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Evaluating the intended and unintended consequences of opioid prescribing interventions on primary care in British Columbia, Canada: protocol for a retrospective population-based cohort study

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ABSTRACT

Introduction: Between 2015 and 2018, there were over 40,000 opioid-related overdose events and 4,551 deaths among residents in British Columbia (BC). In response, the province mobilized a variety of policy levers to encourage physicians to expand access to opioid agonist treatment (OAT) and the College of Physicians and Surgeons of British Columbia (CPSBC) released practice standards establishing legally enforceable minimum thresholds of professional behaviour. Our goal is to conduct a comprehensive investigation of the intended and unintended consequences of these policy changes.
Methods and analysis: This is a population-level, retrospective cohort of all BC primary care physicians who prescribed any opioid medication for opioid use disorder or chronic non-cancer pain during the study period, and their patients. The study period is 1 January 2013 to 31 December 2018, with a one year wash-in period (1 January 2012 – 31 December 2012) to exclude patients on long term opioid treatment (LTOT) whose pain type (i.e. "chronic non-cancer", "acute", "cancer or palliative", or "other") cannot be confirmed. The project combines five administrative health datasets under the authority of the BC Ministry of Health, with the CPSBC's Physician Registry, BC Cancer's Cancer Registry, and Vital Statistics' Mortality data. We will create measures of prescribing concordance, access, continuity, and comprehensiveness to assess primary care delivery and quality at both the physician and patient level. We will use generalized estimating equations, interrupted time series, mixed effects models and funnel plots to

identify factors related to changes in prescribing and evaluate the impact of the changes to prescribing policies.

Ethics and dissemination: This study has been approved by McGill University's Institutional Review Board (#A11-M55-19A), and the University of British Columbia's Research Ethics Board (#H19-03537). We will disseminate results via a combination of open access peer-reviewed journal publications, conferences, lay summaries, and OpEds.

ARTICLE SUMMARY

STRENGTHS AND LIMITATIONS

- This is a population level study of all primary care physicians in British Columbia (approximately 6000, 1200 of which prescribed at least one OAT during the study period) and their patients (>4.6 million) over six years (2013 – 2018)
- By working with a comprehensive dataset, master drug lists and validated coding algorithms in a context where the majority of health services are provided at no cost and all prescription drug dispensations are recorded, we have minimized the potential for misclassification and capture as many patients as possible outside of a strict longitudinal cohort study.
- We use a combination of methods and explore the effects of the prescribing policies from both the physician and patient perspectives
- We are unable to operationalize and evaluate adherence to all stipulations in the practice standards (i.e. documentation of discussions for non-pharmaceutical alternatives or take home naloxone kits, pill counts or urine tests)

Introduction

Between 2015 and 2018, there were over 40,000 opioid-related overdose events and 4,551 deaths among residents in British Columbia (BC).[1-4] The annual provincial overdose mortality rate rose to 30.8 deaths per 100,000 population, and for Vancouver's Downtown Eastside exceeded 100 deaths per 100,000 population.[5,6] In response, the province mobilized a variety of policy levers to encourage physicians and nurse practitioners to expand access to opioid agonist treatment (OAT) including open listing buprenorphine in the PharmaCare and First Nations Health Benefits programs,[7] and amending existing fees and introducing new ones to better compensate physicians who provide treatment for opioid use disorder (OUD).[8,9] Concurrently, the BC Centre on Substance Use (BCCSU) developed provincial guidelines and began offering comprehensive education and training for prescribers of OAT.[10] Meanwhile, the College of Physicians and Surgeons of British Columbia (CPSBC) released *Safe Prescribing of Drugs with Potential for Misuse/Diversion* practice standards (Box 1) to "prevent an increasing toll of prescription drug misuse and overdose deaths".[11] These practice standards established legally enforceable minimum thresholds of professional behaviour; and non-compliant physicians can be disciplined or fined.[12,13]

People with OUD are consistently marginalized and stigmatized from mainstream healthcare delivery systems,[14,15] relying on expensive and fragmented care from emergency departments and walk-in clinics to address their acute and chronic medical conditions.[16,17] Policies aimed at expanding the provision of OAT may therefore have positive spillover effects beyond the benefits of the treatment itself. An expanded pool of prescribers, mostly family medicine physicians, may enable access to primary care services; improving continuity of care and reducing the use of walk-in clinics and emergency departments.[18-21]

Conversely, the CPSBC's practice standards may have inadvertently restricted access to quality primary care for patients with chronic-non cancer pain.[22] Across Canada and the United States there is growing anecdotal evidence that opioid prescribing guidelines have negatively affected people who could benefit from opioids.[23,24] Incorrect interpretations of the standards can result in aggressive weaning without consent, cause debilitating pain and serious withdrawal symptoms, strain patient-physician relationships, and increase risk of overdose for patients who self-medicate for pain relief.[25-31]

Study Objectives

Our goal is to conduct a comprehensive investigation of the intended and unintended consequences of the changes to OAT prescribing and the CPSBC's practice standards for patients and primary care physicians in British Columbia. To meet this objective, we will:

1. *Examine the uptake of OAT prescribing and the adoption of the CPSBC's practice standards among primary care physicians*:
   - RQ[1] 1.1 How do physicians who begin prescribing OAT between 2016 and 2018 differ from those who do not, and with providers already offering OAT prior to recent prescribing changes?
   - RQ 1.2 To what extent do physicians vary in adopting the CPSBC's practice standards?
   - RQ 1.3 What are the effects of the practice standards on prescribing patterns of long-term opioid treatment (LTOT)?
   - RQ 1.4 What physician characteristics are associated with ceasing prescription of controlled substances, and with terminating primary care for patients on LTOT?
2. *Determine the effects of the changes to opioid prescribing on primary care for patients:*
   - RQ 2.1 What are the characteristics of patients who are newly-prescribed OAT (2016 – 2018)?
   - RQ 2.2 What are the characteristics of patients who experience rapid tapering and/or termination with their primary care provider following the release of the CPSBC's practice standard?

[1] RQ=Research Question

RQ 2.3 Do patients who begin receiving OAT experience changes in primary care access, continuity, or comprehensiveness?

RQ 2.4 Do patients treated with LTOT experience changes in primary care access, continuity, or comprehensiveness following implementation of the new practice standards?

Methods and Analysis

Study Setting

British Columbia is Canada's most western province, and has a population of approximately 4.8 million residents. There are over 1200 OAT prescribers[32] among approximately 6000 primary care physicians and addictions specialists[33].

In 2012, fentanyl was first detected in the illicit drug supply, and 4% of the province's 270 overdose deaths were fentanyl-related.[2] By 2018, fentanyl was detected in over 80% of the province's 1,535 drug overdose deaths.[34] In response to rapidly escalating rates of opioid-related overdose events and deaths, Dr. Perry Kendall, the Provincial Medical Health Officer at the time, declared a public health emergency in April 2016.[35] The declaration enabled the BC Centre for Disease Control, Ministry of Health, Regional Health Authorities, BC Coroner Services and related stakeholders to quickly expand surveillance efforts and adopt new harm reduction interventions (e.g. overdose prevention sites, Take Home Naloxone programs), while the Ministry of Health and the College of Physicians focused on supply side interventions to prevent overdose deaths.[35]

Data Sources and Linkages

This project combines five administrative health datasets under the authority of the BC Ministry of Health, with the CPSBC's Physician Registry, BC Cancer's Cancer Registry, and Vital Statistics' Mortality data (Table 1). Population Data BC, a multi-university data resource, will provide secure access to individual level, linked and de-identified data for our research purposes.

Study Design and Study Population

This is a population-level, retrospective cohort of all BC primary care physicians who prescribed any opioid medication for opioid use disorder or chronic non-cancer pain during the study period, and their patients. The study period is 1 January 2013 to 31 December 2018, with a one year wash-in period (1 January 2012 – 31 December 2012) to exclude patients on LTOT whose pain type (i.e. "chronic non-cancer", "acute", "cancer or palliative", or "other") cannot be confirmed (Figure 1).

The cohort will include all primary care physicians and their patients using the CPSBC's Physician Registry, and MSP billings. We will use PharmaNet data to identify all physicians (including specialists) who prescribed any opioid during the study period so we can determine the physician who initiated each opioid prescription. For all patients, MSP, NACRS and DAD will provide complete health service use history during the wash-in and study periods; indicate the types of services the prescription initiating physician provides; and enable us to control for patient level comorbidities. DAD and Mortality data will be used to identify patient sub-populations who are disproportionately harmed by the changes. All records in the MSP, NACRS, DAD and PharmaNet files include de-identified physician and referring practitioner numbers for referral pattern purposes.

Operationalized measures:

We will operationalize a series of variables using our linked dataset (Tables 2 and 3).

Analysis Plan for Each Objective

[2] Illicit overdose events include indication of street drugs (controlled and illegal: heroin, cocaine, MDMA, methamphetamine, illicit fentanyl), and medications not prescribed to the decedent but obtained/purchased on the street, from unknown means, or where origin of drug not known.

Data will be prepared using SAS (V.9.4, SAS Institute, Cary, USA) and statistical analyses will be performed using R (V.3.2.5). In general, missing and incomplete data will be excluded from analyses and the number of observations omitted from analyses due to missing data will be documented. If any imputation is used, the method and extent will be reported. We will report p-values <0.05 and 95% confidence intervals.

Physicians' uptake of OAT prescribing and the adoption of the CPSBC's standards:

To examine the differences between primary care physicians who begin prescribing OAT to patients with OUD and those who do not **(RQ1.1)** – we will restrict our analysis to OAT-naïve physicians (i.e. never prescribed OAT during the three year wash-in period: 2012 – 2014, inclusive), and saw OAT-naïve patients with indication of an OUD between 2015 and 2018, inclusive. This will allow us to examine the cohort of physicians who were susceptible to OAT expansion interventions. We will use generalized estimating equations (GEE) for logistic regression to identify physician-level characteristics (e.g. age, sex, years since training completion, geography, practice type, and prescribing history) associated with OAT prescribing. These nonparametric models allow us to account for the repeated measures and hierarchical structure of our data by specifying joint distribution in their random effects terms, and are well-suited to identifying population average differences.[36,37] We will repeat the analysis to compare physician characteristics associated with new OAT prescribing (i.e. first prescription post-2015) compared with early adopters (i.e. primary care physicians prescribing OAT pre- 2015).

To understand the extent to which physicians vary in adopting the CPSBC's practice standards **(RQ1.2)** – we will restrict analysis to physicians who prescribed LTOT between June 2014 and May 2016 and again during the effective period of the CPSBC's practice standards (June 2016 – May 2018). We will use funnel plots[38] to quantify the extent of deviation in prescription concordance[3] at the physician-level before and after the implementation of the practice standards. Physicians whose observed proportion of non-concordant prescriptions remains above the upper 95% control limits of the expected proportion of non-concordant fills (given the number of prescriptions they prescribed, and controlling for patient and geographic differences) following the implementation of the standards, will be compared with primary care peers whose prescribing becomes concordant. We will use mixed effects models to identify physician characteristics associated with non-concordance.[39-43]

To estimate the effects of the practice standards (June 2016) on usual prescribers of care's LTOT prescriptions **(RQ1.3)** – we will use interrupted time series (ITS) analysis. ITS is a quasi-experimental study design that estimates the effects of service or policy interventions before and after implementation in contexts where randomized controlled trials are not feasible or ethical.[44,45] The advantage of this before-after comparison with a single population is that selection bias and confounding due to between-group differences are limited; and within-group characteristics that change slowly over time (e.g. physician characteristics), secular changes, random fluctuations from one time point to the next and regression to the mean are also controlled.[46] The primary assumption for ITS is that without the intervention (here the introduction of the CPSBC's practice standards) the observed pre-intervention outcome trends would continue unchanged into the post-intervention period.[47] This assumption is supported by Crabtree et al.'s (2019)[48] work which found no change in trends of defined daily dose of opioids prescribed pre- vs. post-implementation of the practice standards. Additionally, to our knowledge there were no other interventions that would affect physician prescribing of LTOT implemented during our study period. Using this method, we will look at the effects of the practice standards on the number of LTOT prescriptions filled with: a) a daily dose greater than 90 MME; b) a benzodiazepine co-prescription; and c) a supply that exceeds 3 months or 250 tablets (whichever is less). We will also look at d) the number of physicians who terminate any controlled substance; and e) the number of LTOT prescriptions terminated. We selected these outcomes because the CPSBC's primary aim for establishing the practice standards was to reduce prescription drug misuse. However, we would also like to quantify the extent of inappropriate treatment cessation, as suggested by mounting anecdotal evidence.

[3] Concordance prior to the implementation of the CPSBC's practice standards (June 2014 – May 2016) will be an artificial measure used to identify physician outliers susceptible to the effects of the practice standards post-implementation.

Given the potential rarity of the outcomes, we will aggregate counts to eight quarterly periods pre- and post-implementation (pre-intervention: June 2014 – May 2016; post-intervention: June 2016 – May 2018). We will use the 2-sided Durbin-Watson test, plot of residuals, and autocorrelation plots to identify and adjust for autocorrelation and moving averages where necessary. We will test the hypothesis that the practice standards had no effect on these outcomes using ordinary least squares and segmented regression.

Lastly, we will use GEE for logistic regression, and GEE for Poisson or negative binomial distribution to identify physician characteristics associated with any controlled substances cessation, and with counts of treatment termination between 2016 and 2018, respectively (**RQ1.4**). Negative binomial models are similar to Poisson models with the exception that the mean and variance of the count data do not have to be the same. These models include an additional parameter to handle over-dispersion in the data, and are well-suited for zero inflation, and unobserved heterogeneity in the data.[49,50] To determine which of the two model types is best suited to the data, we will use Pearson chi-square dispersion statistics and residual plots.[50,51]

Effects of the changes to opioid prescribing on primary care for patients:

We will use GEE for logistic regression to identify patient-level characteristics (e.g. age, sex, geography, comorbidities,[52] contraindications) associated with OAT initiation between 2015 and 2018 among OAT naïve patients (no OAT prescription filled between 2012 and 2014, inclusive) with indication of OUD **(RQ 2.1)**. For patients on LTOT as of June 2016, we will use GEE to identify patient-level characteristics associated with inappropriate treatment termination (including rapid tapering) **(RQ2.2)**.

For **RQ 2.3** – we will use a variety of multiple linear (or linearized, where appropriate) regression models to measure the population-level association between expanded provision of OAT defined as the number of primary care physicians newly prescribing OAT as of 2015 (OAT prescribing naïve 2012 – 2014) and changes to patients' access, continuity and comprehensiveness of primary care (independently), while controlling for patient-level characteristics (e.g. age, sex, geography, indication of OUD, comorbidities,[52] and contraindications). Models will include a lag for the potential delayed effects between expanded provision of OAT and our outcomes. Lags between the number of physicians prescribing OAT and primary care outcomes will be estimated using the weighted cumulative approach[53-55] and informed with expert input from our knowledge users/stakeholders[56,57]. We anticipate at least a one year lag between expanded OAT provision and changes in access, continuity and comprehensiveness of care given how these measures will be constructed.

To measure the effects of the practice standards on patients' access, continuity and comprehensiveness of primary care **(RQ2.4)** – we will use controlled ITS analysis. This modified method allows us to account for time-varying confounders that may have influenced the delivery of primary care. Patients on LTOT just before the implementation of the practice standards will be matched with diabetic patients whose pharmacotherapy is overseen by the same physician, and on age, sex, Charlson comorbidity index, and treatment initiation month.[52] Diabetes patients were selected as our negative control group because:

1. The majority of diabetes care is provided in primary care settings;
2. There were no contemporaneous policies affecting diabetes pharmacotherapy prescribing behaviours during the study period;
3. Opioid prescribing standards are not expected to affect diabetes pharmacotherapy prescriptions;
4. There are clear practice guidelines for physicians treating patients with diabetes, including frequency of physician oversight, which are similar to the guidelines for patients on long-term opioid treatments;[58] and
5. Prescription disruptions (e.g. termination, change in prescriber) are unusual for this patient population.

We will use 24 monthly intervals pre- and post-implementation for a total of 48 time periods between June 2014 and May 2018 (inclusive). At each interval, the outcome measure will be assessed for each patient dispensed a prescription during that month (LTOT for exposed, diabetes drug for matched controls). We

will test our hypothesis of no change in access, continuity or comprehensiveness of care using ordinary least squares and segmented regression, by fitting the following regression model, per outcome:

$$\begin{aligned}\text{Outcome}_{jkt} = {} & \beta_0 + \beta_1 \text{time}_t + \beta_2 \text{group}_k + \beta_3 \text{group}_k \text{time}_t + \beta_4 \text{level}_{jt} + \beta_5 \text{trend}_{jt} + \beta_6 \text{level}_{jt} \text{group}_k \\ & + \beta_7 \text{trend}_{jt} \text{group}_k + \varepsilon_{jkt}\end{aligned}$$

where *j* is the intervention, *t* is the study time in monthly intervals pre- (negative time) and post-intervention (positive time), and *k* distinguishes between intervention and control group. Significant values for coefficients β_6 and β_7 will indicate an effect of the practice standards on patients' access, continuity and comprehensiveness of primary care after accounting for level and trend changes among diabetic controls.

Ethics and dissemination

McGill University's Institutional Review Board (Certificate Number: A11-M55-19A) and the University of British Columbia's Research Ethics Board (Certificate Number: H19-03537) approved this study.

All data used in this project will be linked using de-identified personal health numbers or physician practice numbers. The data will be stored in Population Data BC's Secure Research Environment, a central server for data storage and analysis, including encrypted backups, software, and other services to ensure compliance with data access requirements.[59] All members of the research team who will have access to the data have had the necessary tri-council privacy training and will complete privacy training provided by Population Data BC. Study results will be screened by data stewards prior to publication to ensure privacy and confidentiality requirements are maintained, there is no gross misuse of the data, and data is appropriately referenced. Linked data will remain within Population Data BC's Red Zone (terminals with no external connection) for up to seven years after project completion before being destroyed by authorized data personnel.

Patient and Public Involvement

As part of the project's development, we recruited a patient-partner with lived experience from the Patient Voices Network. Through a series of meetings, the patient-partner has informed the research aims of the project, and outcome measures of interest. This patient-partner will remain an integral member of the team assisting in the interpretation of patient-level results and knowledge dissemination efforts. As this project uses secondary administrative data, no additional patients were recruited for the conduct of the study.

Discussion

Our objective is to evaluate the effects of interventions aimed to improve access to OAT and limit overprescribing of opioid analgesics on physician prescribing behaviour and patient access to comprehensive primary care. Given the potential for patient harm, it is important to understand the effects of the interventions to prevent over/under-prescribing of opioids, and to mitigate the effects of exacerbating or introducing new inequities in access to health care. We will use a variety of health service delivery outcomes and address limitations of existing research. Results from Aim 1 will be useful for isolating the effects of the interventions on physician prescribing behaviour, and to identify physician characteristics associated with high-error prescribing in light of the new standards. Results from Aim 2 will estimate the effects of the interventions on patients' recent primary care experiences; and enable policy makers and physicians to identify potential subgroups harmed by the recent changes in prescribing. Together, these results will provide invaluable information on the effects of recent opioid prescribing policies at both the patient and prescriber level, and equip policy makers and regulatory colleges with the much-needed information to understand the intended and unintended consequences of opioid prescribing interventions to fine-tune their policies.

The primary challenge of this project relates to the use of administrative health data to create quantifiable measures of access, continuity and comprehensiveness of care. In settings without comprehensive records of service use or where access to services and treatment is restricted, such methods can lead to under-ascertainment and estimation of key patient groups (e.g. people with OUD) and undercounting primary care

service use/provision.[60] For example, reliance on administrative data to accurately identify patient health needs (e.g. opioid use disorder, chronic pain) may lead to misclassification. However, by working with the comprehensive dataset described above in a context where the majority of health services are provided at no cost, and by applying modern surveillance methods[61] we minimize the potential for misclassification, and capture as many patients as possible outside of a strict longitudinal cohort study[62]. Of note, while most provinces (e.g. Quebec) lack access to complete drug dispensation records for their populations, BC is unique in that it includes all outpatient prescription fills for all residents, irrespective of payer within PharmaNet's data file. These complete records, along with the BC Cancer Registry enable the cross-validation of patient pain type identified using algorithms which rely on inpatient and outpatient records only, and allow us to work around the issue of inadequate specificity in ICD coding described elsewhere.[63] Further, recognizing the limitations of working with administrative data, we have intentionally recruited primary care physicians, members of the BCCSU and CPSBC, and a patient-partner living with chronic pain in BC to inform all stages of the project including the operationalization of performance measures, their analysis and the interpretation of results. For all health system performance measures, we will also conduct extensive sensitivity analyses.

Knowledge translation is integrated throughout the proposed study. Our team includes a primary care provider in active clinical practice, experts in substance use treatment, policymakers, and a patient-partner with pertinent lived experience. The inclusion of diverse stakeholders within the project team has helped to confirm relevance of research aims and refine specific research questions. As the project progresses, we will meet with stakeholder groups to share interim findings and identify emergent policy areas where information from our project may inform decision-making. In addition to communicating results to stakeholders and policymakers, and through traditional academic channels (publications and conference presentations) we will also work to ensure research findings are accessible to people prescribed opioids in BC and to the public. We will disseminate results via a combination of open access peer-reviewed publications in high-impact journals, conferences, lay summaries, OpEds and ongoing meetings with our stakeholders/knowledge users.

The overdose epidemic in BC is unique to that observed elsewhere in North America. In the United States, the opioid epidemic is described as a triple wave of overdose deaths starting with prescription opioids, followed by heroin, and more recently, fentanyl.[64,65] Other regions in Canada demonstrate a similar epidemiological transition from prescription opioids to illicit substances. For BC, contamination of the illicit drug supply seems to have driven the epidemic since the beginning.[66] Although the underlying drivers of BC's overdose epidemic differ from those described in other parts of Canada and the United States, many of the responses to the epidemic parallel those observed elsewhere. The removal of the federal Section 56 exemption from the *Controlled Drugs and Substances Act* for physicians to methadone, along with coverage on public insurance programs expanded access to OAT for residents in Alberta,[67] Ontario[68] and Quebec[69,70]. Similarly, while enforceable practice standards for the prescribing of opioid analgesics have not been implemented in other jurisdictions, provinces and states are struggling with purported effects of changes in prescribing guidelines.[25,28-30] Given these response similarities, we expect findings will be of international relevance.

Author contributions

Panagiotoglou and McCracken are the co-Principal Investigators of the study. Panagiotoglou, McCracken and Lavergne conceived the study and overall design, with critical revisions from Gomes, Strumpf, Fischer, Brackett, Johnson, and Kendall. All co-authors developed the analysis plan, with specific methodology input from Gomes and Strumpf. Panagiotoglou drafted the manuscript. All authors provided feedback on the manuscript, approved the final version to be published and agree to be accountable to all aspects of the work ensuring the project's accuracy and integrity.

Funding statement

This proposal is currently under review for funding. To date, it has received no specific grant from any funding agency in the public, commercial or not-for-profit sectors, and is supported by new hire start-up funds from McGill University.

Competing interests statement

The authors declare no competing interests.

Box 1. Safe Prescribing of Drugs with Potential for Misuse/Diversion Practice Standards, June 2016

Physicians must:

1. Review patients' current medications before prescribing opioids, sedatives or stimulants.
2. Base long-term treatment with medications with known risks, including opioids, sedatives and stimulants, upon clinical diagnosis and objective evidence. Continuing to prescribe medication solely on the basis that they have been previously prescribed is not acceptable.
3. Document discussion with patients that non-pharmacologic therapy and non-opioid analgesics are preferred for chronic non-cancer pain, and that the potential benefit of long-term opioid treatment (LTOT) is modest and risk significant.
4. Advise patients that LTOT is not indicated for certain medical conditions including headache disorders, fibromyalgia and axial low back pain.
5. Always prescribe the lowest effective dosage of opioid medication. Doses >50 morphine milligram equivalents (MME) per day warrant careful reassessment and documentation. Doses >90 MME per day warrant substantive evidence of exceptional need and benefit. (This advice excludes treatment with methadone.)
6. When treating patients with acute pain conditions, prescribe only immediate release opioids in quantities that the patient will need before community follow-up will be resumed (three to seven days is often adequate).
7. When discharging patients from acute-care settings, or post-operatively, prescribe only the quantities of opioids, sedatives or stimulants that the patient will need before community follow-up will be resumed.
8. Base decisions to prescribe long-term psychoactive medications, including LTOT, on well-documented, comprehensive initial assessments and frequent (at least every three months) reassessments. These assessments and reassessments must include documented history and physical examination of the patient. There must also be documentation that the patient has been screened regularly for the presence or emergence of mental health and substance use disorders and risk factors and advised about safety-sensitive occupational risks, child care responsibilities and driving.
9. Document the offer of a take-home naloxone prescription to all patients who are at risk of respiratory depression as a consequence of receiving opioid medications.
10. Document having directed and regularly reminded patients for whom they are prescribing LTOT to abstain from alcohol and non-prescription sedatives.
11. Order at least annual random urine drug testing and/or random pill counts for all adult patients on long-term opioids, benzodiazepines, sedative hypnotics or stimulants.

Further, physicians must not:

12. Prescribe benzodiazepines or sedative hypnotics to patients on LTOT, other than as a documented taper.
13. Prescribe combinations of opioids with benzodiazepines and/or sedative hypnotics.
14. Provide prescriptions allowing dispenses of opioids, sedatives and stimulants, which exceed a three-month supply or 250 tablets, whichever is less.
15. Initiate treatment with drugs with a high risk-profile such as methadone and fentanyl without relevant training and experience.

Table 2. Administrative datasets used to build cohort

Database	Description	Source
PharmaNet	All prescriptions dispensed from community and hospital outpatient pharmacies to BC residents for home use, irrespective of payer	BC MoH
Cancer Registry	In BC, cancer is a reportable disease and the registry captures all cancers diagnosed for BC residents and their treatment	BC Cancer
Physician Registry	Demographic information on all registered and practicing physicians including practice status (active or retired), and specialty	CPSBC
Physician Billing	All inpatient and outpatient fee-for-service physician billings records; includes ICD-9 diagnosis codes	BC MoH
Patient Registry File	Demographic data on all patients covered by the provincial Medical Services Plan	BC MoH
National Ambulatory Care Reporting System (NACRS)	All ambulatory care visits to hospitals, community and private clinics; includes ICD-9 primary diagnosis	BC MoH
Discharge Abstract Database (DAD)	All BC hospital discharge records (inpatient and day surgeries); including up to 25 ICD-10 diagnostic codes and up to 25 Canadian Classification of Health Interventions (CCI) procedure codes	BC MoH
Mortality	All deaths registered in the province; includes ICD-10 underlying case of death and record axis codes	Vital Statistics

Table 2. Prescribing Measures

Variable	Type	Level	Definition	Frequency	Data Source(s)
Primary purpose	Categorical	Patient	Classify each opioid prescription fill as "chronic non-cancer", "acute", "cancer/palliative", "OAT", "other" or "unknown" using the BC Cancer Registry, PharmaCare's Plan B (residential) and Plan P (palliative care) claims records, College of Pharmacists of British Columbia's and Health Quality Ontario's lists of non-analgesic formulations (i.e. for treatment of cough or diarrhea), the BC CDC's master drug list classification, existing validated coding algorithms and time since prescription initiation.[71-73]	Per Rx	BC Cancer Registry, PharmaNet, Physician Billing, DAD, master drug lists (College of Pharmacists, HQ Ontario, BCCDC)
Daily Dose	Continuous	Patient	Convert prescriptions to daily morphine milligram equivalents using the BC CDC drug classification list conversion factor developed from WHO guidelines	Per Rx	PharmaNet
Release	Categorical	Patient	Distinguish between "short-acting" and "long-acting/extended release formulations" using BC CDC drug list classification[74]	Per Rx	PharmaNet
Usual prescriber of care	Categorical	Patient	Assigned as the primary care physician who initiated the LTOT or OAT prescription. Where prescriptions were initiated by specialists or in-hospital, or where patients have been transferred between practices (e.g. following physician retirement), the primary care physician that renews the prescription at least once is assigned usual prescriber of care. For the purposes of a control group, usual prescriber will be assigned as the primary care physician who initiates or continues diabetes specific pharmacotherapy (e.g. metformin)[75] **Value:** Unique de-identified physician practice number	Per Rx	PharmaNet, Physician Billing, Patient Registry, DAD
Rx concordance	Categorical	Patient	For each LTOT prescription filled for chronic, non-cancer pain, determine whether or not it concordant with the CPBSBC's practice standards (Figure 2). Non-concordant fills will be dispensations contraindicated or where dosing exceeds recommended levels. **Values**: Binary (yes/no)	Per Rx	PharmaNet, Physician Billing, DAD
Controlled substances cessation	Categorical	Physician	For physicians who ever prescribed a controlled substance (e.g. buprenorphine, hydromorphone),[76] we will distinguish physicians who terminated any prescription abruptly for at least three months from those who did not (excluding physicians who have retired, died, or moved; and prescriptions appropriately tapered over time)	Per Rx	PharmaNet, Physician Registry

			Values: Binary (yes/no)		
Treatment termination	Categorical	Patient	For patients on LTOT whose treatment was abruptly stopped or rapidly tapered by their usual prescriber of care. Patients who move, are safely tapered (<20% dose difference week to week), are overseen by a new physician with less than 30 day gap between prescription, or whose usual prescriber retired, moved or died will be excluded.	Annual	PharmaNet, Physician Registry, Patient Registry File

Table 3. Quality of Primary Care Measures

Variable	Type	Level	Definition	Frequency	Data Source(s)
Access to primary care	Continuous	Patient	The proportion of all non-urgent (e.g. Canadian Triage and Acuity Scale of 4 or 5) ambulatory visits that are with a primary care physician, in the preceding year, at the time of each prescription. **Values:** Numerical, bound between 0 and 1	Per Rx	Patient Registry, Physician Billing, Physician Registry, NACRS
Continuity of care	Continuous	Patient	Number of contacts with the usual prescriber of care, divided by the number of all ambulatory contacts, in the preceding year, at the time of each prescription. **Values:** Numerical, bound between 0 and 1	Per Rx	Patient Registry, Physician Billing, Physician Registry, NACRS
Practice type	Categorical	Physician	We will apply Schultz and Glazier's (2017) approach[77] to create an empirical threshold for primary care comprehensiveness and classify each primary care physician by the number of distinct activity areas they bill. **Values:** Focused practice = # of activity areas < empirical threshold Comprehensive practice = # activity areas ≥ empirical threshold	Per Rx	Physician Billing, Physician Registry
Comprehensiveness of care	Continuous	Patient	The proportion of all primary care visits with a physician providing comprehensive care (practice type), in the preceding year, at each prescription fill.	Per Rx	Physician Billing, Physician Registry

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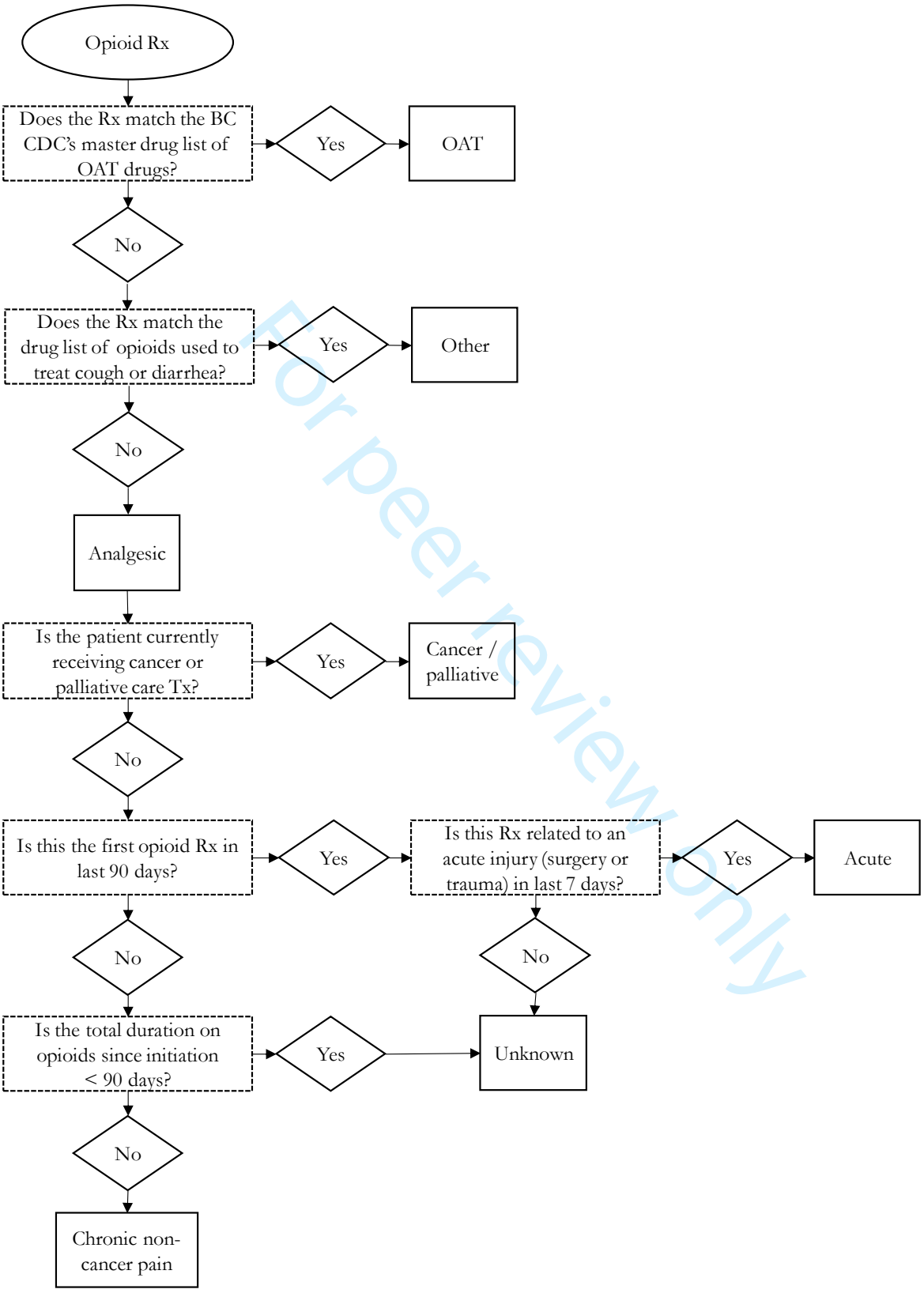
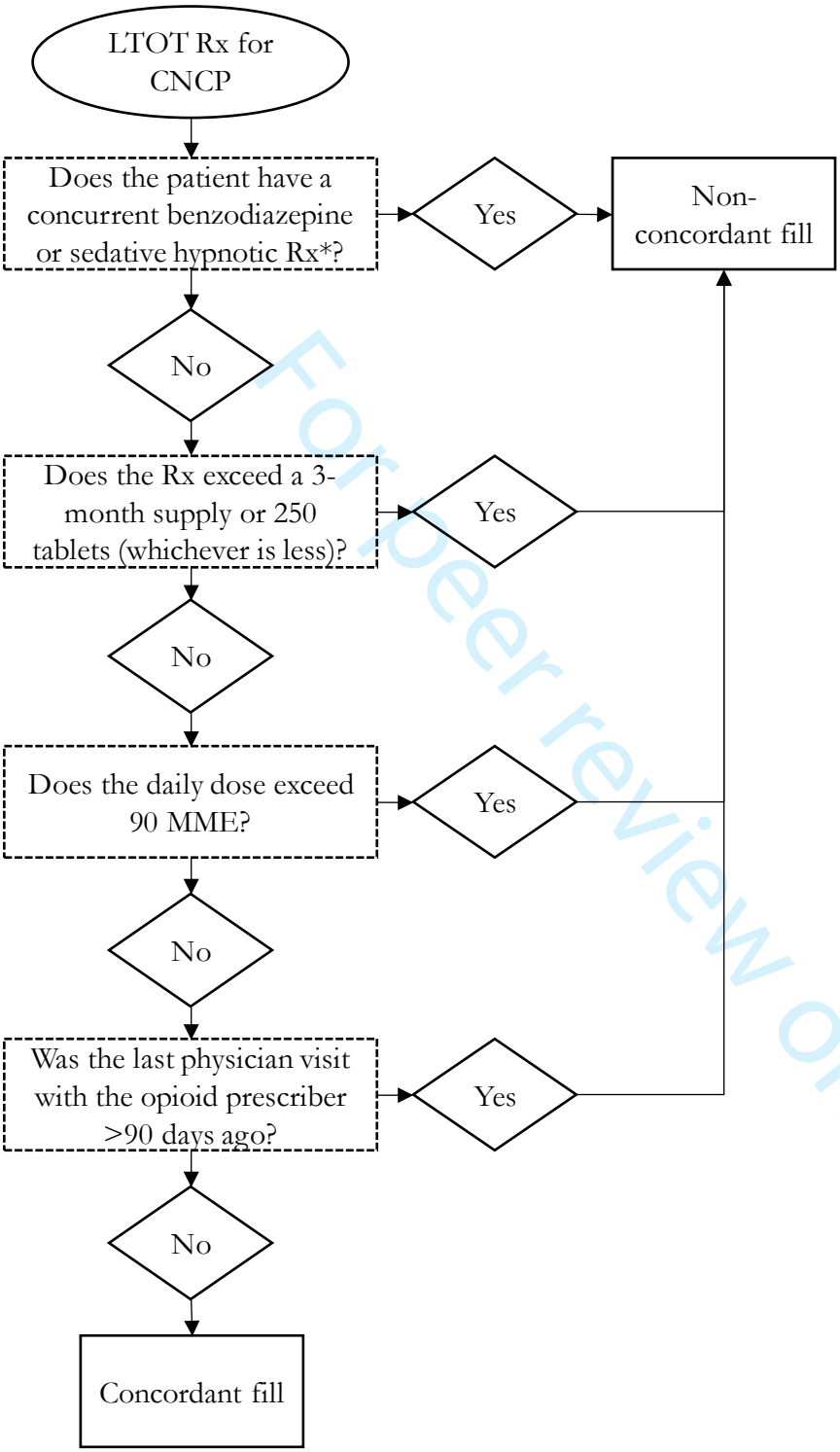
Figure 1. Primary use decision tree



Rx=prescription; BC CDC=British Columbia Centre for Disease Control; Tx=treatmen

Figure 2. Long-term opioid treatment concordant fill decision tree



*Excluding benzodiazepine and sedative hypnotic tapers.

LTOT=long term opioid treatment; CNCP=chronic, non-cancer pain; Rx=prescription; MME=morphine milligram equivalents

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Evaluating the intended and unintended consequences of opioid prescribing interventions on primary care in British Columbia, Canada: protocol for a retrospective population-based cohort study

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Evaluating the intended and unintended consequences of opioid prescribing interventions on primary care in British Columbia, Canada: protocol for a retrospective population-based cohort study

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ABSTRACT

Introduction: Between 2015 and 2018, there were over 40,000 opioid-related overdose events and 4,551 deaths among residents in British Columbia (BC). During this time the province mobilized a variety of policy levers to encourage physicians to expand access to opioid agonist treatment (OAT) and the College of Physicians and Surgeons of British Columbia (CPSBC) released a practice standard establishing legally enforceable minimum thresholds of professional behaviour in the hopes of curtailing overdose events. Our goal is to conduct a comprehensive investigation of the intended and unintended consequences of these policy changes. Specifically, we aim to understand the effects of these measures on physician prescribing behaviours, identify physician characteristics associated with uptake of the new measures, and measure the effects of the policy changes on patients' access to quality primary care.

Methods and analysis: This is a population-level, retrospective cohort study of all BC primary care physicians who prescribed any opioid medication for opioid use disorder or chronic non-cancer pain during the study period, and their patients. The study period is 1 January 2013 to 31 December 2018, with a one year wash-in period (1 January 2012 – 31 December 2012) to exclude patients who initiated long term opioid treatment (LTOT) prior to our study period or whose pain type (i.e. "chronic non-cancer", "acute", "cancer or palliative", or "other") cannot be confirmed. The project combines five administrative health datasets under the authority of the BC Ministry of Health, with the CPSBC's Physician Registry, BC

Cancer Agency's Cancer Registry, and Vital Statistics' Mortality data. We will create measures of prescribing concordance, access, continuity, and comprehensiveness to assess primary care delivery and quality at both the physician and patient level. We will use generalized estimating equations, interrupted time series, mixed effects models and funnel plots to identify factors related to changes in prescribing and evaluate the impact of the changes to prescribing policies. Results will be reported using appropriate EQUATOR guidelines (e.g. STROBE).

Ethics and dissemination: This study has been approved by McGill University's Institutional Review Board (#A11-M55-19A), and the University of British Columbia's Research Ethics Board (#H19-03537). We will disseminate results via a combination of open access peer-reviewed journal publications, conferences, lay summaries, and OpEds.

ARTICLE SUMMARY

STRENGTHS AND LIMITATIONS

- This is a population level study of all primary care physicians in British Columbia (approximately 6000, 1200 of which prescribed at least one OAT during the study period) and their patients (>4.8 million) over six years (2013 – 2018)
- By working with a comprehensive dataset, master drug lists and validated coding algorithms in a context where the majority of health services are provided at no cost and all prescription drug dispensations are recorded, we have minimized the potential for misclassification and capture as many patients as possible outside of a strict longitudinal cohort study
- We use a combination of methods and explore the effects of the prescribing policies from both the physician and patient perspectives
- We are unable to operationalize and evaluate adherence to all stipulations in the practice standard (i.e. documentation of discussions for non-pharmaceutical alternatives or take home naloxone kits, pill counts or urine tests)

INTRODUCTION

Between 2015 and 2018, there were over 40,000 opioid-related overdose events and 4,551 deaths among residents in British Columbia (BC).[1-4] The annual provincial overdose mortality rate rose from 4.7 per 100,000 population in 2009 to 30.8 per 100,000 population in 2018., and for Vancouver's Downtown Eastside exceeded 100 deaths per 100,000 population.[5,6] In an attempt to curtail the number of overdose events, the province launched new policies to encourage physicians and nurse practitioners to expand access to opioid agonist treatment[1] (OAT) including open listing buprenorphine/naloxone in the PharmaCare and First Nations Health Benefits programs.[7] Further, the province amended existing fees and introduced new ones to better compensate physicians who provide treatment for opioid use disorder (OUD).[8,9] Concurrently, the BC Centre on Substance Use (BCCSU) developed provincial guidelines and began offering comprehensive education and training for prescribers of OAT.[10]

Meanwhile, the College of Physicians and Surgeons of British Columbia (CPSBC) released the *Safe Prescribing of Drugs with Potential for Misuse/Diversion* practice standard (Box 1) to "prevent an increasing toll of prescription drug misuse and overdose deaths".[11] Recently renamed *Safe Prescribing of Opioids and Sedatives*, the CPSBC's practice standard evolved from the *CDC Guideline for Prescribing Opioids for Chronic Pain – United States, 2016,* the College's *Prescribing Principles* (2012), and the National Opioid Use Guideline Group's *Safe and Effective Use of Opioids for Chronic Non-Cancer Pain* (2010). The practice standard reflects the findings that opioids compared with placebo modestly improve physical functioning and quality of life for people living with chronic non-cancer pain;[2] but that the risks of adverse health effects outweigh the benefits[12-14]. Unlike its predecessors which recommended courses of action and allowed physicians to "exercise reasonable discretion in their decision to act on guidance provided", the practice standard established legally enforceable minimum thresholds of professional behaviour.[15] Non-compliant physicians can be disciplined or fined under the Health Professions Act, RSBC 1996, c.183 (HPA) and College Bylaws.[15,16]

People with OUD are consistently marginalized and stigmatized from mainstream healthcare delivery systems,[17,18] relying on expensive and fragmented care from emergency departments and walk-in clinics to address their acute and chronic medical conditions.[19,20] Policies aimed at expanding the provision of OAT may therefore have positive spillover effects beyond the benefits of the treatment itself. An expanded pool of prescribers, mostly family medicine physicians, may enable access to primary care services; improving continuity of care and reducing the use of walk-in clinics and emergency departments.[21-24]

Conversely, the CPSBC's practice standard may have inadvertently restricted access to quality primary care for patients with chronic-non cancer pain.[25] Across Canada and the United States there is growing anecdotal evidence that opioid prescribing guidelines have negatively affected people who could benefit from opioids. Incorrect interpretations of the standard can result in aggressive weaning without consent, cause debilitating pain and serious withdrawal symptoms, strain patient-physician relationships, and increase risk of overdose for patients who self-medicate for pain relief.[26-32]

Our goal is to conduct a comprehensive investigation of the intended and unintended consequences of the changes to OAT prescribing and the CPSBC's practice standard for patients and primary care physicians in British Columbia. To meet this objective, we will:

1. *Examine the uptake of OAT prescribing and the adoption of the CPSBC's practice standard among primary care physicians*:

RQ[3] 1.1 How do physicians who begin prescribing OAT between 2016 and 2018 differ from those who do not, and with providers already offering OAT prior to recent prescribing changes?

RQ 1.2 To what extent do physicians vary in adopting the CPSBC's practice standard?

[1] Opioid agonist treatment refers to a set of pharmacological antagonists (e.g. methadone, buprenorphine or naltrexone) for addiction to opioids such as heroin, fentanyl, hydromorphone and oxycodone.

[2] Lasting longer than three months.

[3] RQ=Research Question

RQ 1.3 What are the effects of the practice standard on prescribing patterns of long-term opioid treatment (LTOT)?

RQ 1.4 What physician characteristics are associated with ceasing prescription of controlled substances, and with terminating primary care for patients on LTOT?

2. *Determine the effects of the changes to opioid prescribing on primary care for patients:*

RQ 2.1 What are the characteristics of patients who are newly-prescribed OAT (2016 – 2018)?

RQ 2.2 What are the characteristics of patients who experience rapid tapering and/or termination with their primary care provider following the release of the CPSBC's practice standard?

RQ 2.3 Do patients who begin OAT experience changes in primary care access, continuity, or comprehensiveness?

RQ 2.4 Do patients treated with LTOT experience changes in primary care access, continuity, or comprehensiveness following implementation of the new practice standard?

METHODS AND ANALYSIS

This project is set to start September 2020 and end August 2024.

Study Setting

British Columbia is Canada's most western province, and has a population of approximately 4.8 million residents. There are over 1200 OAT prescribers[33] among approximately 6000 primary care physicians and addictions specialists[34]. The province provides single payer coverage of inpatient and outpatient health services through its Medical Services Plan (MSP). Residents excluded from the insurance program include newly landed immigrants and people covered under federal insurance programs including refugees, asylum seekers, military personnel and First Nations' members (representing less than 4% of the population)[35].

In 2012, fentanyl was first detected in the illicit drug supply, and 4% of the province's 270 overdose deaths were fentanyl-related.[4] By 2018, fentanyl was detected in over 80% of the province's 1,535 drug overdose deaths.[36] Dr. Perry Kendall, the Provincial Medical Health Officer at the time, declared the opioid overdose epidemic a public health emergency in April 2016.[37] The declaration enabled the BC Centre for Disease Control, Ministry of Health, Regional Health Authorities, BC Coroner Services and related stakeholders to quickly expand surveillance efforts and adopt new harm reduction programs (e.g. overdose prevention sites, Take Home Naloxone programs), treatment, and recovery interventions. Meanwhile, the Ministry of Health and the College of Physicians focused on supply side interventions to prevent overdose deaths and reduce harms.[37] A variety of studies are currently underway to evaluate the effects of these interventions.

Data Sources and Linkages

This project combines five administrative health datasets under the authority of the BC Ministry of Health, with the CPSBC's Physician Registry, BC Cancer Agency's Cancer Registry, and Vital Statistics' Mortality data (Table 1). Population Data BC, a multi-university data resource, will provide secure access to individual level, linked and de-identified data for our research purposes.

Patient and Public Involvement

As part of the project's development, we recruited a patient-partner with lived experience from the Patient Voices Network. Through a series of meetings, the patient-partner has informed the research aims of the project, and outcome measures of interest. This patient-partner will remain an integral member of the

[4] Illicit overdose events include indication of street drugs (controlled and illegal: heroin, cocaine, MDMA, methamphetamine, illicit fentanyl), and medications not prescribed to the decedent but obtained/purchased on the street, from unknown means, or where origin of drug not known.

team assisting in the interpretation of patient-level results and knowledge dissemination efforts. As this project uses secondary administrative data, no additional patients were recruited for the conduct of the study.

Study Design and Study Population

This is a population-level, retrospective cohort study of all BC primary care physicians who prescribed any opioid medication for opioid use disorder or chronic non-cancer pain during the study period, and their patients. The study period is 1 January 2013 to 31 December 2018, with a one year wash-in period (1 January 2012 – 31 December 2012) to exclude patients who initiated LTOT before 2012 or whose pain type (i.e. "chronic non-cancer", "acute", "cancer or palliative", or "other") cannot be confirmed (Figure 1).

The cohort will include all primary care physicians and their patients using the CPSBC's Physician Registry, and Medical Services Plan (MSP) billings. We will use PharmaNet data to identify all physicians (including specialists) who prescribed any opioid during the study period so we can determine the physician who initiated each opioid prescription. For all patients, MSP, NACRS and DAD will provide complete health service use history during the wash-in and study periods; indicate the types of services the prescription initiating physician provides; and enable us to control for patient level comorbidities. The Cancer Registry and PharmaNet will allow us to identify and exclude patients being treated for cancer and palliative care. DAD and Mortality data will be used to identify patient sub-populations who are disproportionately harmed by the changes. All records in the MSP, NACRS, DAD and PharmaNet files include de-identified physician and referring practitioner numbers for referral pattern purposes.

Operationalized measures:

We will operationalize a series of variables using our linked dataset (Tables 2 and 3).

Analysis Plan for Each Objective

Data will be prepared using SAS (V.9.4, SAS Institute, Cary, USA) and statistical analyses will be performed using R (V.3.2.5). In general, missing and incomplete data will be excluded from analyses and the number of observations omitted from analyses due to missing data will be documented. If any imputation is used, the method and extent will be reported. We will report p-values <0.05 and 95% confidence intervals. Results will be reported using appropriate EQUATOR guidelines (e.g. STROBE).

Physicians' uptake of OAT prescribing and the adoption of the CPSBC's practice standard:

To examine the differences between primary care physicians who begin prescribing OAT to patients with OUD and those who do not **(RQ1.1)** – we will restrict our analysis to OAT-naïve physicians (i.e. never prescribed OAT during the three year wash-in period: 2012 – 2014, inclusive), and saw OAT-naïve patients with indication of an OUD between 2015 and 2018, inclusive. This will allow us to examine the cohort of physicians who were susceptible to OAT expansion interventions. We will use generalized estimating equations (GEE) for logistic regression to identify physician-level characteristics (e.g. age, sex, years since training completion, geography, practice type, and prescribing history) associated with OAT prescribing. These nonparametric models allow us to account for the repeated measures and hierarchical structure of our data by specifying joint distribution in their random effects terms, and are well-suited to identifying population average differences.[38,39] We will repeat the analysis to compare physician characteristics associated with new OAT prescribing (i.e. first prescription post-2015) compared with early adopters (i.e. primary care physicians prescribing OAT pre- 2015).

To understand the extent to which physicians vary in adopting the CPSBC's practice standard **(RQ1.2)** – we will restrict analysis to physicians who prescribed LTOT between June 2014 and May 2016 and again during the effective period of the CPSBC's practice standard (June 2016 – May 2018). We will use funnel

plots to quantify the extent of deviation in prescription concordance[5] (Figure 2) at the physician-level before and after the implementation of the practice standard. Physicians whose observed proportion of non-concordant prescriptions remains above the upper 95% control limits of the expected proportion of non-concordant fills (given the number of prescriptions they prescribed, and controlling for patient and geographic differences) following the implementation of the standard, will be compared with primary care peers whose prescribing becomes concordant. We will use mixed effects models to identify physician characteristics associated with non-concordance.

To estimate the effects of the practice standard (implemented June 2016) on usual prescribers of care's LTOT prescriptions **(RQ1.3)** – we will use interrupted time series (ITS) analysis. ITS is a quasi-experimental study design that estimates the effects of service or policy interventions before and after implementation in contexts where randomized controlled trials are not feasible or ethical.[40,41] The advantage of this before-after comparison with a single population is that selection bias and confounding due to between-group differences are limited; and within-group characteristics that change slowly over time (e.g. physician characteristics), secular changes, random fluctuations from one time point to the next and regression to the mean are also controlled.[42] The primary assumption for ITS is that without the intervention (here the introduction of the CPSBC's practice standard) the observed pre-intervention outcome trends would continue unchanged into the post-intervention period. This assumption is supported by Crabtree et al.'s (2019)[43] work which found no change in trends of defined daily dose of opioids prescribed pre- vs. post-implementation of the practice standard. Additionally, to our knowledge there were no other interventions that would affect physician prescribing of LTOT implemented during our study period. Using this method, we will look at the effects of the practice standard on the number of LTOT prescriptions filled with: a) a daily dose greater than 90 MME; b) a benzodiazepine co-prescription; and c) a supply that exceeds 3 months or 250 tablets (whichever is less). We will also look at d) the number of physicians who terminate any controlled substance; and e) the number of LTOT prescriptions terminated. We selected these outcomes because the CPSBC's primary aim for establishing the practice standard was to reduce prescription drug misuse. However, we would also like to quantify the extent of inappropriate treatment cessation, as suggested by mounting anecdotal evidence. Given the potential rarity of the outcomes, we will aggregate counts to eight quarterly periods pre- and post-implementation (pre-intervention: June 2014 – May 2016; post-intervention: June 2016 – May 2018). We will use the 2-sided Durbin-Watson test, plot of residuals, and autocorrelation plots to identify and adjust for autocorrelation and moving averages where necessary. We will test the hypothesis that the practice standard had no effect on these outcomes using ordinary least squares and segmented regression.

Lastly, we will use GEE for logistic regression, and GEE for Poisson or negative binomial distribution to identify physician characteristics associated with any controlled substances cessation, and with counts of treatment termination between 2016 and 2018, respectively (**RQ1.4**). Negative binomial models are similar to Poisson models with the exception that the mean and variance of the count data do not have to be the same. These models include an additional parameter to handle over-dispersion in the data, and are well-suited for zero inflation, and unobserved heterogeneity in the data.[44,45] To determine which of the two model types is best suited to the data, we will use Pearson chi-square dispersion statistics and residual plots.[45,46]

Effects of the changes to opioid prescribing on primary care for patients:

We will use GEE for logistic regression to identify patient-level characteristics (e.g. age, sex, geography, comorbidities, contraindications) associated with OAT initiation between 2015 and 2018 among OAT naïve patients (no OAT prescription filled between 2012 and 2014, inclusive) with indication of OUD **(RQ 2.1)**. For patients on LTOT as of June 2016, we will use GEE to identify patient-level characteristics associated with inappropriate treatment termination (including rapid tapering) and regression models to estimate risk of mortality **(RQ2.2)**.

[5] Concordance prior to the implementation of the CPSBC's practice standard (June 2014 – May 2016) will be an artificial measure used to identify physician outliers susceptible to the effects of the practice standard post-implementation.

For **RQ 2.3** – we will use a variety of multiple linear (or linearized, where appropriate) regression models to measure the population-level association between expanded provision of OAT defined as the number of primary care physicians newly prescribing OAT as of 2015 (OAT prescribing naïve 2012 – 2014) and changes to patients' access, continuity and comprehensiveness of primary care (independently), while controlling for patient-level characteristics (e.g. age, sex, geography, indication of OUD, comorbidities, and contraindications). Models will include a lag for the potential delayed effects between expanded provision of OAT and our outcomes. Lags between the number of physicians prescribing OAT and primary care outcomes will be estimated using the weighted cumulative approach[47-49] and informed with expert input from our knowledge users/stakeholders[50,51]. We anticipate at least a one year lag between expanded OAT provision and changes in access, continuity and comprehensiveness of care given how these measures will be constructed.

To measure the effects of the practice standard on patients' access, continuity and comprehensiveness of primary care **(RQ2.4)** – we will use controlled ITS analysis. This modified method allows us to account for time-varying confounders that may have influenced the delivery of primary care. Patients on LTOT just before the implementation of the practice standard will be matched with diabetic patients not on opioids for pain management (e.g. for neuropathic pain)[52] or OAT whose pharmacotherapy is overseen by the same physician, and on age, sex, Charlson comorbidity index, and treatment initiation month. Diabetes patients were selected as our negative control group because:

1. The majority of diabetes care is provided in primary care settings;
2. There were no contemporaneous policies affecting diabetes pharmacotherapy prescribing behaviours during the study period;
3. The opioid prescribing standard is not expected to affect diabetes pharmacotherapy prescriptions;
4. There are clear practice guidelines for physicians treating patients with diabetes, including frequency of physician oversight, which are similar to the guidelines for patients on long-term opioid treatments;[53] and
5. Prescription disruptions (e.g. termination, change in prescriber) are unusual for this patient population.

We will use 24 monthly intervals pre- and post-implementation for a total of 48 time periods between June 2014 and May 2018 (inclusive). At each interval, the outcome measure will be assessed for each patient dispensed a prescription during that month (LTOT for exposed, diabetes drug for matched controls). We will test our hypothesis of no change in access, continuity or comprehensiveness of care using ordinary least squares and segmented regression, by fitting the following regression model, per outcome:

$$\begin{aligned}\mathrm{Outcome}_{jkt} &= \beta_0 + \beta_1 \mathrm{time}_t + \beta_2 \mathrm{group}_k + \beta_3 \mathrm{group}_k \mathrm{time}_t + \beta_4 \mathrm{level}_{jt} + \beta_5 \mathrm{trend}_{jt} + \beta_6 \mathrm{level}_{jt} \mathrm{group}_k \\ &\quad + \beta_7 \mathrm{trend}_{jt} \mathrm{group}_k + \varepsilon_{jkt}\end{aligned}$$

where *j* is the intervention, *t* is the study time in monthly intervals pre- (negative time) and post-intervention (positive time), and *k* distinguishes between intervention and control group. Significant values for coefficients β_6 and β_7 will indicate an effect of the practice standard on patients' access, continuity and comprehensiveness of primary care after accounting for level and trend changes among diabetic controls.

ETHICS AND DISSEMINATION

This study has been approved by McGill University's Institutional Review Board (#A11-M55-19A), and the University of British Columbia's Research Ethics Board (#H19-03537).

All data used in this project will be linked using de-identified personal health numbers or physician practice numbers. The data will be stored in Population Data BC's Secure Research Environment, a central server for data storage and analysis, including encrypted backups, software, and other services to ensure compliance with data access requirements.[54] All members of the research team who will have access to the data have had the necessary tri-council privacy training and will complete privacy training provided by Population Data BC. Study results will be screened by data stewards prior to publication to ensure privacy

and confidentiality requirements are maintained, there is no gross misuse of the data, and data is appropriately referenced. Linked data will remain within Population Data BC's Red Zone (terminals with no external connection) for up to seven years after project completion before being destroyed by authorized data personnel.

Discussion

Our objective is to evaluate the effects of interventions aimed to improve access to OAT and limit overprescribing of opioid analgesics on physician prescribing behaviour and patient access to comprehensive primary care. Given the potential for patient harm, it is important to understand the effects of the interventions to prevent over/under-prescribing of opioids, and to mitigate the effects of exacerbating or introducing new inequities in access to health care. We will use a variety of health service delivery outcomes and address limitations of existing research. Results from Aim 1 will be useful for isolating the effects of the interventions on physician prescribing behaviour, and to identify physician characteristics associated with high-error prescribing in light of the new standard. Results from Aim 2 will estimate the effects of the interventions on patients' recent primary care experiences; and enable policy makers and physicians to identify potential subgroups harmed by the recent changes in prescribing. Together, these results will provide invaluable information on the effects of recent opioid prescribing policies at both the patient and prescriber level, and equip policy makers and regulatory colleges with the much-needed information to understand the intended and unintended consequences of opioid prescribing interventions to fine-tune their policies.

The primary challenge of this project relates to the use of administrative health data to create quantifiable measures of access, continuity and comprehensiveness of care. In settings without comprehensive records of service use or where access to services and treatment is restricted, such methods can lead to under-ascertainment and estimation of key patient groups (e.g. people with OUD) and undercounting primary care service use/provision.[55] For example, reliance on administrative data to accurately identify patient health needs (e.g. opioid use disorder, chronic pain) may lead to misclassification. However, by working with the comprehensive dataset described above in a context where the majority of health services are provided at no cost, and by applying modern surveillance methods we minimize the potential for misclassification, and capture as many patients as possible outside of a strict longitudinal cohort study[56]. Of note, while most provinces (e.g. Quebec) lack access to complete drug dispensation records for their populations, BC is unique in that it includes all outpatient prescription fills for all residents, irrespective of payer within PharmaNet's data file. These complete records, along with the BC Cancer Agency's Cancer Registry enable the cross-validation of patient pain type identified using algorithms which rely on inpatient and outpatient records only, and allow us to work around the issue of inadequate specificity in ICD coding described elsewhere. Further, recognizing the limitations of working with administrative data, we have intentionally recruited primary care physicians, members of the BCCSU and CPSBC, and a patient-partner living with chronic pain in BC to inform all stages of the project including the operationalization of performance measures, their analysis and the interpretation of results. For all health system performance measures, we will also conduct extensive sensitivity analyses.

Knowledge translation is integrated throughout the proposed study. Our team includes a primary care provider in active clinical practice, experts in substance use treatment, policymakers, and a patient with pertinent lived experience. The inclusion of diverse stakeholders within the project team has helped to confirm relevance of research aims and refine specific research questions. As the project progresses, we will meet with stakeholder groups to share interim findings and identify emergent policy areas where information from our project may inform decision-making. In addition to communicating results of research to stakeholders and policymakers, and through traditional academic channels (publications and conference presentations) we will also work to ensure end-of-grant research findings are accessible to people prescribed opioids in BC and to the public. We will disseminate results via a combination of open access peer-reviewed publications in high-impact journals, conferences, lay summaries, OpEds and ongoing meetings with our stakeholders/knowledge users.

The overdose epidemic in BC is unique to that observed elsewhere in North America. In the United States, the opioid epidemic is described as a triple wave of overdose deaths starting with prescription opioids, followed by heroin, and more recently, fentanyl.[57,58] Other regions in Canada demonstrate a similar epidemiological transition from prescription opioids to illicit substances. For BC, contamination of the illicit drug supply seems to have driven the epidemic since the beginning.[59] Although the underlying drivers of BC's overdose epidemic differ from those described in other parts of Canada and the United States, many of the responses to the epidemic parallel those observed elsewhere. The removal of the federal Section 56 exemption from the *Controlled Drugs and Substances Act* for physicians to prescribe methadone, and subsequent provincial requirements for buprenorphine, along with coverage on public insurance programs, expanded access to OAT for residents in Alberta, Ontario and Quebec[60,61]. Similarly, while enforceable practice standards for the prescribing of opioid analgesics have not been implemented in other jurisdictions, provinces and states are struggling with purported effects of changes in prescribing guidelines. Given these response similarities, we expect findings will be of international relevance.

AUTHORS' CONTRIBUTIONS

Panagiotoglou and McCracken are the co-Principal Investigators of the study. Panagiotoglou, McCracken and Lavergne conceived the study and overall design, with critical revisions from Gomes, Strumpf, Fischer, Brackett, Johnson, and Kendall. All co-authors developed the analysis plan, with specific methodology input from Gomes and Strumpf. Panagiotoglou drafted the manuscript. All authors provided feedback on the manuscript, approved the final version to be published and agree to be accountable to all aspects of the work ensuring the project's accuracy and integrity.

FUNDING STATEMENT

This proposal is currently under review for funding. To date, this research has received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. It is supported by new hire start-up funds from McGill University.

COMPETING INTERESTS STATEMENT

The authors declare no competing interests.

Figure 1. Primary use decision tree

Rx=prescription; BC CDC=British Columbia Centre for Disease Control; Tx=treatment

Figure 2. Long-term opioid treatment concordant fill decision tree

*Excluding benzodiazepine and sedative hypnotic tapers.

LTOT=long term opioid treatment; CNCP=chronic, non-cancer pain; Rx=prescription; MME=morphine milligram equivalents

Box 1. Safe Prescribing of Drugs with Potential for Misuse/Diversion Practice Standard, June 2016

Physicians must:

1. Review patients' current medications before prescribing opioids, sedatives or stimulants.
2. Base long-term treatment with medications with known risks, including opioids, sedatives and stimulants, upon clinical diagnosis and objective evidence. Continuing to prescribe medication solely on the basis that they have been previously prescribed is not acceptable.
3. Document discussion with patients that non-pharmacologic therapy and non-opioid analgesics are preferred for chronic non-cancer pain, and that the potential benefit of long-term opioid treatment (LTOT) is modest and risk significant.
4. Advise patients that LTOT is not indicated for certain medical conditions including headache disorders, fibromyalgia and axial low back pain.
5. Always prescribe the lowest effective dosage of opioid medication. Doses >50 morphine milligram equivalents (MME) per day warrant careful reassessment and documentation. Doses >90 MME per day warrant substantive evidence of exceptional need and benefit. (This advice excludes treatment with methadone.)
6. When treating patients with acute pain conditions, prescribe only immediate release opioids in quantities that the patient will need before community follow-up will be resumed (three to seven days is often adequate).
7. When discharging patients from acute-care settings, or post-operatively, prescribe only the quantities of opioids, sedatives or stimulants that the patient will need before community follow-up will be resumed.
8. Base decisions to prescribe long-term psychoactive medications, including LTOT, on well-documented, comprehensive initial assessments and frequent (at least every three months) reassessments. These assessments and reassessments must include documented history and physical examination of the patient. There must also be documentation that the patient has been screened regularly for the presence or emergence of mental health and substance use disorders and risk factors and advised about safety-sensitive occupational risks, child care responsibilities and driving.
9. Document the offer of a take-home naloxone prescription to all patients who are at risk of respiratory depression as a consequence of receiving opioid medications.
10. Document having directed and regularly reminded patients for whom they are prescribing LTOT to abstain from alcohol and non-prescription sedatives.
11. Order at least annual random urine drug testing and/or random pill counts for all adult patients on long-term opioids, benzodiazepines, sedative hypnotics or stimulants.

Further, physicians must not:

12. Prescribe benzodiazepines or sedative hypnotics to patients on LTOT, other than as a documented taper.
13. Prescribe combinations of opioids with benzodiazepines and/or sedative hypnotics.
14. Provide prescriptions allowing dispenses of opioids, sedatives and stimulants, which exceed a three-month supply or 250 tablets, whichever is less.
15. Initiate treatment with drugs with a high risk-profile such as methadone and fentanyl without relevant training and experience.

Table 2. Administrative datasets used to build cohort

Database	Description	Source
PharmaNet	All prescriptions dispensed from community and hospital outpatient pharmacies to BC residents for home use, irrespective of payer	BC MoH
Cancer Registry	In BC, cancer is a reportable disease and the registry captures all cancers diagnosed for BC residents and their treatment	BC Cancer Agency
Physician Registry	Demographic information on all registered and practicing physicians including practice status (active or retired), and specialty	CPSBC
Patient Registry File (MSP)	Demographic data on all patients covered by the provincial insurance program	BC MoH
Physician Billing (MSP)	All inpatient and outpatient fee-for-service physician billings records; includes ICD-9 diagnosis codes	BC MoH
National Ambulatory Care Reporting System (NACRS)	All ambulatory care visits to hospitals, community and private clinics; includes ICD-9 primary diagnosis	BC MoH
Discharge Abstract Database (DAD)	All BC hospital discharge records (inpatient and day surgeries); including up to 25 ICD-10 diagnostic codes and up to 25 Canadian Classification of Health Interventions (CCI) procedure codes	BC MoH
Mortality	All deaths registered in the province; includes ICD-10 underlying case of death and record axis codes	Vital Statistics

Table 2. Prescribing Measures

Variable	Type	Level	Definition	Frequency	Data Source(s)
Primary purpose	Categorical	Patient	Classify each opioid prescription fill as "chronic non-cancer", "acute", "cancer/palliative", "OAT", "other" or "unknown" using the BC Cancer Agency Cancer Registry, PharmaCare's Plan B (residential) and Plan P (palliative care) claims records, College of Pharmacists of British Columbia's and Health Quality Ontario's lists of non-analgesic formulations (i.e. for treatment of cough or diarrhea), the BC CDC's master drug list classification, existing validated coding algorithms and time since prescription initiation. [62-64]	Per Rx	BC Cancer Agency Cancer Registry, PharmaNet, Physician Billing, DAD, master drug lists (College of Pharmacists, HQ Ontario, BCCDC)
Daily Dose	Continuous	Patient	Convert prescriptions to daily morphine milligram equivalents using the BC CDC drug classification list conversion factor developed from WHO guidelines	Per Rx	PharmaNet
Release	Categorical	Patient	Distinguish between "short-acting" and "long-acting/extended release formulations" using BC CDC drug list classification[65]	Per Rx	PharmaNet
Usual prescriber of care	Categorical	Patient	Assigned as the primary care physician who initiated the LTOT or OAT prescription. Where prescriptions were initiated by specialists or in-hospital, or where patients have been transferred between practices (e.g. following physician retirement), the primary care physician that renews the prescription at least once is assigned usual prescriber of care. For the purposes of a control group, usual prescriber will be assigned as the primary care physician who initiates or continues diabetes specific pharmacotherapy (e.g. metformin)[66] **Value:** Unique de-identified physician practice number	Per Rx	PharmaNet, Physician Billing, Patient Registry, DAD
Rx concordance	Categorical	Patient	For each LTOT prescription filled for chronic, non-cancer pain, determine whether or not it concordant with the CPBSBC's practice standard (Figure 2). Non-concordant fills will be dispensations contraindicated or where dosing exceeds recommended levels. **Values**: Binary (yes/no)	Per Rx	PharmaNet, Physician Billing, DAD
Controlled substances cessation	Categorical	Physician	For physicians who ever prescribed a controlled substance (e.g. buprenorphine, hydromorphone),[67] we will distinguish physicians who terminated any prescription abruptly for at least three months	Per Rx	PharmaNet, Physician Registry

			from those who did not (excluding physicians who have retired, died, or moved; and prescriptions appropriately tapered over time) **Values**: Binary (yes/no)		
Treatment termination	Categorical	Patient	For patients on LTOT whose treatment was abruptly stopped or rapidly tapered by their usual prescriber of care. Patients who move, are safely tapered (<20% dose difference week to week), are overseen by a new physician with less than 30 day gap between prescription, or whose usual prescriber retired, moved or died will be excluded.	Annual	PharmaNet, Physician Registry, Patient Registry File

Table 3. Quality of Primary Care Measures

Variable	Type	Level	Definition	Frequency	Data Source(s)
Access to primary care	Continuous	Patient	The proportion of all non-urgent (e.g. Canadian Triage and Acuity Scale of 4 or 5) ambulatory visits that are with a primary care physician, in the preceding year, at the time of each prescription. **Values:** Numerical, bound between 0 and 1	Per Rx	Patient Registry, Physician Billing, Physician Registry, NACRS
Continuity of care	Continuous	Patient	Number of contacts with the usual prescriber of care, divided by the number of all ambulatory contacts, in the preceding year, at the time of each prescription. **Values:** Numerical, bound between 0 and 1	Per Rx	Patient Registry, Physician Billing, Physician Registry, NACRS
Practice type	Categorical	Physician	We will apply Schultz and Glazier's (2017) approach[68] to create an empirical threshold for primary care comprehensiveness and classify each primary care physician by the number of distinct activity areas they bill. **Values:** Focused practice = # of activity areas < empirical threshold Comprehensive practice = # activity areas ≥ empirical threshold	Per Rx	Physician Billing, Physician Registry
Comprehensiveness of care	Continuous	Patient	The proportion of all primary care visits with a physician providing comprehensive care (practice type), in the preceding year, at each prescription fill.	Per Rx	Physician Billing, Physician Registry

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