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Opioid Poisonings and Opioid Adverse Effects in Workers in Washington State

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Objective *To examine trends in opioid poisonings and adverse effects in Washington (WA) State and nationally.*

Methods *We calculated rates of opioid poisonings and adverse effects and examined opioid prescriptions in the WA workers' compensation system, 2004–2010. Using Health Care Cost and Utilization Project (HCUP), Nationwide Inpatient Sample (NIS) data, we also calculated national rates of opioid poisonings and adverse effects, 1993–2010.*

Results *We identified 96 opioid poisonings and 312 opioid-related adverse effects in WA, 2004–2010. The rates did not change substantially over these years. Most poisonings and adverse effects occurred in cases without chronic opioid use and with prescribed doses <120 mg/day morphine-equivalent dose. Nationally, the rates of opioid poisonings and adverse effects increased significantly from 1993 to 2010.*

Conclusions *Many poisonings and adverse effects occurred in patients without high dose or long-term opioid therapy, suggesting that opioid dosing and duration guidelines may not be sufficient to reduce morbidity related to prescription opioid use.* Am. J. Ind. Med. 56:1452–1462, 2013. *© 2013 Wiley Periodicals, Inc.*

KEY WORDS: opioid; opioid morbidity; opioid poisoning; opioid adverse effect; workers' compensation; Nationwide Inpatient Sample

INTRODUCTION

As the use of prescription opioids has increased [Sullivan et al., 2008; Boudreau et al., 2009; Fischer et al., 2011], overdoses and deaths associated with opioid use have increased [Paulozzi et al., 2006; Paulozzi and Annest, 2007; Coolen et al., 2009; Warner et al., 2009; Coben et al., 2010; Green et al., 2011; Paulozzi et al., 2011; Xiang et al., 2012]. Higher prescribed morphine-equivalent doses have been associated with both an increased risk of opioid overdoses [Dunn et al., 2010] and of opioid-related deaths [Bohnert et al., 2011; Gomes et al., 2011]. Studies have examined risk factors and trends for opioid-related fatalities, but fatalities represent only a small percentage of the possible adverse outcomes associated with prescription opioid use. Two recent studies have examined hospitalizations [Coben et al., 2010] and emergency department visits [Xiang et al., 2012] for opioid poisonings, but there are few population-based studies of the broader category of opioid

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adverse events [Solomon et al., 2010a,b]. Further, opioid prescribing prior to opioid adverse effects has not been examined.

As the nature and extent of the adverse events related to prescribed opioids became known, health agencies in Washington State (WA) initiated efforts to reduce opioid-related morbidity and mortality. In 2006 a consortium of Washington State agencies (the Washington State Agency Medical Directors' group) collaborated with clinical and academic experts in pain management (the Clinical Advisory Group) to develop an opioid dosing guideline for prescribing physicians in WA. The Washington State Interagency Guideline on Opioid Dosing for Chronic Non-Cancer Pain (the Guideline) suggested that physicians seek pain management consultation for patients reaching morphine-equivalent doses of >120 mg per day if they were not improving in both pain and function. The WA Guideline was released online March 22, 2007. To disseminate the Guideline, a website [AMDG, 2010] was developed that included "best practice" guidance, web-based continuing medical education training, and an opioid dosing calculator.

In order to determine if there were any changes in opioid morbidity in the 3 years after compared to the 3 years before implementation of the WA Guideline, we conducted a population based study among injured workers in the Washington State workers' compensation system from 2004 through 2010. Most prior studies have focused on opioid fatalities or non-fatal overdoses, which may only represent a small fraction of opioid related morbidity. In this study, we included both opioid poisonings (opioid overdoses) and opioid adverse effects. Since opioid poisonings and adverse effects may differ in both clinical severity and opioid prescription history, we examined poisonings and adverse effects separately. Four objectives guided our study: (1) to estimate the rates of opioid poisoning and opioid adverse effects among injured workers in the Washington workers' compensation system between 2004 and 2010; (2) to determine whether the trends in the rates of opioid-related morbidity changed after dissemination of the Guideline in 2007; (3) to compare patient demographic characteristics and opioid prescription history (including the duration, type, dose, and timing of opioid prescriptions) prior to opioid poisonings versus adverse effects; and (4) to compare Washington trends in opioid poisonings and adverse effects to national trends using the Nationwide Inpatient Sample [HCUP, 2011].

MATERIALS AND METHODS

Study Sample

The study sample consisted of injured workers in Washington State who were at least 18 years of age, had an allowed workers' compensation claim for an occupational injury or illness, and had a paid medical or hospital bill for an opioid poisoning or opioid adverse effect occurring between January 1, 2004 and December 31, 2010. Cases were excluded if they had any bills with a cancer diagnosis in their workers' compensation claim. The study was approved by the University of Washington Institutional Review Board which waived the requirements for informed consent because the research involved no more than minimal risk and could not be practicably carried out without the waiver.

Data Source

We obtained data from the Washington State Department of Labor and Industries (L&I) Workers' Compensation State Fund, which insures approximately two-thirds of non-federal workers in Washington (over 2.3 million workers in 2010). The remaining one-third work for large self-insured companies and were not included in our analyses because medical billing data are unavailable. The Department of Labor and Industries maintains administrative medical bill payment databases for all medical, hospital, and pharmacy bills for State Fund workers' compensation claims. The pharmacy bill database includes information on each prescription filled, including the National Drug Code, drug class, drug strength, number of pills dispensed, and total days' supply. In addition, the schedule of controlled substances, which is assigned by the Drug Enforcement Administration as a measure of potential abuse and dependence, is recorded. The medical and hospital bill databases include the date of service, diagnosis codes [International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM)], location, and billing and payment information. The hospital bills also include the supplementary Classification of External Causes of Injury and Poisoning Codes (E-codes), which indicate whether poisonings were accidental or intentional.

We obtained information on age, gender, type of occupational injury, and the date of injury from the L&I claims data. The care setting (emergency department, hospital inpatient, or outpatient) and other diagnoses on the day of the opioid-related event were obtained from the medical bill file. Cases that were initially treated in an emergency department and then were admitted to a hospital were classified as inpatient.

Outcome Measures

We identified opioid poisonings and opioid adverse effects using ICD-9-CM and E-codes (Table I). Drug poisonings involve either an overdose of a medication (taking a greater quantity than recommended) or the wrong substances given or taken in error. Poisonings exclude adverse effects of the drug [ICD, 2003]. Opioid poisonings include both intentional and unintentional opioid overdoses.

TABLE I. ICD-9-CM Diagnosis and Supplementary Classification of External Causes of Injury and Poisoning E-Codes Used to Identify Opioid Poisonings and Opioid Adverse Effects

Opioid poisoning codes	
965.00	Poisoning by opium, unspecified
965.02	Poisoning by methadone
965.09	Poisoning by other opioids and related narcotics
E850.1	Accidental poisoning by methadone
E850.2	Accidental poisoning by other opiates
Opioid adverse event codes	
E935.1	Adverse effects of methadone
E935.2	Adverse effects of other opioids and related narcotics

TABLE II. Number of Opioid Poisonings and Opioid Adverse Effects Identified With ICD-9-CM and E-Codes in WA State Workers Compensation, January 2004 Through December 2010

Opioid poisonings	Opioid adverse effects
Poisoning by other opioids (965.09) with or without additional diagnoses	
965.09 alone	37
965.09 + 965.00	2
965.09 + 965.02	1
965.09 + E850.2	19
965.09 + E935.2	5
965.09 + 965.0 + E850.2	1
965.09 + 965.02 + E850.1 + E850.2	1
Poisoning by opium, unspecified (965.00) with or without additional diagnosis	
965.00 alone	16
965.00 + E850.2	3
965.00 + E935.2	1
Poisoning by methadone, (965.02) with or without additional diagnoses	
965.02 alone	3
965.02 + E850.1	2
965.02 + E935.1	1
965.02 + E850.1 + E935.2	1
Accidental poisoning by other opiates (E850.2)	
E850.2 alone	3
Adverse effects of methadone (E935.1) and other opioids (E935.2), without an opioid poisoning code	
E935.1 alone	9
E935.2 alone	302
E935.1 + E935.2	1

The instructions for coding an adverse effect of a drug state that the correct drug was administered in therapeutic doses and the drug was the cause of the adverse effect. Adverse effects may include allergic or hypersensitivity reactions and exclude accidental or intentional overdoses [ICD, 2003]. Opioid adverse effects can include, but are not limited to, urticaria/pruritis, nausea and vomiting, constipation, intestinal obstruction, difficulty in breathing, acute respiratory arrest, respiratory failure, and alteration of consciousness. Table II shows the combinations of codes used to define cases of opioid poisonings and opioid adverse effects and the number of cases identified from 2004 through 2010.

When cases had bills for opioid adverse effects or poisonings on more than 1 day, the first event between 2004 and 2010 was considered the index event. Cases with subsequent bills that were less than 7 days from the first event were considered one event. Subsequent bills for opioid-related events that were 7 or more days after the index event were considered a new event.

Medication History

For each opioid poisoning or adverse effect, we identified paid bills in the pharmacy database for opioid medications between the time of the occupational injury and the date of the opioid-related event. (Opioid medications dispensed to patients in an emergency department or hospital are not included in the pharmacy database.) We used the pharmacy data to determine the number of paid prescriptions for opioids in the year (365 days) prior to the event, the days' supply of opioids dispensed in the year before the event, the types of drug(s) dispensed, the number of days between the event and the most recent opioid prescription, and the morphine-equivalent dose in the week prior to the event.

We classified opioid medications in the month before the opioid event according to the duration of action and the U.S. Drug Enforcement Administration schedule for potential abuse. Medications with a high potential for abuse and dependence are classified as Schedule II. We created four mutually exclusive categories: short-acting Schedule II, long-acting Schedule II, both short- and long-acting Schedule II, or only non-Schedule II opioids (which included Schedule III, Schedule IV, and unscheduled [tramadol] opioids). Cases with both Schedule II and non-Schedule II opioids were classified as Schedule II. We estimated the total days' supply of opioids dispensed in the year prior to each event. For cases with non-overlapping prescriptions, the total days' supply was the sum of the days' supply for each prescription. For cases with dispensed prescriptions on dates such that the days' supply of one medication overlapped with the days' supply of the second, each calendar day was counted only once. For each time period of interest, we determined whether medications were available in that time period based on the date dispensed and the days' supply. We defined chronic opioid use as $\geq$90 days' supply of opioid medications during the year before the opioid event.

The daily morphine-equivalent dose for each medication was calculated by multiplying the number of pills per day (the number of pills dispensed divided by the days' supply) by the opioid dose per pill, then multiplying by a morphine conversion factor [Vieweg et al., 2005; Von Korff

et al., 2008; AMDG, 2010]. When cases had more than one opioid medication available on the same day, we calculated the total daily dose by summing the daily doses for each medication. Because potential drug interactions can lead to an increased risk of adverse effects, we also determined whether benzodiazepines, muscle relaxants, or other sedative-hypnotic medications were available in the 30 days before the event (based on the date the medication was dispensed and the days' supply).

Nationwide Inpatient Sample

We estimated the national numbers and rates of hospitalizations for opioid poisonings and opioid adverse effects from 1993 through 2010 using the Nationwide Inpatient Sample (NIS), Healthcare Cost and Utilization Project (HCUP), Agency for Healthcare Research and Quality [HCUP, 2011]. The Nationwide Inpatient Sample is a stratified sample of 20% of U.S. community hospitals. The data include up to 15 diagnoses and up to four E-codes for each hospital discharge. We selected discharges with an ICD-9-CM code for opioid poisoning (965.09) and discharges that had an E-code for an opioid adverse effect (E935.2). To compare the rate of poisonings using different methods to identify cases, we selected all opioid poisonings from the principal diagnosis field and all poisonings coded in any diagnosis field.

Statistical Analysis

The rates of opioid poisonings and opioid adverse effects in WA workers' compensation were calculated as the number of events (per quarter and per year) divided by the number of workers with at least one filled prescription for an opioid medication each year. For cases with multiple events during this time period, only the index event was included in the analysis. We used descriptive statistics to summarize worker demographic characteristics, type of injury, diagnoses on the day of the event, and prescription history prior to the event. We used time series analysis to determine whether there were statistically significant changes in the trends in opioid adverse effects and poisonings in the WA workers' compensation system after implementation of the Opioid Guideline in 2007, controlling for random and seasonal effects [Eccles et al., 2003; Lagarde, 2012]. Specifically, we compared the rates of opioid poisonings and opioid adverse effects for the 13 quarters before the implementation of the Guideline (1st quarter 2004 through the 1st quarter 2007) to the corresponding rates in the 15 quarters after the implementation of the Guideline (2nd quarter 2007 through 4th quarter 2010).

From the Nationwide Inpatient Sample, we estimated the rate of opioid poisonings and adverse effects using the total U.S. population each year as the denominator. Because previous studies have used different methods to identify cases [Coben et al., 2010; Xiang et al., 2012], we examined the rate of poisoning based on an opioid poisoning diagnosis in any field and the rate based on opioid poisonings in the principal diagnosis field.

RESULTS

There were 420 injured workers with at least one opioid poisoning or opioid adverse effect with paid medical bills in the WA workers' compensation State Fund between January 1, 2004 and December 31, 2010. For nine cases with more than one opioid event during this time period, the index event was used in the analysis. Twelve cases were excluded because of a cancer diagnosis. The final dataset consisted of 96 cases with an opioid poisoning and 312 cases with an opioid adverse effect (total N = 408).

Description of Cases With Opioid Poisonings and Opioid Adverse Effects

Table III provides information on the sample characteristics for poisonings and adverse effects. Overall, 67% of the cases were men and the mean age was 44 years (SD = 11.8; range, 18–78 years). The most common types of occupational injuries were back sprains (20%), other sprains (29%), and fractures (13%).

Two-thirds of the poisonings and over 40% of the adverse effects occurred >1 year after the occupational injury. The time between the occupational injury and the opioid event was shorter on average for opioid adverse effects than for opioid poisonings: 25% of opioid adverse effects occurred less than 1 week after injury, in contrast to only 5% of poisonings. Of the eligible cases, the percent admitted to the hospital for treatment was the same for opioid poisonings and for opioid adverse effects.

A diagnosis of alteration of consciousness was present on the day of the opioid event for 23% of cases with poisonings and 8% of cases with adverse effects. Severe respiratory diagnoses (acute respiratory failure, respiratory arrest, hypoxemia, pulmonary collapse, pulmonary insufficiency, or acute lung edema) occurred in 11% of cases with poisonings and 6% of those with adverse effects. A large proportion (44%) of the cases with opioid poisonings also had diagnoses for poisonings by other medications on the same day. Cases with an opioid poisoning were more likely to have had at least one prescription for a sedative-hypnotic, benzodiazepine, or muscle relaxant medication available in the 30 days before the opioid event (27%) than were cases with adverse effects (12%). Among the opioid poisonings, 39% were coded as accidental and 17% were coded as intentional (data not shown).

TABLE III. Characteristics of 408 Opioid Poisonings and Opioid Adverse Effects in Washington State Workers Compensation 2004–2010

	Opioid poisonings (n = 96)		Opioid adverse effects (n = 312)		
	n	%	n	%	*P*-value
Age, years					0.05
<30	11	12%	43	14%	
30–39	20	21%	74	24%	
40–49	33	35%	91	29%	
50–59	28	29%	65	21%	
60+	3	3%	38	12%	
Gender					0.36
Female	35	36%	98	31%	
Male	61	64%	214	69%	
Work injury					0.85
Back sprains	22	23%	60	19%	
Other sprains	26	27%	93	30%	
Fractures	10	10%	45	14%	
Finger amputations	2	2%	4	1%	
Multiple injuries	7	7%	23	7%	
Others	29	30%	87	28%	
Time between date of injury and opioid-related event					<0.01
<7 days	5	5%	79	25%	
7–29 days	7	7%	30	10%	
30–89 days	3	3%	20	6%	
90–364 days	18	19%	52	17%	
365–729 days	21	22%	37	12%	
730–1,094 days	8	8%	24	8%	
≥1,095 days	34	35%	70	22%	
Year of event					0.33
2004	13	14%	34	11%	
2005	14	15%	45	14%	
2006	10	10%	55	18%	
2007	15	16%	48	15%	
2008	14	15%	46	15%	
2009	19	20%	37	12%	
2010	11	11%	47	15%	
Setting					0.63
Outpatient	3	3%	5	2%	
Emergency department	54	56%	175	56%	
Hospital inpatient	39	41%	132	42%	
Diagnoses on day of event					
Alteration of consciousness	22	23%	25	8%	<0.01
Respiratory (all)	23	24%	64	21%	0.47
Severe respiratory diagnoses[a]	11	11%	19	6%	0.08
Cardiac	20	21%	80	26%	0.34
Digestive	10	10%	73	23%	<0.01
Urticaria/pruritus	3	3%	37	12%	0.01
Poisoning by other medications[b]	42	44%	2	0.6%	<0.01
Other medications prior to the opioid event					<0.01
Sedative-hypnotics, benzodiazepines, or muscle relaxants in 30 days before event	26	27%	38	12%	

[a]Acute respiratory failure, hypoxemia, respiratory arrest, pulmonary collapse, pulmonary insufficiency, acute lung edema.
[b]Diagnoses of poisonings by other (non-opioid) medications.

Opioid Prescription History

Almost all cases (97%) with opioid poisonings had at least one paid prescription for opioid medications in the pharmacy database and 90% (86 poisoning cases) had at least one paid bill for an opioid medication in the year before the event. The remaining cases had a paid prescription >1 year prior to the event (3%), had paid prescriptions only after the event (4%), or had no paid opioid prescription in the pharmacy database (3%). A larger percent of cases with adverse effects than with poisonings did not have paid bills for opioid medications in the pharmacy database. Among 312 cases with opioid adverse effects, 81% had at least one paid opioid prescription in the database (64% in the year before the event, 6% more than a year before the event, and 12% only after the event), while 19% had no paid opioid prescriptions in the database.

Table IV provides information regarding the opioid prescription history for the 286 injured workers with paid opioid prescriptions in the year prior to the event. Cases with opioid poisonings had more opioid prescriptions dispensed in the prior year than did cases with opioid adverse effects. Cases with opioid adverse effects were more likely to have had only one prescription dispensed in the past year (31%) than were cases with opioid poisonings (14%). Although a larger percentage of cases with opioid poisonings (49%) received at least 90 days' supply of opioids in the year before the event than did cases with opioid adverse effects (29%), the majority of both groups would not be considered chronic opioid users.

The distribution of opioid dosing in the week before the opioid event was very similar for cases with opioid poisonings and opioid adverse effects. Among the workers who had opioids available (based on the date the prescription was filled and the days' supply) during that time period, the prescribed morphine-equivalent dose in the week before the event was less than 50 mg/day for 33% of the poisonings and 28% of the adverse effects. Prescribed opioid doses were below the "yellow flag" guideline of 120 mg/day for 72% of cases with poisonings and 70% of cases with adverse effects. The median daily dose in the week prior to the event was 75 mg/day in both groups. However, the mean daily dose was higher among opioid poisoning cases (mean = 124 mg, SD = 178) than among the cases with opioid adverse effects

TABLE IV. Opioid Prescription History Prior to Event, 286 WA Workers With Paid Opioid Prescription Bills in the Year Prior to an Opioid Poisoning or Opioid Adverse Event

	Opioid poisonings (n = 86)		Opioid adverse effects (n = 200)		*P*-value
Number of opioid prescriptions in year before event					<0.01
1	12	14%	61	31%	
2–10	38	44%	89	45%	
>10	36	42%	50	25%	
Total days' supply in year before event					<0.01
1–29	19	22%	108	54%	
30–89	25	29%	35	18%	
90+	42	49%	57	29%	
MED/day in week prior to event					0.63
1–19	4	7%	6	4%	
20–49	16	26%	36	24%	
50–89	14	23%	46	30%	
90–119	10	16%	17	11%	
≥120	17	28%	46	30%	
Length of time between last opioid prescription and opioid event					0.15
Same day	12	14%	48	24%	
1–2 days	12	14%	35	18%	
3–7 days	20	23%	35	18%	
8–30 days	17	20%	46	23%	
31–90 days	8	9%	12	6%	
91+days	17	20%	24	12%	
Drug type in 30 days before opioid event					0.15
Schedule II, both long- and short-acting	10	16%	24	14%	
Schedule II, short-acting	28	44%	86	52%	
Schedule II, long-acting	12	19%	14	8%	
Non-schedule II only	14	22%	43	26%	

(mean = 98 mg, SD = 86) owing to higher doses in the top 10% of the opioid poisoning cases (90th percentile = 282 mg/day) than in cases with opioid adverse effects (90th percentile = 180 mg/day).

Among the 86 opioid poisonings, 44 (51%) had an opioid prescription available within the prior 7 days and 61 (71%) within the prior 30 days. Among the 200 opioid adverse effects, 118 (59%) had an opioid prescription within the prior 7 days and 164 (82%) within the past 30 days. For 20% of opioid poisonings and 12% of opioid adverse events, the most recent paid prescription was more than 90 days prior to the event. Of those with opioids available in the 30 days before the event, 35% of opioid poisonings and 22% of cases with adverse effects had Schedule II long-acting opioids.

In both groups, oxycodone was the most common opioid medication available in the month before the event (57% of poisonings and 56% of adverse effects), followed by hydrocodone (47% of each group). Methadone was dispensed infrequently in this population (12% of poisoning cases and 2% of cases with adverse effects).

Rates of Opioid Poisonings and Opioid Adverse Effects

Figure 1 shows the rates, in each year from 2004 through 2010, of opioid poisonings and adverse effects among all injured workers with at least one filled opioid prescription in that year. The rate of opioid poisonings among opioid users remained relatively steady from 2004 (3.6/10,000) through 2010 (3.4/10,000). The rate of opioid adverse effects increased between 2004 and 2006, then decreased from 2007 to 2009, and increased again in 2010. The rate of opioid adverse effects was 9.4/10,000 opioid users in 2004 and 14.7/10,000 in 2010. The time series analysis revealed no statistically significant changes in the quarterly rates of opioid poisonings ($P = 0.47$) or opioid adverse effects ($P = 0.69$) associated with implementation of the Guideline.

Nationwide Inpatient Sample

The Nationwide Inpatient Sample data (Figures 2 and 3) show substantial increases from 1993 to 2010 in the national rates of opioid poisonings (from 2.7 to 12.6 per 100,000 persons) and adverse effects (from 9.9 to 34.2 per 100,000). In 2010, the rate of opioid poisonings was more than 4.5 times and the rate of opioid adverse effects was more than 3 times the rates in 1993. About twice as many cases were identified when opioid poisoning codes were found in any diagnosis field than when only the principal diagnosis field was used to identify poisonings.

We also examined national data for the same years the workers' compensation data were available (2004–2010). Over these years, the national rate of opioid poisonings increased 72% and the rate of adverse effects increased 45%.

DISCUSSION

In this population-based study of injured workers in Washington State, most opioid poisonings and adverse effects occurred among workers who would not be classified as having chronic opioid use. Less than half of the cases of

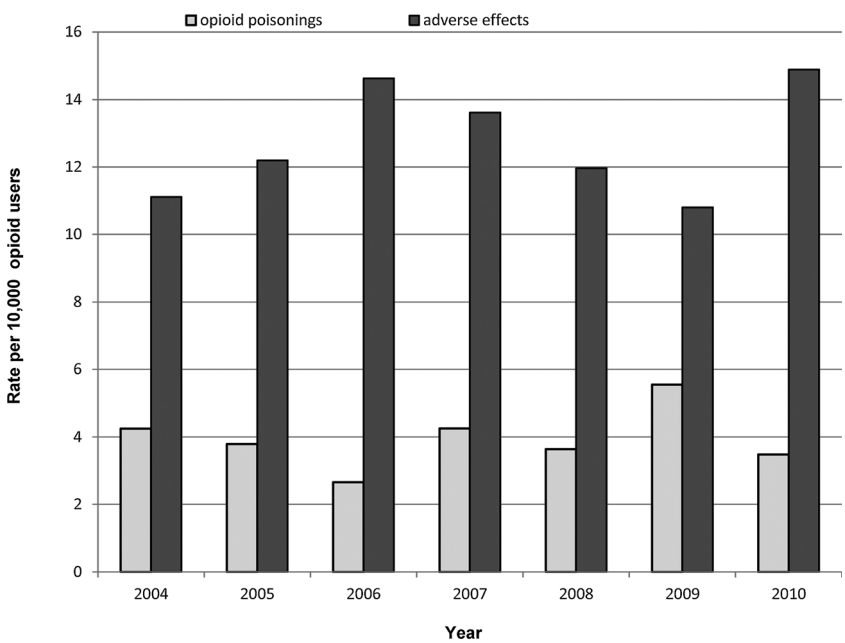

FIGURE 1. Rates of opioid poisoning and opioid adverse effects, WA State Workers Compensation, 2004–2010.

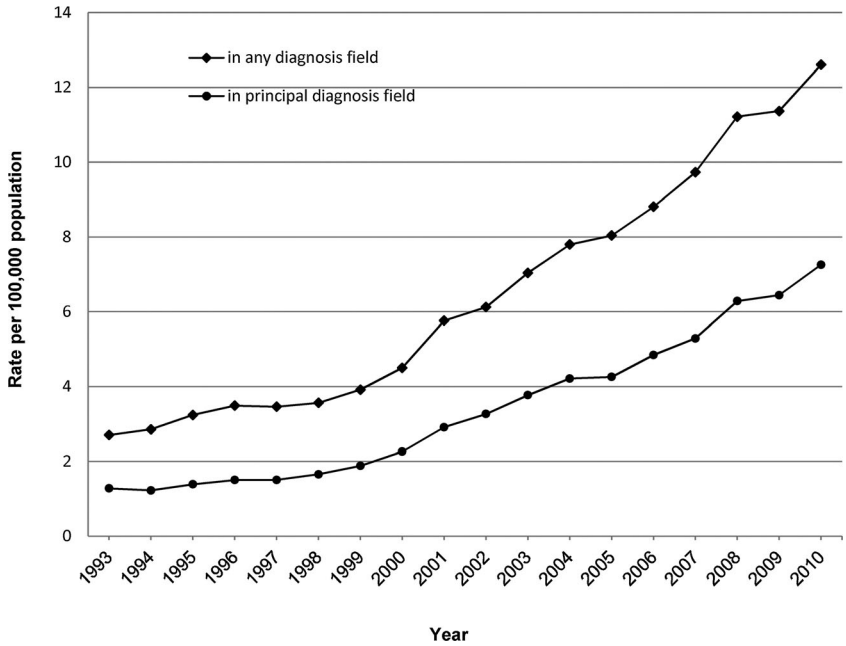

FIGURE 2. Rate of opioid poisonings in the US, Nationwide Inpatient Sample, 1993–2010.

poisonings and only a quarter of the cases of adverse effects had 90 or more days' supply of opioids (an indicator of chronic use) in the year before the event. Those with adverse effects were more likely to have new opioid use as compared with cases of poisonings. Among adverse effect cases, 28% had only one paid prescription prior to the event and 25% occurred within a week of the occupational injury. Although adverse effects cases were less likely than the poisoning cases to have chronic opioid use, the prescribed opioid doses were very similar for both types of events (median, 75 mg morphine-equivalent dose/day) and approximately 25% of each group had prescribed doses above 120 mg/day. Although the median dose is below the yellow flag threshold dose of 120 mg/day in the WA Guideline, it is substantially

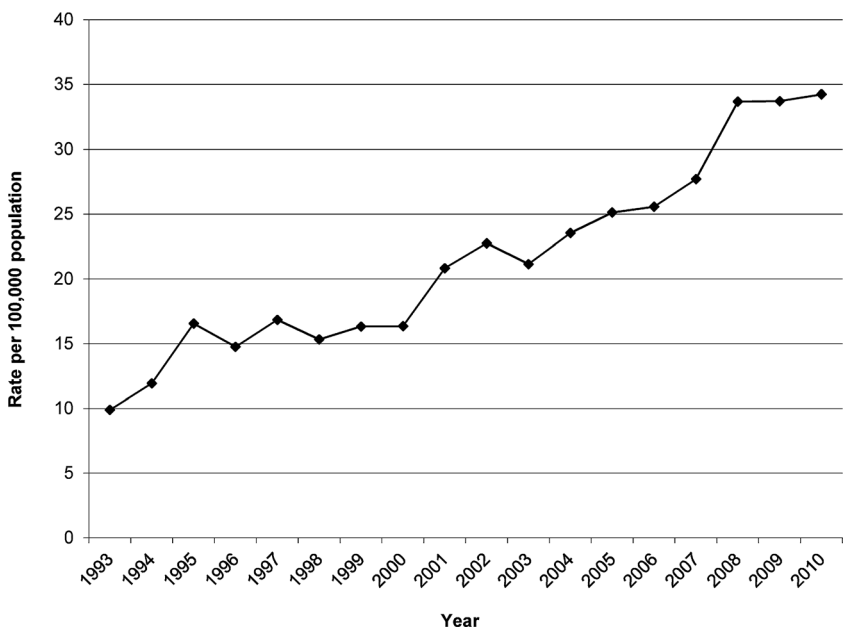

FIGURE 3. Rate of opioid adverse effects in the US, Nationwide Inpatient Sample, 1993–2010.

higher than the average prescribed doses previously reported for back pain patients treated with opioids (30–40 mg/day) [Edlund et al., 2010; Deyo et al., 2011].

We found a wide range of diagnoses on the day of the event for cases having an opioid adverse effect. In addition, higher risks of serious adverse events requiring hospitalization including cardiovascular events, falls, and fractures have been reported for Medicare beneficiaries who were taking opioids than was the case with other pain medications [Solomon et al., 2010b]. Although opioid adverse effects can include relatively minor complications, the percent of cases admitted to the hospital in our sample (over 40%) was the same in cases with adverse effects as with poisonings. Because of the risks involved with opioid therapy, patients need continuous monitoring. Risks are present at the initiation of opioids and throughout the time they are taken.

The combination of benzodiazepines, muscle relaxants, or other sedative-hypnotic medications with opioids can exacerbate respiratory depression and increase the risk of adverse effects, but concomitant use of these medications is common. We found that 27% of poisoning cases and 12% of adverse effect cases had sedative-hypnotic medications available within the month prior to the opioid event. However, this may be an underestimate since it does not include medications that were self-paid, covered by other insurers, or were dispensed more than 30 days before the event. Prior studies of chronic opioid users have found that 29–75% of patients also have concurrent sedative-hypnotic use [Braden et al., 2010; Dunn et al., 2010; Saunders et al., 2012].

The rates of opioid poisonings (about 3/10,000) and opioid adverse effects (about 9–15/10,000) based on our data are low. However, they are likely underestimates of true rates, as emergency department and hospital visits not paid for by workers' compensation, as well as all office or clinic visits, were not captured in our data.

Findings regarding possible impact of the Washington State Interagency Guideline on Opioid Dosing for Chronic Non-cancer Pain on opioid poisonings and adverse effects in the workers' compensation system were ambiguous. Although the rates of opioid poisonings and adverse effects among those who received opioids in WA workers' compensation did not show significant declines after implementation of the Guideline, the national rates of opioid poisonings and adverse effects rose over this time period. However, caution is needed in interpreting these patterns because the rates in the national data are based on the general population whereas the rates in WA workers' compensation are based on individuals who have paid claims for opioid medications. Thus, the WA rates would be expected to be much higher than the U.S. rates. Although the rates of opioid poisoning and adverse effects in the WA workers' compensation population are not strictly comparable to the rates generated by the Nationwide Inpatient Sample, we believe it is useful to include national data in our analysis to compare the WA workers' compensation trends to broader trends in prescription opioid overdose and adverse effects rates outside WA.

A complicating factor in evaluating the impact of the Guideline is that full dissemination was delayed 2 years after first being placed online in 2007 due to legal action that was eventually dismissed. During this period, a statewide survey of primary care prescribers suggested that fewer than half were familiar with the Guideline [Morse et al., 2011]. Because of the lag between implementation of the Guideline and more widespread provider knowledge of the Guideline, we might expect a delayed impact on opioid morbidity. In addition, it was not until late 2009 that the average dose of the most potent opioids began to substantially fall and not until 2010 that opioid-related deaths declined [Franklin et al., 2012]. We would expect a drop in poisonings and adverse effects to follow the drop in average dose. Further evaluation of opioid morbidity rates is needed after wider dissemination of the Guideline.

This study has a number of limitations. First, it may be difficult to detect significant changes in the rates of poisonings and adverse effects in WA workers' compensation due to very small numbers of cases per quarter. Second, we only know of opioid poisonings and adverse effects that are paid by the workers' compensation system; we do not have information on hospital or emergency department visits paid by other insurers. In addition, there are limitations related to the use of administrative pharmacy data. Pharmacy billing data provide a record of the medication dispensed and not the amount actually used. The billing data may underestimate recent opioid use if workers receive opioids covered by other insurers, are self-paid, or take opioid medications saved from a previous episode of care. Likewise, it is not known if workers take more than the prescribed dose, or if workers use non-prescribed opioids. Also, the pharmacy billing data does not include opioid medications dispensed in a hospital or in an emergency department. Administrative pharmacy data will overestimate medication use when patients take less medication than dispensed. However, some of the advantages of using administrative pharmacy records include more complete information on drug name, dose, and timing of use than self-reported data [West et al., 1995, 1997].

Another limitation is possible misclassification of opioid poisonings and opioid adverse effects. We did not validate the ICD-9 CM and E codes in the computerized billing data against the actual medical records related to the event. However, we did observe differences between the poisonings and the adverse effects in the other diagnoses on the day of the event and in the opioid prescription history that support the diagnoses. Cases with opioid poisonings were more likely than cases with adverse effects to have alteration of consciousness or severe respiratory diagnoses. Digestive problems and urticarial/pruritus diagnoses were more likely

in cases with opioid adverse effects than in opioid poisonings. In addition, acute opioid use was more common in cases with opioid adverse effects and chronic use was more common in opioid poisonings. While the diagnosis of an overdose versus an adverse effect may not always be clear to the treating physician, any misclassification in coding poisonings and adverse effects would lead to a conservative bias with fewer differences observed between the two groups.

Finally, the results in WA workers' compensation may differ from those that would be found in the general population. It would be of interest to conduct similar analyses in other, non-workers' compensation populations.

Strengths of this study include the population-based sample, the inclusion of both opioid poisonings and adverse effects, and the inclusion of both acute and chronic opioid use. While a number of studies have examined opioid poisonings, this is the first population-based study to examine the rates of opioid adverse effects resulting in hospitalization or emergency department visits in a working-age population. In addition, this is the first study to examine the opioid dosing patterns prior to adverse effects and poisonings among both acute and chronic opioid users.

CONCLUSION

Although the widespread concern about opioid poisonings has largely focused on patients receiving chronic opioid therapy, we found that over 50% of the opioid poisonings and over 70% of opioid adverse effects occurred in injured workers who would not be classified as having chronic opioid use. Although some aspects of opioid prescription history differed between injured workers with opioid poisonings and those with adverse effects, the opioid dose in the prior week did not differ substantially. The opioid dose in the majority of poisoning and adverse effects cases was substantially lower than the "yellow flag" dose of 120 mg/day morphine-equivalent dose in the WA Guideline. Thus, although patients may have additional prescription opioids from other sources or may take more than the prescribed dose, opioid poisonings and adverse effects can occur at lower doses and during acute use. These data suggest that opioid dosing and duration guidelines that focus primarily on higher dose use may not be sufficient to achieve a substantial reduction in morbidity related to prescription opioid use. Even at modest dosing levels over short time intervals, prescription opioid use can have serious health consequences.

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