Original Investigation

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

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IMPORTANCE 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 unprecedented increase in unintentional overdose events, both fatal and nonfatal, 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 to treat moderate to severe pain has contributed to increases in overdose injury.[1-6] However, few controlled studies have examined the extent to which observations from aggregate-level data about parallel increases in opioid prescribing and overdose injuries reflect risk among patients receiving opioids,[7-11] let alone whether some opioid regimens are safer than others.

The relationship between particular opioid regimens and the risk of overdose remains poorly understood for several reasons. First, randomized clinical trials have been too small to produce meaningful risk estimates for overdose events (either fatal or nonfatal). Although unintentional drug overdose claimed approximately 33 000 lives in 2010[12] (nearly the number of individuals who died in motor vehicle crashes) and an estimated 10 times as many emergency department visits each year,[13] event rates are still too rare to assess with randomized trials. Second, most nonrandomized (ie, observational) studies[1-6] that have examined this issue have relied on ecologic data and thus are subject to the ecologic fallacy (ie, drawing inferences about individuals based on analyses of group data). Third, the few individual-level observational studies that have most thoughtfully investigated the relationship between opioid prescription regimens and unintentional overdose risk have focused on opioid dose[8-11] rather than more readily modified attributes of prescriptions, such as whether the particular opioid agent or type of opioid chosen matters when the dose is controlled. Drawing actionable inferences about preventing unintentional overdose from existing studies is further compromised by limitations in design and analysis, including failure to distinguish between intentional and unintentional overdose outcomes[7,9,10,14] (and other sources of measurement error, such as ascertaining potential confounders after initiation of opioid therapy[7,9,10,15,16]) and selection bias, especially because of the inclusion of prevalent users in the analytic sample.[7-11]

The present cohort study used clinical and pharmacy data from the Veterans Administration (VA) Healthcare System and appropriate pharmacoepidemiologic techniques to examine whether the risk of unintentional overdose injury is associated with the duration of opioid action (ie, long-acting vs short-acting opioid formulations) and, if so, whether the overdose risk is modified by the duration of continuous opioid use. To our knowledge, the present study is the first to address these questions using an incident-user design (ie, a study that sets the cohort's inception date according to patients' new use of opioids, in contrast with studies that follow a prevalent user design and enroll patients who were already receiving opioids when follow-up began).

Methods

Study Design and Data Collection

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[11] 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 formu-

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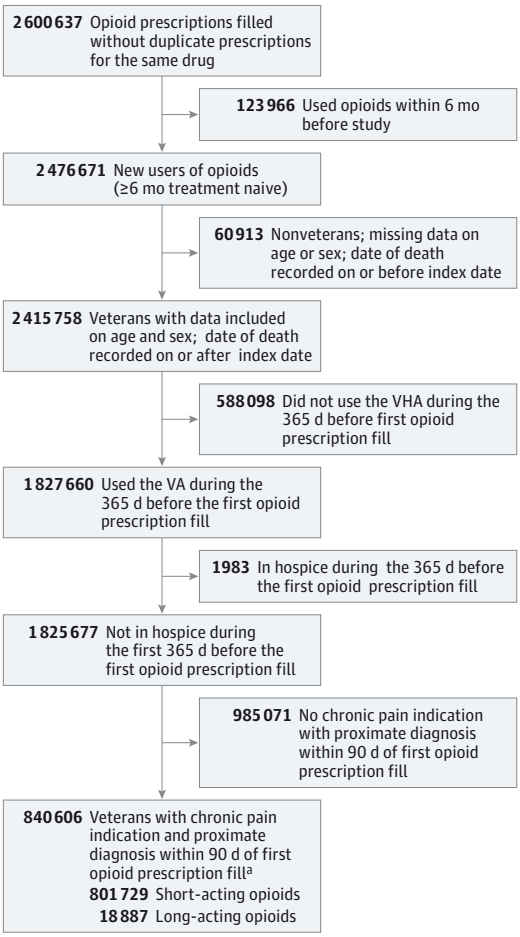
Figure. Sample Population Flowchart



VHA indicates Veterans Health Administration.

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

lation used by the VHA in treating opiate addiction. Short-acting opioids (ie, codeine phosphate, hydrocodone, and oxycodone) used in our study were orally administered and were packaged as single agents or as combination products containing acetaminophen or aspirin. Opioids that were combined with other agents in elixirs (eg, promethazine/codeine syrup) and injectable opioids were excluded.

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-860.x) or undetermined intent (E980.x or drug poisoning [960.x-980.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-

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tional hazards regression models with multivariate and stabilized inverse probability treatment weights were used to assess risk adjusted for potential confounders.[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 (1) 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 monotherapy with 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, posttraumatic 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 patents initiating therapy with short-acting opioids (Table 2).

The crude hazard ratio (HR) of unintentional overdose events 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 agents (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 opioid 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 more than 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 shorter-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,[10] did not distinguish between unintentional and intentional overdose events. In that study, which focused on patients who used

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Table 1. Selected Baseline Characteristics Among Patients Initiating Single Opioid Agents at the Index Time[a]

Characteristic	Short-Acting Opioid[b]				Long-Acting Opioid[c]				
	Total	Hydrocodone Bitartrate	Codeine Phosphate	Oxycodone Hydrochloride	Total	Morphine Sulfate SR	Fentanyl	Methadone Hydrochloride	Oxycodone SR
Veterans, No. (%)	801 729 (97.7)	390 981 (48.8)	244 877 (30.5)	165 871 (20.7)	18 887 (2.3)	7724 (40.9)	4802 (25.4)	3429 (18.2)	2932 (15.5)
Age, median (IQR), y	60 (51-71)	60 (51-71)	61 (52-74)	59 (50-70)	59 (51-72)	59 (51-72)	69 (55-79)	55 (49-63)	59 (50-72)
Male sex, No. (%)	749 552 (93.5)	365 689 (93.5)	229 301 (93.6)	154 562 (93.2)	17 836 (94.4)	7299 (94.5)	3226 (94.1)	4531 (94.4)	2780 (94.8)
Race, No. (%)									
White	568 828 (71.0)	282 388 (72.2)	166 564 (68.0)	119 876 (72.3)	14 351 (76.0)	5822 (75.4)	2615 (76.3)	3648 (76)	2266 (77.3)
Black	147 866 (18.4)	59 829 (15.3)	55 224 (22.6)	32 813 (19.8)	2265 (12.0)	970 (12.6)	340 (9.9)	586 (12.2)	369 (12.6)
Other	85 035 (10.6)	48 764 (12.5)	23 089 (9.4)	13 182 (7.9)	2271 (12.0)	932 (12.1)	474 (13.8)	568 (11.8)	297 (10.1)
Baseline opioid use, median (IQR)									
Initial days' supply	30 (10-30)	30 (10-30)	30 (10-30)	15 (7-30)	30 (30-30)	30 (30-30)	30 (30-30)	30 (30-30)	30 (30-30)
Initial mean daily dose[d]	15 (10-22.5)	15 (10-21)	13.5 (9-18)	22.8 (15-37.5)	45 (30-97)	30 (30-60)	97 (97-179.5)	45 (30-80)	30 (30-60)
Chronic pain indication diagnoses, No. (%)									
Rheumatoid arthritis	10 960 (1.4)	4915 (1.3)	3574 (1.5)	2471 (1.5)	354 (1.9)	132 (1.7)	88 (2.6)	53 (1.1)	81 (2.8)
Osteoarthritis	170 210 (21.2)	81 328 (20.8)	54 549 (22.3)	34 333 (20.7)	3615 (19.1)	1421 (18.4)	759 (22.1)	771 (16.1)	664 (22.6)
Back/neck pain	304 792 (38.0)	157 172 (40.2)	88 375 (36.1)	59 245 (35.7)	10 930 (57.9)	4494 (58.2)	1868 (54.5)	3047 (63.5)	1521 (51.9)
Other arthropathies	347 761 (43.4)	169 499 (43.4)	106 227 (43.4)	72 035 (43.4)	5992 (31.7)	2545 (32.9)	1047 (30.5)	1414 (29.4)	986 (33.6)
Headache	41 186 (5.1)	19 081 (4.9)	13 631 (5.6)	8474 (5.1)	824 (4.4)	322 (4.2)	138 (4.0)	242 (5.0)	122 (4.2)
Neuropathy	24 509 (3.1)	11 157 (2.9)	7181 (2.9)	6171 (3.7)	962 (5.1)	358 (4.6)	183 (5.3)	293 (6.1)	128 (4.4)
Chronic pain	2682 (0.3)	1758 (0.4)	344 (0.1)	580 (0.3)	332 (1.8)	146 (1.9)	38 (1.1)	134 (2.8)	14 (0.5)
Previous injuries and fractures, No. (%)									
Falls	2842 (0.4)	1333 (0.3)	825 (0.3)	684 (0.4)	74 (0.4)	40 (0.5)	18 (0.5)	11 (0.2)	<11
Fracture	13 633 (1.7)	5851 (1.5)	3958 (1.6)	3824 (2.3)	381 (2.0)	152 (2.0)	79 (2.3)	76 (1.6)	74 (2.5)
Comorbidities, No. (%)									
Depression	168 093 (21.0)	83 871 (21.5)	49 011 (20)	35 211 (21.2)	5956 (31.5)	2316 (30)	962 (28.1)	1845 (38.4)	833 (28.4)
Alcohol-related disorders	69 241 (8.6)	32 860 (8.4)	20 536 (8.4)	15 845 (9.6)	1864 (9.9)	726 (9.4)	251 (7.3)	661 (13.8)	226 (7.7)
Drug-related disorders	40 486 (5.0)	18 595 (4.8)	12 427 (5.1)	9464 (5.7)	1724 (9.1)	521 (6.7)	171 (5.0)	842 (17.5)	190 (6.5)
Dementia	22 645 (2.8)	11 097 (2.8)	7299 (3.0)	4249 (2.6)	650 (3.4)	246 (3.2)	202 (5.9)	122 (2.5)	80 (2.7)
Diabetes mellitus	190 520 (23.8)	91 721 (23.5)	59 382 (24.2)	39 417 (23.8)	4313 (22.8)	1831 (23.7)	867 (25.3)	959 (20.0)	656 (22.4)
Hypertension	454 203 (56.7)	220 771 (56.5)	141 301 (57.7)	92 131 (55.5)	10 233 (54.2)	4257 (55.1)	1975 (57.6)	2461 (51.2)	1540 (52.5)
Stroke	30 443 (3.8)	13 689 (3.5)	10 235 (4.2)	6519 (3.9)	743 (3.9)	297 (3.8)	188 (5.5)	139 (2.9)	119 (4.1)
Osteoporosis	15 813 (2.0)	7712 (2.0)	4952 (2.0)	3149 (1.9)	644 (3.4)	263 (3.4)	204 (5.9)	102 (2.1)	75 (2.6)

(continued)

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[10] and the observational study that separated prevalent from incident opioid users,[11] we found an increasing risk of overdose among patients initiating higher doses of opioids. Similar to Paulozzi et al,[19] 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-

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

Characteristic	Short-Acting Opioid[b]				Long-Acting Opioid[c]				
	Total	Hydrocodone Bitartrate	Codeine Phosphate	Oxycodone Hydrochloride	Total	Morphine Sulfate SR	Fentanyl	Methadone Hydrochloride	Oxycodone SR
Concomitant medications[e]									
NSAIDs	405 106 (50.5)	195 581 (50.0)	127 555 (52.1)	81 970 (49.4)	7576 (40.1)	3031 (39.2)	1129 (32.9)	2126 (44.3)	1290 (44.0)
Selective COX-2 inhibitors	21 282 (2.7)	7218 (1.8)	8085 (3.3)	5979 (3.6)	931 (4.9)	252 (3.3)	242 (7.1)	169 (3.5)	268 (9.1)
Corticosteroids	69 686 (8.7)	33 479 (8.6)	20 692 (8.4)	15 515 (9.4)	1747 (9.2)	791 (10.2)	378 (11.0)	322 (6.7)	256 (8.7)
Benzodiazepines	95 152 (11.9)	45 364 (11.6)	27 569 (11.3)	22 219 (13.4)	3662 (19.4)	1524 (19.7)	688 (20.1)	812 (16.9)	638 (21.8)
Sedative-hypnotics	29 657 (3.7)	14 351 (3.7)	8683 (3.5)	6623 (4.0)	1022 (5.4)	396 (5.1)	163 (4.8)	288 (6.0)	175 (6.0)
Antidepressants	251 543 (31.4)	122 978 (31.5)	75 547 (30.9)	53 018 (32.0)	8812 (46.7)	3398 (44.0)	1464 (42.7)	2606 (54.3)	1344 (45.8)
Gastric medications	313 093 (39.1)	149 347 (38.2)	97 909 (40.0)	65 837 (39.7)	8437 (44.7)	3465 (44.9)	1690 (49.3)	1997 (41.6)	1285 (43.8)
Diuretics	208 187 (26.0)	99 252 (25.4)	66 705 (27.2)	42 230 (25.5)	4873 (25.8)	2005 (26.0)	1049 (30.6)	1056 (22.0)	763 (26.0)
Anticonvulsants	124 987 (15.6)	60 510 (15.5)	36 593 (14.9)	27 884 (16.8)	5842 (30.9)	2298 (29.8)	984 (28.7)	1672 (34.8)	888 (30.3)
Healthcare Utilization									
Pain clinic	9523 (1.2)	4037 (1.0)	2764 (1.1)	2722 (1.6)	1690 (8.9)	540 (7.0)	221 (6.4)	740 (15.4)	189 (6.4)
Inpatient hospitalization	160 105 (20.0)	68 432 (17.5)	39 351 (16.1)	52 322 (31.5)	3544 (18.8)	1564 (20.2)	701 (20.4)	734 (15.3)	545 (18.6)

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] A complete listing of baseline characteristics appears in eTable 1 in the Supplement.

[b] Other short-acting agents were hydromorphone hydrochloride, morphine, meperidine hydrochloride, and pentazocine.

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

[d] Morphine-equivalent mean daily dose.

[e] Gastric medications included proton pump inhibitors and H_2 inhibitors, and diuretics included loop and thiazide diuretics.

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)[20-30] 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.[31,32] As is the case for all observational studies, however, our ability to adjust fully for underlying risk at baseline depends on our ability to accurately classify baseline confounders and is compromised to the extent that measurement and reporting of conditions coded in claims are misclassified.[33] However, if unmeasured baseline risk factors were responsible for the

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

Characteristic	No. of Events	No. of Person-years	Crude Rate (95% CI)[b]	Crude HR (95% CI)	Adjusted HR (95% CI)	
					Age, Sex, Index Dose[c]	sIPWT
Overall						
Short-acting	282	194 683	14.49 (12.79-16.18)	1 [Reference]	1 [Reference]	1 [Reference]
Long-acting	37	10 623	34.83 (23.61-46.05)	2.84 (2.01-4.02)	2.56 (1.67-3.93)	2.33 (1.26-4.32)
Strata of Opioid Duration						
≤14 d						
Short-acting	70	27 762	25.21 (19.31-31.12)	1 [Reference]	1 [Reference]	1 [Reference]
Long-acting	10	697	143.4 (54.51-232.20)	5.70 (2.94-11.06)	5.25 (2.61-10.54)	5.25 (1.88-14.72)
15-60 d						
Short-acting	79	49 266	16.04 (12.50-19.57)	1 [Reference]	1 [Reference]	1 [Reference]
Long-acting	6	1666	36.00 (7.19-64.81)	2.42 (1.05-5.56)	2.19 (0.92-5.19)	2.30 (0.67-7.90)
>60 d						
Short-acting	133	115 398	11.53 (9.57-13.48)	1 [Reference]	1 [Reference]	1 [Reference]
Long-acting	21	8188	25.65 (14.68-36.62)	2.39 (1.50-3.78)	2.14 (1.25-3.65)	1.50 (0.68-3.33)

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.

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.[34-36] 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.[37] 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,[38] 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.

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