Medical Research Archives

European Society of Medicine

OPEN ACCESS

Published: December 31, 2023

Citation: Nadeau SE, Lawhern RA, et al., 2023. The Two Opioid Crises-Problems, Causes, and Potential Solutions: An Analytic Review, Medical Research Archives, [online] 11(12). https://doi.org/10.18103/mra.v11i12.4846

DOI
https://doi.org/10.18103/mra.v11i12.4846

ISSN: 2375-1924

REVIEW ARTICLE

The Two Opioid Crises Problems, Causes, and Potential Solutions: An Analytic Review

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ABSTRACT

Introduction: The United States currently faces two opioid crises, an evolved crisis currently manifesting as widespread abuse of illicit opioids, and a crisis in pain management largely manufactured by the Centers for Disease Control and Prevention 2016 Guideline. Our goal in this paper is to identify root causes, trace the trajectory of forces unleashed over time, and define potential solutions to these crises.

Methods: Analytic review of the scientific, socioeconomic, and historical literature.

Results: The evolved crisis reflects a socioeconomic rift in American society that began in the 1970s and has resulted in disintegration of lives and rising levels of desperation, particularly among the under-educated, rendering them susceptible to the lure of illicit opioids. Present manifestations of that crisis reflect a complex series of events starting with a consensus in the late1990s that opioids were fully acceptable in the management of chronic noncancer pain. This was followed by vast opportunism by pill mills, drug distributors, and the manufacturers that supplied them; aggressive actions by state governments to rein in the pill mills; and ultimately, the development of an enormous black market in heroin and fentanyl. The manufactured crisis reflects intrusion into the medical care of patients in chronic pain by the Centers for Disease Control that had been politicized decades earlier and that, in 2016, issued a Guideline that reflected serious mis-construal of the causes of the opioid crisis. We trace this history and review the literature on treatment of addiction, including medically assisted therapy, treatment of depression, psychosocial interventions, 12-step programs, programs that seek to address the causes of desperation, supervised injection facilities, decriminalization, legalization, and the impact of the comprehensive approach taken by Portugal. We also analyze the problems affecting the Centers for Disease Control that led to the publication of its ill-advised 2016 Guideline.

Discussion: We conclude that many approaches currently being taken to treat addiction are well supported by scientific evidence but that the overall efficacy of treatment programs is not optimal and only a small fraction of all patients actually enter such programs. We also conclude that the Centers for Disease Control should have no future role in the regulation of patient care.

Keywords: opioids, opioid crisis, CDC Guideline, CDC, pain management, illicit opioids, opioid abuse

Introduction

The United States is currently in the grip of two opioid crises, both of which began in the 1970's. The first, which may be termed "the evolved crisis," to be further detailed, involves the nation's illicit drug users. It is a manifestation of a rift in American society that began to develop in the 1970s between the economic haves and have nots — particularly affecting non-Hispanic white people with less than a college education [1,2]. This rift has inexorably deepened over the years. It has been politically manifest in various ways but the nature of the rift, hence the potential ability to deal with it, has only recently been recognized. The second, which we term "the manufactured crisis," also to be further detailed below, involves the 15-20 million Americans in disabling chronic pain. Its proximate cause is the 2016 CDC guideline [3], which has been shown to be deeply flawed [4]. However, its deeper cause is substantially the product of very unfortunate decisions made by two American presidents, in 1977 and 1984, that violated the integrity of the science at the Centers for Disease Control and Prevention (CDC), at that time regarded as one of the world's highest ranked scientific institutions (also to be detailed below).

Our premise in writing this paper is that solutions to the two crises cannot be achieved until we understand the root causes. Our goal has been to drill down to these root causes, trace the trajectory of the forces unleashed over time, identify potential future threats, and define potential solutions. The paper is primarily based upon science but it also weaves in a broad ranging context of history, socioeconomics, and politics (see Table 1). It is an expansive review because the evolution of the sustaining causes of both crises has been complex, even as they are closely intertwined and most of the errors made in our efforts to deal with these enormous challenges have stemmed from conflation of the two crises.

Table 1. Timeline of the Development of the Two Opioid Crises.

1865	Opioid use becomes widespread among soldiers injured in the U.S. Civil War
1970s	Early phases of a progressive rift in American society particularly affecting non-Hispanic white people with less than a college education, leading to gradual disintegration of the fabric of their lives and increasing susceptibility to the appeal of opioids as a temporary respite from desperation and despair.
1977	Firing of CDC Director and the beginnings of politicization of the CDC.
1984	CDC Directorship position designated a presidential appointment.
1995	Introduction of the concept that clinicians had an obligation to treat chronic noncancer pain and that opioids were an acceptable means of doing so.
1997-2010	Marked expansion in prescription of opioids for chronic noncancer pain
2000-2010	The advent and proliferation of pill mills, aided and abetted by drug distribution firms and manufacturers, creating a large population of people with addiction —initiating the modern evolved opioid crisis.
2005-2010	The DEA attempts, ultimately unsuccessfully, to constrain opioid distributors and thereby, rein in the pill mills.
2010-2012	US states, through direct legislative action and the universal acceptance of state prescription drug monitoring programs, largely eliminate the pill mills.
2012	Mexican drug cartels and Chinese illicit fentanyl organizations step in to replace the sudden loss of pill mill prescribed opioids with heroin and fentanyl
2008-2015	Growing consensus by legitimate pharmacies that prescription opioids were to blame for the evolved opioid crisis and resistance to filling legitimate opioid prescriptions; promotion by Physicians for Responsible Opioid Prescribing of the idea that opioids were harmful and that overprescribing was responsible for the crisis — the beginnings of the manufactured opioid crisis among 15-20 million Americans in disabling chronic pain.
2010	Beginnings of reduction in opioid prescriptions for patients in chronic pain.
2016	Publication of the first CDC Guideline, most notably ascribing the evolved opioid crisis to over-prescribing by conscientious physicians and asserting that 50 MMED was the point of diminishing returns and increasing risks, despite lack of supporting scientific evidence.
2016	Marked further reduction in opioid prescriptions and the alignment of prescribers, health care provider organizations, health insurance agencies, pharmacies, boards of medicine, state legislatures, and the DEA with the *de facto* CDC mandate. The maturation of the manufactured crisis.
2016-	Legislatures in most states enact laws constraining opioid prescriptions.

2016-2021	No change in annual rate of prescription opioid deaths. Eventual doubling of the rate of illicit opioid-associated deaths.
2016-	Progressive forced tapering of opioids in patients in chronic pain, "firing" of patients and decline in number of physicians willing to provide comprehensive pain management.
2017	Key study (Oliva et al. [5]) demonstrating that overdose and suicide events and deaths among patients prescribed opioids are largely predictable and due to mental health disorders.
~2017-	DEA initiates prosecution of physicians for prescribing medically indicated quantifies of opioids.
2021	No detectable change in prescription opioid overdose death rates. Increase in mortality related to illicit opioids to 85% of the total of greater than 75,000/year.
2022	CDC publishes revision of 2016 guideline — largely a replication of the 2016 Guideline, explicitly ignoring scientific advances and scientific input during the public commentary period and strongly promoting tapering of opioid dosage.
2023-	Manufactured opioid crisis continues unabated and mortality associated with use of illicit opioids continues to grow.
2023-	Vastly undertreated pain persists in 15-20 million Americans with disabling chronic pain.

This analysis predominantly focuses on the American opioid crises. However, the lessons learned likely apply to all countries.

Methods

This is an analytical review. Papers were identified from PubMed, reference lists in papers and books, and selectively, through Google search. Criteria for inclusion included relevance, methodological rigor, and completeness, transparency, and cogence of the results. Concurrence with results of other papers was not a selection criterion. Newspaper articles were selected on the basis of relevance, the standards of the journal (e.g., Washington Post), and the consistency of the reporting with known events. Books were selected from reference lists and through Google search; some were known to the first author from leisure reading. All source materials were subjected to critical analysis and potential sources of weakness are identified in this paper.

The Evolved Crisis

Widespread opioid abuse first surfaced in America in the latter part of the 19th century. It was markedly potentiated by the enormous numbers of civil war soldiers living in chronic pain [6]. Opioid abuse has waxed and waned ever since. Relentless growth since 1970 has culminated in the current illicit drug crisis, which accounted for over 87% of the 70,930 opioid-associated deaths in this country reported in 2020 [7]. The complicated history of the current illicit drug crisis reflects the interaction of a number of contributors that has evolved over time [8,9].

Beginning in about 1995, clinical prescription opioid use expanded as a consensus emerged that chronic noncancer pain needed to be treated and that opioids were an acceptable treatment option, a consensus strengthened by the 1996 action of the American Pain Society, designating "pain as the fifth vital sign" [10]. Intractable pain treatment acts were passed in many states to assure that patients achieved adequate relief [10,11]. Between 1997 and 2002, the number of prescriptions of Oxycontin for noncancer pain increased from about 670,000 to about 6.2 million [10]. This sea change was almost certainly highly beneficial to a large number of patients (including today's legacy patients). However, the policy change also enabled the development of pill mills operated by individual clinicians or organizations that collaborated with selected pharmacies to distribute vast quantities of opioid pills that were shipped about the country and extensively diverted. Pill mills facilitated the development of prevalent addiction in susceptible populations [8,12,13] (see below).

Late in the first decade of this century, a growing consensus began to emerge among legitimate pharmacies, enhanced by the influence of Physicians for Responsible Opioid Prescribing (PROP) and others, that eventuated in the 2016 CDC Guideline [3]. This led to a sharp contraction of opioid availability for clinically managed patients [4,8].

Pill mill operations were strongly aided and abetted by the major drug distribution firms [12]. The Controlled Substances Act (CSA), created by Congress in 1970 (Pub.L.No.91-513,84 Stat.1236), provides the Attorney General of the United States with expansive authority to monitor and regulate manufacturing, distribution, dispensing and prescription of controlled substances, including opioids [14]. Provisions require individuals and entities working with controlled substances to register with the government, take steps to prevent diversion and misuse, and report certain information to regulators. Trafficking provisions establish penalties for the production, distribution, and possession of controlled substances outside the legitimate scope

of the registration system. The CSA defines stringent reporting responsibilities for opioid distribution firms, including reporting of pharmacies that are outliers in quantities of drugs dispensed.

The Drug Enforcement Agency (DEA) was established in 1973 to implement and enforce the CSA (28 CFR § 0.100, 0.101). The Automated Reports and Consolidated Orders System Online Reporting System (ARCOS) [15] enables the DEA to monitor drug distribution. However, efforts by the DEA to meet its regulatory responsibilities with respect to opioids, which began in about 2005, were stymied by the major drug distribution firms [12,16], which, by virtue of their size, have enormous power. In 2017, the combined income of the three largest drug distribution companies, McKesson Corporation, AmersourceBergen Corporation, and Cardinal Health, Inc., was 480 billion dollars [16]. These firms egregiously failed to meet their reporting responsibilities (particularly not identifying outlier pharmacies) [12,16]. They instead mounted massive legal efforts to deter DEA actions, appealed to Congress to threaten DEA funding, and succeeded in having legislation passed that substantially elevated the standard of evidence required of the DEA to take legal action [12]. Drug distribution firms were abetted by drug manufacturers, which provided volume-based discounts to incentivize increased purchasing [12]. Mallinckrodt was the largest volume manufacturer of opioids, shipping some 30 times as many pills as Purdue [12].

Recently, suits by multiple states against some of the major drug distribution firms (McKesson, AmerisourceBergen, and Cardinal Health) and a major manufacturer, Johnson and Johnson, yielded settlements of $26 billion [17]. In 2022, the attorney general of New York secured a $3.1 billion settlement by Walmart [18]. While these are large sums, they represent a very small fraction of the annual income of these companies. Furthermore, the settlements are to be paid out over years — 18 in the case of the $21.12 billion suit against McKesson, AmerisourceBergen, and Cardinal Health [19]. It therefore remains to be seen whether the settlements will have any deterrent power or merely be accepted as a cost of doing business.

Pill mill operations continued unabated until two major actions were taken. First, legislative action was taken against them in 12 states in the 2010-2012 period, most importantly by Florida, the epicenter of pill mill activity [13,20]. Second, progressive implementation of prescription drug monitoring plans (PDMPs) expanded to 49 states and the District of Columbia (27 by 2005, 42 by 2010, and now all states — Missouri joined in 2022 [13,21]). The key contribution of PDMPs has likely been to render pill mill operations more transparent. Pill mill operations largely came to a halt by 2012 [8]. However, the highly desirable outcome of shutting down pill mills inadvertently left large addicted populations without a prescription opioid supply, paving the way for a marked increase in the activity of Mexican drug cartels supplying heroin and Chinese organizations supplying illicit fentanyl. Fentanyl, because it is 50 times more potent than heroin, made this development particularly deadly as small errors in quantity of fentanyl added to heroin or other drugs carried a high risk of death.

Many studies suggest that addiction is best viewed as predominantly a disease of despair [1,9,22-30]. Homelessness and a history of imprisonment are highly prevalent [31]. In this context, opioids and other mind-altering drugs, including alcohol, provide a highly effective but short-lived escape from intolerable psychological, social, and economic conditions [32]. One of the most dramatic demonstrations of this phenomenon is that, while 20% of servicemen in Viet Nam were addicted to heroin, 95% of those addicted did not continue heroin use once they returned to American soil [33,34]. Ultimately, Robins' work suggests that heroin addiction is not primarily about the drug (currently the mainstream conceptualization) [35]: it is instead about the people who use it and the circumstances they live in.

Jalal et al. [36] have provided evidence that the current opioid crisis is simply the latest phase of an exponential rise in drug abuse that began in 1979 (Figure 1). They surmised that "sociological and psychological 'pull' forces may be operative to accelerate demand, such as despair, loss of purpose, and dissolution of communities." This fundamental idea was eloquently expanded by Introcaso [26], who drew heavily from the recently published book by Case and Deaton [1]. Case and Deaton note that the exponential rise in deaths from drugs of abuse accurately tracks a number of profound social, economic, and cultural changes that have taken place in the United States over the past fifty years — changes that have particularly impacted non-Hispanic white people with less than a college education (see also [2,30]).

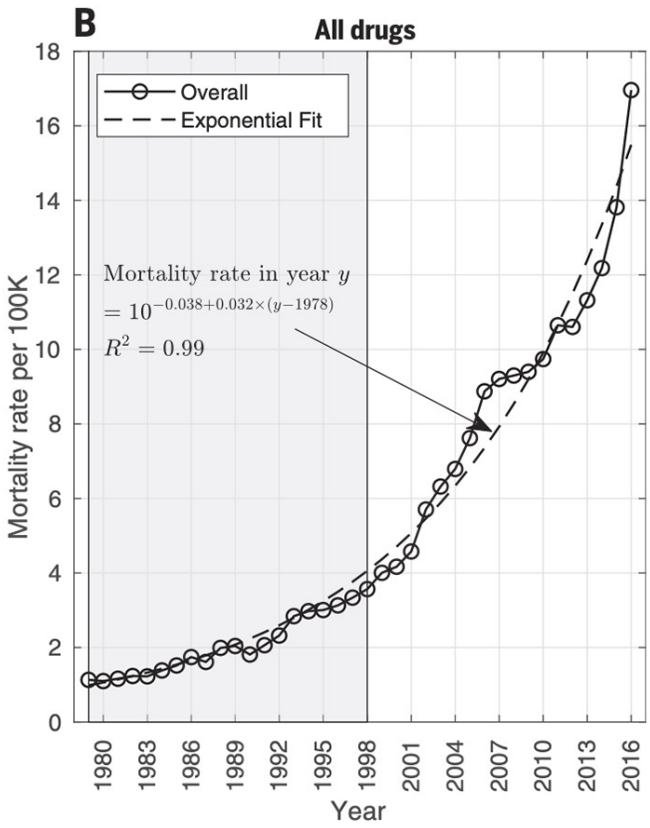

Figure 1. Mortality rates from all unintentional drug overdoses and exponential equation and fit. From Jalal H, Buchanich JM, Roberts MS, Balmert LC, Zhang K, Burke DS. Changing dynamics of the drug overdose epidemic in the United States from 1979 through 2016. Science. 2018;361:eaau1184. Reprinted with permission from AAAS. https://www.science.org/doi/10.1126/science.aau1184?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed

The most influential factor in the evolution of the resultant societal rift has been education [1,37]. Those with a college degree have enjoyed the best that America has to offer, experiencing richer and more socially and intellectually stimulating lives, living in ever more luxurious homes, seeing even better prospects for their children, and thus seeing many causes for opportunity and hope. Those with less than a college education, and even more so, those with less than a high school education, have seen the very fabric of their lives slowly disintegrate [1]. Single parent families have grown in prevalence. Religion has declined as a source of succor and togetherness. Unions, community organizations, and other sources of social support have dramatically declined. Culture has eroded. Whole industries have almost disappeared — most conspicuously coal —and many jobs have been automated or sent overseas [1].

The economic foundation of once-flourishing cities and towns, most in America's heartland, has disintegrated [1]. The days of working for a manufacturing corporation for life and developing a sense of belonging and pride in work, however menial one's job, have largely disappeared. Instead, corporations now commonly outsource menial work to faceless service firms, often with reduced or no benefits. Other undereducated workers have had to go to work for service industries (e.g., fast food). Real wages have declined, steadily eroded by loss of well-paying jobs, inflation, and most seriously, the increasing cost and declining efficiency of health care [1]. These changes appear to reflect a fundamental change in the relationship between business and labor that has evolved as a result of the widespread acceptance of neoliberal ideology [29]. The prevalence of pain and disability, often of occupational origin [23,29], has increased and mental health has declined. Social isolation and loneliness have increased and are now recognized as important contributors to poor health [38]. This complex of factors has led to lives of desperation, a search for even transient respite through drugs of abuse, most particularly deadly fentanyl, and deaths of despair, most often via drug overdose or suicide [1].

As Case and Deaton show, from a socioeconomic perspective, the present opioid crisis was predictable decades ago. In fact, there is reason to believe that the levels of alcohol abuse, illicit drug

use and suicide might usefully be regarded as a barometer of the general health of our entire society and individual states and counties.

Cross-sectional studies have reinforced the case made by Case and Deaton. Affected populations are disproportionately young, male, high school or less educated, poor (income below twice the federal poverty level), and unemployed. They are also more likely to report fair or poor health, a chronic health condition (often pain), disability, and impairment in mental health [4,24]. This population is medically underserved. The narrow focus of the CDC on clinical populations as the alleged cause of the opioid crisis, rather than on illicit drug users, has also meant that insufficient action has been taken on behalf of those caught up in the illicit drug market.

Case and Deaton detailed the major factors that set the stage for the opioid crisis and identified the single most powerful variable modulating susceptibility to opioid abuse: education. However, as noted by Jalal [36](see also [39]), there is considerable local variability in the demographics of those most susceptible and in drugs of choice. Local populations of people with addiction may differ because of variations in local demographics, socioeconomic conditions, policing practices, patterns of inequities, culture, drug availability, local prescribing patterns, local pharmacy practices, insurance company practices, and support infrastructure (see e.g., [40])(Figure 2). As Jalal et al. [36] also noted, the evolved crisis, reflecting these various factors, is nothing if not dynamic. Over recent years, there has been an increase in illicit opioid use and associated overdose deaths among black and Hispanic populations [41-44]. Gibbons et al. [45] review the potential reasons for this trend among blacks. They suggest that the reason may lie in their impaired access to addiction treatment that has become increasingly available to whites over the past 10 years.

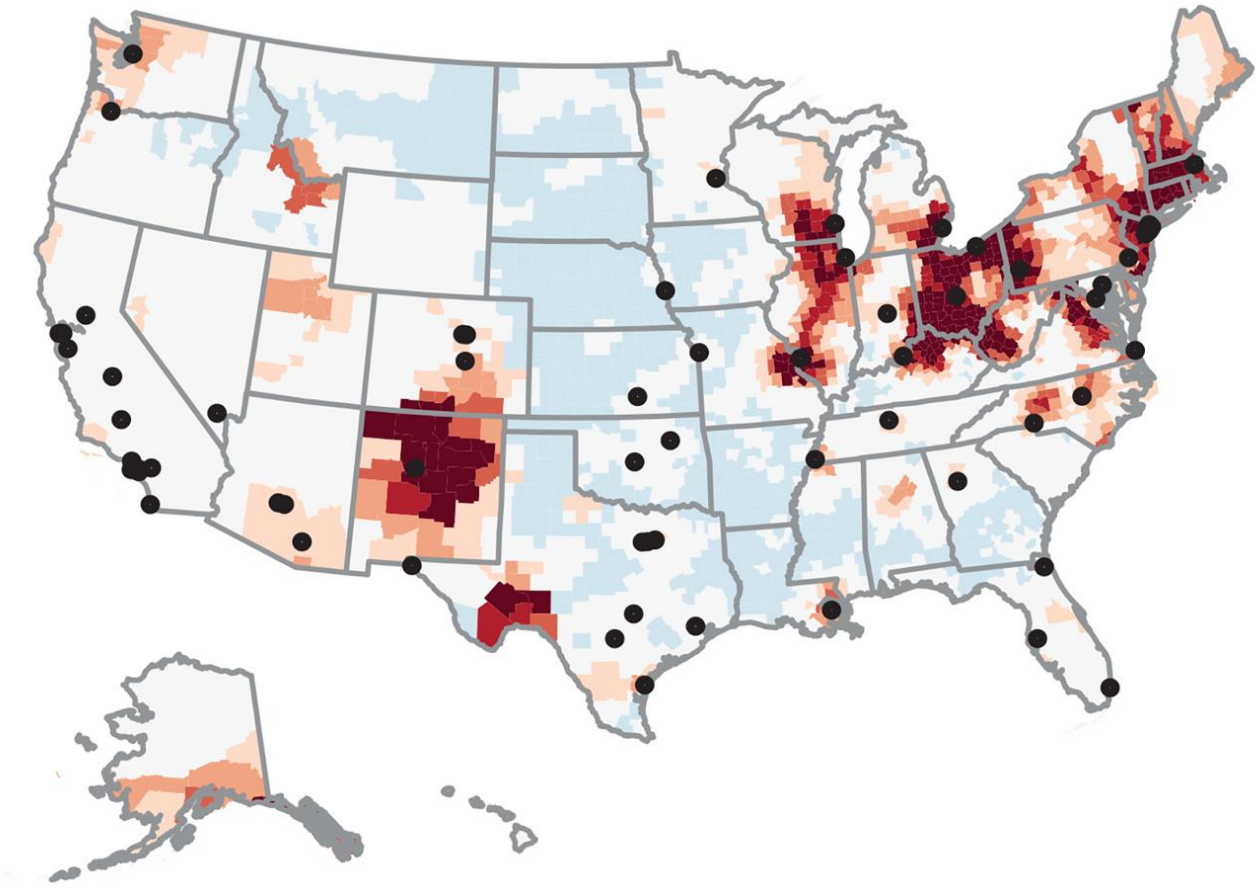

Figure 2. Geography of heroin overdose deaths/100,000, 2012-2016. Dots are cities with >300,000 population. From Jalal H, Buchanich JM, Roberts MS, Balmert LC, Zhang K, Burke DS. Changing dynamics of the drug overdose epidemic in the United States from 1979 through 2016. Science. 2018;361:eaau1184. Reprinted with permission from AAAS.
https://www.science.org/doi/10.1126/science.aau1184?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed

The Manufactured Crisis

The second crisis, involving the 15-20 million Americans in chronic disabling pain [46,47], started to emerge late in the first decade of this century as a consequence of the rising tide of opioid associated deaths. The term "pharmacy crawl" had emerged by at least 2012, describing the plight of patients in pain who had to go from pharmacy to pharmacy to find one that would fill a prescription [48]. The concept that prescription opioids were responsible for the growing crisis was very effectively promoted by the PROP organization. In actual fact, however, there is not now and there never has been evidence that prescribing by conscientious physicians contributed significantly to the opioid crisis [4,49].

Physicians for Responsible Opioid Prescribing (PROP) was heavily represented among the authors of the CDC Opioid Pain Management Guideline published in 2016 [3] (hereinafter termed the 2016 Guideline). The Guideline quickly became the *de facto* law of the land. CDC actions would also have far-reaching institutional ramifications — on the US Department of Veterans Affairs, the US Department of Defense [50], health care provider organizations, health-insurance companies, pharmacies, boards of medicine, state governments, and the DEA [4,8]. CDC actions also put conscientious clinicians in a dire dilemma: 1) observing their patients suffer as they struggled to provide treatments that were seriously suboptimal; 2) abandoning the field of pain management; or 3) daring to provide optimal care and face potential loss of their hospital clinical privileges, and potentially, actions by their boards of medicine and the DEA, the latter sometimes leading to imprisonment [13]. Finally, the actions of the CDC have further stigmatized conscientious physicians prescribing opioids and patients taking them [4,8].

The Guideline had profound ramifications for patients in chronic pain, immeasurably contributing to the pain, suffering, dysfunction, and even mortality of this population, thereby creating a full second crisis [4,8].

Following its failures to rein in the drug distribution firms and opioid manufacturers, the DEA has turned to the practice of harvesting data from PDMPs and other databases to identify physicians who, in the course of conscientious care of patients, could be charged with prescribing "outside the standards of medical care," simply by virtue of the number of opioid prescriptions and the size of these prescriptions [13]. Because there is no general agreement on such standards, virtually any practice involving prescribing opioids has become susceptible to DEA prosecution. Conscientious physicians have been sentenced to prison, sometimes with decades-long sentences [13]. These actions have had a profoundly negative effect on treatment of chronic pain.

The ramifications of the 2016 Guideline, now reinforced by a 2022 revision, have had another effect: many of the fallacies propagated by PROP and incorporated in the 2016 Guideline have now become opioid memes [51,52], thereby substantially escaping the gauntlet of scientific scrutiny, even within scientific publications. As we have seen with controversies surrounding the COVID epidemic, memes can often be more powerful and enduring than scientific facts. This evolution of opioid memes has likely been energized by their congruence with memes about opioids that have been percolating in American society since the 19th century.

Scientifically false memes about opioids appear to be widely accepted as "truths" and bandied about by the lay public, journalists, authors, movie makers, scientists, editors of prestigious journals, lawyers, pharmacies, health insurance companies, boards of medicine, the DEA, and legislatures. The imposition by the majority of state legislatures of strict limits on short-term opioid prescriptions is an excellent example: the incidence of long-term use of opioids following a short perioperative course has now been definitively shown in excellent studies to be very low (0.6% in the subsequent year [53]) and there is good reason to believe that this 0.6% consists of patients with chronic pain [4](see also [54]). Nevertheless, the meme that brief exposure leads to future addiction persists and empowers legislation.

Our prior analysis of the clinical evidence bearing on opioid use to treat chronic pain [4] revealed a number of additional false memes: that overprescribing of opioids is responsible for the opioid epidemic (there is actually no correlation at all between rates of prescribing and overdose deaths [49]); that opioids are ineffective in treating chronic pain (the apparent lack of evidence of efficacy is an artifact of experimental designs that are inadequate to effectively test the effects [55]); clinical use of opioids is associated with high risk of overdose and death (the risk has been shown to be low [56,57] — a false meme that derives from the CDC failure to distinguish prescription opioids from synthetic opioids (e.g., fentanyl); the risk of developing OUD is high (various papers differ by over 1000% in estimation of risk and a best estimate is actually about 3% [4]); and nonmedical approaches to treating chronic pain are to be preferred (when, in the absence of comparative

effectiveness studies, it is impossible to gauge the absolute effectiveness of these methods).

There is strong reason to believe that the populations caught up in the two opioid crises are almost entirely different (Figure 3). First, prescription drug related mortality has changed very little over the past 10 years even though the CDC Guideline has been very effective in curbing opioid prescription rates [7,49]. On the other hand, deaths associated with synthetic opioid analgesics, excluding methadone, have increased by a factor of 17.8 and now account for >85% of all opioid-associated deaths. Had there been significant overlap between the two populations, we would have seen a major impact of the CDC Guideline on total mortality —unless all people in the overlap group fully compensated loss of prescription opioids with illicit opioids (in which case they would have disqualified themselves as members of the prescription opioid group). Second, the demographics of these two populations are very different [8,58]. Nevertheless, the two crises and the causes for them continue to be conflated.

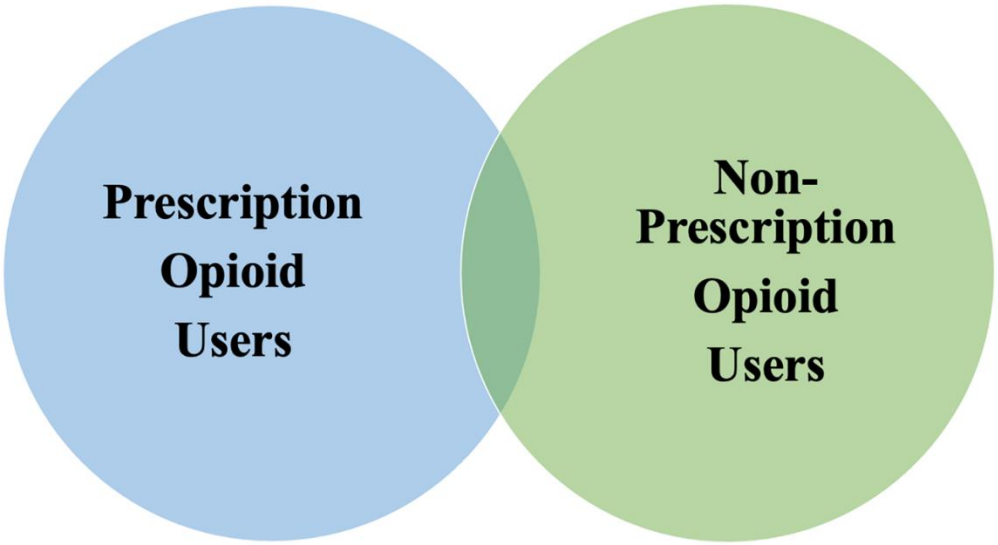

Figure 3. Venn diagram of opioid users. Patients treated for chronic pain by conscientious physicians presently constitute the vast majority of prescription drug users. Illicit drug users likely consist largely of people, many if not most with drug addiction, escaping lives of despair by using street drugs. However, this group also includes the difficult to quantify population of recreational drug users [59]. The overlap group, which has been markedly reduced by actions taken by the states between 2010 and 2012, consists of a heterogeneous population of individuals, the make-up of which constantly changes with time and locale. It includes patients followed in clinics who are driven to street drugs because of serious undertreatment of pain; patients with uncontrolled pain to whom spouses and friends donate opioids; patients followed in clinics who divert prescription drugs, for sale, to aid a partner in pain, or under threat by a partner with addiction; patients followed in clinics who misuse opioids because of events in their lives that have driven them to despair or who use opioids to cope with intolerable situations, e.g., soldiers in Vietnam [33,34]; family members or burglars who filch opioids from the medicine cabinet for sale or personal use; and people with addiction who routinely use street drugs but who intermittently obtain prescriptions in pain clinics [22,60-62]. The existence of this overlap population may account for evidence that prescription opioid associated drug deaths, most particularly in West Virginia but also in some other states, are again climbing [63].

Overdoses, suicide attempts, and deaths associated with opioid use

The question remains as to why patients taking prescription opioids are experiencing opioid-associated deaths. The incidence of death — estimated at 0.25%/year for dosage greater than 100 MMED [57] — though low, is nevertheless of great concern, the more so as understanding the causes may provide the basis for reducing the incidence. This mortality appears to bear only a weak relationship to opioid dosage *per se*: in a Veterans Administration study (2004-2009), the median opioid dosage in patients dying an opioid-associated death was 60 MMED (interquartile interval 30-120) [64].

If not primarily opioid dosage, then what? In a VA population of 1,135,601 patients [5], 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, total event incidence 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 it was high 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%. The leading risk factors were prior overdose/suicide event, odds ratio (OR) 23.1, detoxification 18.5, inpatient mental health treatment 16.1, the 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 OR 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 was an important factor [4].

In aggregate, the data on overdoses/suicides/deaths in clinic populations and the data on illicit opioid use populations suggest that the reasons for opioid-associated death are fundamentally the same in the two populations: desperation and despair.

Addiction and Opioid Use Disorder

We us the term addiction throughout this paper, rather than opioid use disorder (OUD) (see also [65]). Addiction can be defined as the irrepressible use of mind-altering drugs, most particularly illicit opioids, cocaine, and methamphetamine, but also alcohol. This use is typically at considerable risk of serious health consequences or even death, a risk undertaken to achieve euphoria but also to escape the physical and psychic pain of life.

We avoid the DSM-5 term OUD, which is defined as the combination of opioid abuse and opioid dependence [66] because 1) it is operationally an imprecise term [4]; 2) use of the term has done much to conflate victims of the manufactured crisis with victims of the evolved crisis; and 3) dependence is a pharmacodynamic phenomenon, shared by many classes of central nervous system active drugs, that has little to do with addiction (although withdrawal symptoms certainly play a role in the daily dynamic of addiction). It is our impression that the OUD concept, as operationally defined by DSM 5, has had another very serious consequence: it appears to have served to legitimize the scientifically unsupported suspicions of clinicians that every patient chronically prescribed opioids might be an abuser. The 2016 Guideline then put a fine point on it: no longer did clinicians need to worry about a set of criteria; instead, they could assume that if the patient was taking more than 50 mg morphine equivalent/day (MMED), then the probability that they faced serious risks and might become a drug abuser was significantly increased.

It may be that the strongest argument for using the term addiction in lieu of OUD is the operational one. Addiction defines almost the entire population of consumers of illicit drugs (save for those who successfully use them for recreational purposes) and largely, if not entirely, excludes clinically managed populations. OUD includes the entire population of illicit drug users as well as highly varying percentages of the clinical pain population, depending on which study you read [4]. The term therefore lacks discriminatory value.

Our statement about causes of addiction might be construed as an argument against the mainstream conceptualization of addiction as a brain-based disorder induced by use of opioids (and other CNS-active drugs) [35]. This is not the case. However, there is now a compelling body of science, detailed above, that indicates that this model is too narrow. It does not take into account the psychosocial and economic conditions that appear to be the major driving factors behind addiction. Thus, addiction might be misinterpreted as solely a direct impact of the drugs on the brain when it is predominantly driven by the effect of drugs in mitigating the impact of psychosocial and economic conditions (however briefly). Both the euphoria associated with taking an opioid (or other drug) and the relief from suffering it provides can engage brain motivational systems to produce an experience of reward (see [67]).

This conceptualization applies no less to patients in chronic pain treated with opioids. Their major source of reward is relief of suffering from physical pain. However, if a patient's life becomes sufficiently destitute that despair creeps in, opioids might provide either temporary surcease from that misery or a potential means for suicide.

The importance of psychosocial conditions has also been shown in animal studies: rats housed in isolation (a desolate condition for these highly social animals) will consume a substantial dosage of

opioids if they are made available. In rats living in what have been called "rat parks" where they may interact with many peers in a quasi-natural environment, opioid consumption is markedly less [68,69].

The mainstream conceptualization of addiction also cannot account for the complicated dynamics of the current phase of the drug crisis. As we have noted, opioids and addiction have been around for a very long time. The concept that the current phase owes simply to overprescribing by conscientious physicians is strongly contradicted by published evidence [4,49]. Demonstrations that addiction is driven far more by people and their circumstances, such as the studies by Robins of Vietnam war soldiers [33,34], provide further evidence that the mainstream conceptualization of the mechanisms of addiction is too narrow.

Potential Solutions

ILLICIT DRUG CONSUMERS AND THE EVOLVED CRISIS

In developing strategies to deal with the current illicit drug crisis, the results of the unfortunate 1920-1933 experiment by the United States in prohibiting alcohol are instructive. From that experiment, we learned that prohibition had no effect on consumption; it transformed a nation of beer drinkers into a nation of consumers of distilled beverages, simply because the latter were far easier to smuggle (the iron law of prohibition [9,70,71]); and it bred a black market, which in the 1920s came to be dominated by a fledgling criminal organization, the Mafia, which was then catapulted to enormous power. The effects of prohibition of mind-altering drugs have proven no different than the prohibition of alcohol [72]. Enormous efforts devoted to interdiction, prosecution, and punishment have failed to stem illicit drug use [9]. The twenty first century opioid crisis has also paved the way for more potent drugs, e.g., fentanyl. Yesterday's Al Capone has been replaced by today's El Chapo. Clearly, any real solution must instead address the demand side of the equation. Unfortunately, this reality has not yet been accepted as a component of US national drug policy.

Detoxification

Simple drug "detoxification," in and of itself, is of no value [73] and yet as few as 13% of patients who undergo inpatient detoxication receive rehabilitative services [74].

Medically assisted therapy: methadone, buprenorphine, naltrexone and naloxone

Many meta-analyses of randomized controlled trials (RCTs) have addressed the use of methadone, buprenorphine, sustained release morphine, heroin supplementation, and naltrexone in the long-term management of patients with opioid addiction.

Older RCTs demonstrated that both methadone and buprenorphine were effective in reducing illicit opioid use and promoting retention in treatment [75]. More recent meta-analyses directly comparing the two drugs have shown that there is enormous heterogeneity in patient retention between RCTs and ultimately, there is no clear difference in the effect of the two drugs when used in optimal dosage, on retention rates [76]. However, Lim et al. [77], in a network meta-analysis of 79 RCTs, found that the average percentage of treatment retention across all studies was 77.6% for sustained release morphine, 64.1% for methadone, 54.3% for buprenorphine, 41.0% for naltrexone, and 30.1% for control (standard of care, usual care, treatment as usual, behavioral counseling, or placebo); there was too much heterogeneity in definition of continued illicit use to provide the basis for a meta-analysis. Four RCTs suggest that slow-release oral morphine is equivalent to methadone in its effects on treatment retention and reduction of heroin use [78] and there is no difference in adverse effects.

In a meta-analysis of 19 retrospective and prospective cohort studies, it was determined that methadone treatment was associated with an average reduction in overdose mortality rate of 80% and buprenorphine treatment with a reduction of 70% (statistical comparison not warranted because the populations were different) [79] (see also [80]). Use of these drugs is also associated with substantial reductions in all-cause mortality [80,81]. Buprenorphine may be safer because methadone is a full agonist at the mu-receptor, it has a long half-life, and it often prolongs QT interval. There is also a ceiling effect on buprenorphine suppression of respiration. Therefore, the effects of methadone may be additive to those of concurrently used illicit drugs when beginning treatment and when patients go off treatment — a particular problem in patients who repeatedly cycle in and out of treatment [79].

The opioid receptor antagonist naltrexone, particularly in extended release or implant forms, may be highly effective in reducing all-cause mortality, opioid use, and overdose associated mortality [80,82,83]. The short acting mu-receptor antagonist naloxone can be highly effective in reversing respiratory depression due to opioid overdose. However, dosing is not straightforward, acceptance by vulnerable populations represents a challenge, and the magnitude of naloxone distribution effect on illicit opioid use mortality is likely not great [84].

Medically assisted therapy (MAT) lowers the risk of acquiring human immunodeficiency virus infection, either via sharing of needles or unprotected intercourse [85-87], as well as the risk of acquiring hepatitis C virus infection [31].

Unfortunately, only about 30% of patients entering opioid specialty treatment for addiction receive MAT [88] and there are also reasons to question translatability of these trials to clinical practice [89]. In the 32 methadone vs buprenorphine or buprenorphine+naloxone RCTs reviewed by Lim et al. [77], median duration was 24 weeks (mean 23, range 2-52). The retention rate was actually slightly greater in trials with duration ≥24 weeks (0.53) than it was in the trials of duration of <24 weeks (0.49). Retention rates do not seem to be sustained over time. In a recent retrospective propensity score matched population-based study of participants in State of Maryland substance use specialty treatments, overdose death rates were lowest during medication treatment (0.48/1000 person-years), followed by non-medication treatment (4.13/1000 person-years), after non-medication treatment (13.22/1000 person-years) and after medication treatment (17.21/1000 person-years)(follow-up of up to 700 days) [90]. Death rates after the first month following treatment declined to 11.92 and 12.32/1000 person years after non-medication and medication treatment, respectively. In other words, MAT exerts a dramatic effect so long as it is sustained but that effect disappears after the patient leaves treatment. MAT was associated with a substantially greater duration of treatment compared to non-medical treatment (248 days versus 22 days). Longitudinal studies suggest that time in treatment is strongly associated with increased likelihood of successful completion of treatment without re-presentation within six months [91].

Longitudinal cohort studies can address some questions not answerable by RCTs. In an English national, five-year, prospective, observational cohort study of publicly funded, specialist treatment services for addiction [91], successful completion of treatment without re-presentation within six months was achieved in 21.9% of patients. Treatment consisted of MAT plus some mixture of other measures, including contingency management, motivational interviewing, and adjunctive support services such as facilitated access to mutual aid and family, housing, employment, and education and training supports. The process of achieving stable recovery from addiction may involve several cycles of treatment extended over a decade or more [92,93].

Depression

From clinical experience, it can be said that the major challenges to management of chronic pain are the pain itself, depression, adverse home environments, and unemployment, not necessarily in that order. Patients with addiction are likely to struggle with the same complex of problems, albeit in different measure, the overbearing existential challenge being the most salient. This being the case, it is remarkable that depression is rarely even mentioned in the treatment of addiction — despite evidence of a strong association between psychiatric disorders, particularly depression, and opioid overdose [4,5,94]. Furthermore, there is a paucity of studies on the effect of pharmacological treatment of depression on addiction.

In a claims-based analysis, Litz and Leslie [95] found that patients with major depressive disorder or bipolar disorder were less likely to adhere to buprenorphine prescribed to manage addiction (OR 0.80). Petrakis et al. [96], in a 12-week RCT of fluoxetine (20-60 mg, titrated) in participants on methadone maintenance found no effect of the drug on either depression or on heroin use. Given the time needed to achieve steady state levels of fluoxetine (4 months), dose titration effects were likely very modest. Dean et al. [97], in a 12-week RCT of fluoxetine 20 mg in 49 participants, reported similar results. Carpenter et al. [98], in a 12-week RCT of titrated sertraline (mean maximum dose 169 mg/day) in 95 participants on methadone maintenance, demonstrated significant sertraline-associated reductions in depression and opioid use only among those participants living in a more positive environment (precisely defined through a multi-dimensional rating system). Poling et al. [99], in a 12-week RCT of 60 methadone-stabilized participants not selected for depression, randomized to placebo, citalopram 40 mg, or citalopram 40 mg + bupropion 50 mg, found no antidepressant effect on illicit opioid use.

These studies, in aggregate, provide some evidence of antidepressant effect but by no means a scientific basis for introducing treatment of depression as standard practice during MAT. However, in clinical practice, depression is not treated with a fixed dose of a single pharmacological agent — it is treated to remission using a combination of an SSRI/SNRI ± adjuvant bupropion, optimally titrated, ± a mood-stabilizing anticonvulsant ± a neuroleptic + some form of psychotherapy, if it is available.

Psychosocial interventions

A Cochrane review in 2011 demonstrated the potential value of psychosocial intervention in treating addiction [100]. Any psychosocial treatment

(11 studies of five interventions involving a total of 1592 patients, were reviewed) compared with any pharmacological treatment was shown to significantly reduce dropouts (relative risk, RR 0.71), use of opioids during the treatment (RR 0.82) and at follow up (RR 0.66), and clinical absences during the treatment (RR 0.48). The studies considered a number of different psychosocial interventions and two pharmacological treatments (methadone and buprenorphine). Compared to pharmacological treatment alone (methadone or buprenorphine), combination with any psychosocial intervention significantly reduced dropouts (RR 0.71), use of opioids during the treatment (RR 0.82) and at follow up (RR 0.66), and clinical absences during the treatment (RR 0.48).

The results of subsequent studies (none included in the Cochrane review) have been decidedly more mixed: four RCTs suggested that adjunctive psychosocial intervention is of no value and four suggested that it is [101](see also [102]). The potential reasons for these discrepancies are complex (see excellent analytic reviews by [101] and [103]). The mixed results of these studies raise the question as to whether psychosocial interventions are sufficient to the problem. Given that these patients live lives of desperation, it may be that personal interventions may have superior efficacy, e.g., family counseling seeking to resolve domestic sources of stress, job training, providing a pathway to getting a job, and providing stable housing (see section 6.6.2 of WHO guidelines [104]).

12-step programs

Humphreys and Moos [105] reported the results of a non-randomized study of patients enrolled in 12-step–oriented or cognitive behavioral therapy inpatient programs (with continuing outpatient care) participating in the Department of Veterans Affairs nationwide multisite substance abuse treatment outcome study. The 12-step programs emulated those of Alcoholics Anonymous (AA), Cocaine Anonymous, and Narcotics Anonymous (NA). They demonstrated better 2-year abstinence rates (49.5%) than the cognitive behavioral therapy programs (37%) and at significantly lower cost (see also [106]). The existence of an AA or NA program in virtually every town and city in the United States provides a robust infrastructure for provision of this type of treatment [105].

Rehabilitation of people with addiction

Addiction treatment and treatment research have focused substantially on drugs, hence perhaps the longstanding emphasis on medically assisted treatment in our rehabilitation approaches. We suspect that this is at least in part because of the pervasiveness of the concept that addiction is related to purely neurobiological mechanisms, rather than to psychosocial mechanisms. Given the evidence presented in this paper, most notably by Case and Deaton [1], it seems clear that rehabilitation of addiction must involve rescuing these people from their lives of desperation and that pharmacotherapy can serve, at best, as an adjuvant to this process.

There is considerable evidence that dealing with the factors that are primarily responsible for lives of desperation is important. These factors include absence of meaningful employment, isolation, poor social support, prevalence of exposure to violence, unstable housing [107,108], and stress in general [32]. However, programs to address these problems are seldom used even though patients want them [108,109]. There has been relatively little research on the potential value of these programs.

Longitudinal cohort studies such as that of Eastwood et al. [91] (reviewed above under MAT) highlight the importance of what might be termed personal factors. In that study, successful treatment was positively associated with being employed (adjusted odds ratio (AOR) 1.27), negatively associated with having no fixed abode (AOR 0.86), degree of social deprivation (AOR for worst quintile 0.77), and referral from the criminal justice system (AOR 0.68). Heroin users who have achieved abstinence often cite moving away from drug-using social networks and receiving support from non-using friends as a contributory factor to their success [110].

There is evidence that abstinence-contingent partial support of housing, food and recreational activities, abstinence-contingent access to social skills training and job finding group therapy, and non-contingent individual counseling may be of considerable value. These programs substantially increase enrollment in outpatient treatment, reduce return to any drug use, and increase urine drug testing-confirmed abstinence from heroin and cocaine [111](see also [112,113]). Enrollment of a partner, particularly when from the parental family, in an extended training program to assist the partner in using behavioral principles to increase the patient's treatment retention and reduce their drug use, may have a substantial effect on improving retention [114]. Even providing a personal escort plus a financial incentive may substantially increase the success of transition from a detoxification unit to aftercare [115] as many patients with addiction harbor misconceptions that may deter them for entering MAT programs [116] and they may not have the transportation required.

Longitudinal studies of factors affecting cessation of opiate use and maintenance of abstinence also generally suggest the importance of engagement in rewarding nondrug activities (e.g., employment, vocational training) and relationships (e.g., friends, family, spouse), and provision of social support [65]. Unfortunately, there is a paucity of such studies, statistical association does not establish causation, and one can argue that for many factors, causality may flow in both directions. On the other hand, the dramatic results of the truly comprehensive program initiated in Portugal in 2001 (see below: Decriminalization) provide strong evidence that marked reductions in ongoing opioid use can be achieved.

Supervised Injection Facilities

Supervised Injection Facilities (SIFs) are facilities in which health care professionals assist illicit drug users in the antiseptic use of mind-altering drugs (e.g., opioids, cocaine, or methamphetamine). Their goal is harm reduction through treatment of overdoses, prevention of diseases often transmitted by needle sharing (e.g., human immunodeficiency virus and hepatitis C virus), mitigation of public nuisance (e.g., public injection and publicly discarded syringes), enhanced entry into addiction treatment programs, reduction of stigma, and ideally, provision of a platform for assistance by social services, vocational rehabilitation staff, and addiction specialists in an effort to enable addicts to eventually achieve normal, productive, and happy lives [117,118] (see also [82,119-124]). SIFs generally depend upon users bringing their own drugs. However, there has been a large multicenter RCT comparing clinic-provided heroin with methadone in treatment of addiction [27]. This study provided strong evidence of the superiority of heroin treatment. Some SIFs are today providing pharmaceutical grade heroin and dextroamphetamine [125], thereby dealing with the dangerous uncertainties surrounding the dose and extent of contamination of drugs obtained on the street, potentially increasing the bond between the SIF and drug-users, and reducing use of street-drugs and associated criminal activity.

The first SIF was established in Berne, Switzerland in 1986. Presently, more than 200 SIFs are operating internationally, most located in Europe. Only two sanctioned sites operate in the United States, both recently established in New York City [126]. Peer-reviewed studies have shown that, despite the enormous methodologic challenges of the research, SIFs have consistently achieved their objectives, although the beneficial effects have generally been modest (but see the Portugal experience below). SIFs have also been cost-effective [117] (see in particular studies of the Vancouver InSite center, many analysing the complex political obstacles to establishing SIFs and elucidating strategies for overcoming them [127,128]).

Because most SIFs rely on drugs brought in by users, they are not equipped to deal with variability in drug dose or purity. However, safety of dosing in SIFs could be enhanced by the use of fentanyl test strips [129]. There is no evidence that SIFs have negative community consequences, e.g., promoting drug abuse or neighborhood crime [124], an outcome that is consistent with the converging evidence that addiction is a disease of desperation. SIFs and other programs designed to mitigate harm have been favorably viewed by people injecting drugs, particularly with respect to their effect in providing safe havens from violence intrinsic to the drug scene, compounded by violence by police, and their reduction in the risks of injection [120].

It is now reasonably well settled that SIFs do no harm. Remaining questions revolve around whether or not they provide benefit. Despite the extent of science favoring the use of SIFs, and the consistency of findings, these results are not conclusive because of the magnitude of the methodologic challenges [124,130]. Furthermore, most of the data derive from studies in just two cities, Vancouver and Sydney [130]. The single greatest scientific weakness of this entire field of research is the absence of RCTs. There may be ways in which this weakness might be addressed: if a sufficient number of entities (cities, neighborhoods, hospitals) could be engaged, it might be possible to conduct cluster RCTs in which entity served as the unit to be randomized rather than individual patients. The question, after all, is not whether individual illicit drug consumers benefit — they do: there have been no overdose deaths in SIFs [130] — it is whether drug populations and cities benefit. However, many would likely argue that we have passed the point of equipoise on this issue (i.e., that the evidence favoring SIFs is already sufficiently definitive) and that such a trial would be unethical.

If experience is any guide, the establishment of SIFs will face enormous political hurdles [123], as well as opposition by insufficiently informed and recruited community members [118,130]. Finally, SIFs, by their nature, have limited power to address the fundamental drivers of the crisis.

Decriminalization

Decriminalization — allowing the possession of small amounts of specific drugs for personal consumption — would vastly narrow the responsibility of the police and the criminal justice

system, permitting a focus exclusively on dealers. It would also largely eliminate incarceration for possession (see below: the Portuguese experience). It would eliminate the criminal training of mere drug users that is so widespread in prisons, the expansion of addiction in prisons, and the flush of overdose deaths that follows release from prison. Furthermore, it would facilitate the widespread establishment of SIFs that, if permitted to actually administer medical quality drugs, would assure that addicts received precise amounts of drugs administered in the absence of potentially lethal contaminants. Decriminalization has some strong advocates [131].

At least 29 countries have some form of decriminalization [132]. The best test of the effect of decriminalization has been provided by Portugal, the only European country to explicitly decriminalize. In Portugal, persons apprehended for drugs in their possession are referred to an administrative panel. If the panel determines that the quantity of drugs is within stipulated limits for personal use, the person is referred for rehabilitation. If the amount exceeds that, or there is overt evidence of drug trafficking, the case is remanded to the police for adjudication.

In 1999, Portugal had the highest prevalence of drug addiction in Europe (0.5%) and the highest rate of addiction-associated mortality. Heroin posed the greatest challenge. Given favorable political winds, it proved possible in 2001 to embark on a bold experiment. This included decriminalization of the use of drugs, humanistic treatment of drug users, replacement of criminal proceedings with a compulsory meeting with a health department officer, the establishment of harm reduction facilities, including SIFs, in every health district, each incorporating an extensive addiction rehabilitation program, the widespread use of methadone, and the establishment of a central agency to coordinate the response [133] (see also [134]).

In 2017, the most recent year for which detailed data are available, the overdose mortality rate in Portugal associated with *all drugs of potential abuse* was 0.4/100,000 [135] (see also [134,136,137]). That year, the comparable figure across Europe was 2.2/100,000. In the United States, the mortality rate associated with *opioids alone* was 15.2/100,000 in 2017 [138]. New diagnoses of human immunodeficiency virus (HIV) infection declined in Portugal from 500 in 2006 to 18 in 2017. A best estimate of annual expenditures for dealing with drug and alcohol abuse in the 2013-2016 period was 0.03% of gross Portuguese domestic product. The comparable figure for the US in 2022 would have been $6.87 billion — 0.114% of the US budget [139] (see also [140]).

Decriminalization of drugs in Portugal was rapidly transformed into a comprehensive harm reduction and addiction treatment program that has used all available strategies. Therefore, it is impossible to ascribe the gains achieved to any particular component of the intervention. It is also highly uncertain to what extent the dramatic results achieved in Portugal, a poor first-world nation with a relatively homogeneous population, could generalize to the wealthiest nation in the world, albeit one characterized by extraordinary population heterogeneity and structural complexity, a completely different culture, and beset by extreme ideological polarization.

Switzerland has also made major progress in dealing with an addiction and HIV crisis, mainly through harm reduction approaches [141]. Quantitative data are not readily available. Switzerland took a very different pathway than Portugal, reflecting its unique governance system. Its experience may be useful to policy makers in other countries. The United Kingdom, France, and Denmark have also pursued harm reduction strategies [142].

Recently, there has been news of very unfortunate developments in Portugal and the State of Oregon that nevertheless is instructive. In Portugal, the illicit drug crisis has re-emerged in full-blown form after over 17 years of dramatic success [143]. The widespread use of drugs, including injectables, in public places and residential areas has been particularly offensive. The reason is not hard to find. Funding for Portugal's comprehensive addiction program has been cut by 79%. The studies we have reviewed support an unmistakable message: so long as there exist people susceptible to the use of illicit drugs because of desperation and despair, there will be a latent crisis. Only indefinitely sustained programs will keep it at bay.

In 2021, voters in Oregon passed Ballot Measure 110, which decriminalized illicit drugs [144] and earmarked hundreds of millions of dollars in cannabis tax revenue for building a statewide treatment network. Decriminalization was quickly accomplished but the treatment network has failed to materialize, for complex reasons. The result: a marked increase in opioid overdose deaths, was entirely predictable. The measure was inspired by Portugal's approach, but critically, there was insufficient appreciation of the absolute necessity of wedding decriminalization to a systematic referral

system to a robust network of treatment centers. Decriminalization *per se* could, at best, lighten the load on the police, the judicial system, and the prisons.

Legalization

Full legalization of opioids would likely be necessary to achieve the goal of eliminating illicit drugs, drug dealers, and drug cartels because only full legalization could eliminate the pernicious effects of prohibition and the ready availability of drugs of unknown mixture and dose [59]. Legalization has some strong advocates who forcefully argue the case on ethical, social justice, harm reduction, and economic grounds [131,145].

Unfortunately, legalization poses two major challenges: 1) dealing with the extremely variable risk of abuse and addiction among recreational drug users; and 2) establishing an administration and distribution system that has suitable safeguards to prevent a repeat of the disastrous 2000-2012 experiment with "quasi-legalization." It is not clear that either of these aims can be achieved. Furthermore, a proposal by any country to legalize would be in violation of numerous international treaties [134].

Between 2000 and 2012, the United States inadvertently embarked upon a program of "*quasi-legalization*," enabling our entire pharmaceutical drug manufacturing and distribution industry to sell whatever volume of opioids the market would bear. As we now know, this experiment did not end well. The impetus was noble: improving the lives of Americans with chronic noncancer pain by encouraging the use of opioids. Millions of Americans undoubtedly benefited. Only the worst of cynics might have anticipated that substantial numbers of American physicians, pharmacies, drug distribution companies, and drug manufacturers would take advantage, making billions of dollars quite literally at the cost of people's lives. Only the worst of cynics could have anticipated that drug distribution firms and drug manufacturers would effectively leverage Congress to block DEA efforts to rein in their activity. And clearly the states, as they correctly and quite courageously reined in the pill mills between 2010 and 2012, did not foresee that they were also opening up a vast opportunity for Mexican and Chinese drug cartels. Nor did they anticipate the deadly impact of a newcomer to the illicit drug market, fentanyl. We are struggling with the consequences of this initially noble but ultimately tragic experiment in quasi-legalization today. Perhaps this experience can help to guide us as we frame new public policy.

Use of controlled substances for recreation is likely widespread [59], although there are scant data on the epidemiology. As we have noted, the illicit opioid crisis is largely being propelled by the destitute. However, the destitute do not have a monopoly on the hopelessness that can drive one to seek transient or permanent escape in mind-altering drugs. Anyone, regardless of their life situation, faced with grave misfortune, overwhelming situational stress, personal loss, or existential crisis, is potentially susceptible to slipping from recreational use to abuse of mind-altering drugs, no less than with alcohol. Risk may be enhanced by depression or post-traumatic stress disorder. Once addiction is established, suffering is compounded by the dysphoria associated with withdrawal [32]. Patients, faced with inadequately controlled pain, depression, and dire personal circumstances would likely be at risk for slipping into addiction were controlled substances legalized.

Since the introduction of street fentanyl, the result of inadequately constrained opioid access has had the potential for being fatal. Any administrative system must be prepared to catch people "on the slippery slope" before they actually succumb to addiction. Detecting them would require close monitoring of consumption and the ready availability of professionals who could be quick to intervene. At the same time, the cost of the drugs and the administrative burden imposed upon the consumer could not be so great as to motivate them to seek illicit drugs, which would empower the illegal drug industry.

The continued widespread availability in the U.S. of heroin, illicit fentanyl, cocaine, and crystal-meth might also usefully be conceptualized as the result of an "experiment" in *de facto* legalization because of the ineffectiveness of supply-restriction strategies in reducing illicit drug availability [9]. The advent of illicit fentanyl and crystal meth has increased the challenges to interdiction efforts and law enforcement by a quantum level. Because of the tremendous potency of fentanyl, satisfaction of demand can be achieved through importation of very small quantities. Crystal meth can be easily synthesized from readily available materials in myriad tiny hidden laboratories scattered across the country.

The 2000-2012 experiment in quasi-legalization revealed another problem: the enormous power of the pharmaceutic industry, drug distribution firms, and many pharmacies, their cavalier disregard for hundreds of thousands of victims of the crisis, and their ability to manipulate Congress at will [12]. Maintenance of the current state drug regulatory

infrastructures, and most particularly, making participation in PDMPs mandatory in all states, serves to prevent re-development of pill mills. However, if opioids were legalized, it would take great ingenuity to safeguard against a reprise of the 2000-2012 experience with drug distribution and drug manufacturing firms.

While legalization could, in theory, constitute a major advance, it would involve threading a line between the Scilla of prohibition and the Charybdis of the slippery slope to addiction among people at all levels of society rendered susceptible to abuse of opioids and other drugs. This challenge is compounded by the very serious risk of further malfeasance by drug manufacturing and distribution companies and physicians and pharmacies willing to game the system.

Those who have been left behind and deaths of despair

The ultimate solution to the drug overdose crisis lies in dealing with the vast economic, social, and cultural catastrophe that has spawned the opioid crisis, as detailed by Case and Deaton [1] and others [9,29]. It is far beyond our expertise to offer potential solutions but Case and Deaton have proposed a number.

Clinical pain populations and the manufactured crisis

Overdoses, suicide attempts, and deaths associated with prescription opioid use

The important studies by Oliva et al. [5] and Bohnert et al. [64], reviewed above, tell us that long before the CDC weighed in and during a time when there was likely more liberal use of pharmaceutical grade opioids, the major cause of overdoses and suicide attempts (and presumably deaths) was not opioids *per se* but rather mental illness, desperation, and despair. Restriction of opioid use and dosage would not be expected to ameliorate these problems and might worsen them. However, recognition of these issues provides us a clear pathway to what can be done to reduce mortality associated with opioid prescription. A good example is the Stratification Tool for Opioid Risk Mitigation (STORM) program developed by the Veterans Administration on the basis of the results of Oliva et al. [5]. The STORM program has been shown, in a cluster RCT, to reduce all-cause mortality within four months of participant inclusion (RR 0.78) [146].

The CDC

The crisis of pain among clinic populations is almost entirely of the CDC's making and could be ended by prompt departure of the CDC and the various bodies that have been entrained by the 2016 and 2022 Guidelines from the business of regulating medical practice. These include health care provider organizations, state legislatures, insurance companies, pharmacies, and the DEA.

Unfortunately, the CDC recently published a revision of the 2016 Guideline [147] that incorporates mostly cosmetic changes even as it doubles down on some of the most pernicious assertions of its 2016 Guideline: that overprescribing by physicians is responsible for the crisis; that absence of evidence of opioid efficacy constitutes proof of inefficacy; that 50 MMED is the point of diminishing returns and increasing risks from opioid treatment; and that opioids, even judiciously prescribed, pose great harms. These assertions fly in the face of well-established science [4]. Statistical association is constantly misused as evidence of causation. The document does not acknowledge that since 2016, the annual rate of opioid-associated deaths has doubled and, thanks to the 2016 Guideline, an entirely new crisis has been created among patients with chronic pain.

One of the most powerful — and essential — attributes of scientific discourse, dating back to pre-Darwinian times, is that science has been, for the most part [148], open and free-wheeling. The CDC has evolved into a politicized federal bureaucracy [149] and thus has lost this attribute. In the formulation of the 2022 Guideline, it ignored the vast number of scientific publications that might have informed it about problems with the approach being taken. Further, the sources of input that it reviewed in developing the final published 2022 Guideline [147] conspicuously did not include scientists (p15). It ignored the enormous input from patients during the mandatory public commentary period — input that should have informed it of the dire consequences of the 2016 Guideline. It even ignored its own data [49]. The final publication was little different from the draft earlier made available for public commentary.

Why has the CDC arrived at so many conclusions that are contrary to the science [4]? The short answer, which we will enlarge upon below, is that while the CDC employs fine scientists, its publications are no longer reliably scientific. The question raises complex issues that are deserving of extensive inquiry. We can only point to what we suspect to be some major contributing factors. First and foremost, because the CDC Guidelines focus intensively on the clinical management of patients in pain, the formulation of recommendations should have been heavily guided by pain management physicians. However, the review panel was conspicuous for the

paucity of pain clinicians [3]. Those of us who looked at the 2015 publications that preceded the 2016 Guideline were forcibly struck by the vast disparity between the recommendations that were being considered and what we had learned from clinical experience. The review would also have benefited enormously from the inclusion of people with a much deeper understanding of the causes of the evolved crisis, many cited in this paper.

Second, the membership of the CDC 2016 Guideline core expert group and the stakeholder review group strongly suggests that the recommendations were strongly influenced by members of PROP, rather than by a thorough, completely independent review of the science [3 150].

Third, we perceive substantial abandonment of one of the most essential components of scientific inquiry: rigorous skepticism. This has even been evident even in some otherwise excellent studies bearing on the use of opioids. It is flagrant in the two CDC Guideline documents [8].

Fourth, there is a major problem related to over-reliance on meta-analyses. Meta-analyses can certainly be extremely useful. However, in our view, they have, on average, been subjected to insufficient scientific skepticism. There is an inevitable tendency in the conduct of meta-analyses to use individual studies simply because the data provided can readily be entered into the meta-analysis, regardless of the quality of the actual studies or the comparability of the study populations. This is most conspicuous in the innumerable meta-analyses of RCTs of opioid use in chronic pain. These RCTs are deeply flawed because the experimental designs have simply not been adequate to address the questions being asked [55]. Not only has the adequacy of the experimental designs never been questioned — the failure of these flawed studies to yield definitive results has been widely misinterpreted as indicative of lack of opioid efficacy.

Meta-analyses always include consideration of quality of evidence. However, it is very difficult for the reader to use these quality ratings to modify their interpretation of the quantitative data presented. It is all too easy to interpret the results of multiple low-quality studies as having scientific value simply because they seem to arrive at similar conclusions. This is conspicuous in the 2022 Guideline revision [147]. Of 12 recommendations, four (4, 8, 9, and 12) were not controversial. Among the controversial recommendations, two (1 and 11) were based on level 3 evidence, one (10) on level 4 evidence, and one (non-opioid therapies are preferred for subacute and chronic pain) on "level 2" evidence, despite the complete absence of adequate comparative effectiveness studies. Most scientists would view level 3 evidence (observational studies or randomized clinical trials with notable limitations) and level 4 evidence (clinical experience and observations, observational studies with important limitations, or randomized clinical trials with several major limitations) as justification for further research but certainly not a basis for definitive conclusions, much less clinical guidelines.

Fifth, the 2016 Guideline heavily relies on relative risks (RR), odds ratios (OR) and hazard ratios (HR) and often fails to include data on confidence intervals. To be useful to the practitioner, values of this type need to be translated into absolute risks. In considering the risks for any opioid overdose, the Guideline cites figures from Dunn et al. [151]: relative to a baseline risk for patients taking 1-19 MMED range, the HR for the 20-49 range was 1.44 (95% CI 0.57-3.62), for 50-99 MMED range 3.7 (95% CI 1.5-9.5), and for the ≥100 range 8.9 (95% CI 4.0-9.7). The Guideline did not include the confidence intervals and it did not note that the corresponding absolute risks were estimated at 0.16%/year for 0-19, 0.26%/year for 20-49, 0.67%/year for 50-79, and 1.79%/year for ≥100. At the time the Guideline was published, it was also estimated from the work of Gomes et al. [57] that the absolute annual risk of opioid-associated death for patients prescribed >100 MMED was 0.25%, data not noted in the Guideline. Thus, the Guideline provides data in a way that appears intended to cause alarm and understates the degree of uncertainty in the estimates.

Finally, the CDC Guidelines constitute a potentially dangerous intrusion of government bureaucracy into the clinic [4,8]. The two Guidelines make multiple disclaimers that the recommendations proffered represent purely recommendations and should in no way be regarded as regulations (particularly emphatic in the 2022 Guideline). However, many of us, on first reading the 2016 Guideline, immediately recognized that, given the gravitas of the CDC as an institution, the Guideline would have far-reaching ramifications. Because the message of the 2022 Guideline is not fundamentally different from that of the 2016 Guideline — disclaimers notwithstanding — we anticipate continuation along the unfortunate pathway our nation has taken.

Can the CDC be fixed? We believe the answer is yes, but likely with great political difficulty. Through much of its existence, the CDC could justifiably lay claim to being one of the most outstanding scientific

institutions in the world [152]. The quality of its science was impeccable. It was renowned for its steely integrity. The quality of its scientists, their idealism, and their *esprit de corps* were renowned. The CDC made a major, if not the definitive contribution to some extraordinary accomplishments: field-testing Salk's polio vaccine; eradicating smallpox; bringing numerous Third World plagues under control; sounding the alarm on AIDS; and solving the puzzles of Legionnaires' disease, toxic shock syndrome, and hantavirus in Native American reservations in the Southwest.

This began to change in 1977 when the then Director of the CDC, David Sencer, was fired by the new Secretary of Health and Human Services, Joseph Califano. Sencer, a scientist for the ages, had made the mistake of steering significant resources to preparing for the 1976 swine flu epidemic, which seemed to promise a recapitulation of the 1918 epidemic [153]. However, the epidemic never materialized [149]. The first evidence of political meddling came in 1980 when pharmaceutical companies were able to temporarily quash unimpeachable scientific evidence that giving aspirin to children with flu-like illnesses created a serious risk of the development of usually fatal Reye's syndrome [152].

The open door for such meddling was institutionalized in 1984 with the decision by the Reagan Administration to change the position of the Director from one occupied by a career civil service scientist recruited by the CDC to a position to be filled by presidential appointment [149,152]. From that day onward, the actions of the CDC have been profoundly influenced by politics, not science. Entire fields of inquiry (e.g., consequences of abortion, measures to stem the AIDS epidemic, urban violence, and gun violence) were forbidden [152]. Scientific findings that raised the ire of politicians were quashed, never to be published. In the years that have followed, the failed response of the CDC to the SARS-CoV-2 epidemic and its completely misdirected and deeply harmful approach to the opioid crisis are quite representative of the effects of politicization of the organization. The cost in lives lost is now in the millions.

An obvious solution to these problems is to return to the CDC the Director recruitment process that was in place when David Sencer assumed the position in 1966 and thus to reestablish the CDC as the fully independent scientific institution it once was.

Discussion

THE CRISES

The causes of the opioid crises, because of their complexity and continually changing contributory factors, have long remained opaque. No more. The jigsaw puzzle is now largely complete. The course of American history has been marked by progress in increasing equality of opportunity — zig-zag and inhomogeneous, but progress nevertheless. However, in the 1970s, a rift began to develop in the heretofore most privileged socioeconomic class, non-Hispanic whites. It was a rift most economically defined by education. Those with less than a college education, and even more so, those with less that a high school education, began to witness the slow fragmentation of their lives, the steady diminution of opportunity, and increasing grounds for hopelessness — ultimately forming a population susceptible to the escape offered by mind-altering drugs, most particularly opioids.

In the late 1990's, an unrelated sea change occurred in medicine marked by the acceptance of an obligation to treat patients with chronic noncancer pain and acceptance of the use of opioids to do so. Large numbers of patients undoubtedly benefitted. Unfortunately, a number of corrupt physicians and collaborating pharmacies, aided and abetted by drug distribution and manufacturing firms, saw this sea change as an opportunity to make vast amounts of money, however great the cost in lives. The pill mill industry was born and flourished by selling opioids to street resellers, who in turn marketed to those rendered susceptible to the lure of these drugs by the growing desperation in their lives.

Between 2010 and 2012, the states effectively shut down the pill mills —an entirely good thing that, unfortunately then paved the way for a booming market in imported heroin and illicit fentanyl. Groups like PROP and ultimately the CDC, apparently ignorant of the enormous role played by pill mills, incorrectly blamed the growing illicit crisis on overprescribing by conscientious physicians. The CDC, in the wake of tragic actions by Joseph Califano, Secretary of HHS, in 1977 and by the Reagan administration in 1984, had long since become a thoroughly politicized organization in which science is no longer the exclusive guide for its actions — leading to the CDC Guideline of 2016, which generated the manufactured opioid crisis.

POSSIBLE SOLUTIONS

The almost exclusive focus on drug-induced euphoria and the failure to consider the reward value of respite from suffering have had some very perverse consequences for both people with addiction and people with chronic pain and in the directions research has taken. In people with addiction, it has led to a narrow focus on

pharmacologic therapies (methadone, buprenorphine, and naltrexone) and almost no attention to the psychosocial and economic factors that are likely the major drivers of addiction. These drugs have well-demonstrated efficacy but the reality is still that successful completion of treatment without re-presentation within six months is achieved in only 21.9% of patients [91]. It is now accepted that opioid addiction, as currently treated, it a chronic relapsing disorder [65]. Opioid-associated mortality, overwhelmingly due to illicit opioids, continues to rise inexorably. Aggregate drug overdose deaths have now exceeded 100,000/year [154].

In chronic pain populations, there has been an almost obsessive focus on the direct effects of opioids, presumably the induction of euphoria since it is widely assumed that opioids are ineffective (a false assumption that reflects inadequate trial design [55]), and on their alleged risks (actually objectively quite modest given the magnitude of the problem [4]). There has been very little focus on the medical objective — achieving respite from chronic pain, that led to opioid treatment, and on the dire consequences of effectively mandating doses insufficient to control of that pain.

The evolved crisis

From a purely scientific perspective, the solutions to the evolved opioid crisis appear to be fairly well established, even if many may view the scientific evidence as less than robust. The results of the Portuguese experiment have been so dramatic that they define both the benchmark methodology and a benchmark level of success. The initiative was conducted in a poor first world nation that, in the year 2000, had the worst heroin crisis in Europe and an enormous rate of new HIV infections. The solutions involved a comprehensive approach to people with addiction, most importantly including decriminalization (not legalization) and establishment of an extensive network of SIFs, which in turn serve as the point of introduction to comprehensive rehabilitation programs. In 2017, the total mortality associated with all drugs of abuse in Portugal was 2.6% that of US opioid associated mortality — a dramatic demonstration of the effectiveness of the Portuguese program. The establishment of the Portuguese program required buy in from the citizenry, national leadership, police, and communities: no small accomplishment. Unfortunately, the very factors that were key to the success of the Portuguese experiment are likely to be the ones that pose the greatest obstacle to adoption of a similar program in the US: achievement of a consensus program led by the national government and applied uniformly throughout the country, acceptance of the concept of decriminalization, and building the program on the infrastructure provided by a large network of SIFs.

It is now well-established that MAT (particularly methadone and buprenorphine) can have dramatic effects on all-cause mortality, overdose-associated mortality, and treatment retention. There is also an apparently unappreciated benefit: it prolongs by 10-fold the duration of time that patients stay in treatment [90]. The dramatic success of MAT also provides substantial reason for hope as it indicates a substantial prevalence of people with addiction who are willing to block their only means for (transiently) escaping the desolation of their lives by engaging in programs that might offer much greater long-term success and are clearly much safer.

Methadone and buprenorphine are now classified by the World Health Organization as essential medicines for opioid agonist treatment for opioid addiction [155]. However, only about 30% of patients entering opioid specialty treatment for addiction receive MAT [88]. There exist substantial administrative obstacles to prescription of these drugs for patients with addiction. Some have argued convincingly for reducing these barriers, making it possible for emergency department and primary care physicians to prescribe them [156]. On December 29, 2022, the President signed the Consolidated Appropriations Act (Pub. L. No. 117-328) [157] [158], which included sections (1262 and 1263) that revoked the "X-waivers" Now any physician can prescribe buprenorphine for opioid addiction, provided they have taken a mandatory eight-hour course. However, the beneficial effects of methadone and buprenorphine have been demonstrated in populations of patients enrolled in addiction treatment programs. Therefore, it is uncertain whether similar efficacy would be achieved in patients not enrolled in such programs, or whether emergency department and primary care physicians will be willing to prescribe these drugs to people using illicit drugs [159] (see also [160] for additional concerns). Given the evidence we have provided that clinic populations and addicted populations are substantially separate (Figure 3), it is unlikely that most physicians — at least outside emergency rooms and addiction treatment centers — will often encounter people with addiction.

Treatment of depression has theoretical promise. However, studies of the effect of such treatment, because of the limitations of the RCT methodology used, have not yet employed sufficiently vigorous treatment to truly test the hypothesis.

Studies of psychosocial interventions have not, in aggregate, provided sufficient evidence of their efficacy to justify their use. However, there is a clear need for further research of refined interventions.

It seems likely that the ubiquitous 12-step programs (AA, NA and other programs utilizing similar models) make an important contribution to rehabilitating people with addiction. However, there have been very few studies testing their impact.

There is a potential for major gains in achieving successful rehabilitation of people with addiction by dealing with the factors that are primarily responsible for lives of desperation: absence of meaningful employment, isolation, hopelessness, poor social support, prevalence of exposure to violence, and absence of stable housing. The results of the small amount of research that has been done on the impact of such programs are promising but this avenue of treatment needs to be studied much more extensively.

All this said, the most important factor accounting for the lack of effectiveness of rehabilitation from opioid addiction in America may be the enormous variability in the quality of rehabilitation programs and triage pathways to reach them (see [160]). The Substance Abuse and Mental Health Services Administration (SAMSA), an agency within the Department of Health and Human Services, was established in 1992 to regulate and support delivery of mental health services nationally. The passage of the Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment (SUPPORT) for Patients and Communities Act of 2018 [161] (Public Law No 115-271 [162]) established a comprehensive and potentially effective approach to all factors contributing to addiction and strategies for effective rehabilitation [163]. However, given the recency of the passage of this bill, it is too early to assess its effectiveness, we have been unable to find any studies assessing effectiveness, and the illicit opioid crisis so far shows no signs of abating.

The recent NIH initiative, the HEALing Communities Study, appears to be a step in the right direction [164,165]. It clearly recognizes the many obstacles patients face in successfully accessing addiction recovery programs. However, it too seems to overemphasize pharmacological approaches. In its emphasis on evidence-based programs, it has excluded precisely the programs that are both likely to be most essential and which have received the least research attention — approaches designed to rescue people with addiction from their lives of desperation that we have described under "*Rehabilitation of people with addiction*."

The manufactured crisis

The solution to the crisis among patients with chronic pain largely created by PROP and the CDC is much simpler: complete abdication by the CDC from any involvement in the medical management of pain and return of that management to where it has always belonged: the offices of conscientious, compassionate, and well-trained clinicians working carefully with their patients. We also now know from the work of Bohnert et al. [64] and Oliva et al. [5], discussed above, that the key to reducing overdose events and mortality among patients prescribed opioids lies not in reducing opioid dosage but in treating associated mental illness.

We can certainly improve the quality of the care for patients in chronic pain by vastly improving education in pain management that we provide medical students, residents, and post-graduate clinicians. The work of Oliva et al. [5] and Strombotne et al. [146] suggests that we can most effectively reduce risk associated with opioid treatment of pain by providing markedly enhanced support of those at greatest risk for overdose, suicide, and death. We can also improve care of patients in chronic pain by increasing re-imbursement for this complex and demanding service. Unfortunately, the CDC has also set in motion many profound institutional changes, including the passage of laws by the states that seriously interfere with care of patients in pain. These laws have prompted reactive changes by medical provider institutions, pharmacies and insurance companies, and major changes in DEA operational approaches. The CDC has also potentiated a large number of perverse memes that only serve to interfere with medically indicated and scientifically founded treatment.

Given the nature of the 2022 CDC revisions to the original Guideline, it appears that the public must look to executive or legislative intervention for a solution to the manufactured crisis. The ultimate solution to this crisis would be measures to return the CDC to the independent and deeply scientific organization that it was until 1977. Such action could enjoy bipartisan support: on the one hand, the CDC actions represent an example of governmental overreach, and on the other, its actions have been cause for incalculable suffering, loss of capacity, and death.

Addressing the much deeper factors that have created a large population of Americans rendered susceptible to the lure of mind-altering drugs as a

temporary and all too often permanent respite from despair will be a far more challenging proposition. This population consists predominantly but not exclusively of non-Hispanic white people with less than a college education. It will require major changes in the way that capitalism operates in our nation in nearly every sector but particularly in the realm of health care, as discussed by Case and Deaton [1].

Conflicts of Interest

Neither of the authors has any conflicts of interest bearing on this manuscript.

Author Contributions

†SEN was primarily responsible for the literature review, the analyses, and writing the paper.

†RAL and SEN have engaged in an intensive collaborative effort since 2016 to understand the scientific evidence bearing on the prescription opioid crisis, to provide a clinical guideline for management of chronic pain, and in the current paper, to understand the fundamental causes of the current crisis in clinical pain management and illicit opioid use and to propose solutions to these crises. The current manuscript reflects, in substantial part, ideas generated over the years in this intense dialogue. RAL also critiqued the final draft.

Funding

This work was supported by resources provided by the North Florida/South Georgia Veterans Health System, Gainesville, FL. It was not supported by a specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

The contents of this manuscript do not represent the views of the U.S. Department of Veterans Affairs, the United States Government, or the University of Florida.

Data Availability

This paper consists solely of an analytic review and no data were independently collected.

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