Annals of Internal Medicine ORIGINAL RESEARCH

Opioid Prescribing After Nonfatal Overdose and Association With Repeated Overdose

A Cohort Study

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Background: Nonfatal opioid overdose is an opportunity to identify and treat substance use disorders, but treatment patterns after the overdose are unknown.

Objective: To determine prescribed opioid dosage after an opioid overdose and its association with repeated overdose.

Design: Retrospective cohort study.

Setting: A large U.S. health insurer.

Participants: 2848 commercially insured patients aged 18 to 64 years who had a nonfatal opioid overdose during long-term opioid therapy for noncancer pain between May 2000 and December 2012.

Measurements: Nonfatal opioid overdose was identified using International Classification of Diseases, Ninth Revision, Clinical Modification, codes from emergency department or inpatient claims. The primary outcome was daily morphine-equivalent dosage (MED) of opioids dispensed from 60 days before to up to 730 days after the index overdose. We categorized dosages as large (≥100 mg MED), moderate (50 to <100 mg MED), low (<50 mg MED), or none (0 mg MED). Secondary outcomes included time to repeated overdose stratified by daily dosage as a time-varying covariate.

Results: Over a median follow-up of 299 days, opioids were dispensed to 91% of patients after an overdose. Seven percent of patients (n = 212) had a repeated opioid overdose. At 2 years, the cumulative incidence of repeated overdose was 17% (95% CI, 14% to 20%) for patients receiving high dosages of opioids after the index overdose, 15% (CI, 10% to 21%) for those receiving moderate dosages, 9% (CI, 6% to 14%) for those receiving low dosages, and 8% (CI, 6% to 11%) for those receiving no opioids.

Limitation: The cohort was limited to commercially insured adults.

Conclusion: Almost all patients continue to receive prescription opioids after an overdose. Opioid discontinuation after overdose is associated with lower risk for repeated overdose.

Primary Funding Source: Health Resources and Services Administration.

Ann Intern Med. 2016;164:1-9. doi:10.7326/M15-0038 **www.annals.org**
For author affiliations, see end of text.
This article was published online first at www.annals.org on 29 December 2015.

Treatment of chronic noncancer pain with prescription opioids has increased dramatically in recent decades (1–3). Opioid misuse and overdose have increased in parallel, and deaths due to prescription opioids quadrupled to 16 651 between 1999 and 2010 (4, 5). However, overdose deaths alone do not capture the full morbidity from prescription opioids. More than 300 000 patients visited an emergency department in 2008 due to nonmedical use of prescription opioids—more than double the total from 5 years earlier (6).

Presentation to an emergency department or hospital with a nonfatal opioid overdose is an opportunity to identify and refer patients who may be misusing opioids. Prescribing guidelines specify that misuse of opioids and related adverse events are indications to discontinue long-term therapy (7, 8). However, patterns of treatment, including rates of continued prescribing, after an opioid overdose are unknown. Research suggests that opioid overdose is associated with substance use disorders or high opioid dosages (9, 10), but the association between opioid analgesia treatment after an overdose and subsequent overdose is unknown.

In this study, we sought to characterize opioid use after an overdose among patients receiving long-term opioid therapy for noncancer pain. We also aimed to determine whether patients who continued to receive prescription opioids after the index overdose switched providers and whether opioid dosage after an overdose was associated with risk for a subsequent overdose.

Methods

Study Design and Data Source

We did a retrospective cohort study of persons having a nonfatal opioid overdose during an episode of long-term opioid use. We used the Optum database (Optum), comprising complete inpatient, outpatient, and pharmacy claims for patients from a large U.S. health insurer with members in all 50 states. We drew our cohort from 50 million commercially enrolled patients between May 2000 and December 2012 with a median follow-up of 15 months. We obtained study approval through the Harvard Pilgrim Health Care Institutional Review Board.

Patient Selection

We identified 14 725 patients aged 18 to 64 years who had an index opioid overdose, defined as the first emergency department or inpatient claim with an

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Context

Hospitalization or presentation to an emergency department for nonfatal opioid overdose represents an opportunity to identify and refer patients with opioid abuse for substance abuse treatment.

Contribution

Data from a large U.S. health insurer were used to identify patients presenting to a hospital or an emergency department with a nonfatal opioid overdose between 2000 and 2012. Investigators examined whether the patients continued to receive opioid prescriptions and the time to repeated overdose.

Caution

Out-of-hospital overdoses and opioid overdose–related deaths were excluded.

Implication

Nearly all patients having a nonfatal opioid overdose continued to receive prescription opioids, and 7% had a repeated overdose.

International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), diagnosis code of overdose due to a prescription opioid (965.00, 965.02, 965.09, E850.1, or E850.2) or heroin (965.01 or E850.0). This coding classification is consistent with past studies using administrative data and consensus recommendations from the Injury Surveillance Workgroup (11–13). We combined emergency department or inpatient episodes separated by fewer than 2 days into a single episode. We excluded 1711 patients without 90 days of continuous enrollment before the start date of the index overdose to ensure sufficient data to identify prescription opioid dispensing patterns and patient characteristics at baseline (**Appendix Figure 1**, available at www.annals.org).

We limited the cohort to 3379 patients (26% of the remaining 13 014) with evidence of long-term opioid therapy at the time of the index overdose. We defined opioid episodes as consecutive dispensings with 60 or fewer days between the run-out date (fill date plus days supplied) and the fill date of the next dispensing (**Figure 1**, *A*). We defined opioid episodes as long-term if they consisted of 3 or more dispensings at least 21 days apart and lasted at least 84 days (12 weeks) with at least 84 days supplied (**Figure 1**, *B*). We used First Databank (San Francisco, California) drug summary tables to identify National Drug Codes for opiate agonists using American Hospital Formulary Service classification 28080800. We included the following opioids: codeine, dihydrocodeine, meperidine, morphine, oxycodone, hydrocodone, hydromorphone, fentanyl, oxymorphone, propoxyphene, methadone, tramadol, and levorphanol.

We excluded 479 patients with a diagnosis of cancer (except nonmelanoma skin cancer) during their enrollment based on ICD-9-CM diagnosis codes (140.X-208.X, 209.0-209.3, or V10.X [except V10.83]). We excluded 50 patients (2% of the 2900 remaining) for whom we could not confirm that the overdose was nonfatal by proxy of continued health plan enrollment or a subsequent pharmacy or medical claim. We excluded 2 patients with missing demographic variables, yielding a final cohort of 2848 patients (**Appendix Figure 1**).

Patients were followed from 90 days before the index overdose until 1 of the following 5 stopping criteria was met: a second inpatient or emergency department claim for opioid overdose; disenrollment from the health plan; age of 65 years (Medicare eligible); 730 days (2 years) after the index overdose; or December 2012, the end of the study period.

Outcomes

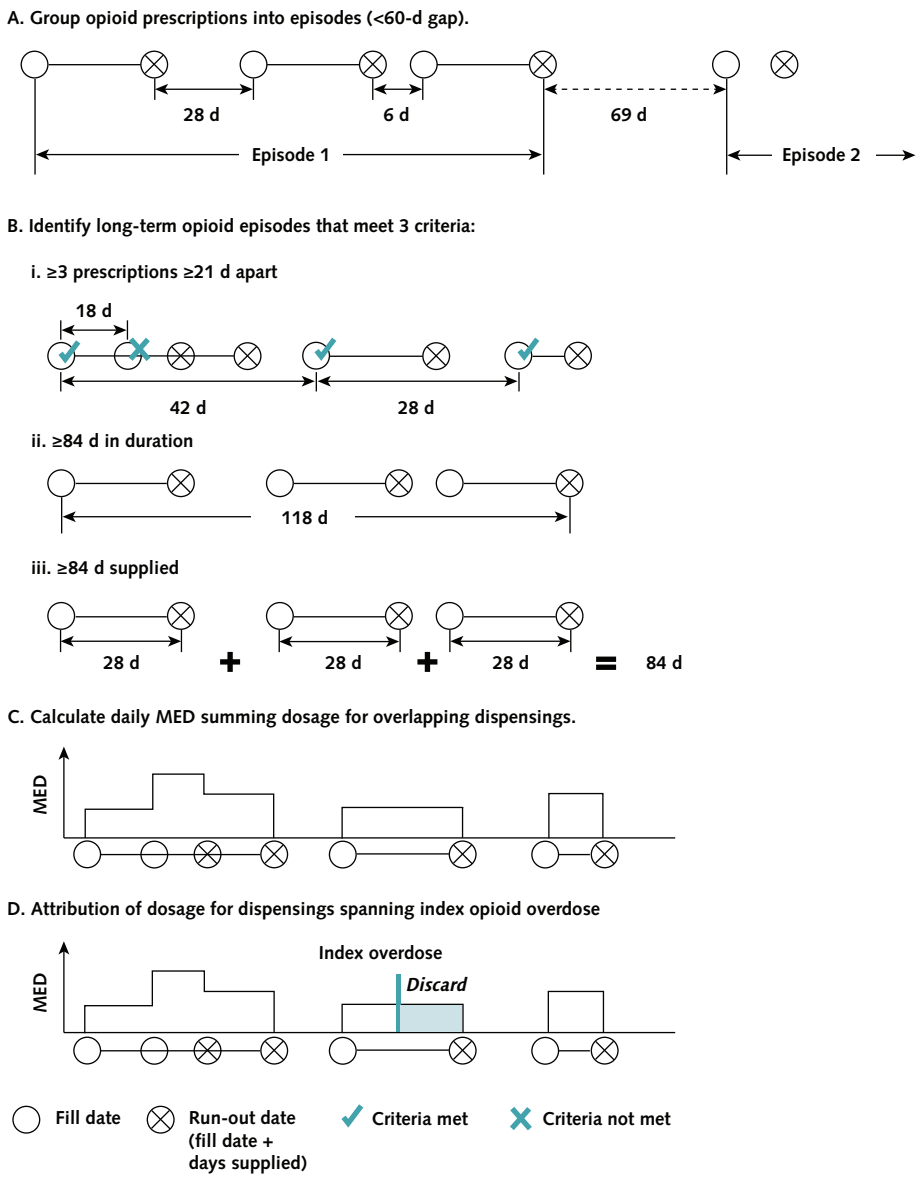
The primary outcome measure was daily opioid dosage. We calculated the morphine-equivalent dosage (MED) for each opioid dispensing using established conversion tables (14). We calculated a daily MED by distributing the total MED for each dispensing over the days supplied and summing the total of overlapping dispensings on each day (**Figure 1**, *C*). For dispensings that spanned the index overdose, we stopped attribution of opioid dosage on the day of the overdose. We set daily dosage to 0 from the first day after overdose until the date of the first opioid dispensing after the overdose, if any (**Figure 1**, *D*). We believe that this attribution scheme best reflects prescriber intent before the overdose and modifiable prescriber behavior after the overdose.

We assessed whether the primary opioid prescriber changed between the 90-day periods before and after the index overdose. We used standard provider identifiers to determine who prescribed each opioid dispensing. We identified the patient's primary prescriber before and after the index overdose as the provider associated with the most opioid dispensings in both periods. Provider identifiers were available for 95% of the prescriptions. We excluded patients whose primary prescriber could not be determined due to missing data for 1 or more opioid dispensings.

We also assessed daily availability of benzodiazepines and buprenorphine after the overdose based on the date of dispensing and days supplied. Benzodiazepines are commonly involved in fatal opioid overdoses and are associated with an increased risk for overdose when combined with opioids (4, 9). Buprenorphine has demonstrated efficacy as an office-based treatment of opioid dependence (15).

We examined time to repeated opioid overdose; patients were censored through use of the criteria identified previously. We sought to determine whether changes in opioid dosage (in particular, opioid discontinuation) after the index overdose led to opioid withdrawal visits. We examined time to a medical claim for drug withdrawal, which was identified with ICD-9-CM diagnosis code 292.0.

Figure 1. Definition of long-term opioid episodes and daily opioid dosage attribution.



MED = morphine-equivalent dose.

We examined characteristics of patients and their treatments in the 90 days before the index opioid overdose. We identified those who had 1 or more claims with a diagnosis of substance use disorder (ICD-9-CM codes 303.X-305.X), mental health disorder (schizophrenic disorder, 295.X; mood disorder, 296.X, 311.X; or anxiety disorder, 300.X), or dispensing for a benzodiazepine (American Hospital Formulary Service classification 28240800). We identified whether patients received immediate-release opioids, extended-release/long-acting opioids (Appendix Table 1, available at www.annals.org), or both. We created clinically relevant categories of pain indications through review of ICD-9-CM diagnosis codes for medical claims in the 90 days before the overdose (Appendix Table 2, available at www.annals.org).

Statistical Analysis

We depicted opioid dosage before and after the index overdose in 3 ways. First, we calculated the mean dosage for the cohort on each day of the study period. Second, we examined the percentages of patients in the cohort with daily opioid dosages of none (0 mg MED), low (>0 to <50 mg MED), moderate (50 to <100 mg MED), or large (≥100 mg MED), consistent with previous studies demonstrating an association between increasing opioid dosage and overdose risk (9, 10, 15). Finally, to examine patterns of change in dosage in individual patients, we examined the category of average

Table 1. Baseline Demographic and Treatment Characteristics of Patients Receiving Long-Term Opioid Therapy Who Have Nonfatal Opioid Overdose*

Characteristic	Value
Patients, *n*	2848
Mean age (SD), *y*	44 (11)
Male	1135 (40)
Daily opioid dosage (MED) before overdose†	
<50 mg/d	928 (33)
50 to <100 mg/d	621 (22)
≥100 mg/d	1299 (46)
Type of opioid prescription in 90 d before index overdose	
Immediate-release only	1216 (43)
Extended-release/long-acting only	206 (7)
Immediate- and extended-release/long-acting	1426 (50)
Benzodiazepine prescription in 90 d before index overdose	1593 (56)
Mental health diagnosis in 90 d before index overdose	1676 (59)
Diagnosis of substance use disorder in 90 d before index overdose	1156 (41)
Pain diagnoses‡	
Extremity	2519 (88)
Neck	1909 (67)
Headache	1720 (60)
Back	1337 (47)
Neuropathic	1267 (44)
Abdomen	1177 (41)
Chest	973 (34)
Chronic pain	561 (20)
Rheumatoid arthritis/lupus	110 (4)
Kidney	63 (2)
Other	590 (21)
Region	
Northeast	158 (6)
Midwest	675 (24)
South	1446 (51)
West	569 (20)
Year	
2000–2003	411 (14)
2004–2006	602 (21)
2007–2009	927 (33)
2010–2012	908 (32)

MED = morphine-equivalent dose.
* Values are numbers (percentages) unless otherwise indicated. Percentages may not sum to 100 due to rounding.
† Average daily dosage for 60 d leading up to and including the date of the index opioid overdose.
‡ See **Appendix Table 2** (available at www.annals.org) for a list of International Classification of Diseases, Ninth Revision, Clinical Modification, diagnosis codes included in each category.

daily dosage for the following 3 periods: 60 days before the overdose, days 31 to 90 after the overdose, and days 91 to 365 after the overdose. We then identified the proportion of patients in each dosage category who moved to a different dosage category in the next period. We excluded the first 30 days before and after the index overdose because we could not correctly classify the dosage before the first prescription in each respective period. We compared benzodiazepine and buprenorphine use daily after the overdose, stratified by whether patients had an active opioid dispensing.

To assess the association between daily opioid dosage and time to repeated overdose and time to medical claim for drug withdrawal, we used an extended Kaplan–Meier estimator allowing for time-varying opioid dosage to generate cumulative incidence curves (16). We developed a multivariable Cox regression model of the time to repeated overdose to assess for predictors of repeated overdose. The main predictor of interest was opioid dosage, incorporated as a time-varying covariate daily. We also added availability of buprenorphine or benzodiazepines as time-varying covariates daily. We incorporated average daily opioid dosage in the 60 days before overdose, sex, age, and preoverdose mental health and substance use diagnoses given their known association with overdose risk (10, 17–20). We used SAS, version 9.3 (SAS Institute), and R, version 3.1.1 (R Foundation for Statistical Computing), for analyses.

Role of the Funding Source

This study was funded by the Health Resources and Services Administration. The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, and approval of the manuscript.

RESULTS

The cohort consisted of 2848 patients followed for a median duration of 299 days (interquartile range, 123 to 639) after the index overdose. The mean age was 44 years (SD, 11), and 40% of patients were men (**Table 1**). In the 60 days before the index overdose, 46% of patients had an average daily dosage of 100 mg MED or more. In the 90 days before the index overdose, 56% of patients were dispensed a benzodiazepine, 59% had claims with a mental health diagnosis, and 41% had claims with a substance use disorder.

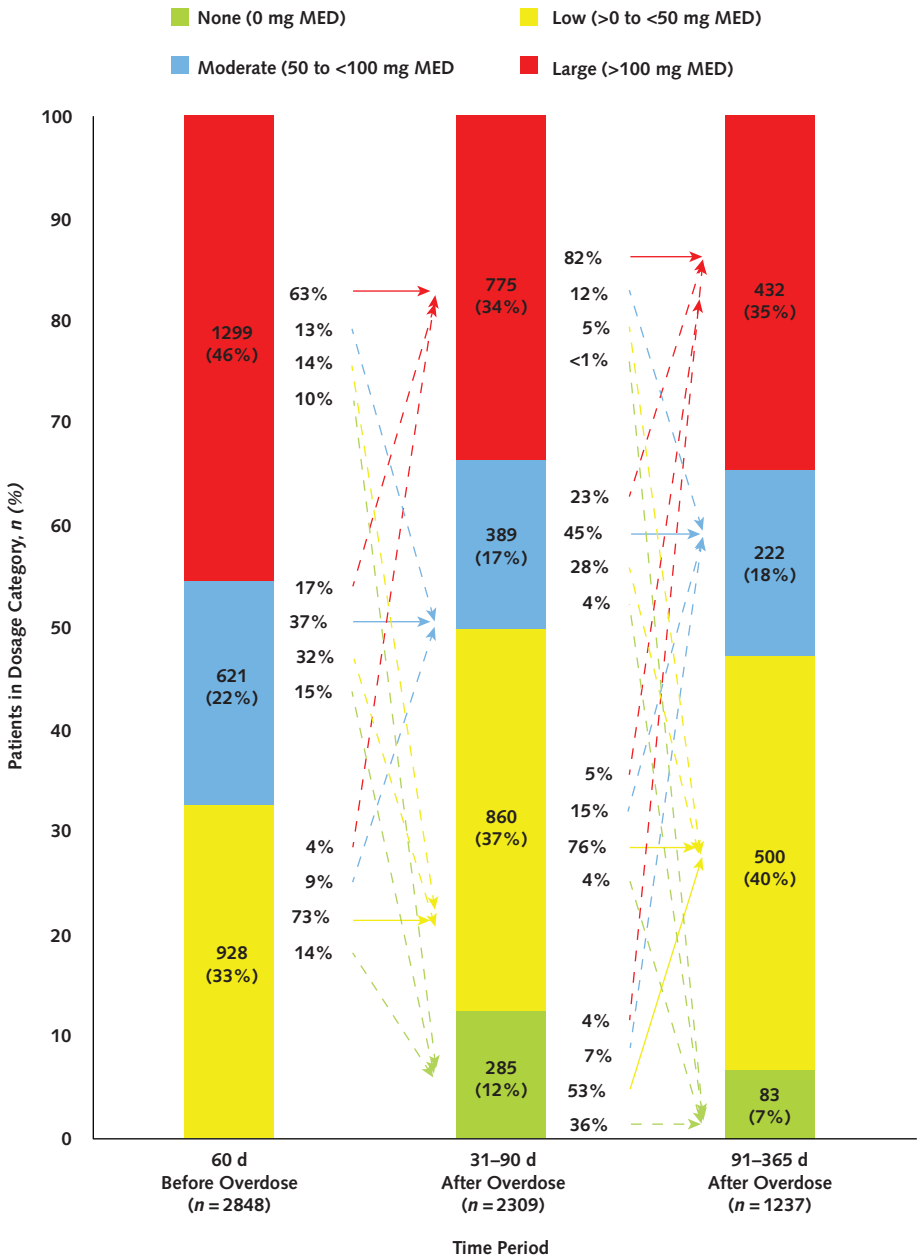
Opioid Dispensing Patterns Before and After the Index Overdose

In the 60 days before the index overdose, the mean daily dosage for the cohort ranged between 152 and 164 mg MED until the week before the overdose when the dosage increased rapidly, peaking at 187 mg MED on the day before the overdose (**Appendix Figure 2**, *A* [available at www.annals.org]). Thirty days after the index overdose, the mean dosage had decreased to 118 mg MED and remained relatively stable, ranging between 111 and 131 mg MED over 2 years of follow-up (**Appendix Figure 2**, *A*).

In the follow-up period after the overdose, 2597 patients (91%) received 1 or more opioid dispensings. On days 31 to 60 after the overdose, 69% to 71% of patients had an active opioid prescription on any given day, which trended down slightly to 63% to 65% in the final month of the 2-year follow-up (**Appendix Figure 2**, *B*). Between 31% and 36% of patients received high daily opioid dosages after postoverdose day 30.

Patients generally stayed in the same dosage category from one period to the next (**Figure 2**). However, most movement was toward lower dosage categories from the 60 days before the overdose to 31 to 90 days after. Similar proportions of patients from each dosage category in the 60-day preoverdose period completely discontinued opioids 31 to 90 days after the overdose

Figure 2. Movement among categories of opioid dosage over time.



The arrows and values depict the percentage of movement from 1 dosage category to another, with the solid arrow representing the path with the most patients. Percentages may not sum to 100 due to rounding. MED = morphine-equivalent dose.

(10% from the large-dosage, 15% from the moderate-dosage, and 14% from the low-dosage categories). Among patients who discontinued opioids 31 to 90 days after the overdose, 64% were dispensed an opioid 91 to 365 days after the overdose.

For the 2597 patients who received opioids both before and after the index overdose, we identified a primary prescriber in both periods for 1964 patients (76%). For 1198 of these (61%), the primary prescriber was the same before and after the index overdose. For an additional 173 patients (9%), the primary prescriber in the postoverdose period was associated with 1 or more preoverdose dispensings. Thus, 593 patients (30%) switched to an entirely new prescriber after the overdose.

Benzodiazepine and Buprenorphine Dispensings After the Overdose

In the postoverdose period, 58% of patients received 1 or more dispensings of a benzodiazepine. Patients with an active opioid dispensing were more likely to have an active benzodiazepine dispensing (33% to

39%) than those without an active opioid dispensing (14% to 22%) (Appendix Figure 3, *A* [available at www.annals.org]). A total of 206 patients (7%) received buprenorphine after the overdose. Active buprenorphine dispensings were less common for patients with an active opioid dispensing (0% to 1%) than for those without an active opioid dispensing (5% to 12%) (Appendix Figure 3, *B*).

Time to Repeated Overdose

Seven percent of patients (n = 212) had a repeated opioid overdose. A total of 2044 patients (72%) were censored before 2 years of follow-up due to health plan disenrollment or becoming 65 years of age. Cumulative incidence curves for repeated overdose by category of daily opioid dosage demonstrate separation over 2 years of follow-up, with higher dosage categories having higher overdose rates (Figure 3, *A*). At the end of 2 years, 17% (CI, 14% to 20%) of patients receiving a high daily dosage had a repeated overdose compared with 15% (CI, 10% to 21%) of those receiving a moderate dosage, 9% (CI, 6% to 14%) of those receiving a low dosage, and 8% (CI, 6% to 11%) of those receiving no opioids.

In the Cox model analyzing daily opioid dosage as a time-varying covariate with no opioid dispensing as the referent, the adjusted hazard ratios of repeated overdose were 1.13 (CI, 0.69 to 1.85) for patients receiving low opioid dosages, 1.89 (CI, 1.18 to 3.04) for those receiving moderate dosages, and 2.57 (CI, 1.72 to 3.85) for those receiving large dosages. Active daily benzodiazepine dispensing was also associated with increased risk for repeated overdose (adjusted hazard ratio, 1.74 [CI, 1.31 to 2.32]). Daily buprenorphine dispensing and opioid dosage before the index overdose were not associated with risk for repeated overdose (Table 2).

Time to Drug Withdrawal

Nine percent of patients (n = 267) had a diagnosis of drug withdrawal after the overdose. Cumulative incidence curves stratified by category of daily opioid dosage demonstrate that patients receiving no opioids had a slightly higher rate of visits for withdrawal (5%) at 30 days than those receiving low, moderate, or large dosages (2% to 4%) (Figure 3, *B*). However, at 2 years, patients receiving large dosages of opioids had the highest cumulative incidence of claims for drug withdrawal (15%).

DISCUSSION

Among patients who had an opioid overdose during long-term therapy for noncancer pain, 91% received 1 or more opioid prescriptions after the overdose. After the overdose, two thirds of patients had an active opioid dispensing and one third were receiving high dosages (≥100 mg MED per day). Higher dosages after the overdose were associated with an increased risk for repeated overdose.

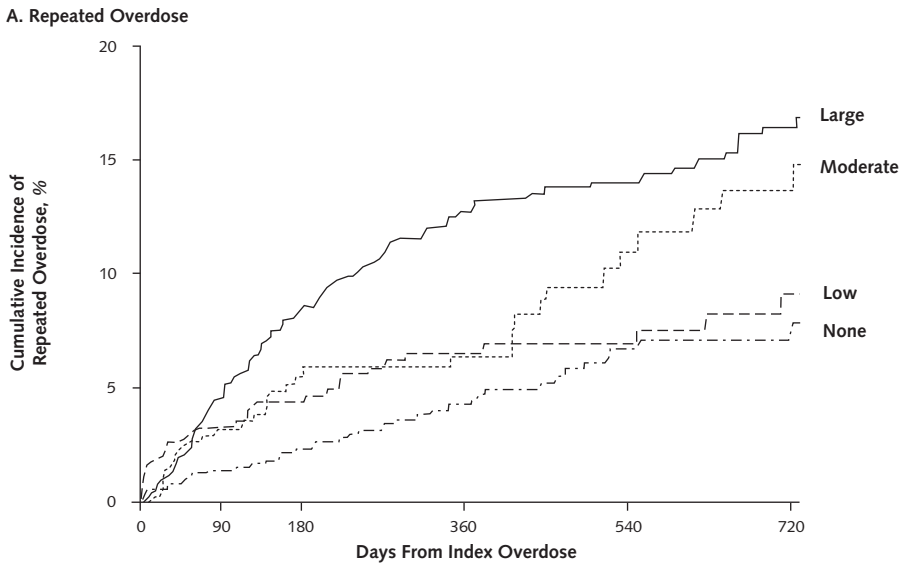
To our knowledge, this is the first study to examine treatment patterns after an overdose and risk for repeated overdose. Prescribing guidelines, updated after the start of our study period, clearly state that misuse of opioids and adverse effects are compelling reasons to discontinue opioids (7, 8). We could not determine reasons for the treatment patterns after the overdose; however, some prescribers may have been unaware that the opioid overdose had occurred. This hypothesis may be supported by the finding that 70% of patients who continued to receive opioids after the overdose obtained them from a prescriber who had treated them before the overdose. In some cases, overdoses may have reflected therapeutic error rather than opioid misuse. In these and other cases, providers may have believed that the risk–benefit ratio favored continued opioid prescribing. Conversely, providers might not have had the knowledge or skills to identify and treat opioid use disorders.

We detected a strong association between opioid dosage after a nonfatal overdose and risk for repeated overdose; however, we cannot conclude that the relationship is causal. Claims data are limited in availability of covariates, and unmeasured confounding is probably substantial. Important contextual factors missing from claims data include the medical and social circumstances surrounding the overdose, quality and degree of counseling, availability of substance abuse treatment, referral to specialist care, and patients' desire to change. We note that this cohort had high levels of known risk factors for overdose in the baseline period, but the only significant predictors of repeated overdose were time-varying daily opioid dosage and active benzodiazepine dispensing.

Our study has several other potential limitations. First, we cannot know the extent of misclassification of opioid dosage because of patients who paid cash as opposed to using insurance to obtain opioids. Second, there is potential misclassification of overdose due to use of ICD-9-CM codes; however, our classification is consistent with consensus recommendations from the Injury Surveillance Workgroup and with past studies (11–13). Third, our study is limited to overdoses treated in emergency department or inpatient settings and excludes out-of-hospital episodes and deaths before a medical encounter. This cohort is limited to commercially insured persons and may not be generalizable to patients in other settings, such as the Medicaid and Veterans Affairs systems, where risk for overdose death is known to be higher (21, 22).

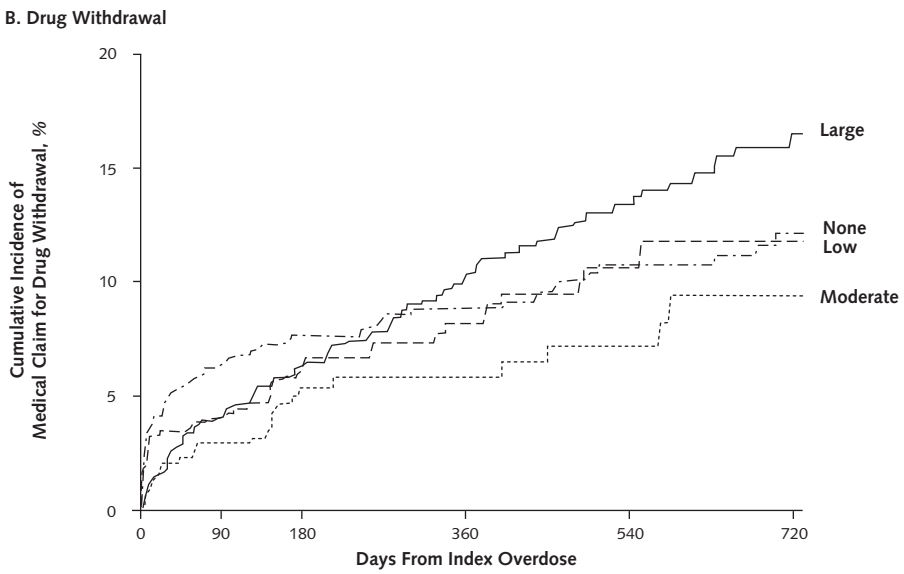
Our finding that almost all patients continue to be prescribed opioids after overdose is highly concerning. The overdoses we detected were captured in routine claims data and treated in emergency departments or inpatient settings and thus represent identifiable events when information sharing might lead to improved care and outcomes. Further research is needed to determine whether providers continuing to prescribe opioids after an overdose are aware of the event and, if so, how they respond in counseling patients. Determining whether patients in integrated health systems fare differently would also shed light on whether fragmented care is a contributing factor.

Figure 3. Extended Kaplan–Meier cumulative incidence curves for repeated opioid overdose and claim for drug withdrawal after overdose stratified by category of opioid dosage (large, moderate, low, or none).



Patients remaining, *n*

None	2719	710	587	417	296	218
Low	52	487	357	223	149	111
Moderate	29	337	254	168	128	71
Large	48	775	624	435	288	205



Patients remaining, *n*

None	2719	642	522	365	256	182
Low	52	475	341	205	136	99
Moderate	29	326	244	158	112	60
Large	48	733	582	397	256	174

Simply eliminating opioid prescribing for patients who had had an overdose is not sufficient for patients with opioid use disorders because some may turn to diverted or illicit opioids. Rather, efforts to identify and treat substance use disorders in these patients are needed. Our study was limited because we could not identify patients receiving methadone maintenance for opioid use disorders and buprenorphine was introduced as an outpatient treatment partway through the study period.

We are not aware of procedures to ensure provider notification after a nonfatal overdose. There are several possible mechanisms for notification. One is direct contact between the hospital where the opioid overdose

Table 2. Adjusted Cox Proportional Hazards Model Results for Time to Repeated Overdose

Variable	Adjusted HR (95% CI)
Age	
18–24 y	1.75 (0.91–3.36)
25–34 y	1.36 (0.86–2.16)
35–44 y	0.88 (0.58–1.34)
45–54 y	1.03 (0.70–1.51)
55–64 y	1.00 (Reference)
Male	1.06 (0.80–1.40)
Average opioid dosage 60 d before index overdose	
Low*	1.00 (Reference)
Moderate†	0.94 (0.62–1.42)
Large‡	0.96 (0.65–1.40)
Mental health diagnosis 90 d before index overdose	0.95 (0.72–1.26)
Diagnosis of substance use disorder 90 d before index overdose	1.03 (0.78–1.37)
Daily opioid dosage after overdose (continuous)	
None§	1.00 (Reference)
Low*	1.13 (0.69–1.85)
Moderate†	1.89 (1.18–3.04)
Large‡	2.57 (1.72–3.85)
Active benzodiazepine dispensing after overdose (daily, continuous)	1.74 (1.31–2.32)
Active buprenorphine dispensing after overdose (daily, continuous)	0.84 (0.26–2.68)
Overdose year	
2000–2003	1.00 (Reference)
2004–2006	0.77 (0.50–1.20)
2007–2009	0.78 (0.52–1.17)
2010–2012	0.72 (0.47–1.10)

HR = hazard ratio.
* <50 mg morphine-equivalent dose per day.
† 50 to <100 mg morphine-equivalent dose per day.
‡ ≥100 mg morphine-equivalent dose per day.
§ 0 mg morphine-equivalent dose per day.

was treated and the opioid prescriber. Forty-nine states now have prescription-monitoring programs that can facilitate such communication (23). Health plans have access to claims for both the overdose and opioid dispensing, and notification programs have been shown to reduce high-risk prescribing (24). However, the effectiveness of provider notification is challenged if patients seek an alternative opioid provider. Health plans could conceivably require prior authorization after an overdose, but patients could still pay cash to obtain opioids. A more centralized approach would mandate reporting of overdoses to a department of public health to facilitate referral to substance abuse treatment or proactive notification of providers and pharmacies. This approach may be limited because of the confidential and sensitive nature of disclosure of substance use disorders.

Almost all members of a commercial insurance plan having opioid overdose continued to receive opioid prescriptions, with one third receiving high-dose opioids over 2 years of follow-up. Patients receiving high dosages had more than twice the risk for repeated overdose. These findings suggest a meaningful opportunity to improve the safety of opioid prescribing through identification and treatment of persons having nonfatal overdose.

From Harvard Medical School, Harvard Pilgrim Health Care Institute, Boston University School of Medicine, and Boston Medical Center, Boston, Massachusetts.

Grant Support: Dr. Larochelle was supported by the Health Resources and Services Administration (grants T32 HP10251 and T32 HP12706), Ryoichi Sasakawa Fellowship Fund, and Harvard Pilgrim Health Care Institute.

Disclosures: Dr. Larochelle reports grants from the Health Resources and Services Administration and Ryoichi Sasakawa Fellowship Fund and nonfinancial support from the Harvard Pilgrim Health Care Institute during the conduct of the study. Authors not named here have disclosed no conflicts of interest. Forms can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M15-0038.

Reproducible Research Statement: *Statistical code:* Available from Dr. Larochelle (e-mail, marc.larochelle@bmc.org). *Study protocol and data set:* Not available.

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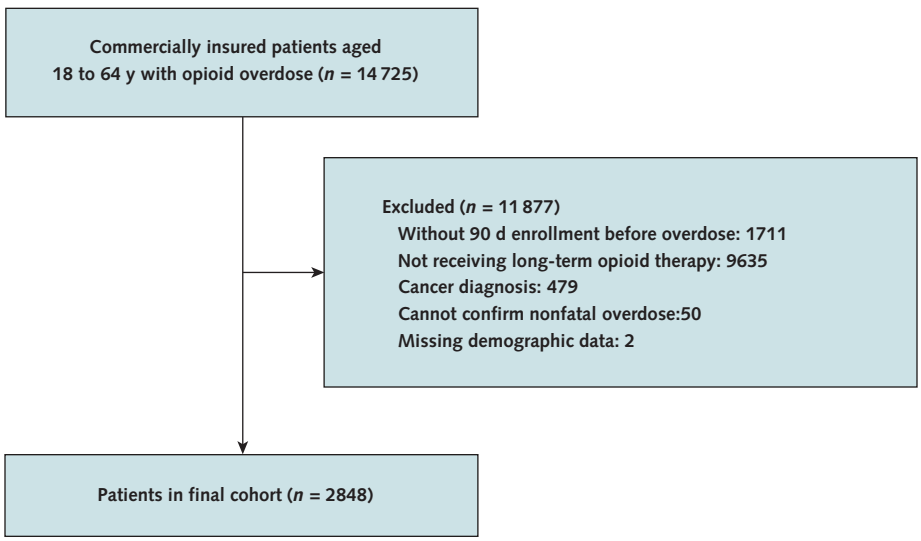
Obtaining of funding: J.F. Wharam.
Administrative, technical, or logistic support: M.R. Larochelle, J.F. Wharam.
Collection and assembly of data: M.R. Larochelle, J.F. Wharam.

Appendix Figure 1. Study flow diagram.



Appendix Table 1. Opioid Formulations Classified as Extended-Release/Long-Acting

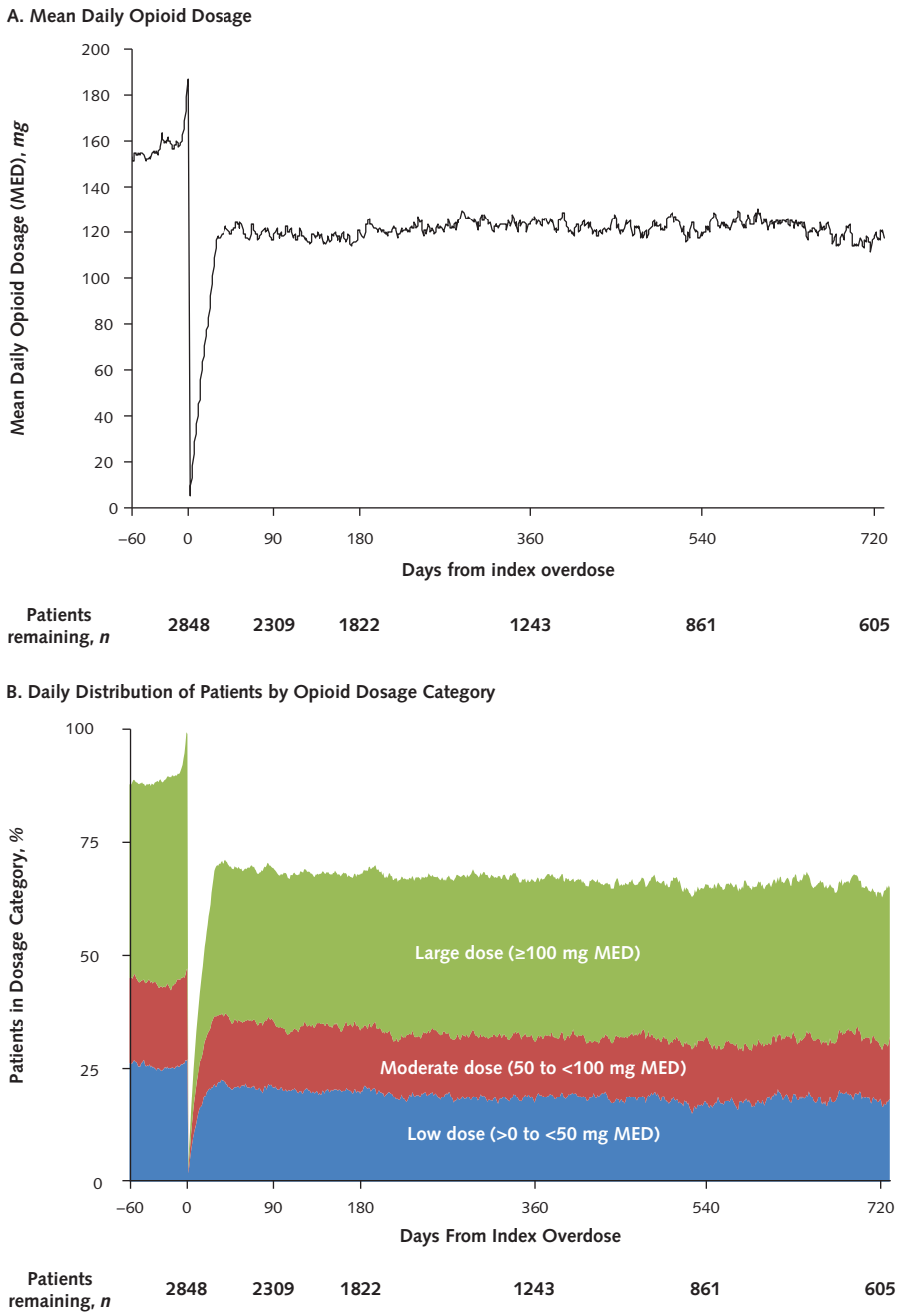
Methadone (all formulations)
Morphine (extended-release capsules or tablets)
Oxycodone (extended-release tablets)
Hydrocodone (extended-release capsules)
Hydromorphone (extended-release capsules or tablets)
Fentanyl (transdermal patch)
Oxymorphone (extended-release tablets)
Tramadol (extended-release tablets)

Appendix Table 2. All ICD-9-CM Diagnosis Codes From 90 d Before the Index Overdose That Were Reviewed by 2 Physicians* and Categorized Into Clinically Relevant Groupings

Pain Diagnosis Category	ICD-9-CM Diagnosis Codes
Extremity	354.0, 715.X, 716.90, 719.4X, 726.X, 728.85, 729.5, 733.90, 836.0, 845.X, 959.7
Neck	721.0X, 721.1X, 722.0X, 722.4X, 722.81, 723.X (except 723.4), 739.1, 847.0, 920
Headache	307.81, 346.X, 784.0
Back	720.X, 721.X (except 721.0, 721.1), 722.X (except 722.0, 722.4, 722.81), 724.X, 737.30, 738.4, 739.2, 739.3, 846.0, 847.1, 847.2
Neuropathic	355.X, 356.X, 357.X, 723.4, 729.2
Abdomen	535.00, 535.50, 555.9, 577.0, 577.1, 620.2, 789.0X
Chest	413.9, 786.5, 959.19
Chronic pain	338.29, 338.4
Rheumatoid arthritis/lupus	710.0, 714.0
Kidney	592.0
Other	307.89, 338.18, 338.19, 729.1

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.
* M.R.L. and J.M.L.

Appendix Figure 2. Daily opioid dosage before and after index overdose.



MED = morphine-equivalent dose.

Appendix Figure 3. Proportion of patients with an active benzodiazepine or buprenorphine dispensing on each day after overdose, stratified by whether the patient also had an active opioid dispensing on that respective day.