

# New Perspectives in the Treatment of Opioid-Induced Respiratory Depression

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According to the Institute of Medicine, chronic pain affects an estimated 100 million individuals in the United States.<sup>1</sup> Lower back pain (27%), severe headache or migraine (15%), and neck pain (15%) are among the most frequently reported pain conditions.<sup>2</sup> The prevalence of pain is likely to increase in the future with the aging of the US population and with the increase in the number of injured military personnel.<sup>1</sup>

## Opioid Use and Abuse in the United States

Opioids include prescription medications, such as buprenorphine, codeine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, and oxycodone, as well as illegal drugs, such as heroin.<sup>3</sup> Opioids prescribed for their analgesic properties are used across a wide range of painful conditions, including injury-related pain, back pain, neck pain, dental pain, postsurgical pain, osteoarthritis, severe or refractory headache, and moderate-to-severe pain associated with cancer.<sup>3-6</sup>

Opioids reduce the perception of pain by binding to specific opioid receptors in the brain, spinal cord, and gastrointestinal tract, and stimulate the reward centers of the brain, resulting in a euphoric response, which may affect other systems of the body that control mood, blood pressure, and breathing.<sup>3,4</sup> The euphoric, mood-altering effects of opioids may lead some individuals to ingest or inject prescription opioids or nonprescription opioids for nonmedical purposes.<sup>4</sup> Although the problem of opioid abuse has been widely publicized, opioids also are sometimes misused unintentionally.<sup>4</sup> Factors explaining the unintentional misuse of opioids include a patient's inability to follow prescribing instructions, accidentally ingesting medication, or mistaking one medication for another.<sup>4</sup>

Opioids can be unintentionally misused by anyone at any age, but this occurs more frequently in older patients with several comorbid conditions requiring multiple medications, as well as in patients with cognitive decline.<sup>4</sup> Although only approximately 13% of the US population is aged  $\geq 65$  years, this age-group accounts for more than 33% of the total outpatient spending on prescription medications, suggesting an increased risk for misuse of opioids in these individuals.<sup>4</sup> In addition, age-related changes in drug metabolism and the potential for drug interactions compound these risks in older individuals.<sup>4</sup>

## Implications of the Increasing Rate of Opioid Prescribing

The prescription sale of opioid analgesics increased 4-fold between 1999 and 2010.<sup>7</sup> This increase coincided with an increase in opioid overdose deaths and substance abuse treatment admissions during the same period (Figure 1).<sup>7</sup>

Given the link between opioid prescribing practices and opioid abuse, the risks for overprescribing these drugs and recommendations for judicious prescribing have been a heated focal topic in the medical community, prompting regulatory scrutiny and position statements from relevant organizations and professional societies.<sup>6</sup> Healthcare providers continue to be challenged with meeting the needs of their patients with chronic pain while addressing the risks associated with the use of opioids.<sup>6</sup> In July 2012, the US Food and Drug Administration (FDA) began requiring a Risk Evaluation and Mitigation Strategy program for extended-release and long-acting opioid medications as part of a broader governmental effort to address the growing problem of prescription drug abuse and misuse.<sup>8</sup>

## Opioid Overdose Is a Burgeoning Problem

An opioid overdose is a life-threatening event that can occur when an individual misuses or abuses a prescribed or an illicit opioid.<sup>3</sup> Opioid overdoses can occur when a patient takes an opioid as directed, but the prescriber erred in calculating the correct opioid dose, the dispensing pharmacist made an error, or the patient misunderstood the instructions for use.<sup>3</sup> An opioid overdose can also occur when an individual takes an opioid that was prescribed for another person; or when an individual combines a prescribed or an illicit opioid with alcohol, another drug, or even an over-the-counter medication that depresses the central nervous system functions.<sup>3</sup>

Overall, 44 individuals in the United States die from a prescription opioid overdose daily.<sup>9</sup> In 2013 alone, an alarming 16,235 deaths were attributed to an opioid overdose, accounting for 37% of all drug-poisoning deaths in 2013 and a 4-fold increase from 1999.<sup>10</sup> In addition, nearly 60% of all drug-poisoning deaths in 2013 involved prescription opioids and/or heroin.<sup>11</sup> Furthermore, among individuals aged 25 to 64 years, deaths from a drug overdose—the majority of which were opioid-

related—exceeded motor vehicle collisions as the leading cause of accidental death in 2013.<sup>9</sup>

The most common drugs associated with prescription opioid overdose deaths include hydrocodone, oxycodone, oxymorphone, and methadone (particularly when prescribed for pain).<sup>12</sup>

### Impact of Opioid Abuse and Misuse

The abuse and misuse of opioids, whether prescription analgesics or illicit drugs, has a resounding and sweeping impact on many aspects of society, including schools and education, employment, relationships, productivity, the criminal justice system, and public health with respect to morbidity, mental health, mortality, and quality of life.<sup>13</sup> Compounding these major issues are the staggering costs of healthcare, including increased emergency department visits and hospitalizations, disability, late opioid use, and the inherent costs of lives lost to overdose.<sup>13</sup> Individuals with substance use disorders may require multiple efforts or programs to recover from their addiction.<sup>4</sup> Addiction to opioids is not always curable but can be effectively managed with medications, behavioral

therapy, treatment programs, and support networks.<sup>1</sup> Furthermore, although some individuals can recover from drug addiction, 40% to 60% of individuals experience a relapse after treatment.<sup>4</sup>

### Adverse Events Associated with Opioid Use

The most common side effects associated with the use of opioid analgesics include constipation, sedation, dizziness, nausea, vomiting, tolerance, physical dependence, and respiratory depression.<sup>14</sup> Of these side effects, opioid-induced respiratory depression (OIRD), defined as the diminished effectiveness of the ventilatory function after opioid administration and often preceded by sedation, is the most serious, resulting in the inability to breathe, and ultimately causing death if the condition is not treated in a timely manner.<sup>14-16</sup> The capacity of these analgesics to cause OIRD is a major contributing factor to the high incidence of drug-related fatalities worldwide, according to the World Health Organization.<sup>17</sup>

### Clinical Risk Factors of Opioid-Induced Respiratory Depression and Opioid Overdose

Multiple clinical factors can increase the risk for OIRD or opioid overdose, including a history of drug use, switching to another opioid, use of concomitant medications, and comorbid conditions, among others; some individuals may have a combination of these risk factors (Table 1).<sup>4,18-29</sup>

In addition, drugs that induce or inhibit the cytochrome (CY)P450 3A4 enzyme can interact with opioids, resulting in potentially fatal respiratory depression.<sup>20</sup> In a 2013 systematic review of 32 published case reports involving 42 patients with chronic pain and experiencing OIRD, Dahan and colleagues found that the predominant contributing factors to OIRD from 2000 to 2012 were pharmacokinetic drug interactions with the CYP450 pathway, which increased the opioid blood concentrations to toxic levels.<sup>21</sup>

OIRD in patients with chronic pain involves an interplay of multiple and complex risk factors.<sup>21</sup> Despite the identification of these risk factors, the occurrence of OIRD is not predictable, underscoring the need for careful dosage titration and continuous monitoring to prevent potentially fatal OIRD.<sup>21</sup>

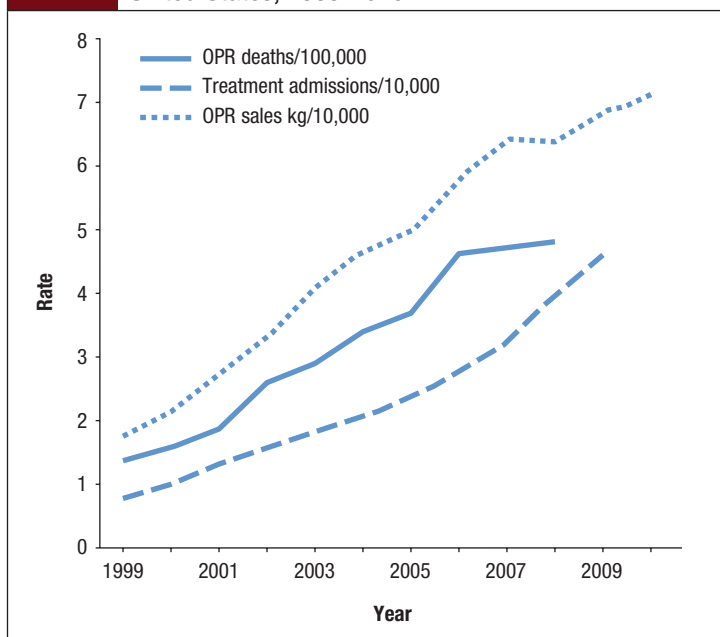
### Demographic Risk Factors for Opioid-Induced Respiratory Depression and Opioid Overdose

In addition to the clinical risk factors of OIRD and opioid overdose, specific demographic factors also increase the risk for these conditions, including sex, age, and income level.<sup>9,30,31</sup>

**Sex.** Although men are still more likely than women to die from a pain medication overdose, the gap be-

Figure 1

Rates of Opioid Pain Reliever Overdose Deaths, Treatment Admissions, and Kilograms Sold in the United States, 1999-2010<sup>a</sup>



<sup>a</sup>Age-adjusted rates per 100,000 population for opioid pain reliever (OPR) deaths, crude rates per 10,000 population for OPR abuse treatment admissions, and crude rates per 10,000 population for kilograms of OPR sold.

Source: Centers for Disease Control and Prevention. *MMWR Morb Mortal Wkly Rep.* 2011;60:1487-1492.

tween men and women is closing.<sup>30</sup> In fact, the number of women who died from prescription painkiller overdoses increased more than 400% from 1999 to 2010 compared with a 265% increase for men during the same period.<sup>30</sup>

**Age.** The majority of opioid overdose deaths occur in individuals aged 25 to 54 years.<sup>31</sup> From 1999 to 2013, the rate of opioid poisoning deaths increased more than 7-fold among adults aged 55 to 64 years.

In addition to adults and teenagers, children also experience opioid overdoses. On average, approximately 3300 children aged ≤5 years receive treatment in emergency departments annually as a result of accidental opioid poisoning; these events are associated with substantial morbidity and healthcare utilization.<sup>32</sup>

**Income level.** Individuals living in rural areas and those with a low income are particularly vulnerable to opioid overdose.<sup>19</sup> From 2004 to 2007, the risk for death from prescription opioid-related overdoses was nearly 6 times higher among Medicaid enrollees compared with those not enrolled in Medicaid.<sup>33</sup>

### Deaths Associated with the Unintentional Misuse of Opioids on the Rise

Some of the clinical and demographic risk factors that increase the risk for opioid overdose are evident, including a history of substance use disorders or obtaining overlapping prescriptions from multiple providers and pharmacies (ie, doctor shopping). Perhaps less evident is that the majority (60%) of deaths related to opioid overdose occur in patients who are prescribed opioids based on prescribing guidelines.<sup>13</sup> Nearly 52% of all drug overdose deaths that occurred in 2013 were related to prescription drugs and not illicit drugs, as may have been expected.<sup>9</sup>

A considerable proportion of opioid overdoses occur when patients take the prescribed opioid doses under the physician's care. Furthermore, the majority (60%) of individuals who overdose on opioid analgesics only have 1 prescriber (Figure 2).<sup>24</sup>

According to a 2012 Centers for Disease Control and Prevention (CDC) report, an estimated 80% of patients are prescribed low doses (<100 mg daily) of opioids by a single provider, accounting for an estimated 20% of all prescription drug overdoses.<sup>24</sup> Another 10% of patients are prescribed high doses (≥100 mg daily) of opioids by single prescribers and account for an estimated 40% of prescription opioid overdoses.<sup>24</sup> The remaining 10% of patients seek care from multiple physicians, are prescribed high daily doses of opioids, and account for another 40% of opioid overdoses (Figure 2).<sup>24</sup>

Furthermore, deaths resulting from the unintentional misuse of prescription drugs, especially opioids, are on the rise. In 2007 alone, approximately 27,000 unintentional

**Table 1** Clinical Risk Factors of Opioid-Induced Respiratory Depression and Opioid Overdose

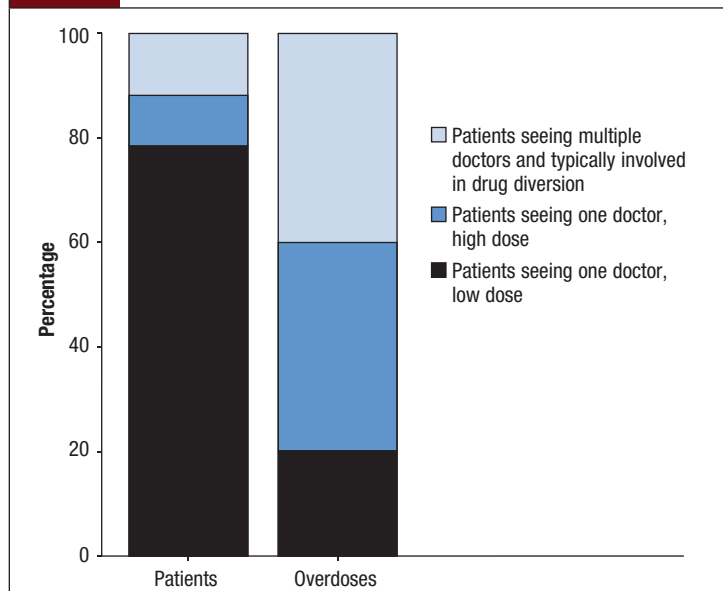
<b>Previous Drug Use Disorder</b>
History of substance abuse, dependence, and/or addiction <sup>18,19</sup>
History or presence of mental illness <sup>18,19</sup>
<b>Dosing and Switching Medications</b>
Use of extended-release formulations and long-acting opioids <sup>19,22,25</sup>
Switching to another opioid <sup>23</sup>
Morphine-equivalent dose ≥20 mg daily <sup>22,25,26</sup>
<b>Accidental Exposure and Unintentional Opioid Misuse</b>
Member of a household who discovers and uses a prescribed opioid inappropriately <sup>23,24</sup>
Inadvertently taking more than prescribed, forgetting whether medication was taken, misunderstanding prescribing instructions, cognitive decline causing confusion <sup>4</sup>
<b>Use of Other Medications</b>
Central nervous system depressants, including benzodiazepines and alcohol <sup>20,27</sup>
Certain monoamine oxidase inhibitors <sup>20</sup>
Initiation of CYP3A4 inhibitors (or discontinuation of CYP3A4 inhibitors) <sup>20,21</sup>
<b>Comorbid Conditions</b>
Chronic pulmonary disease <sup>20,22,26,28,29</sup>
Sleep apnea <sup>22</sup>
Asthma <sup>20,28,29</sup>
Chronic kidney and/or liver impairment <sup>20,22,28,29</sup>
Pancreatitis <sup>22</sup>
Traumatic injury <sup>22</sup>
Skin ulcers <sup>22</sup>
CYP3A4 indicates cytochrome P450 3A4.

drug overdose deaths occurred in the United States at a rate of 1 death every 19 minutes.<sup>24</sup> Since 2003, more overdose deaths have involved opioid analgesics than heroin and cocaine combined (Figure 3).<sup>24</sup> In addition, for every unintentional overdose death related to an opioid analgesic, 9 individuals are admitted for substance abuse treatment, 35 visit emergency departments, 161 report drug abuse or dependence, and 461 report nonmedical uses of opioid analgesics.<sup>24</sup>

### Opioid Prescribing Patterns

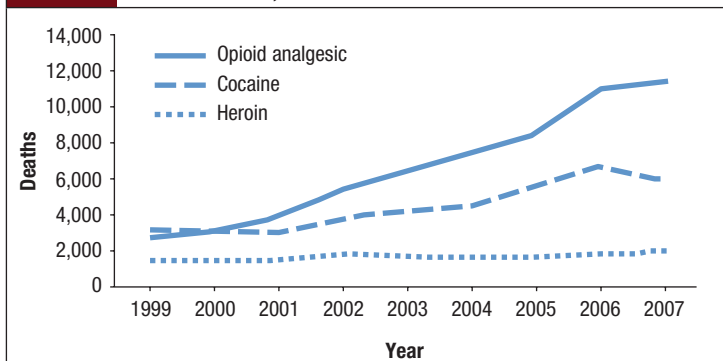
Multiple studies have examined the association between opioid prescribing patterns and the risk for overdose death.<sup>12,18,26</sup> The association between higher opioid doses and overdose events was assessed in a study by Dunn and colleagues.<sup>26</sup> Patients who received ≥100 mg of an opioid daily had nearly a 9-fold increase in the risk

**Figure 2** Percentage of Patients and Prescription Drug Overdoses in the United States



Source: Centers for Disease Control and Prevention. *MMWR Morb Mortal Wkly Rep.* 2012;61:10-13.

**Figure 3** Number of Unintentional Drug Overdose Deaths Involving Opioid Analgesics, Cocaine, and Heroin—United States, 1999-2007



Source: Centers for Disease Control and Prevention. National Vital Statistics System: multiple cause of death dataset. [www.cdc.gov/nchs/nvss.htm](http://www.cdc.gov/nchs/nvss.htm). Accessed August 27, 2015.

for overdose and a 1.8% annual overdose rate compared with patients who received 1 mg to 20 mg of an opioid (0.2% annual overdose rate).<sup>18</sup> In addition, patients who received 50 mg to 99 mg of an opioid had a 3.7-fold increased risk for an overdose and a 0.7% annual overdose rate versus those in the 1-mg to 20-mg group.<sup>18</sup>

Dunn and colleagues acknowledged that the increased risk associated with higher doses may be attributed to the confounding by patient differences and

the use of opioids in a manner other than as directed.<sup>26</sup> Furthermore, a 5-year cohort study by Boehnert and colleagues revealed that higher opioid doses were associated with an increased risk for opioid overdose mortality involving 750 unintentional prescription opioid decedents from a random sample of 154,684 patients who received opioid treatment for pain for a variety of medical conditions.<sup>18</sup>

Findings from this study showed that the adjusted hazard ratio associated with a maximum prescribed dose of  $\geq 100$  mg daily versus a dose of 1 mg to  $< 20$  mg daily was 7.18 in patients with chronic pain, and the adjusted hazard ratio in patients with substance abuse disorders was 4.54.<sup>18</sup> Patients who received as-needed and regularly scheduled opioid doses did not have an increased risk for overdose after adjustment.

Although higher opioid doses are associated with a greater risk for overdose,<sup>18,26</sup> the risk for overdose is also present in individuals taking lower opioid doses.<sup>13</sup> Notably, a 2012 study by Manchikanti and colleagues showed that 20% of individuals who died from an opioid overdose were taking low-dose opioid treatment of  $\leq 100$  mg daily.<sup>13</sup>

### The Need to Integrate Risk Assessment and Risk Reduction Strategies

The findings from these 3 studies examining the prescribing patterns of opioids reinforce the importance of integrating strategies to reduce the risk for overdose in patients who receive opioids for pain, including ongoing patient follow-up.<sup>13,18,26</sup>

Overall, many patient populations are at risk for opioid toxicity and overdose. Considerable work must be done to implement effective strategies and resources that can help avert preventable opioid-induced toxicity and morbidity.<sup>4</sup>

### Treatment of Opioid-Induced Respiratory Depression

Opioid toxicity is characterized by symptoms that typically include OIRD, constricted pupils, stupor, and diminished oxygen saturation.<sup>15</sup> Advancing sedation and OIRD are among the most serious symptoms, and can result in death unless there is a rapid response.<sup>15</sup> Rapid-response interventions include rescue breathing and/or administering naloxone hydrochloride (HCl; naloxone).<sup>16</sup> Naloxone HCl injection, an opioid antagonist, is an antidote to acute opioid toxicity.<sup>3</sup> Naloxone antagonizes opioid effects by competing for the same receptor sites, and, in doing so, reverses the effects of opioids, including OIRD, sedation, and hypotension.<sup>34,35</sup> When injected effectively and soon after an opioid overdose, naloxone restores breathing to individuals who otherwise might have died without treatment.<sup>3,36</sup> It is important to note that naloxone produces no clinical effects

when administered to individuals who are not opioid-intoxicated or -dependent.<sup>3</sup>

Overall, naloxone has a favorable safety profile when used at the recommended doses and titrated appropriately.<sup>3,34,35</sup>

### The History of Naloxone Use

Naloxone HCl injection was initially approved by the FDA in 1971.<sup>37</sup> In the 4 decades since its initial approval, naloxone has become the standard of care for opioid overdose, and emergency medical personnel, healthcare professionals, and patients are increasingly being trained on its appropriate use.<sup>3,38</sup>

Coinciding with the ongoing rise in opioid-related deaths, the use of naloxone was assessed outside of the professional medical setting.<sup>39</sup> In 1996, community-based overdose prevention programs began distributing naloxone kits and educating opioid users and laypersons about their use.<sup>39,40</sup> According to a series of surveys conducted by the Harm Reduction Coalition, these pilot programs achieved positive outcomes. More than 53,000 individuals received training on the use of naloxone, and more than 20,000 opioid-related overdose reversals were recorded between 1996 and 2014.<sup>40</sup>

In August 2013, the Substance Abuse and Mental Health Services Administration (SAMHSA), a division of the US Department of Health & Human Services, published an opioid overdose toolkit, a safety and prevention resource for the community, first responders, prescribers, patients, and family members.<sup>3</sup> Updated in 2014, the SAMHSA toolkit discusses the role of naloxone for reversing respiratory depression during an opioid overdose. The toolkit also provides an overview on the safety of naloxone, and emphasizes the importance of immediate access to naloxone.<sup>3</sup>

### Emergency Medical Responses to Opioid Overdose and Opioid-Induced Respiratory Depression

Many opioid overdoses have been reversed with the help of emergency medical technicians who arrive on the scene in time to administer naloxone and provide other emergent care.<sup>39</sup> However, overdose deaths often occur in the company of individuals who do not call for emergency or other medical assistance for various reasons.<sup>38</sup> Ideally, laypersons who witness an opioid overdose have been trained on how to recognize an opioid overdose, initiate rescue breathing, and administer naloxone. However, relatively few laypersons receive this training.<sup>16,38</sup>

Emergency medical personnel are sometimes limited in their ability to help individuals with opioid overdose, particularly when witnesses to an overdose fail to contact them, when distance affects response time, or when there are disparities in training on naloxone administra-

Data collection period	Organizations reported provided training and naloxone kits (by number of sites), N	Laypersons who received training and naloxone kits, N	Opioid overdose reversals recorded by organizations that collect reversal reports, N
1996-2010	48 (188)	53,032	10,171
1996-2014	136 (644)	152,283	24,463
2013	93 (-)	37,920	8032

*Sources:* Centers for Disease Control and Prevention. *MMWR Morb Mortal Wkly Rep.* 2012;61:101-105; Centers for Disease Control and Prevention. *MMWR Morb Mortal Wkly Rep.* 2015;64:631-635.

tion within emergency medical personnel.<sup>41,42</sup> A 2015 study by Faul and colleagues of the CDC found disparities in naloxone administration between emergency medical technicians in rural areas and those in nonrural areas.<sup>41,42</sup> The findings revealed that basic emergency medical technician staff in rural US regions administered naloxone less frequently than did emergency medical staff in nonrural US regions.<sup>41,42</sup> Although the rate of mortality as a result of opioid overdose was 45% higher in rural areas compared with urban areas, the use of naloxone by rural emergency medical services was only 22.5% higher than the use of naloxone by urban emergency medical services, indicating that if naloxone distribution coincided with the overdose mortality rate, more lives may be saved in rural areas.<sup>42</sup>

To reduce opioid-related overdose deaths, particularly in rural areas, Faul and colleagues recommend expanding training on the administration of naloxone to all emergency medical staff, and facilitating the advanced certification requirements for basic emergency medical staff to prevent drug overdose mortalities.<sup>41,42</sup> Faul and colleagues also recommend the development of universal and national guidelines on the administration of naloxone.<sup>42</sup>

### The Expanding Role of Laypersons Who Witness an Overdose

Laypersons who witness an opioid overdose are in a position to administer potentially life-saving treatment to individuals who overdose on opioids.<sup>16</sup> In a study by Green and colleagues that involved 62 current or former opioid abusers, 72% reported having witnessed an opioid overdose.<sup>16</sup> In addition, a survey conducted from 2002 to 2004 involving 329 drug users revealed that nearly 65% had witnessed a drug overdose, and the majority (88.5%) of the respondents conveyed a willingness to administer

a medication, such as naloxone, to another drug user in the event of an opioid overdose.<sup>43</sup>

### Overdose Treatment and Naloxone Administration Training Programs

The increase in the opioid overdose rate in recent years and its devastating impact on society have led to the development of action plans from federal, state, and local governments, as well as from concerned advocacy groups, professional societies, and communities.<sup>39,40</sup>

**Harm reduction coalition surveys.** As mentioned previously, the Harm Reduction Coalition conducted a series of surveys about the community opioid overdose treatment programs that were initially implemented in 1996.<sup>39,40</sup> From 1996 through 2014, an estimated 26,463 overdose reversals were reported by more than 600 sites in 30 states and the District of Columbia (Table 2).<sup>38,40</sup> Overall, 136 organizations responded to the survey, reporting whether and when they began providing naloxone kits and continue to provide naloxone kits to layper-

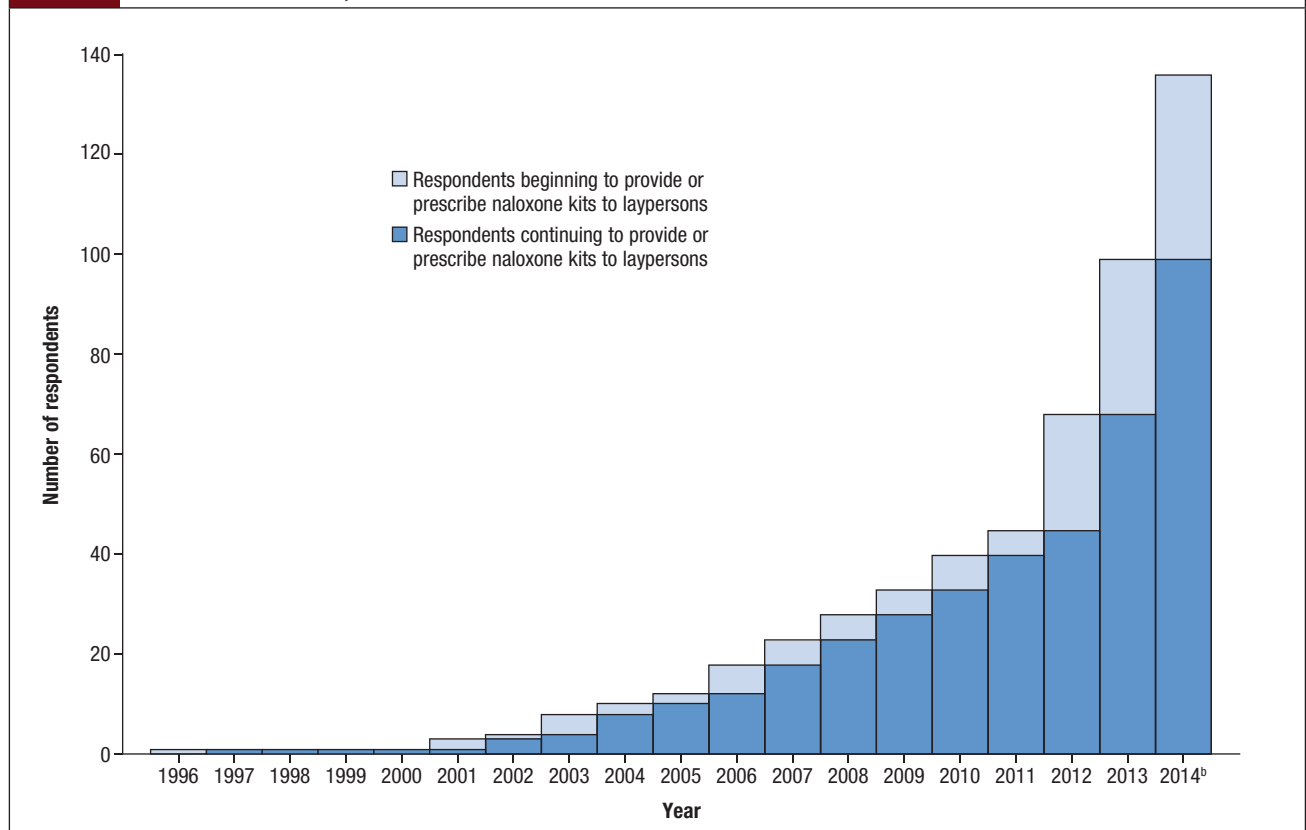
sons (Figure 4).<sup>40</sup> Data revealed that the number of organizations providing naloxone kits to laypersons increased sharply from 2012 to 2014 (Figure 4).<sup>40</sup>

In addition, survey results revealed that from 2010 to 2014, there was a 243% increase (from 188 to 644) in the number of sites providing naloxone kits to laypersons, a 187% increase (from 53,032 to 152,283) in the number of local sites providing naloxone, and a 160% increase (from 10,171 to 26,463) in the number of overdose reversals (Table 2).<sup>40,44</sup>

Despite the major strides achieved through these opioid overdose treatment programs, 29.4% of organizations reported difficulties maintaining an adequate naloxone supply, and 53.7% reported difficulty sustaining or expanding naloxone dissemination efforts because of inadequate resources.<sup>40</sup>

Survey results indicated that providing naloxone kits to laypersons is an important component of responsible opioid prescribing and that effective treatment measures, including educating laypersons on how to respond to

**Figure 4** Number of Survey Respondents Reporting Beginning or Continuing to Provide Naloxone Kits to Laypersons in the United States, 1996-2014<sup>a</sup>



<sup>a</sup>Results of a survey conducted in July 2014 by the Harm Reduction Coalition, in which 136 organizations reported 644 local sites where laypersons were trained to recognize an opioid drug overdose and provided naloxone kits.

<sup>b</sup>As of June 2014.

Source: Centers for Disease Control and Prevention. *MMWR Morb Mortal Wkly Rep.* 2015;64:631-635.

overdoses and on how to administer naloxone, may help prevent opioid overdose fatalities.<sup>40</sup> Additional strategies are needed to provide naloxone kits to individuals who may witness opioid overdoses.<sup>40</sup>

**Massachusetts community analysis.** A 2013 analysis by Walley and colleagues was conducted from 2002 to 2009 within 19 Massachusetts communities (comprising 30% of the state's population) to evaluate the impact of state-supported overdose education and naloxone (intra-nasal) distribution programs on the rates of opioid-related deaths from overdose.<sup>45</sup> Overall, there was a significant reduction in the rate of opioid overdose deaths in communities where overdose education and naloxone distribution programs were implemented—a finding that reinforces the effectiveness of these interventions.<sup>45</sup> The majority of rescue attempts took place in private settings, and the rescuer was usually a friend of the individual who had overdosed.<sup>45</sup>

### **Other Initiatives and Calls to Action**

Momentum to prevent prescription drug overuse, misuse, abuse, and overdose continues to build across the United States at the national, state, and local levels. Some of the many initiatives in progress include the following:

**The CDC Injury Center.** In 2015, the CDC Injury Center announced that it would commit over \$55 million to combat prescription drug overdose, paving the way for the newly created Prescription Drug Overdose: Prevention for States program.<sup>46</sup> This program will fund states to implement prevention strategies designed to reverse the prescription drug overdose epidemic.<sup>46</sup> A total commitment of \$55.6 million over a 4-year period with a maximum of \$1 million per award annually will support approximately 16 states in their efforts to implement prevention strategies.<sup>46</sup>

**FDA collaboration.** In July 2015, the FDA hosted “Exploring Naloxone Uptake and Use,” a 2-day public meeting that was cosponsored by the National Institute on Drug Abuse, the CDC, SAMHSA, and the Health Resources and Services Administration to discuss issues surrounding the use of naloxone, ranging from a review of current naloxone use in clinical and nonclinical settings to a discussion about training and evaluation of naloxone effectiveness.<sup>44</sup>

**The Office of National Drug Control Policy (ONDCP).** The ONDCP recognizes the devastating impact of opioid abuse on public health and safety, and recommends that first responders carry naloxone, and that local law enforcement agencies train their personnel on the use of naloxone.<sup>36</sup> The ONDCP notes that naloxone can save lives, particularly when used jointly with Good Samaritan laws that grant immunity from criminal prosecution to those who witness an overdose.<sup>36</sup>

**American Medical Association (AMA) position statement.** On April 23, 2015, the AMA released a position statement asserting its strong commitment to preventing opioid drug misuse, abuse, overdose, and mortality, while ensuring that patients with pain and opioid use disorders have access to needed treatment.<sup>47</sup> The AMA is collaborating with multiple legislative-focused and patient-focused organizations at the federal and state levels to address these priorities, with emphasis on the need for overdose prevention strategies.<sup>47</sup> According to the AMA position statement, the enactment of new laws addressing overdose prevention, treatment for opioid use disorders, increased access to naloxone, and Good Samaritan protections are showing promise as life-saving initiatives.<sup>47</sup>

**National Governors Association.** On February 19, 2015, the AMA, the Harm Reduction Coalition, and the National Safety Council sent a letter to the Executive Director of the National Governors Association urging the nation's governors to increase their focus on overdose prevention and treatment.<sup>48</sup> Signed by more than 150 other coalitions, professional societies, and advocacy groups from the medical and the public community, this letter drew attention to the potential consequences of unmet overdose prevention and addiction treatment needs.<sup>48</sup>

In addition, the letter emphasized 3 key policies as the cornerstone of an effective demand-side approach to reduce opioid abuse and misuse and curtail opioid-related overdose and mortality, including (1) enhancing access and utilization of naloxone in every state; (2) providing Good Samaritan protections for those who help victims of an opioid overdose; and (3) increasing access to medication-assisted treatment services as well as to nonopioid-based treatments.<sup>48</sup>

### **Changing the Narrative About Access to Naloxone**

Lukewarm support for naloxone distribution programs and other drug abuse treatment programs still lingers in some medical and public communities.<sup>49</sup> This reaction may stem from the stigma of drug use as a moral flaw, and the accompanying view of overdose as the consequence of poor behavior or choices.<sup>49</sup>

A 2015 study by Bachhuber and colleagues showed that there was a substantially higher level of support for overdose prevention policies when individuals received factually accurate information about naloxone, when their concerns about the potential unintended consequences of naloxone were preemptively refuted, and when they were presented with a sympathetic portrayal of someone whose opioid use and untimely death affected others (eg, a mother whose teenaged daughter died of an opioid overdose).<sup>49</sup>

Ongoing education, awareness, support, and resources are warranted to help prevent opioid abuse and overdose wherever possible while responding to the crucial needs of individuals with chronic pain. In addition to education, simpler naloxone administration methods might benefit individuals at risk for OIRD.

### **Novel Strategies for the Administration of Naloxone-Based Treatment**

As efforts expand to engage laypersons to respond to an opioid overdose, there is a corresponding need to provide them with effective training, education, and approaches that help facilitate timely naloxone administration. Part of this training entails reinforcing the concept that naloxone administration is an effective reversal agent in the event of an overdose, but it is not a substitute for emergency medical care.<sup>34,35</sup>

The FDA-approved naloxone formulations and delivery systems include naloxone HCl injection and the naloxone auto-injector.<sup>34,35</sup> The naloxone HCl injection is available as a sterile solution for intravenous, intramuscular, and subcutaneous administration; it is available in a single-dose vial, multiple-dose vial, and in a syringe (without a needle).<sup>34,50</sup>

Approved by the FDA in 2014, naloxone HCl injection 0.4 mg auto-injector (Evzio; kaléo) is intended for intramuscular or subcutaneous use only and delivers a single dose of naloxone in a prefilled auto-injector.<sup>35,51</sup> Intranasally administered naloxone for the reversal of opioid overdose is being developed by several manufacturers.<sup>52</sup> Although some jurisdictions are beginning to use this formulation,<sup>45</sup> intranasal naloxone has not been approved by the FDA.<sup>53</sup>

### **Use of the Naloxone Auto-Injector for Nonclinical Settings**

The naloxone auto-injector was approved by the FDA on April 3, 2014, becoming the first naloxone formulation intended for immediate administration by family members, friends, or caregivers as emergency treatment for opioid overdoses outside of healthcare settings.<sup>51</sup> Specifically, the naloxone auto-injector is indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.<sup>35</sup>

The naloxone auto-injector was approved by the FDA under its priority review program for drugs that may provide safe and effective treatment when no satisfactory alternative treatment exists.<sup>51</sup> It was also granted a fast-track review based on its potential to treat a serious condition and fill an unmet medical need.<sup>51</sup> The naloxone auto-injector comes equipped with an electronic voice instruction system to assist individuals who are not

trained in the administration of naloxone, or in situations where the printed instructions are not readily available.<sup>35</sup> If the voice instruction system does not operate properly, the naloxone auto-injector will still deliver the intended dose of naloxone when used according to the printed instruction on its label.<sup>35</sup>

According to Bob Rappaport, MD, then-Director of the Division of Anesthesia, Analgesia, and Addiction Products in the FDA's Center for Drug Evaluation and Research (CDER), "Overdose and death resulting from misuse and abuse of both prescription and illicit opioids has become a major public health concern in the United States."<sup>51</sup> Dr Rappaport added, "Evzio is the first combination drug-device product designed to deliver a dose of naloxone for administration outside of a health care setting. Making this product available could save lives by facilitating earlier use of the drug in emergency situations."<sup>51</sup>

Douglas C. Throckmorton, MD, Deputy Director for Regulatory Programs in the FDA's CDER, commented, "This approval is the culmination of concerted efforts at FDA and throughout the Department of Health and Human Services (HHS) to spur research into alternative forms of naloxone and to expand its availability."<sup>54</sup> Dr Throckmorton noted that the use of the naloxone prefilled, single-use injection device for an individual who overdoses is similar to devices used by the general public to administer epinephrine to a patient who has a severe allergic reaction.<sup>54</sup> He also outlined many other actions being undertaken by the FDA to combat opioid misuse and abuse, including label changes to improve safe use of opioids, training healthcare practitioners on the responsible prescribing practices of opioids, strengthening surveillance efforts, addressing signs of abuse or dependence, and encouraging the development of abuse-resistant opioids and nonaddictive pain treatments.<sup>54</sup>

The 2014 SAMHSA overdose toolkit includes an announcement about the naloxone auto-injector, stating that the naloxone auto-injector requires no special training, whereas the previously available naloxone kits require training on filling the syringe with naloxone and administering it to the individual.<sup>3</sup>

In addition to its use as an emergency treatment in nonhealthcare settings, the naloxone auto-injector may represent an important alternative to the naloxone injection for those involved in harm-reduction efforts, including emergency medical technicians, law enforcement, and other trained first responders.

### **Usability Study Comparing 2 Naloxone Delivery Systems**

A 2015 study by Edwards and colleagues compared the usability of the naloxone auto-injector with that of a naloxone intranasal delivery system during a simulated



**Table 3** Comparative Usability of the Naloxone Auto-Injector versus the Naloxone Intranasal Delivery System

End points	Before training (N = 42)		After training (N = 42)		P value
	Naloxone auto-injector	Naloxone intranasal delivery system	Naloxone auto-injector	Naloxone intranasal delivery system	
Successful administration of a simulated dose of naloxone, <sup>a</sup> %	90.5	0.0	100	57.1	<.0001
Use of the device according to instructions for use, <sup>b</sup> %	85.7	0.0	100	0.0	<.0001
Average time to task completion for administration attempt, <sup>b</sup> minutes	0.9 ± 0.25	6.0 ± 4.76	0.5 ± 0.15	2.0 ± 2.15	<.0001

<sup>a</sup>Primary end point involved administering the dose into a mannequin during a simulated opioid emergency.  
<sup>b</sup>Secondary end point.  
Source: Edwards ET, et al. *Pain Ther.* 2015;4:89-105.

opioid emergency, before and after 42 healthy participants (aged 18-65 years) received training.<sup>55</sup> In addition, it measured the use of each device according to the instructions for use and the successful completion time of administration for both formulations.<sup>55</sup>

The study findings indicated that a significantly greater proportion of participants were able to successfully administer a simulated dose of naloxone using the naloxone auto-injector compared with participants using the naloxone intranasal delivery system, before and after training (Table 3).<sup>55</sup> Similarly, a significantly greater proportion of the naloxone auto-injector users were able to administer a simulated dose of naloxone according to the instructions for use compared with naloxone intranasal users, before and after training.<sup>55</sup>

The findings of this study confirmed the effective usability of the naloxone auto-injector for trained and untrained individuals, demonstrating its role in facilitating naloxone administration by laypersons during an opioid emergency in nonclinical settings.<sup>55</sup>

### Payer Considerations in the Management of Opioid-Induced Respiratory Depression

When making coverage decisions, payers have a fiduciary responsibility to their customers, which typically include employers, employer groups, public sector agencies, labor unions, individuals who purchase health insurance, and, for public payers such as Medicare and Medicaid, to society at large. Because payers weigh the incremental clinical benefit of a drug or a service relative to its cost, they may be reluctant to extend preferred coverage status to drugs or devices that are perceived to

provide limited value compared with similar drugs or devices with different features and intended uses.

Payers are saddled with the escalating costs of opioid abuse and misuse, particularly with the morbidity and mortality associated with OIRD and overdose. Consequently, there remains a marked need for strategies that improve overall outcomes and reduce costs.

### The Burden of Opioid Abuse and Misuse

Opioid toxicity is associated with a considerable social and economic burden. With the rising trend in opioid abuse and misuse, there is a corresponding increase in hospital admissions, emergency department visits, and overdose fatalities.<sup>56,57</sup>

For every prescription-related opioid mortality in the United States in 2010, there were 10 admissions for abuse treatment, 26 visits to the emergency department for opioid misuse or abuse, 108 individuals who abused or were dependent on opioids, and 733 nonmedical users of opioids.<sup>56,57</sup>

**Emergency department costs.** Medical emergencies resulting from drug misuse or abuse resulted in 2.5 million emergency department visits in 2011—the equivalent of 790 emergency department visits per 100,000 population (500 visits per 100,000 individuals aged ≤20 years; 903 visits per 100,000 individuals aged ≥21 years).<sup>57</sup> An alarming 56% (1.4 million) of these emergency department visits involved prescription drugs.<sup>9,57</sup> According to the CDC, nearly 7000 individuals receive treatment in emergency departments daily for taking prescription pain medications other than as directed by their prescriber.<sup>12</sup> From 2004 to 2011, medical emergencies attributed to the nonmedical use of opioids increased by 183%.<sup>57</sup>

A study by White and colleagues showed that from 1998 to 2002 the annual direct healthcare costs for opioid abusers were, on average, more than 8 times higher than the direct healthcare costs for nonabusers.<sup>58</sup> The hospital inpatient expenses for opioid abusers accounted for 46% of the total costs compared with 17% for nonabusers.<sup>58</sup> A 2014 retrospective study by Hasegawa and colleagues that involved 19,831 patients with 21,609 emergency department visits for opioid overdose demonstrated that frequent visits to the emergency department for opioid overdose were associated with a higher risk for future hospitalizations and near-fatal events; in fact, 7% of patients with opioid overdose had frequent emergency department visits, accounting for 15% of all opioid overdose emergency department visits.<sup>29</sup> In addition, patients with frequent emergency department visits for opioid overdose were nearly 4 times more likely to be hospitalized and more than twice as likely to have a near-fatal event compared with patients with less frequent emergency department visits.<sup>29</sup> These risk factors were evident even after adjusting for patients' demographic factors, healthcare-related factors, and comorbid conditions.<sup>29</sup>

**Quantifying the economic burden of opioid poisoning.** In a US study that used publicly available data sets from 2009, Inocencio and colleagues quantified the economic burden of opioid poisoning.<sup>59</sup> This study was unique in that it estimated the annual costs for opioid-related poisonings, as well as the cost per opioid-related poisoning event.<sup>59</sup>

The study findings revealed that the estimated number of opioid poisoning visits to the emergency department was 534,490, of which 75% involved nonheroin opioids. In addition, poisoning from prescription opioids resulted in 108,106 inpatient admissions after emergency department care.<sup>59</sup>

The results of this study are eye-opening. In 2009, the total annual cost of opioid-related poisonings totaled \$20.4 billion, of which 89% were attributed to indirect costs (Table 4).<sup>59</sup> Mortality-related costs accounted for the majority (87%) of the total costs of opioid poisoning. In addition, prescription opioids accounted for higher costs than those for heroin across multiple categories, including per-poisoning event direct costs, per-poisoning event indirect costs, mean emergency department costs, per-case total direct and indirect costs, and mortality costs.<sup>59</sup> The study researchers concluded that interventions designed to prevent or reverse opioid-related poisoning could reduce the economic burden of opioid misuse and abuse, particularly when fatalities are averted.<sup>59</sup>

**Table 4** Costs Associated with Opioid-Related Poisoning Events in the United States, 2009

Cost variable	All opioids, <sup>a</sup> \$	Prescription opioids, <sup>a</sup> \$	Heroin, <sup>a</sup> \$
<b>Direct costs</b>			
Average direct cost per poisoning event	4006	4255	3199
Mean ED treatment costs	1832	1967	1379
Total annual ED costs	800 million	630 million	169.5 million
Total annual inpatient costs	1.3 billion	1 billion	239 million
Total annual direct costs	2.2 billion	1.7 billion	435 million
<b>Indirect costs</b>			
Estimated indirect cost per poisoning event	33,267	34,285	30,594
Per-case mortality costs	32,657	33,664	30,010
Total annual mortality costs	17.9 billion	13.9 billion	4.1 billion
Total annual indirect costs	18.2 billion	14.1 billion	4.1 billion
<b>Direct and indirect costs</b>			
Per-case total for direct and indirect costs	37,274	38,541	33,793
Total (annual) direct and indirect costs	20.4 billion	15.9 billion	4.6 billion

<sup>a</sup>All costs are reported in 2011 US dollars.

ED indicates emergency department.

Source: Inocencio TJ, et al. *Pain Med.* 2013;14:1534-1547.

### Opioid Risk Management Approaches for Payers

Payers are challenged with ensuring that patients with chronic pain have access to needed opioid analgesics while minimizing the financial risks associated with the misuse and abuse of these drugs.

Risk management approaches that aim to curb the misuse and abuse of opioids include encouragement of prescriber use of prescription drug monitoring programs, patient review and restriction programs, claims reviews, and formulary controls that help identify patients at risk and reduce inappropriate prescribing.<sup>56,60</sup> Other strategies include promoting the use of opioid formulations with lower abuse potential, integrating external policies that encourage and support appropriate prescribing behavior by healthcare providers, and using clinical guidelines or professional society recommendations to set standards or limits.<sup>56,60</sup> Some payers implement claims data surveillance and data sharing with other insurance providers to further their risk management goals.<sup>56,60</sup>

### Reimbursement Considerations: Increasing Naloxone Distribution

The number of overdose prevention and training programs with naloxone distribution has increased dramatically in recent years and is on a rapidly expanding trajectory. In 2013 alone, a total of 37,920 laypersons were

provided with naloxone kits and training; there were 8032 overdose reversals reported in the same year (Table 2).<sup>39</sup>

Recommendations for the increased uptake in naloxone access have been mounting nationwide, from the FDA, the CDC, SAMHSA, the Harm Reduction Coalition, the AMA, and many others. According to a 2014 CDC report on opioid overdose prevention programs, “U.S. and international health organizations recommend providing naloxone kits to laypersons who might witness an opioid overdose; to patients in substance use treatment programs; to persons leaving prison and jail; and as a component of responsible opioid prescribing.”<sup>39</sup>

As treatments become available, payers must decide on coverage and reimbursement for naloxone-based treatments. As mentioned previously, the naloxone auto-injector can be used by laypersons in nonhealthcare settings, including homes, dormitories, or public venues, to help reverse the effects of opioid overdose. The naloxone auto-injector can be used with little to no training.

Nevertheless, there is a cost outlay associated with the naloxone auto-injector, and a considerable portion of the cost will most likely be borne by payers of medical and pharmacy services, including commercial health plans. The following cost model includes data that may be considered in making coverage decisions.

### ***Acquisition Costs and Potential Offsets for the Naloxone Auto-Injector***

A deterministic cost model was designed to evaluate the combined pharmacy and medical resource costs to a health plan and the potential cost offsets associated with the use of the naloxone auto-injector.<sup>61</sup> Developed for a hypothetical health plan with 1 million adult members, the model compared the costs of prescription opioid overdose events for patients dispensed the naloxone auto-injector with that of matched control patients without the naloxone auto-injector.<sup>61</sup> In this model, the number of naloxone auto-injector prescriptions increased from 218 in year 1 to 2527 in year 3.<sup>61</sup> In year 3, overdose events occurred in 86 patients who received the naloxone auto-injector and their matched controls, with fatal overdoses totaling 11.1 in the naloxone auto-injector group versus 14.7 in the control group. In addition, death was prevented in 2.5 individuals in year 3.<sup>61</sup> The acquisition costs for the naloxone auto-injector increased from \$125,000 in year 1 to nearly \$1.5 million in year 3.<sup>61</sup> This cost was offset by medical resource savings of approximately \$84,000 in year 1, increasing to \$975,000 in year 3. In year 3, when the uptake of the naloxone auto-injector was assumed to plateau, the total net cost was \$481,000.<sup>61</sup>

Overall, this model showed that the acquisition costs for the naloxone auto-injector could be offset by reduced medical costs; that is, after 3 years, a representative US

payer organization can recoup approximately 66% of the product acquisition costs.<sup>61</sup> From a clinical perspective, the model suggests that the use of the naloxone auto-injector will likely save lives, reduce the morbidity of patients in the emergency department, and, when appropriately administered to patients experiencing an opioid overdose, will result in less use of emergency department resources and in fewer hospitalizations.<sup>61</sup>

### **Conclusions**

Healthcare professionals are responsible for balancing their patients' pain relief needs against the unintended consequences of abuse or misuse of the opioid analgesics. Conversely, payers must ensure that appropriate patients have access to needed opioid treatment, while managing the financial risks associated with opioid misuse and abuse.

Overdose mortalities from opioid toxicity, including OIRD, have been increasing steadily in recent years. Factors that increase the risk for OIRD and opioid toxicity include substance use disorders, higher opioid doses, pharmacokinetic and pharmacodynamic drug–drug interactions, and certain comorbid conditions. Opioid-related morbidity and mortality exact an immense clinical, societal, and economic toll. Measures to prevent and treat opioid misuse and abuse, while worthy and essential, are costly.

Numerous initiatives are under way to prevent opioid overdose morbidity and mortality at the national, state, and local levels, and through professional societies and advocacy groups. At the heart of these action plans to combat opioid overdose is the immeasurable value of saving a life, and, in doing so, preventing the devastating loss of that individual and its profound ripple effect on families, friends, colleagues, the community, and society as a whole.

These efforts include laws and policies, education, prescription drug monitoring programs, opioid dose limits, judicious opioid prescribing recommendations, and overdose prevention education and training, accompanied by naloxone distribution to laypersons. Naloxone distribution programs, which have gained traction nationwide in recent years, have helped prevent thousands of overdoses from becoming fatal events. An unmet need remains for ongoing prevention and educational campaigns and for novel and effective opioid overdose reversal strategies.

For the past 4 decades, the naloxone injection, administered by trained emergency personnel, has been the standard of care for reversing OIRD. However, OIRD may occur in situations where emergency personnel are not available or cannot reach an individual in a timely manner to prevent death. In these instances, innovative naloxone administration devices may represent particularly valuable treatment options. For example, the nalox-

one auto-injector provides a novel injection system that is readily available and easy to administer, allowing a layperson to do so without medical training. With this device, family members, friends, or caregivers can administer naloxone in nonhealthcare settings. In addition to the clinical and societal benefits afforded by this new approach, US payers can offset some of the acquisition cost of the naloxone auto-injector in averted emergency department visits and hospitalizations. ■

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## NOTES