Bending the Prescription Opioid Dosing and Mortality Curves: Impact of the Washington State Opioid Dosing Guideline

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Background *Opioid use and dosing for patients with chronic non-cancer pain have dramatically increased over the past decade, resulting in a national epidemic of mortality associated with unintentional overdose, and increased risk of disability among injured workers. We assessed changes in opioid dosing patterns and opioid-related mortality in the Washington State (WA) workers' compensation system following implementation of a specific WA opioid dosing guideline in April, 2007.*

Methods *Using detailed computerized billing data from WA workers' compensation, we report overall prevalence of opioid prescriptions, average morphine-equivalent dose (MED)/day, and proportion of workers on disability compensation receiving opioids and high-dose (≥120 mg/day MED) opioids over the past decade. We also report the trend of unintentional opioid deaths during the same time period.*

Results *Compared to before 2007, there has been a substantial decline in both the MED/day of long-acting DEA Schedule II opioids (by 27%) and the proportion of workers on doses ≥120 md/day MED (by 35%). There was a 50% decrease from 2009 to 2010 in the number of deaths.*

Conclusions *The introduction in WA of an opioid dosing guideline appears to be associated temporally with a decline in the mean dose for long-acting opioids, percent of claimants receiving opioid doses ≥120 mg MED per day, and number of opioid-related deaths among injured workers.* Am. J. Ind. Med. *© 2011 Wiley Periodicals, Inc.*

KEY WORDS: chronic pain; guideline; mortality; opioids; population-based; workers' compensation

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INTRODUCTION

In response to the emerging epidemic of deaths from prescription opioids reported from Washington State (WA) [Franklin et al., 2005] and nationally [Paulozzi et al., 2006], the Agency Medical Director's Group (AMDG), representing all of the WA public payers (Medicaid, workers' compensation, corrections, health, public employees), convened in 2006 an advisory group of clinical and academic pain experts. Over the course of five 3-hr meetings, the AMDG, in collaboration with the pain advisors, developed an Interagency Guideline on Opioid Dosing, which was then implemented as a web-based educational pilot in April 2007 [Washington Agency Medical Director's Group]. The hallmark of this Guideline, in addition to widely agreed-upon best practices, was the inclusion of a ''yellow-flag'' warning opioid dose threshold of 120 mg/day morphine-equivalent dose (MED). The Guideline recommended that prescribing providers obtain consultation from a pain medicine expert for patients with chronic non-cancer pain (CNCP) receiving opioid doses greater than 120 mg/day MED whose pain and function had not substantially improved during opioid treatment, before continuing to prescribe daily doses above 120 mg MED. The Guideline also included a web-based opioid dosing calculator that physicians could use to quickly calculate the total daily MED from all opioid medications.

The dosing guidance in the WA Guideline was specifically directed to address the probable mortality risks of chronic high-dose opioid therapy that was not providing clear benefit. There were suggestions in the literature that the harms of chronic opioid therapy had been underestimated and the benefits overestimated [Ballantyne and Mao, 2003]. As we previously reported, doses of the long-acting Schedule II opioids increased by more than 50% in the WA workers' compensation system between 1996 and 2002, concomitant with a dramatic shift from use of Schedule III opioids to Schedule II opioids [Franklin et al., 2005]. The guideline was based on unanimous consensus among the advisory group members. Since initial implementation of the Guideline, epidemiological evidence has corroborated the significant relationship between doses at or above 100–120 mg/day MED and increased risk of opioid-related morbidity and mortality [Braden et al., 2010; Dunn et al., 2010; Bohnert et al., 2011; Gomes et al., 2011]. We now report trends in opioid dosing and mortality in the WA workers' compensation population from 2003 to 2010, updating our earlier reported data, and comparing trends before and after implementation of the AMDG Guideline in 2007. Our objective was to determine whether dissemination of the Guideline may have been associated temporally with changes in trends in opioid dosing and overdose mortality deaths in WA workers' compensation.

METHODS

Setting and Data

The WA Department of Labor and Industries (DLI) is the sole regulator of workers' compensation coverage in WA and is the direct insurer for two-thirds of the non-Federal workforce in the state, covering approximately 2.3 million eligible workers. The remaining one-third of the eligible workforce is covered by approximately 400 larger self-insured companies. The health services and prescription data for the self-insured subset of WA injured workers are insufficient for research purposes and thus are not included in this report. The DLI receives approximately 130,000 claims for work-related injuries and illnesses annually. The study was approved by the University of Washington Institutional Review Board.

We examined data obtained from the DLI administrative database, the Medical Information Payment System (MIPS), which tracks all health care services for which payment is requested. For outpatient prescriptions, MIPS point-of-sale records information includes data such as, but not limited to, national drug code (NDC), drug class, quantity, days' supply, drug strength, prescribing practitioner, and schedules of controlled substances (II, III, IV, or V). Opioids are scheduled by the Drug Enforcement Administration (DEA) according to their potential for abuse and dependence. Schedule II opioids have the greatest potential for abuse and dependence; this category includes formulations of fentanyl, methadone, morphine, and oxycodone. Methadone has a long half-life; fentanyl, morphine, and oxycodone have shorter half-lives but are formulated in slow-release forms. Common Schedule III opioids include formulations of hydrocodone and codeine, and common Schedule IV opioids include formulations of propoxyphene.

Trends in Opioid Prescriptions, 1996–2010

To investigate the temporal trend of opioid use statewide in the workers' compensation system, we examined the total number of prescriptions for all opioids paid annually during 2003–2010. In addition, we investigated changes in prescription of Schedule II opioids compared to prescription of Schedule III and IV opioids. We combined the data for these years with the earlier published data [Franklin et al., 2005] to encompass the entire period from 1996–2010.

Dosing Trends of Longer-Acting Schedule II Opioids

To examine the change in average daily dosages of longer-acting Schedule II drugs, we used published equianalgesic conversions for transdermal fentanyl (25 mcg/hr), oral levorphanol (4 mg), oral methadone (15 mg), oral morphine (45 mg), and oral oxycodone (30 mg). If the published equianalgesic conversion was a range, we used the mid-point of that range [American Pain Society, 1999; Wolters Kluwer Health, 2004]. The daily dose for each Schedule II opioid prescription was calculated as (total quantity / days' supply) $\times$ (drug strength), then converted to the MED. We report the average daily MED for the longer-acting opioids (methadone, levorphanol, and long-acting formulations of morphine, oxycodone, oxymorphone, fentanyl, and hydromorphone) for the years 2003–2010 and include the previously reported data for the years 1996–2002.

We also report the proportion of workers on 120 mg/day or greater MED for the time period 2000–2010. For this analysis, all workers receiving wage replacement in each quarter (timeloss claimants) were included. All such cases receiving at least one prescription of an opioid in that quarter were considered to be ''opioid'' cases, and the proportion of the prevalent cases receiving at or above 120 mg/day MED in that quarter were considered to be ''high-dose opioid'' cases.

Identification of Opioid-Related Unintentional Poisoning Deaths

The DLI is notified of all deaths for persons who are receiving benefits for a work-related injury claim. We requested death certificates for all such workers who had a compensable claim (i.e., a claim where wage replacement benefits for temporary total disability were paid), died between January 2003 and December 2010, and had at least one of the following characteristics: (a) a prescription for a Schedule II or Schedule III opioid within 3 months of death, (b) at least 20 Schedule II or Schedule III opioid prescriptions for their work-related injury over the course of their claim, or (c) were reported to the DLI provider review unit as an opioid-related death.

One of the authors, a pharmacist (JM), reviewed all the cases whose death certificates met the screening criteria and listed the cause of death as accidental, and classified each as definitely, probably, or possibly related to prescription opioid use. We previously described the definitions for these classifications [Franklin et al., 2005], which were also adapted for another prescription opioid mortality report from the WA Medicaid population [MMWR, 2009]. The reviewer obtained information on each of six factors from death certificates and supplementary autopsy reports (factors 1, 2, 3, 5, and 6; described below), and from the computerized DLI pharmacy database (factor 4). Greater weight was given to information obtained from the death records. All cases received autopsies and most had documented toxicology. Factors 2 and 3 were included to increase the certainty that the death was related only to prescription drug use, and not to mixed prescription and non-prescription substance use.

The factors were as follows:

1. Cause of death listed as ''toxic overdose,'' ''acute intoxication,'' ''overdose,'' or ''intoxication'' AND drugs listed included opioids.
2. Other drugs mentioned on the death certificate likely to be prescribed medications (e.g., antidepressants).
3. Terms ''medication'' or ''prescription'' appear in the description of the underlying cause, nature, or associated cause.
4. DLI records indicate worker received schedule II, III, or IV opioids within 3 months of death.
5. Presence or mention of illicit drug use (e.g., methamphetamine, cocaine, heroin).
6. Presence or mention of alcohol use.

We considered the death to be definitely due to prescription opioid use if factor 1 was present, factor 2 or 3 was present, and factors 5 and 6 were both absent. We considered the death to be probably due to prescription opioid use if both 1 and 4 were present and both 5 and 6 were absent. We considered the death to be possibly due to prescription opioid use if the case met criteria for definite or probable and either 5 or 6 was present.

RESULTS

Figure 1 shows the number of paid prescriptions for all claimants in WA workers' compensation. The number of prescriptions for Schedule II opioids increased approximately threefold between 1996 (22,867) and 2006 (66,544), plateaued during 2006–2008, then declined sharply in 2009 (54,484) and 2010 (44,209). The total number of paid prescriptions for Schedule III opioids increased between 1996 (76,935) and 1999 (93,550), then declined modestly through 2008 (79,882), then declined more sharply in 2009 (63,808) and 2010 (52,499).

Figure 2 shows the average daily MED of long-acting opioids prescribed from 1996 through 2010 for all prevalent claimants receiving these opioids. As we previously reported, there was a nearly 50% (47.5%) increase in mean daily MED of the long-acting Schedule II opioid prescriptions between 1996 (mean MED in 1996 = 92 mg/day) and 2002 (mean MED in 2002 = 135.7 mg/day). The mean daily MED was relatively stable between

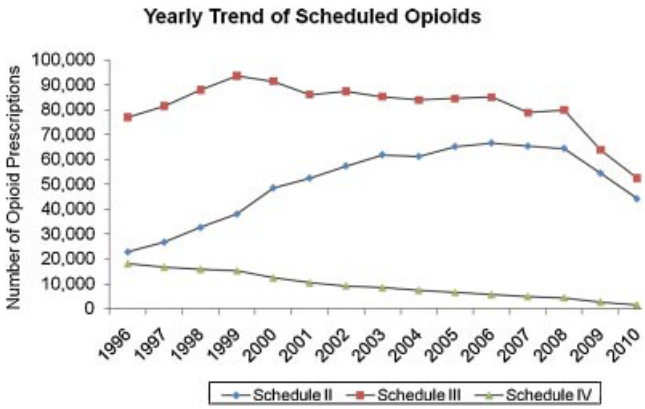

FIGURE 1. Yearly trend of scheduled opioids.

2002–2006, declined slightly in 2008 (129.7 mg/day MED), then declined more sharply beginning in 2009 Q3 (113 mg/day MED), falling to 105 mg/day MED by 2010 Q4, an approximate 27% decline from the peak (144.7 mg/day MED in 2002 Q1) during 2002–2006.

Figure 3 shows both the overall proportion of prevalent claimants on time-loss who received at least one opioid prescription and the proportion of these workers receiving prescriptions for $\geq$ 120 mg/day MED, between 2000–2010. Compared to the two quarters just prior to the release of the AMDG Guideline in April, 2007 (that is, 2006 Q4 and 2007 Q1), both the proportion who received one or more opioid prescriptions and the proportion receiving prescriptions for $\geq$120 mg/day MED fell by approximately 37 and 35%, respectively, by the last two quarters in 2010. For reference, the total number of opioid prescriptions per 1,000 prevalent time loss claims increased from 2,365/1,000 claims in 1997 to 3,222/1,000 claims in 2002, remained unchanged during 2002–2008, then fell to 2,666/1,000 claims in 2009 and to 2,245/1,000 claims in 2010.

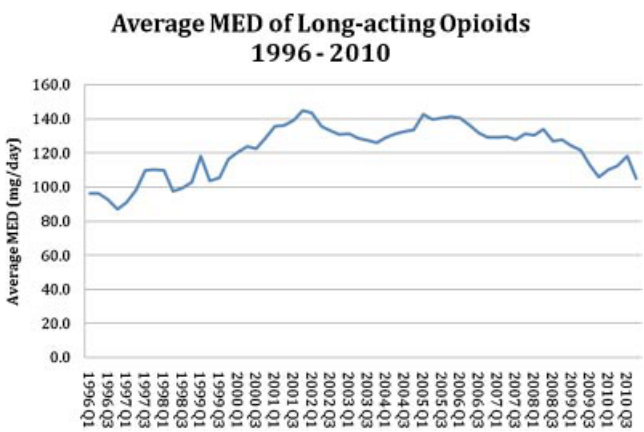

FIGURE 2. Average MED of long-acting opioids 1996–2010.

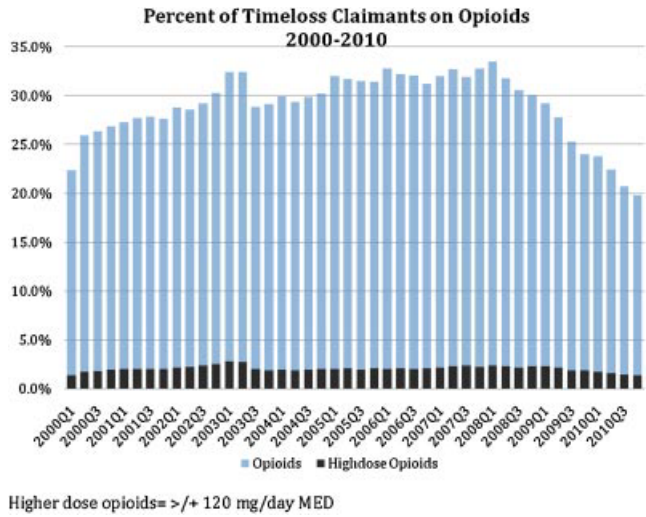

FIGURE 3. Percent of timeloss claimants on opioids 2000–2010.

One thousand two hundred thirty-four death certificates from 2003–2010 met the screening criteria. Of these, 193 listed cause of death as ''overdose'' or ''intoxication'' from opioids, including 15 classified as suicide and 178 as accidental death. One hundred sixty-two cases met criteria for definite, probable, or possible prescription opioid-related death. As can be seen in Figure 4, the overall number of prescription opioid-related deaths in the WA workers' compensation population continued to rise through 2009, then dropped dramatically in 2010.

DISCUSSION

This is the first time that the number of WA workers' compensation claimants treated with opioids, the mean daily opioid dose for long-acting opioids, and the percent of time loss claimants on opioids receiving $\geq$120 mg MED have declined since 1999, when more permissive opioid regulations were implemented in WA. By the 3rd

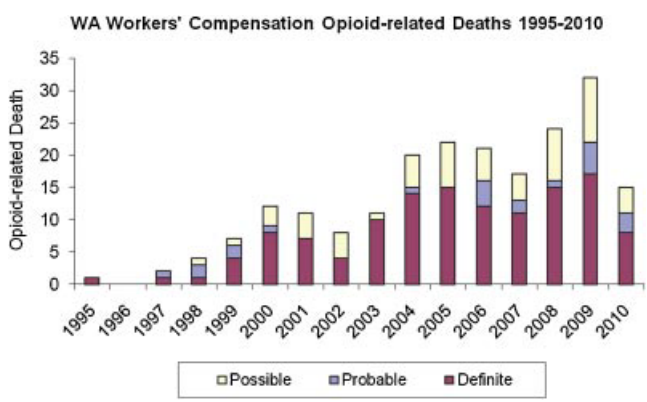

FIGURE 4. WA workers' compensation opioid-related deaths 1995–2010.

quarter 2009, there was a substantial decline in the mean daily long-acting opioid prescription dose among workers' compensation claimants in WA, followed by a dramatic fall in unintentional poisoning deaths related to prescription opioids in this population in 2010. We must emphasize that the drop in deaths represents a single data point and could be due to chance; a sustained drop in subsequent years in the workers' compensation population, or a drop in statewide prescription opioid-associated deaths, would be required to validate the finding. Although it is not possible to determine with certainty the impact of the Guideline relative to other factors affecting prescribing, the decline in average MED/day occurred after the implementation of the Guideline in April 2007 as an educational pilot. The decline in mortality (2010) occurred within two quarters of the most significant initial decline in mean daily dose of the long-acting opioids (2009 Q3–Q4).

The key new idea in the 2007 Guideline was the introduction of the 120 mg/day ''yellow flag'' warning dose, with a specific recommendation to obtain pain management consultation in previously opioid naïve patients who had escalated to that dose but who had not substantially improved in pain and function. No other State [Utah Department of Health, 2008], Federal [VA/DoD, 2010], professional society [Chou et al., 2009], or Canadian [Furlan et al., 2010] guidelines have included any type of specific, actionable dosing recommendation. The absence of any limit on dosing and the inclusion in State regulations of permissive language such as ''No disciplinary action will be taken against a practitioner based solely on the quantity and/or frequency of opioids prescribed'' [Washington Administrative Code, 1999] has likely contributed substantially to the national epidemic of prescription opioid-related morbidity and mortality over the past decade. In WA, these permissive rules have recently been repealed, and new rules reflecting the dosing guidance and other best practices in the AMDG Guideline have been implemented [Sullivan, 2011].

Although diversion and doctor shopping may account for the majority of prescription opioid overdoses in select, more rural regions [Hall et al., 2008] multiple recent well-designed observational studies have demonstrated a strong relationship between prescribed opioid dose and overdose risk [Braden et al., 2010; Dunn et al., 2010; Bohnert et al., 2011; Gomes et al., 2011] among persons with CNCP. Dunn et al. [2010] demonstrated a ninefold increase in risk for a serious adverse event or mortality among enrollees of a large health maintenance organization receiving $\geq$100 mg/day MED compared to doses at or below 20 mg/day MED. Braden et al. [2010] demonstrated that opioid doses over 120 mg/day MED or use of long-acting schedule II opioids increased risk of an alcohol- or drug-related healthcare visit for overdose, intoxication, or withdrawal. In a study of patients receiving opioids for pain from the Veterans Health Administration [Bohnert et al., 2011], the mortality risk related to opioid doses at or above 100 mg/day MED, compared with less than 20 mg/day, was increased sevenfold among patients with CNCP and 12-fold among those with cancer pain. Finally, a population-based study [Gomes et al., 2011] of Canadian residents receiving opioids for non-cancer pain found a near tripling of opioid-related mortality risk at $\geq$200 mg/day MED and a doubling of risk at 100–199 mg/day MED, relative to doses less than 20 mg MED.

This strong evidence of dose-related overdose risk should prompt other states and jurisdictions to take bolder action to stem the tide of opioid-associated morbidity and mortality. With over 13,000 deaths nationally, most of these occurring among 35–54 year olds [Warner et al., 2009; Centers for Disease Control and Prevention, WISQARS], bolder action is necessary. The Federal Centers for Disease Control and Prevention has issued guidelines that include use of a yellow flag warning dose of 120 mg/day MED, particularly for patients whose pain and function have not substantially improved during dosage escalation [Centers for Disease Control and Prevention, Poison Issue Brief]. The Federal government is now taking bolder action, including Risk Evaluation and Mitigation Strategies mandated by the Food and Drug Administration for manufacturers of long-acting opioids, and efforts to expand and improve the effectiveness of State-based Prescription Drug Monitoring Programs [White House Drug Policy, 2011].

It is possible that additional prescription opioid-related deaths could be prevented by more intensive efforts to educate health care providers about opioids. Two years after implementation of the 2007 WA AMDG opioid dosing guideline, only 45% of WA primary care physicians responding to a survey reported being familiar with the guideline [Morse et al., 2011]. This indicates the need for more intensive educational efforts, perhaps including special emphasis on targeting opioid prescribing education to high-frequency prescribers. A recent report suggested that 3% of opioid prescribers were associated with 55% of the Schedule II opioid prescriptions in the CA workers' compensation system [Swedlow et al., 2011]. Similar clustering of opioid prescribing, and a relationship between clustering and mortality, have recently been observed in Ontario [Dhalla et al., 2011].

Further research is needed to increase understanding of other harms that may be associated with opioid use and how to mitigate those harms. Several reports have now documented, in workers' compensation populations, that use of only a modest amount of opioid soon after injury is associated with at least double the odds of long-term disability, even after adjusting for other risk factors [Webster et al., 2007; Franklin et al., 2008; Gross et al., 2009]. Patients who take opioids long-term for pain are at

risk for escalating doses over time and thus at risk for harms associated with higher doses. A prospective study of patients off work due to a recent work-related back injury found that increased doses of opioids over the next year were not associated with clinically meaningful improvement in pain and function for the vast majority of patients [Franklin et al., 2009]. In addition, a recent randomized trial found that, among veterans with chronic pain, pain and function did not improve with dosage escalation over 18 months [Naliboff et al., 2011].

The findings described here point to the possible role for dosing guidance in preventing harms associated with opioid prescribing. Although prescriber education is important, education alone is not likely to be sufficient. It is likely that very specific dosing guidance, coupled with incentives to use best practices, will be crucial. The June 2010 update of the AMDG Opioid Dosing Guideline provides an open source resource of useful tools for prescribing opioids for CNCP [Washington Agency Medical Director's Group]. Other steps may also prove helpful in reducing opioid-related morbidity and mortality. These may include patient education, shared patient–provider decision-making tools to allow informed choices regarding treatments for chronic pain, and payment policy decisions that support use of effective alternatives for the treatment of chronic pain. In addition, wider and more effective use of State-based prescription monitoring programs [PMP Center of Excellence, 2011], including ''pushing'' evidence-based educational content to providers, would also likely be beneficial.

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