Online Supplement 1

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Section 1: Additional information regarding health care administrative databases used

Regarding the Institute for Clinical Evaluative Sciences (ICES) COPD database, COPD health administrative codes were previously validated against an expert respirology panel review of patient medical charts [1]. All patient chart information, including history, physical examination, and investigations, were considered by the expert panel [1]. In addition to the ICES COPD database and the Ontario Drug Benefit (ODB) database, ten other standard health care administrative databases were linked, similar to previous [2], at an individual patient-level in order to identify COPD exacerbations and comorbidities. The Ontario Health Insurance Plan (OHIP) database was used, as it contained information on patient contact by physicians in both ambulatory and hospital settings. The Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD) was used, because it contained information on all hospital admissions. The National Ambulatory Care Reporting System (NACRS) database captured information on all emergency room (ER) visits. Comorbidities were also identified using the Ontario Mental Health Reporting System (containing information on all mental health hospital admissions), the Same-Day Surgery database (containing information on surgical procedures not requiring overnight hospital stays), the Ontario Cancer Registry (a validated provincial cancer registry [3]), and an established validated database of Ontario adults with physician-diagnosed congestive heart failure [4]. Demographic and mortality data were obtained from the Registered Persons Database (RPDB) and cause of death data were obtained from the Office of the Registrar General - Deaths (ORGD) database.

References

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Section 2: Propensity score weighting methods

Since there are significant differences in risk for opioid drug exposure among older adult with COPD [1], inverse probability of treatment weighting using the propensity score was employed to create weighted samples of exposed and control individuals where measured baseline covariates were balanced between the two groups [2-3]. The propensity score reflected the probability of receiving a new opioid for an individual with a specific set of measured baseline factors. A propensity score for new opioid receipt was developed using a logistic regression model with 33 covariates describing patient demographic and health characteristics that were known to be associated with opioid receipt in older adults with COPD [1] and the outcomes of interest (Table 2 in manuscript proper). Indicators of COPD severity, health care utilization, and comorbidities were included in the propensity score.

As clinical items such as respiratory symptoms and pulmonary function were not available in our health administrative databases for inclusion in the propensity score, COPD severity was assessed using other measures, like COPD exacerbation history in the year prior to the index, COPD duration, and use of respiratory-related medications. Canadian [4] and newer global [5] COPD guidelines use COPD exacerbation frequency to distinguish COPD severity. COPD exacerbation history is known to be associated with severity of underlying airflow obstruction [6], risk of future exacerbations [7] and mortality [8], and it is the single best predictor of future exacerbation, regardless of baseline lung function [7]. A cut-off of 1 or more exacerbations in the preceding year was used, as Canadian COPD guidelines use this cut-off [4]. Among individuals who had 1 or more COPD exacerbation in the year prior to index, we separately considered whether the exacerbation(s) were or were not all associated with presentation to hospital, since presenting to hospital likely reflects an exacerbation of greater

severity. Respiratory exacerbations associated with presentation to hospital were defined as an ER visit or a hospitalization for COPD or pneumonia. Respiratory exacerbations not associated with presentation to hospital (i.e., outpatient exacerbations) were defined as receipt of an oral corticosteroid or respiratory antibiotic within +/-7 days of a physician clinic/office visit for COPD or pneumonia and with the corticosteroid or antibiotic prescription having a supply date of 5-21 days. Others have used a similar definition for non-hospital associated respiratory exacerbation [7,9]. Whether or not individuals had had a COPD exacerbation in the 30 days prior to index was also included as covariate in the propensity score. This variable was included to balance opioid users and controls on a marker of recent respiratory status stability at the time of the index date.

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Section 3: Conversion of different opioid drug doses into mg of morphine equivalents per day

Morphine equivalents were calculated based on the data in the following table [1], by dividing the daily dose of the non-morphine formulation by the appropriate number from the list below.

Opioid type	mg morphine equivalents
Morphine sulphate or HCL	1*
Anileridine	1.25
Codeine sulphate or phosphate	3.33
Hydromorphone HCL	0.125
Levorphanol	0.067
Meperidine	5
Oxycodone	0.25
Propoxyphene or Dextropropoxyphene	1.67
Transdermal fentanyl	0.42

*Assuming non-chronic dosing, which applies to our study that examines new opioid use.

References

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Section 4: Additional sensitivity analysis for community-dwelling cohort

We performed three additional sensitivity analysis. We examined for adverse outcomes distinguishing by whether or not the incident opioid contained a caffeine component. Two opioid drugs available in ODB contain a caffeine component, acetaminophen-caffeine-codeine and acetylsalicylic acid-codeine-caffeine. The intention of the caffeine component is to potentially counteract opioid-related sedating side-effects. The purpose of this sensitivity analysis was to evaluate if the association with adverse outcomes would be different between opioids that contain and do not contain a caffeine component. We also evaluated for adverse respiratory outcomes after excluding individuals with a lung cancer diagnosis within five years prior to the index date and separately after excluding individuals with any cancer diagnoses within five years prior to the index date. The purpose of these final two sensitivity analyses was to examine the association between new opioid use and adverse respiratory outcomes after additionally minimizing the potential for confounding by indication by the presence of comorbid malignancy.

Compared to controls, new users of non-caffeine-containing opioids were associated with significantly increased risk of ER visits (HR 1.31, 95% CI 1.12-1.54) and hospitalizations for COPD or pneumonia (HR 1.27, 95% CI 1.10-1.45), as well as increased COPD or pneumonia-related mortality (HR 3.21, 95% CI 2.35-4.40) and all-cause mortality (HR 2.79, 95% CI 2.46-3.16) (Table 1 in this Supplement). New users of caffeine-containing opioids relative to controls were associated with significantly decreased risk of outpatient exacerbations (HR 0.83, 95% CI 0.78-0.89), but increased COPD or pneumonia-related mortality (HR 1.56, 95% CI 1.14-2.13) and all-cause mortality (HR 1.24, 95% CI 1.09-1.40), although the associations with mortality were not as strong as for non-caffeine-containing opioid drugs. No significant associations with other adverse outcomes were observed. Caffeine contained in certain opioid formulations

appears then to provide some protection from opioid-related adverse respiratory events and mortality. The protective effect of caffeine may be related to its stimulating property that may help counteract opioid-related sedating side-effects, and thereby, adverse events possibly related to sedation, like aspiration pneumonia and falls and fractures.

Having excluded individuals with comorbid lung cancer, new opioid users were found to be associated with decreased risk of outpatient exacerbations (HR 0.89, 95% CI 0.84-0.95), but increased risk for ER visits for COPD or pneumonia (HR 1.15, 95% CI 1.01-1.30), COPD or pneumonia-related mortality (HR 2.14, 95% CI 1.60-2.86) and all-cause mortality (HR 1.80, 95% CI 1.59-2.03) relative to controls (Table 2 in this Supplement). No significant associations with other adverse outcomes were observed. When individuals with any pre-existing malignancy were excluded, compared to controls, new opioid users were associated with decreased risk for outpatient exacerbations (HR 0.91, 95% CI 0.85-0.97), but increased risk of ER visits for COPD or pneumonia (HR 1.17, 95% CI 1.02-1.33), COPD or pneumonia-related mortality (HR 2.24, 95% CI 1.66-3.02) and all-cause mortality (HR 1.72, 95% CI 1.51-1.96) (Table 3 in this Supplement). No significant associations with other adverse outcomes were observed. The persistence of increased risk for adverse outcomes among new opioid users with COPD, after having excluding individuals with comorbid malignancy from the analysis (who would be at greater risk for receiving opioids for symptoms, like pain, and who would also be at risk for negative outcomes) supports the robustness of our overall findings. While associations with outpatient respiratory exacerbations were reduced among opioid users relative to controls in these latter two sensitivity analyses, these results are likely explained by the increased and competing risk of death among opioid users.

Table 1. Hazard ratios and confidence intervals for adverse respiratory outcomes for the propensity score weighted community-dwelling cohort, distinguishing by whether or not the incident opioid was caffeine-containing

Opioid drug type	Opioid use status	Outpatient respiratory exacerbations			ER visits for COPD or pneumonia			Hospitalizations for COPD or pneumonia			ICU admissions during hospitalizations for COPD or pneumonia			COPD or pneumonia-related mortality			All-cause mortality		
		Number (%) of events	HR(95% CI)	p-value	Number (%) of events	HR(95% CI)	p-value	Number (%) of events	HR(95% CI)	p-value	Number (%) of events	HR(95% CI)	p-value	Number (%) of events	HR(95% CI)	p-value	Number (%) of events	HR(95% CI)	p-value
Caffeine-containing opioid	New users	1984(3.3%)	0.83(0.78,0.89)	<.0001	611(1.0%)	1.08(0.95,1.23)	0.26	783(1.3%)	1.01(0.90,1.13)	0.89	115(0.2%)	0.95(0.70,1.29)	0.75	129(0.2%)	1.56(1.14,2.13)	0.005	786(1.3%)	1.24(1.09,1.40)	0.0008
	Controls	1667(4.0%)	referent		399(1.0%)	referent		548(1.3%)	referent		85(0.2%)	referent		59(0.1%)	referent		449(1.1%)	referent	
Non-caffeine-containing opioid	New users	1219(4.1%)	0.99(0.91,1.08)	0.84	398(1.3%)	1.31(1.12,1.54)	0.0008	534(1.8%)	1.27(1.10,1.45)	0.0008	80(0.3%)	1.16(0.80,1.70)	0.43	144(0.5%)	3.21(2.35,4.40)	<.0001	990(3.3%)	2.79(2.46,3.16)	<.0001
		1726(4.1%)	referent		428(1.0%)	referent		594(1.4%)	referent		97(0.2%)	referent		64(0.2%)	referent		506(1.2%)	referent	

Table 2. Hazard ratios and confidence intervals for adverse respiratory outcomes among propensity score weighted community-dwelling cohort, excluding individuals with pre-existing lung cancer

Outcomes	Status of opioid use	Number (%) of events	HR (95% CI)	p-value	
Outpatient respiratory exacerbations	New opioid users	3074(3.6%)	0.89(0.84,0.95)	0.0006	
	Controls	1641(4.0%)	referent		
ER visits for COPD or pneumonia	New opioid users	950(1.1%)	1.15(1.01,1.30)	0.04	
	Controls	397(1.0%)	referent		
Hospitalizations for COPD or pneumonia	New opioid users	1229(1.4%)	1.10(0.99,1.23)	0.08	
	Controls	534(1.3%)	referent		
ICU admissions during hospitalizations for COPD or pneumonia	New opioid users	179(0.2%)	1.10(0.83,1.46)	0.49	
	Controls	77(0.2%)	referent		
COPD or pneumonia-related mortality	New opioid users	258(0.3%)	2.14(1.60,2.86)	<.0001	
	Controls	58(0.1%)	referent		
All-cause mortality	New opioid users	1535(1.8%)	1.80(1.59,2.03)	<.0001	
	Controls	410(1.0%)	referent		

Table 3. Hazard ratios and confidence intervals for adverse respiratory outcomes among propensity score weighted community-dwelling cohort, excluding individuals with any pre-existing malignancy

Outcomes	Status of opioid use	Number (%) of events	HR (95% CI)	p-value	
Outpatient respiratory exacerbations	New opioid users	2830(3.6%)	0.91(0.85,0.97)	0.006	
	Controls	1537(4.0%)	referent		
ER visits for COPD or pneumonia	New opioid users	860(1.1%)	1.17(1.02,1.33)	0.02	
	Controls	367(1.0%)	referent		
Hospitalizations for COPD or pneumonia	New opioid users	1117(1.4%)	1.11(0.99,1.24)	0.08	
	Controls	501(1.3%)	referent		
ICU admissions during hospitalizations for COPD or pneumonia	New opioid users	168(0.2%)	1.20(0.90,1.61)	0.20	
	Controls	69(0.2%)	referent		
COPD or pneumonia-related mortality	New opioid users	241(0.3%)	2.24(1.66,3.02)	<.0001	
	Controls	54(0.1%)	referent		
All-cause mortality	New opioid users	1244(1.6%)	1.72(1.51,1.96)	<.0001	
	Controls	361(0.9%)	referent		