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The United States opioid epidemic

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Abstract

The United States opioid epidemic is a nationwide public health crisis. Initially driven by increased consumption and availability of pharmaceutical opioids, an increasing number of opioid overdoses are now related to heroin and illicitly manufactured fentanyl and fentanyl analogs. Addressing this epidemic requires addressing the stigma associated with opioid use disorders and its treatment, improving access to efficacious treatment options, specifically methadone and buprenorphine, and reducing opioid overdose fatalities with distribution of the opioid antagonist and overdose reversal agent naloxone.

Keywords

Opioids; Overdose; Epidemiology

Introduction

The United States is experiencing a nationwide public health crisis that continues to escalate.[1–4] Between 2005 and 2014, the national rate of opioid-related hospitalizations increased 64% to 225 hospitalizations per 100,000 population.[1] Death rates have also increased and in 2016, over 42,000 Americans died from an opioid overdose (OD); a 27% increase in death rate from 2015.[4] While regional and sociodemographic variations exist, the epidemic is widespread.[1–4]

History

The medicinal properties of opiates such as morphine and heroin, drugs naturally derived from the opium poppy, were first recognized in the 1800s and marketed to physicians and patients as a safe and effective way to alleviate the suffering.[5,6] With limited federal and industry oversight, opioids were used freely by doctors and lay persons to treat everyday

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ailments such as cough, diarrhea, anxiety and minor pains. With increased use, some also noted the associated risks of opioids. In 1889, James Adams noted that opium, “while surpassing other remedies in its beneficent effects” was “alike remarkable in its power of harm.”[7] Mirroring sentiment from today, Adams also noted the disadvantages of opium being threefold; “(1) In an overdose it is an active poison. (2) In ordinary doses, its benefits are largely offset by various functional derangements. (3) Its use involves the danger of the opium-habit.” [7]

With pressure from Adams and like-minded colleagues, a change in culture occurred.[5] By the early 1900s, appropriate and advanced medical care was thought to include a restrained approach to opioid use. By 1915, the Harrison Anti-Narcotic Act also took effect, which regulated opioid prescribing and dispensing practices.[8] These initiatives are thought to have led to a decrease in opioid consumption, helping to curtail the nation’s first opioid crisis.

As foreshadowed at the turn of the twentieth century, the modern-day epidemic has also been closely linked to increases in opioid consumption and liberal prescribing practices by clinicians.[9–11] Starting largely in the 1980s, attitudes toward pain management and opioid safety began to shift. Previously, these medications had been reserved for severe cancer pain, end-of-life care and limited episodes of acute pain. However, pain specialists and patient advocacy groups began to raise awareness of the inadequate treatment of non-cancer pain and underutilization of pharmaceutical opioids. For example, in 1985 an editorial published in *Advances in Alcohol and Substance Abuse* reported that physicians “markedly undertreat” pain and expressed concern for “opiophobia” – an “irrational and undocumented” fear that patients will become addicted to opioids when opioids are used appropriately.[12] This sentiment was echoed by the President of the American Pain Society (APS) in a published editorial that advocated for improved pain control and encouraged use of opioids to achieve this, writing “therapeutic use of opiate analgesics rarely results in addiction”.[13] What followed was a movement by the APS to focus on pain and pain control; referring to it as the “fifth vital sign” necessitating repeated monitoring and intervention.[11,14] The Joint Commission (formerly The Joint Commission on the Accreditation of Healthcare Organizations) also intervened and in 2001 set new pain management standards, which tied healthcare quality and patient satisfaction to pain control.[11,14,15]

Reports of pharmaceutical opioid safety often cited a one paragraph letter published in the New England Journal of Medicine in 1980.[16] In this correspondence, the authors briefly reported findings from a retrospective, observational study that assessed the side effects of opioids in hospitalized patients. This limited information was frequently used to highlight safety and promote increased prescribing by clinicians for chronic, non-cancer pain. For example, promotional video conferences and training sessions produced and funded by large pharmaceutical companies, and targeted toward physicians, inaccurately reported the risk of addiction as “less than one percent”.[17]

Compounding this, in 1995 the new extended-release (ER) oxycodone was approved by the Food and Drug Administration (FDA) for use and marketed to physicians as a safe and effective opioid pain reliever. The extended release formulation, it was argued, provided a slow, sustained release of medication which posed a lower risk for a “high” when compared

to immediate release opioids.[18,19] Marketing campaigns seized on this theory, promoting ER oxycodone as an abuse deterrent formulation with very low risk for iatrogenic addiction.[17] At the time however, there were little data to support this claim.[17,20] Studies have since shown that ER oxycodone has a similar efficacy and safety profile as immediate release opioid pain relievers[21–23] and in 2001, the FDA required that this claim be removed from drug labeling.[24]

Paralleling the increased attention to pain management and widespread marketing campaigns, opioid prescribing increased, peaking at 225 million prescriptions dispensed and a rate of 81.2 prescriptions per 100 persons in 2010.[25] In conjunction, diversion and non-medical use (i.e., the use of pharmaceutical opioids without a prescription or in a way that was not intended by the prescribing clinician) also increased,[26–28] and between 1999 and 2009 death rates involving pharmaceutical opioids increased nearly fourfold.[29]

After a period of stabilization, opioid prescribing rates began declining in 2012 and have declined each year from 2012 to 2017.[30] Nonetheless, due in large part to upsurges in fatal overdoses involving heroin and more recently, illicitly manufactured fentanyl (IMF) and highly potent fentanyl analogues, opioid overdose deaths continue to rise.[4,31]

Distinctions between tolerance, dependence, and opioid use disorder

An opioid is any substance that binds to opioid receptors in the central nervous system. Opioids can be (1) endogenous, i. e. endorphins, (2) naturally occurring opium alkaloids derived directly from the opium poppy, or (3) semi-synthetic or synthetic compounds. Naturally occurring opioids such as morphine and codeine may also be referred to as opiates. Heroin, which is made from morphine, and oxycodone, are examples of semi-synthetic opioids. Fully synthetic opioids, such as methadone and fentanyl, have chemical structures different than opium alkaloids but bind to the same opioid receptors in the central nervous system, triggering similar analgesic and euphoric effects.

Although opioid tolerance, dependence and opioid use disorder (OUD) represent distinct phenomena with markedly different clinical implications, their relationship is often misunderstood.[32] Opioid tolerance and dependence are anticipated, physiologic adaptations in the body that occur with repeated meaningful doses of opioid substances, either pharmaceutical or illegal. Tolerance, defined as a diminished response to a substance that occurs with frequent use, often requires that patients use increasing opioid doses to achieve an equivalent analgesic response.[33,34] Dependence means that a person may experience signs or symptoms of withdrawal when their dose is decreased or stopped abruptly.[33,34] Theses responses are not unique to opioids and may occur with other medications or substances such as antihypertensive medications, corticosteroids or even caffeine.

Unlike tolerance and dependence, OUD is not an anticipated or adaptive response to repeated opioid exposure.[33] The hallmark of a use disorder is a problematic pattern of behavior characterized by intense “cravings” that contribute to “compulsive drug seeking and use, despite harmful consequences.”[35] The diagnostic criteria for OUD are outlined in the Diagnostic and Statistical Manuel of Mental Disorders (DSM), Fifth Edition[36] (Table 1).

This diagnosis replaces the separate previous diagnoses from DSM-IV of “substance abuse” and “substance dependence”.[37]

Similar to other substance use disorders, OUD is a complex disease not fully understood by clinicians and researchers. While there are numerous ways to conceive and understand addiction in light of individual and social factors, addiction is commonly understood to be disease of the brain where recurrent exposure to a substance alters its structure and function, ultimately contributing to the compulsive drug-seeking behavior cardinal to OUD.[38,39] However, not all people who are exposed to opioids will develop an OUD.[32] Genetic, environmental and social factors interact to make some patients more vulnerable than others. Further, some medical complications of OUD are the result of limited access to effective preventive strategies, such as sterile syringes, which result from legal policies rather than purely biological phenomena.[40,41]

OUD is often compared to chronic diseases such diabetes and heart disease, where daily medication and lifestyle modification are needed to improve symptoms (e.g. cravings) and reduce adverse health outcomes (e.g. HIV, hepatitis C, overdose).[42,43] Similar to other chronic diseases, treatment adherence is often imperfect and recurrence of use can be common.

Neonatal abstinence syndrome (NAS) is a postnatal withdrawal syndrome that is closely linked to OUD. Strictly speaking, NAS refers to withdrawal syndromes in neonates caused by any substance, however, with the increasing incidence of fetal opioid exposure in-utero, NAS commonly refers to neonatal opioid withdrawal.[44–46] For infants with consistent prenatal opioid exposure of any kind, it is an expected and manageable outcome. Prenatal opioid exposure includes chronic pharmaceutical opioid therapy under a doctor’s supervision for severe pain, methadone or buprenorphine pharmacotherapy for OUD or illicit use of substances such as heroin.

Misunderstandings about NAS are common. For instance, infants who develop NAS are not born “addicted” to opioids.[47] The cardinal feature of addiction is a problematic pattern of behavior, which is not possible in neonates. There is also a common misperception that higher maternal opioid doses are tied to the onset and severity of NAS. However, several studies have examined the relationship between methadone dose and the incidence and severity of NAS with mixed results.[48–50] When restricted to prospective studies using an objective scoring system, a meta-analysis by Cleary et al. found no statistical difference in the incidence and severity of NAS by methadone dose.[51] This suggests that other factors should be considered when determining maternal methadone during pregnancy, such as adequate control of withdrawal symptoms and relapse risk.

Both methadone and buprenorphine can be used to treat women with OUD during pregnancy. A multicenter, double blind randomized control trial, the Maternal Opioid Treatment; Human Experimental Research (MOTHER) study, examined neonatal outcomes in pregnancies with maternal exposure to methadone or buprenorphine.[52] Investigators demonstrated that, while there was no difference in the number of infants requiring treatment for NAS between the groups, buprenorphine pharmacotherapy was associated with

lower morphine requirements, shorter duration of NAS treatment, and shorter infant hospital stays. This study suggested less severe NAS with buprenorphine treatment when compared to methadone. Similarly, a 2013 Cochrane review, which included the MOTHER study, also suggested less severe NAS with buprenorphine. However, the authors also reported increased treatment retention in those receiving methadone compared to buprenorphine. Citing variation across outcomes, as well as the small body of evidence, the authors concluded there was insufficient evidence to support one treatment over the other.[53]

Epidemiology

According to the National Survey on Drug Use and Health, a national, population-based household survey, in 2016, 11.8 million Americans 12 or older reported misuse of opioids (i.e., non-medical use of pharmaceutical opioids or use of heroin) in the last year. Of these, 92% misused pharmaceutical opioids only, 5.4% misused pharmaceutical opioids and heroin and 2.6% used heroin only.[54]

In 2016, over 42,000 Americans died from an opioid overdose, representing a 27% increase in death rates from opioid overdoses from 2015 (13.3 per 100,000 population).[4] Heroin, IMF and highly potent fentanyl analogs are now implicated in the majority of fatal opioid overdoses. The Centers for Disease Control and Prevention (CDC) estimate that over 80% of the opioid overdose deaths in 2016 involved heroin or a synthetic opioid other than methadone (i.e., fentanyl).[55] Between 1999 and 2016, the rate of deaths involving heroin increased seven-fold (from 0.7 per 100,000 in 1999 to 4.9 in 2016) and the rate of deaths involving synthetic opioids increased twenty-fold (from 0.3 per 100,000 in 1999 to 6.2 per 100,000 in 2016). This includes a 100% increase in synthetic opioid overdose death rates from 2015 to 2016.[55]

Historically, men have been disproportionately affected by opioids with higher overall rates of OUD and overdose mortality than women, however the prevalence of OUD and its complications are rising in women.[3] Between 2005 and 2014, opioid-related hospitalizations increased for both men and women. However, rate increases were more for women than for men (75% vs 55%) and by 2014, in most states, the rate of opioid-related inpatient stays for women exceeded that of men.[1]

Mirroring increases in the general population, opioid use and OUD in women who are pregnant have increased.[56–59] Between 1999 and 2014, the rate of antepartum opioid use disorder quadrupled (from 1.5 to 6.5 per 1000 hospital births)[60] and opioids are now the most common reason for seeking drug treatment during pregnancy.[61] Concurrently, the incidence of NAS increased 400% from 2000 to 2012,[62,63] and national medical costs for NAS were estimated at $316 million in 2012 alone.[64]

Confronting the opioid epidemic

Reducing stigma

The language used in discussing and treating patients with substance use disorders is important. Incorrect terminology may unknowingly contribute to misunderstandings about

OUD, perpetuate stigma and bolster stereotypes; collectively reinforcing treatment barriers for patients.[65,66]

Studies have found that terms such as “addict” and “substance abuser” elicit strong negative feelings toward individuals suffering from OUD.[67] This can imply that addiction occurs as a fault of the person, such as a personality flaw or moral failing, requiring punitive measures,[68] rather than as a result of a medical condition.[38,39]

“Person first” language has been suggested as a way to address stigma and stereotypes in OUD.[65,69] In person first language, words describing individuals precede words describing their disease or disorder.[70] For example, consider “patient with a history of opioid use disorder” versus “opioid abuser” or “addict”. The former, helps to focus on the person and not their disorder, conveying that while they may suffer from OUD, it is not their only identity.

The language used to describe medications used to treat OUD can also be pejorative.[71,72] Treatment with the opioid agonists methadone or buprenorphine is often referred to as “opioid substitution therapy” or “medication assisted treatment”. Experts argue that this terminology supports the false notion that these medications are “replacing one addiction for another” and suggests that pharmacotherapy is merely an adjunct to other aspects of addiction care.[71,73] Contrary to this, the scientific literature strongly supports the use of methadone and buprenorphine as a safe and effective way to reduce illicit drug use and improve societal engagement.[74]

Improving prescribing practices

Although prescribing rates have declined in recent years, the increased availability and use of opioid pain medications played an important role in the modern-day epidemic. In 2016, the amount of prescription opioid medications in the United States was roughly three times as high as in 1999,[25,75] and in 2016, over 17,000 died from a pharmaceutical opioid overdose.[4] Several studies have shown a temporal and spatial relationship between the availability of pharmaceutical opioids and overdose mortality.[10,27,76,77] Even when prescribed by a physician and taken as instructed, use of pharmaceutical opioids can lead to adverse health outcomes including addiction and fatal overdoses.[78] Evidence suggests that these risks are increased with long acting opioid formulations, long term opioid therapy, high morphine equivalent doses, concurrent benzodiazepine use, and past history of substance use disorders, tobacco use, and mental health diagnoses.[79–83]

In 2016 the CDC released guidelines with 12 specific recommendations (Table 2) to assist clinicians in prescribing pharmaceutical opioid medications to treat pain and recognize and treat patients with high-risk behaviors or OUD.[84] The primary focus of these recommendations pertained to medical management of pain lasting >3 months and did not pertain to cancer or end-of-life care. Acute pain management was also briefly addressed.

Prescription drug monitoring programs (PDMP) have also been established in nearly every state to improve prescribing practices. Several states report PDMP effectiveness in process outcomes such as improving physician confidence,[85,86] identifying patients with multiple

prescribers, and reducing availability of controlled substances.[87] Patrick et al also demonstrated that state PDMP implementation was associated with a decrease of 1.12 opioid-related overdose deaths per 100,000 population annually. States that monitored four or more drug schedules and updated their PDMP regularly had even great reductions in mortality rates.[88] Current CDC guidelines suggest reviewing PDMP data prior to all opioid prescriptions and at minimum, prior to initiating long-term opioid therapy and periodically during its course.[84]

Increasing utilization of medications for opioid use disorder

There are three FDA-approved medications to treat patients with OUD–methadone, buprenorphine and naltrexone. Methadone and buprenorphine are long-acting opioid receptor agonists that provide consistent systemic drug levels and have been shown to reduce opioid cravings[89] and prevent withdrawal syndromes.[90] Naltrexone, an opioid receptor antagonist, is available as an oral medication requiring daily dosing or as an injectable medication requiring monthly dosing. When taken appropriately, naltrexone blocks the effects of opioids and can prevent relapse. However, adherence to daily dosing is challenging and a 2011 Cochrane Review suggested that oral naltrexone was no better than placebo or no pharmacotherapy in preventing relapse or improving treatment retention.[91] Studies investigating the efficacy of extended-release naltrexone have been more promising;[92,93] however, concerns remain regarding the overdose risk in patients treated with naltrexone only.[94,95]

Studies have repeatedly shown that methadone and buprenorphine reduce illicit opioid use, increase retention in drug treatment, and reduce mortality.[96–101] For example, a systematic review and meta-analysis of cohort studies published in the British Medical Journal in 2017 found that patients who received maintenance buprenorphine or methadone had substantially reduced all-cause and overdose mortality rates when compared to patients who did not receive opioid agonist medications.[102] A Cochrane review by Mattick et al in 2009 and 2014 also showed that when compared to placebo, both buprenorphine and methadone were effective in retaining people in treatment.[74,99]

Despite a substantial evidence base, agonist pharmacotherapy for OUD remains underutilized. Barriers are multifold and include a lack of trained prescribers to initiate and maintain medications, misperceptions by patients and providers about how medications work and their intended outcomes and fear of stigma or criminalization by patients.

Unlike methadone, which can only be dispensed by licensed, specialty treatment programs with daily dosing, the Drug Addiction Treatment Act of 2000 (DATA 2000) allows buprenorphine to be prescribed by waivered physicians and advanced practice providers in an office-based setting to treat OUD.[103] Studies suggest this has improved access to pharmacotherapy for many patients with OUD; however, access remains poor. For example, Jones et al estimated that in 2012, if all available methadone treatment slots were filled and all buprenorphine waivered physicians saw the maximum number of patients allowed, over 900,000 patients would still be in need of pharmacotherapy.[104] This shortfall is particularly dire in rural areas of the country where over half (56.3%) of all counties lack a single buprenorphine provider.[105] Patrick et al also found that while most providers were accepting

new patients in Appalachia, providers were less likely to accept women who were pregnant (91% vs 75%).

In addition to problems with access, pregnant women with OUD may also face fears of criminalization when seeking pharmacotherapy to treat OUD. In 2014, Tennessee was the first state to pass a statute specifically allowing women to be prosecuted for assault if they engaged in illegal drug use during pregnancy. Currently, 23 states and the District of Columbia consider substance abuse during pregnancy to be child abuse and 24 states mandate healthcare workers to report substance abuse if suspected.[106] This legal trend is concerning considering, the data suggest that women who are pregnant and receive methadone or buprenorphine are less likely to relapse on illicit opioids and more likely to engage in routine prenatal care,[53,107–109] leading to better health outcomes for mother, fetus and infant.

Reducing fatal overdoses

Naloxone, an opioid receptor antagonist, is an antidote to opioid overdoses.[110] Observational studies have repeatedly shown that take home naloxone is a safe and effective way to reduce OD mortality in patients with OUD[111–114] and is not known to lead to an increase in substance use.[115,116]

The effectiveness of naloxone requires that overdose bystanders can (1) easily access the medication, (2) promptly recognize the signs and symptoms of OD and (3) effectively administer a life-saving dose. As such, most states have moved beyond traditional prescription models for distribution; allowing for third party prescriptions for anyone who may encounter an overdose and non-patient specific prescriptions where pharmacies and community health programs may distribute naloxone to any individual and provide education and training on OD recognition and medication administration.[117] Guidelines suggest that clinicians offer naloxone to patients with OUD and consider offering it to patients on chronic opioid therapy when risk factors for opioid overdose are present such as concomitant benzodiazepine use, opioid doses over 50 morphine milligram equivalents per day, history of opioid overdose or other substance use disorder.[84] A risk prediction model has been developed to help providers select patients prescribed chronic opioid therapy who could benefit from naloxone.[83]

Conclusion

Initially driven by increases in the availability of pharmaceutical opioids, fatal overdoses are now largely related to the emergence of illegally manufactured fentanyl and fentanyl analogues. Mortality statistics are grim; however, research has consistently shown improved outcomes with the use of pharmacotherapy to treat OUD, including for women who are pregnant. Clinicians can help reduce the stigma associated with OUD and barriers to treatment by using appropriate terminology that is non-judgmental and non-punitive. These efforts may help to address the opioid epidemic.

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Table 1

DSM V diagnostic criteria for opioid use disorder.[36]

Two or more of the following within a 12-month period:
• Using larger amounts of opioids or over a longer period of time than was intended
• Persistent desire to cutback or unsuccessful efforts to control use
• Substantial amount of time spent obtaining, using or recovering from use
• Craving or strong desire to use opioids
• Failure to fulfill obligations at work, home or school due to use
• Continued use despite recurrent social or interpersonal problems caused or exacerbated by use
• Giving up or reducing social, occupational or recreational activities due to use
• Recurrent opioid use in situations that may be physically dangerous
• Continued use despite knowledge of having a physical or psychological problem caused or exacerbated by opioids
• Tolerance *
• Development of withdrawal syndrome if use stopped *
Opioid use disorder severity:
• Mild 2-3 symptoms or signs
• Moderate 4-5 symptoms or signs
• Severe 6 or more symptoms or signs

* Tolerance and withdrawal criteria not met if opioids only used under medical supervision and as intended.

Table 2

CDC guidelines for prescribing opioids for chronic pain.[84]

When to initiate or continue opioids:
1. on-pharmacologic therapy and non-opioid pharmacologic therapy are preferred treatment for chronic pain. If used, opioids should be given in combination with non-pharmacologic therapy and non-opioid pharmacologic therapy when appropriate.
2. Realistic treatment goals should be established prior to initiating therapy.
3. Before starting and periodically during treatment, clinicians should discuss risks and benefits with the patient.
Opioid selection, dosing and duration:
1. Immediate release opioids should be used instead of long acting opioids.
2. The lowest effective dose should be prescribed.
3. When treating acute pain, the lowest effective dose of immediate release opioids should be used for a limited duration; typically 3 days or less, rarely more than 7 days.
4. Clinicians should reevaluate benefits and harms with the patient 1-4 weeks after starting chronic opioid therapy and re-assess risk-benefit of medication.
Assessing risk and addressing harms:
1. Evaluate risk factors for adverse events before initiation and during treatment. Consider naloxone for higher risk patients.
2. Review prescription drug monitor program (PDMP) database before initiating and during treatment.
3. Urine drug testing should be used before initiating and periodically during treatment.
4. Avoid prescribing opioids and benzodiazepines together.
5. Offer treatment or refer patients to treatment if opioid use disorders is expected.

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