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

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Chapter 2:
Overall study methods

Overview

This chapter summarizes key data sources and study methods used throughout the studies described in Parts II, III and IV of this thesis. This includes considerations related to the populations studied, databases used, and general methods implemented.

Data Sources

IMS BROGAN GEOGRAPHIC PRESCRIPTION MONITOR (IMS BROGAN)

The analyses reported in Chapters 8 and 9 used the IMS Brogan Geographic Prescription Monitor database which provides aggregated estimates of both publicly and privately funded prescriptions for long-acting oxycodone dispensed in Canada over the relevant study periods. This database captures data from a representative sample of 5700 retail pharmacies across Canada, which is projected to estimate monthly dispensing estimates by geographic area at the levels of product formulation and strength. In these estimates several factors are taken into account, including the number of pharmacies in a given region, the distance between IMS-captured and uncaptured pharmacies, and the size of the pharmacies. IMS Brogan continuously monitors data received from retail pharmacies to ensure they meet standards set for quality control, and that the resulting product-level volume estimates are representative of all pharmacies in Canada. For Chapters 8 and 9, this database was used to determine the volume of long-acting oxycodone dispensed in regions close to the United States-Canada border.

INSTITUTE FOR CLINICAL EVALUATIVE SCIENCES (ICES)

The Institute for Clinical Evaluative Sciences (ICES) is a not-for-profit research institute in Ontario, Canada that houses a large, linked repository of health databases that are accessible to the research community (www.ices.on.ca). The remaining studies reported here leverage these administrative databases to conduct population-based observational studies among residents of Ontario. Two key databases that are used regularly in these analyses are:

Ontario Drug Benefit (ODB) Database

The Ontario Drug Benefit (ODB) database captures all prescription medications dispensed at retail pharmacies in Ontario and reimbursed by the Ontario Public Drug Programs (OPDP). The eligible population for OPDP includes people with low socio-economic status, receipt of disability support or home care services, high drug costs compared to income, residence in a long-term care facility, or age ≥65 years. This database captures detailed drug information, patient identifiers, quantity

dispensed and days' supply for all such reimbursed prescriptions and is linked to other health databases housed at ICES. Therefore, these data were used to identify individuals in receipt of publicly-funded opioid prescriptions throughout our studies.

Opioid-Related Death Database

All deaths that are sudden and unexpected or unnatural are investigated by the Office of the Chief Coroner of Ontario (OCCO) to ascertain cause and manner of death. All charts for deaths that involved opioids (either alone or in combination with alcohol) between 1991 and 2013 were abstracted from the OCCO to capture key information relating to cause of death, results of post-mortem toxicology, manner of death, and patient demographics and identifiers. Opioid-related deaths were defined by the coroner as those deaths in which postmortem toxicologic analyses revealed opioid concentrations sufficiently high to cause death, or if a combination of drugs (including at least one opioid at clinically significant levels) contributed to death. Deaths were not defined as opioid-related if another drug was present on the toxicologic analysis at concentrations sufficient to cause death. This database has been regularly updated over the past 7 years with new data as it becomes available using consistent abstraction tools and methods, and has been linked to the data warehouse at ICES for research purposes.

Study Population

Because ICES only collects prescription data for Ontarians eligible for public drug benefits, studies relying on linked prescribing data (Chapters 5, 6, 7, 10, and 11) are limited to the OPDP population represented in the ODB database. As described above, this generally represents a group of individuals of lower socioeconomic status, those requiring disability support, and those aged 65 or older. In contrast, studies using IMS Brogan data (Chapters 8 and 9) and those using the Coroners' Opioid-Related Death Database (Chapters 3, 4) do not have such restrictions and are representative of the general population.

Converting Opioid Dose

Several studies reported here rely on the conversion of oral and transdermal opioid doses into milligrams of morphine equivalents (MME). Approximate conversion ratios reported in the Canadian guidelines[1] were used in these calculations as described in Table 2.1 below. These conversion ratios are aligned with those reported in several other international sources.[2]

Table 2.1: Morphine equivalents for oral opioid analgesics*

Opioid	Ratio (opioid to morphine)
Morphine	1:1
Codeine	1:0.15
Oxycodone	1:1.5
Hydromorphone	1:5
Meperidine	1:0.1
Transdermal fentanyl	
25 µg/h	*1:97*
50 µg/h	*1:202*
75 µg/h	*1:292*
100 µg/h	*1:382*

*Adapted from Canadian guideline for safe and effective use of opioids for chronic non-cancer pain[1]

Disease Risk Score

A disease risk score was used in the nested case-control studies reported in Chapters 5, 6, and 7 to minimize differences in patient characteristics between cases and controls. This index was derived using a multivariate regression model to generate predicted probabilities of becoming a case for all individuals in the nest, adjusting for a number of potential confounders, as outlined in Table 2.2 below.[3] Controls were then matched to cases on this risk score within ±0.2 standard deviations.

Table 2.2: Components of Disease Risk Score used to Match Cases to Controls on past comorbidities

Variable	ICD9 Diagnosis Code	ICD10 Diagnosis Code	OHIP Diagnosis Code
Demographic Characteristics (measured on index date)			
Age	Age on index date		
Sex	Patient sex		
Estimated residential income quintile	Neighbourhood Income Quintile based on location of residence on index date (1=lowest, 5=highest)		
Residence in a long-term care facility	Based on Long-Term Care flag on most recent Ontario Drug Benefit database prescription in past 1 year		
Rurality of Principal Residence	Rural community defined as community with ≤10,000 residents		
Medical disorders (measured by presence in 3 years prior to index date)			
Acute myocardial infarction	410	I21	410, 413
Alcohol abuse	V113, 291, 303.0, 303.9, 305.0, 357.5, 425.5, 535.3, 571.0, 571.1, 571.3, 790.3, 980.0	F10, G31.2, G62.1, G72.1, I42.6, I70.0, K29.2, K70.1, K70.4, K70.9, K86.0, R78.0, T51.0, X65, Y15, Y91, Z50.1, Z71.4, Z86.40	291, 303
Atherosclerotic disease	414.0, 440	I251, I70	440
Chronic lung disease	490.0, 491, 492.0, 494.0, 496.0	J40-J44, J47	491, 492, 494, 496
Dementia	290, 331.0, 331.1, 331.2, 797	F00, F01, F02.0, F02.1, F03, F05.1, G30, G31.0, G31.1, R54	290, 331, 797
Diabetes mellitus	Defined as diagnosis date in Ontario Diabetes Database that precedes the index date		
Dyslipidemia	272.0-272.6, 272.9	E78.0-E78.6, E78.9, E88.1, H02.6	272
Gastrointestinal hemorrhage	531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.2, 533.4, 533.6, 534.0, 534.2, 534.4, 534.6, 578.0, 578.1, 578.9	K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K92.0, K92.1, K92.2	
Glaucoma	365	H40, H42	365
Gout	274	M10	274
Heart failure	428	I50	428

Hypothyroidism	244.1, 244.3, 244.8, 244.9	E01.8, E02, E03.2, E03.3, E03.5, E03.8, E03.9, E89.0	244
Injury other than poisoning	8XX, 90-95	S* T00-T35	
Osteoarthritis	715	M15.0-M15.2, M15.4, M16-M19, M89.41-M89.43, M89.45-M89.46, M89.48	715
Other coronary heart disease	411.0, 412.0, 413.0, 414.0, 414.8, 414.9	I20, I24.0, I24.8, I24.9, I25.1, I25.2, I25.5, I25.6, I25.8, I25.9	412
Parkinson's disease	332.0-332.1	G20, G21.1, G21.2, G21.3, G21.8, G21.9, G22	332
Pneumonia	480-486	J10-J18	486
Poisoning or drug toxicity	96-98	T36-T65	977
Rheumatoid arthritis	714.0-714.4, 714.8	M05, M06, M08.0, M08.2-M08.4, M08.8, M08.9, M09, M12.0	714
Seizure disorder	780.3, 345	R56.0, R56.8, G40, G41	345
Sepsis	038	A40, A41	
Stroke	430-438	I60, I61, I62, I63, I64, G45	432-436
Urinary incontinence	788.3	N39.3, N39.4, R32	
Psychiatric disorders (measured by presence in 3 years prior to index date)			
Affective disorder	296	F30, F31, F32.2, F32.3, F32.8, F33, F34.8, F34.9, F38, F39	296
Anxiety or sleep disorders	300	F32.0, F34.1, F40-F42, F44, F45.0-F45.2, F48, F68.0, F99	300

Psychoses, agitation, and related disorders	292, 293.0, 293.8, 294, 295, 297.1, 297.3, 297.8, 297.9, 299	F02.2-F02.4, F02.8, F04, F05.0, F05.8, F05.9, F06.0-F06.6, F06.8, F06.9, F09, F11.0, F11.3-F11.9 F12.0, F12.3-F12.9 F13.0, F13.3-F13.9 F14.0, F14.3-F14.9 F15.0, F15.3-F15.9 F16.0, F16.3-F16.9 F17.0, F17.3-F17.9 F18.0, F18.3-F18.9 F19.0, F19.3-F19.9 F20-F22, F23.2, F24, F25, F53.1, F84	295, 297
All other mental disorders	301, 302.2-302.9, 304.0-304.6, 304.9, 305.1-305.7, 305.9, 306.4, 306.5, 306.8, 306.9, 307, 308.3, 308.9, 309.0, 309.2, 309.8, 310.1, 310.2, 310.8, 310.9, 311.0, 312.0-312.3, 312.8, 312.9, 313.0, 313.2, 313.3, 313.8, 313.9, 314.0, 314.2, 314.8, 314.9, 315, 316.0	F06.7, F07, F11.1, F11.2 F12.1, F12.2 F13.1, F13.2 F14.1, F14.2 F15.1, F15.2 F16.1, F16.2 F17.1, F17.2 F18.1, F18.2 F19.1, F19.2 F32.9, F43, F45.3, F45.4, F45.8, F45.9, F50, F51, F52, F53.0, F54-F59, F60-F66, F68.1, F68.8, F69, F80-F83, F88-F95, F98, G44.2	301, 302, 304, 305, 306-316
Other Variables			
Suicide attempt in 3 years prior to index date	95.0-95.9	X60-X84	
Number of visits to a physician in the past 1 year prior to index date	Count only one Ontario Health Insurance Plan claim per person per physician per day.		
Care by a psychiatrist in 1 year prior to index date	Main Specialty in ICES Physician Database = "PSYCHIATRY"		
Days in hospital during 1 year prior to index date	Sum of total length of stay of all hospitalizations discharged in prior year		

References

1. National Opioid Use Guideline Group. Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain. 2010; http://nationalpaincentre.mcmaster.ca/opioid/. Accessed November 27, 2016.
2. Nielsen S, Degenhardt L, Hoban B, Gisev N. A synthesis of oral morphine equivalents (OME) for opioid utilisation studies. *Pharmacoepidemiology and drug safety.* 2016;25(6):733-737.
3. Arbogast PG, Ray WA. Use of disease risk scores in pharmacoepidemiologic studies. *Stat Methods Med Res.* 2009;18(1):67-80.