

## **Executive Summary**

### **Introduction**

Fatal poisonings related to prescription opioids are a serious public health problem in the United States, more than tripling between 1999 and 2006 [1]. The alarming increase in deaths has paralleled the rise in prescriptions for pain [2], prompting the U.S. Food and Drug Administration (FDA) to call for a risk evaluation and mitigation strategy (REMS) for opioids. Given the substantiation of the relationship between opioid prescribing and opioid-related harms, it may appear indisputable that a simple reduction in the availability of opioids per unit would solve the problem of heightened danger from overdose. However, the deaths are multifactorial, dictating that solutions must be also. Numerous factors contribute to opioid-related deaths, and these must be analyzed and understood in relation to one another. To do otherwise risks replacing one public health problem (death from overdose) with another (non or under treatment of pain), a scourge that can also be deadly.

On July 31, 2009, a panel of national pain experts, regulators, health-care policy makers and epidemiologists met to explore the existing evidence on the causes of opioid-related overdose deaths and to suggest possible solutions. A list of panel members and their affiliations appears in Appendix A. The objectives of the panel were to:

- Examine the national and state data on the frequency of opioid-related deaths
- Evaluate the best evidence available on the possible root causes and risk factors for opioid-related deaths
- Review the factors common to known deaths and extrapolate this information to help determine solutions

The expert analysis and commentary that followed led to the publication of this special supplement of *Pain Medicine*. The expectation is that the supplement will advance research, inform public discussion, help craft quality medical education programs, and facilitate safer opioid prescribing and use.

### **Summary of Articles**

The supplement is divided into two sections: *Defining the Problem and Finding Solutions*. The Table of Contents complete with a full listing of authors can be viewed in Appendix B.

### *Defining the Problem*

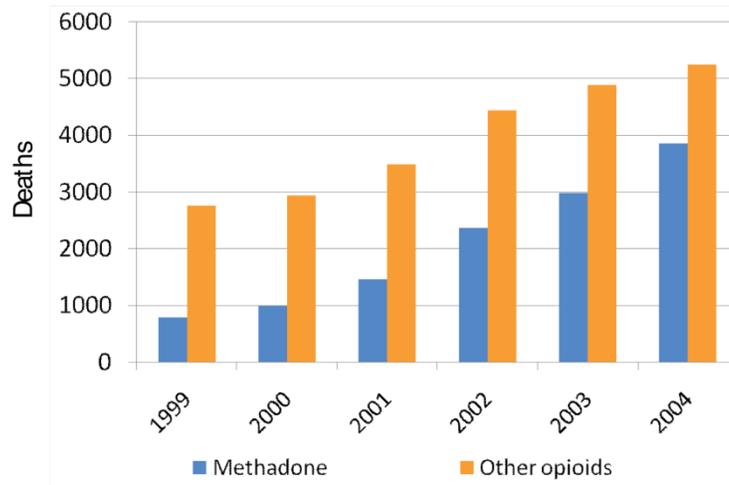
The expert panel's collaboration produced the central manuscript of the supplement, "An Analysis of the Root Causes for Opioid-Related Overdose Deaths in the United States." It presents a summary of state and national data showing a pattern of increasing overdose deaths related to prescription opioids beginning in the early 2000s. Although the literature is limited, certain risk factors and demographic trends emerged.

Methadone represented a disproportionate percentage of opioid deaths. Analysis revealed methadone involvement in a third of opioid-related deaths nationwide (Figure 1), although methadone represents less than 5% of total opioid prescriptions dispensed (Figure 2).

Additional factors in opioid-related deaths included:

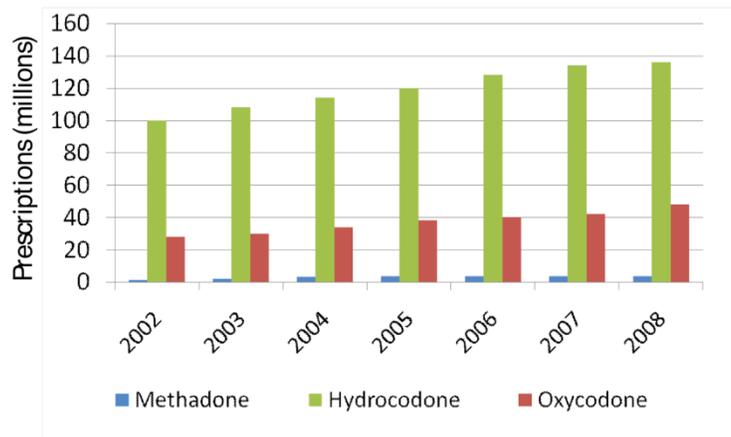
- Prescribing errors by medical providers
- Nonadherence to medical direction by patients
- Nonmedical use by nonpatients
- Misuse in connection with anxiety, depression, substance-use disorders, or other mental illness
- Complications arising from medical conditions, including sleep apnea and cardiac irregularities
- Unauthorized mixing of opioids with other central nervous-system depressants, such as other opioids, benzodiazepines or other tranquilizers, and antidepressant drugs.
- Mixing of opioids with illicit drugs or alcohol
- Payer policies that mandate methadone as first-line therapy
- Middle age
- Male gender, although females death rates are catching up
- Greater increase in deaths in nonmetropolitan vs. metropolitan counties

**Figure 1. Methadone and Other Opioid Deaths in the United States**



Source: National Drug Intelligence Center, Drug Enforcement Administration, U.S. Department of Justice. Methadone diversion, abuse, and misuse: deaths increasing at alarming rate. Product No. 2007-Q0317-001. Johnstown, PA: November 2007.

Figure 2. Total Prescriptions Dispensed in the United States



Source: IMS Health, National Prescription Audit Plus™ (NPA Plus™)

Adapted from: Methadone Associated Overdose and Mortality Assessment Meeting, Drug Enforcement Administration, Office of Diversion Control; June 29-30, 2009; Arlington, VA.

Several states began examining the problem with Utah among the leaders. In answer to reports of rising harm from prescription drugs, epidemiologists at the Utah Department of Health (UDOH) began in 2004 to collect and analyze records from multiple datasets. By linking data from vital statistics, emergency departments, and the state prescription registry, among other sources, the analysts began to find answers about the scope of the problem, the types and sources of implicated drugs, the involvement of legitimate prescriptions, and the individual risk factors for opioid-related death. The findings are summarized in “Studying Adverse Events Related to Prescription Drugs: the Utah Experience,” by Christina A. Porucznik, PhD, MSPH, and colleagues.

A key section describes results from a survey of family and friends of the deceased that is the first of its kind to our knowledge. Its findings are revealing. Of 240 decedents whose deaths involved prescription drugs:

- 63% were unemployed during the last 2 months of life.
- 27% of individuals were uninsured at the time of death (compared with the state uninsured rate of 14%).
- 49% had ever received treatment for substance abuse.
- Specific drugs that the decedent had ever used during his or her lifetime included high rates of marijuana (48%), cocaine (25%), methamphetamine (23%), and heroin (17%).
- 49% were reported to have been diagnosed with a mental illness by a healthcare provider.
- 24% of decedents had been hospitalized for psychiatric reasons.

Another article further examines risky behaviors sometimes displayed by opioid-treated patients. In “Psychological Variables Potentially Implicated in Opioid-Related Mortality as Observed in Clinical Practice,” noted pain psychologists Steven Passik, PhD, and his colleague, Amy Lowery, PhD, shed light on many mental-health and behavioral disorders as supported by the scientific literature and seasoned clinical observation. The discussion covers certain personality disorders as well as traits like impulsivity, catastrophizing, chemical coping, demoralization, and sensation seeking. The authors characterize such behaviors as likely contributors to opioid-related morbidity and mortality and suggest opioid-management strategies and psychotherapeutic interventions.

To round out the discussion of vulnerable patients, Martin Cheatle, MD, discusses the possible contribution of suicides to the total deaths related to opioids in “Depression, Chronic Pain, and Suicide by Overdose: On the Edge.” In examining the unrelenting toll of chronic pain, depression, and other challenges experienced by opioid-treated patients, Cheatle posits that some deaths due to

opioids may be unrecognized suicides. Recommendations are offered for screening, suicide prevention, and interventions.

System dynamics modeling is an emerging science that has been used to study cocaine abuse and prevention policy, among other public health problems. It works by simulating interactions among the key elements of a system with the aim of creating a model that replicates system behavior. Its potential value is examined in the context of opioid-related mortality in “Reducing Overdose Deaths Associated with Pharmaceutical Opioid Treatment of Chronic Pain: Analyzing Interventions Using a System Dynamics Model.” Authors Wayne Wakeland, PhD, et al, explore various interventions, including prescriber education programs and tamper-resistant opioid formulations, and report on their potential outcomes for opioid-related harm. The investigators report that prescriber education is likely to decrease deaths but through decreased prescribing that could reduce availability of medication for patients in pain. The simulation found that less abuseable formulations reduced deaths but increased prescribing, which caused overall deaths to rise. Therefore, the model appears to have value if metrics are carefully selected and negative impacts managed.

To reduce opioid-related harm, it is clear that patients need counseling on regimen adherence. Medical providers also need clarification on safe prescribing methods. In “A Review of Forensic Implications of Opioid Prescribing with Examples from Malpractice Cases Involving Opioid-Related Overdose,” authors Ben A. Rich, JD, PhD, and Lynn R. Webster, MD, analyze the impact of legal and regulatory proceedings on prescribing habits, particularly pertaining to provider error. The analysis takes place against the backdrop of 20 fatal overdoses that led to malpractice suits against physicians. In a review of decedent medical records to determine the main causes for the fatalities, methadone again emerges as a key factor, determined to be the principal cause of death in 10 or 50% of the cases. Hydrocodone was second at 4 deaths (20%). Thirteen deaths (65%) occurred within the first week after a prescription dosage change. Additional factors are presented in Table 1.

**Table 1. Summary of Medical Records Review**

Observation	N=20	%
Morphine equivalent dose > 60 mg at time of death	20	100
Pain level at proximate time of death > 6/10	20	100
Decedents had been taking opioids > 6 months	20	100
Complaint of or signs of respiratory infection at time of death	3	15

History of snoring	12	60
Known history of sleep apnea	6	30
Evidence of current or past substance-use disorder	8	40
Diagnosis of mental-health disorder	14	70

## *Finding Solutions*

Long-term studies are needed for precise analysis of opioid-related deaths but take time to fund, complete, analyze and publish. Until such time, it is critical to implement solutions based on current evidence to reverse the trend of unnecessary deaths. This section of the supplement presents descriptions of selected programs and initiatives aimed at curbing opioid-related death and their outcomes. The potential for replication in other states or by other institutions is unknown but bears investigation.

In 2008, the Utah legislature funded a state prescription pain medication program to provide for physician and patient education and to launch a media campaign to raise public awareness of prescription drug-related danger. The program's activities and outcomes are summarized in "State-Level Strategies for Reducing Prescription-Drug Overdose Deaths: Utah's Prescription Safety Program," authored by the program's manager, Erin Johnson, and colleagues. The "Use Only As Directed" media campaign was one arm of this effort, airing TV commercials between May 2008 and April 2009. Clinical guidelines on prescribing opioids for the treatment of pain were published and made available to providers in March 2009 [3]. The program distributed more than 2,800 copies of the prescribing guidelines and more than 120,000 copies of print materials, including bookmarks, patient information cards, and posters. Following program implementation, non-illicit prescription drug deaths decreased by 14% in 2008 compared 2007, the largest such decrease since 1994.

Utah's quality improvement agency, HealthInsight, conducted the provider education component of Utah's prescription drug program. An overview of the program is given in "Provider detailing: an intervention to decrease prescription opioid deaths in Utah," a manuscript contributed by Susan Cochella, MD, MPH, and Kim Bateman, MD.

Three of the key messages of the detailing were:

- 1) Avoid using long-acting opioids for acute pain
- 2) Access prescription monitoring data to help detect diverters
- 3) Realize the critical importance of risk assessment and increased monitoring

A total of 581 physicians and numerous nonphysician health-care workers participated in 46 presentations. Among the program materials were six provider prescribing practices (Table 2). Follow-up surveys completed by 366 participants at 0 months, 82 participants at 1 month, and 29 participants at 6 months revealed the impact of the program as follows:

- 60% to 80% of providers reported no longer prescribing long-acting opioids for acute pain or with sedatives.
- 50% noted using Utah’s controlled-substances database during patient care and utilizing lower starting doses and slower escalations.
- 30% to 50% reported obtaining EKGs and sleep studies on appropriate patients, using patient education tools, and implementing Utah’s prescribing guidelines.

Because knowledge deficits on the part of healthcare providers require an educational remedy, this example of a state-based educational initiative may be helpful in crafting similar programs.

**Table 2: Six Practices for Safe Opioid Prescribing**

- 1 Start low and go slow (refers to dosing)
- 2 Obtain sleep studies for all patients on moderate or high doses of any long-acting opioid
- 3 Obtain EKGs for methadone dose increases to and above 50mg/day (to address potential QT prolongation)
- 4 Avoid sleep aids and benzodiazepines with opioids
- 5 Avoid long-acting opioids in acute pain
- 6 Educate patients and their families about risks

Sources: Website of the “Use Only as Directed” campaign. Utah Department of Health. Available at <http://www.useonlyasdirected.org>. Adapted from website of the Zero Unintentional Deaths campaign. Available at <http://www.zerodeaths.org>.

In another state, North Carolina, a single project united multiple state and local agencies and community groups in working toward a reduction of prescription drug overdose deaths. Su Albert, MD, MPH, and co-authors summarize the program’s components and impact in Wilkes County, which posts some of the country’s highest overdose rates, in “Project Lazarus: Community-Based Overdose Prevention in rural North Carolina.” The components include community activation and coalition building, monitoring and surveillance data, and the provision of naloxone, a medication that reverses the effects of opioids, to opioid-treated patients judged to be at high risk for overdose.

Results are preliminary, but unadjusted data for Wilkes County showed:

- The overdose death rate dropped from 46.6 per 100,000 in 2009 to 29.0 per 100,000 in 2010

- The number of victims who had received prescriptions for the substance implicated in their fatal overdose from a Wilkes County physician decreased from 82% in 2008 to 10% in 2010.

The next topic addressed within the supplement is the need for better death-causation reporting and analysis in deaths related to opioids and other prescription drugs. “Obtaining adequate data to determine causes of opioid-related overdose deaths,” by Lynn R. Webster, MD, and Nabarun Dasgupta, MPH, call for an expanded death certificate to more precisely delineate the involvement of opioids as a cause or contributory factor and to record patient characteristics to aid analysis, including, body mass index (BMI), duration of opioid usage, daily average dose during the last two weeks of life, and histories of chronic pain/medical conditions, substance abuse, and mental illness/psychiatric diagnoses. In addition, the article argues for improvements to opioid toxicology categories that are used to classify and code cause-of-death data to improve identification of individual drugs and classes most often associated with overdose deaths.

## **Main Conclusions**

Constructive solutions to counteract opioid-related harm must be founded on sound analysis, must not impede access to pain therapy, and will require the cooperation of health-care professionals, patient advocates, regulatory agents, crafters of public policies, and all other stakeholders. Analysis of death causation is complicated, requiring that the scientific method be applied to all public health initiatives intended to improve patient outcomes.

This collection of articles, written by experts in their respective fields, represents a starting point for discussion, research, and education. The effort must continue and conform to new realities. For example, as U.S. military veterans return home with physical and psychological wounds of war, it is critical to treat their pain to the optimal degree, while minimizing the danger of death from the very agents of healing.

## References

1. Warner M, Chen LH, Makuc DM. Increase in fatal poisonings involving opioid analgesics in the United States, 1999-2006. NCHS Data Brief 2009; (22):1-8.
2. Paulozzi LJ, Budnitz DS, Xi Y. Increasing deaths from opioid analgesics in the United States. Pharmacoepidemiol Drug Saf 2006; 15(9):618-27.
3. Utah Department of Health (2009). *Utah Clinical Guidelines on Prescribing Opioids for Treatment of Pain*. Salt Lake City, UT: Utah Department of Health.
4. Bunten H, Liang WJ, Pounder D, Seneviratne C, Osselton MD. CYP2B6 and OPRM1 gene variations predict methadone-related deaths. Addict Biol. 2011;16(1):142-4.

## Appendix A. Expert Panel Assembled for LifeSource Conference

Panel members and their affiliations are as follows:

Lynn R. Webster, MD, FACPM, FASAM, Lifetree Clinical Research, Salt Lake City, Utah

Susan Cochella, MD, MPH, Department of Family and Preventive Medicine, University of Utah

Nabarun Dasgupta, MPH, Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina, Chapel Hill, North Carolina

Keri L. Fakata, PharmD, Lifetree Clinical Research, Salt Lake City, Utah;

Perry G. Fine, MD, Department of Anesthesiology of the School of Medicine, Pain Research Center, University of Utah

Scott M. Fishman, MD, Division of Pain Medicine, University of California, Davis

Todd Grey, MD, Utah Office of the Medical Examiner;

Erin Johnson, MPH, Prescription Pain Medication Program, Utah Department of Health;

Lewis K. Lee, MS, SM, Department of Biomathematics, Geffen School of Medicine, University of California, Los Angeles;

Steven D. Passik, PhD, Department of Psychiatry and Behavioral Sciences, Memorial Sloan-Kettering Cancer Center

John Peppin, DO, FACP, The Pain Treatment Center of the Bluegrass, Lexington, Ken.

Christina A. Porucznik, PhD, MSPH, Division of Public Health, Department of Family and Preventive Medicine, University of Utah

Albert Ray, MD, The LITE Center, Miami, Fla.

Sidney H. Schnoll, MD, PhD, Internal Medicine and Psychiatry, Medical College of Virginia, Virginia Commonwealth University, and Pinney Associates, Inc.

Richard L. Stieg, MD, MHS, National Pain Foundation;

Wayne Wakeland, PhD, Systems Science, Portland State University

Also participating were:

Andy Murphy, then-director of operations with LifeSource.

Beth Dove, medical writer with Lifetree Clinical Research and Pain Clinic and supplement managing editor. Beth Dove also served as medical writer for this executive summary.

The one-day conference was sponsored by the nonprofit foundation, LifeSource ([www.lsource.org](http://www.lsource.org)), which also paid author honorariums for supplement articles. LifeSource, formed in 2007 and based in Salt Lake City, takes as its mission the furtherance of education, research, and media outreach to combat misuse and

overdose deaths due to opioids. LifeSource operates in accordance with Section 501(c)(3) of the Internal Revenue Code.

## **Appendix B. Table of Contents for *Pain Medicine* Supplement**

### *Section 1: Defining the Problem*

1. Ending unnecessary opioid-related deaths: a national priority [Introduction].  
Author: Lynn R. Webster, MD.
2. Studying adverse events related to prescription opioids: the Utah experience.  
Authors: Christina A. Porucznik, PhD, MSPH, Erin Johnson, MPH, Brian Sauer, PhD, Jacob Crook, MS, Robert T. Rolfs, MD, MPH.
3. An analysis of the root causes for opioid-related overdose deaths in the United States.  
Authors: Expert panel assembled July 31, 2009, Salt Lake City, Utah, as participants in LifeSource conference.
4. Psychological variables potentially implicated in opioid-related mortality as observed in clinical practice.  
Authors: Steve D. Passik, PhD; Amy Lowery, PhD.
5. Depression, chronic pain, and suicide by overdose: on the edge.  
Author: Martin Cheatle, PhD.
6. Reducing overdose deaths associated with pharmaceutical opioid treatment of chronic pain: using a system dynamics model to analyze potential interventions.  
Authors: Wayne Wakeland, PhD, Teresa Schmidt, MA, Aaron M. Gilson, PhD, David Haddox, DDS, MD, Lynn R. Webster, MD.
7. A review of forensic implications of opioid prescribing with examples from malpractice cases involving opioid-related overdose.  
Authors: Lynn R. Webster, MD, Ben Rich, PhD, JD.

### *Section 2: Finding Solutions*

8. State-level strategies for reducing prescription-drug overdose deaths: Utah's prescription safety program.  
Authors: Erin Johnson, MPH, Christina A. Porucznik, PhD, MSPH, Jonathan W. Anderson, MPH, Robert T. Rolfs, MD, MPH.

9. Provider detailing: an intervention to decrease prescription opioid deaths in Utah. Author: Susan Cochella, MD, MPH, Kim Bateman, MD.

10. Project Lazarus: community-based overdose prevention in rural North Carolina.

Authors: Su Albert, MD, MPH, Fred Wells Brason II, Chaplain, Catherine (Kay) Sanford, MSPH, Nabarun Dasgupta, MPH, Jim Graham, Beth Lovette, MPH

11. Obtaining adequate data to determine causes of opioid-related overdose deaths.

Authors: Lynn R. Webster, MD, Nabarun Dasgupta, MPH.