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

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Chapter 6:
Opioid dose and risk of road trauma in Canada: A population-based study

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Abstract

BACKGROUND

Use of opioids may predispose drivers to road trauma, yet the impact of dose on this association is unknown.

METHODS

We conducted a population-based nested case-control study of patients aged 18 to 64 years who received at least one publicly-funded prescription for an opioid between April 1, 2003 and March 31, 2011. Cases were defined using health administrative databases as those with an emergency department visit related to road trauma. Patients without road trauma acted as controls and were matched to cases on age, gender, year, prior road trauma and a disease risk index. We compared the risk of road trauma among patients treated with various doses of opioids ranging from low (<20 morphine equivalents daily) to very high (≥ 200 morphine equivalents daily). In a subgroup analysis, we stratified our analysis by driver status.

RESULTS

Among 549,878 eligible adult patients, we identified 5,300 cases with road trauma who were matched to an equal number of controls without road trauma. Multivariate adjustment yielded no significant association between escalating opioid dose and odds of road trauma (adjusted odds ratio [aOR] ranged between 1.00 and 1.09). However, a significant association between opioid dose and road trauma was observed among drivers. Compared with those prescribed low opioid doses, drivers prescribed moderate doses had a 21% increased odds of road trauma (aOR 1.21, 95% confidence interval (CI) 1.02 to 1.42), those prescribed high doses had a 42% increased odds (aOR 1.42, 95% CI 1.15 to 1.76), and those prescribed the highest doses had a 23% increased odds of road trauma (aOR 1.23, 95% CI 1.02 to 1.49).

CONCLUSIONS

Among drivers prescribed opioids, a significant relationship exists between drug dose and risk of road trauma. This association is distinct and does not appear with passengers, pedestrians, and other road users injured in road trauma.

Introduction

Road trauma and prescription drug toxicity represent two leading causes of accidental death in North America[1,2], resulting in substantial avoidable public health and economic losses. In 2009, 2.3 million adults in the United States attended the emergency department for a motor vehicle crash, and 475,000 visited the emergency department for reasons related to misuse and abuse of prescription painkillers.[3,4] Over the past two decades, several studies investigating the effects of prescription medications on driving performance have highlighted how these drugs can influence reaction time, cognition, and concentration in simulated driving situations.[5-7] Although the potential effects of opioids on driving ability are particularly concerning given their increasing use and misuse, major gaps persist in understanding the impact of dose, concomitant medication use, and opioid formulation.[8]

Opioid-related drug toxicity is becoming increasingly prevalent, amounting to more than 40% of deaths from drug toxicity in the United States.[1] Opioids can interfere with attention and impair reaction time[9,10], leading to concerns regarding impaired driving performance. However, two small randomized controlled trials of driving simulations found no significant impact of opioids on driving performance, reaction time or cognition[5,6] although one study suggested that patients receiving opioids experienced reduced alertness and increased sedation while driving.[5] Further, several small observational studies indicate a moderate but significant increased risk of road trauma among drivers prescribed opioids as compared to controls[11-13], while others show no such association.[14-16] It is unknown how these divergent observations translate to driver performance outside of a controlled experimental setting, at a population level.

While the association between opioid use and risk of road trauma is disputed, no studies have investigated whether dose may explain these inconsistencies. This distinction is particularly timely given recent evidence indicating that opioids are being prescribed at increasingly high doses.[17] For example, more than one-quarter of patients prescribed publicly-funded long-acting opioids in Ontario in 2008 received doses exceeding 200 mg morphine (or equivalent)[17], a threshold identified as important in clinical guidelines.[18,19] Therefore, we sought to characterize the relationship between opioid dose and risk of road trauma among patients receiving public drug coverage in Ontario, Canada.

Methods

SETTING

We conducted a population-based nested case-control study of Ontario adults aged 18 to 64 years who were eligible for prescription drug coverage under the Ontario provincial Public Drug Program and who were prescribed opioid analgesics between April 1, 2003 and March 31, 2011. All residents of Ontario receive publically-funded physician and hospital care. The study protocol was approved by the research ethics board of Sunnybrook Health Sciences Centre, Toronto, Ontario.

DATA SOURCES

We used the Ontario Drug Benefit (ODB) database to identify all prescription medications dispensed to eligible residents of Ontario. Eligibility for drug coverage among people aged 18 to 64 included unemployment, disability, high prescription drug costs relative to net household income, or receipt of home care services. We used the Canadian Institute for Health Information's Discharge Abstract Database to identify inpatient hospitalizations, and the National Ambulatory Care Reporting System to identify emergency department visits. Claims for physicians' services (including palliative care services) were obtained from the Ontario Health Insurance Plan database. Finally, the Institute for Clinical Evaluative Sciences Physician Database was used to determine physician specialty, and the Registered Persons Database was used to define patient demographic information.

IDENTIFICATION OF PATIENTS AND OUTCOMES

Opioids included in the exposure definition in this study were oral formulations of codeine, morphine, oxycodone or hydromorphone, and transdermal fentanyl patches. We did not include in our calculation of opioid dose prescriptions for injectable opioids and rarely used drugs such as anileridine, levorphanol tartrate, meperidine, oxymorphone, pentazocine and propoxyphene, as well as methadone, which is most often prescribed in Ontario for opioid addiction rather than pain. Furthermore, hydrocodone was not included because its oral formulation is not covered by the public drug plan in Ontario.

Cases were defined as people who attended an emergency department (ED) with an external cause of injury related to road trauma (*International Classification of Diseases 10th Revision* codes V00 to V89) over the study period. This definition includes drivers, passengers, pedestrians and patients in miscellaneous positions (e.g. bicycle or unknown location). Details of these codes and the stratification by

patient position can be found in Table 6.1. The date of the emergency department visit served as the index date for cases. If patients had multiple incidents of road trauma during the study period, only the first event was considered in the analyses. Potential controls were selected as those individuals who did not attend an ED with road trauma over our study period. The temporal distribution of the index dates for all cases was determined. To ensure that cases and controls were similarly dispersed over time, each potential control was randomly assigned an index date such that the temporal distribution of index dates among controls mirrored that of the cases.

Table 6.1: Place of occurrence codes used to identify Road Trauma in emergency departments.

Place of Occurrence Code	Suffix	Patient Position	Vehicle Involved
V01-V09	all	Pedestrian	Various vehicles
V10-V19	all	Miscellaneous	Pedal bicycle
V20-V29	0, 2, 3, 4, 6, 8, 9	Driver	Motorcycle
V20-V29	1, 5	Passenger	Motorcycle
V30-V39	0, 3, 4, 5, 8, 9	Driver	All-terrain vehicle
V30-V39	1, 6	Passenger	All-terrain vehicle
V30-V39	2, 7	Pedestrian	All-terrain vehicle
V40-V49	0, 3, 4, 5, 8, 9	Driver	Automobile
V40-V49	1, 6	Passenger	Automobile
V40-V49	2, 7	Pedestrian	Automobile
V50-V59	0, 3, 4, 5, 8, 9	Driver	Small truck
V50-V59	1, 6	Passenger	Small truck
V50-V59	2, 7	Pedestrian	Small truck
V60-V69	0, 3, 4, 5, 8, 9	Driver	Big truck
V60-V69	1, 6	Passenger	Big truck
V60-V69	2, 7	Pedestrian	Big truck
V70-V79	0, 5	Driver	Bus
V70-V79	1, 3, 4, 6, 8, 9	Passenger	Bus
V70-V79	2, 7	Pedestrian	Bus
V80	all	Miscellaneous	Animal rider
V81-V82	all	Passenger	Train or Streetcar
V83-V86	0, 3, 4, 5, 9	Driver	Industrial
V83-V86	1, 6	Passenger	Industrial
V83-V86	2, 7	Pedestrian	Industrial
V87-V89	all	Miscellaneous	Uncertain

Cases and controls were eligible for inclusion only if they had at least 6 months of continuous eligibility for public drug coverage prior to their index date and at least one opioid prescription with a duration that overlapped their index date. Cases and controls were excluded if they had invalid patient identifiers, missing age or gender information, received palliative care services in the 6 months prior to their index date, lived in a long-term care home at the time of index date, or had a prescription for a non-study opioid with a duration that overlapped the index date.

We generated a disease risk index for all cases and potential controls to generate predicted probabilities of road trauma. This index was based on measured demographic characteristics, medical disorders, and psychiatric conditions (see Table 2.2). The components of this risk score have been published previously.[20] We selected one control for each case using incidence density sampling.[21] Cases were matched to controls on gender, age (within 3 years), index year (within 1 year), ED visit for road trauma in the past 1 year, and disease risk index (within 0.2 standard deviations). Cases with no matched controls were excluded from analyses.

EXPOSURE DEFINITION

Computerized medication records were used to identify all prescriptions for study opioids with a duration that overlapped the patient's index date (Figure 6.1). The daily dose for each prescription was defined as the total number of pills dispensed multiplied by the strength of the pill in milligrams and divided by the total days' supply of the prescription. The daily dose was converted to morphine equivalents (MEQ) using the morphine equivalence ratios defined by the Canadian National Opioid Use Guideline Group[19], and each patient's total opioid exposure was defined as the sum of all opioid prescriptions overlapping their index date. The primary analysis stratified the average daily dose at index date into 5 categories: very low (less than 20 MEQ), low (20 to 49 MEQ), moderate (50 to 99 MEQ), high (100 to 199 MEQ) and very high (200 MEQ or more). In a secondary analysis, we defined new users of opioids as those whose first prescription for an opioid over the study period occurred in the 14 days prior to their index date.

STATISTICAL ANALYSIS

Patient characteristics were summarized using descriptive statistics and cases and controls were compared using standardized differences. A standardized difference greater than 0.10 was defined as a meaningful difference.[22] We used conditional

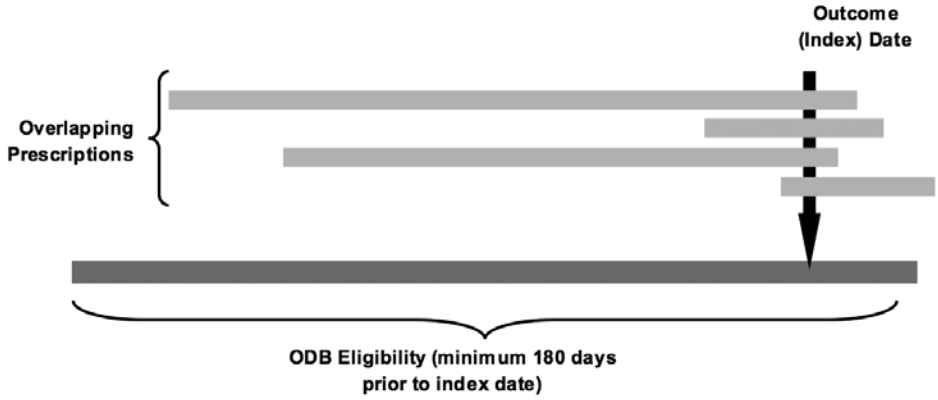


Figure 6.1: Study Design.

Opioid dose was defined based on all prescriptions dispensed to cases and controls with a prescribed treatment duration that overlapped their index date. For each study subject, the total daily dose (converted into morphine equivalents) for each overlapping prescription was summed to generate a total prescribed daily dose.

logistic regression to examine the relationship between opioid dose and odds of an emergency department visit for road trauma. The very low dose category (less than 20 MEQ) was used as the reference group. In a subgroup analysis, we stratified cases into drivers visiting the emergency department for road trauma and non-drivers, under the assumption that drivers might have the strongest association with road trauma risk. In a sensitivity analysis to test the robustness of our findings, we used logistic regression to examine the relationship between dose and road trauma in our entire cohort of cases and controls prior to matching.

We adjusted all models for a variety of potential confounders including age, past hospitalization or physician visit for alcoholism, past emergency department visits for alcoholism, past medication use (selective serotonin reuptake inhibitors, other antidepressants, antipsychotics, benzodiazepines and other depressants of the central nervous system, separately), total number of drugs dispensed in the past 180 days, number of physician visits in the past year, and number of emergency visits in the past year. Furthermore, duration of publically-funded opioid use was included in all models, and was defined as the period of time between the patient's first opioid prescription in our records (starting April 1, 1990) and their index date. This duration does not include any prior use of opioids that were not covered by the provincial public drug program. All analyses were performed using SAS statistical software (version 9.2; SAS Institute Inc, Cary, North Carolina) and used a type 1 error rate of 0.05 as the threshold for statistical significance.

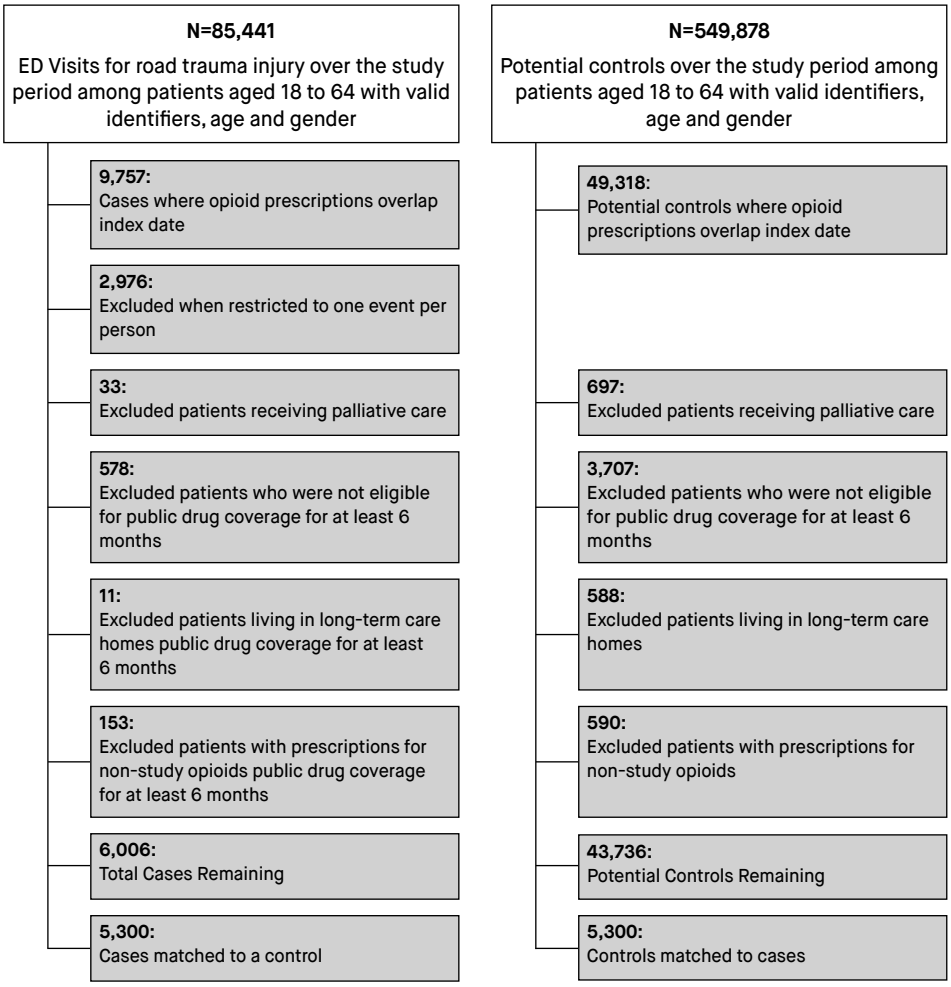


Figure 6.2: Exclusion Criteria Applied to Cases and Potential Controls

Results

A total of 549,878 patients aged 18 to 64 years of age were dispensed at least one opioid over the 8 year study period. Among these patients, we identified 85,441 emergency department visits for road trauma. After applying exclusion criteria, 6,006 cases were eligible for our study (Figure 6.2); of these, 5,300 (88.2%) cases were matched to a control. Among eligible cases, 2,428 (45.8%) were the driver, 840 (15.8%) were passengers, 579 (10.9%) were pedestrians, and 1,453 (27.4%) were in unknown or miscellaneous positions.

Overall, cases were similar to controls with respect to several important demographic and comorbid characteristics (Table 6.2). However, cases visited the emergency department more frequently in the preceding year and were more likely to have visited an emergency department for alcohol-related reasons in the past year. Furthermore, the majority of patients in each group had averaged at least one visit to a physician monthly during the year prior to the index date.

In our primary analysis, we found no association between escalating opioid dose and odds of road trauma (Figure 6.3), with adjusted odds ratios (aOR) ranging between 1.00 and 1.09 for each dose category compared with patients prescribed very low doses of opioids (<20 MEQ). However, in a subgroup analysis of drivers, we found a significantly increased odds of road trauma among patients prescribed moderate, high and very high opioid doses. Compared with those prescribed very low opioid doses, patients prescribed low and moderate doses had a 21% to 29% increased odds of road trauma (aOR 1.21, 95% confidence interval (CI) 1.02 to 1.42 and aOR 1.29, 95% CI 1.06 to 1.57, respectively). Similarly, patients prescribed higher doses of opioids (100-199MEQ and ≥200MEQ) were associated with a 42% and 23% increased odds of road trauma when compared with patients prescribed very low doses (aOR 1.42, 95% CI 1.15 to 1.76 and aOR 1.23, 95% CI 1.02 to 1.49, respectively). As expected, we found no association between opioid dose and risk of road trauma among non-drivers. An analysis of new opioid users found no significant difference in risk of road trauma between individuals who initiated opioids in the prior 2 weeks compared with longer-term opioid users (aOR 1.33, 95% CI 0.84 to 2.12).

The results of our sensitivity analysis were consistent with those of our primary, matched analysis (Table 6.3 and Figure 6.4).

Table 6.2: Characteristics of cases and matched controls

	Cases N=5,300	Controls N=5,300	Standard. Difference
Demographics			
Age (Mean, SD*)	45.76 ± 9.86	45.75 ± 9.85	0
Gender (Male)	2,725 (51.4%)	2,725 (51.4%)	0
Income Quintile			
1	2,280 (43.0%)	2,292 (43.2%)	0.01
2	1,286 (24.3%)	1,305 (24.6%)	0.01
3	737 (13.9%)	720 (13.6%)	0.01
4	560 (10.6%)	552 (10.4%)	0.01
5	404 (7.6%)	399 (7.5%)	<0.01
Missing	33 (0.6%)	32 (0.6%)	<0.01
Urban Residence	4,439 (83.8%)	4,451 (84.0%)	0.01
ODB Plan Coverage			
Social Assistance	1,169 (22.1%)	1,113 (21.0%)	0.03
Disability Support	3,601 (67.9%)	3,528 (66.6%)	0.03
Other	530 (10.0%)	659 (12.4%)	0.08
Charlson Comorbidity Index			
No Hospitalization	3,273 (61.8%)	3,328 (62.8%)	0.02
0	1,242 (23.4%)	1,187 (22.4%)	0.03
1	363 (6.8%)	335 (6.3%)	0.02
2 or more	422 (8.0%)	450 (8.5%)	0.02
Duration of Opioid Use in Years (Mean, SD*)	7.09 ± 3.67	6.84 ± 3.72	0.07
Comorbidity Measures in Past 1 year			
Emergency Department (ED) Visit for Alcohol Abuse	287 (5.4%)	147 (2.8%)	0.13
ED Visit for road trauma	332 (6.3%)	332 (6.3%)	0
ED visit for Drug Toxicity	212 (4.0%)	155 (2.9%)	0.06
Total Number of ED visits (Mean, SD*)	3.93 ± 5.40	2.07 ± 4.48	0.38
Total Number of Physician Visits (Median, IQR**)	21 (12-36)	21 (12-36)	0.01
Total Number of Visits to a Family Physician (Median, IQR**)	13 (7-20)	12 (6-19)	0.04
Visit to a Psychiatrist	1,021 (19.3%)	1,030 (19.4%)	<0.01

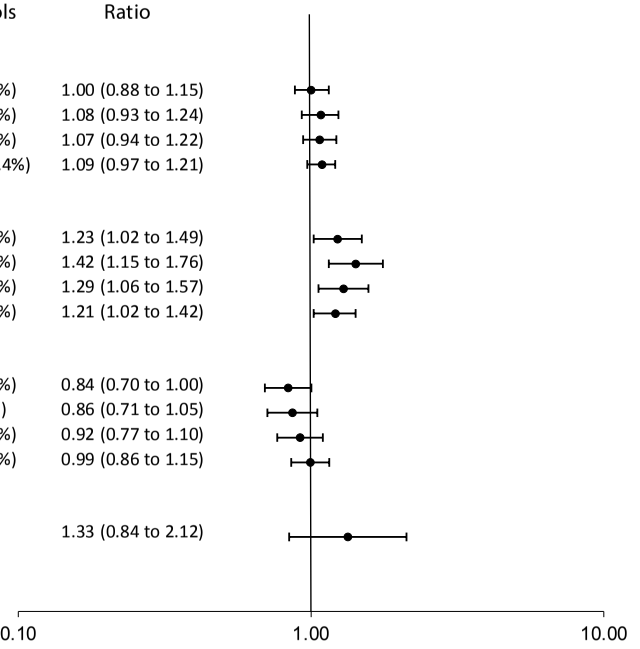
Medication Use in past 180 days			
Number of drugs dispensed (Median, IQR**)	11 (7-16)	11 (7-16)	0.07
SSRI	1,959 (37.0%)	1,963 (37.0%)	<0.01
Other Antidepressant	1,783 (33.6%)	1,842 (34.8%)	0.02
Antipsychotic	898 (16.9%)	886 (16.7%)	0.01
Benzodiazepines	2,764 (52.2%)	2,649 (50.0%)	0.04
Other CNS Depressants	344 (6.5%)	381 (7.2%)	0.03
Comorbidity Measures in past 3 years			
Hospitalization for Poisoning or drug toxicity	991 (18.7%)	971 (18.3%)	0.01
Alcohol Abuse	646 (12.2%)	661 (12.5%)	0.01
Affective Disorder	590 (11.1%)	541 (10.2%)	0.03
Anxiety or Sleep Disorders	3,694 (69.7%)	3,700 (69.8%)	<0.01
Psychoses	406 (7.7%)	404 (7.6%)	<0.01
Other Mental Disorders	3,026 (57.1%)	2,986 (56.3%)	0.02
Injury	291 (5.5%)	324 (6.1%)	0.03
Osteoarthritis	1,951 (36.8%)	1,912 (36.1%)	0.02
Rheumatoid Arthritis	334 (6.3%)	356 (6.7%)	0.02

**SD: Standard Deviation*

***IQR: Interquartile Range*

Figure 6.3: Association between Opioid Dose and Road Trauma

	No. Exposed Cases	No. Exposed Controls	Adjusted Odds Ratio
Primary Analysis: Any Road Trauma*			
≥200 MEQ**	902 (17.0%)	963 (18.2%)	1.00 (0.88 to 1.15)
100 to 199 MEQ	679 (12.8%)	669 (12.6%)	1.08 (0.93 to 1.24)
50 to 99 MEQ	880 (16.6%)	858 (16.2%)	1.07 (0.94 to 1.22)
20 to 49 MEQ	1,591 (30.0%)	1,507 (28.4%)	1.09 (0.97 to 1.21)
Secondary Analyses: Drivers***			
≥200 MEQ	466 (19.2%)	447 (18.4%)	1.23 (1.02 to 1.49)
100 to 199 MEQ	360 (14.8%)	316 (13.0%)	1.42 (1.15 to 1.76)
50 to 99 MEQ	414 (17.1%)	380 (15.7%)	1.29 (1.06 to 1.57)
20 to 49 MEQ	690 (28.4%)	676 (27.8%)	1.21 (1.02 to 1.42)
Non-Drivers†			
≥200 MEQ	140 (16.7%)	150 (17.9%)	0.84 (0.70 to 1.00)
100 to 199 MEQ	93 (11.1%)	99 (11.8%)	0.86 (0.71 to 1.05)
50 to 99 MEQ	139 (16.5%)	142 (26.9%)	0.92 (0.77 to 1.10)
20 to 49 MEQ	244 (29.0%)	227 (27.0%)	0.99 (0.86 to 1.15)
New Users of Opioids‡	42 (0.8%)	39 (0.7%)	1.33 (0.84 to 2.12)



*5,300 cases and controls; Reference Group: 1 to 19 mg MEQ
**MEQ: milligrams of morphine (or equivalent)
*** 2,428 cases and controls; Reference Group: 1 to 19 mg MEQ
† 840 cases and controls; Reference Group: 1 to 19 mg MEQ
‡ 5,300 cases and controls; Reference Group: 1 to 19 mg MEQ

Adjusted for age, past hospitalization for alcoholism (3 years), past emergency department (ED) visit for alcoholism (1 year), duration of opioid treatment, medication use in past 180 days (selective serotonin reuptake inhibitors, other antidepressants, antipsychotics, benzodiazepines and other depressants of the central nervous system, separately), number of drugs dispensed in the past 180 days, number of physician visits in the past 1 year and number of ED visits in the past 1 year

Table 6.3: Characteristics of all Cases and Potential Controls

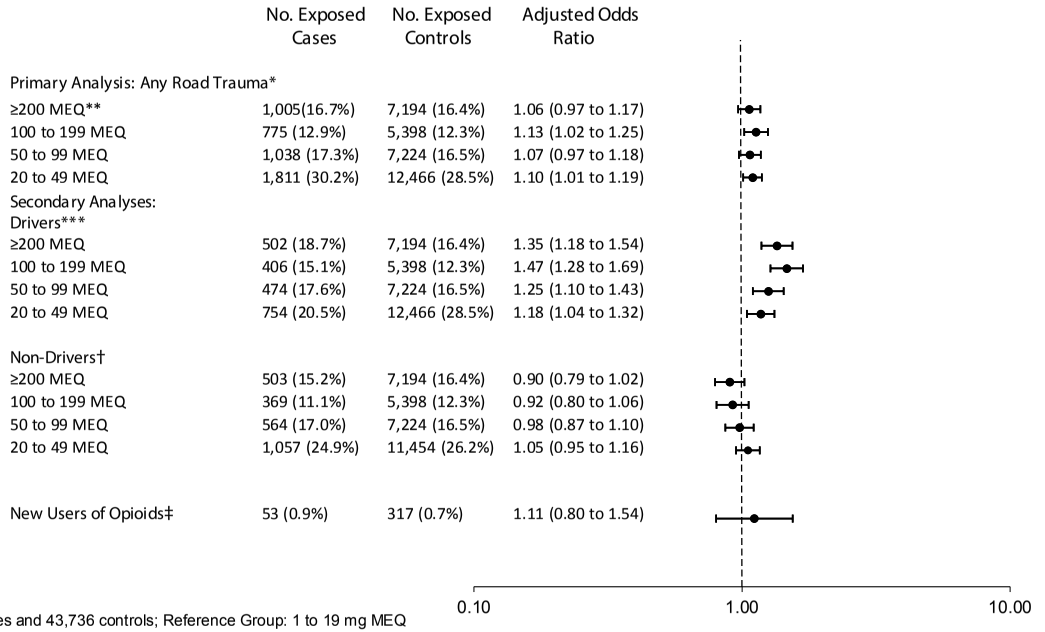
	Cases N=6,006	Controls N=43,736	Standard. Difference
Demographic Characteristics			
Age (Mean, SD*)	45.51 ± 9.95	48.89 ± 9.72	0.35
Gender (Male)	3,151 (52.5%)	20,054 (45.9%)	0.13
Income Quintile			
Missing	39 (0.6%)	261 (0.6%)	<0.01
1	2,587 (43.1%)	18,694 (42.7%)	<0.01
2	1,440 (24.0%)	10,235 (23.4%)	0.01
3	838 (14.0%)	6,479 (14.8%)	0.02
4	644 (10.7%)	4,852 (11.1%)	0.01
5	458 (7.6%)	3,215 (7.4%)	0.01
Urban Residence	5,031 (83.8%)	36,770 (84.1%)	<0.01
ODB Plan Coverage			
Social Assistance	1,370 (22.8%)	7,007 (16.0%)	0.18
Disability Support	4,059 (67.6%)	29,945 (68.5%)	0.02
Other	577 (9.6%)	6,784 (15.5%)	0.17
Charlson Comorbidity Index			
No Hospitalization	3,621 (60.3%)	28,591 (65.4%)	0.11
0	1,459 (24.3%)	7,931 (18.1%)	0.16
1	437 (7.3%)	3,004 (6.9%)	0.02
2 or more	489 (8.1%)	4,210 (9.6%)	0.05
Duration of Opioid Use	7.07 ± 3.68	7.23 ± 3.82	0.04
Comorbidity Measures in Past 1 year			
Emergency Department (ED) visit for Alcohol Abuse	355 (5.9%)	757 (1.7%)	0.28
ED visit for road trauma	990 (16.5%)	404 (0.9%)	0.99
ED visit for Drug Toxicity	262 (4.4%)	809 (1.8%)	0.17
Total Number of ED visits (Mean, SD*)	4.68 ± 8.03	1.59 ± 3.72	0.69
Total Number of Physician Visits (Median, IQR**)	22 (13-38)	18 (10-31)	0.20
Total Number of Visits to a Family Physician (Median, IQR**)	13 (7-21)	10 (5-17)	0.26
Visit to a Psychiatrist	1,209 (20.1%)	6,779 (15.5%)	0.13

Medication Use in past 180 days			
Number of drugs dispensed (Mean, SD*)	12.53 ± 7.27	12.17 ± 6.87	0.05
SSRI	2,210 (36.8%)	15,672 (35.8%)	0.02
Other Antidepressant	2,011 (33.5%)	15,102 (34.5%)	0.02
Antipsychotic	1,052 (17.5%)	6,423 (14.7%)	0.08
Benzodiazepines	3,158 (52.6%)	21,333 (48.8%)	0.08
Other CNS Depressants	381 (6.3%)	2,901 (6.6%)	0.01
Comorbidity Measures in past 3 years			
Hospitalization for Poisoning or drug toxicity	1,229 (20.5%)	6,073 (13.9%)	0.19
Alcohol Abuse	806 (13.4%)	3,576 (8.2%)	0.19
Affective Disorder	683 (11.4%)	3,946 (9.0%)	0.08
Anxiety or Sleep Disorders	4,234 (70.5%)	26,834 (61.4%)	0.19
Psychoses	505 (8.4%)	2,482 (5.7%)	0.12
Other Mental Disorders	3,495 (58.2%)	20,901 (47.8%)	0.21
Injury	425 (7.1%)	1,559 (3.6%)	0.18
Osteoarthritis	2,184 (36.4%)	15,956 (36.5%)	<0.01
Rheumatoid Arthritis	362 (6.0%)	2,958 (6.8%)	0.03

**SD: Standard Deviation*

***IQR: Interquartile Range*

Figure 6.4: Association between Opioid Dose and Road Trauma among all cases and potential controls



*6,006 cases and 43,736 controls; Reference Group: 1 to 19 mg MEQ
**MEQ: milligrams of morphine (or equivalent)
*** 2,686 cases and 12,466 controls; Reference Group: 1 to 19 mg MEQ
† 3,320 cases and 43,736 controls; Reference Group: 1 to 19 mg MEQ
‡ 6,006 cases and 43,736 controls; Reference Group: 1 to 19 mg MEQ

Adjusted for age, gender, public drug plan, Charlson score, past hospitalization for alcoholism (3 years), past emergency department (ED) visit for alcoholism (1 year), number of ED visits in past 1 year, ED visit for road trauma (past 1 year), number of physician visits (past 1 year), number of visits to a family physician (past 1 year), visit to a psychiatrist (past 1 year), hospitalization for drug poisoning (past 1 year), ED visit for drug poisoning (past 1 year), duration of opioid use, medication use in past 180 days (selective serotonin reuptake inhibitors, other antidepressants, antipsychotics, benzodiazepines and other depressants of the central nervous system, separately), number of drugs dispensed in past 180 days, history of sleep disorders, psychoses, other mental disorders, or injury in the past 3 years.

Discussion

In this population-based study spanning 8 years, we did not find an association between opioid dose and risk of road trauma among adults aged less than 65 and eligible for public drug coverage. However, after restricting our analysis to drivers, we found that prescribed daily doses exceeding 20 MEQ were associated with a 20% to 42% increased odds of road trauma. Together, these findings agree with past studies suggesting that increasing opioid doses can impair drivers and contribute to road risks.[5,10-14]

Interestingly, we found that, compared with people receiving very low opioid doses, the odds of road trauma among drivers in the highest dose category was slightly more attenuated than that in the high dose category. Although this is difficult to explain, it is possible that risks are attenuated at the extremes for several reasons. Possible explanations include increased likelihood of medication diversion in this subgroup, or physiologic opioid tolerance among patients who are treated chronically at a fixed dose which may actually offset the detrimental effects of these drugs on driver performance.[10] Therefore, our observed attenuation of risk at the extremes may reflect either behavioural or biologic explanations.

Several limitations of our study merit discussion. First, our population was restricted to younger adults eligible for public drug coverage in Ontario. This constitutes a socioeconomically disadvantaged population and our findings may not be generalizable to individuals with higher socioeconomic status, older adults and other jurisdictions. Second, we are unable to determine the indication for opioid therapy, and thus cannot elucidate how pain severity influenced our findings. Third, we have no information regarding access to motor vehicles or the frequency of driving among patients in our cohort. Fourth, our definition of road trauma has not been validated, and therefore we may not have identified all ED visits related to road trauma over our study period. Fifth, we defined opioid dose on the basis of publicly funded prescriptions, and we do not know how unused prescription drugs, *pro re nata* (PRN) use, illegal drug diversion, quantities obtained illicitly or those paid privately would influence our calculations. All of these limitations likely serve to attenuate our findings, particularly among patients receiving the highest doses. Finally, it is possible that 'adverse selection' – the tendency for patients with substance abuse disorders and mental health conditions to receive chronic opioid therapy – may be influencing our findings.[23] Although we have attempted to address this by adjusting for various factors in our models, it is possible that this selection among high dose opioid users may contribute to the dose response relationship observed in this study.

In summary, although the relationship between use of opioids and risk of road trauma has been frequently described in small samples, this is the first study to demonstrate the relationship between opioid dose and this risk among drivers in a population-based setting. Our findings have important implications in clinical practice and suggest that physicians may want to warn patients about potentially decreased driving ability when escalating to high opioid doses, particularly during the period before acclimatization to a fixed dose develops. Furthermore, policy-makers could improve public education surrounding the potential risks of opioid medications and could consider restricted drivers licenses for patients treated at high doses.

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