

# 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.

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*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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Disclosures: None.

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Emerg Med Clin N Am ■ (2015) ■–■  
<http://dx.doi.org/10.1016/j.emc.2015.11.002>

[emed.theclinics.com](http://emed.theclinics.com)

0733-8627/15/\$ – see front matter © 2015 Published by Elsevier Inc.

49 efforts to curb this abuse and we present a review of the current state of these laws.  
50 Naloxone, an opioid antagonist, has made a profound impact in the care of these pa-  
51 tients if they present for medical care early enough. This paper discusses naloxone  
52 pharmacodynamics, its use in the medical setting and how its use is now being  
53 expanded to include nontraditional providers with take home naloxone (THN)  
54 programs.

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

61 The use of opiates dates back to the Sumerians of Mesopotamia who first cultivated  
62 the opium poppy around 3400 BC. The plant was known as *Hul gil* or “joy plant.”<sup>1</sup>  
63 Opium use, both recreationally and for the treatment of various medical ailments,  
64 spread along routes of trade and conquest. Its use was abandoned in most of Europe  
65 during the Medieval Inquisition. Philippus von Hohenheim (1493–1541), known as Par-  
66 acelsus and sometimes called the “father” of toxicology, is credited with the reintro-  
67 duction and promotion of laudanum, a tincture of opium, for medical treatment in  
68 Europe.<sup>2</sup> Thomas Sydenham (1624–1689) further popularized the medical use of  
69 laudanum and related products. Friedrich Sertüner first isolated morphine in 1804.<sup>3</sup>  
70 In an effort to find a nonaddictive alternative to morphine, Charles R. A. Wright first  
71 synthesized diacetylmorphine, or heroin, in 1874. Bayer Pharmaceutical Products  
72 later marketed heroin as an analgesic and cough suppressant.<sup>4</sup> It was also touted a  
73 medication to help those addicted to morphine.<sup>5</sup>

74 In modern times, there have been multiple swings in prevailing attitudes regarding  
75 the use of opioids for analgesia. For example, the first edition of the classic text,  
76 *Cope’s Early Diagnosis of the Acute Abdomen*, in 1921 directed the provider to with-  
77 hold opioid analgesics until a diagnosis was certain in patients with undifferentiated  
78 abdominal pain. This practice persisted to some degree until recent times, despite  
79 numerous studies that demonstrated that the use of opioid analgesics does not inter-  
80 fere with the diagnostic process in these patients.<sup>6–9</sup> The use of opioids for acute trau-  
81 matic injuries or other acute painful conditions is less controversial.

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

92 Chronic pain has been estimated by the World Health Organization to be present in  
93 up to 22% of patients attending primary care clinics.<sup>12</sup> Through most of the 20th cen-  
94 tury, physicians avoided the use of opioids in treating chronic noncancer pain. This  
95 practice was owing to fear of addiction, overdose, and lack of effectiveness. The  
96 concern over addiction started to wane in 1980 with the publication of a 1-paragraph  
97 letter in which the authors stated there were only 4 instances of addiction in review of  
98 more than 11,000 cases of patients receiving at least one opioid prescription.<sup>13</sup> In  
99 1986, Portenoy and Foley<sup>14</sup> 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.<sup>15,16</sup>

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.<sup>17</sup> James Campbell<sup>18</sup> 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.<sup>19,20</sup> 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.<sup>21</sup> 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.<sup>22</sup> 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.<sup>23,24</sup> 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.<sup>25</sup> 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.<sup>26</sup> Put into perspective, in that year, opioid analgesics contributed to more than twice as many deaths as heroin and cocaine combined.<sup>27</sup> In 2009, deaths attributed to drug overdose surpassed mortality from motor vehicle collisions for the very first time.<sup>25</sup> More than three-quarters of these drug overdose deaths are unintentional.<sup>26</sup> 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.<sup>28</sup>

### ***Morbidity and Economic Burden***

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

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

### ***Demographics: Who Is at Risk?***

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172 Chronic nonmedical use of opioids is almost twice as high in men, although women  
173 have higher rates of being prescribed types drugs that are prone to abuse. Men  
174 also have a higher rate of death related to opioids compared with women. Use of  
175 emergency departments for abuse or misuse of opioids seems to be similar across  
176 the sexes.<sup>35</sup> About 13% of high school seniors report having used prescription opioids  
177 for nonmedical purposes at some time in their life.<sup>36</sup> For adults, the rate of nonmedical  
178 use of opioids is highest among 18 to 25 year olds and decreases with increasing  
179 age.<sup>37</sup> Despite that trend, death rates from opioid overdoses are highest in 45 to  
180 54 year olds.<sup>35</sup> Overdose death rates of non-Hispanic whites and Native Americans  
181 have been 3 times as high as Hispanic whites and African Americans.<sup>32</sup>

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

### ***Which Prescription Opioids Are Most Common?***

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192 Hydrocodone has been the most frequently reported drug exposure for cases called  
193 into United States poison centers.<sup>42</sup> According to data analyzed from 2009 involving  
194 13 states in the Drug Abuse Warning Network Medical Examiner System, oxycodone  
195 (OxyContin; Purdue Pharma), closely followed by methadone, were the 2 most  
196 frequently implicated drugs in fatal overdoses. Methadone has been associated in  
197 the most single-drug deaths, twice as many as any other opioid.<sup>43</sup> From 1999 to  
198 2009, the rate of overdose death from methadone increased by 5-fold. Methadone  
199 is not a medicine prescribed frequently from the emergency department, but patients  
200 may be taking it as a replacement therapy or for chronic pain management, so  
201

202 exceptional caution should be exercised with patients on chronic therapy, or those  
203 who admit to recreational use.

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

### 215 **Limitations of Data**

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

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

### 237 **RECENT TRENDS**

238  
239 According to data from the Researched Abuse, Diversion, and Addiction-Related Sur-  
240 veillance system, prescriptions for opioid analgesics increased substantially from  
241 2002 through 2010 in the United States, but then decreased slightly from 2011 through  
242 2013. Similarly, the diversion and abuse of prescription opioid medications also  
243 increased between 2002 and 2010 and plateaued or decreased between 2011 and  
244 2013.<sup>46</sup> Furthermore, data analyzed by the Centers for Disease Control and Prevention  
245 from 28 states indicated that the death rate from prescription opioids in their study  
246 population decreased from 6.0 per 100,000 in 2010 to 5.6 per 100,000 in 2012.<sup>47</sup> Com-  
247 parable patterns were seen in the Researched Abuse, Diversion, and Addiction-  
248 Related Surveillance data.

249 Although the longevity of these changes is yet to be determined, it is nevertheless  
250 encouraging and may be representative of a general trend toward recognition of the  
251 problem and improvement of care on a nationwide scale. Multiple factors likely  
252 contribute. Most states now have active and functional PDMPs<sup>48</sup> and local, state

253 and federal efforts aimed at reducing questionable practices such as doctor shopping  
254 and so-called pill mills have likely had an impact. Introduction of abuse-deterrent  
255 formulations of opioids, such as the transition of oxycodone in 2010, have been shown to  
256 decrease the popularity of their misuse.<sup>49</sup> Unfortunately, these recent downtrends  
257 have also been accompanied by a marked increase of heroin use, and therefore, for  
258 some, 1 drug may have been supplanted or supplemented with another.

## 260 HEROIN EPIDEMIC

262 Unlike the slight decrease that has recently been seen with prescription opioid-related  
263 deaths, there has been a noticeable growth in the abuse of heroin and the number of  
264 heroin-related deaths since 2010. From 1999 to 2010, deaths from prescription opi-  
265 oids essentially quadrupled whereas deaths from heroin increased by less than  
266 50%. However, in the span of the next 3 years, the heroin overdose death rate nearly  
267 tripled from 1.0 per 100,000 in 2010 to 2.7 per 100,000 (8257 total deaths) in 2013.  
268 Heroin overdose death rates increased in both genders, all age groups, all geographic  
269 regions, and all ethnicities except Native Americans.<sup>47,50,51</sup>

### 271 *Demographics: Who Is at Risk?*

272 In 2013, there were an estimated 517,000 people who were dependent on or abusers  
273 of heroin, which included 169,000 new users.<sup>52</sup> A well-identified trend is that the over-  
274 all demographic of heroin users has changed over time. Primarily affecting urban mi-  
275 norities in the 1980s and 1990s, heroin abuse has become more prevalent in suburban  
276 and rural areas.<sup>53</sup> New heroin users over the past decade are also now predominantly  
277 Caucasian (90.3%), and although heroin use was previously much more common in  
278 men, it is now similar between the sexes. Heroin overdose deaths remain nearly 4  
279 times more frequent in men.<sup>54</sup> People with annual household income less than  
280 \$20,000, the uninsured and Medicaid recipients are also at increased risk for depen-  
281 dence and overdose.<sup>55</sup>

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

296 It would seem to make intuitive sense then that the recent decline in opioid-related  
297 deaths is simply the result of a shift to heroin use. However, in 1 study across multiple  
298 states from 2010 to 2012, decrease in opioid pain reliever deaths were not found to be  
299 associated with increased heroin death rates. In other words, independent of whether  
300 a state had an increase, decrease or no change in opioid deaths, all of the included  
301 states had an increase in heroin deaths during that time.<sup>47</sup> This illustrates that although  
302 populations that utilize either type of drug are known to overlap to a certain extent, us-  
303 age, 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 and opioid pain medication death rather than a heroin itself. This has been demonstrated in several states.<sup>44</sup>

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.<sup>58</sup>

### 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 ( $\mu$ )-opioid receptor and effectively reverses the effects of both exogenous and endogenous opioids.<sup>59–61</sup> 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.<sup>62</sup> Naloxone has no pharmacologic or adverse effects regardless of dose when administered in the absence of opioid agonist.<sup>59,63</sup> 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).<sup>64</sup> 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.<sup>64–66</sup>

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.<sup>65,67</sup> 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).<sup>64,68–70</sup> Two commonly used emergency medicine textbooks adopted similar dose recommendation.<sup>71,72</sup> 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.<sup>62,73,74</sup> 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.<sup>68</sup> 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.

355 Hypoxic end-organ injury owing to ventilatory depression, irrespective of the type or  
356 dose of opioid, is responsible for opioid overdose deaths. Opioid-induced central nervous  
357 system depression alone is usually of limited clinical consequence. Therefore,  
358 the indication for naloxone administration should be to reverse the opioid-induced  
359 ventilatory depression. Diagnostic use of naloxone to determine acute opioid intoxication  
360 in patients in the emergency department with central nervous system depression  
361 alone provides limited clinical benefit and should be avoided. In apneic patients, assisted  
362 manual ventilation (via bag–valve–mask) should be initiated until naloxone is available.  
363 It has been demonstrated in animal studies that an increase in partial pressure of  
364 CO<sub>2</sub> (P<sub>CO<sub>2</sub></sub>) potentiated the catecholaminergic response to naloxone-assisted reversal  
365 of opioid intoxication, which may increase the risk of OWS.<sup>75,76</sup> Therefore, normalizing  
366 P<sub>CO<sub>2</sub></sub> via assisted manual ventilation may decrease the risk of precipitating OWS.<sup>64</sup>

367 Naloxone can be administered by several different routes: IV, intraosseous, intramuscular,  
368 subcutaneous, intranasal, inhalational (nebulized), and, less commonly,  
369 via intralingual injection. The onset of action of naloxone can range widely, from  
370 30 seconds (intralingual) to 6 minutes (intramuscular), depending on the route of  
371 administration. The duration of action of naloxone is approximately 20 to 90 minutes.  
372<sup>64,69</sup> The duration depends on the type and dose of the opioid agonist, as  
373 well as the dose and route of naloxone administration.<sup>64</sup> The short duration of action  
374 of naloxone compared with many opioid agonists (eg, methadone) can lead to recrudescence  
375 of opioid intoxication, requiring repeat administration of naloxone or a  
376 continuous infusion (two-thirds of the response dose per hour).<sup>77</sup> Patients in the emergency  
377 department who received naloxone for the opioid-induced ventilatory depression  
378 should be observed in the emergency department for possible recurrence of  
379 intoxication. The observation period of 2 hours may be adequate for the majority of  
380 acute opioid intoxication as the opioid receptor antagonism effect of naloxone is short  
381 lived.<sup>78</sup> Based on several case reports of delayed recurrence of opioid intoxication in a  
382 setting of long-acting opioid exposure, a longer observation of 4 hours has been  
383 suggested.<sup>64,79–81</sup>

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

### 395 **Take Home Naloxone**

397 Distribution of naloxone to opiate users at high risk for overdose is gaining momentum  
398 in the United States. The first THN programs in the United States started in Chicago in  
399 the mid 1990s as an extension of harm reduction practices for IV drug users.<sup>84</sup> Robust  
400 programs are now in place in many other cities and states.<sup>85–88</sup> The World Health Organization  
401 placed naloxone on its Model List of Essential Medicines in 2012 and released a manual titled  
402 “Community Management of Opioid Overdose” in 2014.<sup>89</sup>  
403 From 2010 to 2014, there was an increase in the number of local sites that dispense  
404 naloxone from 188 to 644. Despite this increase, in 2013 there were 20 states that  
405 had no local dispensing sites.<sup>90</sup>



406 Detractors of THN programs cite multiple reasons why they should not exist. There  
407 is concern that providing this rescue medication encourages the use of opioids. This  
408 view is based in drug control rather than public health policy. Similar arguments have  
409 been made regarding provision of condoms and needle exchange programs. The  
410 practice of “flat lining” was purported to be the practice of 1 person using a high  
411 dose of opioid with another person standing by with naloxone in case of overdose.  
412 There was also concern that naloxone may be used as a weapon against other opioid  
413 abusers.<sup>91</sup> A survey of opioid addicts enrolled in a methadone program revealed that  
414 6% of the respondents felt that having naloxone available might lead to them  
415 increasing their heroin dosages.<sup>92</sup> Despite these concerns, these issues do not  
416 seem to be present in the many successful THN programs that exist today.

417 Another argument is that laypersons do not have the medical knowledge to admin-  
418 ister this medication appropriately. The use of lifesaving medications and devices by  
419 laypersons is not a novel concept. Epinephrine autoinjectors have been given to pa-  
420 tients with anaphylaxis for more than 30 years. Patients with hereditary angioedema  
421 are now being given icaltiban for self-administration at the onset of life-threatening  
422 symptoms.<sup>93</sup> Training for both of these medications often involves caregivers or fam-  
423 ily, and they may sometimes be administered by a third party in a life-threatening sit-  
424 uation. Automated external defibrillator availability is widespread and their use by  
425 people with no or minimal training is encouraged.

426 Other concerns regarding layperson administration of naloxone include the short  
427 duration of action of this antidote. People who are treated successfully may be given  
428 the false sense that they are no longer at risk from the current overdose. The risk is  
429 greatest when the overdose was with long-acting opioids, especially methadone.  
430 THN programs stress the importance that administration of naloxone by a layperson  
431 should be followed by prompt medical attention. Often patients who are given  
432 naloxone by medical providers leave once they experience the unpleasant symptoms  
433 of withdrawal that this may precipitate. In a review of 552 refusals of care after pre-  
434 hospital administration of naloxone, no patient was found to have died within  
435 48 hours.<sup>94</sup>

436 The assertion that THN programs saves lives is less clear. The data are mostly anecd-  
437 otal.<sup>85,95</sup> One analysis of the Massachusetts’s Overdose Education and Nasal  
438 Naloxone Distribution program showed an association of fewer opioid overdose fatal-  
439 ities in communities where Overdose Education and Nasal Naloxone Distribution was  
440 implemented.<sup>87</sup> The N-ALIVE trial is an ongoing study assessing the impact of distri-  
441 bution of naloxone to a high-risk population.<sup>96</sup> The population being studied is pris-  
442 oners at the time of release. There is an increased rate of opioid overdose in the  
443 weeks after release owing to reduced tolerance after a period of prolonged absti-  
444 nence. This study plans to randomize 56,000 participants to either receiving a supply  
445 of naloxone or standard care (no naloxone).

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

457 Some THN programs have also adopted intranasal delivery devices. Recently, the only  
458 manufacturer of naloxone that makes it in a dose appropriate for intranasal delivery  
459 doubled the price of the medication to \$40.<sup>97</sup>

460 In 2014, the US Food and Drug Administration approved a handheld naloxone auto-  
461 injector (EVZIO; kaléo, Inc, Richmond, VA, USA) that uses technology that was first  
462 successfully used for an epinephrine autoinjector made by the same company. One  
463 benefit of the autoinjector is that it eliminates the need for assembly of parts to admin-  
464 ister the medication. Cost of this product may limit its widespread adoption. In a recent  
465 interview, it was announced that the wholesale cost of the kit, which includes a trainer  
466 device and 2 naloxone autoinjectors, is \$575.<sup>98</sup> Third-party payers who are able to  
467 negotiate bulk discounts may easily absorb this cost. Community and small municipal  
468 programs may be unable to afford this when compared with alternative delivery  
469 mechanisms.

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

## 479 OPIOID ANTAGONISTS AND PUBLIC HEALTH LAWS: BARRIERS AND SOLUTIONS

481 Legislative responses to increasing opioid use in the United States initially focused on  
482 taxing the commercial trade of the product. Later, the Harrison Narcotics Tax Act  
483 passed by the US Congress of 1915 not only regulated the taxation and trade of opi-  
484 oids, but also regulated their medical use. The Controlled Substances Act of 1970 is  
485 the current federal legislative basis for most opioid regulation. Under this act, drugs  
486 are classified based on their abuse potential and medical use into 5 schedules.  
487 Schedule 1 drugs have a high abuse potential and no accepted medical use. Schedule  
488 5 drugs have the least abuse potential.<sup>103</sup>

489 In light of the current epidemic of opioid abuse, state legislatures have implemented  
490 a patchwork of laws in an effort to overcome barriers to the dispensing and use of  
491 naloxone for narcotic overdoses.<sup>104,105</sup> Generally, there are 2 main varieties of laws  
492 that have been promulgated to combat the current epidemic: laws that increase ac-  
493 cess and use of naloxone and laws that promote reporting of overdoses.

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

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

### ***Laws Encouraging Access to Naloxone by Limiting Liability***

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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.<sup>113</sup> Currently, New Mexico and several other states have an Opioid Antagonist Administration Training Program that provides naloxone to certified lay rescuers.<sup>105</sup>

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).<sup>104</sup> 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.<sup>105</sup>

### ***Laws to Promote Prescribing of Opioid Antagonists***

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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.<sup>105,106</sup> Strategies to circumvent this issue have included third-party prescriptions, standing orders, and collaborative practice agreements.<sup>105–108</sup> 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.”<sup>114</sup> 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).<sup>106</sup> In other jurisdictions, standing orders signed by a physician allow other providers to dispense opioid antagonists through established protocols.<sup>106,108</sup> 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.<sup>106,107</sup> 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.<sup>106</sup>

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.<sup>105,106</sup>

### ***Good Samaritan Laws: Providing Immunity to Bystanders Who Report Overdose***

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Opioid overdose is commonly witnessed by individuals who also use opioids.<sup>85,90,112</sup> 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.<sup>90,115</sup> Another study surveyed 1184 drug abusers, of which 797 (67.3%) had witnessed a nonfatal

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<b>Table 1</b>				
<b>Opioid antagonist liability protection and third-party prescribing laws as of July 2015</b>				
<b>Civil Liability or Disciplinary Protection for Prescribers</b>	<b>Criminal Liability Protection for Prescribers</b>	<b>Civil Liability Protection for Lay Rescuers</b>	<b>Criminal Liability Protection for Lay Rescuers</b>	<b>Third-party Prescription Allowed</b>
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. Accessed September 2, 2015.

610 or fatal overdose.<sup>90</sup> Of these, 278 (23.5%) had seen an overdose within the previous  
611 6 months.<sup>110</sup>

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

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

## 628 629 **SAFE OPIOID PRESCRIBING PRACTICE IN THE EMERGENCY DEPARTMENT**

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

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

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**Table 2****State Good Samaritan laws as of July 2015**

<b>No Charge for Controlled Substance Possession</b>	<b>No Charge for Drug Paraphernalia</b>	<b>Protection from Other Crimes</b>	<b>Reporting Overdose Can Mitigate Prosecution of a Crime</b>
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. Accessed September 2, 2015.



are not standardized and vary in their complexity and completeness.<sup>24</sup> 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.<sup>138–142</sup> 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.<sup>24,138,140</sup> 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.<sup>138</sup> 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%.<sup>143</sup> However, these mandates face opposition from health care providers to owing to limitations of PDMPs and their intrusion into clinical practice.<sup>138</sup>

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%.<sup>144</sup> 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.<sup>145</sup> 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%).<sup>145</sup> 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.<sup>146,147</sup>

## 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

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

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