

# The Continued Rise of Opioid Misuse: Opioid Use Disorder

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**T**he abuse and misuse of prescription drugs is the fastest growing drug problem in the United States. According to a CDC report, enough opioid pain relievers were sold in 2010 to “medicate every adult in the United States with the equivalent of a typical dose of 5 mg of hydrocodone every 4 hours for 1 month.”<sup>1</sup>

In 2013 in the United States, 40,982 deaths by drug overdose occurred. Of these, 16,235 were the result of opioid analgesics<sup>2</sup>—the equivalent of 46 deaths every day.<sup>3</sup> While the age-adjusted rate for drug overdose deaths related to opioid analgesics increased at a rate of 19% per year from 2000 to 2006, the rate did slow down to 2% from 2006 to 2013. The age-adjusted rate for opioid-analgesic overdose deaths declined from 5.4 to 5.1 per 100,000 from 2010 to 2013.<sup>2</sup> Overdose deaths involving opioid analgesics exceeded those due to heroin and cocaine combined.<sup>4</sup> Between 2002 and 2009, deaths involving oxycodone, hydrocodone, and methadone increased by 109%.<sup>5</sup> Specifically, opioid-related deaths more than tripled between 2000 and 2010.<sup>2,6-8</sup> Concurrently, chronic nonmedical use of opioid analgesics (defined as use of prescriptive pain relievers for 200 days or more during the previous 12 months without a prescription or for recreational purposes) increased by almost 75% from 2003 to 2010.<sup>5</sup> Although reports state that prescriptions for opioid analgesics decreased slightly from 2011 through 2013,<sup>9</sup> 259 million prescriptions were nonetheless written for opioid or narcotic pain relievers in 2012, enough to provide every American adult with 1 bottle of pills.<sup>3</sup>

The rise in overdose death rates and their chronic nonmedical misuse was paralleled by the 300% increase in opioid analgesic consumption between 1999 and 2010.<sup>5,6,10</sup> The same period also saw substantial increases in overdose death rates, sales of prescription analgesics, and opioid-abuse treatment admissions (Figure 1).<sup>4</sup> For each opioid-related accidental overdose death, there were 9 treatment

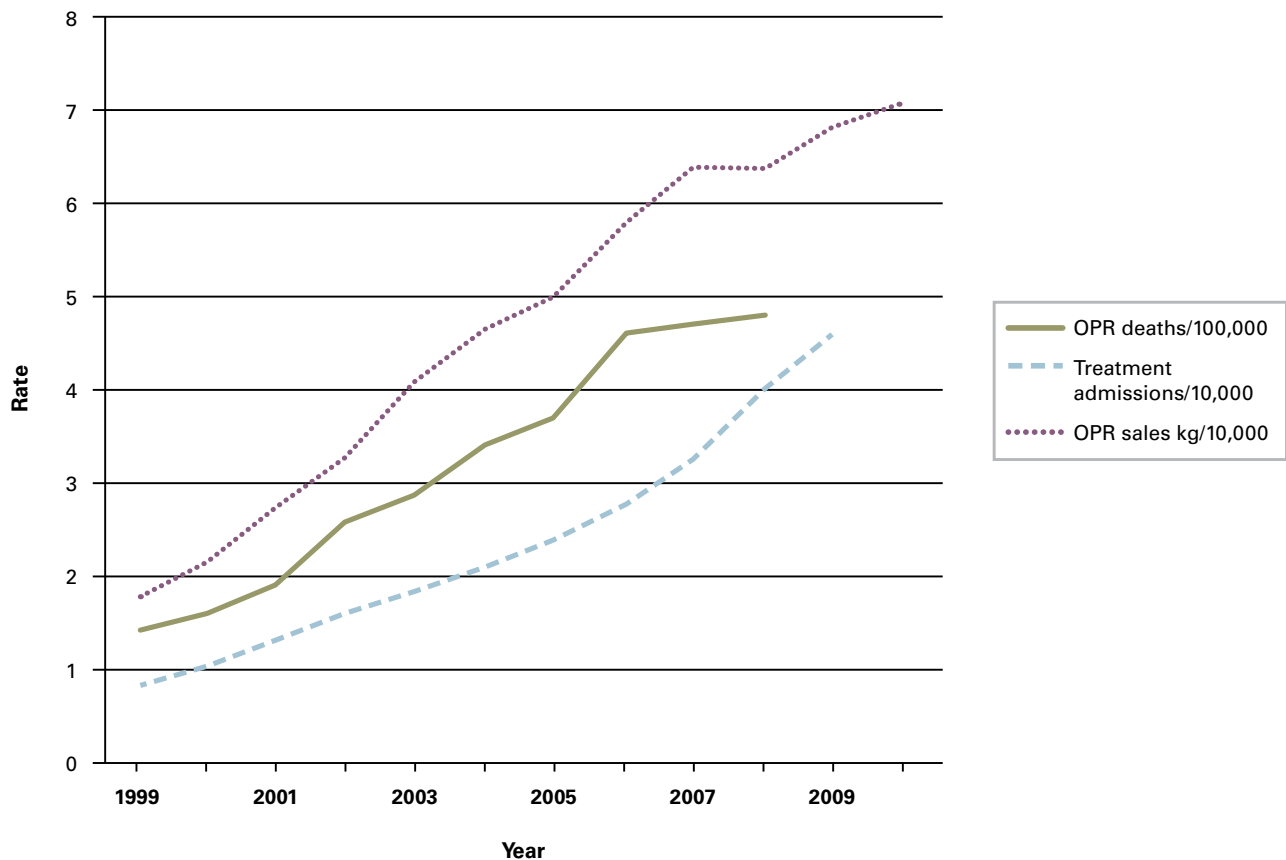
## Abstract

Abuse and misuse of prescription opioids is a national epidemic among adults and adolescents in the United States. Increases in deaths due to overdose and chronic nonmedical use of opioids have been paralleled by a 300% rise in opioid consumption. The development of opioid abuse begins early, with prevalence increasing with age through the early 20s. Diagnosis of opioid use disorder (OUD) is based on the individual’s medical and family history. Risk factors include individual, family, peer, social, and environmental factors, with genetically driven characteristics playing a direct or indirect role within these domains. Men, non-Hispanic whites, and those between 16 and 45 years of age are most at risk of death due to opioid misuse or abuse. Curtailing abuse requires a concerted effort on the part of federal and state regulatory agencies to initiate programs that monitor the prescribing and dispensing of opioids, along with consensus among healthcare professionals on treatment guidelines for pain management.

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■ **Figure 1.** Rates of Opioid Pain Reliever Overdose Death, Treatment Admission, and Kilograms Sold—United States, 1999-2010<sup>4</sup>



OPR indicates opioid pain reliever. Age-adjusted rates per 100,000 population for 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. Reprinted from: CDC. Vital signs: overdoses of prescription opioid pain relievers—United States, 1999-2008. *MMWR*. 2011;60(43):1487-1492.

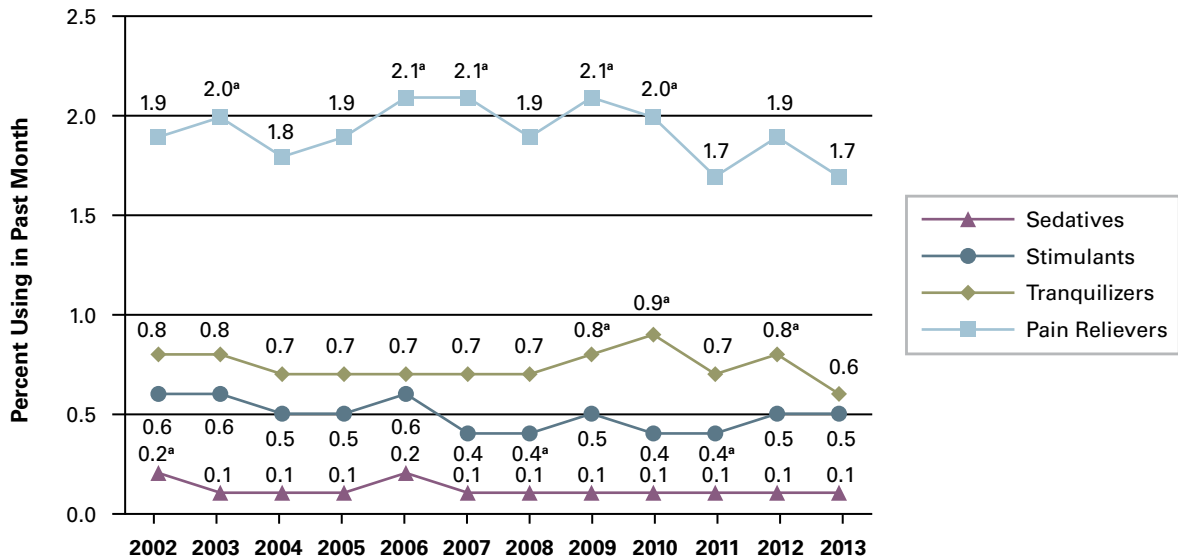
admissions for abuse, 35 visits to an emergency department (ED), 161 reports of abuse or dependence, and 461 reported nonmedical users of opioids.<sup>11</sup> In 2011, 420,040 ED visits were specifically related to the misuse and abuse of opioid analgesics.<sup>12</sup> Together, these numbers translate to \$72.5 billion in annual direct healthcare costs for nonmedical use of prescription analgesics.<sup>13</sup>

This epidemic is not limited to adults. In 2013, nearly 2 million Americans 12 years and older either abused or were dependent on opioid analgesics,<sup>14</sup> and more than 35 million people in the United States age 12 years and older had used an opioid analgesic for a nonmedical purpose at some point in their life, a significant increase from the 30 million estimated for 2002.<sup>15,16</sup> Nearly 10% of high school seniors report nonmedical use of hydrocodone,<sup>17</sup> making hydrocodone abuse second in prevalence only to mari-

juana abuse.<sup>18</sup> This issue has become so pervasive that in its *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*, the American Psychiatric Association replaced the separate diagnoses definitions of opioid dependence and opioid abuse with a single diagnosis definition, termed opioid use disorder (OUD).<sup>19</sup>

OUD is defined by the *DSM-5* as mild, moderate, or severe substance abuse or substance dependence, resulting from prolonged self-administration of opioids either for no legitimate medical purpose, or in doses that greatly exceed what is needed for the medical condition. The disorder results in significant social, functional, and clinical impairment; these problems can increase to the extent that activities of daily living must be scheduled around the procurement and administration of opioids.<sup>19</sup>

**Figure 2.** Past Month Nonmedical Use of Types of Psychotherapeutic Drugs Among Persons 12 Years or Older: 2002-2013<sup>20</sup>



<sup>a</sup>Difference between the estimate for the year shown and the 2013 estimate is statistically significant at the .05 level. Reprinted from: Results from the 2013 National Survey on Drug Use and Health: Summary of National Findings, NSDUH Series H-48, HHS Publication No. (SMA) 14-4863. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2014.

### The Development of Opioid Use Disorder

Statistics covering opioid usage published over the past decade highlight the challenges and controversies surrounding opioid use and misuse in this country, as well as the personal and economic impact of OUD on patients, their families, and society. Although dependency can start at any age, initial addiction and misuse of opioids tends to be most commonly observed in the late teens and early 20s.<sup>16</sup>

In 2013 in the United States, 1 out of 5 cases in which an individual 12 years or older used an illicit drug for the first time involved the nonmedical use of a prescription drug. Pain relievers were the second-most common choice among individuals using a drug illicitly for the first time, with 1.5 million new initiates to their nonmedical use. Nonmedical users 12 years or older totaled 4.5 million (Figure 2<sup>20</sup>), including 4.6% of 12-to-17-year-olds. In the same year, an average of about 0.9% of 12-to-13-year-olds had at any given time used pain relievers nonmedically during the previous month. The same was true for 1.8% of 14-to-15-year-olds, 2.3% of 16-to-17-year-olds, and 3.3% of 18-to-25-year-olds.<sup>20</sup>

More than half of children between 12 and 17 years of age obtained prescription opiate analgesics for free from a friend or a relative, while over 20% got the drug through a prescription from a doctor. Only 15% paid for the prescription, and of these, almost 11% purchased the drug from a friend or a relative.<sup>20</sup>

The prevalence of developing OUD is highest among those between 18 and 29 years of age.<sup>21</sup> After OUD develops, it usually continues over a prolonged period of time, with periods of abstinence and relapses. After the early 20s, increasing age is associated with a decrease in prevalence of developing the disorder, partly due to early mortality, and partly due to a remission of symptoms after reaching 40 years of age.<sup>19</sup>

### Diagnosing Opioid Use Disorder

The diagnostic criteria for OUD include 11 possible scenarios that represent a pattern of opioid use resulting in significant health or social impairment, or distress. Patients meeting 2 of the 11 criteria within a 12-month period, excluding situations in which the medication is prescribed and taken as directed, may be diagnosed with OUD.<sup>19</sup>

Although tolerance and withdrawal will occur after prolonged use in patients who adhere to prescribed use, opioid abusers tend to have significant levels of tolerance and will show symptoms of withdrawal if they abruptly discontinue use. They will also develop cravings or conditioned responses to drug-related stimuli that may hinder abstinence and result in relapses, regardless of the length of abstinence. Social or personal features that may support the diagnosis of OUD include a history of drug-related crimes such as possession or distribution of drugs, forgery, or robbery. In individuals who may have access to opioids, this may translate to illegal activities involving problems with hospital staff or administrative agencies or licensing boards. Personal factors such as divorce, unemployment, or irregular employment are also associated with OUD.<sup>19</sup>

Diagnostic markers for OUD include urine toxicology tests, which can detect the presence of an abused agent for 12 to 36 hours after administration of an opioid. Other commonly abused agents, such as fentanyl, methadone, buprenorphine, and LAAM (L-alpha-acetylmethadol), require more specialized tests that can identify the presence of the agents for several days after administration.<sup>19</sup>

### *Risk Factors for Opioid Use Disorder*

Multiple risk factors can contribute to vulnerability to opioid abuse. These include individual, family, peer, social, and environmental factors, with genetically driven characteristics playing an important direct or indirect role within these domains.<sup>22,23</sup> Understanding who is at risk for misuse, abuse, or overdose can help healthcare professionals diagnose these patients as well as monitor at-risk patients. Data show that some groups are more vulnerable than others. Death rates show more men than women die each year from opioid overdose, along with more middle-aged adults (between 35 and 54 years) and non-Hispanic whites (Figure 3).<sup>6</sup> Those living in rural areas are also more vulnerable, with rates of overdose due to prescription pain medications almost double those of residents of large cities.<sup>13</sup>

### *Assessing Risk for Opioid Use Disorder*

In the primary care setting, risk for opioid abuse among adult patients can be assessed based on the Opioid Risk Tool (ORT) developed by Lynn R Webster, MD. The ORT categorizes patients based on likelihood of risk for future aberrant drug use. However, the ORT is not recommended for use in non-pain populations. The tool assigns points based on gender, personal or family history of substance abuse, age, history of preadolescent sexual abuse, and psychological disease.<sup>24,25</sup>

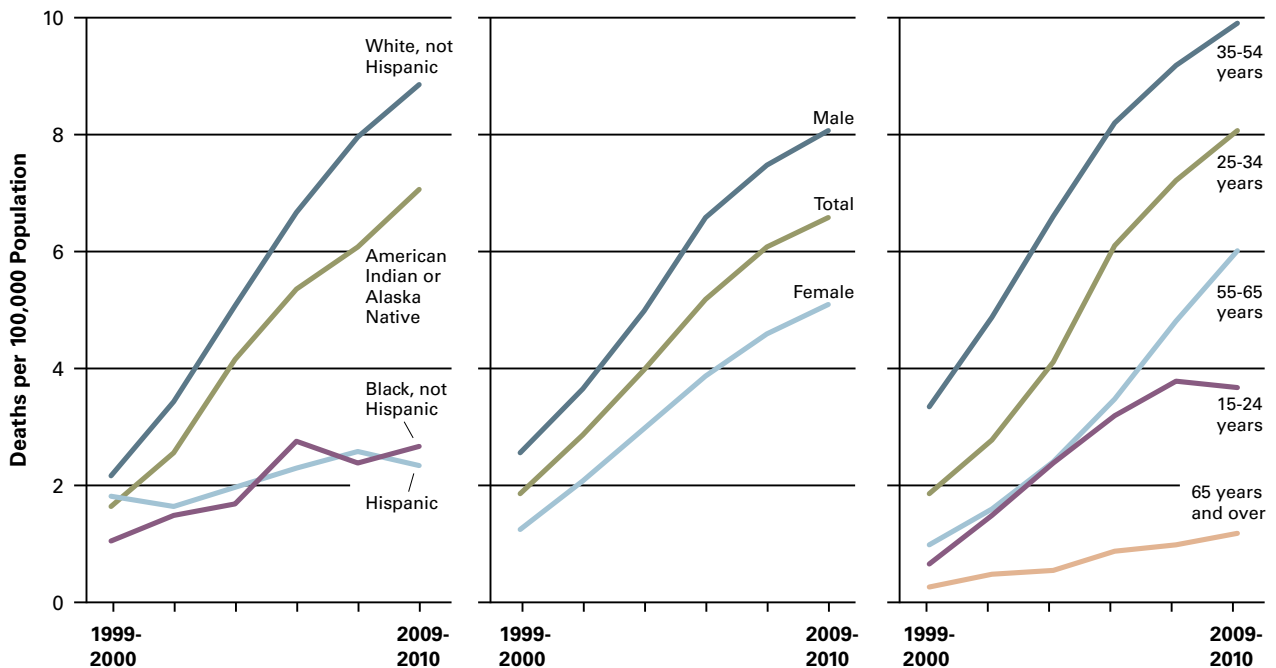
Signs of OUD may not be obvious, especially in patients tolerant of a drug's effects. Clinicians must perform a careful patient history to aid in the diagnosis and assessment of OUD by establishing a good rapport with the patient and asking questions about past use and treatment efforts. Key factors include amount of recent drug use, route of administration, last use, treatment history, and problems resulting from use.<sup>26</sup> A problematic pattern of use can be pinpointed using factors outlined in the most recent DSM, including an increase in the time in the amounts of drug use, unsuccessful attempts to cut down or control use, and lifestyle (work, family, and social obligations) being negatively impacted by drug use, among others.<sup>19,26</sup> Furthermore, it is important that patients on long-term opioid treatment be monitored closely with urine checks, follow-up visits to assess for aberrant behaviors, and possible addiction treatment.<sup>17</sup> Physicians should not dismiss or refuse to treat the patient instead of making a diagnosis of OUD.

Urine drug screening is key to appropriate management; it can detect most opioids for at least 48 hours and up to 4 days after the opioids are administered.<sup>17,27</sup> Blood, hair, saliva, sweat, and nails can also be used in laboratory drug testing, each offering different levels of specificity, sensitivity, and accuracy. Urine testing is the most common because of its ease of administration and sample collection, and because of the speed with which results are available. However, false-negative tests are not uncommon in urine testing—not all opioids can be detected with screening, and false-positive tests can occur with use of common non-opioid drugs or foods (eg, rifampin, poppy seed).<sup>27</sup>

### *Differential Diagnosis*

It is important to distinguish clinically between OUD and the opioid-induced disorders that frequently occur in individuals taking opioids. Opioid-induced disorders are characterized by symptoms such as depressed moods that have their onset during intoxications, as opposed to primary mental disorders. Opioid withdrawal may also result in symptoms of depression, which may require independent clinical attention. Furthermore, OUD should be differentiated from other types of substance intoxication, such as alcohol, sedative, hypnotic, or anxiolytic. However, these substance intoxications can be ruled out based on the presence of pupillary constriction or an adverse reaction to naloxone. The situation may be more complicated when more than 1 drug is being abused. When making a differential diagnosis, symptoms of opioid withdrawal should be considered.

**Figure 3.** Death Rates for Poisoning Involving Opioid Analgesics Among Persons 15 Years and Older, by Race/Hispanic Origin, Sex, and Age: 1999-2000 Through 2009-2010<sup>6</sup>



Rates are age-adjusted, except for age group data. Drug poisoning deaths with the drug type unspecified (up to 25% of the total) are not included. Reprinted from: Health, United States, 2013: with special feature on prescription drugs. Hyattsville, MD: National Center for Health Statistics; 2014.

These include anxiety, restlessness, rhinorrhea, lacrimation, and pupillary dilation, in addition to adverse events associated with opioid use.<sup>19</sup>

Pseudoaddiction should also be considered when diagnosing opioid addiction. Pseudoaddiction is characterized by problematic behaviors resulting from the anxiety associated with pain that is not effectively controlled. The symptoms associated with pseudoaddiction are similar to those of addiction; symptoms may involve escalating doses or impulsively taking doses beyond the prescribed schedule, complaining about the need for more drugs, or aggression. However, in pseudoaddiction, these symptoms tend to disappear when the dose is increased and the pain is adequately controlled.<sup>28</sup>

**Comorbidities**

Individuals with OUD are also at risk for developing depression and antisocial personality syndrome,<sup>19,29</sup> and OUD is considered a risk factor for suicide, including accidental and intentional overdosing.<sup>19</sup> Abuse of other substances, such as alcohol, cannabis, stimulants, and benzodiazepines, are often associated with OUD

because users may depend on them to alleviate opioid withdrawal symptoms. Abuse of intravenous opioids is further associated with other viral infections, such as hepatitis A, B, and C, and human immunodeficiency virus (HIV).<sup>19</sup>

**Functional and Economic Consequences of Opioid Use Disorder**

OUD frequently manifests in symptoms and clinical problems other than intoxication. Infection (ie, hepatitis C, HIV), increased sensitivity to pain (hyperalgesia), narcotic bowel syndrome, and history of accidents and legal problems are common in these patients.<sup>26</sup> Overdose can occur at any time with usage and is more common with the nonmedical use of opioids. In 2010, approximately half of all overdose deaths in the United States (16,652 of 38,329) were caused by prescription opioids.<sup>10,26,30</sup>

Improper use of any opioid drug can result in serious adverse events, including overdose and death, and this risk can be greater with extended-release/long-acting formulations.<sup>15</sup> The age-adjusted death rate for opioid poisoning in those 15 years and older increased from 1.9 deaths per

100,000 population in 1999-2000 to 6.6 in 2009-2010. This rate increased for both males and females, across all age and racial groups. The rate was highest among non-Hispanic white persons 15 years and older (8.9 deaths per 100,000)—3 times the rate among the non-Hispanic black and Hispanic populations (2.7 and 2.4, respectively). Death rates involving opioid analgesics were also higher among males than females (8.1 per 100,000 compared with 5.1), and were the highest in those aged 35 to 54 years (9.9).<sup>6</sup>

Use of opioids in prescribed doses has been associated with a variety of side effects, including activation of the chemoreceptor trigger zone for emesis, reducing gastrointestinal motility, and increasing vestibular sensitivity, resulting in nausea, vomiting, and severe constipation.<sup>31-33</sup> Opioid use is also associated with reduced mucous membrane secretions, causing dry mouth and nose.<sup>19</sup> Other adverse effects of opioids include somnolence, mental confusion, euphoria, and, in high doses, respiratory depression.<sup>32-34</sup>

It is common for those experiencing a euphoric response to an opioid to misuse or abuse the drug by snorting the drug or injecting it, in order to intensify the experience. These modes of administration can increase the risk of medical complications that result from opioid use, including overdose.<sup>35</sup>

In patients abusing the drug by injecting it, sclerosed veins, or tracts, and puncture marks are visible on their upper extremities. Up to 90% of injection opioid users test positive for hepatitis A, B, or C virus, for either the hepatitis antigen or the antibody. The prevalence of HIV infection is also high in patients with OUD. The resulting immune suppression may lead to other infections, such as tuberculosis.<sup>19</sup>

Opioid misuse, abuse, and dependence creates a considerable economic burden for managed care organizations, because abusers have high direct medical and pharmacy costs. In 2011, approximately 420,040 ED visits were related to use of opioid analgesics.<sup>12</sup> Patients who misuse opioids had higher rates of comorbidities and greater healthcare resource use, placing a significant economic burden on healthcare payers. Annual healthcare costs related to opioid abuse are estimated to be \$25 billion per year.<sup>36</sup> Based on claims data filed between 2003 and 2007, it is estimated that mean excess annual cost per privately insured opioid abuse patient was \$20,546, and the mean excess cost per caregiver \$1010. For Medicaid patients in the state of Florida, the mean excess cost per patient was \$15,183.<sup>37</sup> The total societal cost of prescription opioid abuse was estimated at \$55.7 billion in 2007. This included \$25.6 billion in workplace costs due to absenteeism, dis-

ability, or lost earnings because of death, and \$5.1 billion in criminal justice costs, including correctional facility use and police costs.<sup>36</sup>

### Demographic Trends in Opioid Use Disorder

Opioid prescribing has been found to vary widely among different states in this country. For example, higher prescription rates are seen in the South, and this cannot be explained by differences in the underlying health status of the patients in these regions.<sup>3</sup>

Southern states, especially Alabama, Tennessee, and West Virginia, have the highest number of prescriptions for opiates per person (138-143 prescriptions per 100 people). Alabama and Tennessee had 2.5 times more prescriptions written per person than Hawaii and California, the 2 states with the lowest numbers per person. However, even in the cases of Hawaii and California, there were 52 and 57 prescriptions written per 100 people, respectively—more than 1 prescription for every 2 people. States in the Northeast, especially Maine and New Hampshire, had the most prescriptions for long-acting and high-dose opioid analgesics per person.<sup>3</sup>

The geographic variation may be due in part to the lack of consensus throughout the country on how and when to prescribe opiates, and in what dosages. However, states have individually taken action to curtail this abuse. Florida, which had the highest prescription opiate sales per person in 2010,<sup>13</sup> reduced the state's overdose deaths from oxycodone by more than 50% in 2012 by regulating pain clinics and drug monitoring programs, and by stopping healthcare providers from dispensing prescription pain medication from their offices. Florida now ranks below average in prescriptions for opiates per person (73 per 100 persons).<sup>3</sup> New York, which now has the fourth-lowest number of prescriptions per person for opiates in the nation, achieved a 75% reduction in patients shopping for multiple prescribers between 2012 and 2013 by requiring that prescribers check the state's prescription drug monitoring program before writing prescriptions for opioid analgesics. Tennessee saw a 36% reduction in prescription shoppers during the same time frame by enacting a similar policy.<sup>3</sup>

### Management Solutions and Interventions

Curtailling abuse requires a concerted effort on the part of regulatory agencies, pharmaceutical companies, and prescribers. Federal and state regulatory agencies need to implement programs that monitor and limit the prescriptions being written and filled. Pharmaceutical

agencies have initiated development of abuse-deterrent formulations that may meaningfully deter abuse, even if they cannot fully prevent it. Education and consensus on the part of healthcare professionals on prescribing habits and recognizing appropriate patients are important in preventing abuse and intervening when abuse is detected.

Federal support to state programs includes increasing access to mental health and substance abuse treatments and treatment centers through the Affordable Care Act. National healthcare agencies can support healthcare practitioners by providing evidence-based guidance for decision making in the management of opioid use and the treatment of OUD.<sup>3</sup>

Following the examples set by Florida, New York, and Tennessee, states can increase use of prescription drug monitoring programs, track prescriptions, and limit office-based dispensing of prescription pain medication. States also need to consider altering policies to reduce risky prescribing practices and detect and address the problem of inappropriate prescribers. Additionally, ensuring access to substance abuse treatment is important for addressing the needs of existing addicts and potentially curbing future abuse.<sup>3</sup>

Abuse-deterrent technologies manipulate the delivery system of the opiate with the intention of making misuse less appealing or less rewarding, although most can do little to deter abusers from nullifying effectiveness simply by swallowing an excess amount of pills. Common abuse-deterrent strategies include<sup>38</sup>:

- *Physical and/or chemical barriers*: Using physical and chemical barriers that limit drug release, alter the drug upon mechanical manipulation, or resist extraction of opioid using common solvents.
- *Agonist/antagonist combinations*: Adding an opioid antagonist, which becomes clinically active when the dosage form is physically manipulated (crushed or diluted for injection or snorting) and limits or interferes with the euphoria associated with abuse.
- *Aversion*: Addition of substances that result in unpleasant effects, such as irritating the nasal mucosa, if the dosage form is manipulated or used inappropriately at a higher dosage than directed.
- *Delivery system (including use of depot injectable formulations and implants)*: Designing a sustained-release injectable formulation or a subcutaneous implant that may be difficult to manipulate.

Finally, healthcare providers need to educate themselves to better identify patients at risk for abuse or diversion of opioids, and ensure that their patients are also educated

on the risks and benefits of treatment with opioids. This includes educating patients on the possibility of addiction, the importance of appropriate use, and alternative strategies for pain management. Healthcare practitioners need to ensure that they are screening their patients for substance abuse and mental health problems, and monitoring them throughout their treatment process, to identify those at high risk for abuse, and discern between patients taking their medications appropriately and those who are becoming addicted to, abusing, or diverting their prescription pain medication. Managing patients with OUD while they undergo treatment with methadone or buprenorphine is also critical to a successful withdrawal process.

## CONCLUSION

The continued increase in misuse and abuse of opioid analgesics stems from their increased use over the past 25 years. The staggering increases seen in the amount of opiates prescribed and sold in the United States do not represent an overall change in the amount of pain that Americans report. Therefore, it can be surmised that overprescribing of these drugs has helped enable abuse and overdose deaths by increasing diversion rates and/or access for the patient abuser. Implementing strategies to target patients at risk for abuse or misuse of opioids requires a concerted and coordinated effort on behalf of federal and state governments along with healthcare practitioners, both primary care physicians and specialists, to change prescribing habits, treatment options, and monitoring strategies.

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