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VIEWPOINTS

Prevalent Misconceptions About Opioid Use Disorders in the United States Produce Failed Policy and Public Health Responses

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The current opioid crisis in the United States has emerged from higher demand for and prescribing of opioids as chronic pain medication, leading to massive diversion into illicit markets. A peculiar tragedy is that many health professionals prescribed opioids in a misguided response to legitimate concerns that pain was undertreated. The crisis grew not only from overprescribing, but also from other sources, including insufficient research into nonopioid pain management, ethical lapses in corporate marketing, historical stigmas directed against people who use drugs, and failures to deploy evidence-based therapies for opioid addiction and to comprehend the limitations of supply-side regulatory approaches. Restricting opioid prescribing perversely accelerated narco-trafficking of heroin and fentanyl with consequent increases in opioid overdose mortality As injection replaced oral consumption, outbreaks of hepatitis B and C virus and human immunodeficiency virus infections have resulted. This viewpoint explores the origins of the crisis and directions needed for effective mitigation.

Keywords. opioids; overdose; pain; injection drug use.

President Trump has repeatedly stated that the crisis of opioid use disorder (OUD) and consequent overdoses constitute a national emergency requiring a massive response [1–3]. His administration has, conversely, taken no action to commit federal funds at a scale needed to implement effective programs. This gap between words and actions typifies the response of the United States as a whole to the opioid epidemic. At the national and local levels, the sometimes-lurid stories and more serious, probing, evidence-based investigations have failed to promote and disseminate evidence-based actions. These failures are, we believe, rooted in a set of prevailing misconceptions that holds that the crisis was driven primarily by financial gain sought by corrupt pharmaceutical manufacturers abetted by duped or corrupt medical personnel, that treating patients suffering from chronic pain with opioids is a fundamental driver of addiction, that addiction itself is an individual moral failure, and that abstinence-based recovery is the most desirable treatment for those suffering from OUD. These oversimplified explanations need critical examination and historical context that recognizes that we are now in the third critical period of expanding OUD.

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THE FIRST CRISIS: 1865–1913

Some of the misconceptions prevalent during the third crisis predate it and have historical roots in earlier periods of expanding opioid use. During the first crisis period, between the Civil War and the passage of the Pure Food and Drug Act (1906), opioid use grew through 2 mechanisms: (1) the ability to administer morphine using newly invented hypodermic syringes; and (2) even more pervasively, through the inclusion of unregulated opioids (as well as cocaine and alcohol) in patent medicines [4].

Passage of the Harrison Narcotics Tax Act (1914) and court rulings in its wake changed how opioid misuse was perceived. Enforcement of opioid abstinence replaced a medical approach that saw addiction as a treatable disease, a view that figured in the first Supreme Court ruling on interpretations of the Harrison Act [5]. To promote enforced abstinence, it was necessary to create the misconception that people with OUD were not suffering from a disease treatable with medication but from a self-imposed condition maintained through lack of moral fiber [6, 7]. This change in attitude is reflected in Supreme Court rulings about the meaning of the Harrison Act after 1916 [8, 9]. This misconception persisted until 1962, when the Court ruled that addiction was a disease rather than a specific act [10].

THE SECOND CRISIS: 1960–1975

Heroin smuggling and associated problems began appearing in New York City and other large cities as early as 1958 [11, 12], yet it was only in the next decade that the Vietnam War and rising youth disenchantment with 1950s America saw the spread

of heroin to a large swath of the country. In the midst of this crisis, in the late 1960s, medication-based treatment for OUD using methadone was experimented with, gained acceptance, and was scaled up [13]. Unfortunately, adverse events resulting from the rapid and poorly monitored expansion led to the institution of a highly regulated system of methadone clinics [14]. Access to medication was tightly controlled for both clinic and patient under Federal Regulation 37 F.R. 26 806 through directly observed, often daily dosing at clinic sites, mandated drug screening and supplemental counseling, and onerous reporting requirements. These regulations produced a clinic system that stands divorced from the rest of the US healthcare system. And this separation has isolated and stigmatized medication-based treatment for OUD, making it seem medically unacceptable and even suspect. Importantly, this allowed for a return to abstinence-based approaches as the more socially acceptable form of treatment for OUD. This divorce of OUD treatment from mainstream medical care contributed to the detrimental paradox of the Drug Abuse Treatment Act of 2000 that requires an additional 8 hours of mandated training for physicians and a subsequent waiver to prescribe buprenorphine, an effective, office-based, schedule III medication for the treatment of OUD: Physicians can prescribe thousands of opioid pills with relatively minimal oversight but are unqualified to prescribe the much safer partial agonist.

THE THIRD CRISIS: 1995–TODAY

The misconception unique to this current third crisis is the role played by legal and highly regulated opioid medications. Natural opiates had for millennia been a useful tool to treat many kinds of pain and were refined for medical use in the 19th century [15]. Since then, health providers have had a growing array of options for pain relief beginning with morphine, then a variety of semisynthetic opiate derivatives, and later, as pharmacology and pharmaceutical science grew more sophisticated, a wide range of fully synthetic opioids. At present, there are at least 36 opioids listed as schedule II (eg, fentanyl, oxycodone) and/or schedule III (eg, codeine, dihydrocodeine) drugs by the Drug Enforcement Administration of the US Department of Justice [16]. The pharmaceutical industry has labored to supply these products in a range of formulations. Opioids for rapid short-term treatment in response to acute needs differ from extended-release preparations for longer-term relief of chronic or terminal pain.

A review of the origins of the third crisis that began 30 years ago reveals efforts to shift American health systems toward "patient-centered" medical care, including better management of pain [17, 18]. This was seen as a way to improve recovery after surgery or trauma, reduce suffering among the terminally ill, and allow people with chronic pain a higher quality of life. All 3 conditions seemed to justify the increased use of opioids. Treatment decisions to reduce pain have relied on self-reported pain assessment that lacks an objective reference point, which could misinform caregivers and result in inappropriate treatment [19]; yet when there is a comprehensive tool such as opioids, as the saying goes, "when you have a hammer, everything looks like a nail." However, the effectiveness of opioids for treating most kinds of chronic pain—musculoskeletal, neurological, or autoimmune—has been insufficiently studied [20, 21]. Experience has made clear that opioids often are not reasonable solutions for chronic pain [22], but too little work has been done to develop and deploy effective alternatives for clinical use.

Public awareness of the third opioid crisis began to emerge in the late 1990s as pharmaceutical companies developed extended-release formulations of opioids to deliver opioids to people with chronic pain. Rapidly expanding prescribing was abetted by deceptive marketing, especially by Purdue Pharma L.P., manufacturers of Oxycontin. The company falsely claimed that extended-release formulations held reduced abuse potential and were effective for 12 hours, used a range of incentives to promote sales, and obtained endorsements from prominent physicians who received company retainers and/or speaker's fees [23, 24]. Some of these activities violated provisions of the Food, Drug, and Cosmetics Act. Companies marketing extended-release formulations reaped enormous profits, but it is important to note that opioid availability was increased most through the prescribing of traditional, shorter-acting opiates such as hydrocodone (eg, Vicodin) and oxycodone (eg, Percocet), which comprised three-quarters of the US opioid market when prescribing peaked during 2010–2012 [25]. The opioid epidemic was fueled by overprescribing of all forms of opioid medication, not just the extended-release formulations [25, 26]. Other interrelated factors subsequently influenced opioid overprescribing for chronic pain. At the patient–provider level, the factors include the enforced brevity of appointments that make opioid prescribing easier than laying out behavioral approaches to chronic pain management and the providers' desire to satisfy patient requests, a desire that may or may not be heightened by the widespread use of standardized patient satisfaction surveys [18, 27–29]. At the structural level, the factors include the unwillingness of health insurance companies to reimburse for alternative medications or therapies and an employment system that does not permit long stretches of compensated time off needed for physical recovery.

The Automation of Reports and Consolidated Orders System (ARCOS) is used by the US Drug Enforcement Administration to track opioids and some other controlled substances from manufacturing to retail distribution. ARCOS data documented a doubling of opioid analgesic use, measured in milligrams per 100 people, from 2000 to 2010 [30]. Despite this large increase in opioid prescribing for chronic pain, we believe that this alone is not the cause of increased rates of OUD that occurred concurrently with increasing prescribing. Our work, exploring the life histories of adults with co-occurring chronic pain and OUD, has failed to find a trajectory in which opioid prescribing for chronic pain preceded the development of OUD in individuals experiencing chronic pain. In 2 separate studies conducted

10 years apart, experimentation and nonmedical opioid use preceded the onset of chronic pain for 80% of adult participants [31, 32]. This should not be surprising, since experimentation is a feature of adolescence and early adulthood whereas chronic pain appears toward middle and older age. This, then, is the second prevailing misconception: that the prescribing of opioids for chronic pain is the principal cause of rising addiction rates in adults during the third opioid crisis.

Only a small percentage of adults progress to OUD after being prescribed opioids after an episode of acute pain. Studies of opioid prescribing for acute pain from conditions as diverse as surgery, burns, or sickle cell disease found that progression to OUD was rare, <3% for all 3 conditions [33–35]. A more recent, large study explored chronic opioid use 1 year after surgery for 11 surgical conditions covering 640 000 opioid-naive patients. Seven conditions had low levels of ongoing opioid use 1 year after the episode causing acute pain; prevalence of ongoing opioid use ranged from 0.12% for cesarean delivery to 1.4% for total knee replacement [36]. In a comparison group of >18 million nonsurgical, opioid-naive acute pain patients prescribed opioids, prevalence of ongoing opioid use at 1 year was 0.14%.

The very low prevalence of the development of OUD following opioid prescribing to opioid-naive patients does not mean that early initiation of opioid use for pain is without adverse consequences. A pattern of antecedent pain followed by opioid overuse is common among adolescents, especially those with adverse childhood experiences including trauma or living with parents who have their own drug use problems [37–39]. One approach to preventing the development of OUD in young people is to omit or limit the quantity of opioids prescribed and monitor the substance use patterns of patients whose first exposure followed injury or surgery. Additional research is needed to understand the role of experimentation after initial experiences with opioid use for acute pain management and the identification of predisposing factors. For older individuals, an important strategy is for prescribers to screen for past nonmedical opioid use and substance use disorders before prescribing opioids.

SHIFTS IN OPIOID AVAILABILITY AND ROUTE OF ADMINISTRATION

The current crisis has its roots in the expansion of opioid prescribing and their diversion to illicit markets, but has been worsened more recently by supply-side efforts to limit opioid availability. Care must be taken when efforts are made to decrease community access to prescription opioids, as the unforeseen consequences can be catastrophic. Multiple attempts to crack down on unethical pharmaceutical marketing practices and on large-volume prescribers or wholesalers whose practices have been deemed criminal or suspect have not reduced rates of new OUD diagnoses. The supply-side approach has been applied without shifting demand by expanding evidence-based treatment for individuals suffering from opioid use disorders.

The unintended effect has opened many communities to narco-trafficking. New markets for heroin have emerged to take the place of "pill mills" and other sources for diverted pharmaceuticals. We believe that the new, cartel-supplied black markets for heroin/fentanyl have produced more dire consequences than if misuse of pharmaceuticals had continued. Since 2015, fatalities associated with street drugs containing illicitly manufactured, nonprescribed fentanyl and ultra-potent analogues such as carfentanil, acetyl fentanyl, and furanyl fentanyl combined with, or in place of, heroin have been reported with increasing frequency [40, 41]. Instead of purchasing illicit drugs with a fixed dose of an opioid, individuals now have a markedly elevated risk of fatal and nonfatal overdose every time they use a bag of heroin or a fentanyl congener, or a counterfeit pill procured on the black market. This certainly has contributed to the rapidly rising rates of overdose deaths in places that have reduced pharmaceutical opioid prescribing such as Florida, Ohio, and Connecticut, states that otherwise do not share many characteristics. Once OUD has progressed, injection becomes the preferred route of administration, and with this transition are associated increases in human immunodeficiency virus (HIV) and hepatitis C virus infection rates [42–44]. An outbreak of HIV among illicit drug injectors in Lawrence and Lowell, Massachusetts, that detected upwards of 125 new HIV cases is just the latest example [45, 46]. These consequences of reduced pharmaceutical opioid access demonstrate the futility of approaches to epidemic control that neglect to expand effective, evidence-based treatment—that is, opioid agonist therapy for those already affected with OUD.

OPIOID USE DISORDER AS A DISEASE

The third prevailing misconception views addiction as a moral failure, and has its roots, as described above, in the 2 previous opioid crises. This completely discounts the preponderance of evidence demonstrating the genetic and neurobiological basis of the disease of addiction [47–50]. Although pharmaceutical companies engaged in aggressive, non-evidence-based, and even illegal marketing campaigns [23, 51], the etiology of OUD is multifactorial; corporate malfeasance is only part of the explanation of the massive opioid use expansion in this third crisis. A major goal of clinical medicine is promoting patients' well-being, and if this requires prescribing exogenous opioids for acute pain and palliative care, such prescribing may be indicated. Rather than blame the crisis on the moral failures of those who succumb to OUD and exploiters of market forces, it is time to identify and change the social and economic structures that created the conditions conducive to the expansion of opioid misuse. And most importantly, it is time to expand evidence-based treatment for those who now have OUD.

This takes us to the fourth prevailing misconception: that the ultimate goal of treatment for OUD is abstinence from any opioid use. Abstinence-based "recovery" models are based

on the false notion that OUD can be treated like an acute ailment. One recovers from influenza or a broken arm, but not from a chronic disease that recurs if treatment stops. Opioid use disorder is much more like hypertension or diabetes; it can be effectively managed but is rarely cured, though abstinence is possible for some after many years. Acceptance of this fact is rendered difficult because the organ system compromised by opioid use disorder is the brain. We like to believe that we have control over our brain, but much of our experience should disabuse us of this notion. Once continued opioid misuse has altered brain chemistry and neural pathways, the chances of restoring the brain's original homeostasis are slim. Under such circumstances, the presence of an exogenous opioid such as buprenorphine or methadone can restore one's sense of homeostasis, by treating withdrawal symptoms, curbing cravings, and blocking the action of supplemental illicit opioids whether they be pharmaceuticals or heroin/fentanyl.

In contrast, studies going back a century reveal that failure rates for abstinence-based approaches to managing OUD are exceedingly high; recidivism rates of >90% within 6 months support neurobiology observations [52–55]. Along with recidivism, there is compelling evidence for heightened rates of opioid overdose deaths in the wake of relapse as a result of reduced tolerance, which can occur in days to weeks. This is certainly true following periods of enforced abstinence in the criminal justice system. The rates of fatal overdose in the first few weeks following release are 5–10 times higher than at any other time in an individual's life [56–58]. In Connecticut, one-quarter of the opioid overdose deaths in the year following release from incarceration occurred within the first month, attributed to prompt relapse and use of now-stronger heroin–fentanyl combinations [59]. Similarly, detoxification, the first step in abstinence-based approaches, has been associated with increased risk of opioid overdose when individuals resume nonprescribed opioid use [60, 61]. With this compelling medical information, one must conclude that detoxification followed by abstinence is neither a safe nor effective treatment.

In contrast, opioid agonist–based treatment sharply reduces overdose mortality. A recent meta-analysis found that the overdose risk for those in methadone treatment is 21% of that for individuals not in treatment, and for those in buprenorphine treatment the risk is 30% of that for individuals not in treatment [62]. The preponderance of evidence, based on studies in the United States and abroad, supports additional health and social benefits and cost-effectiveness of agonist medications (methadone or buprenorphine) [63, 64]. Individual studies have demonstrated decreased transmission of hepatitis C and HIV, decreased crime, decreased opioid use, and increased social functioning [65, 66]. These treatments have been endorsed by the World Health Organization, American Medical Association, National Institute on Drug Abuse, Office of National Drug Control Policy, and Centers for Disease Control and Prevention for the effective long-term treatment of OUD. And yet, in the United States, less than half of substance abuse treatment facilities for OUD offer their patients agonist-based medication-assisted treatment (MAT). In 2016, >345 443 patients were receiving methadone for the treatment of OUD, and 61 486 patients were prescribed buprenorphine, increases of 34% and 291% since 2006 and 2008, respectively, but this is far short of the 2.6 million Americans who could benefit from agonist-based MAT [67]. Reasons for this shortfall in treatment availability may be plentiful, but stigma associated with drug addiction has created a climate in which abstinence is valued over effective treatment. Often this preference is centered on an ethical argument that agonist therapy is merely replacing one drug with another. This misguided concern is never expressed for other diseases produced by combinations of lifestyle and genetics that are treated with medications such as insulin to treat diabetes or antihypertensives to treat high blood pressure. The situation seems unique to OUD even though effective management of any of these diseases with behavioral modification alone is the exception.

WHAT CAN BE DONE?

This all begs the question of primary prevention of opioid misuse. Why has the desire for the euphoric and pain-dulling effects of opioids increased in so many places in the United States during this third crisis? The answers are complex and most likely not easily remediated because they lie in social and economic transformations over the last 3 decades. Large numbers of young and middle-aged people are unemployed or underemployed, adrift without adequate social support, and seeking escape within the context of an eroded social safety net. Until these problems are addressed, we must mitigate the immediate problems of often-untreated OUD, relapse, and overdose. This will require destigmatizing OUD by recognizing it as a treatable chronic disease, with a favorable prognosis if properly treated. Large-scale expansion of MAT must be supported by ancillary services to educate and reintegrate treated individuals whose OUD has interfered with their development of successful life skills. We must expand overdose prevention programs and community-based distribution of naloxone, made available free of charge by health and government entities to reverse overdoses and reduce the number of deaths. Furthermore, more research and clinical trials are needed for nonopioid medication and nonmedication alternatives for treating chronic musculoskeletal, neurological, and autoimmune pain. If the research and clinical trials confirm that alternative approaches are best practice, then funding systems must be altered to allow paid medical leave, reduced copays, and access to nonpharmaceutical approaches.

All of these efforts to address the opioid epidemic and its co-occurrence with chronic pain will take large-scale

expenditures of state and federal money, estimated to be billions of dollars per year over the next decade, to manage untreated OUD [68]. In this instance, current federal and state government procrastination [69] mirrors the national status quo, which has let this epidemic fester for 2 decades.

Notes

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