Association Between Opioid Prescribing Patterns and Opioid Overdose-Related Deaths

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THE RATE OF OVERDOSE MORTALITY increased sharply in the United States in the past decade and overdose mortality is a pressing public health problem.[1] Between 1999 and 2007, the rate of unintentional overdose death in the United States increased by 124%,[2] largely because of increases in prescription opioid overdoses.[1,3] Achieving a better understanding of the factors contributing to prescription opioid overdose death is an essential step toward addressing this troubling and dramatic increase in overdose mortality.

There is some evidence that higher prescribed doses increase the risk of drug overdose among individuals treated with opioids for chronic noncancer pain.[4] Specifically, the risk of drug-related adverse events is higher among individuals prescribed opioids at doses equal to 50 mg/d or more of morphine. The association of opioid prescribing patterns with risk of overdose may vary across groups of patients; opioid treatment recommendations for pain are typically specific to particular

Context The rate of prescription opioid–related overdose death increased substantially in the United States over the past decade. Patterns of opioid prescribing may be related to risk of overdose mortality.

Objective To examine the association of maximum prescribed daily opioid dose and dosing schedule ("as needed," regularly scheduled, or both) with risk of opioid overdose death among patients with cancer, chronic pain, acute pain, and substance use disorders.

Design Case-cohort study.

Setting Veterans Health Administration (VHA), 2004 through 2008.

Participants All unintentional prescription opioid overdose decedents (n=750) and a random sample of patients (n=154 684) among those individuals who used medical services in 2004 or 2005 and received opioid therapy for pain.

Main Outcome Measure Associations of opioid regimens (dose and schedule) with death by unintentional prescription opioid overdose in subgroups defined by clinical diagnoses, adjusting for age group, sex, race, ethnicity, and comorbid conditions.

Results The frequency of fatal overdose over the study period among individuals treated with opioids was estimated to be 0.04%. The risk of overdose death was directly related to the maximum prescribed daily dose of opioid medication. The adjusted hazard ratios (HRs) associated with a maximum prescribed dose of 100 mg/d or more, compared with the dose category 1 mg/d to less than 20 mg/d, were as follows: among those with substance use disorders, adjusted HR=4.54 (95% confidence interval [CI], 2.46-8.37; absolute risk difference approximation [ARDA]=0.14%); among those with chronic pain, adjusted HR=7.18 (95% CI, 4.85-10.65; ARDA=0.25%); among those with acute pain, adjusted HR=6.64 (95% CI, 3.31-13.31; ARDA=0.23%); and among those with cancer, adjusted HR=11.99 (95% CI, 4.42-32.56; ARDA=0.45%). Receiving both as-needed and regularly scheduled doses was not associated with overdose risk after adjustment.

Conclusion Among patients receiving opioid prescriptions for pain, higher opioid doses were associated with increased risk of opioid overdose death.

JAMA. 2011;305(13):1315-1321   www.jama.com

subgroups such as those with chronic noncancer pain,[5] cancer-related pain, and substance use disorders.[6] However, potential subgroup differences in overdose risk related to opioid prescribing have not been examined.

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Additionally, the use of supplemental "as-needed" opioid doses to augment regularly scheduled opioid regimens has yet to be examined as a risk factor for overdose. Short-term studies (10-16 weeks) suggest that prescribing an opioid to be taken as needed to supplement a regularly scheduled opioid is an effective strategy for addressing pain exacerbations,[7,8] but recent treatment guidelines[5,9] concluded that there is no evidence of the long-term safety of this practice. To address these gaps in the evidence base, we examined the relationship between opioid prescribing patterns and risk of opioid-related deaths over 5 years among diagnostic subgroups of patients (chronic pain, cancer, acute pain, and substance use disorders) in a national sample of Veterans Health Administration (VHA) patients.

METHODS

Design and Sample

This study used a case-cohort design.[10] In this design, all incident cases in a defined cohort are sampled in addition to a random sample from this same cohort. We included two 5% random samples of VHA patients (one each for fiscal year [FY] 2004 and FY2005), as well as all FY2004 and FY2005 VHA patients who died of an opioid overdose before the end of FY2008 ("cases"). The study sample was further restricted to individuals treated with opioids. Individuals with indicators of palliative care consultations or hospice care in their VHA medical records were excluded. The sample size was 155 434.

For cases, observation time began on the date of the first opioid fill that occurred after the first medical visit within the study period to avoid potential immortal person-time.[11,12] Similarly, for all noncases, observation time began on the date of the first opioid fill that occurred after the first medical visit in the year for which the individuals were in the random sample. Observation time ended on the day of death or the end of FY2008, whichever came first.

Data Collection Procedures

We used data from the VHA's National Patient Care Database to identify all VHA encounters. Outpatient prescription medication data came from the VHA's Pharmacy Benefits Management Services. We obtained cause of death indicators from the National Death Index,[13] which compiles death certificates from all state vital statistics offices and has the greatest sensitivity among population-level sources of mortality data.[14] The National Death Index searches for the VHA population have been described elsewhere.[15] We used established methods[16] to ascertain "true" matches with these 2 definitions of a match: (1) full match on Social Security number (SSN) and sex and match on at least 2 of the 3 parts (day, month, year) of date of birth; or (2) match on at least 7 digits of the SSN plus full match on date of birth, sex, first name, and last name and middle initial when present. More than 99% of deaths among VHA patients had a full match on SSN. Study procedures received approval from the Ann Arbor VA human studies committee, which waived the requirement for informed consent.

Opioid Overdose Deaths

Opioid overdose death was determined using National Death Index files and defined as death with an underlying cause-of-death code from the *International Statistical Classification of Diseases, Tenth Revision* (*ICD-10*) of X42, X44, Y12, or Y14, in combination with a T-code of 40.2.[17] These underlying cause-of-death codes include all deaths due to medications and narcotics that were ruled unintentional (X42 and X44) or indeterminate in intent (Y12 and Y14). Intentional overdoses, which are represented with underlying cause-of-death codes X60 through X69, were not included. The T-code restricts the cases to overdoses due in whole or in part to prescription opioids.

Opioid Prescribing

The opioid analgesic medications dispensed by VHA pharmacies during FY2004 through FY2008 were codeine, morphine, oxycodone, hydrocodone, oxymorphone, and hydromorphone. Morphine-equivalent doses were calculated using established methods.[18,19] Semisynthetic opioids were not included because they correspond with *ICD-10* T-code 40.4, which includes opioids not currently used for pain in VHA (ie, buprenorphine). Methadone (*ICD-10* T-code 40.3) was not included in this analysis because of its uniqueness in indications, duration of action, and inconsistent morphine equivalency.[20]

Maximum daily opioid dose was measured as a time-varying covariate. We used an "as-prescribed" approach,[21] which assumes that patients take all prescribed opioids at the maximum dose and on the schedule recommended by their clinicians. Patients who received refills or new prescriptions for the same drug at the same dose and schedule while they still had opioid medication on hand from a prior fill were assumed to have taken the medication from the prior fill, as prescribed, before taking medication from the second fill. However, patients taking opioid medications who received prescriptions for a different dose or schedule or a different opioid medication were assumed to have begun taking the new prescription on the date that it was filled.

Next, each patient's total maximum daily dose for each day of the study observation period was calculated by adding the daily doses of all fills that covered that particular day. The specific daily dose contributed by each fill was determined by dividing the total morphine-equivalent milligrams dispensed in that fill by the number of days supplied. This measurement of dose reflects the maximum daily dose prescribed and not necessarily the actual amount consumed. Morphine-equivalent maximum daily dose was converted into a categorical variable with the values of 0 mg, 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 more.[4] In addition, a time-varying in-

dicator of whether patients were prescribed a regularly scheduled opioid plus a simultaneous as-needed opioid was coded for each day of the study observation period that a patient had at least 1 opioid prescription using the following 3 mutually exclusive categories: 0, only regularly scheduled opioids; 1, only as-needed opioids; or 2, both a regularly scheduled opioid and as-needed opioid prescriptions.

Other Variables

We obtained demographic variables and diagnosis codes from the *International Classification of Diseases, Ninth Revision, Clinical Modification,* from patient records. Race (white, black, other) and Hispanic ethnicity were determined by VA clinicians in the course of medical care and recorded in the medical records for purposes related to evaluation. All diagnoses reflected whether the patient had been diagnosed with each specific condition in the year prior to the start of observation time. We combined all non–substance use psychiatric disorders into 1 category and combined a number of chronic bodily pains into 1 category. Acute pains were defined using codes for injuries, acute pain, and post-surgery pain. Cardiovascular disease (CVD), chronic obstructive pulmonary disease (COPD), and sleep apnea were combined to capture diseases affecting the cardiovascular and pulmonary systems. For the purposes of subgroup analyses, the "chronic pain" category included all individuals who had a diagnosis for at least 1 of the following: headache, neuropathy, or chronic bodily pains.

Data Analyses

We examined bivariate associations of patient characteristics with case status using χ^2 tests. We developed Cox proportional hazards models to examine the relationship of opioid prescribing and risk of opioid overdose death adjusting for demographic and clinical characteristics. Multivariable modeling was restricted to periods when individuals were prescribed at least 1 opioid. We used a risk-sets approach and

a robust variance estimator for the multivariable modeling.[22] We calculated approximated absolute risk differences for significant associations by first estimating the overall rate of opioid overdose among individuals receiving opioid treatment, next multiplying this rate by the hazard ratio (HR), and then taking the difference between these 2 estimated rates.

All individuals were included in modeling when possible. Ten individuals were missing data on age. Analyses were conducted using SAS version 9.2 (SAS Institute, Cary, North Carolina) and Stata version 11.1 (StataCorp, College Station, Texas). The threshold for statistical significance was $P < .05$. Power calculations for Cox proportional hazards models in Stata indicated that 66 overdose deaths would need to be observed to detect an HR of 2.0 and 191 deaths to detect an HR of 1.5 at 80% power and $\alpha = .05$.

RESULTS

Of the 1136 individuals who died of a prescription opioid overdose during FY2004 to FY2008 in the source population, 752 were treated with prescription opioids for pain during FY2004 to FY2008. Two of the opioid overdose deaths among individuals who received opioid therapy for pain occurred among the 2112 individuals who had received palliative care or hospice (who were not included in analyses). The source population included 5 719 542 individuals, and 31.92% of individuals in the random sample were treated with opioids for pain but did not receive palliative or hospice care. Consequently, we estimated that the 750 deaths occurred among approximately 1 834 250 individuals in the base population who would have met study criteria if they had been selected for the random sample. We therefore approximated the rate of overdose among in-

Table 1. Characteristics of the Sample of Veterans Health Administration Patients Receiving Opioid Therapy

Characteristic	No. (%)		P Value
	Opioid Overdose Decedents (n = 750)	All Others (n = 154 684)	
Male sex	700 (93.3)	144 304 (93.3)	.96
Age, y			
18-29	31 (4.1)	3995 (2.6)	<.001
30-39	60 (8.0)	8407 (5.4)	
40-49	313 (41.7)	23 888 (15.4)	
50-59	297 (39.6)	50 216 (32.5)	
60-69	38 (5.1)	29 985 (19.4)	
≥70	11 (1.5)	38 183 (24.7)	
Race			
Black	52 (6.9)	25 409 (16.4)	<.001
White	625 (83.3)	110 965 (71.7)	
Other/missing	73 (9.7)	18 310 (11.8)	
Hispanic ethnicity	23 (3.1)	6342 (4.1)	.15
Pain-related diagnoses[a]			
Cancer	91 (12.1)	36 712 (23.7)	<.001
Chronic bodily pains	588 (78.4)	107 158 (69.3)	<.001
Headache	90 (12.0)	10 208 (6.6)	<.001
Neuropathy	32 (4.3)	8339 (5.4)	.17
Injuries and acute pain	222 (29.6)	29 522 (19.1)	<.001
Other diagnoses[a]			
Substance use disorders	296 (39.5)	15 195 (9.8)	<.001
Other psychiatric disorders	498 (66.4)	51 929 (33.6)	<.001
COPD, CVD, and sleep apnea	467 (62.3)	123 025 (79.5)	<.001

Abbreviations: COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease.
[a] All conditions were measured in the year up to and including the first opioid fill during the observation period and are not mutually exclusive.

dividuals treated with opioids to be 0.04%. Opioid overdose decedents were statistically significantly more likely to be middle-aged and white; more likely to have chronic or acute pain, substance use disorders, and other psychiatric diagnoses; and less likely to have cancer (TABLE 1).

TABLE 2 reports the unadjusted rate of opioid overdose within the study sample for each clinical subgroup. For 326 of 750 cases (43.5%), opioid over-

dose death occurred when the maximum prescribed dose was equal to 0. The overdose rate was higher at higher maximum daily doses compared with lower maximum daily doses across all subgroups examined. Of the different dosing schedules (as-needed, regularly scheduled, and both), the periods with the highest unadjusted overdose rate were those when patients had concurrent fills for both as-needed and regularly scheduled opioids. Across all opioid regimens, the unadjusted rate of overdose in the sample was highest in the group with substance use disorders.

The models reported in TABLE 3 included maximum prescribed dose, dosing schedule, and demographic and clinical characteristics entered simultaneously into Cox proportional hazards models of risk of opioid overdose death. The association of simultaneous as-needed and regularly scheduled opioids was not significant after adjustment. Having as-needed opioids only compared with having regularly scheduled opioids was associated with an increase in risk of opioid overdose among patients with cancer (HR=2.75; 95% confidence interval [CI], 1.31-5.78; absolute risk difference approximation [ARDA]=0.072%). For those in the cancer subgroup, maximum prescribed doses of 100 mg/d or more were associated with an HR of 11.99 (95% CI, 4.42-32.56; ARDA=0.45%). The HRs associated with the same comparison were as follows: among those with substance use disorders, HR=4.54 (95% CI, 2.46-8.37; ARDA=0.14%), among those with chronic pain, HR=7.18 (95% CI, 4.85-10.65; ARDA=0.25%), and among those with acute pain, HR=6.64 (95% CI, 3.31-13.31; ARDA=0.23%).

We repeated the models substituting a continuous variable (where 0=dose of 1 to <20 mg/d, 1=dose of 20 to <50 mg/d, etc) in place of the categorical variable (eTable 1, available at http://www.jama.com). The estimates for this variable for each subgroup were as follows: chronic pain, HR=1.96 (95% CI, 1.74-2.21); cancer, HR=2.42 (95%

Table 2. Unadjusted Rate of Prescription Opioid Overdose Death by Opioid Dose and Fill Type

	Overdose Deaths, No.	Person-Months	Overdose Death Rate per 1000 Person-Months (95% CI)
Patients With Chronic Noncancer Pain Diagnoses			
Maximum prescribed daily opioid dose, mg/d			
0	243	2 729 022.7	0.09 (0.08-0.10)
1-<20	44	395 205.0	0.11 (0.08-0.15)
20-<50	108	458 296.2	0.24 (0.19-0.28)
50-<100	86	129 491.6	0.66 (0.53-0.82)
≥100	125	100 479.3	1.24 (1.04-1.48)
Fill types			
Regularly scheduled only	115	323 304.7	0.36 (0.29-0.43)
As needed only	152	672 276.0	0.23 (0.19-0.27)
Simultaneous as needed and regularly scheduled	96	87 891.5	1.09 (0.88-1.33)
Patients With Cancer Diagnoses			
Maximum prescribed daily opioid dose, mg/d			
0	32	859 278.3	0.04 (0.03-0.05)
1-<20	7	91 108.9	0.08 (0.03-0.16)
20-<50	14	96 778.6	0.14 (0.08-0.24)
50-<100	14	28 809.7	0.49 (0.27-0.82)
≥100	24	24 380.1	0.98 (0.63-1.46)
Fill types			
Regularly scheduled only	11	68 153.9	0.16 (0.08-0.29)
As needed only	31	151 865.6	0.20 (0.14-0.29)
Simultaneous as needed and regularly scheduled	17	21 057.9	0.81 (0.47-1.29)
Patients With Acute Pain Diagnoses			
Maximum prescribed daily opioid dose, mg/d			
0	97	786 769.5	0.12 (0.10-0.15)
1-<20	17	81 006.8	0.21 (0.12-0.34)
20-<50	34	95 109.1	0.36 (0.25-0.50)
50-<100	33	29 080.7	1.13 (0.78-1.59)
≥100	41	22 537.9	1.82 (1.31-2.47)
Fill types			
Regularly scheduled only	42	65 163.2	0.64 (0.46-0.87)
As needed only	52	142 311.5	0.37 (0.27-0.48)
Simultaneous as needed and regularly scheduled	31	20 259.8	1.53 (1.04-2.17)
Patients With Substance Use Disorder Diagnoses			
Maximum prescribed daily opioid dose, mg/d			
0	159	378 244.9	0.42 (0.36-0.49)
1-<20	24	44 630.0	0.54 (0.34-0.80)
20-<50	42	53 584.0	0.78 (0.56-1.06)
50-<100	27	17 019.2	1.59 (1.05-2.31)
≥100	44	14 809.2	2.97 (2.16-3.99)
Fill types			
Regularly scheduled only	44	38 722.0	1.14 (0.83-1.53)
As needed only	59	78 314.2	0.75 (0.57-0.97)
Simultaneous as needed and regularly scheduled	34	13 006.3	2.61 (1.81-3.65)

Abbreviation: CI, confidence interval.

CI, 1.76-3.34); acute pain, HR = 1.97 (95% CI, 1.58-2.46); and substance use disorders, HR = 1.69 (95% CI, 1.38-2.07). These findings indicate a dose-response relationship between maximum daily prescribed dose of opioid and risk of opioid overdose death. We further modeled risk of death by opioid overdose within the subgroups of chronic pain, cancer, and acute pain stratified by substance use disorder status. The HRs of the dose categories 50 mg/d to less than 100 mg/d and 100 mg/d or more compared with 1 mg/d to less than 20 mg/d were elevated for all subgroups except in the subgroup of individuals with acute pain and a substance use disorder, for which the HR estimates were not statistically significant (eTable 2).

COMMENT

Dunn et al[4] found that risk of drug-related adverse events among individuals treated for chronic noncancer pain with opioids was increased at opioid doses equivalent to 50 mg/d or more of morphine. Our analyses similarly found that the risk of opioid overdose increased when opioid dose was equivalent to 50 mg/d or more of morphine. The present study also extended prior research in several important ways. We used a large, national sample of individuals and focused exclusively on opioid overdose deaths. Because the circumstances that lead to overdose death may vary by the condition for which the opioid is prescribed and substance use disorder status, we conducted analyses for subgroups of patients, including those with cancer, acute pain, and substance use disorders.

The present study also extended the prior research by exploring a novel risk factor, ie, concurrent prescriptions of regularly scheduled and as-needed opioids. We found that those patients who

Table 3. Cox Proportional Hazards Models of Risk of Death by Prescription Opioid Overdose[a]

	Risk of Opioid Overdose Death, HR (95% CI)			
	Chronic Pain **(n = 111 759)**	**Cancer** **(n = 36 803)**	**Acute Pain** **(n = 29 739)**	**Substance Use** **Disorders** **(n = 15 491)**
Opioid fill type				
Regularly scheduled only	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
As needed only	1.10 (0.85-1.43)	2.75 (1.31-5.78)	0.94 (0.59-1.49)	0.97 (0.64-1.46)
Simultaneous as needed and regularly scheduled	1.34 (0.99-1.79)	1.84 (0.83-4.05)	1.12 (0.68-1.86)	1.22 (0.72-2.05)
Maximum prescribed daily opioid dose, mg/d				
1-<20	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
20-<50	1.88 (1.33-2.67)	1.74 (0.69-4.35)	1.58 (0.87-2.86)	1.42 (0.85-2.38)
50-<100	4.63 (3.18-6.74)	6.01 (2.29-15.78)	4.73 (2.55-8.79)	2.76 (1.54-4.94)
≥100	7.18 (4.85-10.65)	11.99 (4.42-32.56)	6.64 (3.31-13.31)	4.54 (2.46-8.37)
Pain-related diagnoses				
Cancer	0.99 (0.72-1.36)		0.66 (0.35-1.23)	1.03 (0.63-1.69)
Chronic bodily pains	0.69 (0.35-1.33)	1.53 (0.74-3.16)	0.56 (0.34-0.94)	0.74 (0.46-1.21)
Headache	1.02 (0.74-1.41)	0.72 (0.29-1.80)	1.17 (0.69-1.98)	0.76 (0.43-1.34)
Neuropathy	0.64 (0.38-1.08)	0.21 (0.03-1.56)	0.84 (0.40-1.79)	0.43 (0.16-1.18)
Injuries and acute pain	1.37 (1.08-1.74)	0.94 (0.50-1.77)		1.24 (0.86-1.80)
Other diagnoses				
Substance use disorders	2.53 (1.99-3.22)	3.08 (1.73-5.51)	2.27 (1.55-3.34)	
Other psychiatric disorders	1.87 (1.48-2.38)	1.68 (0.95-3.00)	1.77 (1.19-2.65)	1.73 (1.10-2.72)
COPD, CVD, and sleep apnea	0.63 (0.50-0.80)	0.73 (0.38-1.42)	0.77 (0.50-1.16)	1.01 (0.66-1.54)
Male sex	1.43 (0.91-2.24)	1.58 (0.44-5.63)	2.83 (0.99-8.06)	1.19 (0.50-2.85)
Age, y				
18-29	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
30-39	0.56 (0.27-1.17)	0.85 (0.09-7.86)	0.51 (0.18-1.45)	0.33 (0.11-1.02)
40-49	0.94 (0.49-1.80)	0.33 (0.04-2.96)	0.68 (0.28-1.65)	0.32 (0.12-0.83)
50-59	0.43 (0.22-0.83)	0.22 (0.03-1.93)	0.37 (0.15-0.93)	0.16 (0.06-0.44)
60-69	0.18 (0.08-0.40)	0.06 (0.01-0.64)	0.11 (0.03-0.42)	0.06 (0.02-0.25)
≥70[b]	0.06 (0.02-0.18)		0.12 (0.03-0.52)	
Race				
White	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Black	0.37 (0.24-0.59)	0.76 (0.32-1.83)	0.53 (0.27-1.03)	0.34 (0.17-0.65)
Other/missing	1.00 (0.69-1.44)	0.72 (0.22-2.38)	1.21 (0.63-2.30)	0.63 (0.28-1.41)
Hispanic ethnicity	0.84 (0.45-1.56)	2.59 (0.84-7.93)	0.87 (0.31-2.44)	0.49 (0.15-1.59)

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; HR, hazard ratio.
[a] All variables entered simultaneously into 1 model for each subgroup.
[b] There were not enough cases among patients 70 years and older in the cancer or substance use disorder subgroups to estimate the effect of being in this age group on overdose risk.

were simultaneously treated with as-needed and regularly scheduled opioids, a strategy for treating pain exacerbations,[7,8] did not have a statistically significant increased risk of opioid overdose in adjusted models. Recent treatment guidelines have indicated that the long-term safety of this strategy for pain exacerbation has not been established,[5,9] and in the present study we did not find evidence of greater overdose risk associated with this treatment practice after accounting for maximum daily dose and patient characteristics.

The analyses of opioid risk among subgroups of patients resulted in several novel findings. Prior work on overdose risk has excluded patients with cancer.[4] The present findings indicate that although the overall rate of overdose is lower among patients with cancer compared with other patients, there was a statistically significant association of prescribing patterns with overdose risk among patients with cancer receiving opioid therapy. Renal and liver impairment can interfere with the metabolism of opioids, and high doses of opioids may place patients with cancer at risk for overdose. Patients with cancer were also at an increased risk of overdose if they were prescribed as-needed opioids alone compared with being prescribed regularly scheduled opioids alone, adjusting for total dose. Pain for patients with cancer can be particularly rapid in onset, unpredictable, and severe,[23] and taking opioid doses as needed may result in high doses being taken without the benefit of tolerance developed through a regularly scheduled opioid.

Despite "double effect," which allows use of high doses of opioids for patients in palliative care settings regardless of potential risk (without intention to hasten death),[24] only 2 deaths were observed among individuals who had palliative or hospice care. This may be the result of misclassification of cause of death, but this finding provides some preliminary evidence that overdose death is not common among patients in pallia-tive care. Patients in these settings may be better monitored in a way that mitigates the risk of overdose.

There were several aspects of opioid-taking behavior not examined in the present study but that may further explain risk for opioid overdose. Patients may obtain opioids from non-VHA medical settings (eg, through doctor shopping[25]) or from individuals who are not clinicians. Patients may save medications and take them later in large doses for pain relief or recreationally, particularly when a dose change occurs before the end of a fill or with as-needed doses. These factors may play a particularly important role in opioid overdose among patients with substance use disorders and in explaining those overdoses that occurred when maximum prescribed dose was equal to 0 in the present study.

The present findings highlight the importance of implementing strategies for reducing opioid overdose among patients being treated for pain. McLellan and Turner[6] recommended the following: ascertaining patient history of substance use and dependence, using treatment contracts, and scheduling frequent follow-up visits that include a urine toxicological screen for patients at special risk. Increasing use of specialty pain care may reduce the burden on primary care clinicians for these frequent follow-up visits.

The present study found large HRs in the association of maximum daily dose with risk of death by opioid overdose. However, the estimated overall risk of opioid overdose among individuals treated with opioids (0.04%) and the approximated absolute risk increases for significant associations, which ranged between 0.072% and 0.45%, were small. Opioid overdose death represents a particularly important outcome, but a rare one, and the findings should be interpreted accordingly.

We were not able to measure actual dose consumed by patients on any given day. Semisynthetic opioids, which may have particularly high risk for over-dose,[26] were excluded from analysis, and use of nonopioid medications was beyond the scope of this analysis. Some of the deaths may have been suicides misclassified as unintentional overdoses. However, misclassification of suicides as unintentional overdose is uncommon.[27] Additionally, the use of medical records likely results in underdetection of medical conditions. Nonetheless, this study used a large national sample linked to mortality data. Although we were not able to measure opioid dose consumed, the method we used to measure opioid dose reflects the clinician's intention for the maximum frequency for taking the medication.

CONCLUSIONS

This study documents a relationship between opioid prescribing and opioid overdose in a large, national, prospective cohort of individuals receiving opioid therapy for a variety of medical conditions. The risk of opioid overdose should continue to be evaluated relative to the need to reduce pain and suffering and be considered along with other risk factors.

REFERENCES

1. Okie S. A flood of opioids, a rising tide of deaths. *N Engl J Med*. 2010;363(21):1981-1985.
2. Web-based Injury Statistics Query and Reporting System: leading causes of death reports. Centers for Disease Control and Prevention. http://www.cdc .gov/injury/wisqars/index.html. Accessed March 4, 2011.
3. Paulozzi LJ, Budnitz DS, Xi Y. Increasing deaths from opioid analgesics in the United States. *Pharmacoepidemiol Drug Saf*. 2006;15(9):618-627.
4. Dunn KM, Saunders KW, Rutter CM, et al. Opioid prescriptions for chronic pain and overdose: a cohort study. *Ann Intern Med*. 2010;152(2):85-92.
5. Chou R, Fanciullo GJ, Fine PG, et al; American Pain Society–American Academy of Pain Medicine Opioids Guidelines Panel. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain*. 2009;10(2):113-130.
6. McLellan AT, Turner B. Prescription opioids, overdose deaths, and physician responsibility. *JAMA*. 2008; 300(22):2672-2673.
7. Portenoy RK, Messina J, Xie F, Peppin J. Fentanyl buccal tablet (FBT) for relief of breakthrough pain in opioid-treated patients with chronic low back pain: a randomized, placebo-controlled study. *Curr Med Res Opin*. 2007;23(1):223-233.
8. Simpson DM, Messina J, Xie F, Hale M. Fentanyl buccal tablet for the relief of breakthrough pain in opioid-tolerant adult patients with chronic neuropathic pain: a multicenter, randomized, double-blind, placebo-controlled study. *Clin Ther*. 2007; 29(4):588-601.
9. VA/DoD Clinical Practice Guideline: management of opioid therapy for chronic pain [2010]. Department of Veterans Affairs, Department of Defense. http://www.healthquality.va.gov /Chronic_Opioid_Therapy_COT.asp. Accessed March 4, 2011.
10. Prentice RL. A case-cohort design for epidemiologic cohort studies and disease prevention trials. *Biometrika*. 1986;73:1-11.
11. Lash TL, Cole SR. Immortal person-time in studies of cancer outcomes. *J Clin Oncol*. 2009;27 (23):e55-e56.
12. Suissa S. Immortal time bias in pharmacoepidemiology. *Am J Epidemiol*. 2008;167(4):492-499.
13. National Death Index. Centers for Disease Control and Prevention. http://www.cdc.gov/nchs/ndi .htm. Accessed March 4, 2011.
14. Cowper DC, Kubal JD, Maynard C, Hynes DM. A primer and comparative review of major US mortality databases. *Ann Epidemiol*. 2002;12(7):462-468.
15. McCarthy JF, Valenstein M, Kim HM, Ilgen M, Zivin K, Blow FC. Suicide mortality among patients receiving care in the Veterans Health Administration health system. *Am J Epidemiol*. 2009;169(8):1033-1038.
16. Sohn MW, Arnold N, Maynard C, Hynes DM. Accuracy and completeness of mortality data in the Department of Veterans Affairs. *Popul Health Metr*. 2006; 4:2.
17. Wysowski DK. Surveillance of prescription drug-related mortality using death certificate data. *Drug Saf*. 2007;30(6):533-540.
18. Gammaitoni AR, Fine P, Alvarez N, McPherson ML, Bergmark S. Clinical application of opioid equianalgesic data. *Clin J Pain*. 2003;19(5):286-297.
19. Prommer E. Oxymorphone: a review. *Support Care Cancer*. 2006;14(2):109-115.
20. Lawlor PG, Turner KS, Hanson J, Bruera ED. Dose ratio between morphine and methadone in patients with cancer pain: a retrospective study. *Cancer*. 1998; 82(6):1167-1173.
21. Valenstein M, Taylor KK, Austin K, Kales HC, McCarthy JF, Blow FC. Benzodiazepine use among depressed patients treated in mental health settings. *Am J Psychiatry*. 2004;161(4):654-661.
22. Langholz B, Jiao J. Computational methods for case-cohort studies. *Comput Stat Data Anal*. 2007; 51(8):3737-3748.
23. Portenoy RK, Payne D, Jacobsen P. Breakthrough pain: characteristics and impact in patients with cancer pain. *Pain*. 1999;81(1-2):129-134.
24. Lo B, Rubenfeld G. Palliative sedation in dying patients: "we turn to it when everything else hasn't worked." *JAMA*. 2005;294(14):1810-1816.
25. Hall AJ, Logan JE, Toblin RL, et al. Patterns of abuse among unintentional pharmaceutical overdose fatalities. *JAMA*. 2008;300(22):2613-2620.
26. Schumann H, Erickson T, Thompson TM, Zautcke JL, Denton JS. Fentanyl epidemic in Chicago, Illinois and surrounding Cook County. *Clin Toxicol (Phila)*. 2008;46(6):501-506.
27. Donaldson AE, Larsen GY, Fullerton-Gleason L, Olson LM. Classifying undetermined poisoning deaths. *Inj Prev*. 2006;12(5):338-343.

Patience is necessary, and one cannot reap immediately where one has sown.

—Sóren Kierkegaard (1813-1855)