Original Investigation

Prescription Opioid Duration of Action and the Risk of Unintentional Overdose Among Patients Receiving Opioid Therapy

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IMPORANCE The unprecedented increase in unintentional overdose events that has occurred in tandem with escalating sales of prescription opioids over the past 2 decades has raised concerns about whether the therapeutic use of opioids has contributed to increases in overdose injury. Few controlled studies have examined the extent to which ecologic measures of increases in opioid prescribing and overdose injuries reflect risk among patients prescribed opioids, let alone whether some opioid regimens are safer than others.

OBJECTIVE To examine whether the risk of unintentional overdose injury is associated with the duration of opioid action (ie, long-acting vs short-acting formulations).

DESIGN, SETTING, AND PARTICIPANTS A propensity score-adjusted cohort study was conducted using population-based health care utilization data from the Veterans Administration Healthcare System. The patients were veterans with chronic painful conditions who began therapy with opioid analgesics between January 1, 2000, and December 31, 2009.

MAIN OUTCOMES AND MEASURES Unintentional overdoses that are explicitly coded using International Classification of Disease, Ninth Revision codes as drug or medication poisonings of accidental intent (E850.x-860.x) or undetermined intent (E980.x or drug poisoning [960.x-980.x] without an accompanying external cause of injury code).

RESULTS A total of 319 unintentional overdose events were observed. Patients initiating therapy with long-acting opioids were more than twice as likely to overdose compared with persons initiating therapy with short-acting opioids. After adjustment for age, sex, opioid dose, and other clinical characteristics, patients receiving long-acting opioids had a significantly higher rate of overdose injury than did those receiving short-acting opioids (hazard ratio [HR], 2.33; 95% CI, 1.26-4.32). The risk associated with long-acting agents was particularly marked during the first 2 weeks after initiation of treatment (HR, 5.25; 1.88-14.72).

CONCLUSIONS AND RELEVANCE To our knowledge, the findings of the present study provide the first evidence that the risk of unintentional overdose injury is related to the prescribed opioid’s duration of action. If replicated in other cohorts, our findings suggest that clinicians weighing the benefits and risks of initiating different opioid regimens should consider not only the daily dose prescribed but also the duration of opioid action, favoring short-acting agents whenever possible, especially during the first 2 weeks of therapy.

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The present cohort study examined the relationship between opioid prescription use and nonfatal overdose among veterans receiving care within the US Department of Veterans Affairs Healthcare System between January 1, 2000, and December 31, 2009. All analyses were conducted at the Massachusetts Veterans Epidemiology Research and Information Center, VA Cooperative Studies Coordinating Center, VA Boston Healthcare System. The institutional review board of the VA Boston Healthcare System approved the study. Since health care utilization data stripped of identifiers were used, the need for informed consent was waived.

National pharmacy and administrative data from the Veterans Health Administration (VHA) were linked. Data from the National Patient Care Database includes patient demographics, the location and clinic where services were provided, International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes, Current Procedural Terminology codes (for outpatient procedures), and ICD-9 procedure codes (for inpatient procedures) for all years since 1997. We obtained deidentified outpatient prescription medication data for opioid agents and concomitant medications from the Pharmacy Benefits Management Database. Pharmacy data include all prescriptions, dosages, days’ supply, and quantities dispensed as well as the date dispensed, in a VA facility and outpatient prescription orders filled at a VA pharmacy or consolidated mail outpatient pharmacy.

### Study Population

We identified all patients who filled an opioid analgesic prescription between January 1, 2000, and December 31, 2009 (Figure). The index date was defined as the first day on which an opioid prescription was filled during this period. Our sample was restricted to new users of opioids, defined as persons having a minimum of 6 months without the use of an opioid before the index opioid prescription (ie, we required a 6-month washout period). We further limited the sample to new users with chronic noncancer pain as the likely indication for treatment prior to or including the index date. Chronic pain was characterized using the definition of Bohnert et al in their study of fatal opioid overdose among VHA beneficiaries, including ICD-9 diagnostic codes for general chronic pain; headache (other headache syndromes; migraines; tension, not otherwise specified; and atypical face pain); back and neck pain; arthritis, arthropathies, and other bodily pain; and neuropathies. We excluded patients who were not eligible for VHA benefits, did not have at least 1 inpatient or outpatient encounter in the year prior to their index opioid prescription, or were enrolled in hospice in the year before their index date.

### Opioid Exposure

Our study included the most commonly prescribed short-acting and long-acting opioids in the VHA system during the 10-year study period. Long-acting agents have either an inherently long serum half-life or a delivery vehicle that allows less-frequent administration (ie, at most, twice daily). The long-acting opioids in the present study included orally administered sustained-release morphine sulfate, methadone hydrochloride, controlled-release oxycodone hydrochloride, levorphanol tartrate, and fentanyl patches. Liquid methadone hydrochloride was excluded because this is the formul-


Figure. Sample Population Flowchart

| 260637 | Opioid prescriptions filled without duplicate prescriptions for the same drug |
| 123966 | Used opioids within 6 mo before study |
| 2476671 | New users of opioids (26 mo treatment naive) |
| 60913 | Nonveterans; missing data on age or sex; date of death recorded on or before index date |
| 2415758 | Veterans with data included on age and sex; date of death recorded on or after index date |
| 588098 | Did not use the VHA during the 365 d before first opioid prescription fill |
| 1827660 | Used the VA during the 365 d before the first opioid prescription fill |
| 1983 | In hospice during the 365 d before the first opioid prescription fill |
| 1825677 | Not in hospice during the first 365 d before the first opioid prescription fill |
| 985071 | No chronic pain indication and proximate diagnosis within 90 d of first opioid prescription fill |
| 840606 | Veterans with chronic pain indication and proximate diagnosis within 90 d of first opioid prescription fill |

VHA indicates Veterans Health Administration.

*An additional 19 900 opioid users were excluded because they used opioids other than those specified in the Methods section.

Duration of Opioid Use

Patients began to contribute information to analyses from their index opioid prescription date and continued to do so until they experienced an overdose event, died, switched opioid agents, discontinued opioid treatment, entered hospice, became ineligible for VHA benefits, or reached the end of the study period, whichever came first. When a refill for an opioid prescription was dispensed on a date that occurred before the calculated end date of the prior prescription, the new prescription was assumed to begin the day after the calculated end date of the old prescription, and the days’ supply was accumulated. If a patient accumulated more than 180 days' supply on a given day, the supply was truncated at 180 days. We provided a grace period of 1.5 times the days' supply for any given prescription before censoring a patient for discontinuing their opioid medication (ie, patients must have refilled their opioid prescription within this grace period or they were classified as discontinuers at the end of the grace period).

Dose

To assess and control for the effect of the opioid dose, we converted each opioid agent to the morphine-equivalent dose following the method of Von Korff et al.17 We computed the morphine-equivalent mean daily dose by dividing the total quantity prescribed by days' supply and converted the daily dose thus calculated into a corresponding morphine-equivalent dose. After the conversion, prescriptions in morphine-equivalent mean daily doses were categorized as 1 mg to less than 20 mg, 20 mg to less than 50 mg, 50 mg to less than 100 mg, and 100 mg or greater.

Outcome

Our primary outcome of interest was unintentional overdoses that were coded as drug or medication poisonings of accidental intent using ICD-9 codes (E850.x-E860.x) or undetermined intent (E980.x or drug poisoning [E960.x-E980.x] without an accompanying external cause of injury code). If an e-code indicated that the poisoning was self-inflicted (E950.x) or assault-related (E962.x), it was not counted as an event. Events were recorded at VA institutions and via billing to the VA from outside hospitals.

Covariates

We obtained baseline demographic and clinical characteristics pertaining to the 12 months prior to and including the index date. Demographic variables included age, sex, race (white, black, other, and unknown or missing), and the percentage of any service-connected disability. Service-connected disability percentage is a measure of the severity of a disability, ranging from 0% to 100% and assigned in 10% increments. Zero percent service-connected disability indicates that an individual did not have such a disability. Clinical characteristics included prior falls and fractures, other medical diagnoses, and psychiatric diagnoses. We categorized VA health care utilization as the use of general mental health clinic services, services provided in the posttraumatic stress disorder clinic, and use of specific therapies, including intensive therapy, rehabilitation, and substance abuse disorder treatment; emergency department and urgent care visits; and inpatient hospitalizations. We characterized comedication with nonopioid agents, including selective cyclooxygenase 2 inhibitors and other nonsteroidal anti-inflammatory drugs.

Statistical Analysis

Propensity score adjustment modeled the probability of receiving a long-acting opioid and included baseline covariates and significant 2-way interaction terms. We trimmed the top and bottom 1% in the propensity score distribution to eliminate patients who almost always would and those who would almost always not receive long-acting opioids. Cox propor-
tion of hazards regression models with multivariate and stabilized inverse probability treatment weights were used to assess risk adjusted for potential confounders.\textsuperscript{18} To correct the standard errors in the weighted analysis, we used the robust sandwich estimate of the covariance matrix (ie, the covs[aggregate] option and identification statement in the phreg procedure in SAS, version 9.2). Survival models were conducted in a piecewise fashion to account for variable hazards over time.

Sensitivity analyses excluded people with (i) methadone as the index opioid owing to concern that providers may preferentially prescribe methadone for pain control when unmeasured factors lead them to suspect a patient is at increased risk of abusing their medication and (2) overdose events for which an e-code was unavailable. All analyses were performed using SAS, version 9.2 (SAS Institute Inc).

## Results

Of the 840,606 eligible patients with chronic pain diagnoses within 90 days of their first opioid prescription, the majority of those who filled index prescriptions for opioid monotherapy received short-acting agents (n = 801,729); 18,887 filled prescriptions for long-acting opioids (Figure). New users of long-acting opioid monotherapy in our study represent 17.5\% of all new long-acting opioid prescriptions received by VHA beneficiaries during our study period (ie, 83.2\% of patients receiving long-acting opioids were given concomitant short-acting opioids). Thus, our cohort of incident users of long-acting opioids constituted 2.3\% of patients who used the VA during the year before their index opioid prescription fill (and had a chronic pain indication within 90 days of their index dose).

Selected characteristics of the cohort are described in Table 1. Complete data are provided in eTable 1 in the Supplement. Most of the patients were men. The most common chronic pain diagnoses included osteoarthritis, back or neck pain, and other arthropathies. Hydrocodone was the most commonly prescribed opioid. Patients who were given prescriptions for long-acting opioids were more likely to receive higher daily doses than were those receiving short-acting opioids as well as to have back and neck pain, depression, anxiety, post-traumatic stress disorder, and substance use disorders. The long-acting opioid group also was more likely to be receiving concomitant antidepressants and benzodiazepines.

A total of 319 unintentional overdose events were observed during the study period among patients analyzed in an as-treated fashion (ie, according to our primary censoring criteria). Of these events, 282 occurred among patients initiating therapy with short-acting opioids and 37 among patients initiating therapy with long-acting opioids (Table 2). Approximately half of all the events occurred within the first 60 days after the start of opioid therapy. The crude rate of overdose events observed for both short-acting and long-acting opioids was higher during the first 2 weeks after opioid initiation than thereafter, but the heightened risk immediately after initiation therapy was far more marked among patients initiating therapy with long-acting opioids than for patients initiating therapy with short-acting opioids (Table 2).

The crude hazard ratio (HR) of unintentional overdose during the study period was more than 2.5 times higher for persons initiating therapy with long-acting opioids (35 per 10,000 person-years) compared with persons initiating therapy with short-acting opioids (14 per 10,000 person-years) (HR, 2.84; 95\% CI, 2.01-4.02). After adjustment for age, sex, and opioid dose, the patients receiving long-acting opioids still had a 2.5-fold higher risk of overdose (HR, 2.56; 95\% CI, 1.67-3.93). Adjustment using all available covariates slightly reduced the relative risk, but the risk remained significantly higher among patients who initiated therapy with long-acting opioids (HR, 2.33; 95\% CI, 1.26-4.32). Overdose risk during the first 2 weeks after treatment initiation was more than 5-fold higher for patients who began receiving long-acting opioids compared with those receiving short-acting opioids (HR, 5.25; 1.88-14.72). Relative risk decreased to approximately 2-fold thereafter (higher with long-acting opioids) (Table 2). These general findings remained in sensitivity analyses that excluded patients who initiated therapy with methadone and when analyses were restricted to patients with definitive e-coded event outcomes (eTable 2 and eTable 3 in the Supplement). Of the overdose events in our study, 23.2\% were coded as opioid overdose events per se. Overdose risk was greater for patients initiating higher-dose therapy, with the risk among those receiving therapy with more than 50-mg equivalents of morphine being at most twice the risk of overdose events compared with those receiving opioids at 1- to 20-mg equivalents.

## Discussion

To our knowledge, this is the first study to provide estimates of the relative risk of unintentional overdose events in relation to equianalgesic doses of long-acting vs short-acting opioids. In our study, which was restricted to patients with chronic medical conditions to reduce confounding by indication, patients who initiated opioid therapy with long-acting agents were at significantly higher risk of unintentional overdose events compared with those given prescriptions for short-acting agents. Risk was especially high shortly after opioid therapy began (5-fold higher) and remained elevated throughout the 1-year study period (relative risk was approximately 50\% higher for patients receiving long-acting opioids beyond 60 days of continuous opioid use). The exceptionally high relative risk observed during the first 2 weeks of therapy was driven by a very high rate of unintentional overdose injury among patients receiving long-acting agents rather than a particularly low rate of injury among those receiving short-acting agents, making it less likely that differentially poor initial adherence to opioid therapy by patients receiving short-acting agents accounts for our findings.

The only other large observational study to examine opioid therapy in relation to overdose risk in a cohort of patients with chronic painful conditions, conducted by Dunn et al,\textsuperscript{10} did not distinguish between unintentional and intentional overdose events. In that study, which focused on patients who used...
long-acting opioids and assessed opioid overdose risk for patients who continued treatment for at least 90 days after initiating therapy, overdose risk was elevated with increasing mean daily doses. Consistent with the findings of Dunn et al and the observational study that separated prevalent from incident opioid users, we found an increasing risk of overdose among patients initiating higher doses of opioids. Similar to Paulozzi et al, we found that opioid overdoses represented approximately 1 of every 3 to 4 unintentional overdose events.

Our decision to restrict analyses to patients with documented diagnoses of chronic painful conditions who were be-
ginning new opioid therapy confers several advantages over designs that include prevalent opioid users. The primary advantages include the ability to detect adverse events that occur soon after drug therapy is started, assess risks over time, and control for selection bias with baseline patient characteristics that are not influenced by the effects of opioid treatment. In addition, incident-user designs also mitigate potential selection bias owing to a drug-related history that might affect current treatment assignment. Because we were interested in adverse outcomes most directly linkable to the opioid regimen a patient was receiving, our primary analytic strategy was to censor people at the time of opioid regimen changes. Our decision to censor data for patients at treatment discontinuation and to use a proportional hazards analysis adjusts for differences in treatment persistence. By censoring patient follow-up as soon as an individual switched opioid agents or augmented therapy with a different opioid, we avoided the problematic comparison of patients who change treatment in response to adverse effects, refractory pain, or worsening symptoms (any of these factors might be indications of elevated overdose risk) with patients who do not change treatment.

Several caveats should be considered when interpreting the findings from the present study. First, as in all analyses relying on claims databases, we had limited ability to adjust for the severity of substance use disorders, physical illness, and psychiatric illness, all of which might place patients at heightened risk of unintentional overdose without regard to the opioid regimen. Patients who received long-acting opioids in our study were, in fact, more likely to have baseline risk factors for unintentional overdose injury (eg, more substance use disorders, psychiatric morbidity, and comedication with barbiturates, antidepressants, and sedative-hypnotics) compared with patients who received shorter-acting opioids. Nevertheless, after adjustment for these differences, unintentional overdose risk remained substantially higher, especially soon after the initiation of long-acting opioid therapy. Propensity scores offer an advantage in studies of rare outcomes (eg, unintentional overdose events) because propensity scores model the relationship of covariates and their interactions with the drug exposure (which is relatively frequent) and not directly with the study outcome (which is often rare), thereby mitigating the risk of overfitting in a traditional outcome model.

### Table 1. Selected Baseline Characteristics Among Patients Initiating Single Opioid Agents at the Index Time (continued)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Short-Acting Opioid</th>
<th>Long-Acting Opioid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hydrocodone Bitartrate</td>
<td>Codeine Phosphate</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>405.106 (50.5)</td>
<td>195.581 (50.0)</td>
</tr>
<tr>
<td>Selective COX-2 inhibitors</td>
<td>21.282 (2.7)</td>
<td>7218 (1.8)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>69.686 (8.7)</td>
<td>33.479 (8.6)</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>95.152 (11.9)</td>
<td>45.364 (11.6)</td>
</tr>
<tr>
<td>Sedative-hypnotics</td>
<td>29.657 (3.7)</td>
<td>14.351 (3.7)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>251.543 (31.4)</td>
<td>122.978 (31.5)</td>
</tr>
<tr>
<td>Gastric medications</td>
<td>313.093 (39.1)</td>
<td>149.347 (38.2)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>208.187 (26.0)</td>
<td>99.252 (25.4)</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>124.987 (15.6)</td>
<td>60.510 (15.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Healthcare Utilization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain clinic</td>
</tr>
<tr>
<td>Inpatient hospitalization</td>
</tr>
</tbody>
</table>

Abbreviations: ACE, angiotensin-converting enzyme; CAD, coronary artery disease; CHF, congestive heart failure; COX-2, cyclooxygenase-2; GI, gastrointestinal; IQR, interquartile range; MI, myocardial infarction; NSAIDs, nonsteroidal anti-inflammatory drugs; PTSD, posttraumatic stress disorder; PVD, peripheral vascular disease; SR, sustained release.

* A complete listing of baseline characteristics appears in Table 1 in the Supplement.

* Other short-acting agents were hydromorphone hydrochloride, morphine, meperidine hydrochloride, and pentazocine.

* Levorphanol tartrate was excluded from the table because fewer than 11 patients were receiving it as the index medication.

* Morphine-equivalent mean daily dose.

* Gastric medications included proton pump inhibitors and H2 inhibitors, and diuretics included loop and thiazide diuretics.
differential risk we observed, it is not clear why such risk would be so much higher soon after initiation of therapy than thereafter.

Second, we used administrative data and therefore did not directly measure opioid adherence. Using automated prescription data may, however, more accurately measure use of the medication than studies that rely on data from self-report surveys. A related point is that we defined drug exposure in our primary analysis in a way that seeks to capture how patients fill their prescriptions (ie, analyses are "as treated"), but in so doing admit possible selection bias owing to censoring. Nevertheless, our findings were robust to analyses in which exposure was defined using first treatment carried forward, which would tend to bias findings toward the null. In addition, it is possible that some patients we classified as incident users were, in fact, prevalent users of opioids if they were taking opioids prescribed outside the VA or illicitly at the time our data suggest incident use.

Third, the event rates that we report are necessarily underestimates of the actual unintentional overdose event rate because events may go unreported if patients with unintentional overdose events (1) die without coming to medical attention for their fatal event, (2) do not seek medical attention for a nonfatal event, or (3) receive medical attention that is neither treated nor reimbursed by the VHA system. Since we do not have any reason, a priori, to believe that ascertainment of outcomes would be biased with respect to duration of opioid action, the relative risks that we report are unlikely to be affected by this consideration.

Fourth, our findings apply to patients with chronic painful conditions who received care within the VHA system, the vast majority of whom are male and older than 50 years. The applicability of our findings to females, patients without chronic medical conditions, and younger patients is not known. Given the elevated prevalence of chronic pain and opioid use among a recent sample of active-duty infantry soldiers who are not seeking treatment, many of whom will become eligible for VA services upon separation from the military, future work focusing on opioid duration of action and overdose risk among recently separated military personnel may be warranted.

Conclusions

Despite the study's limitations, we believe that our findings provide the first evidence that the risk of unintentional opioid overdose injury is related to the prescribed drug's duration of action. If replicated in other cohorts, our findings suggest that clinicians weighing the benefits and risks of different opioid regimens should take into account not only the daily dose prescribed but also the duration of opioid action, favoring short-acting opioids whenever possible, especially during the first 2 weeks after initiation of therapy.

Table 2. Incidence Rate and HR for Unintentional Overdose Comparing Long-Acting With Short-Acting Opioids

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Events</th>
<th>No. of Person-years</th>
<th>Crude Rate (95% CI)</th>
<th>Crude HR (95% CI)</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>282</td>
<td>194,683</td>
<td>14.49 (12.79-16.18)</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Short-acting</td>
<td>282</td>
<td>194,683</td>
<td>25.21 (19.31-31.12)</td>
<td>1.74 (1.34-2.26)</td>
<td>1.74 (1.34-2.26)</td>
</tr>
<tr>
<td>Long-acting</td>
<td>37</td>
<td>10,623</td>
<td>143.4 (54.51-232.2)</td>
<td>2.84 (2.01-4.02)</td>
<td>2.56 (1.67-3.93)</td>
</tr>
<tr>
<td>Overall</td>
<td>106</td>
<td>10,623</td>
<td>34.83 (23.61-46.05)</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Short-acting</td>
<td>106</td>
<td>10,623</td>
<td>16.04 (12.50-19.57)</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Long-acting</td>
<td>10</td>
<td>697</td>
<td>36.00 (14.64-64.71)</td>
<td>2.42 (1.05-5.56)</td>
<td>2.19 (0.92-5.19)</td>
</tr>
</tbody>
</table>

Abbreviations: HR, hazard ratio; sIPWT, stabilized inverse probability weight.

a Seventy-five of the 319 unintentional overdose events were noted to be opioid overdoses. Stabilized inverse probability weights were used to balance potential confounding of the relationship between opioid use and overdose. All baseline characteristics from Table 1 were included in the propensity score model for receipt of a long-acting opioid. In addition, all significant 2-way interactions of characteristics from Table 1 were included when modeling the probability of receiving a long-acting opioid. These included, among many other baseline factors, interactions of benzodiazepines, pain clinic visits, and antidepressant use. Other recurring factors with significant interactions were the use of cyclooxygenase 2 inhibitors, baseline hyperlipidemia, and baseline liver disease. These propensity scores were then used to adjust the association between opioid use and overdose for all included covariates and interactions.

b Per 10,000 person-years.

c Morphine-equivalent mean daily dose.


