

The Opioid Epidemic in the United States

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KEYWORDS

• Opioids • Opioid epidemic • Heroin • Prescription drugs • Overdose • Legal liability

KEY POINTS

- There is an epidemic of opioid abuse in the United States.
- The risk of heroin abuse has been appreciated for more than a century with it now being considered to have no justifiable medical use.
- Opioids commonly prescribed to treat painful conditions have had a dramatic increase in the rate of abuse, addiction, overdose, and death.
- The increase in complications corresponds with a dramatic increase in the rate of opioid prescriptions that resulted from pressures placed on practitioners to avoid undertreatment of pain.
- Naloxone is a competitive opioid antagonist that is used to reverse the adverse effects of opioid intoxication. It is increasingly being prescribed for emergent outpatient administration.

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

—Dr Albert Schweitzer, 1931.

INTRODUCTION

The United States is currently experiencing an epidemic of opioid abuse. This article discusses the history of opioid use for pain management and how epidemiologic data demonstrate a convincing degree of association between the increasing rate of opioid prescriptions and the increasing rate of adverse effects, aberrant use, and unintentional death from opioids. There is a clear but not complete overlap between prescription opioid abuse and heroin use. Regardless of drug of choice, abusers of opioids are at great risk of harm. There have been increasing legislative

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efforts to curb this abuse and we present a review of the current state of these laws. Naloxone, an opioid antagonist, has made a profound impact in the care of opioid overdose patients who present for medical care early enough. This paper discusses naloxone pharmacodynamics, its use in the medical setting and how its use is now being expanded to include nontraditional providers with take home naloxone (THN) programs.

Opioid is the term used to describe a substance that is able to bind the opioid receptors. The more specific term, *opiate*, refers to a class of agents that are directly derived from naturally occurring opium. The opiate class includes morphine and codeine. The term *narcotic* is less informative, has a negative connotation, and tends to be reserved for law enforcement and the lay public when referring to an opioid that is used illicitly.

The use of opiates dates back to the Sumerians of Mesopotamia who first cultivated the opium poppy around 3400 BC. The plant was known as *Hul gil* or “joy plant.”¹ Opium use, both recreationally and for the treatment of various medical ailments, spread along routes of trade and conquest. Its use was abandoned in most of Europe during the Medieval Inquisition. Philippus von Hohenheim (1493–1541), known as Paracelsus and sometimes called the “father” of toxicology, is credited with the reintroduction and promotion of laudanum, a tincture of opium, for medical treatment in Europe.² Thomas Sydenham (1624–1689) further popularized the medical use of laudanum and related products. Friedrich Sertürner (1783–1855) first isolated morphine in 1804.³ In an effort to find a nonaddictive alternative to morphine, Charles R. A. Wright first synthesized diacetylmorphine, or heroin, in 1874. Bayer Pharmaceutical Products later marketed heroin as an analgesic and cough suppressant.⁴ It was also touted a medication to help those addicted to morphine.⁵

In modern times, there have been multiple swings in prevailing attitudes regarding the use of opioids for analgesia. For example, the first edition of the classic text, *Cope's Early Diagnosis of the Acute Abdomen*, in 1921 directed the provider to withhold opioid analgesics until a diagnosis was certain in patients with undifferentiated abdominal pain. This practice persisted to some degree until recent times, despite numerous studies that demonstrated that the use of opioid analgesics does not interfere with the diagnostic process in these patients.^{6–9} The use of opioids for acute traumatic injuries or other acute painful conditions is less controversial.

Opioid use for patients with chronic pain owing to cancer has long been a mainstay of therapy. The goal of this therapy is to maintain pain relief to tolerable levels to allow for improved quality of life. The risk of addiction or overdose is ethically justified through application of the principle of double effect. This principle dates back to St. Thomas Aquinas (1225–1274) and states that it is moral to perform an action in the pursuit of a good outcome with the knowledge that a foreseeable harm may occur. The action must fulfill the following conditions: the action cannot of itself be morally wrong, the good outcome cannot be directly caused by the harm, the potential harm cannot be the intention of the action, and the harm cannot be disproportionate to the good outcome.^{10,11}

Chronic pain has been estimated by the World Health Organization to be present in up to 22% of patients attending primary care clinics.¹² Through most of the 20th century, physicians avoided the use of opioids in treating chronic noncancer pain. This practice was owing to fear of addiction, overdose, and lack of effectiveness. The concern over addiction started to wane in 1980 with the publication of a 1-paragraph letter in which the authors stated there were only 4 instances of addiction in review of more than 11,000 cases of patients receiving at least one opioid prescription.¹³ In 1986, Portenoy and Foley¹⁴ published a retrospective review showing addiction in

only 2 of 38 patients treated with chronic opioid therapy. Both patients had a history of prior drug abuse. After this, there was a campaign of editorials proclaiming the safety of chronic opioid therapy for noncancer pain.^{15,16}

The drumbeat to eradicate pain continued despite no quality efforts to research the effects of opioid use in chronic pain. The term “oligoanalgesia” was coined in 1989 and worked to shift the blame onto the provider if the patient experienced pain.¹⁷ James Campbell¹⁸ introduced the concept of pain as the fifth vital sign in his 1995 Presidential Address to the American Pain Society. Numerous medical societies and organizations adopted policies of pain control that championed the use of opioids.^{19,20} The Veterans Health Administration adopted “Pain: the 5th vital sign” as the name of its 1999 pain management initiative that mandated evaluation and treatment of pain at all clinical encounters.²¹ The Joint Commission on Accreditation of Healthcare Organizations (now known as The Joint Commission) began assessing pain management as a requirement for accreditation in 2000.²² The balance shifted toward treatment of pain with less regard given for contributing to development of abuse and risk of opioid overdose.

Despite the increase in opioid addiction and deaths that contemporaneously occurred with the dramatic increase in prescriptions for opioid pain medications, there has been a very slow response in the medical community. Numeric pain scores remain a part of the vital signs collected at clinical encounters, regardless of the reason for the encounter and often without consideration of the score given in a broader context. Within the past few years there has been some increased momentum to control the opioid epidemic.^{23,24} This paper looks at some of the responses to the epidemic including the implementation of prescription drug monitoring programs (PDMPs) and the use of THN. To effectively manage this problem, there will need to be increased research into pain, pain management, and opioid abuse.

EPIDEMIOLOGY

Opioid Prescription Epidemic

The first decade of the new millennium saw a significant increase in the availability, use, and abuse of prescription opioid medications and the development of an unprecedented drug overdose epidemic. This situation slowly garnered the attention of medical organizations, news media and individual practitioners. As described previously, this phenomenon is complex and multifactorial in etiology, owing in part to increased emphasis on treating pain, a push toward the philosophy that opioid pain medications are “safe,” insufficient or ineffective oversight, and a marked growth in nationwide consumption and demand in the United States. As general medical use became more commonplace, so too did nonmedical use. This parallel relationship led to an estimated 25 million Americans engaging in the nonmedical use of prescription opioids from 2002 to 2011.²⁵ The general epidemic seems to have peaked around 2010, the eleventh consecutive year that saw an increase in the number of prescription opioid-related deaths with 16,651 fatalities.²⁶ Put into perspective, in that year, opioid analgesics contributed to more than twice as many deaths as heroin and cocaine combined.²⁷ In 2009, deaths attributed to drug overdose surpassed mortality from motor vehicle collisions for the very first time.²⁵ More than three-quarters of these drug overdose deaths are unintentional.²⁶ Although medication overdoses frequently involve multiple classes of drugs, 4903 of 16,651 opioid deaths (29.4%) in 2010 involved solely the ingestion of opioids, a proportion nearly 3 times higher than fatal single-class ingestions of any other psychotropic or central nervous system medicine.²⁸

Morbidity and Economic Burden

Prescription opioid-associated deaths notwithstanding, there are other considerable health consequences associated with these medications, and the morbidity associated with prescription drug overuse has also increased in recent years. Prescription opioids are associated with chronic constipation and narcotic bowel syndrome,²⁹ falls and orthopedic injuries in the elderly,³⁰ neonatal abstinence syndrome, and transition to intravenous (IV) drug use with further associated health risks such as infectious complications and human immunodeficiency virus and hepatitis C virus exposure.

The resource costs associated with opioid abuse are considerable. Over the past decade, there has been a general increase in the number of emergency department visits and inpatient hospitalizations related to prescription drug use.^{31,32} From 2004 to 2011, the number of emergency department visits related to opioid abuse or misuse increased by 183%. In 2011, there were 420,040 emergency department visits for prescription opioid abuse.³¹ The increase in patient volume alone is yet another affliction on an already overtaxed health care system, but the financial cost is substantial as well. It is estimated that the abuse and misuse of prescription opioids are responsible for somewhere between \$53 to \$72 billion in cumulative costs annually.^{33,34} These figures account for insurance payments and fraud, lost productivity, criminal justice costs, drug abuse treatment, and general medical complications.

Demographics: Who Is at Risk?

Chronic nonmedical use of opioids is almost twice as high in men, although women have higher rates of being prescribed types of drugs that are prone to abuse. Men also have a higher rate of death related to opioids compared with women. Use of emergency departments for abuse or misuse of opioids seems to be similar across the sexes.³⁵ About 13% of high school seniors report having used prescription opioids for nonmedical purposes at some time in their life.³⁶ For adults, the rate of nonmedical use of opioids is highest among 18 to 25 year olds and decreases with increasing age.³⁷ Despite that trend, death rates from opioid overdoses are highest in 45 to 54 year olds.³⁵ Overdose death rates of non-Hispanic whites and Native Americans have been 3 times as high as Hispanic whites and African Americans.³²

Certain socioeconomic and clinical factors have also seemed to play a role in differential opioid prescribing, misuse, and poor outcomes. Patients who have lower educational attainment, are eligible to receive Medicaid, or have history of previous substance abuse and/or psychiatric disease all tend to be prescribed more opioids and at higher doses.³⁸ Perhaps predictably, the rate of opioid overdose death is higher in Medicaid-eligible populations, and also in those with previous substance abuse or psychiatric histories.^{39,40} It has been shown previously that patients with psychiatric conditions are at risk for opioid overuse and abuse.⁴¹

Which Prescription Opioids Are Most Common?

Hydrocodone has been the most frequently reported drug exposure for cases called into United States poison centers.⁴² According to data analyzed from 2009 involving 13 states in the Drug Abuse Warning Network Medical Examiner System, oxycodone, closely followed by methadone, were the 2 most frequently implicated drugs in fatal overdoses. Methadone has been associated in the most single-drug deaths, more than as many as any other opioid.⁴³ From 1999 to 2009, the rate of overdose death from methadone increased by 5-fold. Methadone is not a medicine prescribed frequently from the emergency department, but patients may be taking it as a replacement

therapy or for chronic pain management, so exceptional caution should be exercised with patients on chronic therapy, or those who admit to recreational use.

Providers should also take caution with patients who are taking other types of prescription medications, especially psychiatric or central nervous systems agents, when considering prescribing an opioid. Opioid analgesics are by far the most commonly involved medications for pharmaceutical overdose deaths, followed distantly by benzodiazepines and antidepressants. However, overdose deaths are frequently owing to coingestions, and opioids are often implicated in many deaths from other medications. For instance, opioids have been identified in the majority of overdose deaths involving benzodiazepines (77.2%), antiepileptics/anti-Parkinsonian medication (65.5%), antipsychotic and neuroleptic drugs (58.0%), antidepressants (57.6%), other analgesics, antipyretics, and antirheumatics (56.5%), and other psychotropic drugs (54.2%).²⁸

Limitations of Data

One shortcoming of the data used for reporting the amount of prescription opioid abuse is that the true incidence is likely underreported. Much of the research is culled from numerous sources, encompassing a patchwork-like pattern that involves self-reporting, criminal databases, poison control center data, autopsy or death certificate results, pharmacy data, and hospital billing coding. All of these sources have limitations.

As with any other illegal activity, self-reporting is likely limited to the degree to which any individual may be forthcoming. Overdoses of prescription opioid medications are coingested frequently with other medications, street drugs, and alcohol.²⁸ Furthermore, deaths can be multifactorial, and unless there is a known ingestion or autopsy performed, suspected cause of death by the certifying physician may be incorrect. Another problem underlying the reliance on data from death certificates is that a specific drug is not reported in almost a quarter of all reports.⁴⁴ Fluctuating criminal justice priorities and state/regional variance in reporting, rates of abuse, or prescribing of opioids affect the generalizability of information available from those sources. A majority of the opioid prescribing and abuse has been dominant in the Southeast and Western United States,⁴⁵ and although no area of the country has been immune, research studies that focus exclusively on particular regions may not capture the full picture. Complete representative data from the entire country are lacking.

RECENT TRENDS

According to data from the Researched Abuse, Diversion, and Addiction-Related Surveillance system, prescriptions for opioid analgesics increased substantially from 2002 through 2010 in the United States, but then decreased slightly from 2011 through 2013. Similarly, the diversion and abuse of prescription opioid medications also increased between 2002 and 2010 and plateaued or decreased between 2011 and 2013.⁴⁶ Furthermore, data analyzed by the Centers for Disease Control and Prevention from 28 states indicated that the death rate from prescription opioids in their study population decreased from 6.0 per 100,000 in 2010 to 5.6 per 100,000 in 2012.⁴⁷ Comparable patterns were seen in the Researched Abuse, Diversion, and Addiction-Related Surveillance data.

Although the longevity of these changes is yet to be determined, it is nevertheless encouraging and may be representative of a general trend toward recognition of the problem and improvement of care on a nationwide scale. Multiple factors likely contribute. Most states now have active and functional PDMPs⁴⁸ and local, state

and federal efforts aimed at reducing questionable practices such as doctor shopping and so-called pill mills have likely had an impact. Introduction of abuse-deterrent formulations of opioids, such as the transition of oxycodone in 2010, have been shown to decrease the popularity of their misuse.⁴⁹ Unfortunately, these recent downtrends have also been accompanied by a marked increase of heroin use, and therefore, for some, one drug may have been supplanted or supplemented with another.

HEROIN EPIDEMIC

Unlike the slight decrease that has recently been seen with prescription opioid-related deaths, there has been a noticeable growth in the abuse of heroin and the number of heroin-related deaths since 2010. From 1999 to 2010, deaths from prescription opioids essentially quadrupled whereas deaths from heroin increased by less than 50%. However, in the span of the next 3 years, the heroin overdose death rate nearly tripled from 1.0 per 100,000 in 2010 to 2.7 per 100,000 (8257 total deaths) in 2013. Heroin overdose death rates increased in both genders, all age groups, all geographic regions, and all ethnicities except Native Americans.^{47,50,51}

Demographics: Who Is at Risk?

In 2013, there were an estimated 517,000 people who were dependent on or abusers of heroin, which included 169,000 new users.⁵² A well-identified trend is that the overall demographic of heroin users has changed over time. Primarily affecting urban minorities in the 1980s and 1990s, heroin abuse has become more prevalent in suburban and rural areas.⁵³ New heroin users over the past decade are also now predominantly Caucasian (90.3%), and although heroin use was previously much more common in men, it is now similar between the sexes. Heroin overdose deaths remain nearly 4 times more frequent in men.⁵⁴ People with annual household income less than \$20,000, the uninsured and Medicaid recipients are also at increased risk for dependence and overdose.⁵⁵

Heroin use has become more commonly accepted among individuals who engage in nonmedical prescription opioid use. The odds of heroin use in prescription opioid abusers from 2008 to 2011 were double what they were in 2002 to 2005. Prescription opioids also seem to have served as a “gateway” for this new breed of heroin user. Among new heroin initiates from 2009 to 2011, 86.1% reported abusing prescription opioids before their first use of heroin.⁵⁶ A major factor that has been attributed to the recent increase in overall heroin use is the introduction of a higher volume and lower cost product into the drug marketplace.⁵⁷ Research on this transition is limited, but evidence suggests that many users adopt heroin because it is cheaper and easier to obtain than similarly potent or injectable prescription opioids.⁵⁴ As mentioned, this overall trend seems to have coincided with reformulation of common medications previously associated with abuse, such as the introduction of abuse-deterrent extended-release oxycodone hydrochloride,⁴⁶ and an uptick in the regulation and monitoring of prescription drugs.

It would seem to make intuitive sense then that the recent decline in opioid-related deaths is simply the result of a shift to heroin use. However, in 1 study across multiple states from 2010 to 2012, decrease in opioid pain reliever deaths were not found to be associated with increased heroin death rates. In other words, independent of whether a state had an increase, decrease or no change in opioid deaths, all of the included states had an increase in heroin deaths during that time.⁴⁷ This illustrates that although populations that utilize either type of drug are known to overlap to a certain extent, usage, demographic patterns, and factors contributing to these deaths remain partially

independent. Overall, there seems to be a rapidly worsening problem with heroin, superimposed on a continued problem with nonmedical use of prescription opioids.

Limitations of Data

Data for heroin abuse are fraught with the same limitations as prescription opioids; however, some heroin overdose deaths may also be underreported owing to death certificate reporting. Because heroin is metabolized to morphine, listing of that metabolite on an autopsy report or death certificate may lead to misclassification of an opioid pain medication death rather than from heroin itself. This has been demonstrated in several states.⁴⁴

Furthermore, there have been 2 major reported outbreaks of overdoses related to fentanyl being sold as heroin or being mixed with heroin in 2005 to 2007 and 2013 to 2014. This caused a number of overdose deaths, even among veteran heroin users, because of the relative potency of fentanyl or its analogs and its surreptitious introduction into the marketplace. Between the 2 spikes there were more than 1700 fatalities, although this number is likely underestimated. Fentanyl may not be tested for by medical examiners at autopsy. Adulteration of heroin with fentanyl was initially most prevalent in the Northeast and Midwest, but became much more widespread during the more recent outbreak.⁵⁸

OPIOID ANTAGONIST AGENTS

Naloxone hydrochloride (Narcan) is a competitive opioid antagonist that is frequently administered to reverse the adverse effects of opioid intoxication (ie, opioid-induced central nervous system and ventilatory depression). It has a high affinity for the mu (μ)-opioid receptor and effectively reverses the effects of both exogenous and endogenous opioids.^{59–61} Unlike opioid antagonists that were used before its availability (eg, nalorphin and levallorphan), naloxone is a pure antagonist that is devoid of any opioid receptor agonism.⁶² Naloxone has no pharmacologic or adverse effects regardless of dose when administered in the absence of opioid agonist.^{59,63} However, in the opioid-dependent population, excessive dosing of naloxone may precipitate acute opioid withdrawal syndrome (OWS). Abstinence-related OWS typically has limited clinical consequence (eg, piloerection, vomiting, diarrhea, dysphoria).⁶⁴ In contrast, clinical effects of pharmaceutically precipitated OWS can result in significant morbidity including acute agitation, delirium, seizure, acute respiratory distress syndrome, and cardiac dysrhythmias.^{64–66}

A patient's history of opioid use is often not available when caring for patients in the emergency department with signs and symptoms of acute opioid intoxication. Several case reports have shown that the standard recommended initial dose of naloxone (0.4 mg) can precipitate acute OWS in opioid-dependent patients.^{65,67} To minimize the risk of precipitating acute OWS, several resources advocate for the use of low-dose naloxone (0.04 mg IV with titration every 2–3 minutes).^{64,68–70} Two commonly used emergency medicine textbooks adopted similar dose recommendation.^{71,72} Outside of the standard dose of 0.4 mg, which was established from anesthesiology research from the 1960s, there is limited clinical evidence to support the use of low-dose naloxone.^{62,73,74} A recent small case series ($n = 15$) demonstrated that low-dose naloxone with titration reversed methadone-induced ventilatory depression with a median total dose administration of 0.08 mg IV.⁶⁸ There is insufficient evidence to advocate the use of low-dose naloxone as the standard of care. However, the use of low-dose naloxone may be a prudent approach to minimize potential harm to patients in the emergency department while reversing opioid-induced ventilatory depression.

Hypoxic end-organ injury owing to ventilatory depression, irrespective of the type or dose of opioid, is responsible for opioid overdose deaths. Opioid-induced central nervous system depression alone is usually of limited clinical consequence. Therefore, the indication for naloxone administration should be to reverse the opioid-induced ventilatory depression. Diagnostic use of naloxone to determine acute opioid intoxication in patients in the emergency department with central nervous system depression alone provides limited clinical benefit and should be avoided. In apneic patients, assisted manual ventilation (via bag–valve–mask) should be initiated until naloxone is available. It has been demonstrated in animal studies that an increase in partial pressure of CO₂ (P_{CO₂}) potentiated the catecholaminergic response to naloxone-assisted reversal of opioid intoxication, which may increase the risk of OWS.^{75,76} Therefore, normalizing P_{CO₂} via assisted manual ventilation may decrease the risk of precipitating OWS.⁶⁴

Naloxone can be administered by several different routes: IV, intraosseous, intramuscular, subcutaneous, intranasal, inhalational (nebulized), and, less commonly, via intralingual injection. The onset of action of naloxone can range widely, from 30 seconds (intralingual) to 6 minutes (intramuscular), depending on the route of administration. The duration of action of naloxone is approximately 20 to 90 minutes.^{64,69} The duration depends on the type and dose of the opioid agonist, as well as the dose and route of naloxone administration.⁶⁴ The short duration of action of naloxone compared with many opioid agonists (eg, methadone) can lead to recrudescence of opioid intoxication, requiring repeat administration of naloxone or a continuous infusion (two-thirds of the response dose per hour).⁷⁷ Patients in the emergency department who received naloxone for the opioid-induced ventilatory depression should be observed in the emergency department for possible recurrence of intoxication. The observation period of 2 hours may be adequate for the majority of acute opioid intoxication as the opioid receptor antagonism effect of naloxone is short lived.⁷⁸ Based on several case reports of delayed recurrence of opioid intoxication in a setting of long-acting opioid exposure, a longer observation of 4 hours has been suggested.^{64,79–81}

The reversal of buprenorphine-induced ventilatory depression, unlike other opioids, has been shown to be delayed and to require large doses of naloxone (>2 mg IV).^{82,83} This has been attributed to the slow association and dissociation rate between buprenorphine and opioid receptors, which limits the competitive antagonism of naloxone by reducing its ability to displace buprenorphine from opioid receptors.^{64,82,83} Administration of naloxone doses of greater than 4 mg have resulted in an inverse dose–response relationship with a decrease in the reversal of ventilatory depression.^{82,83} Caution should be exercised when caring for patients in the emergency department with suspected buprenorphine-induced ventilatory depression because their response to naloxone may be inconsistent and/or delayed compared with other opioid overdoses.

Take Home Naloxone

Distribution of naloxone to opiate users at high risk for overdose is gaining momentum in the United States. The first THN programs in the United States started in Chicago in the mid 1990s as an extension of harm reduction practices for IV drug users.⁸⁴ Robust programs are now in place in many other cities and states.^{85–88} The World Health Organization placed naloxone on its Model List of Essential Medicines in 2012 and released a manual titled “Community Management of Opioid Overdose” in 2014.⁸⁹ From 2010 to 2014, there was an increase in the number of local sites that dispense naloxone from 188 to 644. Despite this increase, in 2013 there were 20 states that had no local dispensing sites.⁹⁰

Detractors of THN programs cite multiple reasons why they should not exist. There is concern that providing this rescue medication encourages the use of opioids. This view is based in drug control rather than public health policy. Similar arguments have been made regarding provision of condoms and needle exchange programs. The practice of “flat lining” was purported to be the practice of 1 person using a high dose of opioid with another person standing by with naloxone in case of overdose. There was also concern that naloxone may be used as a weapon against other opioid abusers.⁹¹ A survey of opioid addicts enrolled in a methadone program revealed that 6% of the respondents felt that having naloxone available might lead to them increasing their heroin dosages.⁹² Despite these concerns, these issues do not seem to be present in the many successful THN programs that exist today.

Another argument is that laypersons do not have the medical knowledge to administer this medication appropriately. The use of lifesaving medications and devices by laypersons is not a novel concept. Epinephrine autoinjectors have been given to patients with anaphylaxis for more than 30 years. Patients with hereditary angioedema are now being given ibrucicant for self-administration at the onset of life-threatening symptoms.⁹³ Training for both of these medications often involves caregivers or family, and they may sometimes be administered by a third party in a life-threatening situation. Automated external defibrillator availability is widespread and their use by people with no or minimal training is encouraged.

Other concerns regarding layperson administration of naloxone include the short duration of action of this antidote. People who are treated successfully may be given the false sense that they are no longer at risk from the current overdose. The risk is greatest when the overdose was with long-acting opioids, especially methadone. THN programs stress the importance that administration of naloxone by a layperson should be followed by prompt medical attention. Often patients who are given naloxone by medical providers leave once they experience the unpleasant symptoms of withdrawal that this may precipitate. In a review of 552 refusals of care after pre-hospital administration of naloxone, no patient was found to have died within 48 hours.⁹⁴

The assertion that THN programs saves lives is less clear. The data are mostly anecdotal.^{85,95} One analysis of the Massachusetts’s Overdose Education and Nasal Naloxone Distribution program showed an association of fewer opioid overdose fatalities in communities where Overdose Education and Nasal Naloxone Distribution was implemented.⁸⁷ The N-ALIVE trial is an ongoing study assessing the impact of distribution of naloxone to a high-risk population.⁹⁶ The population being studied is prisoners at the time of release. There is an increased rate of opioid overdose in the weeks after release owing to reduced tolerance after a period of prolonged abstinence. This study plans to randomize 56,000 participants to either receiving a supply of naloxone or standard care (no naloxone).

THN programs have used multiple delivery systems for the administration of naloxone to overdose patients. Currently, naloxone is approved by the US Food and Drug Administration for IV, intramuscular, and subcutaneous administration. The recommended route is IV, but this recommendation is for medical providers and not laypersons. Naloxone kits that come as a syringe with a separate ampule of medication require the person administering the medication to successfully draw up and then inject the medication. Owing to concern over needle stick injuries, some Emergency Medical Services (EMS) systems have moved to intranasal delivery despite its lack of US Food and Drug Administration approval. Using an approved medical device called the mucosal atomization device (MAD Nasal, Wolfe Tory Medical, Inc), naloxone can be administered without risk of needle stick to the provider.

Some THN programs have also adopted intranasal delivery devices. Recently, the only manufacturer of naloxone that makes it in a dose appropriate for intranasal delivery doubled the price of the medication to \$40.⁹⁷

In 2014, the US Food and Drug Administration approved a handheld naloxone autoinjector (EVZIO; kaléo, Inc, Richmond, VA, USA) that uses technology that was first successfully used for an epinephrine autoinjector made by the same company. One benefit of the autoinjector is that it eliminates the need for assembly of parts to administer the medication. Cost of this product may limit its widespread adoption. In a recent interview, it was announced that the wholesale cost of the kit, which includes a trainer device and 2 naloxone autoinjectors, is \$575.⁹⁸ Third-party payers who are able to negotiate bulk discounts may easily absorb this cost. Community and small municipal programs may be unable to afford this when compared with alternative delivery mechanisms.

When naloxone from a THN program is administered, it is often done so by a person other than the overdose victim.^{99,100} This is owing to the nature of the overdose and the fact that most overdoses occur in the presence of other people, who are often opioid users themselves. Training family members and other people likely to witness an overdose in the administration of naloxone may be beneficial.¹⁰¹ There may also be additional benefit in training these groups in cardiopulmonary resuscitation.¹⁰² Overall, there is a growing body of evidence that naloxone can be safely and effectively administered to victims of opioid overdose.

OPIOID ANTAGONISTS AND PUBLIC HEALTH LAWS: BARRIERS AND SOLUTIONS

Legislative responses to increasing opioid use in the United States initially focused on taxing the commercial trade of the product. Later, the Harrison Narcotics Tax Act passed by the US Congress of 1915 not only regulated the taxation and trade of opioids, but also regulated their medical use. The Controlled Substances Act of 1970 is the current federal legislative basis for most opioid regulation. Under this act, drugs are classified based on their abuse potential and medical use into 5 schedules. Schedule 1 drugs have a high abuse potential and no accepted medical use. Schedule 5 drugs have the least abuse potential.¹⁰³

In light of the current epidemic of opioid abuse, state legislatures have implemented a patchwork of laws in an effort to overcome barriers to the dispensing and use of naloxone for narcotic overdoses.^{104,105} Generally, there are 2 main varieties of laws that have been promulgated to combat the current epidemic: laws that increase access and use of naloxone and laws that promote reporting of overdoses.

First, there are laws that provide greater access and use of naloxone. They do this by allowing physicians to engage in third-party prescribing (prescriptions for patients not examined), prescribing by standing order and broadening the personnel who can prescribe antagonists (eg, pharmacists).^{104–108} Other laws have been created to encourage distribution and use of opioid antagonists by limiting the civil and criminal liability of prescribing physicians and laypersons administering the reversal agents.^{104,105}

The second type of laws addresses the reluctance of overdose witnesses to call EMS for fear of criminal prosecution.^{64,109–111} This is owing to the fact that witnesses to overdoses are often themselves engaging in the criminal use of controlled substances, are in possession of such substances, or are afraid of arrest for other reasons (eg, possession of illegal drugs or outstanding warrants).^{109,110,112} To combat this, many states have enacted Good Samaritan laws that provide limited criminal immunity to bystanders who report an overdose.

Laws Encouraging Access to Naloxone by Limiting Liability

In 2001, New Mexico became the first jurisdiction to create a law to specifically provide liability protection for providers who dispensed and lay rescuers who administered naloxone.¹¹³ Currently, New Mexico and several other states have an Opioid Antagonist Administration Training Program that provides naloxone to certified lay rescuers.¹⁰⁵

As of July 2015, 40 states and the District of Columbia of have made changes to their laws to allow the prescribing of naloxone with varying limits to civil and criminal liability (Table 1).¹⁰⁴ Some of these laws provide for both civil and criminal liability protections to varying degrees for both prescribers and lay rescuers, whereas others only protect either providers or rescuers but not both. Some states have enacted laws that protect providers from disciplinary action by the state medical board. Interestingly, despite a flurry of legislation that would seem to indicate prosecution of prescriber and layperson rescuers was a major issue, but in reality prosecution is extremely rare.¹⁰⁵

Laws to Promote Prescribing of Opioid Antagonists

To increase the distribution of opioid antagonists, many states have enacted laws to facilitate the prescription of this medication. Usually a provider cannot prescribe medication to a patient unless the provider has examined that patient personally.^{105,106} Strategies to circumvent this issue have included third-party prescriptions, standing orders, and collaborative practice agreements.^{105–108} Third-party prescriptions allow physicians to prescribe medication for patients they have neither seen nor examined. For example, under the Massachusetts law, an “opioid antagonist may lawfully be prescribed and dispensed to a person at risk of experiencing an opiate-related overdose or a family member, friend or other person in a position to assist a person at risk of experiencing an opiate-related overdose.”¹¹⁴ Similar strategies have been adopted to combat sexually transmitted diseases using Expedited Partner Therapy.

Many jurisdictions have created similar legislation specifically for opioid antagonists third-party prescriptions (see Table 1).¹⁰⁶ In other jurisdictions, standing orders signed by a physician allow other providers to dispense opioid antagonists through established protocols.^{106,108} Another way of facilitating dispensing of naloxone is through the use of collaborative practice agreements that allow for pharmacists to prescribe opioid antagonists on behalf of and in conjunction with licensed physicians.^{106,107} New Mexico, a state that has led the way in legislative solutions for the opioid epidemic, recently was the first state to give pharmacists the authority to dispense opioid antagonists independently.¹⁰⁶

These legislative efforts demonstrate attempts to increase opioid antagonist availability through standing orders, pharmacist prescribing, and third-party prescriptions. An even better way to distribute antagonists to the public might be to simply provide the medication as an over-the-counter drug. However, for naloxone to be approved by the US Food and Drug Administration for over-the-counter use, some entity would have to fund clinical trials and then the application process. This process would take years and would likely be cost prohibitive.^{105,106}

Good Samaritan Laws: Providing Immunity to Bystanders Who Report Overdose

Opioid overdose is commonly witnessed by individuals who also use opioids.^{85,90,112} In 1 survey study of 329 drug users, 34% stated that they had experienced an unintentional overdose and 64% stated that they had witnessed an overdose.^{90,115} Another study surveyed 1184 drug abusers, of which 797 (67.3%) had witnessed a nonfatal

Table 1
Opioid antagonist liability protection and third-party prescribing laws as of July 2015

Civil Liability or Disciplinary Protection for Prescribers	Criminal Liability Protection for Prescribers	Civil Liability Protection for Lay Rescuers	Criminal Liability Protection for Lay Rescuers	Third-party Prescription Allowed
AL, AR, CA, CO, CT, DE, FL, GA, ID, IN, LA, MA, MD, ME, MI, MN, MS, NC, ND, NH, NJ, NM, NV, OH, PA, SC, TN, TX, UT, VA, VT, WA, WI, WV	AL, AR, CA, CO, CT, DE, FL, GA, ID, IL, LA, MN, MS, NC, ND, NE, NH, NJ, NM, NV, OH, PA, SC, TX, VT, WA, WI, WV	AL, AR, CA, CO, CT, DC, FL, GA, ID, IL, IN, KY, LA, MD, MI, MN, MS, NC, ND, NH, NJ, NM, NV, NY, OH, OR, PA, RI, SC, TX, UT, VA, VT, WA, WI, WV	AL, AR, CA, CO, CT, DC, GA, ID, IL, KY, LA, MA, MD, MN, MS, NC, ND, NE, NH, NJ, NM, NV, NY, OH, PA, RI, SC, TX, VA, VT, WA, WI, WV	AL, AR, CA, CO, FL, GA, ID, IL, IN, KY, LA, MA, MD, ME, MI, MS, NC, ND, NE, NH, NJ, NV, NY, OH, OK, OR, PA, SC, TN, TX, UT, VA, VT, WA, WI, WV

Data from The Network for Public Health Law. Legal intervention to reduce overdose mortality: naloxone access and overdose Good Samaritan laws. 2015. Available at: https://www.networkforphl.org/_asset/qz5pvn/network-naloxone-10-4.pdf. Accessed September 2, 2015.

or fatal overdose.⁹⁰ Of these, 278 (23.5%) had seen an overdose within the previous 6 months.¹¹⁰

Despite bystanders' familiarity with potentially deadly overdoses, they often do not call EMS. Survey data estimate that only 10% to 60% of bystander witnesses actually call EMS when drug overdoses occur.^{85,109,110,112} The primary reason that bystanders do not call is fear of arrest and criminal prosecution.^{109,110} In a survey of 301 bystanders who delayed or did not call for help during an overdose, 152 (52%) stated that they feared police response and potential arrest.^{64,109,110} Although prior surveys of police officers indicate that they are unlikely to arrest an overdose victim or bystander, the fear of legal action remains a significant barrier to calling for assistance.^{110,111} Although uncommon, the legal risk to the bystander is not completely absent.^{105,112,116,117}

To address this fear of arrest and to encourage bystanders to call for EMS, many states have passed laws that create limited criminal immunity for bystanders who report an overdose.^{64,104,105,109} As of July 15, 2015, 31 states and the District of Columbia have passed Good Samaritan laws (**Table 2**).¹⁰⁴ Most of these laws provide protection from criminal charges regarding possessing a controlled substance, whereas others also provide protection from possession of drug paraphernalia.

SAFE OPIOID PRESCRIBING PRACTICE IN THE EMERGENCY DEPARTMENT

As many as 42% of all emergency department visits are owing to pain-related conditions.¹¹⁸ Between 2001 and 2010, there has been a 49% increase in the percentage of total emergency department visits where an opioid was prescribed for pain.¹¹⁹ In 2010 alone, enough morphine milligram equivalents were prescribed by all specialties nationwide to provide every adult American with enough to take 5 mg every 4 hours for a month.³² Although primary care providers and dentists prescribe the majority of opioids in the United States, emergency medicine ranks among the top 5 specialties (for ages 0–39 years) for opioid prescribing in the ambulatory setting.¹²⁰ Some data suggest that there is an increased rate of diversion and abuse of opioids that are prescribed from emergency departments, especially by young people.³⁶ The primary challenge for emergency department providers in the current opioid abuse epidemic is how to balance the need to provide adequate pain control for patients in the emergency department while minimizing the availability of opioids for abuse or diversion. Recently, the American College of Emergency Physicians, American Academy of Emergency Medicine, 14 states (AK, AZ, CA, CT, DE, HI, MA, MD, ME, OH, OK, OR, PA, and WA), and New York City have established opioid prescribing guidelines specifically for emergency medicine providers.^{121–133} In addition, numerous other states have adapted opioid prescribing and pain treatment guidelines for all health care providers.¹²¹ Emergency department–specific guidelines generally recommend prescribing small quantities (eg, a 3-day supply) of short-acting opioids for acute pain. They also discourage replacing lost, stolen, or destroyed prescriptions.^{24,124,132,133} These guidelines also advocate for the use of PDMP to review prescription history and to identify potential at-risk patterns for “doctor shopping.”^{24,123,134} Some health care providers have expressed concerns that these guidelines may result in undertreatment of pain, especially for those patients who use emergency department as their source of primary care. Others argue that prescribing guidelines can interfere with their professional independence and judgment.¹³⁵

PDMPs have been advocated as a promising tool to decrease inappropriate opioid prescribing and to identify patients with at-risk pattern for misuse. To date, 49 states (except Missouri) have operational PDMPs.^{136,137} However, the state-based PDMPs

Table 2

State Good Samaritan laws as of July 2015

No Charge for Controlled Substance Possession	No Charge for Drug Paraphernalia	Protection from Other Crimes	Reporting Overdose Can Mitigate Prosecution of a Crime
AK, AL, AR, CA, CO, CT, DC, DE, FL, GA, HI, IL, KY, LA, MA, MD, MN, MS, NC, NH, NJ, NM, NV, NY, OR, PA, RI, TN, VA, VT, WA, WI, WV	AL, CA, CO, CT, DC, DE, GA, HI, KY, MD, MN, MS, NC, NJ, NV, NY, OR, PA, RI, TN, VA, WI	AL, AR, CA, CO, DC, DE, GA, HI, IL, LA, MD, MN, MS, NC, NJ, NV, NY, OR, PA, RI, TN, VA, VT, VW	AK, DC, FL, HI, IL, IN, MA, MD, MN, NM, NV, NY, RI, TN, UT, VT, WA, WV

Data from The Network for Public Health Law. Legal intervention to reduce overdose mortality: naloxone access and overdose Good Samaritan laws. 2015. Available at: https://www.networkforphl.org/_asset/qz5pvn/network-naloxone-10-4.pdf. Accessed September 2, 2015.

are not standardized and vary in their complexity and completeness.²⁴ The use of PDMPs has been shown to decrease “doctor shopping”; however, there is inconsistent evidence as to how PDMPs affect health care provider’s opioid prescribing behavior.^{138–142} The possibility that PDMPs have little effect on prescribers’ behavior has been attributed to the difficulty of obtaining PDMP access, lack of use, and incomplete data within PDMPs.^{24,138,140} To improve provider use, 22 of the 49 states with PDMPs mandated all prescribers of controlled substances to query the PDMP for at-risk pattern for misuse and/or diversion.¹³⁸ The mandated query of PDMPs, based on the experience from Kentucky, New York, and Tennessee, did decrease the overall number of opioid prescriptions by 7% to 9%.¹⁴³ However, these mandates face opposition from health care providers to owing to limitations of PDMPs and their intrusion into clinical practice.¹³⁸

The impact of the emergency department opioid guidelines on opioid prescribing practice is unknown. One recent study showed that the introduction of an emergency department opioid guideline in 2 academic affiliated EDs decreased the number of discharged patients with opioid prescriptions from 52.7% to 33.8%.¹⁴⁴ Its impact on outpatient pain management was not assessed and further investigation is needed. The use of opioid prescribing guidelines is voluntary and not a mandated practice. Each emergency department provider must use his or her clinical intuition and judgment to adequately address and treat the pain experienced by each patients in the emergency department. Although emergency department providers are not the leading prescribers of opioids, appropriate prescribing practice is essential to help decrease the availability of opioids for abuse or diversion.

Opioid pain medication abuse is one of the leading public health problems in the United States. Health care providers have contributed to the current opioid abuse epidemic through our prescribing practices. In 2012, 4.2 billion prescriptions were written in the United States; 289 million (6.8%) were for opioids, an increase of 11.7% from 2007.¹⁴⁵ There has been a concerted effort among government, state, and professional organizations, and members of medical specialties to address the increasing incidence of opioid abuse and overdose-related deaths. Nationally, numerous medical specialties have made conscientious effort to decrease inappropriate opioid prescribing. Between 2007 and 2012, large decreases in opioid prescriptions were noted in emergency medicine (–8.9%), followed by dentistry (–5.7%) and surgery (–3.9%).¹⁴⁵ Numerous states have developed emergency department opioid prescribing guidelines, and implemented PDMPs and health care provider education programs. Patient-directed interventions also need to be developed with a focus on remediating the deficiencies in patients’ understanding of the risk of opioid use and the expected outcome of “adequate” pain management.^{146,147}

SUMMARY

There is an epidemic of opioid abuse in the United States. The risk of heroin abuse has been appreciated for more than a century with it now being considered to have no justifiable medical use. Opioids that are prescribed commonly to treat painful conditions have had a dramatic increase in the rate of abuse, addiction, overdose, and death. The increase in complications corresponds with a dramatic increase in the rate of opioid prescriptions that resulted from pressures placed on practitioners to avoid undertreatment of pain.

Naloxone is an opioid receptor antagonist that is used to treat opioid overdoses. Its use as a rescue medication by laypersons is becoming increasingly accepted. Other

efforts to combat the opioid epidemic include the use of PDMPs and implementation of safe opioid prescribing guidelines. The laws that govern these efforts vary from state to state resulting in a wide range of effectiveness. The efforts to reign in the abuse of opioids will require further research and a reexamination of the balance between the need to treat pain and the recognition that opioid medications are not without risk.

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