UPDATED VERSION, Sept. 17, 2021

cmajOPEN

Research

Influence of opioid prescribing standards on health outcomes among patients with long-term opioid use: a longitudinal cohort study

Richard L. Morrow MA, Ken Bassett MD PhD, James M. Wright MD PhD, Greg Carney PhD, Colin R. Dormuth ScD

Abstract

Background: The College of Physicians and Surgeons of British Columbia introduced opioid prescribing standards and guidelines in mid-2016 in British Columbia. We evaluated impacts of the standards and guidelines on health outcomes.

Methods: We conducted a longitudinal study with repeated measures using administrative data from December 2013 to March 2017. The study included BC patients with long-term use of prescription opioids. Those with a history of long-term care, palliative care or cancer were excluded. Patients were followed for a 12-month prepolicy period and 10-month postpolicy period and compared with historical controls. We estimated changes in level (sudden changes) and monthly trend (gradual changes) of rates of opioid overdose hospital admission, and secondary outcomes of all-cause hospital admission, all-cause emergency department visits, opioid overdose mortality and all-cause mortality.

Results: The study included 68 113 patients in the main cohort and 68 429 historical controls. We did not find significant changes to opioid overdose hospital admissions in level (adjusted rate ratio [RR] 0.83, 95% confidence interval [CI] 0.45–1.54) or in trend (adjusted RR 1.00, 95% CI 0.91–1.10). All-cause hospital admissions declined in level but may have increased in trend, suggesting that a temporary decrease in hospital admissions may have occurred. We found no significant changes in all-cause emergency department visits, opioid overdose mortality or all-cause mortality.

Interpretation: Among patients with a history of long-term prescription opioid use, the regulatory prescribing standards and guidelines were not associated with changes in opioid overdose hospital admissions, all-cause emergency department visits, opioid overdose mortality or all-cause mortality, or with a sustained reduction in all-cause hospital admissions, over a 10-month period after they were introduced. Future research should investigate whether opioid prescribing standards or guidelines are associated with use of nonopioid analgesic medications or nonpharmacologic treatments.

In the context of the opioid overdose crisis in the United States, the US Centers for Disease Control and Prevention (CDC) published a guideline on opioid prescribing for chronic pain in March 2016.[1] At the same time, British Columbia was experiencing the highest rates of hospital admissions for opioid overdose and apparent opioid-related deaths among Canadian provinces.[2,3] The opioid overdose deaths in BC in recent years have been associated with the contamination of street drugs with fentanyl and other potent synthetic opioids.[4] Nevertheless, the overdose deaths have raised concerns that the rate of opioid analgesic prescribing has contributed to the province's crisis of opioid-related harms. Rates of opioid prescribing have been associated with opioid-related morbidity and mortality in ecological-level studies of patients in BC, Ontario and the US.[5–9]

Following the publication of the CDC guideline, the College of Physicians and Surgeons of British Columbia endorsed the guideline[10] and subsequently issued its own policy with legally enforceable standards and recommended guidelines related to prescribing of opioid analgesics, which took effect on June 1, 2016.[11] The college noted that the potential benefit of long-term opioid therapy for chronic noncancer pain was modest.[11]

Competing interests: None declared.

This article has been peer reviewed.

Correspondence to: Richard Morrow, richard.morrow@ubc.ca

***CMAJ Open* 2020. DOI:10.9778/cmajo.20190228**

A systematic review published since the standards and guidelines were issued found that opioids compared with placebo were associated with only small decreases in pain and improvements in physical functioning in the treatment of chronic noncancer pain.[12] The college's standards and guidelines were not intended to apply to patients with active cancer or those receiving palliative or end-of-life care.

This study is the second phase of a 2-part research project evaluating the impact of the college's opioid standards and guidelines among patients with a history of long-term opioid use. In the first phase of the project, we found that the standards and guidelines were associated with a modest reduction in opioid utilization, increased switching from high-dose opioid therapy to lower dose opioid therapy, and a decrease in concurrent use of opioids and sedative and hypnotic medications.[13] In this study, we evaluated the impact of the standards and guidelines on health outcomes, including hospital admissions for opioid overdose, all-cause hospital admissions, all-cause emergency department visits, opioid overdose mortality and all-cause mortality.

Methods

Study setting and design

We described our study design and study population in our report on the first phase of our research project evaluating the impact of the college's standards and guidelines,[13] but here we briefly highlight key aspects of the study design and population and include elements unique to our analysis of health outcomes. We used a longitudinal cohort study design with a historical control group.[14,15] The longitudinal data in our study included monthly repeated outcome measures, which allowed us to evaluate the impact of the introduction of the standards and guidelines on health outcomes while controlling for patient covariates.

We analyzed data for BC residents with a history of long-term use of prescription opioids, where long-term use was defined as the receipt of at least 2 opioid prescriptions during a 6-month baseline period, with at least 1 fill in the first 3 months and 1 fill in the last 3 months, comprising at least 60 days' supply. Opioid analgesic medications included buprenorphine (patch), codeine, fentanyl, hydromorphone, meperidine, morphine, oxycodone, tapentadol and tramadol.

Participants

Patients who met our criteria for long-term opioid use during an identification period of Dec. 1, 2014, to May 31, 2015, were followed for a 12-month prepolicy period before the introduction of the standards and guidelines on June 1, 2016, and a 10-month postpolicy period ending on Mar. 31, 2017 (Appendix 1, Figure S1, available at www.cmajopen.ca/content/8/4/E869/suppl/DC1). We designated these patients as the policy cohort, as their follow-up included a period during which the standards and guidelines applied.

Patients who met our criteria for long-term opioid use 1 year earlier, from Dec. 1, 2013, to May 31, 2014, were designated as the historical control cohort. Follow-up of these patients included a 12-month baseline period (June 2014 to May 2015) and a 10-month control period (June 2015 to March 2016), analogous to the prepolicy and postpolicy period of patients in the policy cohort. As the follow-up of the patients in the historical control cohort ended before the introduction of the standards and guidelines, they provided a comparison group to help control for changes in outcome rates in the absence of the policy of interest. It was possible for patients to be members of both cohorts if they met the inclusion criteria during the identification period for both cohorts.

We excluded patients who lacked 1 year of medical services coverage and censored patients if their coverage ended during follow-up. We also excluded patients in long-term residential care and censored patients if they entered long-term care during follow-up, because the first phase of our study evaluated drug utilization and we lacked complete drug information for residents of long-term care facilities. We excluded patients who had a record of palliative care or a medical visit with a diagnosis of cancer in the year before follow-up, and we censored patients who received palliative care or a diagnosis of cancer during follow-up (see Appendix 1, Table S1, for diagnostic codes).

For the outcome of all-cause emergency department visits, we analyzed data for only a cohort of patients who were likely to report to the 29 hospitals in BC that supply data on emergency department visits to an ambulatory care database available for analysis (the National Ambulatory Care Reporting System). We included patients living in areas in which residents were admitted to 1 of these 29 hospitals for at least 95% of all hospital admissions, according to the first 3 digits of patients' postal codes, on the basis of the assumption that we would also capture most emergency department visits for these patients.

Data sources

We had access to patient-level, deidentified, linked data from the BC Ministry of Health's Healthideas data warehouse to conduct the study. This included data from the BC Medical Services Plan, BC PharmaNet, the BC Vital Statistics Agency, the National Ambulatory Care Reporting System and the Canadian Institute for Health Information Discharge Abstract Database. The data cover most of the BC population but not the approximately 4% of the population covered by federally insured drug plans for First Nations, members of the military, members of the Royal Canadian Mounted Police and inmates in federal penitentiaries. See Appendix 1 for further information on the data sources.

Outcomes

The primary outcome was hospital admission for opioid overdose, which was defined as a hospital admission with a diagnostic code for opioid poisoning of the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* (ICD-10) (Appendix 1, Table S2). Secondary health outcomes included all-cause hospital admission, all-cause emergency department visits, opioid overdose mortality

and all-cause mortality. Opioid overdose mortality was defined as a death recorded in vital statistics data with an ICD-10 code for opioid poisoning as a cause of death (Appendix 1, Table S2).

Covariates

We identified patient characteristics to describe the cohorts and adjust for confounding variables, including demographic variables (sex, age category, low-income status and rural residence); medical history, based on outpatient and inpatient records in the 365 days before follow-up; and prescription drug history in the 180 days before follow-up.

Medical history variables included psychiatric illness, mechanical neck or back problems (excluding low back pain), mechanical low back pain, osteoarthritis, rheumatoid arthritis, diabetic neuropathy, peripheral neuropathy (excluding diabetic neuropathy), lumbar radiculopathy, alcohol dependence or harmful use, opioid use disorder and Romano comorbidity score (an index of the patient's comorbidities based on previous diagnoses).[16,17] (See Appendix 1, Tables S3 and S4, for diagnostic codes and definitions for chronic pain conditions.)[18–26]

Prescription history variables included opioid substitution therapy (≥ 1 prescription), sedative and hypnotic medication (including benzodiazepines) (≥ 1 prescription), maximum daily opioid analgesic dose prescribed (≤ 50 mg of morphine equivalents [MME], > 50 to 90 MME, > 90 to 200 MME or > 200 MME)[27] and intensity of opioid analgesic use (60 to < 90 days' supply or ≥ 90 days' supply prescribed).

Statistical analysis

We estimated rate ratios (RRs) for the effect of the opioid policies on health outcomes, using generalized linear models with a log link function, a Poisson error distribution and an autoregressive correlation structure.[15] We used generalized estimating equations in regression models to adjust for correlations among multiple observations from the same patients.[28] In addition, we adjusted estimates by the patient-level covariates to control for confounding.

We estimated RRs for changes to the level and trend of each outcome following the introduction of the opioid prescribing standards and guidelines among patients in the policy cohort in comparison with the historical control cohort. Level changes represent a sudden change in event rates following the introduction of the policy, whereas trend (slope) changes reflect gradual monthly changes in outcome rates occurring during each month (Appendix 1, Figure S2). Our statistical model used interactions between a binary variable for cohort status (policy cohort v. historical control cohort) and level and trend effect variables to estimate postpolicy changes to level or trend[15,29] (see Appendix 1 for additional details).

In addition, we conducted preplanned analyses of our primary outcome in subgroups defined by prescription opioid use during the 180 days before follow-up, including by maximum daily dose (≤ 50 MME v. > 50 MME) and intensity of use (< 90 days' supply v. ≥ 90 days' supply dispensed).

Ethics approval

The study was approved by the University of British Columbia Clinical Research Ethics Board (H18–00494).

Results

The policy cohort included 68 113 patients, and the historical control cohort included 68 429 patients; 47 416 patients were in both cohorts because they met the inclusion criteria at baseline for each cohort. Patients were followed for 1–22 months; 90% were followed for at least 16 months. Approximately 90% of patients in the study were 40 years of age or older, and 54% were female. Patient characteristics are summarized in Table 1.[13]

The crude rates of opioid overdose hospital admissions were 3.2 hospital admissions per 1000 person-years during the prepolicy period in the policy cohort and 3.3 hospital admissions per 1000 person-years in the historical control cohort (Table 2 and Figure 1). In our analysis of the primary outcome of hospital admissions involving opioid overdose, we observed no significant impact of the college's opioid standards and guidelines on either the level of opioid overdose hospital admissions (adjusted RR 0.83, 95% confidence interval [CI] 0.45–1.54) or the trend in opioid overdose hospital admissions (adjusted RR 1.00, 95% CI 0.91–1.10) (Table 2). We also found no change in opioid overdose hospital admissions in subgroup analyses by baseline prescription opioid use (Table 2).

A decrease in the level of all-cause hospital admissions occurred in the policy cohort relative to the historical control cohort following the introduction of the opioid prescribing standards and guidelines (adjusted RR 0.86, 95% CI 0.82–0.91). However, this decrease in level may have been accompanied by an increasing monthly trend of all-cause hospital admissions (RR 1.01, 95% CI 1.00–1.02; $p = 0.002$), although the trend estimate's lower confidence limit overlapped 1.00 (Table 2). This mixed finding for all-cause hospital admissions is reflected in Figure 1, which shows that the crude rate of all-cause hospital admissions for the policy cohort declined in level in the initial months of the postpolicy period before trending upward without showing a clear difference from the data for the historical control cohort. In addition, we found no change following the introduction of the standards and guidelines in all-cause emergency department visits, opioid overdose mortality or all-cause mortality (Table 2, Figure 2 and Figure 3).

Interpretation

The College of Physicians and Surgeons of British Columbia's opioid prescribing standards and guidelines were not associated with a significant change in the primary outcome of opioid overdose hospital admissions among patients with long-term use of prescription opioid analgesics. Our mixed finding that all-cause hospital admissions declined in level but may have increased in trend suggests that a temporary decline in hospital admissions may have occurred. In addition, we

Table 1: Characteristics of patients with long-term opioid use in British Columbia

Characteristic	No. (%) of patients	
	Historical control cohort *n* = 68 429	Policy cohort *n* = 68 113
Demographic characteristics		
Sex		
Female	36 894 (53.9)	36 903 (54.2)
Male	31 535 (46.1)	31 210 (45.8)
Age, yr		
< 25	473 (0.7)	388 (0.6)
25–39	6376 (9.3)	5925 (8.7)
40–54	20 946 (30.6)	19 848 (29.1)
55–64	18 779 (27.4)	19 249 (28.3)
65–74	11 670 (17.1)	12 391 (18.2)
75–84	6921 (10.1)	7015 (10.3)
≥ 85	3264 (4.8)	3297 (4.8)
Low income	13 222 (19.3)	12 683 (18.6)
Place of residence		
Rural	10 766 (15.7)	10 726 (15.7)
Urban	57 663 (84.3)	57 387 (84.3)
Medical history in 365 d before follow-up		
Psychiatric illness	14 994 (21.9)	14 152 (20.8)
Chronic pain conditions		
Mechanical neck or back pain*	9738 (14.2)	9815 (14.4)
Mechanical low back pain	12 900 (18.9)	13 477 (19.8)
Osteoarthritis	6778 (9.9)	6723 (9.9)
Rheumatoid arthritis	1619 (2.4)	1566 (2.3)
Diabetic neuropathy	239 (0.3)	262 (0.4)
Peripheral neuropathy†	230 (0.3)	262 (0.4)
Lumbar radiculopathy	182 (0.3)	221 (0.3)
Alcohol dependence or harmful use	1307 (1.9)	1,311 (1.9)
Opioid use disorder	821 (1.2)	931 (1.4)
Romano comorbidity score		
0	36 447 (53.3)	36 000 (52.9)
1	17 146 (25.1)	16 965 (24.9)
2	7074 (10.3)	7320 (10.7)
≥ 3	7762 (11.3)	7828 (11.5)
Prescription history in 180 d before follow-up		
Opioid substitution therapy	943 (1.4)	909 (1.3)
Maximum daily opioid analgesic dose dispensed		
Lower dose (≤ 50 MME)	41 679 (60.9)	42 565 (62.5)
Intermediate dose (> 50 to 90 MME)	12 987 (19.0)	12 753 (18.7)
High dose (> 90 to 200 MME)	8598 (12.6)	8144 (12.0)
Very high dose (> 200 MME)	5165 (7.5)	4651 (6.8)
Intensity of opioid analgesic use‡		
Lower intensity use (< 90 days' supply)	10 648 (15.6)	10 471 (15.4)
Higher intensity use (≥ 90 days' supply)	57 781 (84.4)	57 642 (84.6)
Sedative and hypnotic medication	30 291 (44.3)	28 737 (42.2)

Note: Patient characteristics were evaluated before cohort entry (prior to June 1, 2014, for the historical control cohort and prior to June 1, 2015, for the policy cohort).
MME = milligrams of morphine equivalent.
*Excluded low back pain.
†Excluded diabetic neuropathy.
‡Based on days' supply dispensed.

Table 2: Impact of the College of Physicians and Surgeons of British Columbia's opioid prescribing standards and guidelines on health outcomes among patients with long-term opioid use

Analysis	No. of patients		Crude event rate per 1000 person-years*				Adjusted rate ratio‡ (95% CI)	
			Months 1–12†		Months 13–22†			
	Historical control cohort	Policy cohort	Historical control cohort	Policy cohort	Historical control cohort	Policy cohort	Impact on outcome level§	Impact on outcome trend§
Primary outcome								
Opioid overdose hospital admission	68 429	68 113	3.3	3.2	3.3	2.8	0.83 (0.45–1.54)	1.00 (0.91–1.10)
Secondary outcomes								
All-cause hospital admission	68 429	68 113	522	530	497	497	0.86 (0.82–0.91)	1.01 (1.00–1.02)††
All-cause emergency department visits	27 778	27 713	828	848	829	815	0.94 (0.88–1.00)	1.00 (0.99–1.01)
Opioid overdose mortality¶	68 429	68 113	1.0	1.3	1.4	2.1	1.38 (0.60–3.21)	0.97 (0.87–1.09)
All-cause mortality	68 429	68 113	17.2	17.5	17.2	19.3	1.08 (0.87–1.35)	1.01 (0.98–1.04)
Opioid overdose hospital admission, by baseline opioid analgesic use								
Maximum daily dose received¶**								
Lower dose (≤ 50 MME)	41 679	42 565	1.8	2.1	1.9	1.7	0.54 (0.21–1.35)	1.07 (0.93–1.24)
Higher dose (> 50 MME)	26 750	25 548	5.7	4.9	5.5	4.7	0.96 (0.44–2.10)	0.98 (0.87–1.10)
Intensity of opioid use¶								
Lower (< 90 d supply)	10 648	10 471	1.7	1.6	1.1	1.3	1.03 (0.16–6.84)	1.05 (0.72–1.51)
Higher (≥ 90 d supply)	57 781	57 642	3.7	3.5	3.7	3.1	0.79 (0.42–1.49)	1.00 (0.91–1.10)

Note: CI = confidence interval, MME = milligrams of morphine equivalents.
*May include multiple events of the same type for the same patient, but not in the same month.
†Months 1–12 and months 13–22 represent the prepolicy and postpolicy periods for the policy cohort and analogous periods for the historical control cohort.
‡Adjusted for patient-level covariates, including demographic variables, medical history and prescription drug use.
§Impact on outcome level measures a sudden change following implementation of a policy, whereas impact on outcome trend measures gradual change occurring each month following implementation of a policy.
¶Because of the small numbers of patients with neuropathic pain, it was not feasible to include covariates for these conditions in analyses of opioid overdose mortality or in subgroup analyses of opioid overdose hospital admission.
**Patient subgroups were defined by opioid analgesic medication use in the 180 d before follow-up.
††$p = 0.002$.

found no significant change in all-cause emergency department visits, opioid overdose mortality or all-cause mortality.

Opioid prescribing practices probably helped to create the current crisis of opioid overdoses and deaths in BC and other jurisdictions in North America, as opioids including high-dose opioids were increasingly prescribed for chronic noncancer pain.[30–32] We previously reported that the standards and guidelines were associated with modestly reduced use of opioid analgesics, increased switching from high-dose to lower dose opioids, and a decrease in concurrent use of opioids and sedative and hypnotic medications among patients with long-term opioid use.[13] Our current analysis suggests that these modest changes in prescription opioid utilization did not translate into reductions in opioid overdose hospital admissions, all-cause emergency department visits, opioid overdose mortality or all-cause mortality and were not associated with sustained reductions in all-cause hospital admissions.

A major contributing factor to the rise in opioid overdoses and deaths in BC in recent years has been contamination of street drugs with synthetic opioids such as fentanyl.[4] Concern has been expressed that policies focused on reducing prescribing of opioid analgesics could increase opioid-related deaths if patients unable to access prescription opioids for adequate pain relief turned to street drugs and were exposed to dangerously high levels of synthetic opioids.[33] Our study did not find evidence that the standards and guidelines had the unintended consequence of increasing opioid overdose hospital admissions or opioid overdose mortality.

It would be valuable for future research to investigate further how opioid prescribing standards or guidelines influence treatment of chronic noncancer pain, such as rates of initiation of or switching to nonopioid analgesic medications or nonpharmacologic treatments. Although the preferred study design will depend on the context, other study designs should be considered in future research, such as use of a concurrent control group or an interrupted time-series design. The impact of opioid prescribing standards or guidelines on health outcomes also merits additional research.

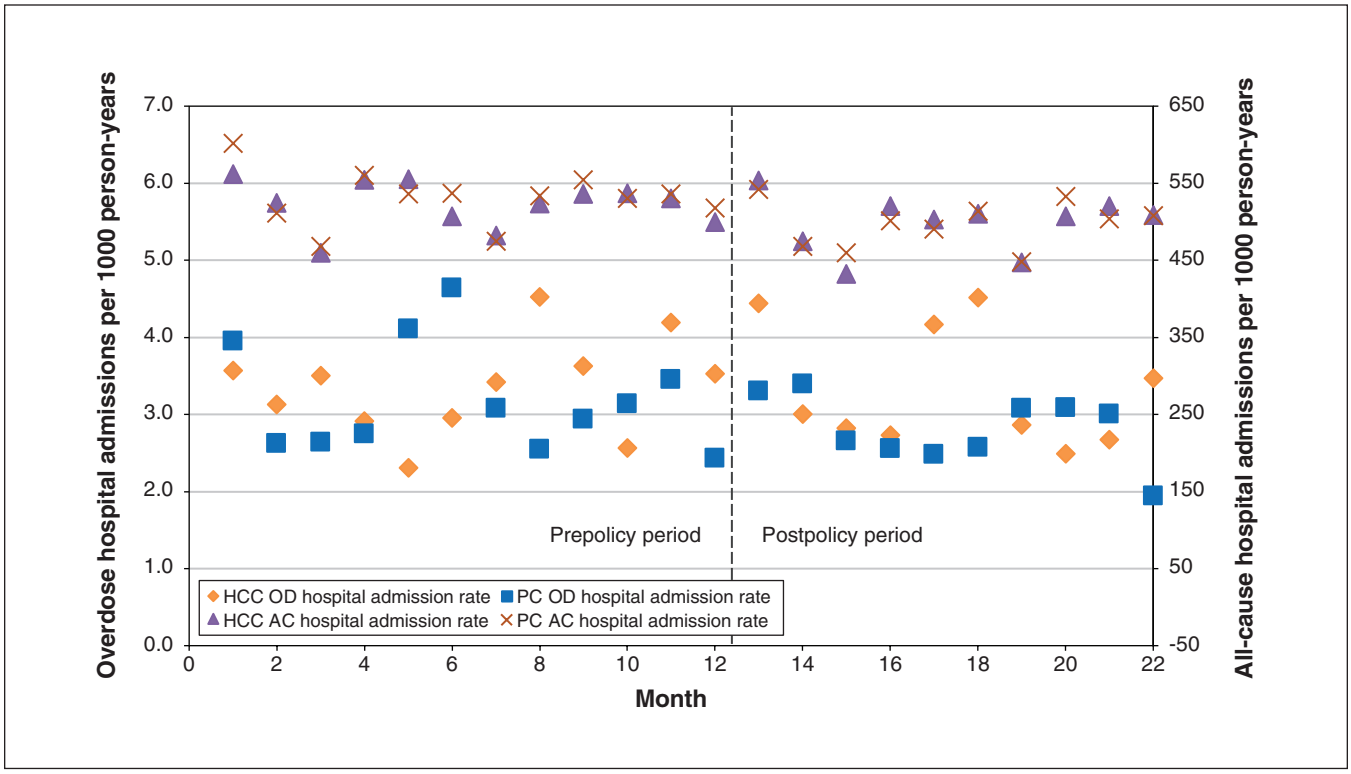

Figure 1: Opioid overdose (OD) hospital admission rates and all-cause (AC) hospital admission rates per 1000 person-years in the policy cohort (PC) versus the historical control cohort (HCC).

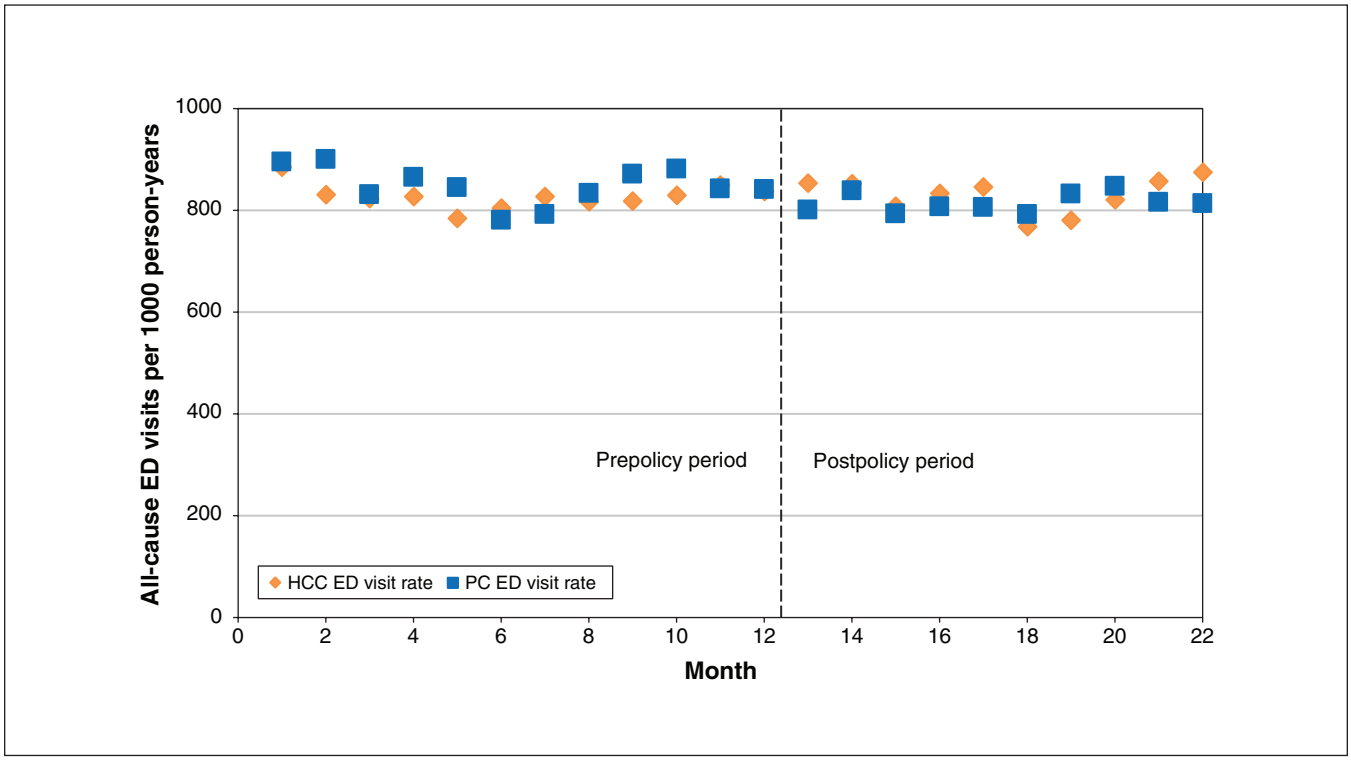

Figure 2: All-cause emergency department (ED) visit rates per 1000 person-years in the policy cohort (PC) versus the historical control cohort (HCC), among patients at least 95% likely to report to a hospital in the National Ambulatory Care Reporting System database.

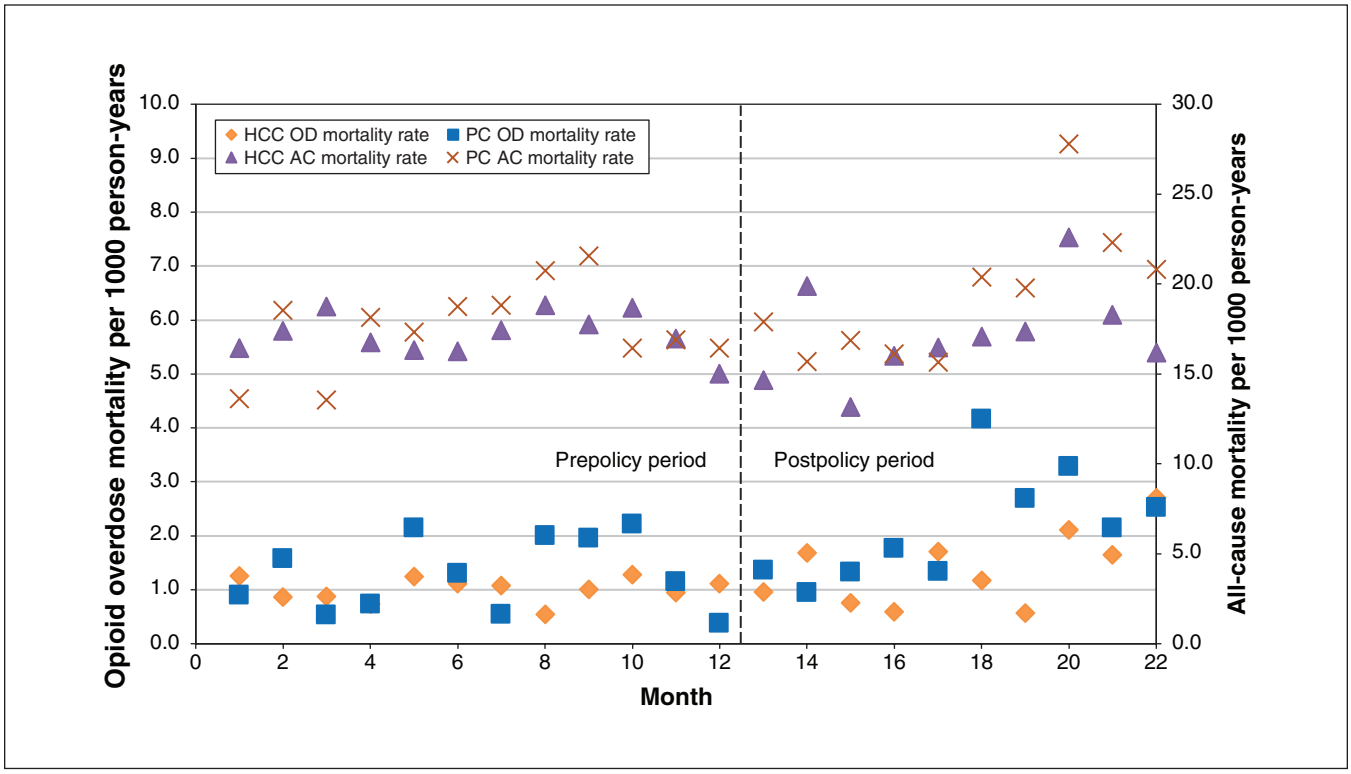

Figure 3: Opioid overdose (OD) mortality and all-cause (AC) mortality rates per 1000 person-years in the policy cohort (PC) versus the historical control cohort (HCC).

Limitations

Our study had several limitations. We used a study design that reused some outcomes from patients who were in both the historical control cohort and the policy cohort, with statistical adjustment for this reuse. We did not evaluate the impact of the policy on pain management. We focused on patients with a history of long-term opioid use and used a 10-month postpolicy period; impacts over the longer term or on other BC residents were beyond the study's scope. Homeless people may be underrepresented in our study population because of the exclusion of people without 1 year of medical services coverage.

Our primary outcome of opioid overdose hospital admission may be biased toward the null because of misclassification bias, as opioid overdoses of patients admitted to hospital may not always be accurately identified in administrative data. Our analyses may have been subject to time-varying confounders such as cointerventions or the exposure of some members of the study population to street drugs contaminated with fentanyl or other potent synthetic opioids at levels that varied over time. Cointerventions included declaring a public health emergency in BC,[34] scaling up the provincial take-home naloxone program[35] and increasing the availability of opioid agonist therapy.[36] Finally, the generalizability of our findings may depend on the similarity of other opioid prescribing policies to the college's standards and guidelines and on contextual factors such as the availability of alternative treatments and the contamination of the street drug supply.

Conclusion

The regulatory opioid prescribing standards and guidelines introduced by the College of Physicians and Surgeons of British Columbia in mid-2016 were not associated with reductions in opioid overdose hospital admissions, all-cause emergency department visits, opioid overdose mortality or all-cause mortality, or with a sustained reduction in all-cause hospital admissions, over a 10-month postpolicy period among patients with a history of long-term opioid use. Conversely, our analyses did not indicate that these policies produced the unintended consequence of increasing risk of these adverse events in this population.

References

1. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain — United States, 2016 [published erratum in *MMWR Recomm Rep* 2016;65:295]. *MMWR Recomm Rep* 2016;65:1-49.
2. Opioid-related harms in Canada. Ottawa: Canadian Institute for Health Information; 2017.
3. Special Advisory Committee on the Epidemic of Opioid Overdoses. National report: apparent opioid-related deaths in Canada (January 2016 to June 2017) Web-based report. Ottawa: Public Health Agency of Canada; 2017.
4. Illicit drug overdose deaths in BC: January 1, 2007–December 31, 2017. Burnaby (BC): British Columbia Coroners Service; 2018 Jan.
5. Gladstone EJ, Smolina K, Weymann D, et al. Geographic variations in prescription opioid dispensations and deaths among women and men in British Columbia, Canada. *Med Care* 2015;53:954-9.
6. Fischer B, Jones W, Rehm J. High correlations between levels of consumption and mortality related to strong prescription opioid analgesics in British Columbia and Ontario, 2005-2009. *Pharmacoepidemiol Drug Saf* 2013; 22:438-42.
7. Fischer B, Jones W, Urbanoski K, et al. Correlations between prescription opioid analgesic dispensing levels and related mortality and morbidity in Ontario, Canada, 2005-2011. *Drug Alcohol Rev* 2014;33:19-26.

8. Dhalla IA, Mamdani MM, Sivilotti ML, et al. Prescribing of opioid analgesics and related mortality before and after the introduction of long-acting oxycodone. *CMAJ* 2009;181:891-6.
9. Wisniewski AM, Purdy CH, Blondell RD. The epidemiologic association between opioid prescribing, non-medical use, and emergency department visits. *J Addict Dis* 2008;27:1-11.
10. College board endorses the US Centers for Disease Control and Prevention's guidelines for prescribing opioids in chronic pain [press release]. Vancouver: College of Physicians and Surgeons of British Columbia; 2016 Apr. 5.
11. Professional standards and guidelines: safe prescribing of drugs with potential for misuse/diversion. Vancouver: College of Physicians and Surgeons of British Columbia; revised 2016 Oct. 28.
12. Busse JW, Wang L, Kamaleldin M, et al. Opioids for chronic noncancer pain: a systematic review and meta-analysis. *JAMA* 2018;320:2448-60.
13. Morrow RL, Bassett K, Wright JM, et al. Influence of opioid prescribing standards on drug use among patients with long-term opioid use: a longitudinal cohort study. *CMAJ Open* 2019;7:E484-91.
14. Fitzmaurice GM, Laird NM, Ware JH. *Applied longitudinal analysis*. Hoboken (NJ): John Wiley & Sons; 2004.
15. Dormuth CR, Maclure M, Glynn RJ, et al. Emergency hospital admissions after income-based deductibles and prescription copayments in older users of inhaled medications. *Clin Ther* 2008;30:1038-50.
16. Schneeweiss S, Seeger JD, Maclure M, et al. Performance of comorbidity scores to control for confounding in epidemiologic studies using claims data. *Am J Epidemiol* 2001;154:854-64.
17. Romano PS, Roos LL, Jollis JG. Adapting a clinical comorbidity index for use with ICD-9-CM administrative data: differing perspectives. *J Clin Epidemiol* 1993;46:1075-9, discussion 81-90.
18. Lavis JN, Malter A, Anderson GM, et al. Trends in hospital use for mechanical neck and back problems in Ontario and the United States: discretionary care in different health care systems. *CMAJ* 1998;158:29-36.
19. Lacasse A, Ware MA, Dorais M, et al. Is the Quebec provincial administrative database a valid source for research on chronic non-cancer pain? *Pharmacoepidemiol Drug Saf* 2015;24:980-90.
20. Harrold LR, Yood RA, Andrade SE, et al. Evaluating the predictive value of osteoarthritis diagnoses in an administrative database. *Arthritis Rheum* 2000; 43:1881-5.
21. Widdifield J, Bernatsky S, Paterson JM, et al. Accuracy of Canadian health administrative databases in identifying patients with rheumatoid arthritis: a validation study using the medical records of rheumatologists. *Arthritis Care Res (Hoboken)* 2013;65:1582-91.
22. Dworkin RH, Malone DC, Panarites CJ, et al. Impact of postherpetic neuralgia and painful diabetic peripheral neuropathy on health care costs. *J Pain* 2010;11:360-8.
23. Berger A, Dukes EM, Oster G. Clinical characteristics and economic costs of patients with painful neuropathic disorders. *J Pain* 2004;5:143-9.
24. Kostev K, Jockwig A, Hallwachs A, et al. Prevalence and risk factors of neuropathy in newly diagnosed type 2 diabetes in primary care practices: a retrospective database analysis in Germany and U.K. *Prim Care Diabetes* 2014;8:250-5.
25. Callaghan B, Kerber K, Langa KM, et al. Longitudinal patient-oriented outcomes in neuropathy: importance of early detection and falls. *Neurology* 2015;85:71-9.
26. Schoenfeld AJ, Laughlin M, Bader JO, et al. Characterization of the incidence and risk factors for the development of lumbar radiculopathy. *J Spinal Disord Tech* 2012;25:163-7.
27. Nielsen S, Degenhardt L, Hoban B, et al. A synthesis of oral morphine equivalents (OME) for opioid utilisation studies. *Pharmacoepidemiol Drug Saf* 2016;25:733-7.
28. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics* 1986;42:121-30.
29. Dormuth CR, Glynn RJ, Neumann P, et al. Impact of two sequential drug cost-sharing policies on the use of inhaled medications in older patients with chronic obstructive pulmonary disease or asthma. *Clin Ther* 2006;28:964-78, discussion 2-3.
30. Smolina K, Gladstone EJ, Rutherford K, et al. Patterns and trends in long-term opioid use for non-cancer pain in British Columbia, 2005-2012. *Can J Public Health* 2016;107:e404-9.
31. Gomes T, Juurlink DN. Opioid use and overdose: what we've learned in Ontario. *Healthc Q* 2016;18:8-11.
32. Levy B, Paulozzi L, Mack KA, et al. Trends in opioid analgesic-prescribing rates by specialty, U.S., 2007-2012. *Am J Prev Med* 2015;49:409-13.
33. Tyndall M. An emergency response to the opioid overdose crisis in Canada: a regulated opioid distribution program. *CMAJ* 2018;190:E35-6.
34. Provincial health officer declares public health emergency [news release]. Vancouver: Government of British Columbia; 2016 Apr. 14. Available: https://news.gov.bc.ca/releases/2016HLTH0026-000568 (accessed 2016 Jul. 16).
35. Responding to BC's opioid overdose epidemic: progress update October 2017. Victoria (BC): BC Ministry of Mental Health and Addictions; 2017.
36. Important notice regarding Suboxone® [announcement]. Vancouver: College of Physicians and Surgeons of British Columbia; 2016 July 4. Available: www.cpsbc.ca/important-notice-regarding-suboxone%C2%AE (accessed 2016 Jul. 16).

Affiliations: Departments of Anesthesiology, Pharmacology and Therapeutics (Morrow, Bassett, Wright, Carney, Dormuth), Family Practice (Bassett), and Medicine (Wright), University of British Columbia, Vancouver, BC

Contributors: Richard Morrow, Ken Bassett, James Wright, Greg Carney and Colin Dormuth contributed to the study design. Richard Morrow conducted the data analysis and drafted the manuscript. All authors contributed to the interpretation of the data, revised the work for important intellectual content, provided final approval for the version to be published and agreed to be accountable for all aspects of the work.

Funding: This work was supported by a 5-year renewable grant to the University of British Columbia from the British Columbia Ministry of Health. Individuals employed by or consulting for the Ministry of Health at the time the research project was planned provided ideas and feedback on development of the research protocol.

Data sharing: The authors do not have permission to share data from this study.

Acknowledgements: The authors thank Brian Emerson (British Columbia Ministry of Health), Kathleen Perkin (British Columbia Ministry of Health), Mikhail Torban (advised while at the British Columbia Ministry of Health, now at the British Columbia Ministry of Mental Health and Addictions) and Kenneth Tupper (British Columbia Ministry of Health), who provided ideas and feedback during the development of the research protocol.

Disclaimer: The analyses and interpretations in this study are those of the authors and do not reflect the opinions or policies of the British Columbia Ministry of Health. All inferences, opinions and conclusions drawn in this article are those of the authors and do not reflect the opinions or policies of the data stewards.

Supplemental information: For reviewer comments and the original submission of this manuscript, please see www.cmajopen.ca/content/8/4/E869/suppl/DC1.