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An Analysis of the Root Causes for Opioid-Related Overdose Deaths in the United States

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Abstract

Objective. A panel of experts in pain medicine and public policy convened to examine root causes and risk factors for opioid-related poisoning deaths and to propose recommendations to reduce death rates.

Methods. Panelists reviewed results from a search of PubMed and state and federal government sources to assess frequency, demographics, and risk factors for opioid-related overdose deaths over the past decade. They also reviewed results from a Utah Department of Health study and a summary of malpractice lawsuits involving opioid-related deaths.

Results. National data demonstrate a pattern of increasing opioid-related overdose deaths beginning in the early 2000s. A high proportion of methadone-related deaths was noted. Although methadone represented less than 5% of opioid prescriptions dispensed, one third of opioid-related deaths nationwide implicated methadone. Root causes identified by the panel were physician error due to knowledge deficits, patient non-adherence to the prescribed medication regimen, unanticipated medical and mental health comorbidities, including substance use disorders, and payer policies that mandate methadone as first-line therapy. Other likely contributors to all opioid-related deaths were the presence of additional central nervous system-depressant drugs (e.g., alcohol, benzodiazepines, and antidepressants) and sleep-disordered breathing.

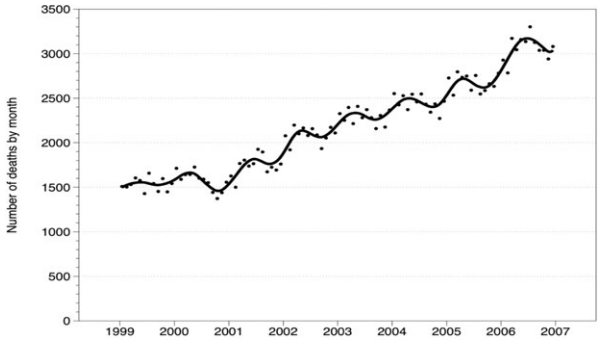

Figure 1 Increase in US overdose deaths related to opioids and unidentified drugs, 1999–2007 [3].

Conclusions. Causes of opioid-related deaths are multifactorial, so solutions must address prescriber behaviors, patient contributory factors, nonmedical use patterns, and systemic failures. Clinical strategies to reduce opioid-related mortality should be empirically tested, should not reduce access to needed therapies, should address risk from methadone as well as other opioids, and should be incorporated into any risk evaluation and mitigation strategies enacted by regulators.

Key Words. Chronic Pain; Methadone; Opioids; Opioid-Related Death; Overdose; Mortality

Introduction

Simultaneous with the recognition that chronic pain often goes undertreated, the United States is experiencing a significant public health threat from overdose deaths involving prescription opioids. The National Center for Health Statistics reports that the number of fatal poisonings involving opioid analgesics more than tripled from 4,000 to 13,800 from 1999 through 2006 [1]. Figure 1 shows an estimate of deaths by month based on a derivative of the Australian opioid-overdose surveillance definition [2] drawn from a derivative of the International Classification of Diseases, 10th Revision (ICD-10) and multiple cause-of-death data from the Centers for Disease Control and Prevention (CDC) [3]. The deaths peaked in 2006, when nearly 100 deaths occurred per day in the United States attributable to intentional and unintentional drug overdoses using the broadest surveillance definition (deaths related to opioids and unidentified drugs, a significant portion of which are prescription drugs).

These reports reveal a pattern of increasing opioid-related deaths; however, the exact number of deaths remains unknown for several reasons: 1) lack of standardized national definitions among death investigators to interpret postmortem toxicology findings, 2) state-level variations in determining the manner of death (e.g., suicide vs accident vs undetermined), and 3) poorly defined toxicology categories used to classify deaths in the ICD-10.

The reasons for the deaths are multifactorial, encompassing prescriber behaviors, patient contributory factors, nonmedical use patterns, and systemic failures. Identifying risk factors among opioid overdose decedents has been difficult due, in part, to the widely varying methods employed by state death investigators to collect mortality data and to report on drug involvement in overdose. One major contributing factor cited by the CDC is the rise in the number of opioid prescriptions [4]. In response, the US Food and Drug Administration (FDA) instituted risk evaluation and mitigation strategies (REMS) for opioids [5].

Although analysis of risk factors is ongoing, pain care providers and public health officials have a duty to act now to prevent as many deaths as possible. To that purpose, an expert panel met to examine the data on root causes and risk factors pertaining to opioid-related deaths, to evaluate the extent to which measures enacted to prevent the deaths have been successful, and to propose recommendations to reduce death rates. Results of this analysis are intended to provide focus to policy debates, to help craft quality medical education programs and other interventions, to identify needed research, and to inform public discussion.

Methods

A search of PubMed and state and federal government sources was conducted to assess frequency, demographics, and risk factors associated with opioid-related overdose deaths over the past decade. Searches were conducted using combinations of the search terms “opioids,” “overdose,” “poisoning,” “deaths,” “respiratory depression,” and “mortality.” The literature yielded 91 documents. A panel of experts in pain medicine and public health met on July 31, 2009 in Salt Lake City, Utah, for a full day of presentations and discussion. The conference was sponsored by the LifeSource Foundation, a nonprofit organization formed in 2006 as an educational and research vehicle to heighten safety in the delivery of pain medicine. The panel reviewed the following resources:

- Results from the assembled documents.
- Results presented through the Utah Department of Health of prevalence and decedent risk factors in opioid-related overdose deaths.
- Data from 35 medical malpractice legal cases involving opioid overdose poisoning, 20 of which were fatal [6].

The panel pursued the following objectives:

- Examined the national and state data on the frequency of opioid-related deaths.
- Evaluated the best evidence available on the possible root causes and risk factors for opioid-related deaths.
- Reviewed the factors common to known deaths and extrapolated this information to help determine solutions.

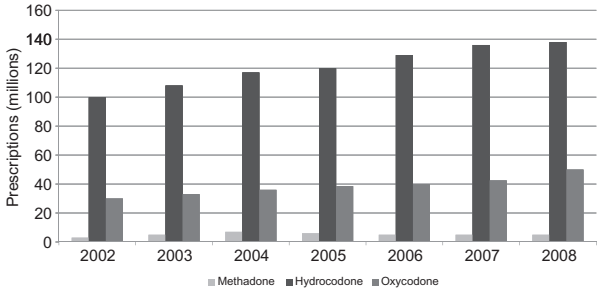

Figure 2 Total prescriptions dispensed in the United States [7]. Source: IMS Health, National Prescription Audit Plus™ (NPA Plus™).

Results

The panel proposed that the risk factors examined were both proximate (e.g., human error) and latent (e.g., relating to systems and organizations). Certain interventions—such as improvement of prescriber education—were characterized as "low-hanging fruit," meaning those interventions are controllable and possess a high potential for direct impact on death rates from opioids.

The panel noted a persistent increase in opioid-related overdose deaths beginning in the early 2000s. The panel also observed a high proportion of methadone-related deaths compared with other opioids when adjusted for the total number of prescriptions issued. Findings related to methadone included the following:

1. *Total prescriptions.* Methadone represents less than 5% of total opioid prescriptions dispensed (Figure 2) [7], but a third of opioid-related deaths nationwide (Figure 3) [8].
2. *Toxic exposures* as quantified by the National Poison Database System, which tracks all cases recorded from 61 regional poison centers. Exposures are defined as nonadministrative, noninformation calls wherein the caller was concerned about an exposure to a substance. Methadone was involved in fewer than 10% of all calls made to poison centers (Figure 4) [7]; however, when adjusted for the number of outpatient prescriptions dispensed, the rate for methadone-related exposure calls was approximately 10 times greater than for hydrocodone and four times greater than for oxycodone (Figure 5) [7]. The rate of deaths reported to poison centers per each 10,000 toxic exposures involving methadone as a single substance was substantially larger than for all other opioids (Figure 6) [7].

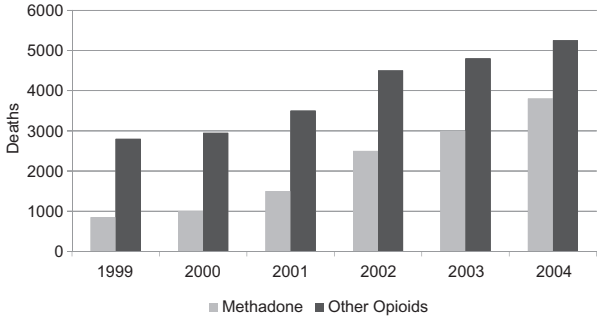

Figure 3 Methadone and other opioid deaths in the United States [8].

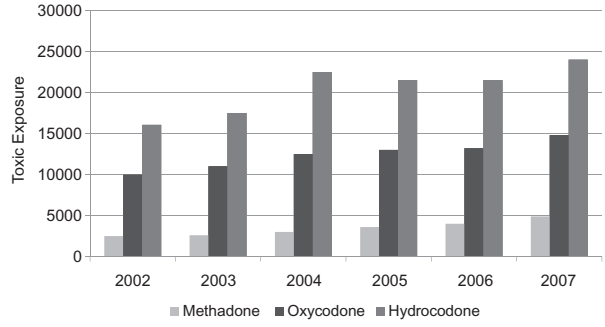

Figure 4 National exposure calls* reported to poison control [7]. Source: National Poison Database System (NPDS), which tracks all cases recorded from 61 regional poison centers. *Exposures are defined by the NPDS as nonadministrative, noninformation calls wherein the caller was concerned about an exposure to a substance.

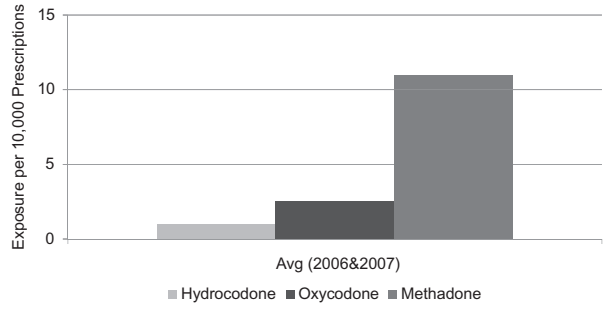

Figure 5 National exposure calls* per 10,000 prescriptions [7]. Sources: National Poison Database System (NPDS), which tracks all cases recorded from 61 regional poison centers, IMS Health, National Prescription Audit Plus™ (NPA Plus™). *Exposures are defined by the NPDS as nonadministrative, noninformation calls wherein the caller was concerned about an exposure to a substance.

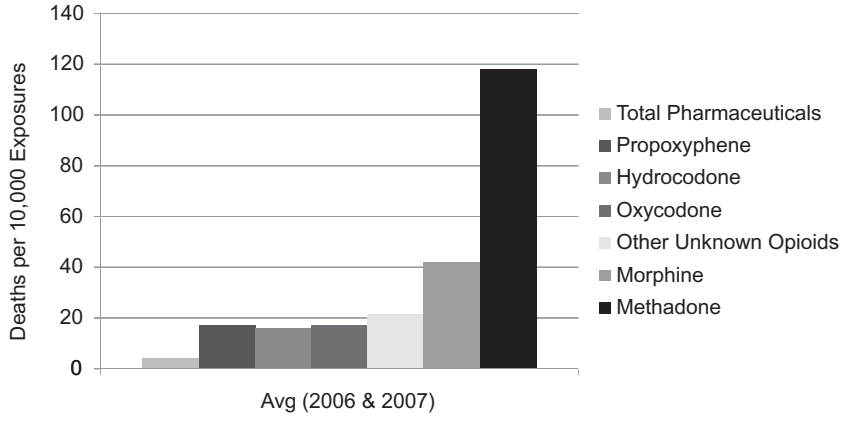

Figure 6 Deaths reported to poison centers per 10,000 single substance exposures* [7]. Source: National Poison Database System (NPDS), which tracks all cases recorded from 61 regional poison centers. *Exposures are defined by the NPDS as non-administrative, noninformation calls wherein the caller was concerned about an exposure to a substance.

3. *Inclusion in reports of forensic drug items*. Methadone represented about 12% of all drugs seized by law enforcement (Figure 7) [7]. However, when adjusted for the number of dispensed outpatient prescriptions, the rate for methadone-related drug seizures was approximately 11 times greater than for hydrocodone and five times greater than for oxycodone (Figure 8) [7].
4. *Emergency department (ED) admissions related to prescription drugs.* Methadone was involved in about 30% of all overdoses treated in EDs (Figure 9) [7,9]. However, when adjusted for the number of dispensed outpatient prescriptions, the rate for methadone-related visits was approximately 23 times greater than for hydrocodone and six times greater than for oxycodone (Figure 10) [7,9].
5. *Review of medical malpractice legal cases*. One of the panel members (LRW) reviewed 35 medical records from 2005 to 2009 of patients with chronic pain who suffered opioid overdose poisonings, leading to malpractice lawsuits against physicians. Twenty of the overdoses were fatal. The reviews were requested by plaintiff and defense attorneys from across the United States with the purpose of determining the cause(s) of overdose. All decedents had been taking at least 60 mg oral morphine equivalent for more than a year. The primary drug responsible for death was determined to be methadone in 10 cases (50%) [6].

The panel discussed factors common to opioid-related deaths and identified several factors that could help explain the disproportionate involvement of methadone. The top factors included:

Physician Error due to Knowledge Deficits

Possible errors include initiating methadone at too high a dose (Utah data show that death occurred within 7 days of

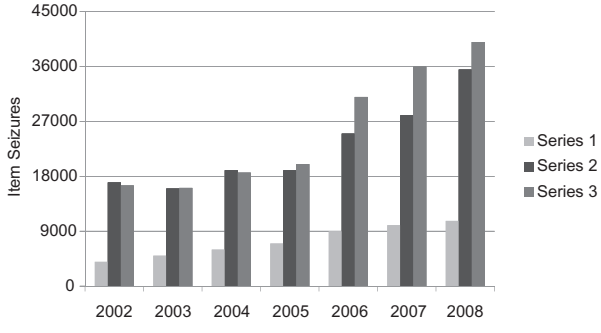

Figure 7 National estimates of forensic drug item seizures [7]. Source: Drug Enforcement Agency National Forensic Laboratory Information System (NFLIS).

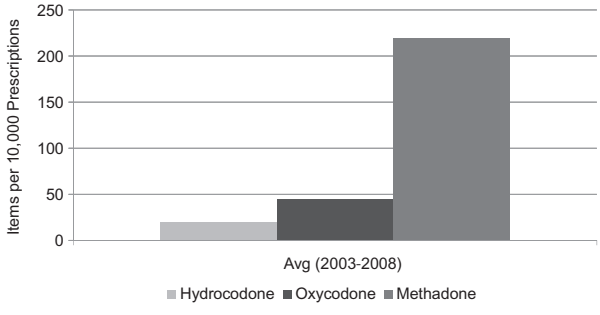

Figure 8 National drug seizures per 100,000 prescriptions [7]. Sources: IMS Health, National Prescription Audit Plus™, Drug Enforcement Agency National Forensic Laboratory Information System.

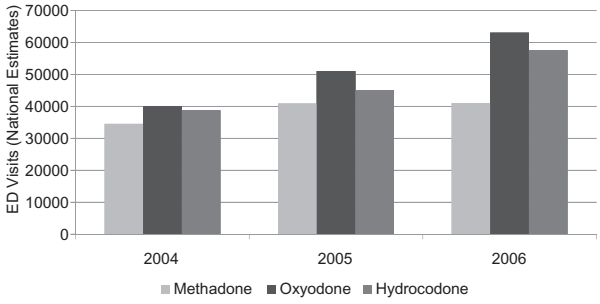

Figure 9 National prescription drug-related emergency department visits [7,9]. ED = emergency department.

beginning treatment for 70% of decedents who held a methadone prescription) [10], over-relying on published equianalgesic conversion tables when converting to methadone from another opioid, titrating doses too rapidly, lacking familiarity with the unique pharmacokinetics and pharmacodynamics of methadone, failing to identify and monitor patients at risk for substance misuse, and overestimating the tolerance to respiratory depression conferred by prior opioid use in patients with chronic pain. Methadone has a long elimination half-life (typically 8 to 59 hours) that long outlasts its analgesia (typically 4 to 8 hours) [11]. Because of individual variations in metabolism, methadone's half-life can range from 5 to 130 hours [12]. Lack of education as to appropriate prescribing practices and lack of resources were cited as drivers of physician errors. The panel expressed concern that the initial ceiling dose of 30 mg per day endorsed in the FDA-approved label for methadone—although revised downward in 2006—may still be too high for some patients [11]. Further knowledge deficits concern the risk of QT interval prolongation and effects on sleep-related respiratory physiology.

Patient Non-Adherence to Medication Regimen

Mistakes by patients include escalating doses without prescriber knowledge or mixing opioids with alcohol, benzodiazepines, or other substances. These actions may reflect pursuit of greater pain relief, attempts to self-medicate a comorbid mental health disease, or manifestation of a substance use disorder. Patients may also fail to take all medication as prescribed, leading physicians to overestimate the degree of opioid tolerance present when converting to or initiating methadone or another new opioid.

Payer Policies that Mandate Methadone as First-Line Therapy

Because methadone is less expensive compared with many other opioids, some insurance companies and other providers of payment, including Medicaid, encourage or even require prescribers to try methadone first. The panel proposed that such policies may lead clinicians who are unfamiliar with the unique pharmacology of methadone to prescribe it.

Unanticipated Mental-Health Comorbidities, Including Substance-Use Disorders

Mental disorders, including depression, anxiety, somatization disorder, and substance use disorders, have been correlated with chronic pain [13,14]. A report describing 500 consecutive opioid-treated pain patients in an interventional pain management setting found that 59% of them had depression and 64% of them had anxiety; furthermore, drug abuse was more likely in patients with depression than in patients without depression (12% vs 5%) [13]. Similarly, 9,279 respondents to a survey weighted to be representative of the US population indicated that users of opioids had higher rates of opioid and non-opioid drug abuse problems, a finding partially mediated by depressive and anxiety disorders [14]. Investigators in the latter study did not draw a causal relationship but concluded that the data were compatible with mental disorders preceding substance abuse.

Mental disorders, with or without pain, are associated with drug abuse. A lifetime mental disorder diagnosis has been associated with twice the risk of having an alcohol disorder and four times the risk of having another drug use disorder [15]. State medical examiners report that a high percentage of people who died of prescription drug overdoses had histories of substance abuse [4,16]. In a discussion of these outcomes, the panel identified as one factor the frequent reluctance by insurance companies and other payers to cover mental health, behavioral, and substance-abuse treatment comprehensively with pain. Also cited was failure by clinicians, often due to lack of training or resources, to screen patients for mental health comorbidities.

Unanticipated Medical Comorbidities

Although no consensus yet exists, some studies have linked sleep apnea to opioid use [17–19]. In one study, a

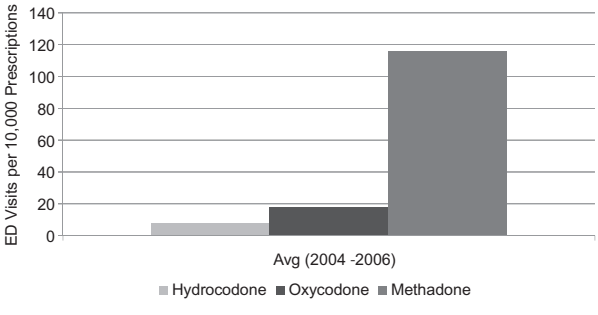

Figure 10 National emergency department visits per 10,000 prescriptions [7,9]. Sources: DAWN, IMS Health, National Prescription Audit Plus™. ED = emergency department.

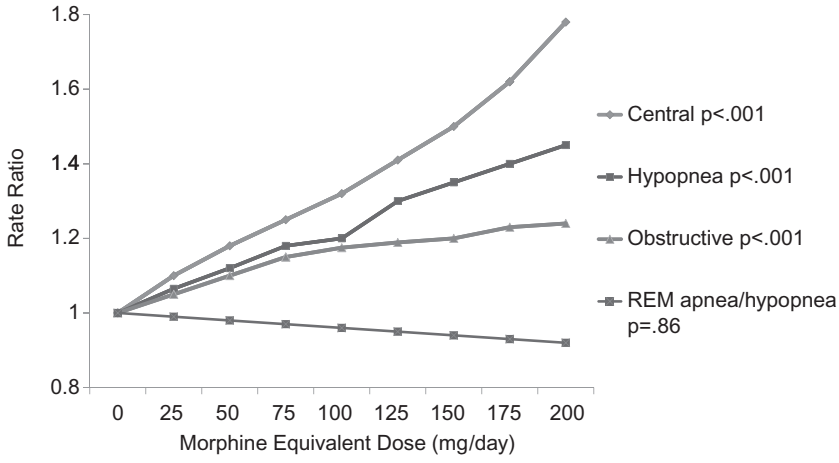

Figure 11 Central sleep apnea: rate ratios by increase of morphine equivalent dose [19]. REM = rapid eye movement.

positive correlation was found between central apnea and the daily dosage of methadone, an effect that was heightened with benzodiazepines [17]. A literature review estimated the prevalence of central sleep apneas of periodic and non-periodic breathing types at 30% among chronic opioid users [18]. Other investigators have found a nearly linear relationship between the morphine equivalent and prevalence of central sleep apnea wherein each 100-mg morphine dose equivalent increased the rate of central apneas by 29.2% (Figure 11) [19].

Methadone is believed to produce *torsades de pointes*, or pathological QTc interval prolongation [20], and the association appears to be dose related. Other drugs that prolong the QTc interval could produce a dangerous additive effect.

The Presence of Additional Central Nervous System (CNS)-Depressant Drugs (e.g., Alcohol, Benzodiazepines, and Antidepressants)

Most opioid-related decedents had multiple substances in their blood at the time of death. Alcohol is found more frequently in opiate (i.e., heroin and opioid) deaths than any other substance, according to epidemiological data [21]. In 2006, about half of all US opioid-related deaths involved more than one type of drug with benzodiazepines mentioned in 17% of the deaths [1]. Multiple substances were evident in almost 80% of opioid-associated deaths from 1999 to 2004 in West Virginia [22]. Benzodiazepines are frequent co-intoxicants in methadone-related deaths [11]. Utah data show other substances were involved in 60% of methadone-related deaths, including benzodiazepines, other opiates, antidepressants, and alcohol [10].

The following decedent and demographic factors were found for deaths related to all opioids, including methadone:

The highest rates of opioid-analgesic poisonings were in the 40- to 49-year-old age group [4]. Men were found to be at higher risk for overdose, accounting for 69.2% of decedents in the opioid analgesic-alone category from 1999 to 2002 [4], but female deaths rates rose faster. From 1999 to 2004, unintentional poisoning deaths increased among females from 2.3 to 4.7 per 100,000 population (103.0%), which was more than twice the increase among males, from 6.5 to 9.5 per 100,000 population (47.1%) [23].

Rates of opioid poisoning showed a greater increase between 1999 and 2004 in nonmetropolitan counties (371%) than in central metro counties (52%) [24]. Rural overdose deaths presented different characteristics from the deaths studied in urban centers, including a high involvement of doctor shopping, different medication combinations, lower presence of illicit drugs, and more polydrug abuse [22,25].

In Utah, an analysis of drug poisoning fatalities from 1999 through 2003 showed a higher death rate (14.25%) in decedents with a body mass index (BMI) of ≥30 than in those with a BMI in the range of 25–29.9 (5.26%) or <25 (3.61%) [26].

Discussion

Data pertaining to all opioid deaths revealed a high proportion of methadone-related deaths when compared with the number of prescriptions issued (Figures 2 and 3). This finding corroborates analysis by the CDC that determined the increase in methadone-related deaths (213%) from 1999 to 2002 is closer to the increase in methadone sales through pharmacies for pain management (175%) than it is to the increase in methadone distribution through opioid treatment programs (43%) [4].

The root cause analysis indicates that some decedents were patients who were legally prescribed methadone and died because 1) they took too much medication or mixed it with unauthorized substances, or 2) they were prescribed too much medication by a physician. The starting dose for methadone appears to be critical for safety as supported by Utah data showing death occurred within 7

days of beginning treatment for 70% of decedents who held a methadone prescription [10].

Deaths also occurred in patients switched to methadone from prior opioids, suggesting that clinicians may have presumed these patients to be opioid tolerant based on past prescribed dosages, although cross tolerance was incomplete. Another reason clinicians may overestimate opioid tolerance is that patients with chronic pain do not always take all medications they are prescribed. For example, a patient who suffers frequently from headaches may take medication only on days when a headache occurs but not on headache-free days. Therefore, before initiating any changes to an opioid dosage, it is important that clinicians clarify with patients precisely how they have been taking their prescribed medications.

When patients with presumed opioid tolerance and no apparent substance use disorder die of respiratory depression after a switch to methadone, suspicion is cast on currently available conversion guidelines. Many older and even recently published conversion tables must be used with extreme caution when rotating from any opioid to methadone. A systematic review of opioid conversion ratios used with methadone for pain found a wide variance in successful conversion ratios and a need to examine patient factors that could help explain that variance [27]. This lack of rigorous science to support published conversion ratios for methadone suggests the need for conservative dosing accompanied by close supervision. A recent review of the literature on the science behind equianalgesic tables recommends substantial reduction in calculated equianalgesic doses when converting to methadone [28], and consensus recommendations from an expert panel [29] suggest a 75–90% decrement in the equianalgesic dose from conventional conversion tables when a switch is made from another opioid to methadone. The significant variability in the speed at which different people metabolize opioids also affects the risk of toxicity [30,31].

In proposing interventions, the panel focused on the clinical aspects of opioid prescribing in the belief that this area is where physicians and other providers may realistically help reduce the number of accidental deaths. However, data also are accumulating to suggest that many deaths occur in people with prior histories of substance abuse [16]. The National Drug Intelligence Center (NDIC) cites illegal diversion and theft as key sources of methadone contributing to deaths [8]; therefore, physicians may be obliged to consider the probable impact of opioid exposure beyond the clinical setting. All clinicians who prescribe opioids long term should intensify efforts to assess and monitor patients to ensure to the best of their ability that opioids are being consumed within the confines of set parameters and to the benefit of patients.

Much of the risk for overdose death comes through patients who make mistakes that put them at grave risk. Patients may be driven to misuse opioids by a desire for greater pain relief, to self-medicate a comorbid mental health disease, or to relieve stress from social, financial, and employment issues related to pain. Patients should be counseled never to escalate doses of methadone or other opioids on their own and should be warned about the danger of mixing unauthorized substances with their medication. Clinicians should beware of behaviors pointing to a patient taking opioids to achieve a secondary benefit such as relief from a psychiatric disorder. Opioids are meant for pain control, and channeling opioids toward disorders for which they are not indicated can be lethal.

Benzodiazepines appear frequently in death investigations in combination with methadone and other opioids. It is important to consider that benzodiazepines may have additive or synergistic effects when combined with opioids [17,32]. It also should be noted that mental health disorders such as anxiety, for which benzodiazepines are prescribed, appear to present their own risks for heightened pain and opioid use [33]. One large study reported that benzodiazepine users who did not use opioids to start with were more likely than non-users of benzodiazepines to later use opioids [34]. When aberrant opioid-related behaviors co-occur with alcohol or benzodiazepine use, lethal toxic levels could be reached at low blood levels of opioid for a given patient. Clinicians using opioids to treat pain should consider using an alternative to benzodiazepines for anxiety disorders or insomnia, limiting the quantity of opioids used for pain, or limiting quantities of both medications if used together.

Certain demographic trends emerged from the data discussed by the panel. Middle age is the most vulnerable time for opioid overdose, differing from the age group most likely to misuse opioids recreationally, which is young people aged 18–25 years [35]. The increase in opioid-poisoning deaths in nonmetropolitan centers has translated to death rates in rural areas that are now comparable with those in urban counties [24]. More men than women die from opioid-related causes, but women are catching up in vulnerability to overdose. In West Virginia, women and people aged 35–44 years were significantly more likely to show evidence of doctor shopping than men and people in other age groups [22].

It appears the presence of sleep-disordered breathing could increase the risk of overdose death. Chronic opioid use and sleep-disordered breathing occur frequently together [18], and future research should focus on understanding the effects of opioids on ventilatory control mechanisms. Additional research should investigate the apparent parallel of risk factors for obstructive sleep apnea to the risk factors for death during chronic opioid therapy (e.g., middle age, above-average BMI).

On November 27, 2006, the FDA issued a public health advisory for methadone, entitled *Methadone Use for Pain Control May Result in Death and Life-Threatening Changes in Breathing and Heart Beat* [36]. The association between methadone and cardiac irregularities does not appear to be a common problem but could be lethal if not detected. Other drugs known to

prolong the QTc interval could produce an additive effect, and QT syndromes may be preexisting but largely asymptomatic.

The presented rates of methadone events (calls, units seized, ED visits) are higher than expected for methadone relative to the other opioid comparators, oxycodone and hydrocodone. However, certain clarifications are necessary regarding how the present data were collected and analyzed. Outpatient dispensed prescriptions comprise the denominator of the rates for Figures 5, 6, 8, and 10, but the numerator can include events from patients in methadone maintenance treatment programs (MMTPs). Prescriptions dispensed onsite in MMTPs or as part of take-home doses are not reflected in the outpatient prescriptions used to calculate the rate denominators. Additionally, event rates per number of outpatient prescriptions for hydrocodone may be higher than comparators, in part, because hydrocodone is a Schedule III medication and so is issued in greater quantities per prescription than are methadone and oxycodone.

Studies are needed to illuminate not only which types of drugs appear most frequently in opioid-related deaths but the patterns of use that lead to the deaths. A study is due from the CDC, whose scientists will compare data from New Mexico's prescription drug monitoring program to data on decedents from the office of the state medical examiner [37]. In this way, it is hoped that risk factors such as quantity and type of prescriptions can be examined. More studies of this type are needed.

The increased availability of opioid analgesics has corresponded to the increase in accidental overdose deaths. However, responding by simply reducing the amount of opioids prescribed would be likely to harm legitimate patients needing pain relief, whereas determined nonmedical users would be likely to seek alternative sources. Rather, the focus should be on physician education leading to appropriate screening and monitoring of opioid candidates. Once health care providers are better trained to conduct assessment and monitoring, outcomes in the clinical setting should improve. Better medical decision making should be the goal, not decreased opioid prescribing, although the volume of prescribing may drop as a result of better screening and monitoring practices. The panel's proposals are aimed at reversing the trend of opioid-related deaths related to legitimate prescriptions for pain. Different strategies will be needed to effect change among nonmedical users of opioids.

Summary

Although methodologies differ, rendering data inconsistent, opioid-related overdose deaths have risen persistently in recent years with methadone representing a disproportionate number of opioid-related deaths. Risk factors identified by the panel included:

- Physician error due to knowledge deficits.
- Patient non-adherence to medication regimen.
- Unanticipated medical and mental health comorbidities, including substance use disorders.
- Payer policies that encourage or mandate methadone as first-line therapy.
- The presence of additional CNS-depressant drugs (e.g., alcohol, benzodiazepines, and antidepressants).
- Sleep-disordered breathing.

All opioids must be used judiciously considering two-thirds of opioid-related deaths are caused by opioids other than methadone. After assessing patients for mental health disorders, clinicians should consider implementing structured care for those with depression, anxiety, or other mental illness to include possible minimization of opioids. Solutions must be multifactorial, should address risk from methadone as well as other opioids, and should be incorporated into any REMS program.

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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 Jauncey ME, Taylor LK, Degenhardt LJ. The definition of opioid-related deaths in Australia: Implications for surveillance and policy. Drug Alcohol Rev 2005;24(5):401–9.

3 Mortality Data—Vital Statistics NCHS's Multiple Cause of Death Data, 1959–2006. National Bureau of Economic Research. Available at: http://www.nber.org/data/multicause.html (accessed October 2010).

4 Paulozzi LJ, Budnitz DS, Xi Y. Increasing deaths from opioid analgesics in the United States. Pharmacoepidemiol Drug Saf 2006;15(9):618–27.

5 Proposed Risk Evaluation and Mitigation Strategy (REMS) for Long-Acting and Extended-Release Opioids. U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Joint meeting of the Anesthetic and Life Support Drugs Advisory Committee (ALSDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM). July 22-23, 2010. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/UCM217510.pdf (accessed July 2010).

6 Webster LR, Dove B, Murphy A. Select Medical-Legal Reviews of Unintentional Overdose Deaths. Presented at: 2010 AAPM Annual Meeting; February 3–6, 2010; San Antonio, TX.

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

8 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.

9 Substance Abuse and Mental Health Services Administration, Office of Applied Studies. *Drug Abuse Warning Network, 2006: National Estimates of Drug-Related Emergency Department Visits.* DAWN Series D-30, DHHS Publication No. (SMA) 08-4339, Rockville, MD, 2008.

10 Sundwall DN, Rolfs RT. Prescription medication deaths in Utah: Summary of findings. Utah Department of Health, Workgroup Meeting, October 24–25, 2005. Available at: http://health.utah.gov/prescription/pdf/Prescription_medication_deaths_in_utah.pdf (accessed April 2008).

11 Prescribing information for Dolophine® Hydrochloride CII (methadone hydrochloride tablets, USP) 5 mg, 10 mg. Roxane Laboratories, Inc. Columbus, Ohio: 27 November 2006. Available at: http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM142842.pdf (accessed May 2010).

12 Eap CB, Buclin T, Baumann P. Interindividual variability of the clinical pharmacokinetics of methadone: Implications for the treatment of opioid dependence. Clin Pharmacokinet 2002;41(14):1153–93.

13 Manchikanti L, Giordano J, Boswell MV, et al. Psychological factors as predictors of opioid abuse and illicit drug use in chronic pain patients. J Opioid Manag 2007;3(2):89–100.

14 Edlund MJ, Sullivan M, Steffick D, Harris KM, Wells KB. Do users of regularly prescribed opioids have higher rates of substance use problems than nonusers? Pain Med 2007;8(8):647–56.

15 Regier DA, Farmer ME, Rae DS, et al. Comorbidity of mental disorders with alcohol and other drug abuse. JAMA 1990;264(19):2511–8.

16 Paulozzi LJ. Testimony on Trends in Unintentional Drug Overdose Deaths. Before the U.S. Senate Judiciary Committee, Subcommittee on Crime and Drugs. Wednesday, March 12, 2008. Available at: http://www.hhs.gov/asl/testify/2008/03/t20080312g.html#_ftn1#_ftn1 (accessed April 2009).

17 Webster LR, Choi Y, Desai H, Grant BJB, Webster L. Sleep-disordered breathing and chronic opioid therapy. Pain Med 2008;9(4):425–32.

18 Teichtahl H, Wang D. Sleep-disordered breathing with chronic opioid use. Expert Opin Drug Saf 2007;6(6):641–9.

19 Walker JM, Farney RJ, Rhondeau SM, et al. Chronic opioid use is a risk factor for the development of central sleep apnea and ataxic breathing. J Clin Sleep Med 2007;3(5):455–61.

20 Kornick CA, Kilborn MJ, Santiago-Palma J, et al. QTc interval prolongation associated with intravenous methadone. Pain 2003;105(3):499–506.

21 Hickman M, Lingford-Hughes A, Bailey C, et al. Does alcohol increase the risk of overdose death: The need for a translational approach. Addiction 2008; 103(7):1060–2.

22 Hall AJ, Logan JE, Toblin RL, et al. Patterns of abuse among unintentional pharmaceutical overdose fatalities. JAMA 2008;300(22):2613–20.

23 Centers for Disease Control and Prevention (CDC). Unintentional poisoning deaths—United States, 1999–2004. MMWR Morb Mortal Wkly Rep 2007;56(5):93–6.

24 Paulozzi LJ, Xi Y. Recent changes in drug poisoning mortality in the United States by urban-rural status and by drug type. Pharmacoepidemiol Drug Saf 2008;17(10):997–1005.

25 Wunsch MJ, Nakamoto K, Behonick G, Massello W. Opioid deaths in rural Virginia: A description of the high prevalence of accidental fatalities involving prescribed medications. Am J Addict 2009;18(1):5–14.

26 Porucznik CA. Update on prescription drug overdose research. University of Utah, School of Medicine. Public Health Program and Utah Department of Health. Available at: http://health.utah.gov/prescription/pdf/steering_com_pdf/Research UpdateApril.pdf (accessed May 2009).

27 Weschules DJ, Bain KT. A systematic review of opioid conversion ratios used with methadone for the treatment of pain. Pain Med 2008;9(5):595–612.

28 Knotkova H, Fine PG, Portenoy RK. Opioid rotation: The science and limitations of the equianalgesic dose table. J Pain Symptom Manage 2009;38(3):426–39.

29 Fine PG, Portenoy RK. Establishing "best practices" for opioid rotation: Conclusions of an expert panel. J Pain Symptom Manage 2009;38(3):418–25.

30 Somogyi AA, Barratt DT, Coller JK. Pharmacogenetics of opioids. Clin Pharmacol Ther 2007;81(3):429–44.

31 Argoff CE. Clinical implications of opioid pharmacogenetics. Clin J Pain 2010;26(suppl 10):S16–20.

32 Pirnay S, Borron SW, Giudicelli CP, et al. A critical review of the causes of death among postmortem toxicological investigations: Analysis of 34 buprenorphine-associated and 35 methadone-associated deaths. Addiction 2004;99(8):978–88.

33 Sullivan MD, Edlund MJ, Zhang L, Unützer J, Wells KB. Association between mental health disorders, problem drug use, and regular prescription opioid use. Arch Intern Med 2006;166(19):2087–93.

34 Skurtveit S, Furu K, Bramness J, Selmer R, Tverdal A. Benzodiazepines predict use of opioids—A follow-up study of 17,074 men and women. Pain Med 2010;11(6):805–14.

35 Substance Abuse and Mental Health Services Administration. *Results from the 2007 National Survey on Drug Use and Health: National Findings* (Office of Applied Studies, NSDUH Series H-34, DHHS Publication No. SMA 08-4343). Rockville, MD: Author; 2008.

36 U.S. Food and Drug Administration. Public Health Advisory: Methadone Use for Pain Control May Result in Death and Life-Threatening Changes in Breathing and Heart Beat. Rockville, MD: Author; 2006.

37 Centers for Disease Control and Prevention, National Center for Injury Prevention and Control. *Unintentional Poisoning: CDC Research & Activities.* Available at: http://www.cdc.gov/homeandrecreationalsafety/poisoning/activities.htm (page last updated: March 12, 2010, accessed July 2010).