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Opioid Prescriptions for Chronic Pain and Overdose

A Cohort Study

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Background: Long-term opioid therapy for chronic noncancer pain is becoming increasingly common in community practice. Concomitant with this change in practice, rates of fatal opioid overdose have increased. The extent to which overdose risks are elevated among patients receiving medically prescribed long-term opioid therapy is unknown.

Objective: To estimate rates of opioid overdose and their association with an average prescribed daily opioid dose among patients receiving medically prescribed, long-term opioid therapy.

Design: Cox proportional hazards models were used to estimate overdose risk as a function of average daily opioid dose (morphine equivalents) received at the time of overdose.

Setting: HMO.

Patients: 9940 persons who received 3 or more opioid prescriptions within 90 days for chronic noncancer pain between 1997 and 2005.

Measurements: Average daily opioid dose over the previous 90 days from automated pharmacy data. Primary outcomes—nonfatal and fatal overdoses—were identified through diagnostic codes from inpatient and outpatient care and death certificates and were confirmed by medical record review.

Results: 51 opioid-related overdoses were identified, including 6 deaths. Compared with patients receiving 1 to 20 mg/d of opioids (0.2% annual overdose rate), patients receiving 50 to 99 mg/d had a 3.7-fold increase in overdose risk (95% CI, 1.5 to 9.5) and a 0.7% annual overdose rate. Patients receiving 100 mg/d or more had an 8.9-fold increase in overdose risk (CI, 4.0 to 19.7) and a 1.8% annual overdose rate.

Limitations: Increased overdose risk among patients receiving higher dose regimens may be due to confounding by patient differences and by use of opioids in ways not intended by prescribing physicians. The small number of overdoses in the study cohort is also a limitation.

Conclusion: Patients receiving higher doses of prescribed opioids are at increased risk for overdose, which underscores the need for close supervision of these patients.

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In response to the growing awareness that chronic pain is an important patient concern, long-term opioid therapy is being prescribed with increased frequency (1–3), with more than 3% of adults now receiving long-term opioid therapy for chronic noncancer pain (2). At the same time, rates of death from opioid analgesic poisoning have increased (4–8). From 1995 to 2004, hospitalizations for opioid-related overdose doubled in Washington (9). A recent study in West Virginia reported that fewer than half (44%) of persons who died of unintentional prescription drug overdose identified at autopsy had received opioids from a physician, which suggests that overdose typically resulted from drug diversion (10, 11). However, overdose risk in patients receiving medically prescribed opioids has not been studied.

Some believe that the increase in overdose is related to excessive use of opioid analgesics in community practice (12). Others are concerned that such interpretations may lead to underprescription of opioids in patients with chronic noncancer pain (13). The association between prescription opioid exposure and overdose risk has been inferred from uncontrolled case series of autopsies subject to selection bias or from ecological time series studies in which individual-level associations cannot be examined. Although opioids provide partial relief of chronic pain (14, 15), the balance of long-term risks and benefits is poorly understood (16–21). Large-scale epidemiologic studies assessing patient use of prescribed opioids are needed to assess whether a relationship exists between medically prescribed opioid therapy and opioid-related overdose. A key unanswered question is whether risk for overdose differs by dose among patients receiving long-term therapy.

Our objectives are to estimate overall overdose rates (nonfatal and fatal) among persons receiving long-term opioid therapy for chronic noncancer pain from medical sources and to compare risks for opioid overdose among patients recently receiving different doses of long-term opioid therapy.

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Context

Information about overdose in patients prescribed long-term opioid therapy is scant.

Contribution

This study found that 51 of 9940 adults receiving long-term opioid therapy for chronic noncancer pain had 1 or more overdose events. Six events were fatal. Estimated annual overdose rates were 0.2%, 0.7%, and 1.8% among patients receiving less than 20 mg/d, 50 to 99 mg/d, and more than 100 mg/d of opioids, respectively.

Caution

Overdose events were assessed primarily through medical record review. Whether the dose-related differences in overdose rates were due to patient differences or direct effects of higher doses was not established.

—The Editors

METHODS

We report findings from the CONSORT (Consortium to Study Opioid Risks and Trends) study (22). The study setting was Group Health Cooperative (GHC), which provides comprehensive care on a prepaid basis to about 500 000 persons in Washington (23). The study was approved by the GHC Institutional Review Board.

Sample

The study cohort consisted of persons who started use of opioid analgesic prescriptions for a pain problem. Specific inclusion criteria were adults aged 18 years or older starting a new episode of opioid use (no opioid prescriptions filled in the past 6 months) from 1997 through 2005, having 3 or more prescriptions filled for opioid analgesics in the first 90 days of the episode, and receiving a diagnosis of chronic noncancer pain from the prescribing physician in the 2 weeks before the initial opioid prescription. Eligible pain diagnoses were back or neck pain; osteoarthritis; headache; extremity pain; abdominal pain or hernia; menstrual pain; temporomandibular disorder pain; and fractures, contusions, and injuries. Persons entered the study cohort on the 90th day of the episode once eligibility was established and remained in the cohort regardless of whether they continued to receive prescription opioids.

Exclusion criteria were persons with a cancer diagnosis (except nonmelanoma skin cancer) in the Cancer Surveillance and End Results Registry up to the end of 2006, 2 or more cancer diagnoses (excluding nonmelanoma skin cancer) from visit or hospital data between the episode start date and the date of censoring, and persons not enrolled for at least 270 days in the year preceding study entry. Persons who disenrolled from GHC after baseline were censored on the date of disenrollment; all other participants were censored on 31 December 2006, the end of the study observation period.

Classification of Opioids

We obtained medication data from GHC automated pharmacy files. These data cover more than 90% of the prescription medications used by GHC enrollees (23). We calculated total morphine equivalents dispensed for each opioid prescription filled during follow-up, defined by the quantity of pills dispensed multiplied by their strength (in milligrams), multiplied by a conversion factor (22). We then calculated the average daily morphine equivalent dose dispensed for 90-day exposure windows (see Statistical Analysis) by adding the morphine equivalents for the prescriptions dispensed during the 90 days and then dividing by 90. For each 90-day exposure window and each person, we calculated the average daily opioid dose dispensed and divided these into 5 categories: none, 1 to 19 mg, 20 to 49 mg, 50 to 99 mg, and 100 mg or more.

Covariate Data Collection

We obtained information on baseline covariates from automated health care data. These included age, sex, tobacco use, and diagnosis of depression or substance abuse in the 2 years before study entry. We identified the type of pain diagnosis at the index visit. We calculated chronic disease comorbidity adjustors at the time of the index visit: RxRisk risk (24) and the Romano version of the Charlson score (25). We calculated the day's supply of sedative-hypnotics dispensed (on the basis of benzodiazepine, barbiturate, and muscle relaxant prescriptions from automated pharmacy files) for 90-day exposure windows. We classified the percentage of days during which sedative-hypnotics were used into 80% of days or more (72 days or more), 50% to 79% of days (45 to 71 days), 25% to 49% of days (23 to 44 days), 1% to 24% of days (1 to 22 days), or none.

Definition of Overdose

We identified potential opioid-related overdoses from electronic medical records and conducted medical record reviews to classify and validate overdose events. We identified potential cases from the electronic medical records by using the following 2 definitions: International Classification of Disease code indicating opioid-related poisoning (case definition 1 in **Appendix Table 1**, available at www.annals.org), or International Classification of Disease code indicating an adverse opioid-related event plus a diagnosis code on the same date considered to identify an overdose (case definition 2 in **Appendix Table 1**). We identified fatal overdoses from the Washington mortality registry, which is linked to the GHC enrollment file annually (23), by using the International Classification of Disease codes listed in **Appendix Table 1**.

We examined the medical records for all potential cases identified and classified them according to the available evidence for an opioid-related overdose (categories: definite, probable, uncertain, probably not, and definitely not) (**Appendix Table 2**, available at www.annals.org). We extracted further information from the medical records on

the severity of consequences (death, serious [for example, hospitalization, unconsciousness, or respiratory failure], or not serious [for example, dizziness]). We reviewed these records without knowledge of opioid exposure status.

We ascertained overdose status (present or absent) for each participant on a daily basis. For each person, we modeled the time to the first overdose event during the study period at which the full case criteria were met (that is, after medical record review). We did not include subsequent overdose events, if they occurred, in the analyses. Separate analyses examined risk for any opioid-related overdoses and serious opioid-related overdoses. In analysis of serious overdoses, persons who had an initial overdose that was not serious were included in analyses until they had a subsequent serious overdose or were censored.

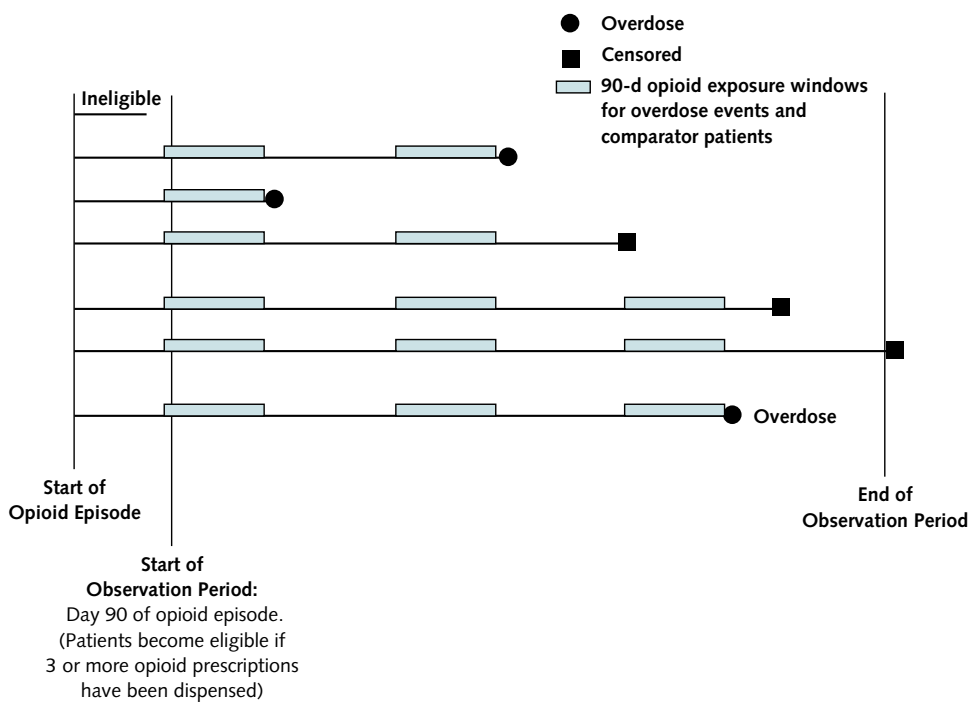
Statistical Analysis

We used a Cox proportional hazards model (PROC PHREG, SAS Institute, Cary, North Carolina) to estimate the risk for overdose across persons as a function of their average daily opioid dose (26, 27). We included opioid dose as a time-varying covariate, estimated for continuously updated 90-day exposure windows. Participants could be classified as either exposed to opioids (at any of 4 dosage levels) or unexposed on any given day, on the basis of their average daily opioid dose during the previous 90 days, including the event date. Estimated hazard ratios for opioid dose were based on comparing the opioid dose for a person who had an overdose (evaluated at the time of the event), with the opioid dose for all other persons at risk for overdose at the time of the event (that is, at the same number of days since entering the study cohort). We included whether each person had started (or restarted) opioid use in the previous 90 days as a time-varying covariate. We classified persons as starting opioid use for the first 30 days of the study period, and subsequently for any 30-day intervals after receiving an opioid prescription when no opioids had been received in the previous 90 days.

The **Figure** depicts the observation period starting at cohort entry (that is, 90 days after the start of a new episode of opioid use if 3 or more opioid prescriptions were received) and shows how the 90-day opioid exposure windows were used to compare patients who had an overdose with comparator patients who remained at risk for overdose. We contrasted opioid dose for patients with an overdose and all eligible comparator patients; patients in both groups were evaluated at the same number of days since cohort entry.

We included sedative-hypnotic use as a time-varying covariate, estimated for continuously updated 90-day exposure windows. We classified participants as either exposed to sedative-hypnotics (at any of the 4 levels of days' supply dispensed) or unexposed on any given day. Hazard

Figure. **Cohort entry, overdose events, and 90-day opioid exposure windows for patients who overdosed and comparators.**



For each patient who overdosed, we compared the average opioid dose in the preceding 90 days with all patients who remained eligible as of the same number of elapsed days since the beginning of observation. We followed patients until their first opioid overdose or until they were censored because of health plan disenrollment, death, or the end of observation.

ratios were also adjusted for the following covariates that were not treated as time-varying: age (included as a continuous variable), sex, smoking, depression diagnosis, substance abuse diagnosis, index pain diagnosis, and chronic disease comorbidity adjustors (included as continuous variables). We assessed the validity of the proportional hazards assumption by using Schoenfeld residuals (28).

Table 1. **Characteristics of Study Patients**

Characteristic	Value
Baseline	
Female, %	59.6
Age, *y*	
Mean (SD)	54 (16.8)
Range	18–99
Tobacco use, %	29.4
Depression diagnosis, %	26.9
Substance abuse diagnosis, %	6.2
Comorbid conditions	
RxRisk score	
Mean (SD)	3057 (2434)
Range	70.7–20 802
Charlson score	
Mean (SD)	0.71 (1.48)
Range	0–14
Pain diagnosis at the index visit, %	
Back pain	37.9
Extremity pain	30.3
Osteoarthritis	12.7
Injury, contusion, or fracture	12.3
Neck pain	8.9
Abdominal pain	6.4
Headache	4.9
Menstrual pain	2.1
Temporomandibular pain	0.4
Follow-up	
Follow-up, *person-months*	
Mean (SD)	42.1 (30.5)
Range	0.1–118.7
Dose of opioids, *mg/d of morphine equivalent**	
Mean	13.3
Median	6.0
Sedative-hypnotic use, %	
Prescribed any sedative-hypnotic during follow-up	74.7
Prescribed muscle relaxants during follow-up	52.3
Prescribed benzodiazepines during follow-up	42.7
At least 45 d of sedative-hypnotics prescribed in ≥1 period of 90 d	31.9
Most common opioids prescribed during follow-up, %†	
Hydrocodone	46.3
Oxycodone	24.5
Codeine combination	11.6
Long-acting morphine	6.2
Propoxyphene	4.9
Oxycodone CR	2.5
Tramadol	1.7
Hydromorphone	0.9
Methadone	0.7
Fentanyl patch	0.6
Type of opioids received most frequently, %	
Any short-acting opioid	90.4
Any long-acting opioid	9.6

CR = controlled release.
* Daily dose in patients prescribed opioids.
† Top 10 shown, based on number of days an opioid was prescribed during follow-up.

Analysis focused on the increased risk for overdose associated with recent receipt of opioids at higher doses versus recent receipt of opioids at the lowest doses (1 to 19 mg). We also compared differences in overdose risk between patients not currently receiving prescribed opioids and patients receiving opioids at the lowest doses. Exploratory analyses examined potential interactions between opioid use and baseline covariates.

Role of the Funding Source

This research was funded by the National Institute of Drug Abuse, which played no role in the analysis of data, the writing of this article, or its submission for publication.

RESULTS

We included 9940 persons starting long-term opioid therapy. We followed them for a mean of 42 months (range, <1 to 119 months) from their initial 90-day exposure window. Of the total cohort, 61% had complete follow-up (from entry into the cohort until the end of the study period, or until an event occurred), 32% left GHC during the study, and 7% died. **Table 1** describes the characteristics of the cohort. Around 60% of the cohort were women, with a mean age of 54 years. Two thirds of the cohort received a diagnosis of back pain or extremity pain at the index visit (38% and 30%, respectively). The mean daily dose of opioids prescribed was 13.3 mg (morphine equivalents). Among 46% of the cohort, hydrocodone was the most commonly prescribed opioid, and 10% of the cohort received predominately long-acting opioids. Cohort patients were using opioids during 51.2% of follow-up, with 40.1% of observation time at the lowest dose (1 to <20 mg/d of morphine equivalents); 6.7% at 20 to fewer than 50 mg/d; 2.6% at 50 to fewer than 100 mg/d, and 1.8% at 100 mg/d or more. Sedative-hypnotics were prescribed to three quarters (74%) of the cohort at some point.

Clinical Description of Identified Opioid Overdoses

We identified 6 fatal opioid-related overdoses and 74 nonfatal overdoses during the study; 13 of these were classified as definite nonfatal opioid overdoses and 32 as probable nonfatal opioid overdoses (10 were uncertain, 17 were probably not, and 2 were definitely not opioid overdoses). By defining opioid-related overdose as death or definite or probable nonfatal overdose, we identified 51 patients who had 1 or more overdose events. Of these, 40 (78.4%) experienced a fatal or otherwise serious overdose, and 11 (21.6%) had only nonserious overdose events. Common clinical contexts for overdose were varied and included accidental excess ingestion of opioids ($n = 8$) and suicide attempts ($n = 6$). We noted 3 persons who obtained additional opioids from nonmedical sources, and drug abuse was noted in the medical record of 4 persons. Four patients had notes indicating overdoses associated with applying extra fentanyl patches or sucking on a patch. The largest

Table 2. **Overdose Rates, by Patient Characteristic**

Sample	Patients Who Overdosed, *n*		Person-Years	Overdose Rate (95% CI) per 100 000 Person-Years	
	All Events*	Serious Events†		All Events*	Serious Events†
Total	51	40	34 362	148 (111–192)	116 (83–155)
Age					
18–44 y	15	11	9208	163 (91–255)	119 (60–200)
45–64 y	18	14	15 219	118 (70–179)	92 (50–146)
≥65 y	18	15	9935	181 (107–274)	151 (85–236)
Sex					
Male	21	17	13 822	152 (94–223)	123 (72–188)
Female	30	23	20 540	146 (99–203)	112 (71–162)
History of depression diagnosis					
No	25	20	25 994	96 (62–137)	77 (47–114)
Yes	26	20	8368	311 (203–441)	239 (146–354)
History of substance abuse diagnosis					
No	45	35	32 541	138 (101–182)	107 (75–146)
Yes	6	5	1821	329 (121–641)	274 (89–562)

* Opioid-related overdose death or nonfatal event.
† Opioid-related overdose death or serious nonfatal event.

category of noted clinical effects of overdose was delirium, loss of consciousness, or confusion ($n = 23$), followed by respiratory problems ($n = 15$) and falls ($n = 4$). The most common initial care settings identified for nonfatal overdose events were the emergency department ($n = 23$), inpatient care ($n = 14$), urgent care ($n = 2$), or other ambulatory care ($n = 6$).

Overdose Rates

The annual rate of overdose for the total sample was 148 per 100 000 person-years overall and 116 per 100 000 person-years for serious overdose (**Table 2**). The overdose rates were somewhat higher among persons aged 65 years or older than among persons in the 2 younger age groups and were similar between men and women. Overdose rates were elevated among persons with a history of depression or treatment of substance abuse (**Table 2**). The overall rate of overdose mortality ($n = 6$) was 17 per 100 000 person-years, so the cohort had more than 7 nonfatal overdoses for each fatal overdose. When stratified by recent receipt of opioids, the annual overdose rate was 256 per 100 000 person-years in patients who recently received medically prescribed opioids compared with 36 per 100 000 person-years in the subsample who did not (**Table 3**). We examined overdose events by clinic and did not observe notable clustering of overdose within any of the 29 clinics included in this study (data not shown).

Relationship Between Dose Dispensed and Overdose

Table 3 shows hazard ratios for the relationship between recently prescribed opioid doses and opioid-related overdose, adjusted for potential confounders. Persons receiving the lowest doses (<20 mg/d) had an annual overdose rate of 160 per 100 000 person-years. The risk for overdose increased with increasing doses. In persons receiving a dose of 100 mg/d or more, the annual overdose rate was 1791 per 100 000 person-years, a 9-fold increase in overdose risk (8.87 [95% CI, 3.99 to 19.72]) compared with persons receiving the lowest doses. When we restricted analysis to serious events, the hazard ratios were of

Table 3. **Hazard Ratios Between Recent Opioid Doses and Overdose***

Opioid Dose	Patients Who Overdosed, *n*	Person-Years	Overdose Rate (95% CI) per 100 000 Person-Years	Hazard Ratio for All Overdose Events (95% CI)†	Hazard Ratio for Serious Overdose Events (95% CI)†‡
None	6	16 780	36 (13–70)	0.31 (0.12–0.80)	0.19 (0.05–0.68)
1 to <20 mg/d	22	13 770	160 (100–233)	1.00	1.00
20 to <50 mg/d	6	2311	260 (95–505)	1.44 (0.57–3.62)	1.19 (0.40–3.60)
50 to <100 mg/d	6	886	677 (249–1317)	3.73 (1.47–9.50)	3.11 (1.01–9.51)
≥100 mg/d	11	614	1791 (894–2995)	8.87 (3.99–19.72)	11.18 (4.80–26.03)
Any opioid use	45	17 582	256 (187–336)	5.16 (2.14–12.48)	8.39 (2.52–27.98)

* Opioid-related overdose death or nonfatal event.
† Adjusted for smoking, depression, substance abuse, comorbid conditions, pain site, age, sex, recent sedative-hypnotic prescription, and recent initiation of opioid use.
‡ Opioid-related overdose death or serious nonfatal event ($n = 40$).

a similar magnitude and demonstrated a similar difference by dose (**Table 3**). Persons recently receiving sedative-hypnotic medications were also at increased risk for opioid overdose, but risk did not increase with the frequency of receiving sedative-hypnotic medications. Relative to persons not receiving any sedative-hypnotic medications in the 90 days before opioid overdose, the overdose hazard ratios were 3.4 (CI, 1.6 to 7.2) for a 1- to 22-day supply; 0.9 (CI, 0.2 to 4.0) for a 23- to 44-day supply; 3.7 (CI, 1.6 to 8.9) for a 45- to 71-day supply; and 2.7 (CI, 1.2 to 6.0) for a 72-day or more supply. In multivariate analyses, recently starting (or restarting) opioid use was not associated with either increased or reduced risk for overdose (data not shown).

We assessed patient differences by the maximum dose received during follow-up. Patients receiving the highest doses (relative to those receiving the lowest doses) more often were men (48.4% vs. 39.5%), were current smokers (40.0% vs. 28.0%), had a history of depression treatment (32.0% vs. 25.9%), had a history of substance abuse treatment (13.7% vs. 5.3%), and had higher Charlson comorbidity scores (mean, 0.93 [SD, 1.61] vs. 0.63 [SD, 1.40]), but did not differ in age. The intermediate-dose groups were generally similar to the lowest-dose group on these variables.

Persons who had not recently received opioids had less than one third the risk for overdose of patients receiving opioids at low doses (**Table 3**), with a hazard ratio of 0.31. In covariate stratified analyses, the consistency of differences in overdose risk was compared between persons recently receiving opioids and persons not recently receiving opioids. Elevated overdose risk was observed in persons recently receiving prescribed opioids in all subgroups (data not shown).

DISCUSSION

In our study, patients receiving higher doses of medically prescribed opioids for chronic noncancer pain were at increased risk for overdose relative to patients receiving lower doses. On the basis of a MEDLINE search in September 2009, we believe this study provides the first estimates of the relationship of prescribed opioid dose and overdose risk in a population with chronic pain. This increased risk remained after controlling for demographic and clinical variables. Patients who received high opioid doses were at somewhat higher risk (for example, somewhat more likely to smoke, with slightly more comorbid conditions) than patients who received the lowest doses. At low doses, the absolute risk for overdose was small. In contrast, the unadjusted, annual overdose rate was 1.8% among patients receiving 100 mg/d or more of morphine equivalents. Although risk for overdose was highest in those receiving higher doses, most overdoses occurred in patients receiving low- to moderate-dose regimens because most patients were receiving these lower doses. More than 7 nonfatal opioid-overdose events occurred for each fatal overdose in the study cohort.

Previous studies (7) indicated that the increase in opioid-related overdoses is paralleled by increased prescription of opioids for chronic noncancer pain, but some evidence suggests that overdose occurs predominately in persons obtaining prescription opioids from nonmedical sources (10). Our study provides the first estimates that directly link receipt of medically prescribed opioids to overdose risk, and suggests that overdose risk is elevated in patients receiving medically prescribed opioids, particularly in patients receiving higher doses. Our study was not designed to identify mechanisms, but information from medical records suggests that accidental ingestion of excess opioids, attempting suicide, obtaining additional opioids from nonmedical sources, using higher doses of opioid than prescribed, and using opioids in the context of drug abuse were clinical contexts, but none of these explanations was predominant.

Our study has limitations. This observational study cannot establish whether overdose risk differences reflect direct effects of differences in opioid dose or patient characteristics. Patients receiving high doses tended to be at higher risk, but differences in risk profile were controlled in multivariate analyses. Because opioid events were uncommon, we could not account for potential correlation of observations by physician or clinic. We found no notable clustering of overdose events by clinic.

Patients receiving higher-dose regimens may have been more likely to deviate from medically prescribed use (for example, increasing dose above prescribed levels, using opioids that were not prescribed, or using other substances that influence overdose risks). Some participants used prescribed opioids in dangerous ways, such as applying multiple fentanyl patches or substituting an opioid obtained from a nonmedical source for a prescribed medication. Further research is needed to understand the specific determinants of overdose risks in patients receiving long-term opioid therapy. However, our results suggest that patients using long-term opioids (particularly persons receiving higher-dose regimens) require close supervision and careful instruction in appropriate use, as recommended by expert guidelines (29, 30). Because few events were observed in the sample, we could not assess overdose risk for specific opioids or risk differences for long- versus short-acting opioids. Further research is needed to assess these risks.

The comparison group was persons who recently received prescribed opioids at low doses. We used this group (rather than the group not receiving opioids) to minimize the possibility of overdose ascertainment bias (for example, physician awareness of a patient's opioid use could influence identification of overdose). Although we adjusted for several potential confounders, the possibility of residual confounding cannot be excluded. Substance abuse and depression history based only on diagnostic codes are probably selective, and adjustment for comor-

bid conditions with the Charlson score and RxRisk is imperfect.

The inclusion of nonfatal overdoses improves understanding of the problem, because most previous work has examined only fatal overdoses. The overall overdose rate in the sample was 148 per 100 000 person-years, indicating that fatal overdose represents only the tip of the iceberg (88% of identified overdose events were nonfatal). Most of the nonfatal overdoses were clinically serious. A limitation is that we ascertained only overdoses that were brought to medical attention and identified by study procedures. Therefore, the overdose rates reported here may be conservative.

Overdose occurs at increased rates in patients prescribed opioids for chronic noncancer pain, and the risk for overdose seems to increase markedly with the average daily dose prescribed. Over the past 20 years, prescription rates of opioid analgesics for chronic noncancer pain have increased substantially (1, 2). However, large-scale, controlled studies evaluating the effectiveness and safety of long-term opioid therapy are not available (17, 31). Observational studies suggest that many patients receiving opioids for chronic noncancer pain often continue to experience appreciable pain and activity limitations (32). Because millions of adults now receive long-term opioids, which have an uncertain risk–benefit profile, large-scale, controlled studies evaluating the effectiveness and safety of long-term use of opioids in community practice are needed.

We observed increased risk for overdose in patients receiving medically prescribed opioids at higher doses. Most overdoses were medically serious, and 12% were fatal. Our study cannot conclusively establish whether dose-related differences in overdose were due to patient differences or to direct or indirect effects of higher doses. Because of uncertainties regarding effectiveness and risks (31), long-term opioid therapy should be prescribed with awareness of risks and close patient monitoring (29, 30), which may not be happening consistently at present (33). Further research on overdose risks of long-term opioid therapy and approaches to reduce associated risks is needed.

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Disclaimer: Dr. Von Korff had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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References

1. **Caudill-Slosberg MA, Schwartz LM, Woloshin S.** Office visits and analgesic prescriptions for musculoskeletal pain in US: 1980 vs. 2000. Pain. 2004;109:514-9. [PMID: 15157714]
2. **Boudreau D, Von Korff M, Rutter CM, Saunders K, Ray GT, Sullivan MD, et al.** Trends in long-term opioid therapy for chronic non-cancer pain. Pharmacoepidemiol Drug Saf. 2009. [Epub ahead of print.] [PMID: 19718704]
3. **Franklin GM, Mai J, Wickizer T, Turner JA, Fulton-Kehoe D, Grant L.** Opioid dosing trends and mortality in Washington State workers' compensation, 1996-2002. Am J Ind Med. 2005;48:91-9. [PMID: 16032735]
4. **Paulozzi LJ, Budnitz DS, Xi Y.** Increasing deaths from opioid analgesics in the United States. Pharmacoepidemiol Drug Saf. 2006;15:618-27. [PMID: 16862602]
5. **Shah NG, Lathrop SL, Reichard RR, Landen MG.** Unintentional drug overdose death trends in New Mexico, USA, 1990-2005: combinations of heroin, cocaine, prescription opioids and alcohol. Addiction. 2008;103:126-36. [PMID: 18028518]
6. **Wysowski DK.** Surveillance of prescription drug-related mortality using death certificate data. Drug Saf. 2007;30:533-40. [PMID: 17536879]
7. **Paulozzi LJ, Ryan GW.** Opioid analgesics and rates of fatal drug poisoning in the United States. Am J Prev Med. 2006;31:506-11. [PMID: 17169712]
8. **Fernandez W, Hackman H, McKeown L, Anderson T, Hume B.** Trends in opioid-related fatal overdoses in Massachusetts, 1990-2003. J Subst Abuse Treat. 2006;31:151-6. [PMID: 16919742]
9. **Washington State Department of Health.** The Health of Washington State, 2007. Olympia, WA: Washington State Department of Health; 2007.
10. **Hall AJ, Logan JE, Toblin RL, Kaplan JA, Kraner JC, Bixler D, et al.** Patterns of abuse among unintentional pharmaceutical overdose fatalities. JAMA. 2008;300:2613-20. [PMID: 19066381]
11. **Kuehn BM.** Efforts aim to curb opioid deaths, injuries. JAMA. 2009;301:1213-5. [PMID: 19318643]
12. **Fishman SM.** Commentary in response to Paulozzi et al.: prescription drug abuse and safe pain management. Pharmacoepidemiol Drug Saf. 2006;15:628-31. [PMID: 16862601]
13. **Reidenberg MM, Willis O.** Prosecution of physicians for prescribing opioids to patients. Clin Pharmacol Ther. 2007;81:903-6. [PMID: 17329989]
14. **Won A, Lapane KL, Vallow S, Schein J, Morris JN, Lipsitz LA.** Long-term effects of analgesics in a population of elderly nursing home residents with persistent nonmalignant pain. J Gerontol A Biol Sci Med Sci. 2006;61:165-9. [PMID: 16510860]
15. **Ballantyne JC.** Opioid analgesia: perspectives on right use and utility. Pain Physician. 2007;10:479-91. [PMID: 17525783]
16. **Hartung DM, Middleton L, Haxby DG, Koder M, Ketchum KL, Chou R.** Rates of adverse events of long-acting opioids in a state Medicaid program. Ann Pharmacother. 2007;41:921-8. [PMID: 17504834]
17. **Ballantyne JC, Mao J.** Opioid therapy for chronic pain. N Engl J Med. 2003;349:1943-53. [PMID: 14614170]
18. **Martell BA, O'Connor PG, Kerns RD, Becker WC, Morales KH, Kosten TR, et al.** Systematic review: opioid treatment for chronic back pain: prevalence, efficacy, and association with addiction. Ann Intern Med. 2007;146:116-27.

[PMID: 17227935]
19. **Furlan AD, Sandoval JA, Mailis-Gagnon A, Tunks E.** Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. CMAJ. 2006; 174:1589-94. [PMID: 16717269]
20. **Breivik H.** Opioids in chronic non-cancer pain, indications and controversies. Eur J Pain. 2005;9:127-30. [PMID: 15737800]
21. **Ballantyne JC, Shin NS.** Efficacy of opioids for chronic pain: a review of the evidence. Clin J Pain. 2008;24:469-78. [PMID: 18574357]
22. **Von Korff M, Saunders K, Thomas Ray G, Boudreau D, Campbell C, Merrill J, et al.** De facto long-term opioid therapy for noncancer pain. Clin J Pain. 2008;24:521-7. [PMID: 18574361]
23. **Saunders KW, Davis RL, Stergachis A.** Group Health Cooperative. In: Strom B, ed. Pharmacoepidemiology. West Sussex, UK: J Wiley; 2005:223-39.
24. **Fishman PA, Goodman MJ, Hornbrook MC, Meenan RT, Bachman DJ, O'Keeffe Rosetti MC.** Risk adjustment using automated ambulatory pharmacy data: the RxRisk model. Med Care. 2003;41:84-99. [PMID: 12544546]
25. **Romano PS, Roos LL, Jollis JG.** Further evidence concerning the use of a clinical comorbidity index with ICD-9-CM administrative data. J Clin Epidemiol. 1993;46:1085-90.
26. **Therneau TM, Grambsch PM.** Modeling Survival Data: Extending the Cox Model. New York: Springer-Verlag; 2000.
27. SAS/STAT 9.2 User's Guide. Cary, NC: SAS Publishing; 2008.
28. **Grambsch PM, Therneau TM.** Proportional hazards tests and diagnostics based on weighted residuals. Biometrika. 1994;81:515-26.
29. **Chou R, Fanciullo GJ, Fine PG, Adler JA, Ballantyne JC, Davies P, et al; American Pain Society-American Academy of Pain Medicine Opioids Guidelines Panel.** Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. J Pain. 2009;10:113-30. [PMID: 19187889]
30. **Trescot AM, Helm S, Hansen H, Benyamin R, Glaser SE, Adlaka R, et al.** Opioids in the management of chronic non-cancer pain: an update of American Society of the Interventional Pain Physicians' (ASIPP) Guidelines. Pain Physician. 2008;11:S5-S62. [PMID: 18443640]
31. **Von Korff M, Deyo RA.** Potent opioids for chronic musculoskeletal pain: flying blind? [Editorial]. Pain. 2004;109:207-9. [PMID: 15157679]
32. **Eriksen J, Sjøgren P, Bruera E, Ekholm O, Rasmussen NK.** Critical issues on opioids in chronic non-cancer pain: an epidemiological study. Pain. 2006;125: 172-9. [PMID: 16842922]
33. **McLellan AT, Turner B.** Prescription opioids, overdose deaths, and physician responsibility [Editorial]. JAMA. 2008;300:2672-3. [PMID: 19066389]

AD LIBITUM

Strong Woman

(for the mom at preschool drop-off)

When I think I'm having a bad morning,
coaxing kids out of the van, late, heading in,
I see her across the parking lot, rail-thin;
her face pale and gaunt, the hair—a warning.

Early May—the Mother's Day Tea's Friday.
***How are you? Fine*, she says, beneath her pain.**
I think, how brave. A smile—brief—she feigns.
Kids run ahead, I want to ask, in some way,

but can't. At night, I lie awake thinking—
of risk factors, and predispositions.
After I have prayed for her remission,
I dream; I'm treading water, swimming, sinking.

I want to ask, despite probable answers.
The next day—I nod and smile, walking past her.

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Appendix Table 1. Codes for Identifying Potential Opioid-Related Overdoses

ICD Code, by Version	Description
Opioid-related poisoning codes (case definition 1)	
ICD-9	
9650*	Poisoning by opioids and related narcotics
E850.1	Accidental poisoning by methadone
E950.0	Suicide and self-inflicted poisoning by analgesics, antipyretics, and antirheumatics
E980.0	Undetermined poisoning by analgesics, antipyretics, and antirheumatics
ICD-10	
T40.0	Poisoning by opium
T40.2	Poisoning by other opioids
T40.3	Poisoning by methadone
T40.4	Poisoning by other synthetic narcotics
X42	Accidental poisoning by and exposure to narcotics and psychodysleptics, not elsewhere classified
X62	Intentional self-poisoning by and exposure to narcotics and psychodysleptics, not elsewhere classified
Y12	Undetermined poisoning by and exposure to narcotics and psychodysleptics, not elsewhere classified
Opioid-specific adverse event codes (case definition 2a)†	
ICD-9	
E935.0	Adverse effects of heroin
E935.1	Adverse effects of methadone
E935.2	Adverse effects of other opioids and related narcotics
ICD-10	
Y45.0	Adverse effects of opioids and related analgesics
Overdose diagnostic codes (case definition 2b)†	
ICD-9	
276.4	Mixed acid–base balance disorder
292.1	Drug-induced psychotic disorders (including 292.11 and 292.12)
292.81	Drug-induced delirium
292.8*	Drug-induced mental disorder (excluding 292.81)
486	Pneumonia, organism unspecified
496	Chronic airway obstruction, not elsewhere classified
518.81	Acute respiratory failure
518.82	Other pulmonary insufficiency, not elsewhere classified
780.0*	Alteration of consciousness
780.97	Altered mental state
786.03	Apnea
786.05	Shortness of breath
786.09	Dyspnea and respiratory abnormalities—other
786.52	Painful respiration
799.0*	Asphyxia and hypoxemia
E950–E959	Suicide and self-inflicted injury

ICD = International Classification of Diseases.
* Includes all subcodes beginning with this code.
† Case definition 2 is met when participants have a diagnostic code from 2a plus one from 2b on the same date.

Appendix Table 2. Criteria for Classifying Events to Their Likelihood of Being an Opioid-Related Overdose, Based on Medical Record Review

Category	Criteria	Example
Definite	Clearly stated as opioid overdose	Accidental methadone overdose
Probable	Mention of overdose with involvement of opioids, or stated as probable opioid overdose; or mention of overdose and mention of opioids but not explicitly stated as opioid-related overdose	Acute alteration in level of consciousness presumed due to narcotic excess; respiratory depression due to narcotics or obstructive sleep apnea
Uncertain	Records not clear	In hospital but no specific mention of overdose
Probably not	Event with no mention of opioids; or mention of opioids but not stated as overdose	Adverse effect in context of operation
Definitely not	Clearly not opioid-related overdose	Opioid therapy withdrawal