LESS IS MORE

Opioid Dose and Drug-Related Mortality in Patients With Nonmalignant Pain

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Background: Opioids are widely prescribed for chronic nonmalignant pain, often at doses exceeding those recommended in clinical practice guidelines. However, the risk-benefit ratio of high-dose opioid therapy is not well characterized. The objective of this study was to characterize the relationship between opioid dose and opioid-related mortality.

Methods: We conducted a population-based nested case-control study of Ontario, Canada, residents aged 15 to 64 years who were eligible for publicly funded prescription drug coverage and had received an opioid from August 1, 1997, through December 31, 2006, for nonmalignant pain. The outcome of interest was opioid-related death, as determined by the investigating coroner. The risk of opioid-related death was compared among patients treated with various daily doses of opioids.

Results: Among 607 156 people aged 15 to 64 years prescribed an opioid over the study period, we identified 498 eligible patients whose deaths were related to opioids and 1714 matched controls. After extensive multivariable adjustment, we found that an average daily dose of 200 mg or more of morphine (or equivalent), was associated with a nearly 3-fold increase in the risk of opioid-related mortality (odds ratio [OR], 2.88; 95% confidence interval [CI], 1.79-4.63) relative to low daily doses (<20 mg of morphine, or equivalent). We found significant but attenuated increases in opioid-related mortality with intermediate doses of opioids (50-99 mg/d of morphine: OR, 1.92; 95% CI, 1.30-2.85; 100-199 mg/d of morphine: OR, 2.04; 95% CI, 1.28-3.24).

Conclusion: Among patients receiving opioids for nonmalignant pain, the daily dose is strongly associated with opioid-related mortality, particularly at doses exceeding thresholds recommended in recent clinical guidelines.

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THE USE OF OPIOID ANALGESICS to treat chronic nonmalignant pain has become increasingly common over the past 20 years.[1-7] Prescribing patterns have recently shifted from short-acting combination products containing opioids with acetaminophen in favor of long-acting opioid formulations, particularly those including oxycodone, and the average daily dose of opioids has increased considerably.[1,2,8]

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Although there is no uniformly accepted definition of what constitutes a high dose of opioids, recently published clinical guidelines recommend 200 mg/d or more of morphine (or equivalent) as a "watchful dose," based on expert opinion and commonly studied doses in the medical literature[9,10] Some data suggest an increasing prevalence of prescriptions for long-acting opioids at doses of 200 mg/d or more of morphine (or equivalent), over time.[1] This is important because opioids can be hazardous at high doses, particularly when taken in combination with sedatives or alcohol. From 1999 through 2006, the number of opioid-related deaths increased by more than 85% in the United States.[11]

Despite such observations, few studies have explored the relationship between opioid dose and serious adverse outcomes. A recently published study conducted among Group Health Cooperative patients in Washington State[12] demonstrated a relationship between opioid dose and overdose. However, the setting was not typical of usual practice,[13] the population studied was small (9940 patients), and only 6 deaths were observed over the 9-year study period.[12] Consequently, there remains a paucity of evidence regarding opioid dose and the far more serious outcome of opioid-related mortality in the medical literature. We conducted a large population-based study to characterize the relationship between opioid dose and opioid-related mortality.

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METHODS

SETTING

We performed 2 population-based nested case-control studies among Ontarians aged 15 to 64 years who were eligible for prescription drug coverage under the Ontario (Canada) Provincial Drug Program and received opioids for nonmalignant pain from August 1, 1997, through December 31, 2006. These individuals had universal access to hospital care, physicians' services, and prescription drug coverage over the study period. This study was approved by the research ethics board of Sunnybrook Health Sciences Centre, Toronto, Ontario.

DATA SOURCES

We obtained prescription drug data from the Ontario Public Drug Benefit Program database, which contains comprehensive records of prescriptions dispensed to eligible Ontario residents. Eligibility criteria for drug coverage among people aged 15 to 64 years include unemployment, disability, high prescription drug costs relative to net household income, receipt of home care services, and residence in a long-term care facility.

We identified patients with a history of cancer using the Ontario Cancer Registry, a computerized database of information on all Ontario residents with cancer, and the Canadian Institute for Health Information's Discharge Abstract Database was used to identify hospitalizations. Claims for physicians' services (including palliative care services) were obtained from the Ontario Health Insurance Plan database, and demographic information was obtained from the Ontario Registered Persons Database, which contains a unique entry for each resident ever issued a health insurance number.

Opioid-related deaths were identified from the Office of the Chief Coroner of Ontario. In accordance with Ontario's Coroners Act, all deaths that are sudden and unexpected, or nonnatural, must be reported to the coroner's office. To determine the cause and manner of death, the coroner, a licensed physician, will order a postmortem examination, generally including detailed toxicologic testing. For this study, opioid-related deaths were defined as those in which the coroner determined that a combination of drugs (including ≥1 opioid) resulted in death, or those in which forensic toxicologic testing revealed opioid concentrations sufficiently high to cause death, as described previously.[2] During the study period, coroners in Ontario followed a protocol that required toxicologic testing when drug-related paraphernalia was present at the scene or if an anatomic cause of death was not found on autopsy. Furthermore, toxicologic testing was frequently ordered when an anatomic cause of death was present on autopsy so as to identify multiple, contributory causes of death. Coroners are provided with standardized information from the toxicology laboratory in Ontario but ultimately use their individual judgment in determining the cause of death, including consideration of an individual's opioid tolerance.

IDENTIFICATION OF PATIENTS AND OUTCOMES

We studied a cohort of patients aged 15 to 64 years who were dispensed at least 1 prescription for an opioid over the study period, including codeine phosphate, morphine sulfate, oxycodone hydrochloride, hydromorphone hydrochloride, meperidine hydrochloride, or transdermal fentanyl. Prescriptions for parenteral or intranasal opioids and those for methadone were excluded, the latter because it is principally used for opioid addiction rather than chronic pain in Ontario.

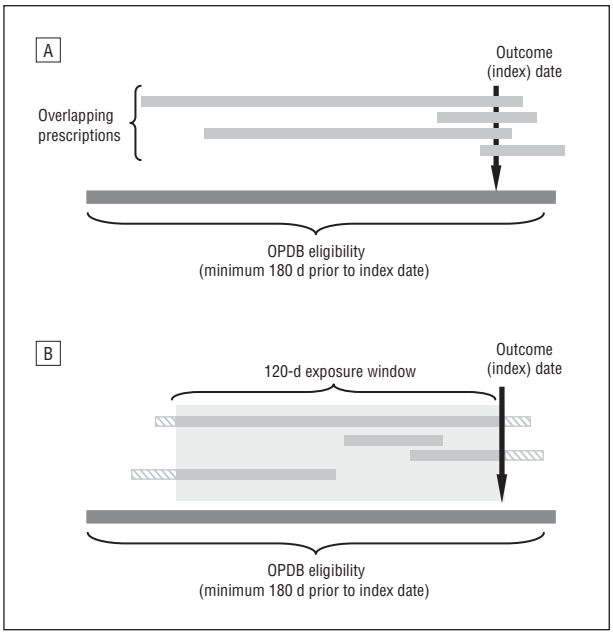

Figure 1. Study design. A, Primary exposure defined as the sum of the daily dose for all prescriptions overlapping with the index (opioid-related mortality) date. B, Secondary analysis; the average daily dose was calculated for all opioids dispensed for use in the 120-day interval preceding the index date. OPDB indicates Ontario Public Drug Benefit.

We defined cases as people who died of an opioid-related cause. The date of death was used as the index date for all analyses. Cases and potential controls were excluded if they had a diagnosis of cancer at any time or had received palliative care services in the 6 months prior to their index date. All patients were required to have at least 6 months of continuous eligibility for public drug coverage.

In order to better match cases and controls, we developed a disease risk index[14] to generate predicted probabilities of opioid-related deaths among cases and potential controls. The components of the risk score model are outlined in the eTable (http://www.archinternmed.com). From within the cohort of opioid users, we selected up to 4 controls for each case using incident density sampling.[15] Controls were matched on the disease risk score using a caliper of 0.2 standard deviations, as well as age (within 3 years), sex, index year, and Charlson comorbidity index,[16,17] and were assigned the same index date as their matched case. When fewer than 4 control patients could be matched to a case, we studied only those who could be matched and did not alter the matching algorithm. Cases with no matched controls were excluded from the analysis.

EXPOSURE DEFINITION

Prescription records were used to ascertain the average daily dose of opioids on the index date using 2 different approaches. The primary exposure definition considered only prescriptions overlapping the index date and therefore provides an indicator of the average daily dose of opioid the time of death (**Figure 1**). Any cases or potential controls without such a prescription were excluded prior to matching. The dose of opioid was calculated as the number of tablets dispensed multiplied by the strength of the pills (in milligrams) for each prescription. The average daily dose for each of these prescriptions was then calculated as the dose (in milligrams) divided by the number of days' supply for which the prescription was written, converted to morphine equivalents using morphine equivalence ratios used by the Canadian National Opioid Use Guideline

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Table 1. Oral Opioid Analgesic Equivalence Table[a]

Opioid	Ratio (Opioid: Morphine)
Morphine sulfate	1:1
Codeine phosphate	1:0.15
Oxycodone hydrochloride	1:1.5
Hydromorphone hydrochloride	1:5
Meperidine hydrochloride	1:0.1
Transdermal fentanyl	25 mcg/h→ 1:97
	50 mcg/h→ 1:202
	75 mcg/h→ 1:292
	100 mcg/h→ 1:382

[a] Adapted from the Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain.[9]

Group (**Table 1**).[9] When we identified multiple concurrent opioid prescriptions, the total average daily dose was defined as the sum of the average daily dose of all prescriptions overlapping the patient's index date.

In a sensitivity analysis to test the robustness of this analysis, we developed a secondary exposure definition—the average daily dose of opioids in the 120 days preceding the index date—which estimates a patient's average opioid dose over the 4-month period preceding death. For this analysis, we included all opioid prescriptions extending into or dispensed during the 120 days preceding the index date. For prescriptions dispensed prior to but extending into the 120-day window, we excluded the quantity intended for use before the start of the 120-day window. Similarly, for prescriptions dispensed during the 120-day window, we excluded any doses intended for use after the index date (Figure 1). Cases and potential controls without an eligible prescription were excluded prior to matching. We estimated the average daily dose as the total quantity of opioids intended for use in the 120 days prior to the index date (in milligrams of morphine equivalents) divided by 120. If a patient was newly treated with opioids during the 120-day window, the time interval between the first opioid prescription and index date was used as the denominator for this calculation.

STATISTICAL ANALYSIS

Descriptive statistics were calculated for baseline characteristics. Standardized differences were used to test for differences between groups. A standardized difference that is greater than 0.10 is generally considered a meaningful difference.[18] We used conditional logistic regression to estimate the odds ratio (OR) for the association between average daily opioid dose and opioid-related mortality. Patients were categorized according to their average daily opioid dose: less than 20 mg, 20 to 49 mg, 50 to 99 mg, 100 to 199 mg, and 200 mg or more of morphine equivalents. The lowest dose stratum (<20 mg) was used as the reference group for all analyses.

We adjusted all models for duration of opioid treatment as well as several other potential risk factors, including income, history of alcohol abuse (based on hospital admissions and physician visits), prescriptions for potential interacting drugs (methadone, selective serotonin reuptake inhibitors, other antidepressants, benzodiazepines, other psychotropic drugs, and central nervous system depressants) total number of different drugs dispensed, treatment with a long-acting opioid, number of physicians prescribing opioids, the number of pharmacies dispensing opioids, and the presence of a long-acting opioid prescription during the exposure window. All analyses used a type 1 error rate of 0.05 as the threshold for statistical significance and were performed using SAS statistical software (version 9.2; SAS Institute Inc, Cary, North Carolina).

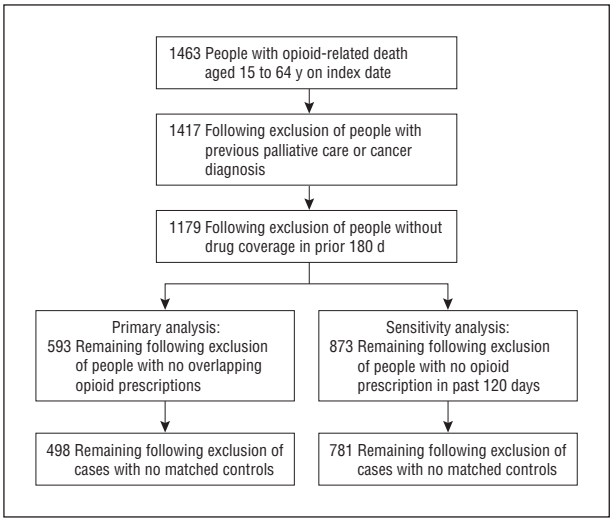

Figure 2. Exclusion criteria applied to cases.

RESULTS

Over the 113-month study period, we identified 607 156 people aged 15 to 64 years with at least 1 opioid prescription paid by the Ontario public drug plan. From this cohort, 1463 individuals had an opioid-related death. The manner of death was accidental in 863 instances (59.0%), suicide in 246 (16.8%), and undetermined in the remaining 354 (24.2%). All manners of death were eligible for inclusion in this study. The mean (SD) age at the time of death was 42.7 (8.8) years.

In the primary analysis, 593 deaths met the inclusion criteria for this study (**Figure 2**), including eligibility for public drug coverage, receipt of an opioid prescription overlapping the index date, and no evidence of cancer or palliative care. Of these, 498 (84.0%) were matched to at least 1 control. The coroner's toxicologic screening detected more than 1 opioid type in 193 (38.8%), benzodiazepines in 301 (60.4%), and ethanol in 92 (18.5%) of these cases. The baseline characteristics of cases and controls are presented in **Table 2**. Patients whose deaths were related to opioids were similar to controls with respect to demographic characteristics and comorbidities but were more likely to have received antidepressants, benzodiazepines, methadone, psychotropic drugs, or other sedating medications prior to death. They were also more likely to have a history of alcoholism and to have obtained opioids from multiple physicians and pharmacies. Over two-thirds of cases (67.7%) were in the lowest 2 income quintiles.

In the primary analysis, after extensive multivariate adjustment, we found a significant relationship between the average daily opioid dose and opioid-related mortality (**Figure 3**). Compared with patients receiving less than 20 mg/d, those prescribed opioids at daily doses of 200 mg or more of morphine (or equivalent) had a much higher risk of opioid-related mortality (OR, 2.88; 95% confidence interval [CI], 1.79-4.63). A significant but attenuated association was found between 2 moderate opioid dose categories and opioid-related mortality (50-99 mg/d of morphine equivalents: OR, 1.92, 95% CI, 1.30-2.85; and 100 to 199 mg/d of morphine equivalents: OR, 2.04; 95% CI, 1.28-3.24).

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Table 2. Baseline Characteristics of Individuals Who Died of Opioid-related Causes (Cases) and Matched Controls

Variable	Exposure: Opioid Prescription Overlaps Index Date[a]		
	Cases (n=498)	Controls (n=1714)	Standardized Difference
Age, y			
Mean (SD)	44.49 (8.25)	44.72 (8.20)	0.03
Median (IQR)	44 (38-50)	45 (39-51)	0.03
Sex	293 (58.8)	994 (58.0)	0.02
Past drug use (in past 180 d)			
Antidepressants, SSRIs	247 (49.6)	663 (38.7)	0.22
Antidepressants, other	258 (51.8)	668 (39.0)	0.26
Benzodiazepines	421 (84.5)	1104 (64.4)	0.44
Other psychotropic drugs and CNS depressants	180 (36.1)	444 (25.9)	0.23
Methadone hydrochloride	35 (7.0)	56 (3.3)	0.19
Income quintile			
1	226 (45.4)	777 (45.3)	0.00
2	111 (22.3)	381 (22.2)	0.00
3	76 (15.3)	231 (13.5)	0.05
4	51 (10.2)	201 (11.7)	0.05
5	32 (6.4)	121 (7.1)	0.03
Missing	≤5 (0.4)	≤5 (0.2)	0.05
Rural or urban			
Rural	58 (11.6)	238 (13.9)	0.07
Urban	439 (88.2)	1474 (86.0)	0.06
Missing	≤5 (0.2)	≤5 (0.1)	0.02
Distinct drugs used (in past 180 d), No. (IQR)	10 (7-15)	9 (6-13)	0.26
Charlson score (past 3 y of hospitalization)			
No hospitalizations	187 (37.6)	723 (42.2)	0.09
0	170 (34.1)	576 (33.6)	0.01
1	75 (15.1)	223 (13.0)	0.06
≥2	66 (13.3)	192 (11.2)	0.06
History of alcoholism	159 (31.9)	433 (25.3)	0.15
Duration of opioid use, No. (IQR), y	5 (2-7)	4 (2-7)	0.08
Physicians prescribing opioids (in past 180 d), No.			
Incomplete prescriber information	36 (7.2)	107 (6.2)	0.04
1	229 (46.0)	996 (58.1)	0.25
2	128 (25.7)	391 (22.8)	0.07
3	52 (10.4)	122 (7.1)	0.12
4	20 (4.0)	53 (3.1)	0.05
5	16 (3.2)	18 (1.1)	0.18
≥6	17 (3.4)	27 (1.6)	0.13
Pharmacies dispensing opioids (in past 180 d), No.			
1	285 (57.2)	1161 (67.7)	0.22
2	116 (23.3)	370 (21.6)	0.04
3	46 (9.2)	108 (6.3)	0.12
4	32 (6.4)	45 (2.6)	0.21
5	6 (1.2)	18 (1.1)	0.02
≥6	13 (2.6)	12 (0.7)	0.18
Long-acting opioid dispensed in exposure window	228 (45.8)	523 (30.5)	0.33
Physician visits (in past 1 y), No. (IQR)	32 (20-55)	28 (16-47)	0.14

Abbreviation: CNS, central nervous system; IQR, interquartile range; SSRI, selective serotonin reuptake inhibitor.
[a] Data are given as number (percentage) except where noted.

In a sensitivity analysis, 873 cases met revised inclusion criteria in which an opioid prescription was dispensed in the 120 days preceding the index date. Of these, 781 (89.5%) were matched to at least 1 control (Figure 2). The results of this analysis were consistent with those observed in the primary analysis (Figure 3).

COMMENT

In this population-based study spanning more than 9 years, we found a significant association between prescribed average daily dose of opioids and opioid-related mortality in adults with nonmalignant pain. The risk was highest in patients receiving 200 mg or more of morphine (or equivalent), on average per day. The importance of this finding is underscored by the fact that doses in this range are common. In 2008, 27% of Ontario social assistance recipients who were treated with long-acting opioids received daily doses exceeding this threshold.[1]

Previous research on the association between opioid dose and harm has been limited by low event rates and limited generalizability.[12,13] Our study describes a population-

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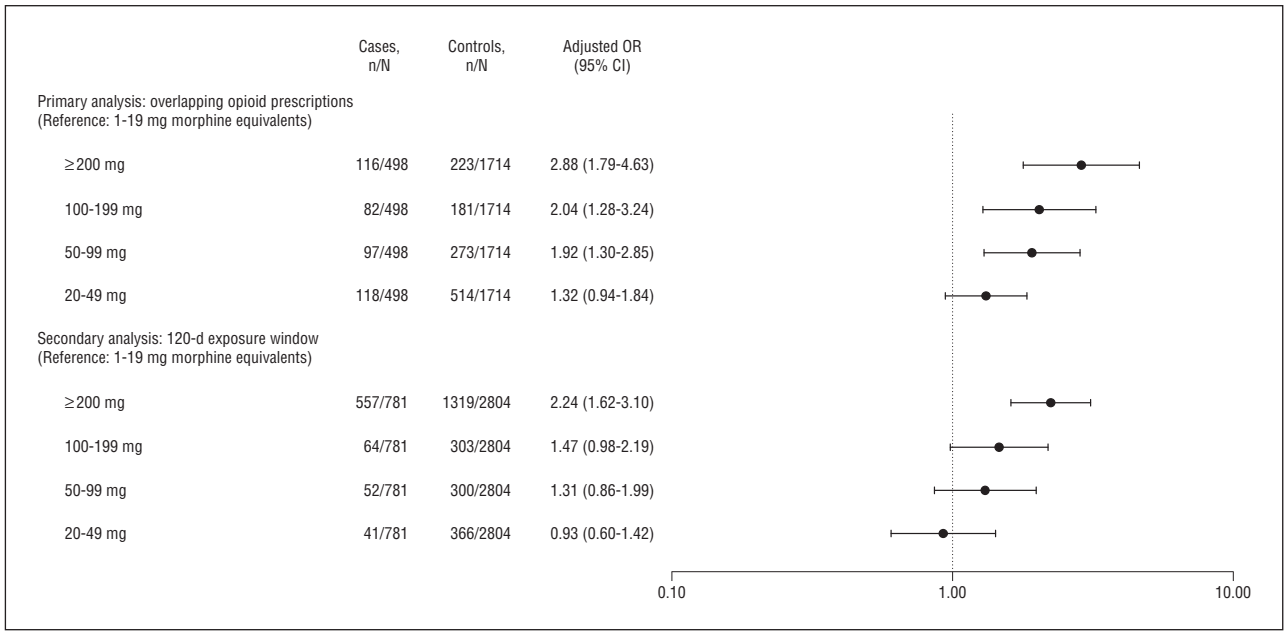

Figure 3. Association between opioid-related death and opioid dose. Adjusted for previous drug use (selective serotonin reuptake inhibitors, other antidepressants, benzodiazepine, other psychotropic drugs and central nervous system depressants, and methadone), the number of drugs used in past 6 months, duration of opioid treatment, the number of physicians prescribing opioids, the number of pharmacies dispensing opioids, and the presence of any long-acting opioid dispensed in exposure window. CI indicates confidence interval; OR, odds ratio.

based analysis with more than 500 opioid-related deaths. Other strengths of our study include the specific assessment of the safety of a "watchful" opioid dose presented in recent guidelines.[9,10] The significant association between daily doses of 200 mg or more of morphine (or equivalent) and opioid-related mortality provides further evidence that, while there is no maximal dose of opioids, very high doses are accompanied by a major increase in the risk of harm. Our results also suggest that average daily doses of 50 to 199 mg of morphine (or equivalent), which are extremely common in clinical practice, may also be associated with increased risk of death. Larger studies are needed to confirm this observation.

While this study demonstrates a substantial increase in the relative risk of opioid-related mortality associated with high opioid doses, our study design does not allow us to estimate the absolute risk of opioid-related mortality among patients prescribed high doses of opioids. In a related study[1] of socioeconomically disadvantaged Ontarians aged 15 to 64 years, the 2-year risk of opioid-related mortality among those prescribed 200 to 400 mg/d of morphine (or equivalent) was 0.8%, and the risk among those prescribed more than 400 mg/d of morphine (or equivalent) was 1.0%. Although these absolute risks may seem small, it bears reiterating that the outcome is mortality, and preventing any number of avoidable deaths should be a major public health priority.

Some limitations of our work merit emphasis. Although Ontarians have universal access to health care services, drug coverage among residents younger than 65 years is restricted to a socioeconomically disadvantaged population. Consequently, our results may not be generalizable to other populations or jurisdictions. Second, opioid dose was estimated from publically funded prescriptions and cannot identify unused prescription drugs, those obtained illicitly, and those paid for out of pocket. However, these limitations would tend to underestimate our dose calculations for cases and controls and, in conjunction with the conservative dose estimates used, would bias our results toward a null finding. Third, it is possible that opioid-related deaths could be classified as non–opioid-related deaths if information available to the coroner was incomplete. However, all unexpected deaths are investigated by the coroner, and toxicologic analyses are conducted when appropriate. Therefore, it is unlikely that misclassification would occur. Furthermore, any misclassification of cases as controls would act to bias the findings toward the null and therefore underestimate the true dose-response relationship. Fourth, we are unable to determine the indication for opioid therapy; however, it is unlikely that this would affect the association between high dose and opioid-related mortality. Finally, as expected, cases and controls differed on several baseline characteristics that may be associated with risk of addiction and drug-related adverse events, such as concomitant use of benzodiazepines, antidepressants, and other central nervous system depressants, along with possible "doctor shopping." However, our cases and controls were similar with respect to several measures of comorbidity, and the models were adjusted for all potential confounders.

In conclusion, we found that a higher daily dose of opioids is associated with large relative and absolute increases in opioid-related mortality, and that daily doses of 200 mg or more of morphine (or equivalent) are associated with a particularly high risk. Our findings have important implications, largely because most opioid-related deaths were avoidable and occurred in young people. We believe physicians should carefully assess the appropriateness of long-term use of opioids to treat chronic, noncancer-related pain, particularly at high doses.[9,10]

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INVITED COMMENTARY

Limiting the Potential Harms of High-Dose Opioid Therapy

Randomized trials provide the gold standard for testing the efficacy of pharmacological therapies. But to obtain reasonable estimates of risk for rare but serious events in the highly comorbid populations in which therapies are actually used, we need to turn to observational studies such as the article by Gomes et al concerning the experience of over 600 000 patients receiving opioids over a nearly 10-year period through

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