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August 5, 2019

U.S Department of Health and Human Services
Office of the Assistant Secretary for Planning and Evaluation
Office of Science and Data Policy
200 Independence Avenue, SW, Room 434E
Washington, DC 20201
Attn: EPAEDEA Report Feedback

Re: Response to Request for Information Directed by Section 3 of the "Ensuring Patient Access and Effective Drug Enforcement Act" of 2016 Federal Register Doc. No: 2019-16145

Dear Deputy Assistant Secretary Destro,

I greatly appreciate the opportunity to respond to your Request For Information by offering the following comments.

My name is Jeffrey A. Singer, MD. I am a Senior Fellow at the Cato Institute in Washington, DC, where I work in the Department of Health Policy studies. The Cato Institute is a 501(c)(3) educational foundation dedicated to the principles of individual liberty, limited government, free markets, and peace. Its scholars conduct independent, nonpartisan 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 publications.

My focus of public policy research is the overdose crisis plaguing the US and much of the developed world, as well as the harmful effects resulting from non-medical use of licit and illicit drugs in an underground market fueled by drug prohibition, seeking best approaches to mitigate those harms. My work at the Cato Institute is also informed and bolstered by the fact that I am a general surgeon in private clinical practice in Phoenix, Arizona for over 35 years, and have directly treated acute and chronic surgical patients in pain, many with cancer or critical surgical illnesses, from the time of presentation, through the postoperative period, and during outpatient recovery. I received my BA in Biology at Brooklyn College (City University of New York), my MD at New York Medical College, and completed my specialty residency in general surgery at the Maricopa Medical Center in Phoenix, AZ, after which I became certified by the American Board of Surgery. I am a Fellow of the American College of Surgeons. My work has appeared in the peer-reviewed medical and scientific literature, as well as in national and regional periodicals and journals read by the general public.

It is my firm belief that current policy regarding the overdose crisis places too much emphasis on the prescribing practices of health care practitioners treating their patients in pain. Undoubtedly some practitioners over-prescribe opioids to their patients in pain. But medical

treatment is nuanced. Patients vary not just in physiology, age, metabolism, and tolerance of medication, but in their experience and ability to tolerate pain. It is the job of clinicians to use their best judgment, based upon their clinical knowledge and experience and their knowledge of their patients, in deciding how to treat their patients' pain. There is no "one-size-fits-all" approach to the diagnosis and management of pain. As in many areas of medicine, respected and experienced clinicians can and often disagree on the rational approach to treating pain in any given circumstance. The same can be said about a vast array of clinical challenges providers face. Experts in various medical specialties often have animated and unresolved disagreements, expressed at conferences and in the literature, regarding the rational use of antibiotics to treat infectious diseases; the proper management of diabetes; the indications for the pharmacologic treatment of hypertension; and numerous other medical and surgical conditions that have varied presentations and responses to treatment.

Prescription Volume and Misuse, Use Disorder, and Overdose Rates

The emphasis on restricting the prescription volume of opioids derives from the erroneous belief that the opioid-related overdose crisis resulted from a pattern of "over-prescribing" of opioids by health care practitioners. However, research using data provided by the National Survey on Drug Use and Health and the US Centers for Disease Control and Prevention clearly shows no correlation between prescription volume per capita and "past month non-medical use" as well as "pain reliever use disorder in the past year" in adults age 12 and over. Furthermore, the data show prescription volume peaked in 2012 and as total prescription volume dropped by 29 percent between 2010 and 2017 the opioid-related overdose death continued to rise, increasing 16 percent from 2016 to 2017. Also changing between 2010 and 2017 were specific drugs that caused the opioid-related deaths. The proportion of opioid-related deaths attributable to heroin and fentanyl has dramatically risen while those due to prescription opioid have fallen off. For example, in 2017, CDC data reveal that fentanyl or heroin were involved in 75 percent of opioid-related overdose deaths, up from 28 percent in 2010. In 2017 just 30 percent of opioid-related overdose deaths involved prescription opioids, down from 52 percent in 2010, and 40 percent of deaths involving prescription opioids also involved heroin or fentanyl. These trends suggest non-medical users are migrating from diverted prescription opioids to heroin and illicitly produced fentanyl as legally produced opioids become more expensive and difficult to obtain in the underground market.[1]

The absence of any relationship between prescription volume and use disorder (addiction) is confirmed by recent research involving the German population. Germany is second only to the US in opioid prescription volume, and the volume curve between 1980 and 2015 closely mirrors the pattern in the US, with volume also peaking in 2012. Researchers there found no significant change in the addiction rate in Germany, with as steady average of 1 per thousand population, over the past 20 years. Yet the opioid-related overdose rate in Germany has remained one of the lowest among the OECD (Organization for Economic Development and Cooperation) nations, the implications of which will be addressed later.[2]

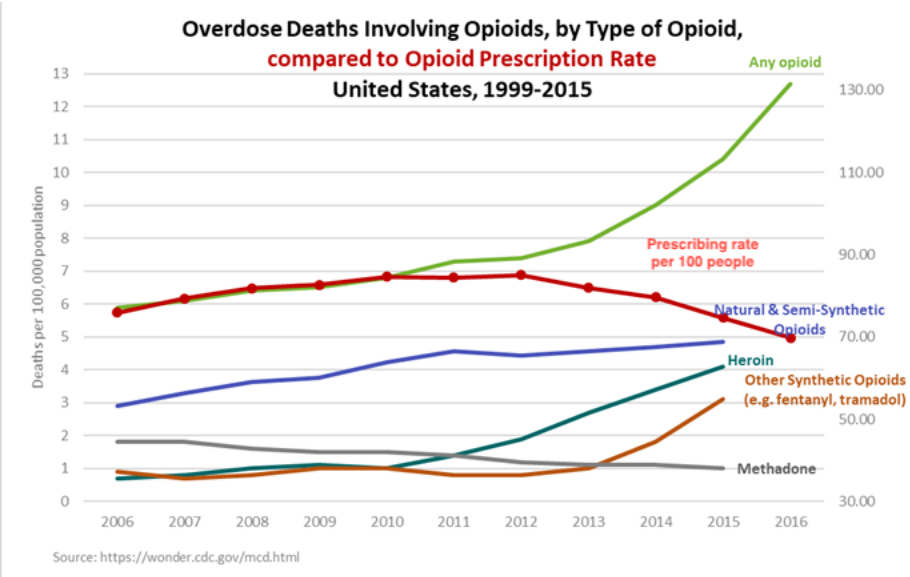
Research from the University of Pittsburgh Graduate School of Public Health finds the overdose rate from the non-medical use of licit and illicit substances has been on a steady,

exponential increase at least since the late 1970s, and is showing no evidence of deviating from that trend. The only thing that has changed over the years is the particular drug in popular use and responsible for those deaths at any given time. In the early part of this century the popular drugs for non-medical users were diverted prescription opioids. Next it became heroin. For the past several years it has been heroin and fentanyl.[3] Recent evidence from the CDC also point to a renewing surge in methamphetamine related deaths.[4] In fact, the CDC preliminary data for 2018 show the number of methamphetamine-related deaths eclipsing those involving prescription opioids. Another worrisome trend is that non-medical users are taking risks that previous generations were less willing to take. For example, Cicero, et al found that 33.3 percent of heroin addicts entering rehab in 2015 initiated non-medical drug use with heroin, as opposed to 8.7 percent 10 years earlier.[5]

The evidence suggests that the overdose crisis from the non-medical use of licit and illicit drugs has sociocultural and psychosocial etiologies and is exacerbated by the dangers inherent in accessing and using drugs in an underground market fueled by drug prohibition. The evidence also suggests the overdose crisis had its beginnings well before prescription opioids began to gain prominence as a cause of death. Furthermore, the evidence indicates that the current emphasis on reducing prescription opioid volume only serves to worsen the situation by driving non-medical users to more dangerous and deadly opioids in the black market (see figure 1).[6]

In addition to exacerbating the overdose death rate among drug users in the underground market, the emphasis on reducing prescription volume— specifically through the actions of Prescription Drug Monitoring Programs in conjunction with law enforcement, and the institution of prescription dosage and amount limitations—has cast a chilling effect on the treatment of pain by health care providers and has caused the under-treatment of many patients in acute and chronic pain as well a the rapid tapering of many chronic pain patients on long-term opioid therapy in ways that can only be characterized as unscientific and cruel.[7]

Figure 1.



Overdose and Addiction Potential of Prescription Opioids

The current emphasis on restricting the production and prescription of opioids to patients is, in part, influenced by a misunderstanding of the overdose and addiction potential of prescription pain relievers used in the medical setting. Numerous studies have shown that prescription opioids have a very low overdose potential when used as directed, and if not taken in combination with other drugs such as alcohol or benzodiazepines, which can potentiate their effect.

For example, a 2011 study by Bohnert, et al, of approximately 155,000 patients in the Veterans Health Administration system from 2004 to 2008 found the frequency of fatal overdose during that period to be 0.04 percent, and that "receiving both as-needed and regularly scheduled doses was not associated with overdose risk after adjustment."[8] Dasgupta, et al reported in 2016 on the results of a prospective cohort study of approximately 2.2 million residents in North Carolina prescribed opioids in one year and found an overdose death rate of 0.022 percent, with 61 percent of the decedent having been found to have other potentiating drugs, such as alcohol or benzodiazepines, in their system at the time of death. The authors concluded, "Dose-dependent opioid overdose risk among patients increased gradually and did not show evidence of a distinct risk threshold."[9] In 2019 Miron, et al analyzed data on noninstitutionalized adult prescribe opioids in 2017, provided by the CDC and the Substance Abuse and Mental Health Services Administration (SAMHSA), and concluded "the number of unintentional nonheroin or synthetic opioid overdoses was about 9,000 or 0.01 percent of the population taking prescription opioids."[10] The role of polydrug use in opioid-related overdoses cannot be over-emphasized. As noted above, roughly 40 percent of overdose deaths involving prescription pain pills involved multiple other drugs, including alcohol, benzodiazepines, cocaine, heroin, fentanyl and methamphetamines. The New York City Department of Health reported 97 percent of opioid-related overdose deaths in 2016 involved multiple drugs, and 46 percent of the time they involved cocaine.[11]

Impacting the misconstruction of the risks of opioids is the tendency to conflate addiction with physiological dependence. Dependence is not the same as addiction. Dependence represents a physiologic adaptation to the drug such that abrupt cessation or a tapering-off of the drug too rapidly can precipitate a withdrawal syndrome.[12] Tolerance is often a feature of this adaptation, referring to the decrease in one or more effects a drug has on a person after repeated exposure, requiring increasing the dose. Physiological dependence is seen with many categories of drugs besides drugs that are commonly abused. Examples include antidepressants, tranquilizers, and even beta-blockers, commonly used to treat hypertension and other cardiovascular conditions. In fact, withdrawal from beta-blockers can have fatal consequences.

Addiction, on the other hand, is a behavioral disorder characterized by compulsive use of a substance despite negative and self-destructive consequences. The American Society of Addiction Medicine defines addiction as a "chronic disease of brain reward, motivation, memory and related circuitry…characterized by the inability to consistently abstain, impairment in behavioral control, craving" that continues despite resulting destruction of relationships,

economic conditions, and health. A major feature is compulsiveness. Addiction has a biopsychosocial basis with a genetic predisposition and involves neurotransmitters and interactions within reward centers of the brain. This compulsiveness is why alcoholics or other drug addicts will return to their substance of abuse even after they have been "detoxed" and despite the fact that they know it will further damage their lives.[13] [14]

Writing in the *New England Journal of Medicine* in 2016, Drs. Nora Volkow and Thomas McLellan of the National Institute on Drug Abuse explained, "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."[15] Two Cochrane systematic reviews of opioid therapy in chronic non-cancer pain patients found addiction rates of roughly 1 percent.[16] [17] Researchers at Harvard and Johns Hopkins Universities and the University of Florida reported in 2018 on over 568,000 "opioid naïve" receiving postoperative opioids between 2008 and 2016 and found a total misuse rate of 0.6 percent. The misuse rate was 0.15 percent per year in patients who had no refills, and 0.29 percent per year in patients receiving one refill.[18]

While opioid prescribing does carry a risk of overdose or addiction, the evidence indicates that the risks of either are extremely small when prescribed by clinicians in the medical setting.

Controversies, Misinterpretations, and Misapplications of the 2016 CDC Guidelines

In 2016 the Centers for Disease Control and Prevention published guidelines regarding opioid prescribing for pain.[19] Many scholars and clinicians specializing in pain management and addiction treatment criticized the guide as lacking a basis in evidence.[20] Despite the fact that the CDC stated its guidelines were meant to be "voluntary rather than prescriptive standards, " and that much of the guidelines were based on "Type 4 evidence" (defined as "based upon clinical experience and observations, observational studies with important limitations, or randomized clinical trials with several major limitations"), policymakers on the federal and state level have been quick to adopt many of these guidelines as statutory limitations on opioid prescribing. The guidelines recognized that "clinical decision making should be based on a relationship between the clinician and patient, and an understanding of the patient's clinical situation, functioning, and life context." But one-size-fits all limitations on prescription dosages and amounts implemented by policymakers are incompatible with that statement.

An outcry from chronic pain patients experiencing the rapid tapering or termination of their chronic opioid treatment that has followed in the wake of statutory enactments of the guidelines led former Food and Drug Administration Commissioner Scott Gottlieb to order a meeting on "Patient-Focused Drug Development for Chronic Pain" on July 9, 2018, stating in the meeting announcement: "In short, having sound, evidence-based information to inform prescribing can help ensure that patients aren't over prescribed these drugs; while at the same time also making sure that patients with appropriated needs for short and, in come cases, longer-term use of these medicines are not denied access to necessary treatments. We will take the first steps toward developing this framework in the coming months, with the goal of

providing standards that could inform the development of evidence based guidelines (emphasis added)." Thus, the Commissioner implied his sympathy with criticisms raised by academic and clinical physicians and their patients regarding the misinterpretation and misapplication of guidelines that lacked a solid basis on the evidence.

In November 2018 the American Medical Association House of Delegates adopted Resolution 235:

RESOLVED, that our AMA affirms that some patients with acute or chronic pain can benefit from taking opioid pain medications at doses greater than generally recommended in the CDC Guideline for Prescribing Opioids for Chronic Pain and that such care may be medically necessary and appropriate, and be it further

RESOLVED, that our AMA advocate against misapplication of the CDC Guideline for Prescribing Opioids by pharmacists, health insurers, pharmacy benefit managers, legislatures, and governmental and private regulatory bodies in ways that prevent or limit patients' medical access to opioid analgesia, and be it further

RESOLVED, that our AMA advocate that no entity should use MME (morphine milligram equivalents) thresholds as anything more than guidance, and physicians should not be subject to professional discipline, loss of board certification, loss of clinical privileges, criminal prosecution, civil liability, or other penalties or practice limitations solely for prescribing opioids at a quantitative level above the MME thresholds found in the CDC Guideline for Prescribing Opioids.[21]

Complaints from clinicians and patients continued to mount in early 2019.[22] [23] On April 24, 2019 the CDC issued a clarification to its guidelines, noting "Some policies, practices attributed to the Guideline are inconsistent with its recommendations." Among the misapplications of the Guidelines it noted were those that result in "hard limits or 'cutting off' opioids," stating the "Guideline does not support abrupt tapering or sudden discontinuation of opioids."

Nevertheless, statutory limitations remain in place, and some leaders in Congress advocate tightening those limitations.[24] Meanwhile, growing fear among health care practitioners that they will be criminally prosecuted or have their licenses revoked cause many of them to severely curtail their opioid prescribing or ceases prescribing opioids altogether.[25] As outlined above, the curtailment in opioid prescribing volume has had no impact on the non-medical use or use disorder associated with prescription opioids, but it has been associated with an increase if opioid-related overdose deaths from heroin and synthetic opioids, and has caused many chronic patients to grow desperate as they get abruptly tapered from their medicine, triggering withdrawal and a return of disabling pain. There are anecdotal reports of some of these patients seeking relief in the dangerous underground market. There are documented reports of many resorting to suicide.[26]

Prescriptions Surged in Germany While Addiction Rate Remained Stable and Overdoses Dropped—Why Is That?

As mentioned above, Germany is second only to the US in opioid prescription volume.[27] The pattern of opioid prescribing, surging from the mid-1990s and then peaking in 2012 after which it receded, mirrors that of the US (see figures 2 and 3).[28]

Figure 2. Prescription Opioid Volume in Germany 1980 to 2015

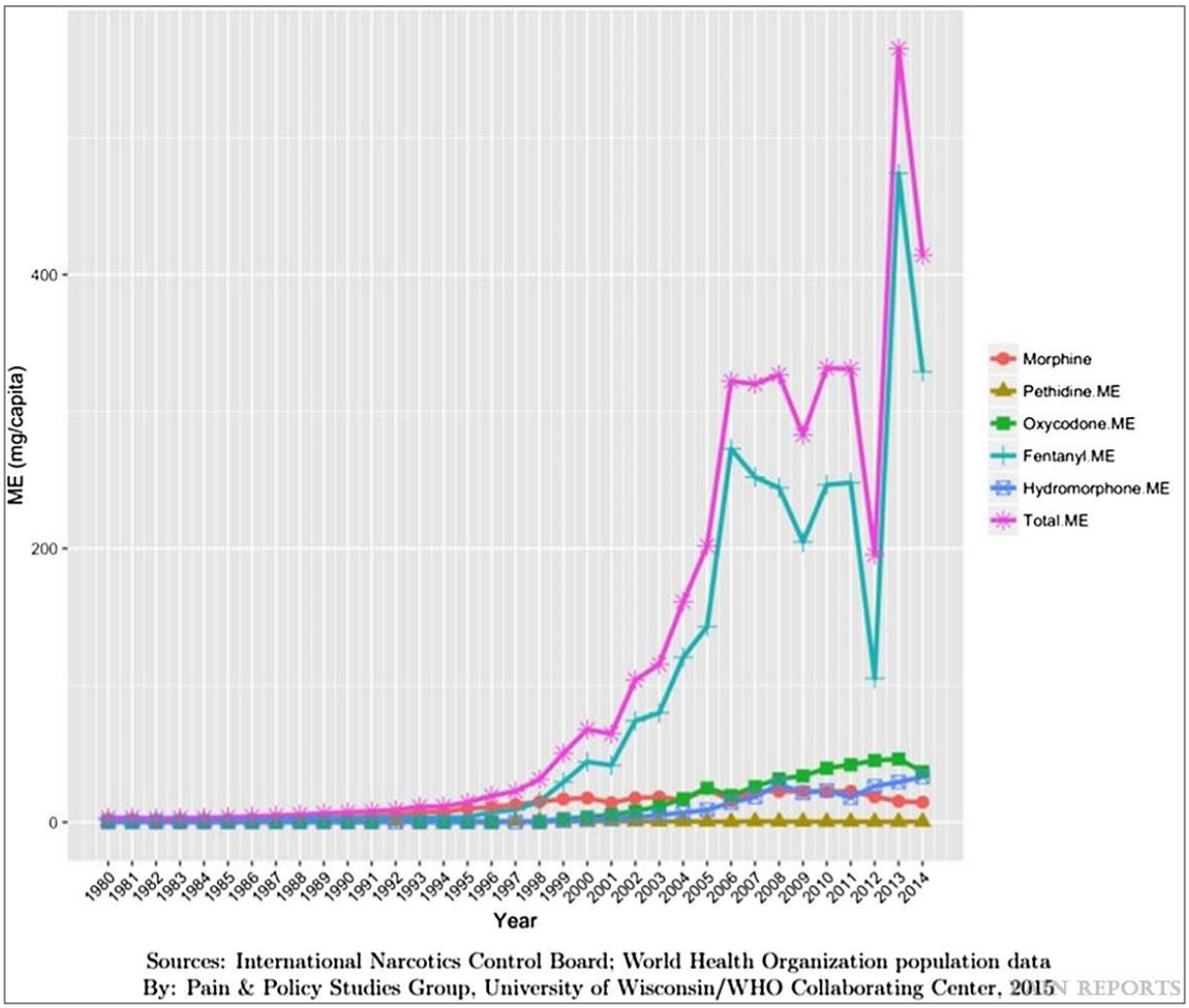
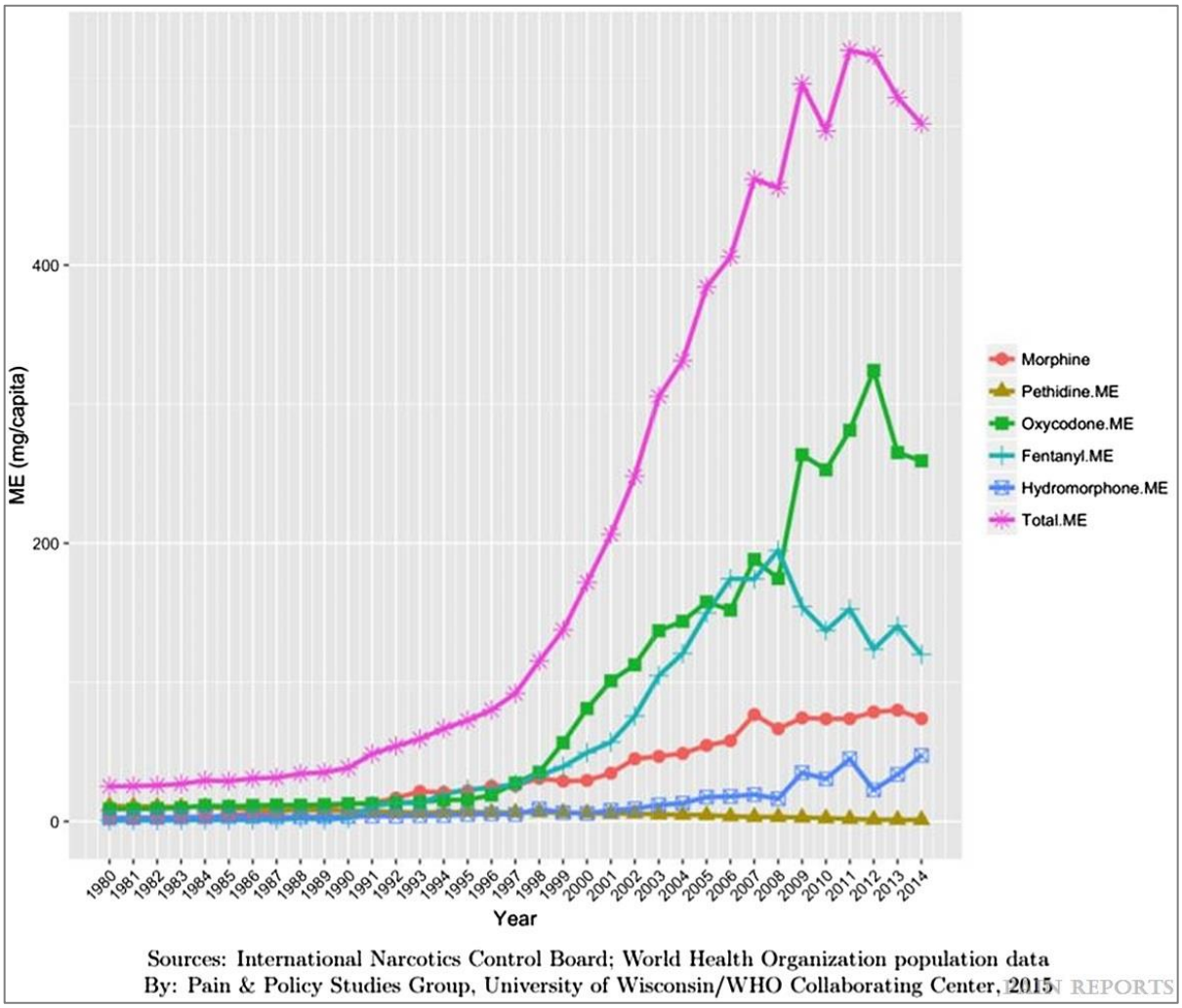


Figure 3. Prescription Opioid Volume in the United States 1980 to 2015



Despite the similarities between Germany and the US with regard to prescribing patterns and their lack of influence on non-medical use or use disorder rates, Germany maintains one of the lowest opioid-related overdose rates among the OECD nations (see figure 4).

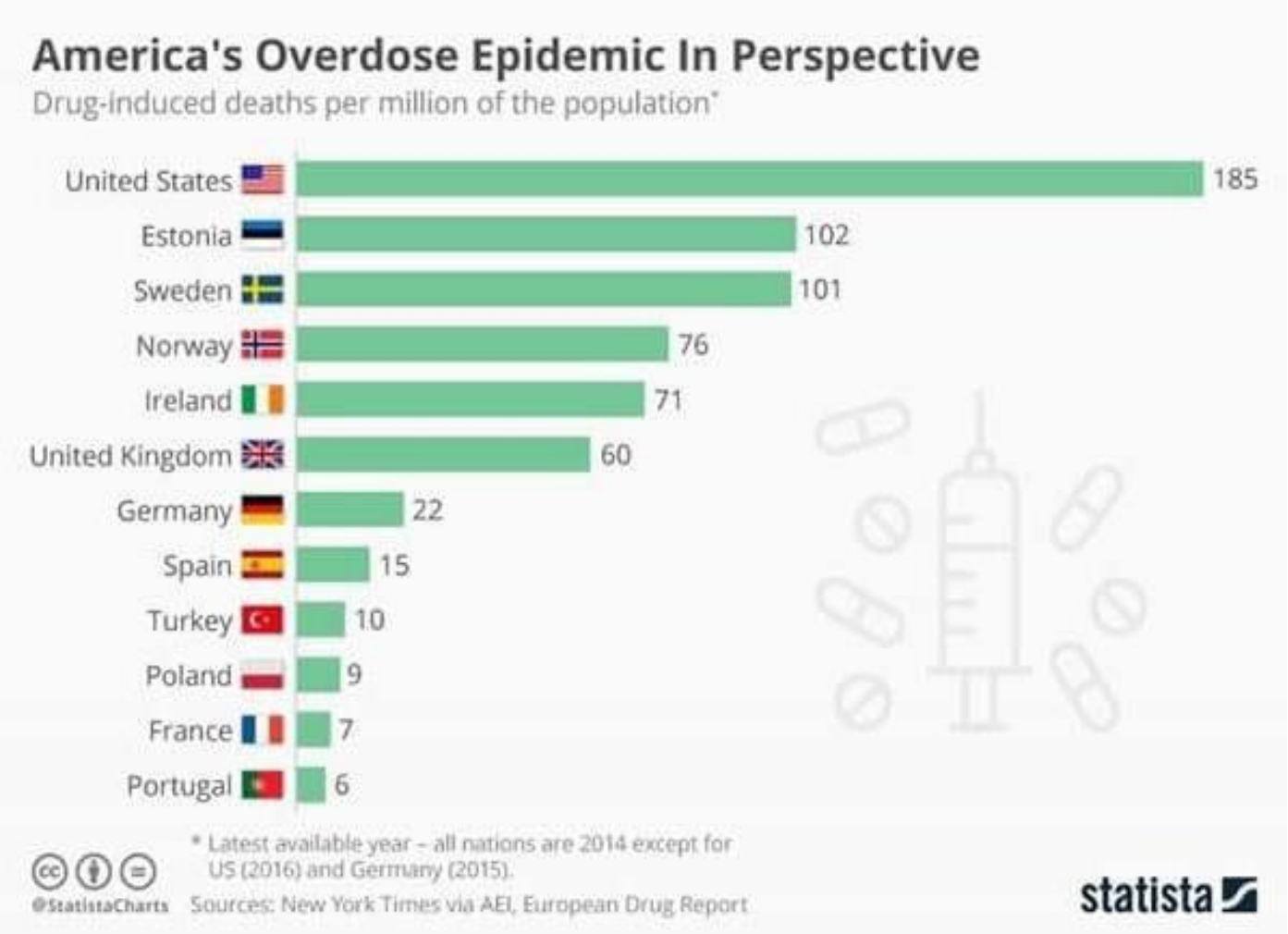


Figure 4. International comparison of overdose deaths

A notable difference between US and German drug policy relates to Germany's decades-long embrace of and emphasis on harm reduction strategies. Unlike prohibition, harm-reduction strategies begin with the realistic and nonjudgmental premise that "there has never been, and will never be, a drug-free society." Akin to the credo of the medical profession-"First, do no harm"-harm reduction seeks to avoid measures that exacerbate the harms the black market already inflicts on nonmedical users and to focus strictly on the goal of reducing the spread of disease and death from drug use. These strategies include needle exchange programs, safe injection facilities (called "Drug Consumption Rooms" in Germany), and Medication Assisted Treatment with drugs such as methadone, buprenorphine, morphine, hydromorphone, and diacetylmorphine (heroin). There is significant empirical evidence that harm reduction strategies successfully reduce overdose deaths, the spread of HIV, hepatitis, and other life-threatening blood-borne infectious diseases, and facilitate rehabilitation from addiction.[29] [30]

As shown in figure 4, Portugal has an even lower overdose rate than Germany. In 2001 Portugal decriminalized personal possession and use of all drugs and redirected resources to harm reduction. It also saw a subsequent drop in its population of heroin addicts as well as in the non-medical use of illicit drugs by teenagers.[31]

Conclusions: Shifting From a War on Drugs to a War on Drug-Related Deaths

Policymakers should remove the statutory dosage and day limits on the prescription of opioids by licensed health care practitioners to their patients in pain. Evidence demonstrates that prescription volume has no impact on the incidence of non-medical use of prescription pain relievers or on pain reliever use disorder. Prescribed in the medical setting and used as directed, prescription opioids have a low overdose and addictive potential. It should permit clinical decision making to be made "based on a relationship between the clinician and patient, and an understanding of the patient's clinical situation, functioning, and life context," as the CDC initially urged in its 2016 Guideline.

Evidence is strong that the policy-induced curtailment in the manufacture and prescription of opioids has driven up the overdose rate by driving non-medical users from diverted prescription pain pills to much more dangerous alternatives in the underground market.

The evidence is so strong that this curtailment has caused unnecessary pain and suffering among chronic pain and other pain patients, that the Food and Drug Administration has been moved to develop its own set of guidelines and the CDC has issued a clarification that states policymakers and practitioners are misinterpreting and misapplying its guidelines on opioid prescribing.

In short, the current emphasis on opioid manufacture and prescribing in addressing the opioid overdose crisis is futile and unintentionally cruel.

Policymakers should shift emphasis to harm reduction strategies. There is already evidence that increased emphasis on harm reduction strategies has reduced deaths in states such as Ohio and Massachusetts, among others.[32]

To facilitate harm reduction efforts, Congress should repeal 21 USC 856, also known as the "Crack House Statute," so that the many US urban centers that wish to join the more than 120 cities throughout Europe, Canada, and Australia, currently reducing overdose deaths with Safe Injection Facilities, will not be blocked from doing so by a federal law that was enacted to address a different problem at a time before Safe Injection Facilities existed.[33]

Congress should also repeal the "X waiver" to make it easier for clinicians to engage in Medication Assisted Treatment with buprenorphine.[34] It should also revise the laws and regulations regarding methadone treatment of addiction, allowing them to come into closer conformity with buprenorphine treatment laws and regulations, as is the case in Canada, the UK, and Australia.[35]

The Food and Drug Administration should make naloxone a truly over-the-counter drug to enhance its dissemination. Increased access to naloxone has been a proven life-saver.[36]

States should ease licensing procedures for providers wishing to establish methadone treatment clinics. They should also repeal anti-paraphernalia laws that inhibit the operation of needle exchange programs, already permitted by federal law and encouraged by the CDC, Surgeon General, and American Medical Association.

A shift to harm reduction strategies will work to reduce disease and deaths related to non-medical use of licit and illicit drugs as it is already accomplishing in much of the developed world.

Progress in combatting the overdose epidemic should not be measured by how much the prescription volume has been reduced, but by how many lives have been saved.

Respectfully submitted,

Jeffrey A. Singer, MD, FACS
Senior Fellow, Cato Institute

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