

# PHARMACY

R E V I E W

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## Opioid Drug Overdoses: A Prescription for Harm and Potential for Prevention

**Abstract:** *This article reviews the burden of accidental poisonings from opioid overdoses in the United States, describes several current federal- and state-level prevention strategies, and illustrates several approaches taken to prevent deaths from opioid overdoses and reduce emergency department visits for chronic pain. One approach, Project Lazarus in North Carolina, is a community-based, secondary prevention program that trains medical care providers to coprescribe naloxone with opioids and provide education to patients who are at risk of opioid overdoses and to their families and peers.*

**Keywords:** prescription drugs; drug overdose; opioid; naloxone; Project Lazarus

The purpose of this review is to document unintentional fatal poisonings in the United States, identify the more prominent substances that cause or contribute to these deaths, and illustrate how prevalence and substance vary by state. We describe interventions that are being used to prevent fatal drug-related overdoses and present a novel approach in North Carolina that serves as a safety net for those who use opioids

and are not yet willing to or capable of responding to efforts to prevent opioid overdose and abuse.

### The Burden of Drug Overdoses in the United States

Injury deaths, like deaths from motor vehicle crashes and firearms, are so commonplace today that they almost go unnoticed. However, deaths from acci-

oxycodone, hydrocodone, and methadone now make the headlines of national newspapers.<sup>5-10</sup> Press coverage on the drug-related deaths of Anna Nicole Smith, Heath Ledger, and Chris Benoit, as well as recovery from addiction by Eminem, Rush Limbaugh, the Osbournes, and Mindy McCready, points to the pervasiveness of the problem. Michael Jackson's death on June 25, 2009, widely alleged at the time of this writing to be related to overdose of a prescription

**In our program model, naloxone distribution is one component of a multifaceted community response, all of which together is intended to reduce opioid overdose mortality.**

dental poisonings or prescription drug overdoses are widely publicized. Almost all (92%) of unintentional poisoning deaths involve drugs.<sup>1-4</sup> Poisoning deaths that involve prescription opioids such as

drug(s), is only the most recent example. Regrettably, these celebrity events belie the universality and the seriousness of the drug overdose problem in the United States.

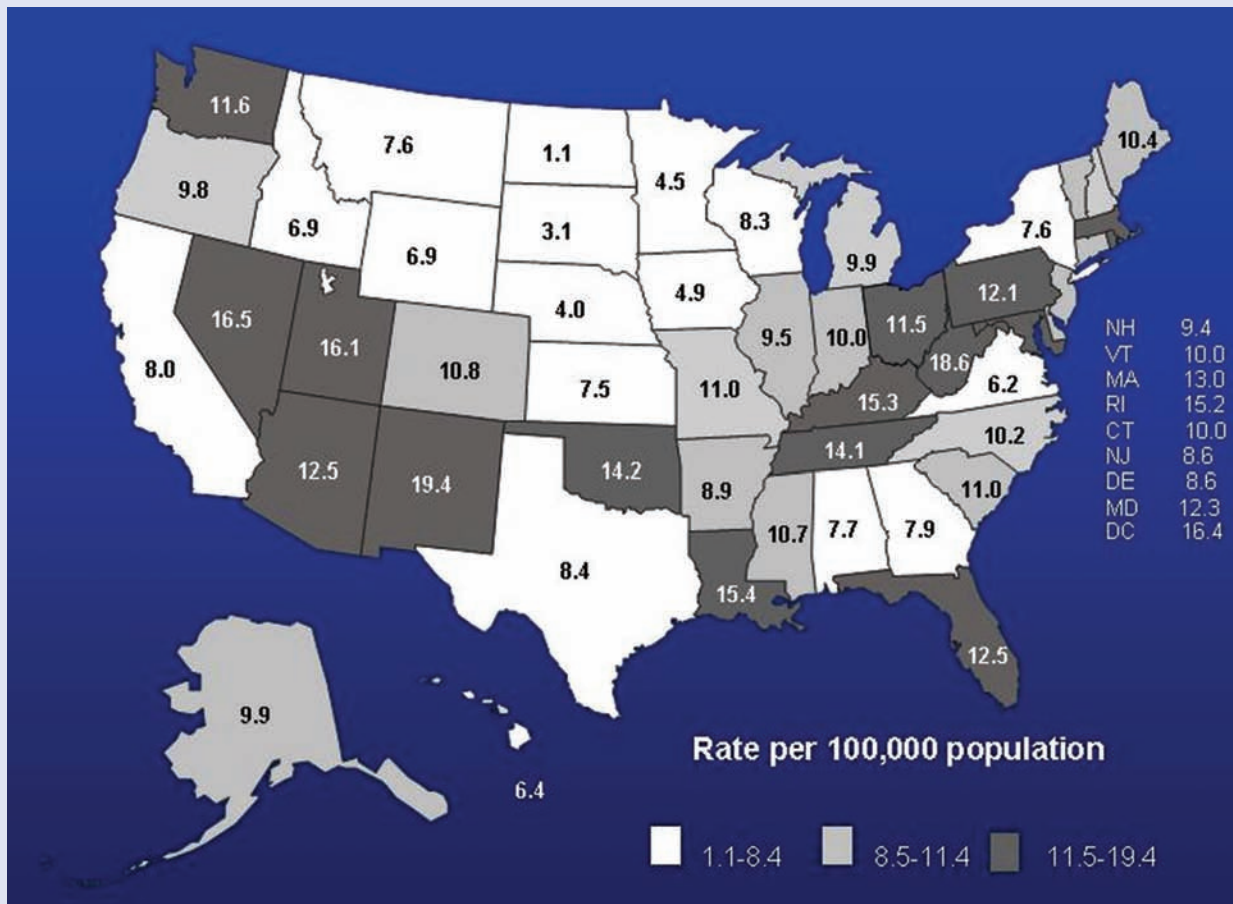
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**Figure 1.**

Drug overdose death rates by state, 2006.



Source: Len Paulozzi, MD, MPH, Division of Unintentional Injury Prevention, National Center for Injury Prevention and Control, Centers for Disease Control and Prevention. Prepared August 2009..

The Centers for Disease Control and Prevention (CDC) *Morbidity and Mortality Weekly Report (MMWR)* data, published the day after Michael Jackson's death, show that the mortality rate for accidental poisonings (the third leading cause of injury death in the United States in 2006) has more than doubled in the past 30 years.<sup>11</sup> From 2005 and 2006, accidental poisoning deaths (almost three quarters of all fatal poisonings) increased 13% to 27 531 deaths in 2006, resulting in an age-adjusted mortality rate of 9.14 per 100 000 people. In contrast, there was no change in the age-adjusted mortality rates per 100 000 population for either motor vehicle traffic (14.43, based on 43 664 deaths) or firearms (10.2, based on 30 896 deaths).<sup>11</sup>

Despite statistical stability from large populations, national mortality statistics for accidental poisonings can be misleading as they often mask the variability that occurs by geography and by substance. In 2006, state accidental poisoning mortality rates ranged from a low of 1.1 deaths per 100 000 in North Dakota to 19.1 deaths per 100 000 in New Mexico (Figure 1).<sup>12</sup> Within-state variation can sometimes be even more pronounced. For example, 2-year (2006-2007) mortality rates for accidental poisonings in North Carolina ranged from a low of 0 deaths to a high of 31.9 deaths per 100 000 residents per year,<sup>13</sup> a rate 3.5 times higher than the 2006 national mortality rate of 9.14 per 100 000 per year, as reported by the CDC.<sup>13</sup>

Of equal importance is the variability in the type/kind of drugs that cause or are implicated in these fatal overdoses in these different locations. Nationally, half (50.1%) of fatal drug-related deaths are due to overdoses of prescription and over-the-counter drugs, and the other half are due to illicit drugs (39.3%) and unspecified narcotics (10.6%).<sup>14</sup> Some geographical areas are responsible for the greatest number of heroin and cocaine deaths. For example, in New Mexico, the state in 2006 with the country's highest mortality rate from accidental poisonings, heroin is associated with more drug-related deaths than any other drugs.<sup>15</sup> However, in most other states, prescription opioids, such as fentanyl, hydrocodone, hydromorphone,

methadone, morphine, and oxycodone, are associated with the greatest number of fatal overdoses.<sup>16-18</sup> There appears to be a linear relationship between the amount of prescribed opioids and the magnitude of misuse and abuse that results in fatal overdoses, but the relationship is complex.<sup>16</sup> For example, the absolute number of methadone-related deaths is less than the total number involving hydrocodone, morphine, or oxycodone,<sup>1</sup> yet sales of methadone for outpatient use increased about 300% between 2000 and 2005,<sup>19,20</sup> whereas the distribution of oxycodone and hydrocodone roughly doubled.

Nevertheless, methadone-related deaths have increased proportionately more than other narcotic-related deaths since 1999.<sup>1</sup> It appears that the lethality of a drug (in this case, methadone) may not be linearly proportional to its prevalence in the community and may be strongly influenced by the pharmacokinetic/pharmacodynamic properties of the drug, the reasons it is used, and the population that uses it.<sup>21</sup> Thus, it takes more than just surveillance and monitoring to understand the problem and potential prevention strategies.

### Prevention of Unintentional Poisoning

Fatal drug overdoses are recognized as a preventable problem.<sup>22,23</sup> Many states with higher than average prescription drug mortality rates have already begun designing, implementing, and evaluating opioid prevention strategies, and federal agencies are beginning to respond. The CDC's National Center for Injury Prevention and Control recently held 2 expert meetings<sup>24</sup> in 2008-2009 to address the problem. There is a National Prescription Drug Abuse Prevention Strategy<sup>25</sup> and a US Department of Justice National Prescription Drug Threat Assessment Program.<sup>26</sup> The Food and Drug Administration (FDA) has initiatives to monitor the safety of long-acting opioids (ie, the Risk Evaluation and Mitigation Strategy [REMS]), the Drug Enforcement Agency (DEA) has requirements for accounting of products in the

pharmaceutical supply chain and investigations into breaches, and the Substance Abuse and Mental Health Services Administrations (SAMHSA) has initiatives intended to expand access to drug treatment services. However, with the exception of SAMHSA's efforts, these programs are largely focused on supply-side reductions and have ignored decades of experience from other countries showing that demand reduction (ie, through widespread and free access to substitution therapy) in the context of harm reduction measures (ie, distribution of sterile injection equipment) can reduce the number of opioid overdose deaths, accompanied by dramatic and sustained decreases in drug-related crime.<sup>27-29</sup>

State-level prevention programs have had a tendency to focus most on physicians who prescribe opioids for pain management and patients who accidentally overdose, misuse, or abuse their prescribed drugs. Physicians need clear, evidence-based best practices that serve as clinical guidelines for prescribing opioids for the management of chronic (noncancer) pain in the emergency room and in the out-patient setting. Dozens of guidelines are already available and can be found at [www.guidelines.gov](http://www.guidelines.gov). Patients also need to be carefully screened to identify those at increased risk of opioid overdose. However, overdose potential must be seen as a separate but parallel phenomenon that can exist in the absence of abuse, diversion, and addiction.

The Utah drug misuse, abuse, and overdose prevention plan ("use only as directed") is a model state-based program that provides guidelines and resources for medical care providers and patients. In 2007, unintentional prescription pain medication overdoses were the number one cause of injury deaths in Utah, exceeding even motor vehicle crash deaths. The Utah Department of Health looked to its community and helped develop patient safety guidelines ([www.useonlyasdirected.org](http://www.useonlyasdirected.org)). The medical care practitioner guidelines developed are evidence based and applicable for the treatment of both acute and chronic pain.<sup>30</sup> Guidelines for patients include safety precautions, signs of abuse/misuse, signs of

addiction, signs of when to seek help, options/locations for treating addiction or substance abuse, and safeguarding and disposal of medications.

The Spokane, Washington, emergency department (ED) protocol, The Consistent Care Program, available at [www.consistentcare.com](http://www.consistentcare.com), is a novel, city-based pilot program for improving the use of opioids for the treatment of patients with chronic pain who inappropriately use the emergency department as their primary source of medical care.<sup>31</sup> The core principles of the program involve procedures to prevent enabling, nontherapeutic (patient) behavior; coordinate care among EDs in the city and in primary care; keep the primary care provider in control; enable patients to treat themselves; and protect patients from prescription overmedication and abuse. If a patient returns to the ED often for symptoms of chronic pain, the chart is flagged. The ED physician reviews the Consistent Care guidelines developed by the ED's Care Guidelines Committee, provides the appropriate diagnostic assessment, does not prescribe an opioid outside of the predetermined guidelines, refers the patient to the ED case manager, and then discharges the patient back to the care of the primary care provider. Pilot study results suggest a 50% drop in the number of visits in the Consistent Care Program, including a substantial decrease in the costs associated with each ED claim.

### Rescue Approaches

A rescue response is often necessary because overdoses are still going to occur despite prevention efforts. Traditional treatment resources that are often used as surrogate rescue programs (eg, emergency medical services and EDs) are often inadequate, and some may even be contributing to the problem. Many drug overdose prevention programs are working with their local emergency departments to review and revise their administrative policies on writing prescriptions for opioids to patients who use emergency rooms as their source of medical care for chronic pain. Review of medical examiner data reveals that well

over half of the people who accidentally died from drug overdoses were dead prior to the arrival of emergency medical services,<sup>32</sup> clearly pointing to the need for community-based rescue tools and education to prevent fatalities.

Among the most promising interventions to date has been the provision of naloxone (a potent mu-opioid receptor antagonist used as the standard antidote for opioid-induced respiratory depression) to those at greatest risk for opioid overdose, accompanied by education to family and peers on how to recognize and reverse an opioid overdose.<sup>33</sup> Used throughout the United States and Europe, these programs have been credited with preventing overdose deaths in thousands of individuals. From our decade of experience with preventing opioid overdoses, we believe that prevention programs will ultimately fall short of the community's expectations if they do not provide a robust rescue component, such as the dispensing of naloxone to at-risk patients and the concurrent education of their families and peers to recognize the symptoms of an overdose and the steps to treat the overdose appropriately before the arrival of traditional medical services. The North Carolina programs in Wilkes County, described below, provide a model for designing and implementing a community-based and accepted opioid overdose rescue program, specifically targeted at preventing opioid overdoses.

Project Lazarus ([www.projectlazarus.org](http://www.projectlazarus.org)) in North Carolina uses a harm reduction approach as an adjunct to its innovative drug prevention program. It is part of the Chronic Pain Initiative (CPI) that was developed by the Northwest Community Care Network (NCCN) in response to the high cost of caring for chronic pain patients and persistent prescription drug-related overdoses among Medicaid recipients. The NCCN is one of 15 state Medicaid networks, with 70 primary care practices, 500 primary care practitioners, and approximately 58 000 Medicaid beneficiaries in 6 rural North Carolina counties. The NCCN, as a member of Community Care of North Carolina, was honored as an award winner for Innovations in American

Government by the Ash Institute for Democratic Governance and Innovation at Harvard's JFK School of Government in 2007. The CPI and broader community efforts in Wilkes County include steps to more appropriately treat chronic pain while reducing the unintended consequences of opioid availability. It includes patient and prescriber education, support groups for pain patients, distribution of a pain management toolkit, and modification of emergency department opioid use. Other important features are case management of chronic pain patients who inappropriately use the ED for primary care, a pharmacy home, expanded use of pain contracts, utilization of the controlled substances reporting system, hiring a dedicated prescription drug diversion law enforcement officer, and increasing access to and convenience of local substance abuse treatment options (including increasing the number of physicians authorized to prescribe buprenorphine for addiction). The program includes teaching and providing tools to encourage the proper storage and disposal of medications and other means of limiting diversion and/or improving medical care. These are the community-level primary prevention strategies for reducing potential fatal exposure to opioids. Providing naloxone rescue medication is a safety mechanism or means of preventing deaths from opioid-induced respiratory depression. In our program model, naloxone distribution is one component of a multifaceted community response, all of which together is intended to reduce opioid overdose mortality.

Evidence suggests that those dying from opioid poisoning in North Carolina are a mix of pain patients taking opioids incorrectly or inappropriately ("misusers"), as well as nonmedical opioid users ("abusers"). Most of those who died from prescription opioid poisoning had received a prescription for the medication in the months prior to death.<sup>32</sup> Death from opioid poisoning often occurs over 1 to 3 hours after exposure to opioids,<sup>33</sup> and most of these deaths occur in the presence of others.<sup>34-50</sup> Because oftentimes emergency assistance is received too late to be effective,<sup>32</sup> the North Carolina

Medical Board determined that peer- or family-administered treatment (eg, naloxone) to opioid overdoses should be considered. Naloxone is the antidote used in emergency medical settings to reverse respiratory depression due to opioid poisoning. It is a prescription medication that is not a controlled substance and has no abuse potential. A review of North Carolina statutes by legal scholars confirmed that prescribing naloxone to prevent an opioid-induced overdose is fully consistent with state and federal laws.<sup>51</sup> As a public health prevention strategy in areas with high heroin overdose rates, naloxone has been successfully given to drug users (along with education) to prevent overdose deaths. No systematic increase in risk taking or drug use has been documented in 13 years of international and domestic experience, and survivors were more likely to reduce injection frequency, discuss substance abuse treatment options, and enter drug treatment in some studies.<sup>39,47,52,53</sup>

The educational component of Project Lazarus is conducted in the privacy of a physician's office and does not require significant additional time from the physician or the office staff. The video covers patient responsibilities in pain management, including storage and disposal of opioid medications, how to recognize an opioid overdose, rescue breathing and the recovery position, naloxone administration, the importance of calling 911, and options for substance abuse treatment. At the end of the video and after completing the enrollment forms, patients receive the naloxone kit free of charge from their medical care provider, alongside any prescriptions for pain management that they may require. Following program models in New Mexico and Massachusetts, a formulation of intranasal naloxone is used in the Project Lazarus naloxone kit. As it is assumed that the patient will not be able to self-administer the naloxone, education of peers and family members is critical, and they are invited to take part in the training with the person receiving naloxone.


For those with substance abuse disorders, harm reduction interventions aimed at preventing the mortality associated



with substance abuse, such as prescription naloxone, do not aim to change the trajectory of substance use progression instantaneously. Rather, the programs are intended to support the more immediate goal of preventing deaths, in the hope that the person who is abusing narcotics is alive long enough to realize the future goal of recovery. Project Lazarus is consistent with this approach while maintaining patient safety as the core principle.

Project Lazarus could potentially save thousands of dollars in medical costs and lost productivity and tens of millions of dollars in North Carolina each year.<sup>54,55</sup> The ongoing and postproject process and outcome evaluation of Project Lazarus will determine the broad feasibility of coprescribing naloxone to patients thought to be at increased risk of opioid-induced respiratory depression in the rest of North Carolina and in the United States.

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