

Introduction to the Opioid Epidemic: The Economic Burden on the Healthcare System and Impact on Quality of Life

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“Pain is a more terrible lord of mankind than even death itself.”

– Albert Schweitzer
French-German physician
1875-1965

Understanding Pain

Pain affects more Americans than diabetes, heart disease, and cancer combined.¹ There are several approaches to classifying pain, including by duration, which is the most common (eg, acute, subacute, or chronic); by type (eg, nociceptive, neuropathic, inflammatory); and by intensity (eg, mild, moderate, or severe).² Data from 2012 estimated that 126.1 million adults in the United States suffer from pain.³ This pain originates from a variety of conditions, diseases, and events. For example, 80% of patients undergoing surgery will experience postoperative pain, with fewer than half reporting adequate pain relief.⁴ Sixty percent of women experiencing their first childbirth rate their pain as severe, with up to 18% reporting persistent pain 1 year after delivery.⁴ According to 2016 survey data from the National Center for Health Statistics, 15.3%, 14.9%, and 28.4% of Americans older than 18 years experienced severe headache or migraine, neck pain, or lower back pain, respectively, within the past 3 months.⁵ Frequent back pain affects more than 26 million Americans between 20 and 64 years, and is the leading cause of disability in those under 45 years; acute headache accounts for 2.1 million emergency department (ED) visits every year.^{4,6} Of individuals seeking help from the ED for pain, 74% are discharged in moderate to severe pain.⁴

Acute pain is short in duration, self-limiting, and typically the result of identifiable causes, such as surgery, acute illness, trauma, labor and childbirth, medical procedures, and cancer or cancer treatment.^{2,7} Although short lived, acute pain stimulates the sympathetic nervous system and causes clinical symptoms of hypertension, tachycardia, diaphoresis, shallow respiration, restlessness, facial grimacing, guarding behavior, pallor, or pupil dilation.⁷ Although acute pain is a normal and necessary response to tissue damage, it may be associated with significant physical, psychological, and

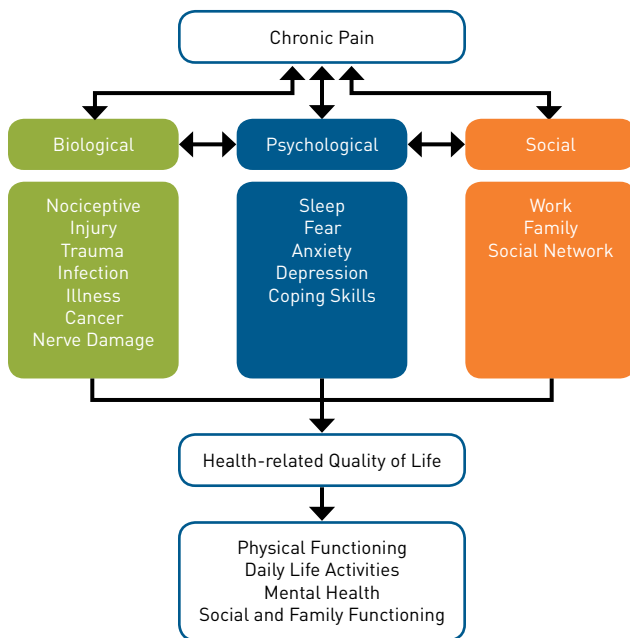
ABSTRACT

Opioid analgesics are commonly used to treat acute and chronic pain; in 2016 alone, more than 60 million patients had at least 1 prescription for opioid analgesics filled or refilled. Despite the ubiquitous use of these agents, the effectiveness of long-term use of opioids for chronic noncancer pain management is questionable, yet links among long-term use, addiction, and overdose deaths are well established. Because of overprescribing and misuse, an opioid epidemic has developed in the United States. The health and economic burdens of opioid abuse on individuals, their families, and society are substantial. Part 1 of this supplement will provide a background on the burden of pain and the impact of opioid abuse on individuals, their families, and society; the attempts to remedy this burden through prescription opioid use; and the eventual downward spiral into the current opioid epidemic, including an overview of opioid analgesics and opioid use disorder and the rise in opioid-related deaths.

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FIGURE 1. Biopsychosocial Model of Pain and Consequences on Daily Life⁹



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emotional distress.⁷ Furthermore, inadequate control of acute pain is a risk factor for developing chronic pain.⁷

Compared with acute pain, chronic pain—defined as pain lasting 3 months or beyond the time of normal tissue healing—is much more complex and challenging to treat.^{2,8} Although acute pain resolves as the body heals, chronic pain may persist for months to years and is often a result of changes to nerve function and transmission.² Chronic pain does not resolve on its own, and, over time, the pain may become more sensitive; hyperresponsive; and able to produce intense, spreading, and unremitting pain, which may be affected by physical, environmental, and psychological factors.⁷ Therefore, chronic pain is often regarded as a disease in and of itself, and has been associated with reduced patient quality of life, well-being, and ability to function over the long term.⁷

Chronic pain affects many aspects of a patient’s life, including daily activities, physical and mental health, family and social relationships, and interactions in the workplace, as shown in **Figure 1**.⁹ For example, a study by Toblin et al found that 44% of US Army infantry soldiers reported chronic pain after a combat deployment; this pain was significantly associated with positive screens for major depressive disorder (odds ratio [OR], 2.3; 95% CI, 1.4-3.6) and post-traumatic stress disorder (OR, 1.7; 95% CI, 1.2.0-2.5).¹⁰

Despite the availability of opioid analgesics and other pharmacotherapies, many patients remain in pain. A 2006 survey in which

303 patients with chronic pain were currently using an opioid for treatment found that 51% of respondents felt as though they had no or little control over their pain.⁶ Additionally, 77% reported feeling depressed, 70% had trouble concentrating, and 86% were unable to sleep well due to pain.⁶

Data from the American Productivity Audit of 28,902 working adults from August 2001 to July 2002 revealed that 53% of the workforce reported headache, back pain, arthritis, or other musculoskeletal pain in the previous 2 weeks, with 13% reporting lost productivity time due to pain during that timeframe.⁶ Additionally, 77% of lost productivity occurred due to reduced work performance rather than absenteeism.⁶ This lost productivity has been estimated to cost several hundred billion dollars annually, including days of work missed (\$11.6 billion to \$12.7 billion), hours of work lost (\$95.2 billion to \$96.5 billion), and lost wages (\$190.6 billion to \$226.3 billion).⁴ Collectively, combining healthcare cost estimates and lost productivity, the total annual economic burden of pain on society ranges from \$560 billion to \$635 billion.⁴

In summary, pain contributes to substantial morbidity, mortality, and disability for millions of Americans. When inadequately or inappropriately treated or managed, the consequences extend beyond the individuals experiencing pain, impacting families, healthcare systems, work performance, and society.⁴

Prescription Opioids for Pain

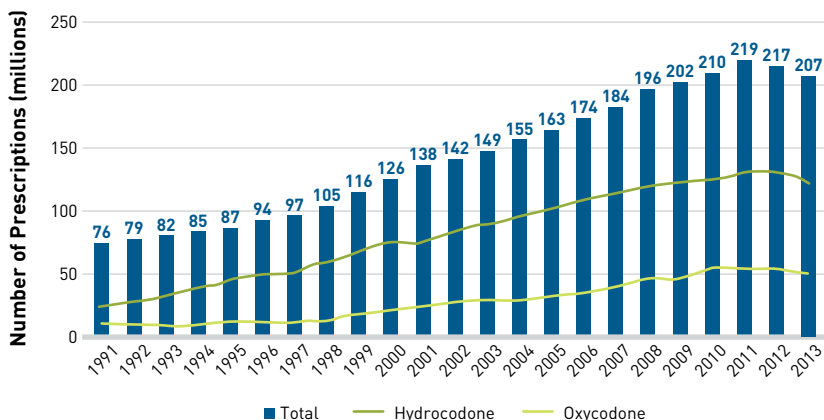
“ If we know that severe pain and suffering can be alleviated, and do nothing about it, then we ourselves become the tormentors. ”

– Primo Levi
Italian-Jewish chemist
Auschwitz survivor
1919-1987

Two decades ago, the burden of pain on American society reached a boiling point in the medical community, and there was a shift toward more compassionate treatment for all patients suffering with chronic pain.¹¹ Following the publication of an observational study of 38 patients touting the use of opioid analgesics for chronic noncancer pain and the 1995 FDA approval of a time-released oxycodone formulation (OxyContin), the prescription opioid market exploded.¹¹⁻¹³ Healthcare providers unwilling to prescribe opioids were considered “opiophobic,” and initiatives promoting stricter controls on opioid prescribing were described as “careless, naïve, and unsympathetic.”¹¹

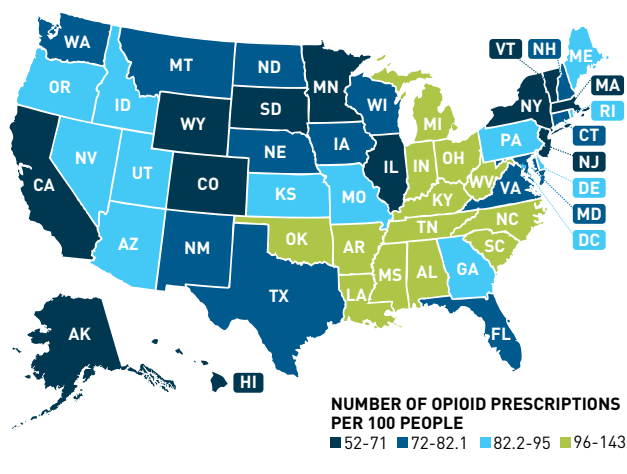
Opioids, including opiates, such as morphine and heroin, and synthetic opioids, such as fentanyl, are derivatives of opium and synthetic surrogates that work on μ -opioid receptors in the body to relieve pain.¹⁴ Additional opioid receptor subtypes include δ and κ nociception/opioid-receptor-like subtype 1 (ORL-1) receptors.¹⁴

FIGURE 2. Opioid Prescriptions Dispensed by US Retail Pharmacies, 1991-2013¹³



IMS Health. National Prescription Audit. Years 1997-2013. Data extracted 2014.

FIGURE 3. Rates of Opioid Prescribing by State, 2012^{23,24}



Pharmaceutical agents may exhibit varying levels of agonism, antagonism, or mixed agonist-antagonist activity at different opioid receptors, depending on their chemical structure, which leads to different adverse effects and analgesic properties.¹⁴ Opioid analgesics are commercially available in oral, intravenous, transdermal, intranasal, epidural, and intrathecal preparations, which contributes to their clinical utility.⁸ Additional formulations, such as oral transmucosal, rectal, inhaled, and topical, may be compounded to meet individual patient needs.¹⁵

In 1998, the Federation of State Medical Boards (FSMB) of the United States released guidelines for the use of controlled substances for the treatment of pain.¹⁶ Although the initial purpose was to curtail controlled substance abuse by outlining the appropriate use of opioids and other pain medications, the guidelines had the opposite effect of

“absolving prescribers from the responsibility of their actions and even promoted more prescriptions under the guise of appropriate medical treatment.”¹¹ Direct statements from the guidelines declare: “...the Board will judge the validity of prescribing based on the physician’s treatment of the patient...rather than on the quantity and chronicity of prescribing;” continuing with “...physicians should not fear disciplinary action from the Board...for prescribing, dispensing, or administering controlled substances, including opioid analgesics;” and “...fears of investigation or sanction by federal, state, and local regulatory agencies may also result in inappropriate or inadequate treatment of chronic pain patients;” and, finally, “...these guidelines have been developed to...alleviate physician

uncertainty and to encourage better pain management.”¹⁶

In addition to these US FSMB guidelines, a review of medical records from 1990 to 1996 concluded that the increased use of opioids to treat pain did not contribute to increased rates of abuse.¹⁷ In late 1996, the American Pain Society initially promoted the phrase “pain as the 5th vital sign,” and by the year 2000, the Department of Veterans Affairs published a document recognizing “pain as the 5th vital sign.”¹⁸ In 2001, the Joint Commission on Accreditation of Healthcare Organizations, now known simply as the Joint Commission, released standards for inpatient and outpatient pain management that emphasized the patient’s right to pain relief as a key shift in the pain management paradigm.^{18,19}

Following these initiatives and others that came after, opioid sales skyrocketed, as demonstrated in **Figure 2**.¹³ In 1991, prescriptions written in the United States for opioids were around 76 million.¹³ At peak in 2011, there were 219 million prescriptions written, an increase of nearly 300%, or 143 million from 1991, making the United States the largest consumer globally of opioid analgesics.²⁰

Approximately 1 of 5 patients with noncancer pain or pain-related diagnoses are prescribed opioid analgesics; of 164 million pain visits in 2010, 20% of patients were treated with an opioid.²¹ In 2016, approximately 66.5 opioid prescriptions were written for every 100 Americans.²² As shown in **Figure 3**, the wide geographic variation in prescribing practices, with overprescribing predominantly occurring in Appalachian and midwestern regions, does not reflect discrepancies in injuries, surgeries, or conditions requiring analgesics.^{23,24} Results of a national county-level analysis by McDonald et al found significant correlations between amounts of prescribed opioids in 2008 and higher population size, lower education level, higher percentage of white non-Hispanic and African American, higher poverty, higher percentage without insurance and younger than 65 years, higher physicians per capita, and higher percentages

among all surgeons, psychiatrists, and pediatricians.²⁴ Although US prescription trends vary considerably from state to state, the dispensing of prescription opioids remains high across the United States.²³

Despite the routine use of opioids for pain, there remains no strong scientific evidence for the use of opioids in chronic noncancer pain.¹¹ Although evidence indicates prescription opioids do reduce pain intensity in patients with chronic noncancer pain by 30%, on average, evidence also indicates that the long-term use of opioids in patients with chronic noncancer pain is not associated with improvements in health-related quality of life assessment scores.^{25,26} A recent study by Krebs et al evaluated pain-related function among 234 opioid and nonopioid users.²⁷ After 12 months, opioid users experienced more adverse events ($P = .03$) but did not differ from nonopioid users in pain-related function. Furthermore, pain intensity was significantly better for nonopioid users ($P = .03$).²⁷

The Opioid Epidemic

“ Nobody will laugh long who deals much with opium: its pleasures even are of a grave and solemn complexion. ”

– Thomas de Quincy
English essayist,
Confessions of an English Opium-Eater
1785-1859

Despite the benefits that prescription opioids offer in acute pain management, the use, abuse, and overuse of these agents has contributed to significant health and economic burdens for patients, their families, and society. As the sales of opioids rose during the first decade of the new millennium, so did the rates of opioid misuse and abuse. By 2016, 11.5 million Americans were misusing prescription opioids, 2.1 million had opioid use disorder (OUD), and more than 42,000 died from overdosing on opioids.²⁸ In October 2017, the US Department of Health and Human Services declared the opioid crisis a public health emergency.²⁹

The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*, defines OUD as “a problematic pattern of opioid use leading to clinically significant impairment or distress.”³⁰ To be diagnosed with an OUD, an individual must have at least 2 of the manifestations outlined in the **Table** over a 12-month period.³⁰ Symptoms of OUD include a strong desire for opioids, the inability to control or reduce use, continued use despite interference with major obligations or social functioning, the use of larger amounts over time, and a great deal of time spent obtaining and using opioids.³¹ Additionally, OUD may involve the development of tolerance and withdrawal.³⁰ Tolerance is a markedly diminished effect with continued use that leads to a need for increased amounts to achieve intoxication or the desired effect; withdrawal is the occurrence of symptoms when the use of opioids is discontinued, including negative mood, nausea or vomiting, muscle aches, diarrhea, fever, and insomnia.^{30,31}

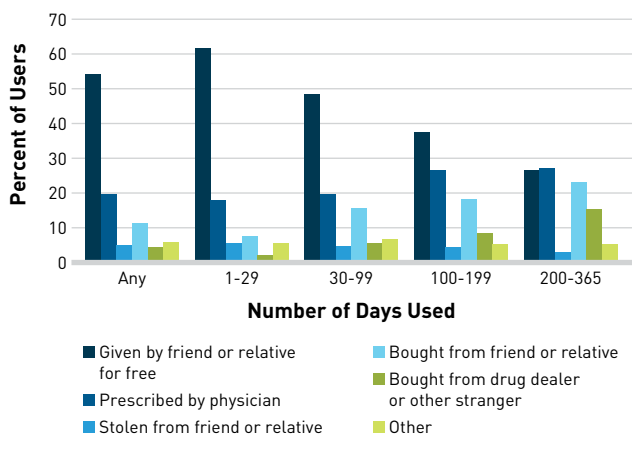
TABLE. DSM-5 Criteria for Opioid Use Disorder³⁰

Opioids are often taken in larger amounts or over a longer period than was intended.
There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
Craving or a strong desire or urge to use opioids.
Recurrent opioid use resulting in failure to fulfill major role obligations at work, school, or home.
Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
Important social, occupational, or recreational activities are given up or reduced because of opioid use.
Recurrent opioid use in situations in which it is physically hazardous.
Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
Tolerance, as defined by either of the following: <ul style="list-style-type: none"> • A need for markedly increased amounts of opioids to achieve intoxication or desired effect • A markedly diminished effect with continued use of the same amount of an opioid (Note: This criterion is not considered to be met for those taking opioids solely under appropriate medical supervision.)
Withdrawal, as manifested by either of the following: <ul style="list-style-type: none"> • The characteristic opioid withdrawal syndrome • Opioids (or a closely related substance) are taken to relieve or avoid withdrawal symptoms. (Note: This criterion is not considered to be met for those individuals taking opioids solely under appropriate medical supervision.)

DSM-5 indicates Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

The terms misuse and abuse are also used in discussion of OUD; according to the FDA, these terms are distinguished from each other by the intention of the person taking the substance.³² However, these definitions may vary by the definer (eg, FDA vs National Institute on Drug Abuse), which may lead to confusion when interpreting the literature, so care must be taken when comparing data across multiple sources without a clear definition of terminology. Whenever a person takes a legal prescription medication for a purpose other than the reason it was prescribed, this is misuse; an example of misuse would be taking an additional hydrocodone tablet beyond the indicated prescription instructions because the patient remains in pain.³² Abuse refers to the intentional seeking of euphoria or “high” associated with misuse of the substance, such as taking several oxycodone tablets for the pleasant or euphoric feeling.³² Nonmedical use of a prescription opioid is defined as use without a prescription, even if for a medical reason such as headache, or use with a prescription for the feeling or experience (ie, the “high”) caused by the drug.³³

FIGURE 4. Source of Opioid Analgesic Most Recently Used Without a Prescription or With a Prescription for Nonmedical Reasons³³



Because opioids vary in potency from one agent to another, comparison of doses and conversion from one opioid to another is considered in terms of morphine milligram equivalents (MMEs). Despite criticism regarding the validity and utility of MME conversions, the total daily dose of MMEs is commonly used to evaluate the need for dose tapering, closer patient monitoring, or other measures to reduce the risk of transition to OUD or overdose.^{34,35} Data have shown that patients who died of an overdose were prescribed an average of 98 MMEs per day, while others who did not die of an overdose were prescribed an average of 48 MMEs per day.³⁵ Accordingly, patients receiving doses above 50 MMEs per day are considered to have at least twice the risk of overdose compared with those receiving less; the Centers for Disease Control and Prevention (CDC) recommends extra precautions with doses greater than or equal to 50 MMEs per day and avoidance or careful justification of doses greater than or equal to 90 MMEs per day.³⁵ Examples of amounts of opioids equivalent to 50 MMEs per day are 50 mg of hydrocodone (10 tablets of hydrocodone/acetaminophen 5 mg/325 mg), 33 mg of oxycodone (approximately 2 tablets of oxycodone sustained-release 15 mg), or 333 mg of codeine (6 tablets of acetaminophen/codeine 60 mg/300 mg).^{35,36} Recent data show a relatively steady average of 50 to 60 MMEs per day per opioid prescription from 2006 to 2015.³⁷

In addition to understanding OUD, the false sense of security a prescription may create is important to consider. Studies have shown that opioids are considered by many to be safer or less addictive than illicit drugs, such as heroin, and are often shared freely between family members or friends, as shown in **Figure 4**.^{33,38} Although obtaining from friends or family for free was the most frequently cited means of acquiring opioids in the lower use groups, (up to 199 days used), the highest use group (200 to 365 days used) depended on several sources more equally, including prescriptions from a

physician and friends or family (free and purchased).³³ These data underscore the impact of both prescribing and dispensing practices and public awareness in combating the opioid epidemic.

The rapid rise in opioid-related deaths is the most devastating aspect of the opioid epidemic. Prescription opioid-related deaths have tripled since 1999; opioid overdose is now responsible for 115 daily deaths of Americans on average, which is roughly 1 death every 13 minutes.^{39,40} National overdose deaths from all opioids, including both prescription and illicit drugs, are shown in **Figure 5**,⁴¹ with a 2.8-fold increase in total number of deaths noted from 2002 to 2015.^{20,41} In 2008, overdose was responsible for 830,652 years of potential life lost before age 65 years.⁴²

Until 2014, prescription opioids were the primary driver of opioid-related deaths in the United States. However, since that time, mortality from illicit opioid use, including heroin and illicitly manufactured fentanyl, has increased significantly (**Figure 6**).^{8,41} A study by Fibbi et al found that among participants denied prescriptions for opioids, approximately half reported self-medicating pain with either illegally obtained prescription opioids or heroin; self-medication was associated with new risk behaviors and more intense drug use.⁴³ Studies evaluating deaths from pharmaceutical opioids in West Virginia, Utah, and Ohio found that 25% to 66% of deaths were from opioids originally prescribed to someone else.¹¹

Overdose-related death is not the only risk associated with prescription opioids; additional dangers include misuse, abuse, and OUD. According to the CDC, 1 in 4 patients in a primary care setting who receive long-term opioids for chronic noncancer pain struggle with OUD.⁴⁴ Every day, more than 1000 people are treated in EDs for misusing prescription opioids, with the most commonly abused agents being methadone, oxycodone, and hydrocodone.⁴⁴ Once an OUD is established, the negative impacts on quality of life and health, as well as economic impacts to individuals, families, and society, are substantial.

A study by Griffin et al found that patients with OUD had worse physical ($P < .001$) and mental ($P < .001$) quality of life compared with the general population.⁴⁵ Among heroin-dependent patients, the prevalence of sleep disturbances was over 75%, which was associated with greater severity of dependence, greater severity of depression, and poorer physical health-related quality of life.⁴⁶ Compared with the general population, medical complications that may be more prevalent in individuals with OUD include infections, such as cellulitis, wound botulism, necrotizing fasciitis, and endocarditis; transmissible diseases, such as HIV/AIDS, hepatitis, syphilis, and tuberculosis; diseases related to heavy tobacco use, such as chronic obstructive pulmonary disease, hypertension, and coronary artery disease; or conditions resulting from intoxication or criminal activity, such as head trauma or gunshot wounds.⁴⁷

The burden associated with diminished quality of life from OUD extends beyond the individual, affecting the physical and

mental health of the individual's family, too.⁴⁸ A study comparing family burdens in injecting versus noninjecting opioid users found that all caregivers reported moderate to severe burdens.⁴⁸ For both groups combined (n = 80), opioid use imposed a moderate to severe burden on finances (100%), disruption of family routine (99%), disruption of family leisure (99%), and disruption of family interaction (98%).⁴⁸ Additionally, 44% and 85% of participants reported a moderate to severe burden on the physical and mental health of family members, respectively.⁴⁸ Similar results were found by Mattoo et al, with 95% to 100% of family caregivers of men with OUD reporting a moderate to severe burden across similar domains.⁴⁹

In addition to the impact to individuals and families, society has been negatively impacted by the opioid epidemic. For example, in 2014, opioid overdoses were responsible for 147,654 ED visits, with estimated direct medical costs of \$152.8 million, with over half of these costs (\$83.7 million) borne by the public sector.⁵⁰ Costs that contribute to the burden to society include those related to healthcare, workplace, and criminal justice.⁵¹ Compared with patients who do not struggle with OUD, those with an OUD use significantly more healthcare resources, such as ED visits, physician outpatient visits, and inpatient hospital stays.^{52,53} Meyer et al estimated the mean annual excess healthcare cost for patients with OUD ranges from \$14,054 to \$20,546, and \$5874 to \$15,183 for those with private insurance and Medicaid, respectively.⁵³ In addition to higher costs, greater usage of healthcare resources may lead to longer wait times, fewer appointment options, and increased staff workload.

Florence et al estimated the total economic burden of prescription opioid overdose, abuse, and dependence to be \$78.5 billion in 2013.⁵⁴ However, a recent executive summary released by the Council of Economic Advisers states that prior publications have underestimated the total cost of the opioid crisis, and it estimated the economic burden in 2015 to be \$504 billion, which was more than 6 times higher than other estimates.⁵² Fatality costs comprise over 85% of total costs.⁵² Aside from fatality and healthcare costs, other costs include foregone earnings from employment and higher costs to the criminal justice system.⁵² Although this estimate is the first to include illicit drug use (eg, heroin, illicitly produced fentanyl), the authors note that only 14% of individuals with an OUD present with heroin use disorder in isolation.⁵²

FIGURE 5. National Overdose Deaths Involving Opioid Drugs⁴¹

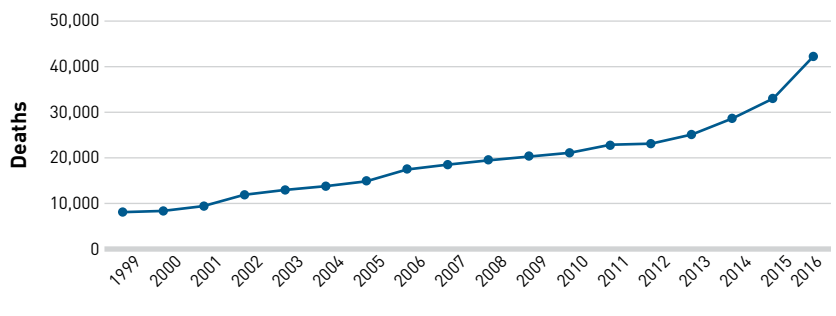
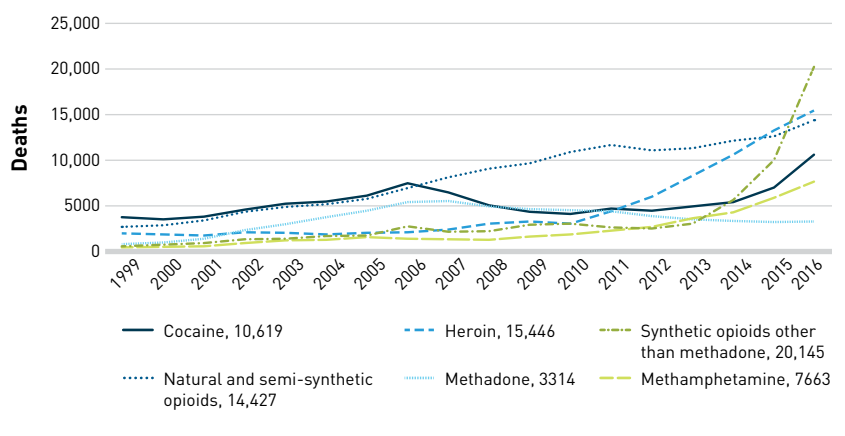


FIGURE 6. Drugs Involved in Overdose Deaths, United States, 2000-2016⁴¹



Conclusions

The opioid epidemic has been responsible for hundreds of thousands of lives lost over the past 2 decades, and millions more individuals and their families have been negatively affected by the misuse or abuse of prescription opioids. Although the origins of increased opioid use were well-intended attempts at optimal pain management, the result has become a costly increase in OUDs and death, with little evidence of improvement in chronic noncancer pain. National and government organizations, particularly the CDC, have recognized and initiated interventions to raise awareness and reduce opioid prescribing practices, and prescription rates have correspondingly stabilized. Additionally, the Comprehensive Addiction and Recovery Act (CARA), which was signed into law in 2016, was the first major federal addiction legislation in 40 years; CARA involves 6 pillars necessary for a complete, coordinated response to the opioid crisis: (1) prevention, (2) treatment, (3) recovery, (4) law enforcement, (5) criminal justice reform, and (6) overdose reversal.⁵⁵ Initiatives such as these will combat both the supply and demand of the opioid epidemic; however, as prescription opioid abuse lessens, illicit abuse of opioids and overdose

deaths from all opioids are increasing, indicating that much work remains to be done. ■

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