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Identifying and evaluating patterns of prescription opioid use and associated risks in Ontario, Canada

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Chapter 5:
Opioid dose and drug-related mortality in patients with nonmalignant pain

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Opioid dose and drug-related mortality
in patients with nonmalignant pain.
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Abstract

CONTEXT

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.

OBJECTIVE

To characterize the relationship between opioid dose and opioid-related mortality.

DESIGN, SETTING AND PATIENTS

We conducted a population-based nested case-control study of Ontario residents aged 15 to 64 who were eligible for publicly-funded prescription drug coverage and received an opioid between August 1, 1997 and December 31, 2006 for non-malignant pain.

MAIN OUTCOME MEASURES

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 prescribed an opioid over the study period, we identified 498 eligible cases whose deaths were related to opioids and 1,714 matched controls. After extensive multivariable adjustment, we found that an average daily dose exceeding 200 mg morphine (or equivalent) was associated with a nearly threefold increase in the risk of opioid-related mortality (odds ratio 2.88, 95% confidence interval 1.79 to 4.63) relative to low daily doses (less than 20 mg morphine or equivalent). We found significant but attenuated increases in opioid-related mortality with intermediate doses of opioids (50 to 99 mg of morphine: odds ratio 1.92 (95% confidence interval 1.30 to 2.85); 100 to 199 mg of morphine: odds ratio 2.04 (95% confidence interval 1.28 to 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.

Introduction

The use of opioid analgesics to treat chronic nonmalignant pain has become increasingly common over the past twenty 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]

Although there is no uniformly accepted definition of what constitutes a high dose of opioids, recently published clinical guidelines recommend 200 mg 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 exceeding 200 mg 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. Between 1999 and 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 demonstrated a relationship between opioid dose and overdose. However, the setting was not typical of usual practice[12], the population studied was small (N=9,940), and only 6 deaths were observed over the 9-year study period.[13] 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.

Methods

SETTING

We performed two population-based nested case-control studies among Ontarians aged 15 to 64 who were eligible for prescription drug coverage under the Ontario Provincial Drug Program and received opioids for nonmalignant pain between August 1, 1997 and 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.

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 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 non-natural, 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 toxicological testing. For this study, opioid-related deaths were defined as those in which the coroner determined that a combination of drugs (including at least one opioid) resulted in death, or those in which forensic toxicology 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 toxicological testing when drug-related paraphernalia was present at the scene or if an anatomic cause of death was not found on autopsy. Furthermore, toxicological 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 one prescription for an opioid over the study period, including codeine, morphine,

oxycodone, hydromorphone, meperidine 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.

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 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 Table 2.2. 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 subjects 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 two 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 5.1a). 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 employed by the Canadian National Opioid Use Guideline Group (Table 2.1).[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.

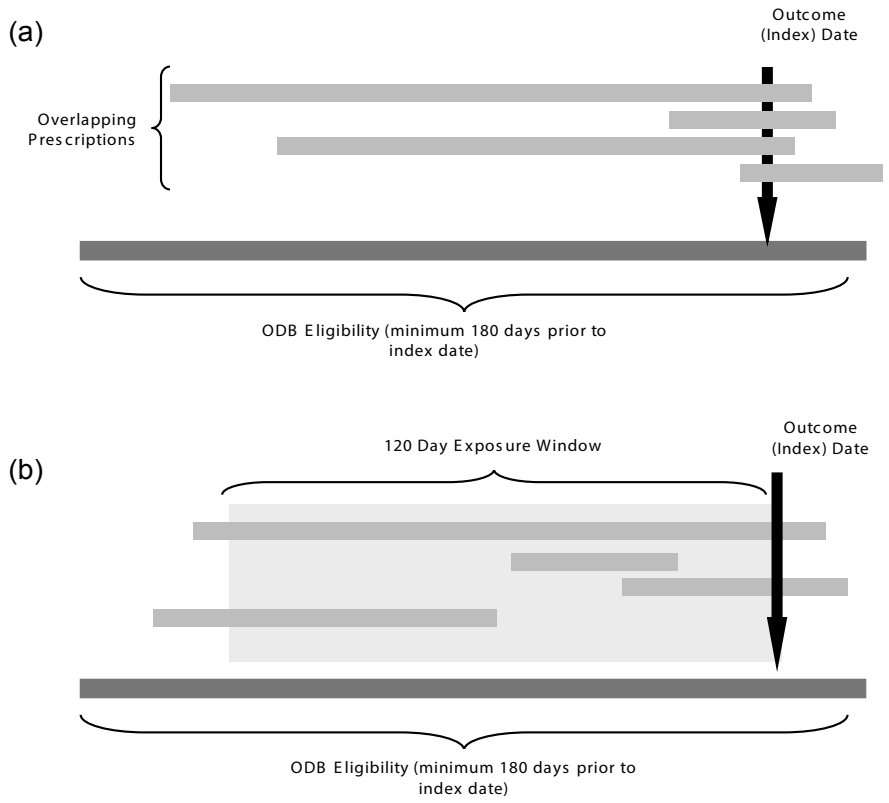


Figure 5.1: Key components of study design.

(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 - average daily dose was calculated for all opioids dispensed for use in the 120 day interval preceding the 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 5.1b). 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 of greater than 0.10 is generally considered a meaningful difference.[18] We used conditional logistic regression to estimate the odds ratio for the association between average daily opioid dose and opioid-related mortality. Subjects 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 greater than 200 mg 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 (CNS) 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 version 9.2 (SAS Institute, Cary, North Carolina).

Results

Over the 113 month study period, we identified 607,156 people aged 15 to 64 with at least one opioid prescription paid by the Ontario public drug plan. From this cohort, 1,463 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 average age of death was 42.7 years (standard deviation 8.8 years).

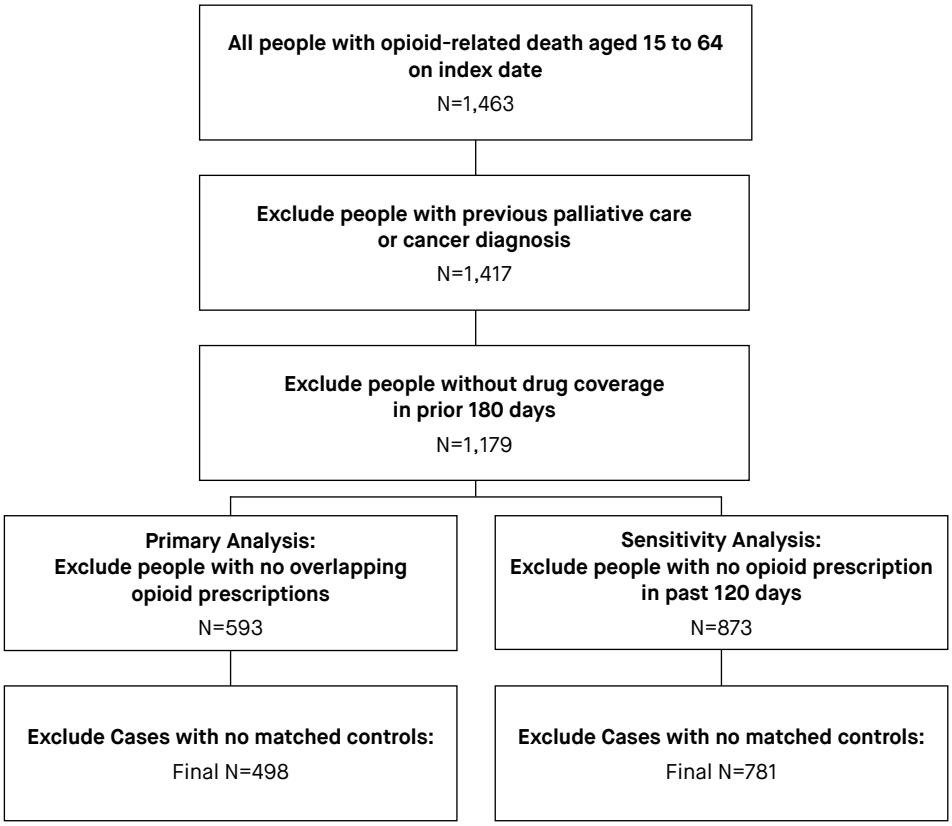


Figure 5.2: Exclusion criteria applied to cases.

In the primary analysis, 593 deaths met the inclusion criteria for this study (Figure 5.2), 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 one control. The coroner's toxicological screening detected more than one opioid type in 38.8% (N=193), benzodiazepines in 60.4% (N=301), and ethanol in 18.5% (N=92) of these cases. The baseline characteristics of cases and controls are presented in Table 5.1. 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 past history of alcoholism and to have obtained opioids from multiple physicians and pharmacies. Over two-thirds of cases (67.7%) were in the lowest two income quintiles.

Table 5.1: Baseline characteristics of individuals who died of opioid-related causes (cases) and matched controls

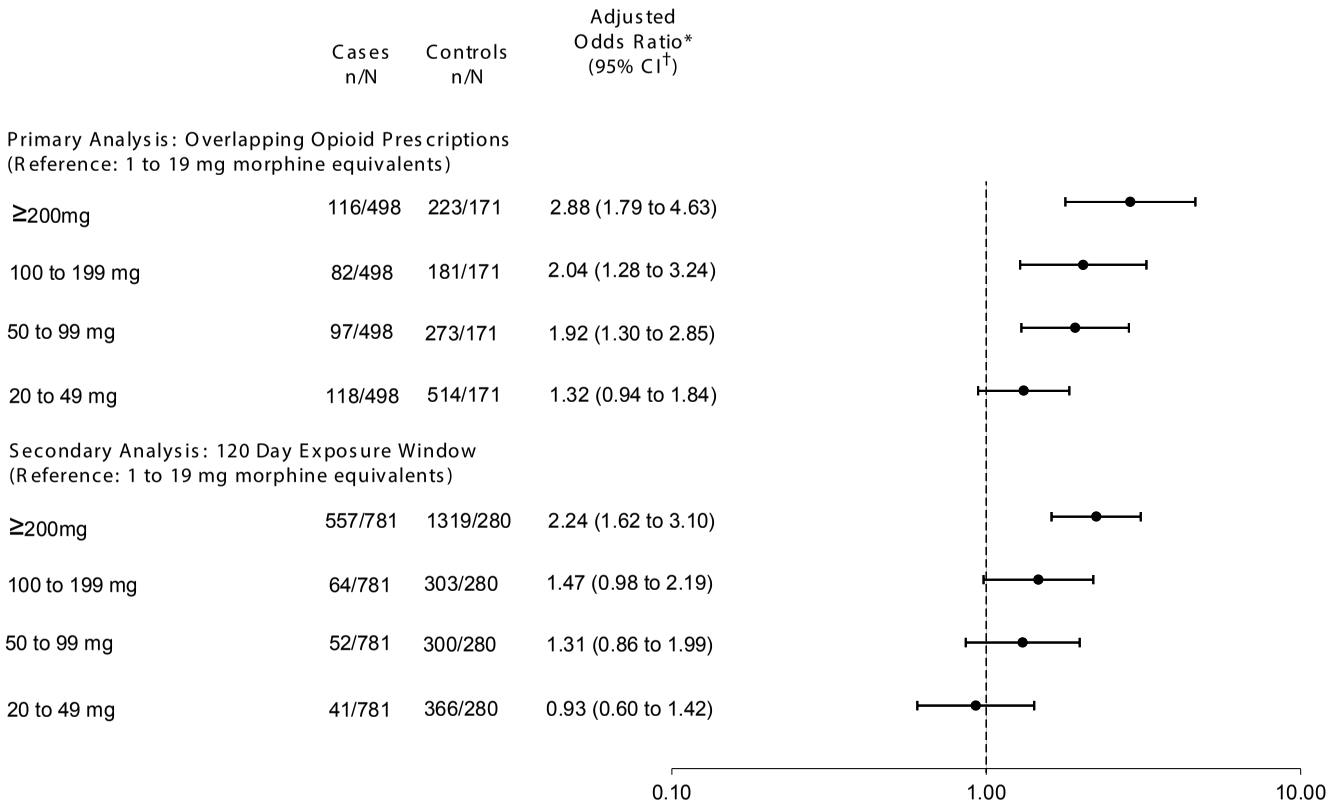
	Exposure: Opioid Prescription Overlaps Index Date		
Variable	**Cases N=498**	**Controls N=1,714**	**Standardized Difference**
Age			
Mean (SD)	44.49 ± 8.25	44.72 ± 8.20	0.03
Median (IQR)	44 (38-50)	45 (39-51)	0.03
Gender	293 (58.8%)	994 (58.0%)	0.02
Past Drug use (past 180 days)			
Antidepressants – SSRIs	247 (49.6%)	663 (38.7%)	0.22
Antidepressants – Other	258 (51.8%)	668 (39.0%)	0.26
Benzodiazepines	421 (84.5%)	1,104 (64.4%)	0.44
Other Psychotropic Drugs and CNS depressants	180 (36.1%)	444 (25.9%)	0.23
Methadone	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			
Missing	<=5 (0.2%)	<=5 (0.1%)	0.02
Rural	58 (11.6%)	238 (13.9%)	0.07
Urban	439 (88.2%)	1,474 (86.0%)	0.06
Number of Distinct Drugs (past 180 days)	10 (7-15)	9 (6-13)	0.26
Charlson Score (past 3 years 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 and up	66 (13.3%)	192 (11.2%)	0.06
History of Alcoholism	159 (31.9%)	433 (25.3%)	0.15
Duration of opioid use	5 (2-7)	4 (2-7)	0.08

Number of physicians prescribing opioids (past 180 days)			
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 or more	17 (3.4%)	27 (1.6%)	0.13
Number of pharmacies dispensing opioids (past 180 days)			
1	285 (57.2%)	1,161 (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 or more	13 (2.6%)	12 (0.7%)	0.18
Long-acting opioid dispensed in exposure window	228 (45.8%)	523 (30.5%)	0.33
Number of Physician Visits (past 1 year)	32 (20-55)	28 (16-47)	0.14

In the primary analysis, after extensive multivariate adjustment, we found a significant relationship between the average daily opioid dose and opioid-related mortality (Figure 5.3). As compared with patients receiving less than 20 milligrams per day, those prescribed opioids at daily doses exceeding 200 milligrams morphine or equivalent had a much higher risk of opioid-related mortality (odds ratio 2.88, 95% confidence interval 1.79 to 4.63). A significant but attenuated association was found between two moderate opioid dose categories and opioid-related mortality (50 to 99 mg morphine equivalents: odds ratio 1.92, 95% confidence interval 1.30 to 2.85; and 100 to 199 mg morphine equivalents: odds ratio 2.04, 95% confidence interval 1.28 to 3.24).

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 one control (Figure 5.2). The results of this analysis were consistent with those observed in the primary analysis (Figure 5.3).

Figure 5.3: Association between opioid-related death and opioid dose



**Adjusted for: previous drug use (SSRIs, other antidepressants, benzodiazepine, other psychotropic drugs and CNS depressants, and methadone), number of drugs in past 6 months, duration of opioid treatment, number of physicians prescribing opioids, number of pharmacies dispensing opioids, presence of any long-acting opioid dispensed in exposure window.*

† CI=confidence interval

Discussion

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 more than 200 mg 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-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 highly significant association between daily doses exceeding 200 mg 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 between 50 mg and 200 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 of socioeconomically disadvantaged Ontarians aged 15 to 64, the two-year risk of opioid-related mortality among those prescribed 200-400 mg morphine or equivalent was 0.8%, and the risk among those prescribed more than 400 mg morphine or equivalent was 1.0%.[1] Though 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 healthcare services, drug coverage among residents younger than 65 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 towards 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 toxicological 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 towards 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 adjusted for all potential confounders.

Conclusion

In conclusion, we found that higher daily dose of opioids is associated with large relative and absolute increases in opioid-related mortality, and that doses exceeding 200 mg morphine (or equivalent) are associated with a particularly high risk. Our findings have important implications, largely because the majority of opioid 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, non-cancer pain, particularly at high doses.[9,10]

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