Data Supplement

Title: Association between Opioid Prescription Profiles and Adverse Health Outcomes in Opioid Users Referred for Sleep Disorder Assessment: A Secondary Analysis of Health Administrative Data

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Text E1: Details on ICES databases used.

Tables

E-References

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Since 1991, ICES (www.ices.on.ca) has housed high-quality administrative datasets on publicly funded services provided, including individual-level information on physician claims, hospitalization, and emergency visits within Ontario.[1] The accuracy of these datasets has been previously validated.[2,3] The Registered Persons Database (RPDB) contains data on demographics, residence location, and date of death; the Discharge Abstract Database records up to 25 diagnoses and procedures performed for each hospital admission; the National Ambulatory Care Reporting System Database records up to 10 diagnoses and procedures for emergency room and urgent care visits; the OHIP database captures all physician billing and technical fees for procedures such as PSG, and the Canadian Census includes neighborhood socioeconomic details. The Narcotics Monitoring System (NMS) collects data on dispensed prescriptions for narcotics, controlled substances, and other monitored drugs such as stimulants, benzodiazepines/zolpidem, and barbiturates. Since November 1, 2011, all dispensers in Ontario are required to submit information to the NMS on date, name, strength, dosage of the monitored drug, quantity dispensed, and length of therapy. Furthermore, for all insured Ontario residents who have been diagnosed with SDB by a sleep physician, funding is provided for PAP systems and documented in the Assistive Devices Program (ADP) database from 2000 onwards.[4] There are several positive airway pressure (PAP) modalities used to treat patients with sleep disordered breathing (SDB): CPAP, autotitrating positive airway pressure (APAP), bilevel positive airway pressure (BiPAP) and adaptive servo-ventilation (ASV). The Respiratory Equipment Pool of the ADP provides 75% of the cost of a basic CPAP/APAP/BiPAP device. The Ventilatory Equipment Pool of the ADP provides ventilators including BiPAP required back up rate and is fully funded by the government. A description of the ICES datasets is available at https://datadictionary.ices.on.ca/Applications/DataDictionary/Default.aspx.

Table E1: Details on the cohort creation and variable definitions.

Cohort of Interest: individuals who underwent diagnostic sleep study, untreated for sleep disordered breathing, with active opioid prescription at the sleep study (the index date)	**Cohort**: All adults (***18+***) who underwent a diagnostic sleep study (***index study date***) identified using the OHIP fee codes (J890, J690, J896, J696, J897, J697) from July 2013 and June 2016 AND with active opioid prescription at the index date (please see details below) **Excluded individuals**: (1) received ***palliative care*** (based on physician service codes in OHIP and CIHI-DAD databases) in the year prior to the index date: admitted to hospital with a patient service code for palliative care (PATSERV = 58) or palliative diagnostic code (Z515) in any diagnosis field; or if a treating physician had billed OHIP for any of the following palliative care fee codes: A945, B998, C945, C882, C982, K023, W872, W882, W972 or W982; or palliative end of life homecare (service code 95 or 54) from home care delivered services OR (2) in ***long-term care*** (LTS) in the year prior to the index date from Continuing Care Reporting System (CCRS - LTC) OR (3) already on ***positive airway pressure (PAP) treatment*** at the index date or requested a repeat PAP prescription in the last 5 years through the Assistive Device Program Database (ADP) OR (4) underwent a ***therapeutic sleep study*** (the OHIP fee codes: J889, J689, J895, J695) in the last 5 years preceding the index date OR (5) were taking opioids that are rarely used and/or with no well-defined morphine equivalencies such as intranasal, injectable, or rectal suppositories opioids at the index date OR (6) Missing age or gender OR (7) Uninsured
Opioids of interest (the Narcotic Monitoring System [NMS] database)	Individuals on opioids will be defined through the NMS database by dispensing of **oral/transdermal** opioids between July 2012 and March 2018. At least one opioid prescription over the study period, including **oral formulations** of morphine, codeine, oxycodone, meperidine, hydromorphone, pentazocine, tramadol, tapentadol, opium (miscellaneous opioids) as well as **transdermal** fentanyl and buprenorphine patches, and opioid maintenance therapy (OMT), that includes buprenorphine for opioid dependence (Subutex), buprenorphine/naloxone, and methadone for opioid dependence.
Active opioid prescription	An opioid Rx that overlaps with the index date (i.e., date of dispensing is < index date and date of dispensing + days supply is >index date)
Exposures: Opioid characteristics at the index date	
Chronic opioid use	Three or more prescriptions for any opioids in the last six months or at least one prescription for a long-acting opioid[5]
The daily opioid dose (morphine equivalent daily dose, MED)	• The daily dose was calculated as the total 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 Group. When multiple concurrent opioid prescriptions were identified, the total average daily dose was defined as the sum of the average daily dose of all prescriptions overlapping the patient's index date. • MED was considered as both a continuous variable and categorical variable (<90 vs. ≥90 mg/day)[6,7]
Outcomes	

Withing the first year since the index date	
Primary outcome: All-cause mortality (from RPDB – Demographic database)	The date of the death from all-causes
Secondary outcomes	
All-cause Hospitalization (from DAD database)	The date of inpatient hospitalization for all-causes
All-cause Emergency Department Visit that does not result in a hospitalization (from NACRS database)	The date of emergency department visit for all-causes
From the index date to the last date of the follow-up (***March 31, 2018***)*	
Opioid Poisoning Related ED Visit and/or Hospitalization [8,9]	The date of hospitalizations and/or ED visits for (ICD-10-CA codes) [10]: – T40.0 (poisoning by opium) – T40.1 (poisoning by heroin) – T40.2 (poisoning by other opioids) – T40.3 (poisoning by methadone) – T40.4 (poisoning by other synthetic narcotics) – T40.6 (poisoning by other and unspecified narcotics)
Variable Definitions (Baseline Characteristics)	
Baseline demographics	– Age, sex – Socioeconomic status (SES): A patient's residential neighbourhood income was defined from the Ontario Census. Ontario neighbourhoods are classified into one of the five approximately equal-sized income quintiles, ranked from poorest (Q1) to wealthiest (Q5) and shown to be related to population health status and health care utilization.[11] The neighborhood income quintiles have previously been shown to be a useful method to stratify individuals by SES and to identify related disparities in health and health care utilization.[11] Research has demonstrated that the neighborhood-level income measures may not only account for the aspects of individual-level SES, such as income and education level, but also measure contextual factors of SES, such as access to resources, availability and quality of local services, rates of crime and violence, unemployment rates, and features of the social environment (e.g., social interaction, physical activity).[12,13] – Location of residence (urban vs. rural)
Information on all medications available in NMS database <u>one year prior to the index date</u>	– being on any opioids prescribed in past year (Yes/No) – being on benzodiazepines (Yes/No) – being on barbiturates (Yes/No) – being on cannabinoids (Yes/No) – being on stimulants (Yes/No) – being on testosterone (Yes/No)
Opioid use disorder	
Individuals who were hospitalized for opioid use disorder in the last five years preceding the index date (from CIHI)	Hospitalizations and/or ED visits for (ICD-10-CA codes): • T40.0 (poisoning by opium) • T40.1 (poisoning by heroin) • T40.2 (poisoning by other opioids) • T40.3 (poisoning by methadone) • T40.4 (poisoning by other synthetic narcotics)

	• T40.6 (poisoning by other and unspecified narcotics)[10]
Individuals who were taking narcotics for opioid use disorder in the last year prior the index date (from NMS database)	Anyone taking orally methadone and buprenorphine (including in combination with naloxone, e.g., Suboxone)
Mental and behavioural disorders due to use of opioids (from DAD, NACRS and OMHRS databases) in the last 5 years	(1) from DAD and NACRS (hospitalizations/ED visits): • ICD-10: F11 (Mental and behavioural disorders due to use of opioids. Details are in the Appendix) (2) from OMHRS: • 304.00: Opioid dependence • 305.50: Opioid abuse
Prior comorbidities: Comorbidities at index date that can also affect prescription of opioids: hypertension, diabetes, depression, psychiatric comorbidities, liver disease, asthma, COPD (including severe COPD which may require an opioid prescription), cardiovascular disorders, chronic renal disorder, prior health care utilization and surgical interventions; comorbidities associated with early mortality (e.g., cancer and being on dialysis); conditions that can contribute to sleep disordered breathing such as neuromuscular disorders and alcohol intoxication/abuse.	
17 ICES chronic conditions at the index date (https://datadictionary.ices.on.ca/Applications/DataDictionary/Default.aspx)	Validated algorithms[14-22] were used to ascertain cases of the following 8 chronic conditions: 1. Acute myocardial infarction[20] 2. Asthma[16] 3. Congestive Heart Failure[14] 4. COPD (sensitive cohort)[15] 5. Dementia[17] 6. Diabetes (the Ontario Diabetes Database)[18] 7. Hypertension (the Hypertension Database)[22] 8. Rheumatoid Arthritis (the Ontario Rheumatoid Arthritis Database)[21] The remaining 10 chronic conditions were defined according to inpatient hospital diagnostic codes (at least 1 from DAD) or outpatient physician billing codes (at least 2 from OHIP within a 2-year period): 1. Arrhythmia 2. Coronary Heart Disease 3. IBD 4. Non-psychotic mood and anxiety disorders 5. Osteoarthritis 6. Osteoporosis 7. Other mental health conditions 8. Stroke
Measure of Comorbidity	The Charlson comorbidity index (CCI)[23] 2 years prior to index, aggregated, n (%): • none (CCI score = 0) • low (score = 1) • moderate (score = 2) • high (score ≥ 3)
Presumably moderate to severe COPD	Prevalent COPD from the ICES-derived COPD specific cohort[15]
Hospitalizations with serious liver disease in the	from DAD/SDS: – ICD-9: 5712, 5715, 5716 – ICD-10: K703, K71.7, K74

last 5 years prior the index date	
End stage renal disease, hemodialysis in the last 5 years prior the index date (from DAD, SDS, NACRS, and/or OHIP databases)	• Any hospitalization or same day record from DAD, or NACRS – ICD-9: 4031, 4039, 585, V45.1 – ICD-10: I12, I13, N18.3, 18.4, 18.5, 18.6, 18.9, E08.22, E09.22, E10.22, E11.22, E13.22, Z99.2 • OHIP codes: G860, G861, G862, G863, G864, G865, G866
Cancer	Prevalent cancer from the Ontario Cancer Registry[24]
Number of the office visit, primary care, in the last year prior the index date	Obtain all OHIP records for the desired period, where visit location was in the physician office, LTC (the physician came to a long-term care facility to see the patient), or home (i.e., patient's home)
Any outpatient or inpatient surgical intervention in the last year	From DAD database, using intervention indicator
In the last 5 years	
Alcohol dependence/ intoxication (from DAD, SDS, NACRS, and/or OHIP databases)	• Any hospitalization, ED visit or same day record from DAD, SDS or NACRS – ICD-9: 303, 3050 – ICD-10: E512, F10, G312, G621, G721, I426, K292, K70, K860, T510, X45, X65, Y15, Y573, Z502, Z714, Z721 • OHIP code: 303
Neuromuscular Disease [25] (from DAD, OHIP databases)	– ICD-9, ICD-10 and OHIP codes for the following conditions: Amyotrophic lateral sclerosis, Cerebral palsy, Guillain-Barre syndrome, Metabolic disorders, Multiple sclerosis, Muscular dystrophy, Myasthenia gravis, Neuromuscular disorders (other), Neuropathy, Post-polio syndrome, Spina bifida, Spinal muscular atrophy – For patients identified with OHIP dx349, including only those with subsequent or previous NMD-related ED, hospitalization visit or with subsequent or previous neurologist visit and EMG
Sleep disordered breathing (SDB)-related treatment (positive airway pressure therapy or surgical interventions) **in follow-up**	
PAP treatment initiation (from ADP. Respiratory and ADP. Ventilatory)	Application for Funding Respiratory Equipment & Supplies forms from which data was extracted is available through the ADP website: https://www.ontario.ca/page/respiratory-equipment-and-supplies. Individuals were defined through the ADP Respiratory and Ventilator Equipment Pool as one who received a government funded CPAP, APAP, and bilevel therapy. The date of the PAP claim will be considered as the date of PAP initiation.
Bariatric surgery (from CIHI/DAD/ SDS, procedures; OHIP)	In-patient Bariatric Procedures: • ICD-10-CA – E66, obesity (all codes in category); AND • the Canadian Classification of Health Interventions (CCI) codes: 1NF78 repair by decreasing size, stomach Outpatient bariatric procedures (OHIP FEECODES): • S120 for gastric bypass with Roux-en-Y anastomosis • S114 for sleeve gastrectomy • S189 for intestines-intestinal bypass for morbid obesity
Maxillomandibular advancement (MMA)/ uvulopalatopharyngoplasty (UPPP) (from CIHI/DAD/ SDS, procedures)	CCI codes: • MMA: 1EE79 • UPPP: 1FQ78LA

ADP, Assistive Devices Program Database; DAD, Discharge Abstract Database (Canadian Institute for Health Information); NACRS, National Ambulatory Care Reporting System Metadata (Canadian Institute for Health Information); CCI, Canadian Classification of Health Interventions; COPD, chronic obstructive pulmonary disease; ED, emergency department; ICD, International Classification of Diseases; NMS, Narcotics Monitoring System; OHIP, the Ontario Health Insurance Plan Database; OMHRS, the Ontario Mental Health Reporting System; PAP, positive airway pressure; RPDB, the Registered Persons Database; SDS, Same Day Surgery; SDB, sleep disordered breathing.

*Given a small sample size for the opioid-related outcome within the first year since the index date, we extended the follow-up for this outcome until the end of the study (March 31, 2018) to increase statistical power.

Table E2: The results of the multivariable Cox regression analysis on the association between opioid-related characteristics and the primary outcome, all-cause mortality within the first year since the diagnostic sleep study, in adults who underwent a diagnostic sleep study between 2013 and 2016 while being treated with prescription opioids. Estimates are presented as adjusted hazard ratios and 95% confidence intervals.

Variables considered in the statistical model		All-cause Mortality within the first year since the diagnostic sleep study Hazard Ratio (95% CI)	
Opioid-related characteristics			
Chronic opioid use vs. not		**1.84**	**(1.12-3.02)**
Being on more than one opioid at the index date vs. not		0.98	(0.67-1.44)
MED >90 vs. ≤90 mg/day		1.18	(0.80-1.74)
Demographics at the index date [the date of the diagnostic sleep study]			
Age, years, per one year increase		**1.04**	(**1.03-1.06)**
Sex: Female vs. Male		0.89	(0.67-1.20)
Neighbourhood Income Quintile (Q)	Q2 vs. Q1 (lowest)	0.75	(0.51-1.10)
	Q3 vs. Q1 (lowest)	0.77	(0.52-1.16)
	Q4 vs. Q1 (lowest)	0.58	(0.36-0.94)
	Q5 (highest) vs. Q1 (lowest)	0.83	(0.52-1.32)
Rurality: No vs Yes		0.78	(0.55-1.12)
Comorbidities, primary health care exposure, surgical interventions and controlled substance use in the last year prior to the sleep study			
Charlson Comorbidity Index (CCI)	High (CCI =3) vs. None (CCI = 0)	**3.67**	(**2.30-5.86)**
	Moderate (CCI =2) vs. None (CCI = 0)	**2.32**	(**1.38-3.89)**
	Low (CCI =1) vs. None (CCI = 0)	**2.00**	(**1.24-3.21)**
Number of Primary Care Visits, per unit increase		1.00	(0.99-1.02)
Surgery/Intervention Indicator: Yes vs. No		0.74	(0.47-1.17)
Number of Hospitalization/ED Visits, per unit increase		1.01	(0.97-1.06)
Benzodiazepines Dispensed		**1.10**	(**0.82-1.48)**
Comorbidities defined in the last five years prior to the sleep study: Yes vs. No			
Alcohol Dependence/intoxication		**1.73**	(**1.05-2.83)**
Neuromuscular Disease		1.40	(0.94-2.08)
Prevalent comorbidities: Yes vs. No			
Arrythmia		1.20	(0.82-1.76)
Chronic heart failure		1.46	(1.00-2.13)
Chronic obstructive pulmonary disease		**2.16**	(**1.58-2.96)**
Coronary artery disease		0.94	(0.67-1.31)
Diabetes		1.04	(0.75-1.43)
Hypertension		1.13	(0.77-1.66)
Non-psychotic Mood and Anxiety Disorders prevalent		0.95	(0.69-1.30)
Cancer		**1.53**	(**1.06-2.21)**
Prior opioid use disorder			
Any Opioid Use Disorder Indication*: Yes vs. No		1.01	(0.55-1.87)
Follow-up-related variables			
OSA-relevant treatment in follow-up		0.86	(0.61-1.23)

In bold: statistically significant associations.

* Any opioid use disorder indication: hospitalizations/ED visits for opioid use disorder or mental and behavioural disorders due to the use of opioids 5-years prior to the index date or taking narcotics for opioid use disorder 1-year prior to the index date.

CCI, Charlson Comorbidity Index; ED, emergency department; MED, morphine equivalent daily dose.

Table E3: The effect of the prescription of benzodiazepines in the last year prior to the sleep study on the relationship between opioid characteristics and the outcome of the interest.

Description	All-cause Mortality-1yr	P-value*	All-cause ED Visit1-yr	P-value*	All-cause Hospitalization-1yr	P-value*	Opioid Poisoning Related ED Visit and/or Hospitalization	P-value*
The effect of chronic opioid use on outcomes								
Prescription of benzodiazepines in the last year: No	1.86 (0.99-3.48)	0.8842	1.08 (0.99-1.18)	0.9579	**1.21 (1.06-1.39)**	0.1665	2.69 (0.81-8.96)	0.5107
Prescription of benzodiazepines in the last year: Yes	1.72 (0.77-3.84)		1.08 (0.95-1.23)		1.03 (0.85-1.25)		1.58 (0.56-4.45)	
The effect of morphine equivalent daily dose (MED) on outcomes								
Prescription of benzodiazepines in the last year: No	**1.95 (1.18-3.23)**	0.0043	1.01 (0.91-1.11)	0.6136	1.10 (0.96-1.27)	0.5609	**3.34 (1.71-6.52)**	0.1591
Prescription of benzodiazepines in the last year: Yes	0.64 (0.36-1.14)		1.05 (0.94-1.16)		**1.17 (1.01-1.36)**		**1.85 (1.14-3.01)**	

*p-values for the statistical interaction term

ED, emergency department

Table E4: The association between opioid maintenance therapy (OMT) at the date of the sleep study and opioid dosage change at the first refill and opioid discontinuation within 180 days of the date of the sleep study. Estimated presented as adjusted hazard ratios and confidence interval.

Opioid-related characteristics	**All-cause Mortality-1yr**	**All-cause ED Visit-1yr**	**All-cause Hospitalization-1yr**	**Opioid Poisoning Related ED Visit and/or Hospitalization**
	N= 205	N= 6,887	N= 3,077	N=213
At the index date (date of the sleep study), N = 15,678				
OMT: Yes vs. No	1.22 (0.43-3.42)	0.85 (0.72-1.00)	0.80 (0.61-1.04)	1.55 (0.93-2.57)
Changes in dose within 180 days since the index date, N = 14,532				
No refill within 180 days: Yes vs. No	**0.06 (0.02-0.18)**	0.95 (0.89-1.01)	**0.88 (0.80-0.96)**	**0.48 (0.31-0.77)**
Dose reduction at the first refill	1.16 (0.83-1.61)	**1.11 (1.04-1.17)**	**1.18 (1.08-1.28)**	1.38 (0.99-1.91)
Dose increase at the first refill	0.89 (0.52-1.50)	**1.24 (1.13-1.35)**	**1.26 (1.11-1.43)**	0.69 (0.37-1.30)
The same dose at the first refill	Reference	Reference	Reference	Reference

In bold: statistically significant associations.

ED, emergency department; OMT, opioid maintenance therapy

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