Risk of opioid-related adverse events among Medicaid and workers' compensation patients receiving long-term opioid therapy

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Abstract

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Background: Death from opioid analgesics has become a national epidemic after a change in federal regulations in 1999 liberalized the use of opioids in long-term treatment for chronic non-cancer pain (CNCP). Opioids were increasingly prescribed for CNCP in the last decade despite weak evidence on the safety and effectiveness of long-term opioid therapy. In 2007, Washington State (WA) agencies implemented an opioid dosing guideline on safe prescribing for CNCP as an educational tool for providers to safely prescribe opioids for CNCP at effective doses. We conducted two population-based observational studies in WA state-funded programs after implementation of the opioid dosing guideline. The objective of the first study was to determine whether opioid dose is associated with the risk of opioid-related mortality using a population-based retrospective cohort study design among opioid users who were enrolled in WA Medicaid.

We also investigated the risk of opioid-related mortality associated with patterns of opioid use such as duration of use, chronic use, opioid duration of action, and other prescription drug use. The objective of the second study was to evaluate opioid use and dosing before and after Guideline implementation in the WA workers' compensation population.

Study 1 Methods and Results: We identified 150,821 patients ages 18-64 years with non-cancer pain who had ≥1 opioid prescriptions in WA Medicaid during April 1, 2006-December 31, 2010. We used bivariate analysis to examine indicators of opioid use with opioid-related death. Overall and stratified rates of opioid-related deaths per 100,000 person-years were calculated among the WA Medicaid study population. Cox proportional hazards models were used to calculate unadjusted and demographic-adjusted hazard ratios (HRs) and 95% Confidence Intervals (CIs) for risk of opioid overdose death with opioid use and dosing factors. The majority of patients were short-term users with <3 months of opioid use overall (76.5%) but almost three-quarters of the opioid deaths (73.4%) occurred in patients who were chronic users. The median average daily dose was 40 mg/day morphine equivalent dose (MED). The majority of patients who died from an opioid overdose had a current opioid prescription (76.9%). Only a small fraction of patients (4.4%) had doses ≥200 mg/day MED at last use, but this group constituted more than a quarter of the opioid overdose deaths (27.8%). The overall rate of opioid-related death was 125.8 per 100,000 person-years, and as high as 684.0 per 100,000 person-years among patients with ≥200 mg/day MED. The overdose death rates among chronic users were higher than the rates among the overall study population, even at moderate doses. Among patients at 50-89 mg/day MED, the rate in chronic users was 425.7 per 100,000 person-years, whereas the rate in all users was 261.8 per 100,000 person-years. The risk of opioid overdose death significantly increased with increasing doses at or above 50 mg/day MED in all

users as well as in chronic users only. Among all users, compared with patients with low doses of 1-19 mg/day MED, patients with 50-89 mg/day MED had almost 3 times the risk of overdose death (adjusted HR: 2.7, 95% CI: 1.5 - 4.8) and patients with ≥200 mg/day MED had more than 5 times the risk (adjusted HR: 5.3, 95% CI: 3.1 - 9.1). The HRs among chronic users were higher than among all users, particularly at doses of 120-199 mg/day MED (adjusted HR: 4.8, 95% CI: 2.3- 10.1) and ≥200 mg/day MED (adjusted HR: 5.9, 95% CI: 3.0-11.4). Chronic users had a 6-fold increased risk of opioid overdose death relative to non-chronic users (adjusted HR: 6.3, 95% CI: 4.8-8.2). Opioid overdose risk increased with cumulative duration of opioid use (continuous and non-continuous days), even at shorter use. Users at 31-89 cumulative days of opioid use were 4 times more likely to have an opioid-related death than users with ≤30 cumulative days of use (adjusted HR: 4.3, 95% CI: 2.7-6.9). Opioid controlled substance Schedule and duration of action were also associated with the risk of opioid overdose death. The greatest risk was among patients with prescriptions for both long-acting and short-acting Schedule II opioids versus those with non-Schedule II opioids only (adjusted HR: 4.7, 95% CI: 3.2-6.8).

Study 2 Methods and Results: We identified 161,283 workers aged 18-64 years with non-cancer pain who had ≥1 opioid prescriptions in WA Workers' Compensation during April 1, 2004-December 31, 2010. Prevalence and incidence rates of opioid use were assessed. We compared pre- and post-Guideline chronic and high-dose use (≥120 mg/day) among incident users. The mean monthly prevalence of opioid use declined by 25.6% between 2004 (14.4%) and 2010 (10.7%). Fewer incident users went on to chronic opioid therapy in the post-Guideline period (4.7%; 95% CI, 4.5%-5.0%) than in the pre-Guideline period (6.3%; 95% CI, 6.1%-6.6%). Compared with pre-Guideline incident users, post-Guideline incident users were 35%

less likely to receive high doses (adjusted odds ratio=0.65; 95% CI, 0.59-0.71).

Conclusion: The results of these studies demonstrate significantly increased risk of opioid overdose death among various groups of opioid users and emphasize the importance of continuous monitoring throughout the course of therapy. The study findings suggest that opioid dosing guidelines that specify a "yellow flag" dosing threshold may be a useful tool in preventing escalation of doses into ranges associated with increased mortality risk. Although the extent to which decreases were due to the Guideline is uncertain, to our knowledge, this was the first report of significant decreases in chronic and high-dose prescription opioid use among incident users. Dosing guidelines have generally targeted CNCP patients, but patients with short-term opioid therapy for acute pain may also be at increased risk of opioid overdose death. Evidence-based strategies for opioid risk management are needed to help abate the epidemic of opioid-related morbidity and mortality.

DISSERTATION INTRODUCTION

In recent years, an opioid overdose epidemic emerged in the United States (US)[1] following increased opioid prescribing for chronic non-cancer pain (CNCP).[2-5] Opioid analgesics (e.g., Percocet, Vicodin, OxyContin) in the treatment and management of CNCP was restricted by federal legislation until the late 1990s, after pain specialists and advocacy groups lobbied for more effective CNCP treatment.[6,7] Changes in state policies and regulations permitted practitioners to prescribe opioids to CNCP patients for long-term use at any rate and dose without being penalized.[8,9] Yet, there was no strong evidence for the safety and effectiveness of long-term opioid therapy.[10-12] Studies used for support were generally of short duration with small samples and different populations.[12,13] Compounding the situation, the long-acting opioid OxyContin was put on the market during the same time with false claims that the risk of addiction was less than 1%.[14] Further, the manufacturers targeted high prescribing providers in areas where opioids were in high demand while increasing manufacturing and supply. Sales of opioids to pharmacies, hospitals, and practitioners soared across the US.[1,14-17]

The Washington (WA) Department of Labor and Industries (L&I) workers' compensation system was one of the first to report increases in opioid overdose deaths.[18,19] L&I identified trends in opioid mortality and patterns in opioid dosing among the workers' compensation population[19-22] which brought to the forefront the increase in opioid-overdose deaths in WA.[23] The WA Department of Health (DOH) increased opioid surveillance that illustrated trends across the state and identified Medicaid as a high risk population for opioid overdose death.[23,24] Beginning in 2006, CDC conducted several descriptive studies to detect national patterns of opioid use and overdose.[1,16,17,25-28] Harms from opioid use included opioid

misuse, abuse and diversion.[1,25,29].

In an immediate response to the emerging epidemic of unintentional poisonings, the WA Agency Medical Directors' Group (AMDG) collaborated with clinical and academic pain experts to develop the *Interagency Guideline on Opioid Dosing for Chronic Non-cancer Pain* (the Guideline).[4,30] The Guideline was implemented in 2007 and was the first to provide specific prescription opioid dosing guidance in treating CNCP patients more safely and effectively. The Guideline included recommendations on best practices for patient selection and risk assessment, initiating and discontinuing opioid therapy, and for transitioning to chronic opioid therapy. A key feature was the recommendation that providers not exceed a dosing threshold of 120 mg/day morphine equivalent dose (MED) for patients who did not have clinically meaningful improvement in pain and function without first consulting with a pain specialist.

A high priority in risk management and shaping health policy is generating evidence for the effectiveness of long-term opioid therapy.[11,12,31] Although several studies have been conducted recently on the risk of opioid overdose, research gaps still exist in quantifying the risks posed by opioid use and understanding the characteristics of high-risk populations that put them at increased risk for opioid overdose death. It is also necessary to evaluate the impact of interventions on opioid overdose so that they can be replicated or improved in other populations.

The purpose of the study in Chapter 1 was to determine whether opioid dose is associated with the risk of opioid-related mortality using a population-based retrospective cohort study design among opioid users enrolled in WA Medicaid. We also investigated the risk of opioid-related mortality associated with patterns of opioid use such as duration of use, chronic use, opioid duration of action, and other prescription drug use.

The purpose of the study in Chapter 2 was to evaluate the impact of the WA *Interagency*

Guideline on Opioid Dosing for Chronic Non-cancer Pain on post-implementation opioid use and dosing patterns, as compared to pre-implementation opioid dosing patterns, among the WA workers' compensation population receiving opioid therapy for CNCP.

CHAPTER 1

Risk of opioid-related adverse events among Medicaid patients receiving opioid therapy

INTRODUCTION

A dramatic increase in fatal opioid overdose has paralleled a rise in use of prescription opioids.[1-5] The number of opioid prescriptions written and dispensed soared[32] following changes to state and federal regulations in the late 1990s to improve the treatment and management of chronic non-cancer pain (CNCP) with long-term opioid therapy.[6] An opioid was prescribed in approximately 20% of office-based medical visits for pain in 2010, as compared to 11% in 2000.[33] Sales to pharmacies, hospitals, and practitioners for opioids across the US suggested that by 2010 opioid use was 4 times higher than in 1999, and sales in the state of Washington (WA) were among the highest.[1] By 2012, the rate of opioid overdose death in the United States was 5.1 per 100,000 persons, over 3.5 times greater than the rate in 1999 (1.4 per 100,000).[34] Accidental poisonings have become the leading cause of unintentional injury death in the United States (US), largely due to deaths associated with prescription opioids.[1] The Centers for Disease Control and Prevention (CDC) has declared opioid overdose deaths to be a national epidemic.

Rates of opioid overdose death in the US were at their highest in 2010-2011 (5.4 per 100,000 in both years).[34] However, in WA, the rate peaked in 2008 at 7.4 per 100,000,[23] which was 50% higher than the national rate that year (4.8 per 100,000).[34] Although rates of opioid overdose death in WA have since been decreasing, the rate remained elevated in 2012 at 5.3 per 100,000 compared to rates prior to the emergence of the opioid overdose epidemic. The decline in opioid overdose death rates reflects the results of efforts by both state and local governmental and non-governmental entities to improve the safety of opioid prescribing practices for

CNCP.[18,35] Yet, the increased risk of opioid-related death persists and risk factors among CNCP patients have not been adequately established.[12,31]

Medicaid has been recognized by CDC as a high-risk population for fatal opioid overdose.[24,29] Nationally, prescriptions for opioids among Medicaid beneficiaries nearly doubled between 1998 and 2003 from 15 million to more than 27.5 million, representing an estimated 4% of the program's total prescription drug expenditures.[3] In Arkansas Medicaid, the proportion of enrollees with CNCP who were prescribed opioids increased by 29% from 17% in 2000 to 22% in 2005.[36] A study by the WA Department of Health (DOH) found that the age-adjusted rate of opioid overdose death among WA Medicaid enrollees during 2004-2007 was 30.8 per 100,000 person-years, almost 6 times the rate of 4.0 per 100,000 person-years in the non-Medicaid population (age-adjusted relative risk 5.7, 95% Confidence Interval (CI) 5.3-6.1).[24] Nearly half (45.4%) of the opioid overdose deaths overall (N=1,668) were among Medicaid enrollees. The decedents included in the study had been enrolled in Medicaid at some point during the year that they died, but whether or not they had previously received a prescription for an opioid through Medicaid was not reported. The authors posited that the higher rate in Medicaid may be due to higher rates of opioid prescribing or a greater proportion of individuals with substance abuse disorders.

Few studies have reported risk factors for opioid-related mortality in Medicaid CNCP populations using long-term opioid therapy. Most studies have focused on drug utilization[37-40] opioid use patterns,[41,42] or opioid dependence/abuse.[39] Some studies of Medicaid beneficiaries have reported opioid overdose death by opioid dosage but were restricted to specific generic forms of opioids without an emphasis on chronic use.[43-45] Previous research has shown that a dose-response relationship exists between opioids and the risk of opioid overdose among CNCP

patients.[46-48] These studies were conducted in unique populations, including a health maintenance organization (HMO) and the Veterans Health Administration (VA). Unlike these groups, Medicaid serves a population with a low socioeconomic status. To our knowledge, the overall relationship between dose and opioid-related death has not been assessed in the Medicaid population.

Additional research is needed to understand the characteristics that may put Medicaid patients at higher risk for opioid overdose death. The association between opioid dose and opioid overdose deaths may be different among Medicaid patients. Further, based on WA's experience with significantly higher rates of opioid overdose deaths in Medicaid than in non-Medicaid populations, the rates of opioid overdose deaths by dose may also differ among chronic opioid users. Alternatively, rates of opioid overdose death may be elevated among acute users which could be indicative of aberrant drug-related behaviors. While there is increased substance abuse in Medicaid populations[24,49] and non-medical use of opioids is a large contributing factor to the rise in opioid overdose[28], the magnitude of opioid overdose risk in Medicaid recipients prescribed an opioid for pain is unclear. The assessment of opioid overdose risk in acute users and by duration of use could help elucidate the risk conferred by opioid abuse in short-term users.

We obtained WA Medicaid pharmacy data for all patients who had an opioid prescription during 2006-2010. These data were linked to WA DOH death data, giving us the ability to examine opioid overdose death and dosing patterns in this population. The purpose of the study was to determine whether opioid dose is associated with the risk of opioid-related mortality using a population-based retrospective cohort study design among opioid users in WA Medicaid. To address the need for more evidence on determinants for fatal opioid overdoses, we also

investigated the risk of opioid-related mortality associated with patterns of opioid use such as duration of use, chronic use, opioid duration of action, and other prescription drug use.

MATERIALS AND METHODS

Study Setting and Population

We obtained WA Medicaid data from the WA Health Care Authority (HCA). The Medicaid administrative databases include automated data on paid and unpaid claims for medical, hospital and pharmacy services. HCA also provided data files for cause of death and enrollment. Patient-level data were available only for claims under the fee-for-service (FFS) program beginning in April 2006. Thus, claims paid through managed care programs are not included. Additionally, methadone prescriptions among patients receiving methadone maintenance treatment for opioid dependence are billed separately so were not included in the pharmacy data. HCA identified 377,056 patients in WA Medicaid aged 18-64 years with at least one paid or unpaid FFS claim for opioid analgesic prescriptions dispensed between April 1, 2006 and December 31, 2010.

The first paid opioid prescription dispensed during the study period for each patient was defined as the index prescription. The index prescription reflects the first available paid opioid prescription in the data and not necessarily a patient's first use of opioids. Patients were excluded (Table 1) if they had (in order) 1) no paid claims for oral or transdermal prescription opioid analgesics (12.8%), 2) a history of cancer (except non-melanoma skin cancer) based on *International Classification of Diseases (ICD), Ninth Revision, Clinical Modification* diagnostic codes or prescriptions for cancer drug treatment up to 1 year after the index prescription (4.6%), 3) a history of opioid dependence treatment indicated by the outpatient procedure code H0020 up

to 90 days after the index prescription (0.8%), 4) dual-eligible coverage (benefits through both Medicaid and Medicare) on or before the index prescription dispense date (9.6%), 5) comprehensive care through a managed care program only (4.5%) or at the time of the index prescription (0.9%), 6) limited FFS enrollment for follow-up at first opioid use because of a switch to managed care/dual-eligible coverage (19.0%) or <90 days of continuous FFS enrollment (7.3%) resulting in unstable enrollment or insufficient information needed to assess opioid use and health outcomes, or 7) did not have any clinic visits within 1 month of the index prescription (0.7%). The final sample consisted of 150,821 non-cancer patients with ≥1 paid oral or transdermal opioid prescription and ≥90 days of continuous FFS enrollment at opioid initiation.

Patients in the final sample were followed for a minimum of 90 days starting with the index prescription date. Follow-up continued until the end of the study period, death, disenrollment from Medicaid, or loss of cohort eligibility. Depending on the reason patients were no longer eligible for the study, follow-up ended on the last day before they either received a cancer diagnosis, entered into an opioid dependence treatment program, switched to managed care or dual eligible coverage, or aged out of the Medicaid program.

Opioid Prescription Use and Dosing

The WA Medicaid pharmacy database contains a record for each medication dispensed with information on drug name, strength, quantity, days' supply and dispense date. Methadone prescriptions for use in methadone maintenance treatment for opioid dependence are not included. For each enrollee's prescription, we defined the start date as the date dispensed and the end date as the date dispensed plus the days' supply minus 1 day. The dates encompassed by a prescription during months of FFS enrollment were counted as the days covered by opioids. If

an individual had 2 or more prescriptions with days' supply covering the same dates, the overlapping dates were counted as one covered day.

We grouped opioids by generic name, short- versus long-acting properties, and Drug Enforcement Administration (DEA) schedule (Appendix 1). The DEA schedule ranks controlled substances with recognized medical uses on a scale of II through V, with Schedule II having the highest abuse potential (Schedule I drugs cannot be legally prescribed). We further categorized opioids as short-acting Schedule II, long-acting Schedule II, or non-Schedule II (including non-scheduled tramadol).[50]

We calculated the daily dose for each opioid prescription as the total number of pills dispensed multiplied by the drug strength, divided by the days' supply. For fentanyl, the daily dose was equivalent to the drug strength delivered by 1 patch. Daily doses were then converted to morphine equivalent doses (MED) using published conversion factors.[30,50,51] If an individual had prescriptions with overlapping dates, the daily dose was defined as the sum of the doses from the different prescriptions for the same day. As a result, we were able to estimate the total opioid dose for each day of follow-up.

We used the daily doses to estimate the average daily dose in 30-day intervals starting with the index prescription. The average daily dose (mg/day MEDs) for each 30-day interval was computed as the sum of the daily doses in that interval, divided by the number of days in that interval covered by an opioid prescription. Patients were classified based on average daily MEDs of 1-19 mg/day, 20-49 mg/day, 50-89 mg/day, 90-119 mg/day, 120-199 mg/day, or 200 mg/day or more.

Duration of opioid use was based on the total number of prescription days' supply, considering overlapping dates in prescriptions. An individual's overall duration of use was

counted as the total number of days covered by opioid prescriptions during the study period. Categories included less than 3 months, 3-5 months, 6-12 months, 13-24 months, or >24 months. Cumulative duration of use was determined on each day of follow-up as the sum of days covered by opioid prescriptions through that point in time. Specific categories of cumulative duration were assigned as 1-30 days, 31-90 days, 91-180 days, 181-365 days, 366-730 days, or >730 days.

We assessed chronic opioid use on each day as having $\geq$90 days of opioid use (consecutive or non-consecutive) within the past 180 days. Once a patient became a chronic user, the patient remained a chronic user for the duration of the study. Recency of opioid use was defined for each day of follow-up according to time since the last run-out day of an opioid prescription. A patient was considered a current user if run-out days for an opioid prescription included the same day or the past 30 days. Recent use was 31-180 days since last use, and past use was over 180 days since last use.

We were able to determine the number of different prescribing providers that patients had in their first year of opioid use by using unique provider codes encrypted by HCA. We grouped patients as having 1-2 providers, 3-5 providers, or $\geq$6 providers in the 365 days after the index prescription.

Opioid-Related Death

Fatal opioid overdoses were identified by WA DOH through a special review of death certificates in 1995-2010 for accidental deaths with ICD 10 codes (T40.0-T40.6 and F11) for poisoning by narcotics or opioid abuse, dependence, or misuse.[24] Briefly, DOH classified such deaths as being related to prescription opioids if the death certificate contained overdose-related terms indicating acute drug intoxication and a prescription opioid was reported on the death

certificate. Because morphine and hydromorphone are metabolites of heroin, these opioids were only considered prescription opioids if there was evidence on the death certificate to support that they were pharmaceutical.

The death data maintained by DOH do not include payer source. However, the WA Health and Recovery Services Administration provided HCA with the data from the DOH prescription opioid death study linked to individuals with Medicaid enrollment in the year of death. In turn, HCA supplied us with these data as part of the data files for cause of death. Based on the study exclusions, we excluded 485 opioid-related deaths, most due to the enrollees with dual-eligible coverage only (n=172) or limited enrollment (n=170) (Table 2). An additional 117 opioid overdose deaths occurred among the included enrollees after study follow-up and could not be used. The final study population included 316 opioid-related deaths among the Medicaid beneficiaries.

Comorbidities

Patients were classified as having a diagnosis for opioid dependence or abuse if a medical visit was coded with an ICD-9 code of 304.0, 304.7, or 305.5.[52,53] Because the index opioid prescription reflects the first available paid opioid prescription in the data and not necessarily first use of opioids, patients could have a history of opioid dependence or abuse at the time of their index prescription. We examined concurrent use of sedative-hypnotics that have been shown to increase risk of opioid-related death.[46] Sedative-hypnotics included barbiturates, benzodiazepines, muscle relaxants, and anti-anxiety medications. We ascertained if sedative-hypnotic prescriptions were dispensed in the first 30 days of opioid use or in the last 30 days of opioid use. We similarly evaluated antidepressants which were also frequently prescribed.

Chronic disease scores are commonly used as a measure of comorbidity in epidemiologic

research.[46,49,54-56] We used the Charlson Comorbidity Index which was designed for use in risk adjustment for comorbidity severity.[54,57-59] A score for prognostic comorbidity is generated based on a weighted classification scheme for chronic diseases that predicted 1-year mortality.[60] The Charlson Index is the sum of the weighted scores, ranging from 0 to 30, and was recoded as 0, 1, or ≥2.

Demographics

The Medicaid data included information on race and Hispanic origin. A person's race/ethnicity was classified as either non-Hispanic white, non-Hispanic black, Hispanic, Asian (including Hawaiian and Pacific Islander), Native American/Alaskan Native, other, or unknown. The region in which the patient resided at first opioid use was based on the classification system by the Rural Health Research Center at the University of Washington and categorized as 1) urban, 2) large, rural city or town, or 3) small or isolated, rural town.[61] Estimates of the median household incomes of patients' residential ZIP Codes at first opioid use were obtained from the U.S. Census Bureau American Community Survey of 2010.[62]

Statistical Analysis

Descriptive statistics were used to characterize opioid users, prescription history, dosing patterns and duration of use during the study period. We used bivariate analysis to examine these indicators of opioid use as potential risk factors or confounders for opioid-related death. Correlations between dose, duration of use, time since last use, and chronic use were examined using Pearson's correlation coefficient. The overall rate of opioid-related deaths per 100,000 person-years was calculated for WA Medicaid recipients aged 18-64 years with ≥1 paid opioid prescription during the study period. In addition to demographics, rates were stratified by average daily dose, duration of use, time since last use, chronic use, opioid drug type and other

prescription drug use. We also present rates of opioid-related death by average daily dose stratified by chronic and non-chronic users.

Cox proportional hazards models were used to assess the associations between the various factors and the risk of opioid-related death. The study entry date was the date of the first paid opioid prescription (the index prescription). Patients were censored at 1) disenrollment from Medicaid, 2) enrollment into managed care or dual-eligible coverage, 3) date of their 65th birthday, 4) cancer diagnosis date, 5) admission into opioid dependence treatment, 6) non-opioid death, or 7) end of the study (December 31, 2010). Several of the variables were included as time-varying covariates, including average daily dose, cumulative duration of use, time since last use, chronic use, and opioid drug type. We calculated unadjusted and demographic-adjusted hazard ratios (HR) and 95% confidence intervals (CIs) to determine if opioid use and dosing factors were associated with the risk of opioid-death. All analyses were conducted using Stata Statistical Software Release 12.[63]

RESULTS

Demographics

The 150,821 Medicaid recipients included in the study were followed for a mean (SD) of 20.3 (16.5) months, with more than half having at least one year of continuous enrollment (median 13.2 months) (Table 3). Half of the opioid users were under 35 years of age (49.5%), and more than one-third were of ages 35-54 years (38.4%). Two-thirds (67.7%) were women. The study population was mostly non-Hispanic white (56.0%), but also consisted of 6.3% non-Hispanic black, 10.5% Hispanic, 3.5% Asian/Hawaiian/Pacific Islander, 7.6% Native American/Alaskan Native, 7.1% other, and 9.1% unknown. The majority of patients resided in

urban areas (79.0%), with fewer residing in smaller rural towns (10.5%).

Almost half of the opioid deaths were among Medicaid enrollees ages 45-54 years (45.3%) and a quarter were among patients ages 35-44 years (26.3%) (Table 4). Opioid deaths were equally divided between men (48.2%) and women (51.8%). The proportions of opioid deaths were highest among non-Hispanic whites (84.5%) and residents of urban areas (78.5%). There were no deaths among Hispanic or Asian patients, and <5% were among non-Hispanic blacks (3.8%) and Native American/Alaskan Natives (4.4%).

Opioid Prescription Use and Dosing

Approximately three-quarters of patients received ≥1 prescription for hydrocodone (74.1%) and half received ≥1 prescription for oxycodone (49.0%). Other opioids that patients ever used included tramadol (18.3%), codeine (16.6%), and propoxyphene napsylate (9.1%). Less than 5% of patients had ever received a prescription for methadone (4.9%) or hydromorphone (4.4%). One of the least used opioids was fentanyl (1.2%).

Slightly more than half of the patients had average daily doses of 20-49 mg/day MED at first opioid use (53.3%) and at last use (52.2%) (Table 5). However, the distribution of average daily doses was skewed with a mean (SD) of 129.3 (338.3) mg/day MED and median (interquartile range) of 40 (23.3-80.4) mg/day MED because some patients had very high doses of opioids. At last opioid use, 3.3% of patients had prescribed doses of 120-199 mg/day MED and 4.4% had prescribed doses of ≥200 mg/day MED. Chronic opioid use within the first 180 days of the first prescription was 12.8% and grew to 20.1% by last use. However, the majority of patients were short-term users with <3 months of opioid use overall (76.5%) and not more than 30 days' supply in the first year of use (70.8%). Over half of patients had only 1-2 opioid prescriptions in the first year of use (52.5%). Almost two-thirds had only non-schedule II

opioids at last use (65.0%). Two-thirds of the patients had 1-2 prescribing providers in the first year of use (69.1%), and 8.2% had ≥6 providers. A fraction of patients had a diagnosis of opioid dependence/abuse before their index opioid prescription (1.1%) or received a diagnosis in the first or second year after their index prescription (2.1% and 1.1%, respectively). Concomitant medications that were commonly prescribed in the first 30 days of opioid use included sedative/hypnotics (20.0%) and antidepressants (21.6%).

More than one-third of opioid deaths were among individuals with average daily doses of 20-49 mg/day MED in the first 30 days of use (36.4%) (Table 6). Opioid users with doses of ≥200 mg/day MED at first recorded use represented 19.9% of opioid deaths and even more deaths with these doses at last use (27.8%). Patients with a total duration of 3-5 months of opioid use comprised the lowest proportion of deaths (13.6%). Just over half of the opioid overdose deaths were among patients with chronic use in the first 180 days (54.7%), but nearly three-quarters of the deaths occurred in all patients who eventually became chronic users (73.4%). Chronic users were more likely than non-chronic users to have an opioid-related death.

Table 6 also shows that 38.3% of patients who had a fatal opioid overdose had >20 opioid prescriptions and 50.0% had >180 days' supply in their first year of opioid use. The majority of patients with an opioid overdose death had a current opioid prescription either on the day of their death (60.8%) or within the previous 30 days (16.1%). Among patients with an opioid overdose death, the last opioid prescription the patient filled was for a Non-Schedule II opioid (34.5%), a Schedule II short-acting opioid (21.8%), a Schedule II long-acting opioid only (24.4%), or for both Schedule II long- and short-acting opioids (19.3%). A small minority of the deaths included patients with a history of opioid dependence/abuse before their first recorded opioid prescription (2.2%), but 17.1% of the patients who died had received a diagnosis during

their first year of opioid use. More than half of the opioid overdose deaths occurred in patients who had current prescriptions for sedative/hypnotics (43.7%) or for antidepressants (33.9%).

Rates of Opioid Overdose Deaths

Overall, the rate of opioid-related death in this Medicaid population was 125.8 per 100,000 person-years (Table 7). The rate of opioid overdose death increased with dose. Rates increased substantially for doses of 50-89 mg/day MED (261.8 per 100,000 person-years) and 90-119 mg/day MED (354.8 per 100,000 person-years). The death rates were as high as 445.2 per 100,000 among patients with doses of 120-199 mg/day MED, and 684.0 per 100,000 person-years among users with $\geq$200 mg/day MED. Rates of fatal opioid overdose exhibited a dose-response among chronic opioid users as well, climbing up to 768.9 per 100,000 person-years in users at $\geq$ 200 mg/day MED (Table 8). The overdose death rates among chronic users were higher than the rates among the overall study population, even at moderate doses. Among patients at 50-89 mg/day MED, the rate in chronic users was 425.7 per 100,000 person-years, whereas the rate in all users was 261.8 per 100,000 person-years. Because the numbers of opioid overdose death were smaller in non-chronic users, their rates of opioid overdose death by dose were variable and unstable in this group. However, the rate in all non-chronic users was 43.7 per 100,000 person-years.

Risk Factors for Opioid Overdose Deaths

Cox proportional hazards models of risk of opioid overdose death among various subgroups are presented in Table 9 for unadjusted HRs and HRs adjusted for age, gender, race/ethnicity and area of residence. Patients ages 45-54 years had twice the risk of a fatal opioid overdose as patients ages 25-34 years (adjusted HR: 2.2, 95% CI: 1.5-3.1). Males were 70% more likely than females to have an opioid overdose death (adjusted HR: 1.7, 95% CI: 1.3-2.1).

Native Americans/Alaskan Natives and non-Hispanic blacks were at least 50% less likely than non-Hispanic whites to fatally overdose from opioids (adjusted HR: 0.5, 95% CI: 0.3-0.9 and adjusted HR: 0.4 95% CI: 0.2-0.7, respectively).

The risk of opioid overdose death significantly increased with increasing doses at or above 50 mg/day MED in all users (Table 9) as well as in chronic users only (Table 10). Among all users, compared with patients with low doses of 1-19 mg/day MED, patients with 50-89 mg/day MED had almost 3 times the risk of overdose death (adjusted HR: 2.7, 95% CI: 1.5 - 4.8) and patients with $\geq$200 mg/day MED had more than 5 times the risk (adjusted HR: 5.3, 95% CI: 3.1 - 9.1). The HRs among chronic users were higher than among all users, particularly at doses of 120-199 mg/day MED (adjusted HR: 4.8, 95% CI: 2.3- 10.1) and $\geq$200 mg/day MED (adjusted HR: 5.9, 95% CI: 3.0-11.4). Additionally, chronic users had a 6-fold increased risk of opioid overdose death relative to non-chronic users (adjusted HR: 6.3, 95% CI: 4.8-8.2) (Table 9).

Overdose risk increased with cumulative duration of use (continuous and non-continuous) (Table 9). Users at 31-89 cumulative days of opioid use were 4 times more likely to have an opioid-related death than users with $\leq$30 cumulative days of use (adjusted HR: 4.3, 95% CI: 2.7-6.9). The risk doubled between 91-180 days and 181-365 cumulative days of use (adjusted HRs: 7.3, 95% CI: 4.6-11.5 to 14.1, 95% CI: 9.1-21.8). At >730 cumulative days of use, the risk of opioid overdose death was over 20 times the risk in users with $\leq$30 cumulative days of use (adjusted HR: 23.8, 95% CI: 13.9-40.6). In addition, patients who hadn't filled an opioid prescription in over 6 months had a marked 90% decreased risk of opioid overdose death compared with patients who had an active opioid prescription within the last 30 days (adjusted HR: 0.1, 95% CI: 0.1-0.2). Patients with opioid prescriptions in the last 2-6 months also had a

significantly lowered risk by 70% (adjusted HR: 0.3, 95% CI: 0.3-0.5).

Opioid controlled substance Schedule and duration of action was also associated with the risk of opioid overdose death. The greatest risk was among patients with prescriptions for both long-acting and short-acting Schedule II opioids versus those with non-Schedule II opioids only (adjusted HR: 4.7, 95% CI: 3.2-6.8). Having Schedule II short-acting opioids only put patients at twice the risk as having non-Schedule II opioids only (adjusted HR: 2.1, 95% CI: 1.4-3.1). Sedative/hypnotic use compared to non-use, regardless of concurrent opioid use, was associated with more than triple the risk of opioid overdose death (adjusted HR: 3.4, 95% CI: 2.7-4.3). Use of antidepressants was associated with more than double the risk (adjusted HR: 2.4, 95% CI: 1.9-3.0).

DISCUSSION

We believe that our study is the first to report increased risks of opioid-related death associated with prescription opioid dose in a Medicaid population among both chronic opioid users as well as opioid users overall. There was a clear dose-response relationship between` opioid dose and the risk of overdose death both overall and among chronic users only. Although <5% of patients had doses $\geq$200 mg/day MED at last use, they constituted more than a quarter of the opioid overdose deaths. In this study population consisting of predominantly short-term opioid users, almost three-quarters of the opioid deaths occurred in patients who were chronic users. Chronic users were at higher risk of opioid overdose death than non-chronic users. The majority of patients who died from an opioid overdose had an active opioid prescription on the same day or within the 30 days prior to their death. Although the risk of opioid overdose death was highest among users with the most cumulative days of opioid use, the risk began to increase

among opioid users at 31-89 cumulative days of opioid use compared to users with ≤30 cumulative days of use. In addition, not only did using long-acting opioids pose more risk of opioid overdose death, but users of short-acting opioids had a smaller but significant increased risk (compared to non-Schedule II medications) as well.

Consistent with other studies, we observed the highest rates of opioid overdose death among chronic opioid users with doses at or above 120 mg/day MED. These high-dose chronic users had an increased risk of opioid overdose death relative to chronic users with low doses (1-19 mg/day MED). A study at a WA health maintenance organization (HMO) was the first to illustrate a dose-response relationship between opioid dose and risk of overdose among incident long-term users.[46] They found that, compared with low-dose opioid users, users of 50-99 mg/day were at 3.73 times higher risk (95% CI 1.47-9.50) and users of 100 mg/day or more were at 8.9 times greater risk (95% CI 3.99-19.72). Although the risk of opioid overdose was greater for persons who received elevated doses of opioids, only a small number of events were observed in this population (6 fatal and 45 non-fatal events between 1997 and 2005). However, we were able to conduct our study in a larger sample and saw similar patterns.

Similarly, US Veterans with CNCP who were taking over 100 mg/day MED, as compared to less than 20 mg/day MED, had a 7-fold increased risk of opioid overdose death (95% CI 4.85-10.65).[47] A case-control study in Ontario, Canada, was also conducted among residents of low socioeconomic status (SES). The chance of dying from opioids in patients on more than 200 mg/day MED was almost three times that of all patients on less than 20 mg/day MED (adjusted OR: 2.88, 95% CI: 1.79-4.63).[48] Direct comparisons are difficult due to differences in dose definitions, study inclusions and populations used. However, the various studies on opioid overdose and dose demonstrate that the risk of opioid mortality can vary

between and within diverse patient populations, and the association between higher opioid dose levels and opioid overdose risk were shown in repeated results.

While high doses of opioids were clearly associated with an increased risk of opioid overdose mortality, patients using lower doses of opioids should not be overlooked. The last opioid dose for half of the patients were at doses 20-49 mg/day MED. The proportion of opioid overdose deaths in these patients was equivalent to the proportion of deaths in patients with doses $\geq$200 mg/day MED at last use. The high proportion of deaths in the low-dose patients could be a reflection of the large prevalence of low-dose users overall. In a recent study we conducted in a larger group of Medicaid patients[64], we showed that more than half of the non-fatal opioid poisonings were in patients who had opioid prescriptions totaling <90 days' supply in the year before the poisoning. The recommendation was that opioid dosing guidelines be revisited to address acute and intermittent opioid use even at low prescribed doses.

Our study appears to be the first to quantify the risk conferred by duration of use for opioid-related death in a population of both chronic and acute users. A recently published study was also conducted among all opioid users to examine differences in durations of opioid use.[65] The results indicated that individuals with extended opioid use had higher rates of opioid overdose morbidity than those who discontinued use earlier. We found that, the more days of use a patient accumulated, the greater the risk of opioid-related death compared to users with $\leq$30 cumulative days of use. Although the rate was lower in short-term users, they were still at increased risk of overdose death. We also demonstrated that, compared with current opioid users, patients who had not received an opioid prescription for at least 6 months were at significantly decreased risk of opioid overdose death.

Long-acting opioids can be dangerous, particularly for patients who are newly placed on

these medications[10,66] (i.e., opioid naïve). However there are few studies that describe this increased risk. If long-acting opioids are taken by individuals who have never used opioids or are not opioid tolerant, delayed adverse effects could occur while the medication is still being metabolized or eliminated.[10,66] In addition, patients may not feel an immediate effect due to the slow release of the drug and take additional doses misconstruing the original dose as ineffective.[16] A recent study of non-fatal opioid overdose found that new users of opioid therapy for CNCP who were using long-acting opioids had an increased risk compared to those using short-acting opioids, especially if they started with the long-acting opioid.[67] Our study may be the first to provide evidence of the increased risk of opioid overdose death with both opioid Schedule and duration of action. Patients using Schedule II long-acting opioids, either taken alone or with Schedule II short-acting opioids, had a higher risk of overdose than users of Non-Schedule II opioids only. The risk was also elevated among users of Schedule II short-acting opioids only compared to non-scheduled opioid medications. We also found that the last opioid prescriptions that the patients in the study population received were typically for Non-Schedule II opioids only. These opioids have less abuse potential than Schedule II opioids, but more than a third of the deaths occurred in these patients. It could be that risk of opioid overdose varies with specific opioid generics within ranked Schedule. For example, while the risk among propoxyphene users compared to hydrocodone users was not significant,[44] methadone users had a higher risk of death than users of sustained-release morphine at doses <60 mg/day MED (HR: 1.59, 95% CI: 1.01-2.51).[45]

Sedative-hypnotics have also been shown to increase opioid overdose risk,[46] and opioid use among patients on sedative-hypnotics is common.[68] The combined effect of opioids and sedative-hypnotics can result in respiratory depression or sedation.[69] Similar to our findings,

benzodiazepines were identified in 31% of opioid overdose deaths nationally, more than twice as many in 1999.[70] Several studies have also illustrated that individuals with mental health or substance use disorders have a high risk of opioid-related mortality.[46,71,72] We observed an increased risk among patients with antidepressant use. Due to possible confounding by indication, the overdose risk should also be assessed among patients diagnosed with depression.

Drug misuse, addiction, and diversion became rampant in the US as opioid prescribing increased.[16,73] Given the rise in non-medical use of prescription opioids nationwide, we explored the frequency of opioid/dependence and opioid overdose death in this population. Because we suspected related deaths would occur among patients who did not have valid prescriptions for opioids, we followed patients during periods of opioid non-use. A notable proportion of the opioid overdose deaths occurred among patients who were diagnosed with opioid dependence/abuse in the first year after their first opioid prescription, but opioid dependence/abuse was not common in this study population. However, it was not within the scope of this study to assess substance abuse disorders or deaths from heroin or other illicit drugs. It may be that most individuals with opioid dependence/abuse obtain opioids diverted from other sources and didn't receive a prescription through Medicaid, at least not during the study period. We would not have captured these individuals because all of the patients in the study had at least 1 FFS-paid opioid during the study period. In addition, patients with a history of methadone maintenance treatment for opioid/dependence were not included in the study or were censored if they were admitted to a treatment program during follow-up because dosing data are not available for these patients. However, they comprised <1% of the subjects altogether.

Evidence for variation in rates by race/ethnicity is scarce. In this low SES population,

non-Hispanic blacks and Native Americans/Alaska Natives were at lower risk of opioid overdose death than non-Hispanic whites. There were no opioid overdose deaths among Hispanics. Although Native Americans/Alaska Natives were at half the risk of overdose compared with non-Hispanic whites, they had one of the highest rates of overdose death by race/ethnicity. A national study conducted by CDC also reported that the highest rates of opioid overdose fatalities occurred in non-Hispanic whites and Native American/Alaska Natives (over 6.0 per 100,000 in each group).[1] The lowest rates, 0.5-2.1 per 100,000, were in Asians/Native Hawaiians or Pacific Islanders, blacks, and white Hispanics. Opioid prescribing patterns have also been shown to vary by race/ethnicity. Black beneficiaries in North Carolina Medicaid were almost 10% less likely to receive an opioid prescription (OR: 0.91, 95% CI: 0.88-0.94).[40] Hispanic and Non-Hispanic black patients were more than 30% less likely than white patients to receive an opioid for pain at an emergency department visit.[74] The racial disparities in both opioid prescribing and opioid overdose death are not understood. The study population was not very diverse with more than half being non-Hispanic white. This group incurred 85% of the opioid overdose deaths, but the high proportion may not only be the reflection of the racial/ethnic distribution. The second largest racial/ethnic group comprising 10% of the study population were Hispanic patients, and there were no opioid overdose deaths among them. Some factors to explore would be health care utilization, access to care, and prescription drug costs to the patients. The quality of race/ethnicity data is poor and needs to be improved.

Our study has several limitations. Medicaid serves a socioeconomically disadvantaged, diverse population and the members may not be representative of higher income groups, other WA residents, or Medicaid populations in other states. With the Medicaid data came several challenges. Variable enrollment for patients was one of the most problematic limitations. First,

patient-level data were only available for individuals with Medicaid FFS and did not include complete outcome data for individuals enrolled in managed care or dual-eligible programs. Some patients were enrolled in one of the non-FFS insurance types only so they were automatically excluded. In many instances, patients switched back-and-forth between non-FFS insurance and FFS, or permanently switched to non-FFS insurance. Lapses in FFS coverage resulted in loss of data on patients' opioid use during those time periods. Incomplete data on the frequency of opioid use, dose levels, and opioid Schedule could have resulted in misclassification of related covariates, such as duration of use and chronic use. Because continuous follow-up was necessary for this study to accurately assess opioid use and outcomes, we censored patients when they switched to either managed care or dual-eligible coverage.

Second, some patients had FFS at their first paid opioid prescription but limited follow-up or enrollment. For instance, they switched to managed care or dual eligible coverage within the next two months or had <3 months enrollment altogether. We had virtually no follow-up data on their opioid use since they would have been censored in the second or third month. In order to avoid including patients with unstable enrollment or insufficient information needed to assess opioid use and health outcomes, our inclusion criteria required that patients have at least 90 continuous days of FFS enrollment from the dispense date of their index prescription.

Third, data were not available before April 2006 due to changes in Medicaid's computerized billing system. Therefore, we had no medical history for a large proportion of patients whose first available opioid prescription was in April 2006. The same applied to other patients who enrolled in Medicaid during a later month in the study period and had an opioid prescription that same month (e.g., enrolled in Medicaid in December 2008 and also had their first paid opioid prescription in December 2008). Without knowledge of prior opioid use, we

were unable to distinguish new opioid users from current opioid users. Treatment with opioid therapy for incident users would be different than treatment for chronic users. Incident users are considered opioid naive and have less tolerance for opioids than chronic users. They would likely initiate opioid therapy at lower dose levels, be prescribed short-acting opioids and try various generics in response to side effects.

Some limitations in our study are inherent in use of pharmacy claims data and may lead to misclassification of exposures and outcomes. Opioid use may be underestimated due to prescriptions that were denied, charged to other insurance, or paid for out-of-pocket. We also could not assess changes in pain and function without patient-reported outcomes. The prescription dispense date may not reflect the actual timing of medication use. We could not determine actual medication intake or duration of use. We assumed patients took medications at the maximum rate allowed as calculated by the dispensing pharmacist, which may have overestimated daily dose and underestimated days used. Some administrative pharmacy datasets include a variable for dosage instructions indicating how often the medication was to be taken, for example, daily, as needed, 10 continuous days, every other day, etc..[75] If we had such a variable, we could more accurately measure daily dose as well as frequency of use.

In response to the then emerging epidemic of unintentional opioid poisonings, the WA Agency Medical Directors' Group (AMDG) collaborated with clinical and academic pain experts in 2007 to develop and implement the first guideline specifically for prescription opioid dosing.[4,30] The goal of the AMDG Guideline was to assist primary care providers in more safely and effectively prescribing opioids to CNCP patients initiating opioid therapy and to prevent these new patients from escalating to high-dose opioid use if they were not benefitting from opioid therapy. A key feature was the recommendation that providers not exceed a dosing

threshold of 120 mg MED/day for patients who did not have clinically meaningful improvement in pain and function without first obtaining a pain specialist consultation. Since then, several states and agencies have followed suit. In WA, new regulations for CNCP management that went into effect in 2010 to enforce best practice use, including attention to the dosing threshold.[76]

Our findings suggest that long-term, high-dose opioid users are not the only patients at high risk for opioid overdose death. Some subpopulations at higher risk may not have been identified or current interventions are not reaching them as indicated by increased proportions of deaths among non-chronic and short-term users. For instance, patients with opioids leftover from a previous injury may not understand the potential deadly effects of using them while not under health care supervision. Alternatively, the accessibility of diverted prescription opioids may not have improved and sources of these opioids may not be detected. WA Labor and Industries designed new guidelines in 2013 to extend opioid prescribing best practices to treatment for acute and subacute pain, perioperative opioid use, opioid tapering, and gauging clinically meaningful improvements in pain and function.[35] Likewise, AMDG recently revised their guidelines to do the same. Guidelines also relay the dangers of early use of long-acting opioids, concurrent opioid use with benzodiazepines, and use among patients with mental health or substance use disorders. These steps have all helped to reduce the harms associated with prescription opioid use, as mirrored in recent declines in opioid overdose death,[35] however, the risk of opioid overdose death is still high.

Additional research is needed to clarify these risks associated with opioid overdose death. Although risk estimates were adjusted for demographics, we have not yet assessed the risks associated with opioid overdose death adjusted for or stratified by clinical factors, such as

concomitant use of sedative/hypnotics or a history of mental/substance use disorder. In addition, there is insufficient evidence on risk of opioid overdose death with opioid generic, either overall or by duration of action. These research questions must be answered with long-term studies, ideally with measurements to track improvements in pain and function, in order to follow patients long enough to reflect the duration of use in practice. States across the nation have launched Prescription Monitoring Programs (PMPs) which may become valuable resources for comprehensive opioid prescribing data that can be used to identify statewide opioid trends, high-risk populations, and inappropriate opioid use.

Table 1. Study exclusions among Washington State Medicaid enrollees aged 18-64 years who had ≥1 pain-related opioid prescription during April 2006-December 2010.

	n	%	Remaining N	Remaining %
Total Number of Subjects Identified by Medicaid	**377,056**			
Exclusion				
No Paid Claims for Opioid Prescriptions	48,275	12.8	328,781	87.2
No Eligible Opioid Prescriptions	101	0.0	328,680	87.2
Incomplete Enrollment Data	231	0.1	328,449	87.1
History of Cancer	12,662	3.4	315,787	83.8
Cancer Diagnosis Within 1st Year of Use	4,546	1.2	311,241	82.5
History of Methadone Maintenance Treatment (up to 3 Months After 1st Use)	2,959	0.8	308,282	81.8
Dual-Eligible Coverage Only	35,016	9.3	273,266	72.5
Comprehensive Managed Care Only	16,917	4.5	256,349	68.0
Limited Enrollment:				
Managed Care at 1st Opioid Prescription	3,432	0.9	252,917	67.1
1st Opioid Rx After Oct 1, 2010	10,511	2.8	242,406	64.3
<3 Months Total Enrollment	1,579	0.4	240,827	63.9
1 Month FFS Enrollment at 1st Use, then Managed Care	39,985	10.6	200,842	53.3
2 Months FFS Enrollment at 1st Use, then Managed Care	29,790	7.9	171,052	45.4
<3 Months FFS Enrollment at 1st Use, then Dual-Eligible	1,825	0.5	169,227	44.9
<3 Months FFS Enrollment Post-Opioid Use and <6 Prior Months	5,821	1.5	163,406	43.3
<3 Months FFS Enrollment Post-Opioid Use and ≥6 Prior Months	2,330	0.6	161,076	42.7
<3 Consecutive Months FFS Enrollment Post-Opioid Use	7,593	2.0	153,483	40.7
No Paid Office Visits	2,662	0.7	150,821	40.0
Total Number of Subjects Eligible for Study Inclusion			**150,821**	

Table 2. Number of deaths included and excluded based on study eligibility among Washington State Medicaid enrollees aged 18-64 years who had ≥1 pain-related opioid prescription during April 2006-December 2010.

	Death Type		
	Opioid	**Cancer**	**Other**
Exclusions			
No Paid Opioid Prescriptions	39	165	492
No Eligible Opioid Prescriptions	1	19	32
Incomplete Enrollment Data	0	0	5
History of Cancer	21	2,253	484
Cancer Diagnosis Within 1st Year of Use	19	252	259
History of Opioid Dependence Treatment (up to 3 Months After 1st Use)	52	6	122
Dual-Eligible Coverage Only	172	24	1,655
Comprehensive Managed Care Only	2	0	21
Managed Care at 1st Use	4	0	28
Limited Enrollment:			
1st Opioid Rx After Oct 1, 2010	1	0	9
<3 Months Total Enrollment	18	0	80
1 Month FFS Enrollment at 1st Use, then Managed Care	43	0	168
2 Months FFS Enrollment at 1st Use, then Managed Care	44	6	153
<3 Months FFS Enrollment at 1st Use, then Dual-Eligible	5	1	79
<3 Months FFS Enrollment Post-Opioid Use and <6 Prior Months	32	0	238
<3 Months FFS Enrollment Post-Opioid Use and ≥6 Prior Months	9	0	150
<3 Consecutive Months FFS Enrollment Post-Opioid Use	18	4	114
No Paid Office Visits	4	0	40
Total Deaths Excluded	**485**	**2,739**	**4,178**
Total Deaths Included	**316**	**0**	**1,792**
Death Occurred After Follow-Up	**117**	**164**	**919**
TOTAL DEATHS	**918**	**2,903**	**6,889**

Table 3. Characteristics of the study population among Washington State Medicaid FFS enrollees aged 18-64 years with ≥1 paid, pain-related opioid prescription during April 2006-December 2010.

	N=150,821	
	n	%
Age at first use (years)		
18-24	34,934	23.2
25-34	39,661	26.3
35-44	28,283	18.8
45-54	29,510	19.6
55-64	18,433	12.2
Sex		
Female	102,134	67.7
Male	48,686	32.3
Race		
White	84,442	56.0
Black	9,439	6.3
Asian/Hawaiian, Pacific Islander	5,343	3.5
Hispanic	15,778	10.5
Native American/Alaskan Native	11,512	7.6
Other	10,656	7.1
Unknown	13,651	9.1
Area of residence*		
Urban	119,171	79.0
Large, Rural City/Town	15,263	10.1
Small/Isolated, Rural Town	15,830	10.5
Median household income of Residential ZIP Code†		
<$25,000	4,037	2.7
$25,000-$49,999	76,383	50.6
$50,000-$74,999	60,981	40.4
$75,000-$99,999	8,944	5.9
≥$100,000	476	0.3
Follow-up time in months (mean=20.3, median=13.2)		
3-5	25,766	17.1
6-12	34,624	23.0
13-24	46,699	31.0
25-36	15,187	10.1
37-48	11,076	7.3
49-57	17,457	11.6

*Source: Rural Health Research Center, University of Washington, 2005.
†Source: U.S. Census Bureau, American Community Survey, 2010.

Table 4: Cause of death by characteristics of the study population among Washington State Medicaid FFS enrollees aged 18-64 years with ≥1 paid, pain-related opioid prescription during April 2006-December 2010.

	Opioid Death N=316		Non-Opioid Death N=1,792		None N=148,713	
	n	%	n	%	n	%
Age at first use (years)						
18-24	10	3.0	76	3.9	37,536	23.6
25-34	54	16.0	113	5.8	42,373	26.7
35-44	89	26.3	304	15.5	30,049	18.9
45-54	153	45.3	793	40.6	30,213	19.0
55-64	32	9.5	668	34.2	18,553	11.7
Sex						
Female	163	51.8	913	50.9	101,058	68.0
Male	153	48.2	879	49.1	47,654	32.0
Race						
White	267	84.5	1,368	76.3	82,807	55.7
Black	12	3.8	125	7.0	9,302	6.3
Asian/Hawaiian, Pacific Islander	0	0.0	29	1.6	5,314	3.6
Hispanic	0	0.0	18	1.0	15,760	10.6
Native American/Alaskan Native	14	4.4	132	7.4	11,366	7.6
Other	11	3.5	47	2.6	10,598	7.1
Unknown	12	3.8	73	4.1	13,566	9.1
Area of residence at first use*						
Urban	248	78.5	1,437	80.2	117,486	79.0
Large, Rural City/Town	29	9.2	192	10.7	15,042	10.1
Small/Isolated, Rural Town	39	12.3	162	9.0	15,629	10.5

*Source: Rural Health Research Center, University of Washington, 2005.

Table 5. Opioid use among Washington State Medicaid FFS enrollees aged 18-64 years with ≥1 paid, pain-related opioid prescription during April 2006-December 2010

	Total Population N=150,821	
	n	%
Average daily dose (mg MED/day) in first 30 days of use		
1-19	16,734	11.1
20-49	80,395	53.3
50-89	35,006	23.2
90-119	7,800	5.2
120-199	4,995	3.3
>=200	5,891	3.9
Average daily dose (mg MED/day) in last 30 days of use		
1-19	18,487	12.3
20-49	78,646	52.2
50-89	34,223	22.7
90-119	7,885	5.2
120-199	4,898	3.3
>=200	6,682	4.4
Overall duration of use (continuous and non-continuous days)		
<90 days	115,414	76.5
90-180 days	10,100	6.7
181-365 days	8,612	5.7
366-730 days	7,269	4.8
>730 days	9,426	6.3
Chronic or non-chronic use in first 180 days of use		
Non-chronic (<90 opioid days)	131,481	87.2
Chronic (≥90 opioid days)	19,340	12.8
Chronic or non-chronic use at last follow-up		
Non-chronic (<90 opioid days)	120,509	79.9
Chronic (≥90 opioid days)	30,312	20.1
Days since last opioid prescription use at last follow-up		
Same day	22,762	15.1
1-30	15,724	10.4
31-90	17,467	11.6
91-180	25,078	16.6
181-365	32,449	21.5
>365	37,341	24.8
Number of opioid prescriptions in first year of use		
1-2	79,191	52.5
3-5	28,833	19.1
6-10	16,750	11.1
11-20	16,603	11.0
>20	9,444	6.3

Table 5 (continued). Opioid use among Washington State Medicaid FFS enrollees aged 18-64 years with ≥1 paid, pain-related opioid prescription during April 2006-December 2010

	Total Population N=150,821	
	n	%
Total days' supply in first year of use		
1-30	106,813	70.8
31-90	16,669	11.1
91-180	10,024	6.7
>180	17,315	11.5
Number of prescribing providers in first year of use		
1-2	104,181	69.1
3-5	34,273	22.7
≥6	12,367	8.2
Drug type in first 30 days of use		
Non-schedule II only	98,553	65.3
Schedule II short-acting only*	43,790	29.0
Schedule II long-acting only*	4,477	3.0
Schedule II short- and long-acting*	4,001	2.7
Drug type in last 30 days of use		
Non-schedule II only	98,009	65.0
Schedule II short-acting only*	43,150	28.6
Schedule II long-acting only*	5,674	3.8
Schedule II short- and long-acting*	3,988	2.6
Diagnosis of opioid dependence/abuse†		
Prior to first use	1,594	1.1
First year of use	3,125	2.1
Second year of use	1,635	1.1
Other prescription medications in first 30 days of use‡		
Sedatives/hypnotics or muscle relaxants	32,006	21.2
Antidepressants	32,930	21.8
Other prescription medications at last follow-up‡		
Sedatives/hypnotics or muscle relaxants	13,683	9.1
Antidepressants	16,636	11.0

*With or without Non-Schedule II opioids.

†Does not include Medicaid recipients who were receiving opioid dependence treatment before or up to 3 months after their first opioid use, as they were excluded from the study.

‡Categories are not mutually exclusive.

Table 6. Cause of death by opioid use factors among Washington State Medicaid FFS enrollees aged 18-64 years with ≥1 paid, pain-related opioid prescription during April 2006-December 2010

	Opioid Death N=316		Non-Opioid Death N=1,792		None N=148,713		
	n	%	n		n	%	*P*§
Average daily dose (mg MED/day) in 1st 30 days of opioid use							
<20	29	9.2	243	13.6	16,462	11.1	<.001
20-49	115	36.4	758	42.3	79,522	53.5	
50-89	66	20.9	358	20.0	34,582	23.3	
90-119	20	6.3	98	5.5	7,682	5.2	
120-199	23	7.3	99	5.5	4,873	3.3	
≥200	63	19.9	236	13.2	5,592	3.8	
Average daily dose (mg MED/day) in last 30 days of opioid use							
<20	35	11.1	238	13.3	18,214	12.2	<.001
20-49	81	25.6	670	37.4	77,895	52.4	
50-89	62	19.6	346	19.3	33,815	22.7	
90-119	23	7.3	111	6.2	7,751	5.2	
120-199	27	8.5	146	8.1	4,725	3.2	
>=200	88	27.8	281	15.7	6,313	4.2	
Overall duration of use (continuous and non-continuous days)							
<90 days	73	23.1	737	41.1	114,604	77.1	<.001
90-179 days	43	13.6	262	14.6	9,795	6.6	
180-365 days	76	24.1	279	15.6	8,257	5.6	
366-730 days	61	19.3	270	15.1	6,938	4.7	
>730 days	63	19.9	244	13.6	9,119	6.1	
Chronic or non-chronic use in first 180 days of use							
Non-chronic (<90 opioid days)	143	45.3	1,141	63.7	130,197	87.5	<.001
Chronic (≥90 opioid days)	173	54.7	651	36.3	18,516	12.5	
Chronic or non-chronic use at death							
Non-chronic (<90 opioid days)	84	26.6	857	47.8	119,568	80.4	<.001
Chronic (≥90 opioid days)	232	73.4	935	52.2	29,145	19.6	

Table 6 (continued). Cause of death by opioid use factors among Washington State Medicaid FFS enrollees aged 18-64 years with ≥1 paid, pain-related opioid prescription during April 2006-December 2010

	Opioid Death N=316		Non-Opioid Death N=1,792		None N=148,713		
	n	%	n		n	%	*P*[§]
Days since last opioid prescription use							
Same day	192	60.8	619	14.8	21,951	14.8	<.001
1-30	51	16.1	458	10.2	15,215	10.2	
31-90	31	9.8	219	11.6	17,217	11.6	
91-180	21	6.7	180	16.7	24,877	16.7	
181-365	11	3.5	176	21.7	32,262	21.7	
>365	10	3.2	140	25.0	37,191	25.0	
Number of opioid prescriptions in 1st year of use							
1-2	20	6.3	372	20.8	78,799	53.0	<.001
3-5	32	10.1	301	16.8	28,500	19.2	
6-10	49	15.5	292	16.3	16,409	11.0	
11-20	94	29.7	443	24.7	16,066	10.8	
>20	121	38.3	384	21.4	8,939	6.0	
Total days' supply in first year of use							
1-30	52	16.5	602	33.6	106,159	71.4	<.001
31-90	44	13.9	290	16.2	16,335	11.0	
91-180	62	19.6	293	16.4	9,669	6.5	
>180	158	50.0	607	33.9	16,550	11.1	
Number of prescribing providers in first year of use							
1-2	80	25.3	947	52.8	103,153	69.4	<.001
3-5	122	38.6	576	32.1	33,576	22.6	
≥6	114	36.1	269	15.0	11,984	8.1	

Table 6 (continued). Cause of death by opioid use factors among Washington State Medicaid FFS enrollees aged 18-64 years with ≥1 paid, pain-related opioid prescription during April 2006-December 2010

	Opioid Death N=316		Non-Opioid Death N=1,792		None N=148,713		
	n	%	n		n	%	*P*[§]
Drug type in first 30 days of use							
Non-schedule II only	136	43.0	900	50.2	97,517	65.6	<.001
Schedule II short-acting[*]	82	25.9	526	29.4	43,182	29.0	
Schedule II long-acting[*]	54	17.1	200	11.2	4,223	2.8	
Schedule II short- and long-acting[*]	44	13.9	166	9.3	3,791	2.5	
Drug type in last 30 days of use							
Non-schedule II only	109	34.5	755	42.1	97,145	65.3	<.001
Schedule II short-acting[*]	69	21.8	568	31.7	42,513	28.6	
Schedule II long-acting[*]	77	24.4	255	14.2	5,342	3.6	
Schedule II short- and long-acting[*]	61	19.3	214	11.9	3,713	2.5	
Diagnosis of opioid dependence/abuse[†]							
Prior to first use	7	2.2	34	1.9	1,553	1.0	<.001
First year of use	54	17.1	97	5.4	2,974	2.0	
Second year of use	17	5.4	41	2.3	1,577	1.1	
Other prescription medications in first 30 days of opioid use[‡]							
Sedatives/hypnotics or muscle relaxants	191	60.4	715	39.9	31,000	20.9	<.001
Antidepressants	178	56.3	781	43.6	31,971	21.5	<.001
Other prescription medications (at time of death)[‡]							
Sedatives/hypnotics or muscle relaxants	138	43.7	371	20.7	13,174	8.9	<.001
Antidepressants	107	33.9	327	18.5	16,202	10.9	<.001

[*]With or without Non-Schedule II opioids.

[†]Does not include Medicaid recipients who were receiving opioid dependence treatment before or up to 3 months after their first opioid use, as they were excluded from the study.

[‡]Use of specific medications compared to non-use; categories are not mutually exclusive.

[§]p-value based on results of chi-square test.

Table 7. Rate of opioid-related deaths among Washington State Medicaid enrollees aged 18-64 years who had ≥1 paid, pain-related opioid prescription during April 2006-December 2010

	ALL USERS		
	Opioid Deaths	**Person-Years**	**Rate/100,000**
Total	316	251,201.6	125.8
Average daily dose (mg MED/day)*			
0	95	156,874.7	60.6
<20	16	15,675.6	102.1
20-49	40	39,908.6	100.2
50-89	44	16,808.4	261.8
90-119	18	5,074.0	354.8
120-199	23	5,166.6	445.2
≥200	80	11,696.2	684.0

*At time of death.

Table 8. Rates of opioid-related death by dose for among Washington State Medicaid enrollees with chronic and non-chronic opioid use during April 2006-December 2010.

	Chronic			Non-Chronic		
	Opioid Deaths	**Person-Years**	**Rate per 100,000**	**Opioid Deaths**	**Person-Years**	**Rate per 100,000**
Total	232	59,001.7	393.2	84	192,202.4	43.7
Average daily dose (mg MED/day)*						
0	44	9,194.6	478.5	51	147,680.0	34.5
1-19	10	8,327.2	120.1	6	7,348.4	81.7
20-49	30	16,672.5	179.9	10	23,236.0	43.0
50-89	34	7,986.7	425.7	10	8,821.7	113.4
90-119	14	3,046.7	459.5	4	2,027.3	197.3
120-199	23	3,759.1	611.8	0	1,407.5	0.0
≥200	77	10,014.8	768.9	3	1,681.4	178.4

*At time of death.

Table 9. Risk factors for opioid-related death among WA Medicaid recipients who had ≥1 prescription opioid prescription, 2006-2010

				Unadjusted		Demographic-Adjusted*	
	Deaths	Person-Years	Rate/ 100,000	HR (95% CI)	*P*	HR (95% CI)	*p*
TOTAL	316	251,201.6	125.8				
Age							
18-24	6	38,451.8	15.6	0.2 (0.1-0.5)	0.001	0.2 (0.1-0.5)	<.001
25-34	41	55,012.7	74.5	1.0 [Ref]		1.0 [Ref]	
35-44	76	46,893.9	162.1	2.1 (1.4-3.0)	<.001	1.8 (1.2-2.6)	0.003
45-54	140	62,735.8	223.2	2.7 (1.9-3.8)	<.001	2.2 (1.5-3.1)	<.001
55-64	53	48,110.0	110.2	1.3 (0.9-2.0)	0.212	1.1 (0.7-1.6)	0.718
Sex							
Female	163	169,022.0	96.4	1.0 [Ref]		1.0 [Ref]	
Male	153	82,181.8	186.2	1.9 (1.5-2.4)	<.001	1.7 (1.3-2.1)	<.001
Race/ethnicity							
Non-Hispanic White	267	155,506.2	171.7	1.0 [Ref]		1.0 [Ref]	
Non-Hispanic Black	12	17,195.2	69.8	0.4 (0.2-0.7)	0.002	0.4 (0.2-0.7)	0.002
Native American/Alaskan Native	14	18,967.6	73.8	0.4 (0.3-0.8)	0.003	0.5 (0.3-0.9)	0.017
Other†	11	43,871.7	25.1	0.2 (0.1-0.3)	<.001	0.2 (0.1-0.4)	<.001
Unknown	12	15,663.4	76.6	0.5 (0.3-0.9)	0.030	0.7 (0.4-1.3)	0.265
Area of residence at first use‡							
Urban	248	198,094.5	125.2	1.0 [Ref]		1.0 [Ref]	
Large, Rural City/Town	29	26,090.9	111.2	0.9 (0.6-1.3)	0.508	0.8 (0.6 - 1.2)	0.301
Small/Isolated, Rural Town	39	26,709.9	146.0	1.2 (0.8-1.6)	0.379	1.1 (0.8 - 1.5)	0.716
Average daily dose (mg MED/day)§							
0	95	156,874.7	60.6	0.6 (0.3-0.9)	0.027	0.7 (0.4 - 1.1)	0.142
1-19	16	15,675.6	102.1	1.0 [Ref]		1.0 [Ref]	
20-49	40	39,908.6	100.2	1.1 (0.6-1.9)	0.777	1.1 (0.6 - 1.9)	0.843
50-89	44	16,808.4	261.8	2.9 (1.6-5.1)	<.001	2.7 (1.5 - 4.8)	0.001
90-119	18	5,074.0	354.8	3.6 (1.9-7.1)	<.001	3.4 (1.7 - 6.6)	<.001
120-199	23	5,166.6	445.2	4.2 (2.2-8.0)	<.001	3.8 (2.0 - 7.3)	<.001
≥200	80	11,696.2	684.0	6.2 (3.6-10.6)	<.001	5.3 (3.1 - 9.1)	<.001
Duration of use (cumulative)§							
1-30 days	36	150,663.5	23.9	1.0 [Ref]		1.0 [Ref]	
31-89 days	37	32,833.9	112.7	5.0 (3.1-7.9)	<.001	4.1 (2.5-6.5)	<.001
90-180 days	45	17,443.7	258.0	9.0 (5.8-14.0)	<.001	7.0 (4.4-11.0)	<.001
181-365 days	74	17,455.6	423.9	18.3 (12.0-27.8)	<.001	13.8 (8.9-21.4)	<.001
366-730 days	61	17,189.8	354.9	18.2 (11.4-29.1)	<.001	13.7 (8.5-22.1)	<.001
>730 days	63	15,617.6	403.4	31.0 (18.4-52.3)	<.001	23.2 (13.6-39.6)	<.001

Table 9 (cont.). Risk factors for opioid-related death among WA Medicaid recipients who had ≥1 prescription opioid prescription, 2006-2010

				Unadjusted		Demographic-Adjusted*	
	Deaths	Person-Years	Rate/ 100,000	HR (95% CI)	*p*	HR (95% CI)	*p*
Time since last prescription§							
Current (Same day/1 Month)	243	106,075.5	230.0	1.0 [Ref]		1.0 [Ref]	
Recent (2-6 Months)	52	68,097.1	74.9	0.3 (0.2-0.4)	<.001	0.3 (0.3-0.5)	<.001
Past (>6 Months)	21	77,031.5	27.3	0.1 (0.1-0.1)	<.001	0.1 (0.1-0.2)	<.001
Chronic use§							
Non-Chronic	84	192,202.4	43.7	1.0 [Ref]		1.0 [Ref]	
Chronic	232	59,001.7	393.2	8.1 (6.2-10.5)	<.001	6.3 (4.8-8.2)	<.001
Opioid drug type in first 30 days of use							
Non-Schedule II only	136	166,291.0	81.8	1.0 [Ref]		1.0 [Ref]	
Schedule II short-acting only¶	82	65,314.2	125.6	1.6 (1.2-2.1)	0.001	1.6 (1.2-2.1)	0.001
Schedule II long-acting only¶	54	11,086.1	487.1	5.5 (4.0-7.6)	<.001	4.2 (3.0-5.7)	<.001
Schedule II long-acting and short-acting¶	44	8,512.8	516.9	6.0 (4.3-8.4)	<.001	4.5 (3.2-6.4)	<.001
Opioid drug type§							
Non-Schedule II only	50	51,258.5	97.5	1.0 [Ref]		1.0 [Ref]	
Schedule II short-acting only¶	47	22,591.9	208.0	2.1 (1.4-3.2)	<.001	2.1 (1.4-3.1)	<.001
Schedule II long-acting only¶	67	11,170.0	599.8	5.2 (3.6-7.4)	<.001	4.5 (3.1-6.5)	<.001
Schedule II long-acting and short-acting¶	57	9,309.0	612.3	5.3 (3.6-7.7)	<.001	4.7 (3.2-6.8)	<.001
None	95	156,874.7	60.6	0.5 (0.4-0.7)	<.001	0.6 (0.5-0.9)	0.013
Other prescription drugs§**							
Sedative-hypnotics or muscle relaxants	138	31,586.6	436.9	5.0 (4.0-6.3)	<.001	4.1 (3.3-5.2)	<.001
Antidepressants	107	36,494.5	293.2	2.8 (2.2-3.5)	<.001	2.3 (1.8-2.9)	<.001
Charlson Comorbidity Index							
0	199	176,953.8	112.5	1.0 [Ref]		1.0 [Ref]	
1	64	48,712.2	131.4	1.1 (0.8-1.4)	0.538	1.0 (0.7-1.3)	0.804
2	53	25,538.1	207.5	1.7 (1.3-2.4)	<.001	1.4 (1.1-2.0)	0.023

*Demographics include age, gender, race/ethnicity and area of residence.

†Asian, Hawaiian/Pacific Islander, and Hispanic were combined with "Other" because there were no deaths in these categories.

‡Source: Rural Health Research Center, University of Washington, 2005.

§At time of death.

¶With or without Non-Schedule II opioids.

**Use of specific medications compared to non-use; categories are not mutually exclusive.

Table 10. Risk of opioid-related death and dose among chronic users among WA Medicaid recipients 2006-2010

	Unadjusted		Demographic-Adjusted*	
	HR (95% CI)	***p***	**HR (95% CI)**	***p***
Average daily dose (mg MED/day)†				
0	4.2 (2.1-8.4)	<.001	4.0 (2.0-8.0)	<.001
1-19	1.0 [Ref]		1.0 [Ref]	
20-49	1.5 (0.7-3.1)	0.261	1.5 (0.7-3.0)	0.304
50-89	3.6 (1.8-7.2)	<.001	3.4 (1.7-6.9)	0.001
90-119	3.9 (1.7-8.7)	0.001	3.7 (1.6-8.3)	0.002
120-199	5.1 (2.4-10.7)	<.001	4.8 (2.3-10.1)	<.001
≥200	6.4 (3.3-12.4)	<.001	5.9 (3.0-11.4)	<.001

*Demographics include age, gender, race/ethnicity and area of residence

†At time of death.

Chapter 2

Changes in Opioid Prescribing for Washington Workers' Compensation Claimants after Implementation of an Opioid Dosing Guideline for Chronic Non-Cancer Pain: 2004-2010

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ABSTRACT: An opioid overdose epidemic emerged in the United States following increased opioid prescribing for chronic non-cancer pain (CNCP). In 2007, Washington State agencies implemented an opioid dosing guideline on safe prescribing for CNCP. The objective of this population-based observational study was to evaluate opioid use and dosing before and after Guideline implementation. We identified 161,283 workers aged 18-64 years with ≥1 opioid prescriptions in Washington Workers' Compensation, April 1, 2004-December 31, 2010. Prevalence and incidence rates of opioid use were assessed. We compared pre- and post-Guideline chronic and high-dose use (≥120 mg/day) among incident users. The mean monthly prevalence of opioid use declined by 25.6% between 2004 (14.4%) and 2010 (10.7%). Fewer incident users went on to chronic opioid therapy in the post-Guideline period (4.7%; 95% Confidence Interval [CI], 4.5%-5.0%) than in the pre-Guideline period (6.3%; 95% CI, 6.1%-6.6%). Compared with pre-Guideline incident users, post-Guideline incident users were 35% less likely to receive high doses (adjusted odds ratio=0.65; 95% CI, 0.59-0.71). Although the extent to which decreases were due to the Guideline is uncertain, to our knowledge, this is the first report of significant decreases in chronic and high-dose prescription opioid use among incident users.

PERSPECTIVE: Evidence-based strategies for opioid risk management are needed to help abate the epidemic of opioid-related morbidity and mortality. The study findings suggest that opioid dosing guidelines that specify a "yellow flag" dosing threshold may be a useful tool in preventing escalation of doses into ranges associated with increased mortality risk.

KEY WORDS: opioids; dosing; trends; guideline; chronic pain

INTRODUCTION

Opioid analgesics were increasingly prescribed for long-term treatment of chronic non-cancer pain (CNCP)[2-5] following advocacy for greater attention to pain and its relief by pain management leaders and subsequent changes in state laws and regulations.[6] In recent years, there has been a national epidemic of overdose deaths and morbidity related to prescription opioids.[1] Accidental poisonings have become the leading cause of unintentional injury death in the United States (US), largely due to the rise in deaths associated with prescription opioids.[1] In 2008, the opioid-related mortality rate in the US was 4.8 per 100,000[1] whereas the rate in Washington State (WA) was more than 50% higher (7.4 per 100,000).[23] The number of opioid-related deaths among WA residents increased from under 50 in 1995 to over 500 in 2008.[23]

Parallel trends were evident in the WA workers' compensation (WC) system, with more than 100 deaths due to accidental overdose from opioids between 2000 and 2010.[4] Prescriptions for Schedule II opioids (the most potent opioids) in WC nearly tripled between 1996 and 2006,[4,19] and mean daily doses for long-acting Schedule II opioids were as high as 140 mg/day morphine equivalent dose (MED) in 2006.[19] Multiple studies have found that opioid-related morbidity and mortality rates were highest among high-dose users.[46-48]

In response to the emerging epidemic of unintentional poisonings, the WA Agency Medical Directors' Group (AMDG) collaborated with clinical and academic pain experts to develop and implement the *Interagency Guideline on Opioid Dosing for Chronic Non-cancer Pain* in 2007.[4,30] The goal of the Guideline was to assist primary care providers in more safely and effectively prescribing opioids to CNCP patients initiating opioid therapy and to prevent these new patients from escalating to high-dose opioid use if they were not benefitting from opioid therapy. The Guideline was intended as a resource for primary care providers who do not

specialize in pain medicine. A key feature was the recommendation that providers not exceed a dosing threshold of 120 mg MED/day for patients who did not have clinically meaningful improvement in pain and function without first obtaining a pain specialist consultation.

The AMDG Guideline was the first to provide specific prescription opioid dosing guidance.[4] The Guideline also included recommendations for best practices for patient selection and risk assessment, initiating and discontinuing opioid therapy, and for transitioning to chronic opioid therapy. Following its online release in 2007, dissemination of the Guideline also included numerous presentations to provider groups, free web-based training for continuing medical education credits, and access on the National Guideline Clearinghouse[77] and WA Medical Association websites.

We previously reported that the number of WA WC opioid prescriptions, the mean daily long-acting opioid dose, the percent of claimants receiving work disability benefits with doses $\geq$120 mg MED/day, and the number of unintentional opioid poisoning deaths all decreased after 2007.[4] However, in that study, examination of high-dose opioid use was restricted to long-acting opioids and claimants receiving work disability compensation, incident and chronic opioid use were not assessed, and pre- vs. post-Guideline prescribing patterns were not compared statistically.

The current study expanded upon this prior work to more closely examine opioid use and dosing patterns in the WA WC population before and after Guideline implementation by assessing the incidence of opioid use, chronic use among incident opioid users, and high-dose opioid use including all prescription opioids and all claimants. Because the main emphasis of the AMDG Guideline was to prevent potentially unsafe opioid dose escalation among patients initiating opioid therapy, we also compared pre- and post-Guideline rates of chronic and high-

dose opioid use among incident users to determine whether these rates decreased after Guideline implementation.

MATERIALS AND METHODS

Study Setting and Population

The WA Department of Labor and Industries (DLI) is the sixth largest WC insurer in the US and the sole regulator of WC in WA. DLI reviews as many as 130,000 claims for work-related injuries and illnesses in one year. The DLI State Fund is the direct insurer for approximately 2.3 million covered workers who account for two-thirds of the non-Federal WA workforce. The remaining one-third work for and are covered by approximately 350 large, self-insured companies. For this study, we examined State Fund claims data. Complete claims data from the self-insured companies are not available for use. Approved State Fund claims typically remain open until a provider certifies that the worker's injury has healed or would not likely benefit from further medical care. The DLI administrative database, the Medical Information Payment System (MIPS), tracks all requests for billing and payment of health care services directly related to the covered injury or illness. The extensive database contains computerized billing data for all allowed claim-related hospital, outpatient medical, and pharmacy services allowed under injury claims and is commonly used for research purposes.[4,19-22,78] The MIPS point-of-sale pharmacy database captures complete information on outpatient prescriptions, including drug name, strength, quantity, days' supply, national drug code, and dispense date for each medication dispensed. We obtained MIPS data for all opioid prescriptions in 2004-2010. The study was approved by the University of Washington Institutional Review Board. Because the research involved no more than minimal risk and included a large number of individuals, the

requirement for informed consent was waived.

We identified 161,283 workers in WA WC aged 18-64 years with an accepted DLI injury claim and at least one paid opioid prescription (oral or transdermal) dispensed between April 1, 2004 and December 31, 2010. Workers who had a medical bill containing an *International Classification of Diseases, Ninth Revision, Clinical Modification* code for cancer other than non-melanoma skin cancer were excluded. For individuals with multiple injury claims, we aggregated prescriptions across all claims.

Opioid-Related Measures

We grouped opioids by generic, short- versus long-acting properties, and Drug Enforcement Administration schedule. This schedule ranks controlled substances with recognized medical uses on a scale of II through V, with Schedule II having the highest abuse potential (Schedule I drugs cannot be legally prescribed). We further categorized opioids as short-acting Schedule II, long-acting Schedule II, or non-Schedule II (including non-scheduled tramadol).[50]

The first opioid prescription dispensed during the study period for each worker was defined as the *index prescription*. For each prescription, we defined the *start date* as the dispense date and the *end date* as the dispense date plus days' supply minus 1. The dates encompassed by a prescription were counted as the days covered by opioids. If an individual had 2 or more prescriptions with days' supply covering the same dates, the overlapping dates were counted as one covered day.

We defined a worker as an *incident user* if no opioid prescriptions were dispensed in the 3 months prior to the index prescription. For users with an index prescription in April-June 2004 (the first 3 months of our study), the 3-month pre-prescription window included the relevant

dates in January-March 2004. An *incident-chronic user* was defined as an incident user who had at least 90 days (consecutive or non-consecutive) covered by opioids in the 180 days after the index prescription start date.

The prevalence of opioid use among all workers in WA WC aged 18-64 years was determined for each year and each quarter as the mean of the monthly rates in each time segment. To obtain monthly prevalence, we divided the number of all opioid users in that month by the total number of claimants with an open claim that month (estimated by DLI). The mean monthly prevalence for a quarter was calculated as the sum of the 3 monthly rates in that quarter divided by 3. The mean monthly prevalence for a year was calculated as the sum of the 12 monthly rates in that year divided by 12 (the calculation for 2004 used 9 monthly rates and divided by 9 since the study began in April 2004). We assessed the quarterly rate of incident users who became chronic by dividing the number of incident-chronic users by the total number of incident users in the quarter.

We computed a worker's daily dose for each opioid prescription as the total number of pills (or patches) dispensed multiplied by the drug strength, divided by the days' supply. Daily doses were then converted to MED using published conversion factors.[30,50,51] If an individual had prescriptions with overlapping dates, the daily dose was defined as the sum of the doses from the different prescriptions for the same day. We estimated the daily dose per quarter for an individual as the sum of the doses on the days in the quarter divided by the number of days in that quarter covered by opioid prescriptions.

For each year, we determined the proportions of incident users and of incident-chronic users who received high daily opioid doses on any 30 days (consecutive or non-consecutive) within one year of the index prescription (i.e., the index prescription start date plus 365 days).

We included prescriptions dispensed in 2011 for workers with an index prescription in 2010. We defined three high-dose categories: ≥60, ≥90, and ≥120 mg MED/day.

Pre- and Post-Guideline Implementation Time Periods

The WA Guideline was released online on March 22, 2007, but for purposes of the study we considered April 1, 2007 as the implementation date. We defined the pre-Guideline period as April 2004-March 2007 and the post-Guideline period as April 2007-December 2010.

Statistical Analysis

Descriptive statistics were used to characterize opioid users, prescriptions, and doses in 2004-2010. To compare the rate of incident users who became chronic users in the pre- versus post-Guideline time periods, we conducted an interrupted time series analysis using a segmented linear regression model.[79] This model allowed us to compare the pre- and post-Guideline trends in quarterly rates while accounting for underlying changes in rates that would be expected had there been no policy change. The model included a linear term for the quarter, an indicator for whether the quarter was before or after Guideline implementation, and a linear term for the time since Guideline implementation. We obtained 95% Confidence Intervals (CI) and performed the Durbin-Watson test[79] for autocorrelation.

We constructed a logistic regression model to compare pre- versus post-Guideline incident users on the odds of receiving ≥120 mg MED/day on any 30 days within the first year, adjusting for worker age and gender. Workers who received their first opioid prescription in April 2006-March 2007 were excluded from this model to ensure that the one-year follow-up did not extend beyond the Guideline implementation date. All analyses were conducted using Stata Statistical Software Release 12.[63]

RESULTS

Among the 161,283 injured workers with a dispensed opioid prescription, the mean (SD) age was 39.2 (11.7) years and the majority were male (68.9%). The annual number of opioid prescriptions ranged from a high of 165,017 in 2006 to a low of 101,278 in 2010 (Table 1). Opioid prescriptions consisted mostly of non-Schedule II medications across all years (57.4%-62.4%). The proportion of prescriptions that were for long-acting Schedule II opioids peaked at 8.6% in 2007, then decreased to a low of 4.1% in 2010. The proportion of prescriptions that were for short-acting Schedule II opioids increased over those years from 32.5% to 38.4%.

Temporal Trends in Opioid Use

Overall, the mean monthly prevalence of opioid use declined by 24.3% between 2004 (14.4%) and 2010 (10.9%) (Table 2). The decrease in prevalence was greatest (24.3%) between 2008 Quarter 1 and 2010 Quarter 4 (Figure 1). Mean monthly incidence rates of opioid use were low across all years (2.9%-4.1%) (Table 2), but decreased by 26.8% overall between 2004 and 2010.

As illustrated in Figure 2, the proportion of incident users who became chronic users decreased overall by 52.7% between 2004 Quarter 1 (7.4%) and 2010 Quarter 4 (3.5%). Results from the segmented regression analysis showed that, on average, significantly fewer incident users became chronic in the post-Guideline period [4.7% (95% CI, 4.5%-5.0%)] than in the pre-Guideline period [6.3% (95% CI, 6.1%-6.6%), (P<0.001)]. Rates of incident-chronic use significantly decreased per quarter in both the pre-Guideline period [-0.10 (95% CI= -0.17, -0.03), P=0.01] and the post-Guideline period [-0.18 (95% CI= -0.23, -0.13), P<0.001]. While the rate of decrease was greater in the post-Guideline period, the comparison between the pre- and post-Guideline trends did not reach statistical significance in the segmented linear regression

model (P=0.07). No significant autocorrelation was present in the data (Durbin-Watson test,[79] P=0.84), thus, further adjustment was not necessary.

High-Dose Use

The median [interquartile range (IQR)] daily opioid dose in each quarter remained fairly stable over the study period, ranging from 36.5 (23.3-58.7) to 37.5 (23.6-60.0) mg MED. For incident users, the median (IQR) daily dose in the first quarter of use changed little over time with doses between 33.3 (25.0-50.0) and 37.5 (25.0-56.3) mg MED.

Between 2004 and 2010, high-dose use among incident users similarly decreased for daily doses of ≥60, ≥90, and ≥120 mg MED (Table 3). In 2004, 1.8% of incident users reached daily doses of ≥120 mg MED/day on 30 days or more within one year. By 2010, the rate of opioid use at this level decreased by 55.6% among incident users to 0.8%. After adjusting for age and gender, post-Guideline incident users were 34.9% less likely to receive doses of ≥120 mg MED/day, as compared with pre-Guideline incident users (odds ratio=0.66; 95% CI, 0.60-0.72, P<0.001). Among incident-chronic users, the proportion with doses ≥120 mg MED/day was highest in 2006 (18.7%) and remained above 15% until dropping to 13.6% in 2010.

DISCUSSION

This study builds on our previous research in the WA WC population and contributes new information on trends in prevalent, incident, incident-chronic, and high-dose opioid use in WA WC between 2004 and 2010, encompassing periods before and after dissemination of the WA Opioid Dosing Guideline. Both prevalence and incidence rates of opioid use decreased by 24% between 2004 and 2010. Most dramatically, the proportion of incident users who transitioned to chronic opioid use declined by more than half. Compared with the pre-Guideline

period, incident-chronic use, on average, was significantly lower following release of the Guideline. Incident users in the post-Guideline period were also less likely to reach high daily doses than were pre-Guideline incident users. Although a substantial minority of incident-chronic users received high opioid doses across study years, the data revealed a decrease in 2010. To our knowledge, this study is the first report of significant decreases in chronic and high-dose use among incident prescription opioid users.

Few studies have examined population-based prescription opioid use rates. In Arkansas Medicaid, 30% of enrollees received opioids in 2005 compared with 26% in 2000.[36] Incident opioid use among enrollees in a WA nonprofit health care system increased from 15% in 1997 to 16% in 2005, and the rate of incident-chronic use was 5% in 2005.[68] Rates in this study appear to be higher than rates in WA WC. However, unlike our study, the health care system members could have multiple incident episodes of opioid use, were counted as chronic if they used opioids episodically before transitioning to chronic use, and tended to have long-term enrollment which permitted extensive follow-up. In Ohio WC, a reported 19% of claimants in 2008-2009 received opioids,[80] but this was likely an underestimate since it excluded non-Schedule II opioids, which are the most frequently prescribed opioids in the US[81] and comprised over half the opioid prescriptions in our study. Another study methodological difference is that we calculated rates of opioid use per month rather than per year to account for changes in the WC population due to claims opening and closing at various intervals. By capturing the population in a shorter time increment, we could better quantify the impact of the Guideline at a specific point in time.

The decline in chronic opioid therapy among incident users may be due, in part, to possible improvements in patient selection and risk assessment using best practices widely recommended for chronic opioid therapy.[10,82-84] Providers are advised to discontinue therapy if

pain and function are not improving or the patient displays aberrant drug-related behaviors or other significant adverse effects. It is plausible that the reduction in incident-chronic use after Guideline implementation may have prevented dose escalation and severe opioid-related adverse events. Lowered incident-chronic use may have also reflected growing concerns regarding the risks of chronic opioid therapy.[85-87] In a survey of WA primary care providers related to Guideline implementation, 54% of the respondents reported concerns over development of opioid dependence, tolerance, or addiction and 30% reported prescribing opioids less frequently.[88] As many as one-third of primary care physicians in low-income clinics in the US reported discontinuing opioid prescribing for CNCP altogether.[89]

Dose escalation is common among chronic users and can result in high prescribed doses[22,90,91] associated with increased risk of fatal and non-fatal overdose.[46-48] The AMDG's main objective for the Guideline was to reduce the risk of opioid overdose in CNCP patients by preventing high-dose use in incident opioid users. Incident users were targeted in an attempt to deter dose escalation among patients beginning chronic opioid therapy. Our finding of a significantly reduced likelihood of reaching $\geq$120 mg MED/day among post-Guideline incident users is consistent with the possibility that the Guideline was successful in reducing dose escalation in the target population and may mitigate known risks of high-dose opioid use. Consistent with the Guideline-recommended dosing threshold, the best current evidence supports 100-120 mg MED/day as a "yellow flag" dosage at which the risk of morbidity and mortality rises significantly.[46-48] Two of these studies also reported increased risk at lower doses (50-100 mg MED/day).[46,47] These results emphasize the importance of screening for risk before starting chronic opioid therapy, and continuous monitoring throughout the course of therapy.

The decrease we observed in high-dose use among incident users coincided with

reductions (in 2010) in mean daily dose of long-acting Schedule II opioids and in opioid-related mortality in WA WC.[4] Our current findings suggest that high-dose use among incident-chronic users may also be decreasing. However, prescribed daily doses still reached 120 mg MED/day for 13% of incident-chronic users in 2010. High doses have also been reported in WC populations in other states. In Ohio WC, 9.2% of Schedule II opioid users in 2008-2009 received doses ≥120 mg MED/day (ever) during the two years.[80] Among workers in Louisiana WC with injuries during 1999-2002, average daily doses were as high as 145.7 mg MED/day 1 year after injury.[92]

We cannot rule out changes in opioid use and dosing after Guideline implementation due to general increased awareness of the risk of opioid overdose related to medical and non-medical opioid use. Professional societies, emergency departments, and other organizations have promoted clinical guidelines for opioid prescribing.[10,82,93-95] The Centers for Disease Control and Prevention (CDC) has been active in educating individuals, providers, health insurers and state policy makers.[1] The Food and Drug Administration and state and local health departments have also aimed to improve opioid safety.[96-99] National media coverage and scientific journal articles have brought much attention to the rising rates of opioid overdose and prescription opioid abuse.

Some limitations in our study are inherent in use of pharmacy claims data. We could not determine actual medication intake or duration of use. We assumed patients took medications at the maximum rate allowed as calculated by the dispensing pharmacist, which may have overestimated daily dose and underestimated days used. Also, the prescription dispense date may not reflect the actual timing of medication use. Opioid use may be underestimated due to prescriptions that were denied, charged to other insurance, or paid for out-of-pocket. Because we could not determine prior opioid use for claimants new to the WC system, incident and

incident-chronic use may be overestimated. For future studies, data on all legally dispensed opioids in WA will be available through the new WA Prescription Monitoring Program (PMP).[100]

Another limitation is the lack of patient-reported outcomes. Although the Guideline underscores the need for monitoring improvements in patient pain and function, our study could not address the impact of the observed prescribing changes on pain-related outcomes. Little is known concerning the effectiveness of chronic opioid therapy for improving pain and function long-term. In a previous WA WC study, the average opioid dose significantly increased by 62% among claimants receiving opioid therapy throughout the year after injury, yet only 27% showed a clinically meaningful improvement in pain and only 16% showed a clinically meaningful improvement in function.[22] In a randomized trial comparing stable opioid dose versus escalating dose prescribing strategies, there was no difference on the primary outcomes of usual pain and functional disability.[101] A recent study found no correlation between changes in dose and pain.[102] A stronger evidence base regarding safety and effectiveness of opioid therapy, and comparative effectiveness of chronic opioid therapy versus alternative therapies for chronic pain, is needed to optimize CNCP patient care, risk management, and health policy decision-making.

Urgent action is needed to prevent additional harms from prescription opioid use that have become a public health crisis.[1] State and federal governmental agencies have an instrumental role in strategic planning for opioid risk management. The CDC has adopted the WA Guideline dosing criteria and advocates its application in practice.[1,29] Under new regulations in WA for CNCP management, the five Boards and Commissions representing prescribers licensed to prescribe controlled substances now have the authority to enforce best practice use, including attention to the dosing threshold.[76] These regulations also repealed earlier

permissive legislation that removed limitations on dose and duration of opioid therapy.[103] Similar laws in other states and collaborations among government agencies may reduce opioid-related morbidity and mortality. State PMPs could be a valuable resource for comprehensive opioid prescribing data that can be used to identify statewide opioid trends, high-risk populations, and inappropriate opioid use. Improved registration, interoperability, and use of PMPs among prescribers may help maximize the benefits of PMPs.

The findings from this study suggest that clinical opioid dosing guidelines for CNCP that specify a "yellow flag" dosing threshold may be a useful tool for improving the safety of opioid prescribing practices by discouraging further dose escalation. Both chronic and high-dose opioid use rates declined among incident users after the WA Guideline implementation. Although the extent to which these decreases may have been due to the Guideline cannot be established, these findings contribute to the evidence base concerning risk management strategies that may help to abate the national epidemic of opioid-related morbidity and mortality among patients with CNCP. Further research is needed on risk factors for opioid-related adverse events, as well as on optimal treatment strategies in chronic opioid therapy.

DISCLOSURES

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The Centers for Disease Control and Prevention had no involvement in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

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Table 1. Opioid Prescriptions and Users, Washington Workers' Compensation, 2004-2010

	Opioid Prescriptions				Opioid Users	
	Total	Short-Acting Schedule II	Long-Acting Schedule II	Non-Schedule II	Total	Incident
Year	n	n (%)	n (%)	n (%)	n	n
2004	120,300[a]	38,365 (31.9)	6,778 (5.6)	75,157 (62.5)	30,208[a]	21,590[a]
2005	163,318	53,227 (32.6)	11,027 (6.8)	99,064 (60.7)	36,412	24,759
2006	165,017	51,631 (31.3)	14,064 (8.5)	99,322 (60.2)	37,127	23,501
2007	156,992	50,960 (32.5)	13,473 (8.6)	92,559 (59.0)	34,812	20,621
2008	155,903	54,318 (34.8)	9,227 (5.9)	92,358 (59.2)	37,953	22,850
2009	125,290	46,594 (37.2)	6,667 (5.3)	72,029 (57.5)	33,753	19,362
2010	101,278	38,977 (38.5)	4,132 (4.1)	58,169 (57.4)	31,127	18,481

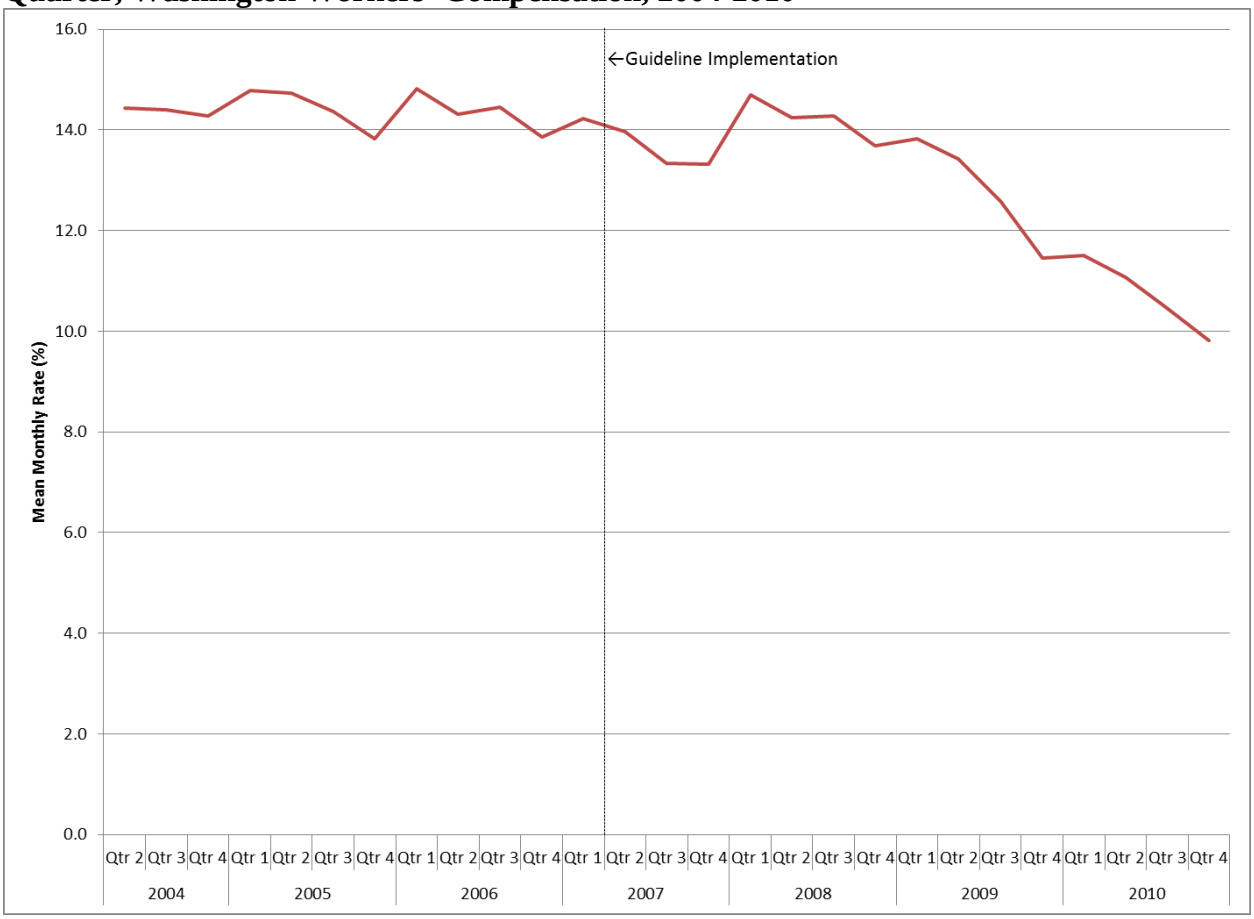
[a]Totals for 2004 are based on Quarters 2-4 (study did not include Quarter 1).

Table 2. Prevalence and Incidence of Opioid Use, Washington Workers' Compensation, 2004-2010

	Mean monthly total WC claimants[a]	Mean monthly total opioid users	Mean monthly incident opioid users
Year	n	n (%)	n (%)
2004	58,311	8,375 (14.4)	2,399 (4.1)
2005	59,013	8,507 (14.4)	2,063 (3.5)
2006	60,248	8,648 (14.4)	1,958 (3.3)
2007	59,620	8,170 (13.7)	1,718 (2.9)
2008	57,691	8,212 (14.2)	1,904 (3.3)
2009	51,634	6,623 (12.8)	1,614 (3.1)
2010	50,729	5,429 (10.7)	1,540 (3.0)

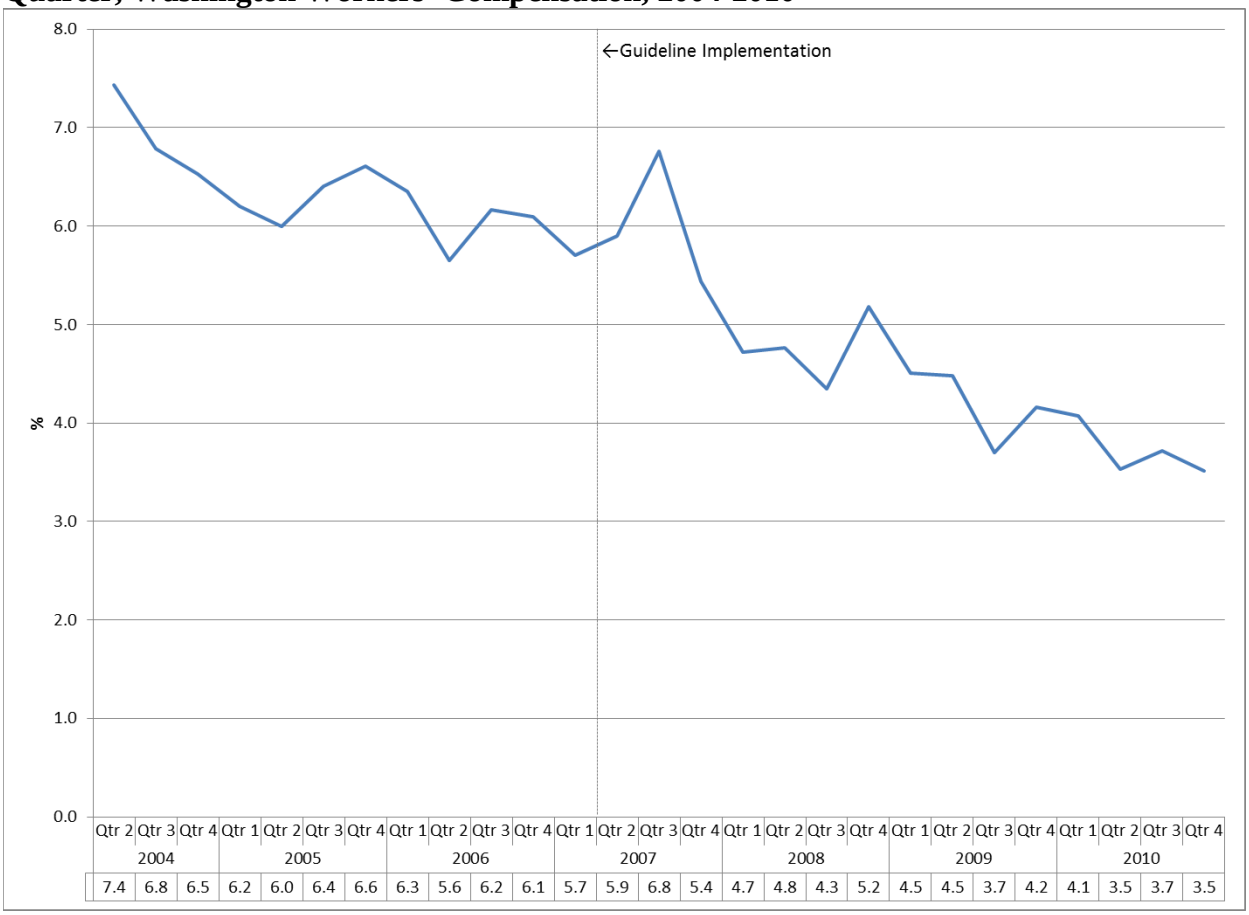
[a]Claimants from the overall WC population were included if they had an open claim at any time during the month.

Figure 1. Prevalence of Opioid Use among Injured Workers, Mean Monthly Rates per Quarter, Washington Workers' Compensation, 2004-2010



The prevalence of opioid use (%) per quarter among all workers in Washington workers' compensation aged 18-64 years. Quarterly rates of opioid use were estimated as the mean of the monthly rates in that quarter.

Figure 2. Rate of Incident Users Who Became Chronic Users, Mean Monthly Rates per Quarter, Washington Workers' Compensation, 2004-2010



The quarterly rate of incident users who became chronic (%) among Washington workers' compensation adults aged 18-64 years. Incident-chronic users had ≥90 days (consecutive or non-consecutive) covered by opioids in the 180 days after their first opioid prescription was dispensed.

Table 3. High-dose opioid use among incident and incident-chronic users in the first year of use, Washington Workers' Compensation, 2004-2010

		Workers who reached specified dose on 30 or more days[a]		
		>=60 mg MED	>=90 mg MED	>=120 mg MED
Year of Incident Use	**n**	**n (%)**	**n (%)**	**n (%)**
ALL INCIDENT USERS				
2004	21,590[b]	1,066 (4.9)	609 (2.8)	386 (1.8)
2005	24,759	1,114 (4.5)	615 (2.5)	380 (1.5)
2006	23,501	1,025 (4.4)	588 (2.5)	383 (1.6)
2007	20,621	809 (3.9)	452 (2.2)	287 (1.4)
2008	22,850	825 (3.6)	451 (2.0)	258 (1.1)
2009	19,362	657 (3.4)	346 (1.8)	226 (1.2)
2010	18,481	511 (2.8)	238 (1.3)	142 (0.8)
INCIDENT-CHRONIC USERS				
2004	1,496[b]	602 (40.3)	374 (25.0)	263 (17.6)
2005	1,559	626 (40.2)	381 (24.4)	260 (16.7)
2006	1,425	595 (41.8)	384 (27.0)	265 (18.6)
2007	1,225	454 (37.1)	279 (22.8)	188 (15.4)
2008	1,082	418 (38.6)	267 (24.7)	166 (15.3)
2009	814	308 (37.8)	194 (23.8)	135 (16.6)
2010	685	249 (36.4)	141 (20.6)	91 (13.3)

[a]Days were within one year of the index prescription start date and could be consecutive or non-consecutive.

[b]Totals for 2004 are based on Quarters 2-4 (study did not include Quarter 1).

Abbreviation: MED=morphine-equivalent dose

DISSERTATION CONCLUSION

Our finding of a significantly reduced likelihood of reaching >120 mg MED/day among post-Guideline incident users is consistent with the possibility that the Guideline was successful in reducing dose escalation in incident users, the target population, and may mitigate known risks of high-dose opioid use. The best current evidence supports 100-120 mg MED/day as a "yellow flag" dosage, the Guideline-recommended dosing threshold. Our study among Medicaid patients confirmed the findings in those population-based samples. There was a clear dose-response relationship between opioid dose and risk of opioid overdose death in, both, users overall as well as chronic users only. Both chronic and high-dose opioid use rates in workers' compensation declined after the WA Guideline implementation among incident opioid users. In the Medicaid study population, consisting of predominantly short-term opioid users, almost three-quarters of the opioid deaths occurred in patients who were chronic users. Chronic users were also at higher risk of opioid overdose death compared with non-chronic users.

Findings suggest that long-term, high-dose opioid users are not the only patients at high risk for opioid overdose death. A typical short-term opioid user in this study would ideally have the lowest doses and the lowest risk for an opioid overdose death. Based on those who had used opioids for <90 days, they would make up three-quarters of the study population. We found that the risk of opioid overdose death significantly increased with duration of use, even among these short-term opioid users. Also, the proportion of opioid deaths among short-term users was similar, if not higher, than the proportions among the patients in longer duration categories. This difference could be because the majority of patients are short-term users. Although it is possible that the short-term users had an opioid overdose death that involved drug diversion or other

aberrant drug-related behaviors, most patients with a fatal opioid overdose in this study population had a current prescription on the day of their death or within the 90 days prior. Short-term users may also include intermittent opioid users who had intervals of short-term use throughout follow-up. Intermittent use may also be reflective of the smaller but significantly increased risk posed by short-acting opioids.

Additional research is needed to clarify these risks associated with opioid overdose death. Although risk estimates were adjusted for demographics, we have not yet assessed the risks associated with opioid overdose death adjusted for or stratified by clinical factors, such as concomitant use of sedative/hypnotics or a history of mental/substance use disorder. In addition, there is insufficient evidence on risk of opioid overdose death with opioid generic form, either overall or by duration of action. Opioid generics that are available as either long-acting or short-acting may result in not only different risks of opioid overdose death, but also different risks of non-opioid deaths related to illicit drug use, substance use disorders or other aberrant drug-related behaviors. Such outcomes among opioid users warrant further investigation.

Our findings contribute to the evidence base concerning risk management strategies that may help to abate the national epidemic of opioid-related morbidity and mortality. The effectiveness of chronic opioid therapy for improving pain and function long-term remains unclear. Further research is needed to better understand risk factors for opioid-related adverse events, as well as on optimal treatment strategies in chronic opioid therapy. These research questions must be answered with long-term studies, ideally with measurements to track improvements in pain and function, in order to follow patients long enough to reflect the duration of use in practice.

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