Prescription opioid treatment for non-cancer pain and initiation of injection drug use: large retrospective cohort study

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ABSTRACT

OBJECTIVE
To assess the association between long term prescription opioid treatment medically dispensed for non-cancer pain and the initiation of injection drug use (IDU) among individuals without a history of substance use.

DESIGN
Retrospective cohort study.

SETTING
Large administrative data source (containing information for about 1.7 million individuals tested for hepatitis C virus or HIV in British Columbia, Canada) with linkage to administrative health databases, including dispensations from community pharmacies.

PARTICIPANTS
Individuals age 11-65 years and without a history of substance use (except alcohol) at baseline.

MAIN OUTCOME MEASURES
Episodes of prescription opioid use for non-cancer pain were identified based on drugs dispensed between 2000 and 2015. Episodes were classified by the increasing length and intensity of opioid use (acute (lasting ‹90 episode days), episodic (lasting ≥90 episode days; with ‹90 days' drug supply and/ or ‹50% episode intensity), and chronic (lasting ≥90 episode days; with ≥90 days' drug supply and ≥50% episode intensity)). People with a chronic episode were matched 1:1:1:1 on socioeconomic variables to those with episodic or acute episodes and to those who were opioid naive. IDU initiation was identified by a validated administrative algorithm with high specificity. Cox models weighted by inverse probability of treatment weights assessed the association between opioid use category (chronic, episodic, acute, opioid naive) and IDU initiation.

RESULTS
59 804 participants (14 951 people from each opioid use category) were included in the matched cohort, and followed for a median of 5.8 years. 1149 participants initiated IDU. Cumulative probability of IDU initiation at five years was highest for participants with chronic opioid use (4.0%), followed by those with episodic use (1.3%) and acute use (0.7%), and those who were opioid naive (0.4%). In the inverse probability of treatment weighted Cox model, risk of IDU initiation was 8.4 times higher for those with chronic opioid use versus those who were opioid naive (95% confidence interval 6.4 to 10.9). In a sensitivity analysis limited to individuals with a history of chronic pain, cumulative risk for those with chronic use (3.4% within five years) was lower than the primary results, but the relative risk was not (hazard ratio 9.7 (95% confidence interval 6.5 to 14.5)). IDU initiation was more frequent at higher opioid doses and younger ages.

CONCLUSIONS
The rate of IDU initiation among individuals who received chronic prescription opioid treatment for non-cancer pain was infrequent overall (3-4% within five years) but about eight times higher than among opioid naive individuals. These findings could have implications for strategies to prevent IDU initiation, but should not be used as a reason to support involuntary tapering or discontinuation of long term prescription opioid treatment.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Several qualitative and observational quantitative studies have assessed the association between prescription opioids and initiation of illicit drug use or injection drug use

Few large longitudinal studies exist, and most studies have instead examined self-reported non-medical prescription opioid use and initiation of heroin use

Non-medical use most commonly involves diverted prescription opioids obtained from sources other than a doctor (eg, friends, family, drug dealers); therefore, less is known about medically dispensed opioid treatment for pain

WHAT THIS STUDY ADDS

In this large longitudinal study of nearly 60 000 individuals, objective measures were used for both prescription opioid use and initiation of injection drug use (as opposed to relying on self-report), and medically dispensed opioid treatment for non-cancer pain (as opposed to non-medical use) was assessed

Although the overall rate of injection drug use initiation among individuals with chronic use of prescription opioids was infrequent (3-4% within five years), the rate was 8-10 times higher than for opioid naive individuals

Introduction

Injection drug use is associated with substantial morbidity and mortality,[1] and the prevalence of this practice is increasing in some jurisdictions.[2 3] Harms associated with injection drug use include HIV, hepatitis C virus, infective endocarditis, skin and soft tissue infections, and overdose.[4 5] In Canada, the estimated number of people who inject drugs increased from 130 000 to 171 900 between 2011 and 2016.[3] In the US, an estimated one million people reported injection drug use in the past 12 months.[6] Identification of populations at higher risk of initiating injection drug use is critical to prevent transitions to this practice and reduce secondary harms.[7]

Medical use of opioids to treat acute and chronic pain is widespread in North America.[4 8] In general,

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prescription opioids are not recommended as first line treatment of chronic non-cancer pain due to limited long term benefit and risk of harms,[9-13] but adequate non-opioid alternatives are often unavailable or inaccessible (eg, owing to limited insurance coverage, poor availability of multidisciplinary pain clinics, or long wait times for pain management specialists).[14] Large increases in opioid prescribing in North America began in the late 1990s—driven in part by aggressive marketing and a heightened focus on pain management—and were followed by increases in opioid overdose deaths.[15 16] A systematic review of prescription opioid treatment for chronic pain estimated average rates of opioid misuse and addiction to be 21-29% and 8-12%, respectively.[11]

People prescribed opioids for pain could be at higher risk of initiating illicit or injection drug use. Individuals on long term opioid treatment tend to have a higher prevalence of potential risk factors for illicit or injection drug use, including chronic pain, lower socioeconomic status, mental health issues, and substance use.[17-20] Further, qualitative studies suggest that prescription opioids can facilitate initiation of heroin or injection drug use, and these transitions can be motivated by increasing tolerance, relief of pain or withdrawal, desire for a better high, or sudden reduced access to opioid drug treatments.[21-25] Recent initiatives to promote appropriate prescription opioid use have raised concerns related to involuntary tapering or discontinuation and subsequent transitions to the illicit drug market to manage pain or withdrawal.[26] These concerns are supported by longitudinal studies identifying a heightened risk of harms after discontinuation of opioid treatment.[27 28]

Little is known about the initiation of injection drug use among individuals medically prescribed opioids to manage pain. Instead, most quantitative research has focused on self-reported, so-called non-medical, prescription opioid use—which most often entails diverted prescription opioids obtained from friends, family members, or drug dealers[29]—and its link to initiation of heroin use.[20] While self-report is also used to measure the initiation of heroin and injection drug use in these studies, interest in the use of administrative data to identify injection drug use is increasing, because of the wide breadth of these databases and limitations with self-report.[6] Overall, most administrative studies conducted so far have aimed to quantify prevalence of injection drug use in various jurisdictions (rather than initiation in specific populations, such people who are prescribed opioids for pain).[3 30] Assessing initiation is important in order to establish temporality and identify potentially causal risk factors for transitioning to this practice. Identification of injection drug use in administrative data is challenged by the lack of specific diagnostic codes for injection, but validated algorithms exist with varying sensitivity and specificity.[30 31]

In this paper, we used a large administrative data source (of about 1.7 million people) with broad capture of the population in British Columbia, Canada (about a third of the province's population; all individuals tested for HIV or hepatitis C virus),[32] to examine the association between prescription opioid treatment for non-cancer pain and subsequent initiation of injection drug use among individuals without a history of substance use at baseline.

Methods

Data sources

We used the Integrated Data and Evaluative Analytics (IDEAs) cohort (also known as the British Columbia Hepatitis Testers Cohort) to conduct our retrospective cohort study. The databases integrated within IDEAs and their linkage have been described previously (supplementary table A).[32] The IDEAs cohort is composed of all individuals tested for hepatitis C virus or HIV at the British Columbia Centre for Disease Control Public Health Laboratory between 1992 and 2015, as well as reported cases of hepatitis B and tuberculosis. The laboratory conducts more than 95% of hepatitis C virus or HIV diagnostic testing in the province. These data are linked to data on medical visits (1990-2015), hospital admissions (1985-2015), emergency department visits (2012-15), cancer diagnoses (1923-2015), deaths (1985-2015), and pharmacy dispensations (1996-2015).

In British Columbia, HIV or hepatitis C virus testing is broadly offered to certain populations (eg, pregnant people, baby boomers, sexually active individuals). The IDEAs cohort is estimated to capture about a third of the province's population and 40-50% of prescription opioid use in the province.[18 32] Importantly, the IDEAs platform captures historical data on all participants, including data before and after an individual met the inclusion criteria (eg, before and after HIV or hepatitis C virus testing).

Long term prescription opioid treatment

Data on opioid medication dispensations were obtained from PharmaNet, a province wide database capturing dispensations from all community pharmacies in British Columbia (1996 onwards), regardless of payer. We identified all episodes of prescription opioid use for non-cancer pain between 1996 and 2015.[33] As defined by others, an episode starts with an incident opioid prescription (defined as no drug supply available in the past six months) and ends once there has been another six months with no drug supply.[33] When creating these episodes, we did not consider low dose codeine formulations (<30 mg per tablet), opioid formulations primarily used for cough suppression or opioid agonist treatment, injectable opioid formulations, or opioid dispensations occurring after a cancer or palliative care record.[18 34]

Based on episode length, we initially characterised each episode as either acute (lasting <90 episode days) or long term (≥90 episode days).[33] Long term episodes were further categorised as episodic or chronic, based on days' of drug supply (that is, the number of calendar days within an episode covered by drug supply) and episode intensity (that is, the percentage

of episode days covered by drug supply). Episodic episodes contained fewer than 90 days' drug supply and/or less than 50% of episode intensity, and chronic episodes contained at least 90 days' drug supply and at least 50% episode intensity.[18][34] We have extensively characterised these definitions in a previous analysis.[18]

Initiation of injection drug use

Participants were considered to have initiated injection drug use when the following two criteria occurred within one year of each other:

- Evidence of a problem related to the use of potentially injectable drugs (eg, diagnostic codes for dependence to opioids, cocaine, amphetamines, or benzodiazepines; prescription of opioid agonist treatment; supplementary table B); and
- Diagnosis of a possible injection related infection (eg, endocarditis, bacteraemia or sepsis, skin or soft tissue infections; supplementary table B).

In a validation study using the IDEAs cohort and linked surveillance data with self-reported injection drug use, this algorithm had a sensitivity of 63% and specificity of 90% for identifying people who inject drugs.[30] Despite the availability of alternative algorithms with a better balance between sensitivity and specificity,[30] we opted for a highly specific algorithm that included a requirement for an injection related infection, because drug related diagnostic codes do not specify the route of drug administration (eg, injection *v* oral) and—given our study population—these codes could be flagging dependence to prescription opioids taken orally.

Study design (matched cohort)

We created a matched cohort to examine the association between long term prescription opioid treatment and initiation of injection drug use. Each matched grouping included one person with a chronic episode of opioid use, one person with episodic opioid use, one person with acute opioid use, and an opioid naive person—all who entered the analysis in the same year and at about the same age (within a difference of 1 year of age). In this article, we refer to these categories within each matched group as the prescription opioid use categories (chronic, episodic, acute, opioid naïve).

To create the matched cohort, individuals with long term opioid use were classified into two groups, according to whether their first long term episode between 2000 and 2015 was episodic or chronic. Individuals with chronic opioid use were matched 1:1 to those with episodic opioid use, based on sociodemographic variables (birth year, sex, ethnic origin) and year of index date. Index date was defined as the initiation date of long term use (that is, start date of the first long term episode plus 90 days).

We next matched individuals with chronic opioid use (based on birth year, sex, and ethnic origin) to two groups of individuals without a history of long term prescription opioid use at baseline (1:1:1 to opioid naive and acute use individuals). These two groups of individuals without long term prescription opioid use were assigned the index date (baseline) of the person with chronic opioid use to whom they were matched.[35] The two groups were defined on the basis of prescription opioid use before their index date (that is, no history of opioid use for opioid naive, and ≥1 acute episode for acute use).

Eligibility criteria (matched cohort)

We applied several inclusion and exclusion criteria before and during the matching process. We included individuals aged between 11 and 65 years at the index date (the injection drug use algorithm was only validated for this age range)[30] and who had a record of living in British Columbia at least five years before index date.

We excluded individuals who had a cancer or palliative care diagnosis or evidence of substance use problems before index date. We were conservative with regards to the second exclusion criteria, and excluded all individuals meeting a more sensitive version of our injection drug use algorithm (sensitivity 91%, specificity 72%; supplementary table B).[30] This algorithm excluded the injection related infection requirement and captured a broader range of substance use diagnostic codes (but did not include alcohol). To further improve sensitivity, we also excluded individuals who were living with HIV or had been given a diagnosis of hepatitis C virus.

Before matching, we also excluded individuals who had missing sex or high level geographical information (health authority). However, we included individuals who were missing social or material deprivation information, because the lack of geographical information could be a proxy for homelessness.

Statistical analysis

Participants were followed from the index date to the earliest of the following: injection drug use initiation, 66 years of age, out-migration (two years after the last record in linked databases), initiation of a long term prescription opioid episode (only applicable to individuals in the acute use and opioid naive categories), study end (end of 2015 or 10 years of follow-up), or death. Individuals in the opioid naive and episodic use categories were not censored at initiation of an acute or chronic episode, respectively.

We used cumulative incidence curves to measure the cumulative probability of injection drug use initiation and Cox models to quantify the relative association between opioid use category (chronic, episodic, acute, opioid naive) and injection drug use initiation. In subanalyses, we stratified individuals with chronic opioid use by average daily dose across their first chronic episode. Average daily dose was calculated as the cumulative morphine equivalents prescribed during the episode divided by number of episode days covered by drug supply.

We weighted Cox models by inverse probability of treatment weights (IPTW).[36] The generalised propensity

scores used to derive IPTW were calculated from a multinomial logistic regression model with opioid use category as the outcome and sex, age, ethnic origin, health authority, material deprivation, major mental illness, alcohol use problem, and chronic pain as independent variables (all measured at the index date; supplementary table B). Weights were truncated at 1st and 99th centiles.[36] Models used a robust sandwich covariate matrix to account for intracluster correlation within each matched group.[37] We used the cumulative sums of Martingale residuals and the Kolmogorov type supremum test to assess the non-proportional hazards assumption.[38]

Sensitivity analyses
We conducted several sensitivity analyses, including a model with death as a competing risk,[39] a model with inverse probability of censoring weights to account for artificial censoring at initiation of a long term episode (only applicable to individuals in the acute use and opioid naive categories),[40] and a model using an alternate matched cohort limited to individuals with a history of chronic pain.[41 42]

Patient and public involvement
This cohort study was developed without patient involvement owing to the retrospective, administrative, and de-identified nature of the data sources. The study was developed in response to concerns expressed by patients and the public regarding the contribution of prescription opioids to the illicit overdose crisis in British Columbia. These concerns were brought forward to members of the research team through peer based organisations of people with lived and living experience of substance use, the media, concerned friends and family members, providers, and provincial committees involved in the overdose response.

Results
Study population
The IDEAs PharmaNet database includes information for about 1.7 million individuals (1996-2015). Of 159 109 eligible individuals who had a first long term prescription opioid episode between 2000 and 2015 (fig 1), 14 975 had a first long term episode that was chronic (that is, lasting ≥90 episode days; with at least 90 days' drug supply and at least 50% episode intensity). Almost all eligible people with a chronic episode (apart from 24 (0.2%) individuals) were matched (1:1:1:1) to an individual in the other opioid use categories (episodic, acute, opioid naive). The final matched cohort included 59 804 people (14 951 in each category).

Characteristics of study participants and success of IPTW weighting
Overall, 30 140 (50.4%) participants were male and the median age was 44 (interquartile range 35-55) years. The footnotes of table 1 show the breakdown of matched sociodemographic variables. With increasing length and intensity of prescription opioid use (that

is, from opioid naive to chronic use), we observed an increasing proportion of people who were more materially deprived or had history of major mental illness, alcohol use problems, or chronic pain (table 1). Standardised mean differences were 0.1 or more for all covariates before weighting by IPTW (except for matched variables) and all were less than 0.1 after weighting (supplementary table C).

Prescription opioid episode characteristics
Half of the chronic opioid episodes were longer than two years, contained more than 1.5 years of drug supply, and had an average daily dose of higher than 32 morphine equivalents (supplementary table D). The corresponding characteristics were lower for episodic episodes (171 days, 22 days, and 22 morphine equivalents, respectively). Supplementary table D contains additional information on episode characteristics (eg, inferred indication, most common opioid formulation). Our previous analysis showed that most acute episodes (about 70%) contain ≤7 days' supply of opioids.[18]

Study follow-up and injection drug use initiation
The 59 804 individuals in the matched cohort were followed for a median of 5.8 years (interquartile range 3.0-9.4), and 1149 participants initiated injection drug use (table 2). Risk of initiation was highest for the chronic use category, followed by the episodic use, acute use, and opioid naive categories (table 2, fig 2). In the chronic use category, risk of initiation was higher at younger ages (table 2, fig 2) and greater average daily dose (table 2, fig 2). Among individuals with chronic use who initiated injection drug use, the median time to identification of injection drug use through the administrative algorithm was 3.6 years (interquartile range 1.7-6.0).

Cox models
The magnitude of association between opioid use category (v opioid naive individuals) and injection drug use initiation increased with greater intensity and length of use (that is, chronic use had a greater association than episodic use, which was in turn greater than acute use; table 3). In the IPTW Cox model, risk of injection drug use initiation was 8.4 times (95% confidence interval 6.4 to 10.9) higher for people in the chronic opioid use category than for opioid naive individuals, 2.7 times (2.1 to 3.6) higher for people in the episodic use category, and 1.4 times (1.0 to 2.0) higher for people in the acute use category. Table 4 shows other characteristics associated with initiation of injection drug use.

Sensitivity analyses
Sensitivity analyses were generally consistent with our primary results (supplementary table E). However, limiting the analysis to individuals with a history of chronic pain lowered the cumulative probabilities of injection drug use initiation but did not lower the hazard ratios (table 3).
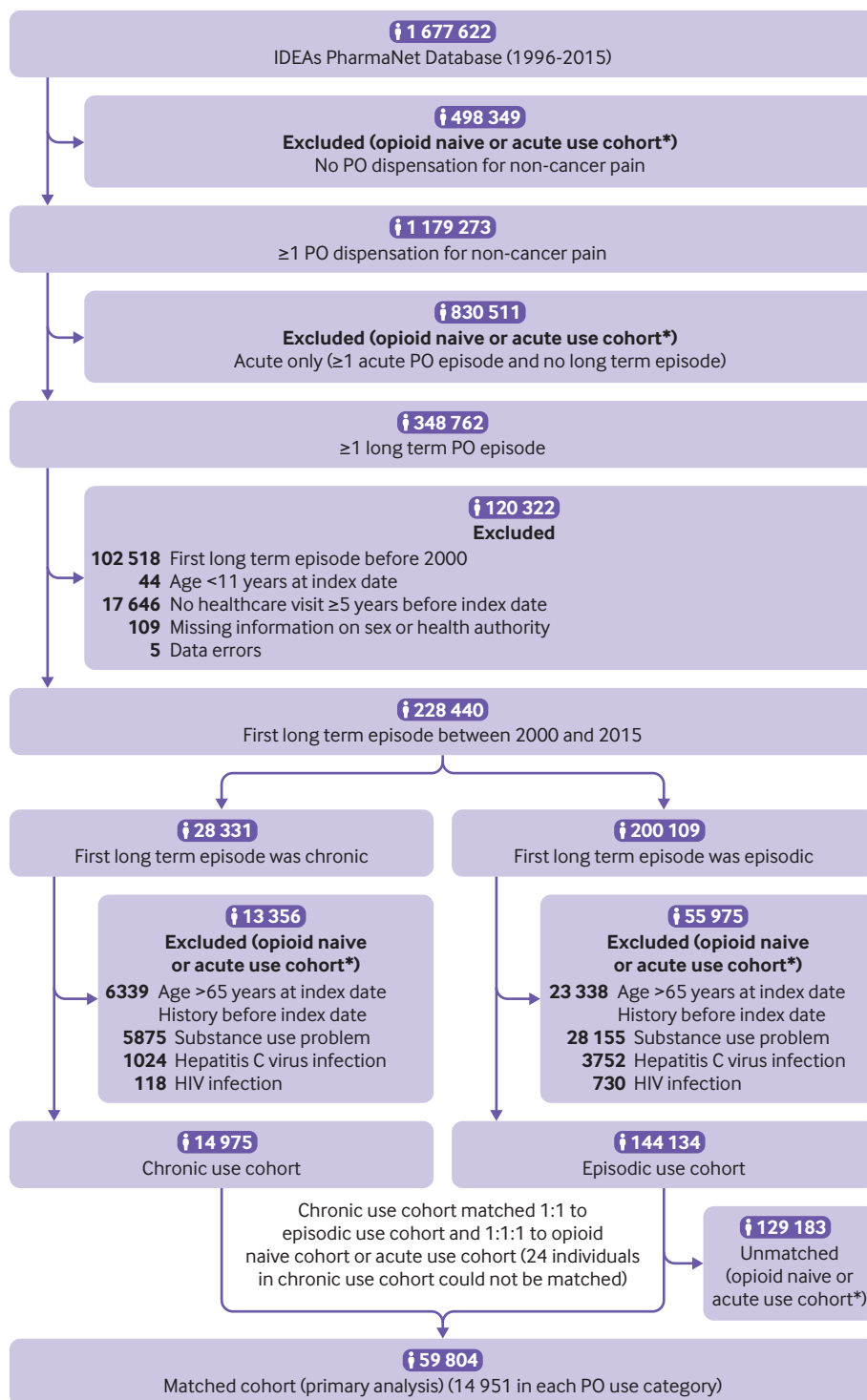
1 677 622
IDEAs PharmaNet Database (1996-2015)

498 349
Excluded (opioid naive or acute use cohort*)
No PO dispensation for non-cancer pain

1 179 273
≥1 PO dispensation for non-cancer pain

830 511
Excluded (opioid naive or acute use cohort*)
Acute only (≥1 acute PO episode and no long term episode)

348 762
≥1 long term PO episode

120 322
Excluded
102 518 First long term episode before 2000
44 Age <11 years at index date
17 646 No healthcare visit ≥5 years before index date
109 Missing information on sex or health authority
5 Data errors

228 440
First long term episode between 2000 and 2015

28 331
First long term episode was chronic

200 109
First long term episode was episodic

13 356
Excluded (opioid naive or acute use cohort*)
6339 Age >65 years at index date
History before index date
5875 Substance use problem
1024 Hepatitis C virus infection
118 HIV infection

55 975
Excluded (opioid naive or acute use cohort*)
23 338 Age >65 years at index date
History before index date
28 155 Substance use problem
3752 Hepatitis C virus infection
730 HIV infection

14 975
Chronic use cohort

144 134
Episodic use cohort

Chronic use cohort matched 1:1 to episodic use cohort and 1:1:1 to opioid naive cohort or acute use cohort (24 individuals in chronic use cohort could not be matched)

129 183
Unmatched (opioid naive or acute use cohort*)

59 804
Matched cohort (primary analysis) (14 951 in each PO use category)

Fig 1 | Study flowchart. IDEAs=Integrated Data and Evaluative Analytics data platform; PO=prescription opioid.
*Opioid naive or acute use cohort contains the pool of potential opioid naive or acute use individuals available for matching to the chronic use category; see methods for more detailed definitions of opioid use episodes

Discussion

Principal findings

In this longitudinal analysis of roughly 60 000 matched individuals selected from a large administrative data source (all individuals tested for HIV or hepatitis C virus in the Canadian province of British Columbia), the rate of injection drug use initiation among individuals who received chronic prescription opioid treatment for non-cancer pain was infrequent overall (3-4% within five years), but 8-10 times higher than among opioid naive individuals. Notably, of the almost 15 000 individuals on chronic opioid treatment, half had used opioid treatments on most days for more than two years, and initiation of injection drug use was more frequent at higher doses and younger ages. We excluded people older than 65 years or with a history of substance use

Table 1 | Characteristics of study participants by prescription opioid use category, matched cohort (n=59 804). Data are number (%) of participants

	Chronic use (n=14 951)	Episodic use (n=14 951)	Acute use (n=14 951)	Opioid naive (n=14 951)
Matched variables (sex, birth year, year of index date, approximate age (±1 year), ethnic origin)	Approximately the same across categories*			
Health authority (British Columbia)				
Vancouver Coastal	2931 (19.6)	3230 (21.6)	4087 (27.3)	4843 (32.4)
Fraser	4904 (32.8)	5220 (34.9)	5228 (35.0)	4998 (33.4)
Vancouver Island	2666 (17.8)	2549 (17.1)	2366 (15.8)	2095 (14.0)
Interior	3216 (21.5)	2564 (17.2)	2216 (14.8)	2130 (14.3)
Northern	1234 (8.3)	1388 (9.3)	1054 (7.1)	885 (5.9)
Urbanicity				
Urban	12 644 (84.6)	12 696 (84.9)	12 999 (86.9)	13 201 (88.3)
Rural	2254 (15.1)	2186 (14.6)	1904 (12.7)	1694 (11.3)
Missing	53 (0.4)	69 (0.5)	48 (0.3)	56 (0.4)
Material deprivation†				
1 (least)	2405 (16.1)	2873 (19.2)	3444 (23.0)	3678 (24.6)
5 (most)	3295 (22.0)	2969 (19.9)	2439 (16.3)	2394 (16.0)
Missing	97 (0.7)	87 (0.6)	67 (0.5)	72 (0.5)
Social deprivation†				
1 (least)	2222 (14.9)	2496 (16.7)	2648 (17.7)	2671 (17.9)
5 (most)	4044 (27.1)	3622 (24.2)	3481 (23.3)	3658 (24.5)
Missing	97 (0.7)	87 (0.6)	67 (0.5)	72 (0.5)
Chronic pain	8452 (56.5)	6905 (46.2)	5232 (35.0)	3197 (21.4)
Major mental illness	2937 (19.6)	2338 (15.6)	1837 (12.3)	1362 (9.1)
Alcohol use problem	996 (6.7)	686 (4.6)	409 (2.7)	255 (1.7)
Elixhauser comorbidity index†				
0	7171 (48.0)	8793 (58.8)	10 206 (68.3)	11 082 (74.1)
≥4	2234 (14.9)	1341 (9.0)	838 (5.6)	649 (4.3)

Index date for measurement of variables was initiation date of long term use (for people in episodic and chronic use categories) or index date of the matched chronic use individual (for people in opioid naive and acute use categories). Individuals were matched on sex, birth year, and ethnic origin.
*Data for sex, birth year, year of index date, approximate age (±1 year), and ethnic origin were similar across all categories (male (50.4%), female (49.6%); <1950s (17.4%), 1950-60s (53.0%), and >1970s (29.6%); 2000-04 (29.3%), 2005-09 (34.1%), and 2010-15 (36.6%); age <25 (7%), 25-34 (17%), 35-44 (23%), 45-54 (28%), and 55-65 (26%) years; and East Asian (2.2%), South Asian (5.6%), and other residents of British Columbia (92.2%), respectively).
†All levels not shown for ease of presentation.

problem (except alcohol) at baseline. Aspects unique to our analysis include the use of a population based, dispensation data source to identify opioid treatment (all prescriptions dispensed from community pharmacies, regardless of payer) and the application of a highly specific administrative algorithm (validated in our data source) to identify initiation of injection drug use.[18] [30] Our analysis fills an important gap in the literature, which has primarily focused on self-reported non-medical prescription opioid use (NMPOU) and heroin use,[20] and also contributes to a relatively new field of research using administrative algorithms to identify injection drug use. Importantly, we were unable to determine the underlying reasons for initiation of injection drug use, or whether these initiations were causally related to opioid treatment.

Table 2 | Number of participants, follow-up time, and rate of injection drug use (IDU) initiation by prescription opioid use category

Category	No of participants	Follow-up (person years)		No of incident IDU initiations	Rate of IDU initiation (per 1000 person years)	5 year cumulative probability of IDU initiation (%)
		Total	Median (interquartile range)			
Full matched cohort*	59 804	350 131	5.8 (3.0-9.4)	1149	3.3	1.6
Opioid naive	14 951	87 939	5.8 (3.1-9.4)	73	0.8	0.4
Acute	14 951	77 878	4.9 (2.4-8.1)	98	1.3	0.7
Long term (all)	29 902	194 314	6.3 (3.4-10.0)	978	5.0	2.6
Episodic	14 951	93 780	6.5 (3.5-10.0)	248	2.6	1.3
Chronic	14 951	90 534	6.2 (3.2-9.8)	730	8.1	4.0
Average daily dose (chronic use only; morphine equivalents)†						
<50	9887	58 499	5.9 (3.0-9.7)	291	5.0	2.4
50-89	2574	15 259	6.0 (3.3-9.0)	139	9.1	4.7
90-199	1695	11 187	7.1 (4.0-10.0)	175	15.6	7.9
≥200	795	5589	7.9 (4.6-10.0)	125	22.4	11.0
Age (chronic use only; years)†						
<25	1083	6953	6.6 (3.8-10.0)	129	18.6	9.4
25-34	2502	15 703	6.4 (3.7-10.0)	209	13.3	6.6
35-44	3382	23 540	7.8 (4.4-10.0)	193	8.2	4.0
45-65	7984	44 338	5.4 (2.7-8.7)	199	4.5	2.3

*See methods for more details on opioid use categories.
†Average daily dose calculated as the cumulative prescribed morphine equivalents during episode divided by the number of episode days covered by drug supply. Age measured at initiation of chronic opioid use.
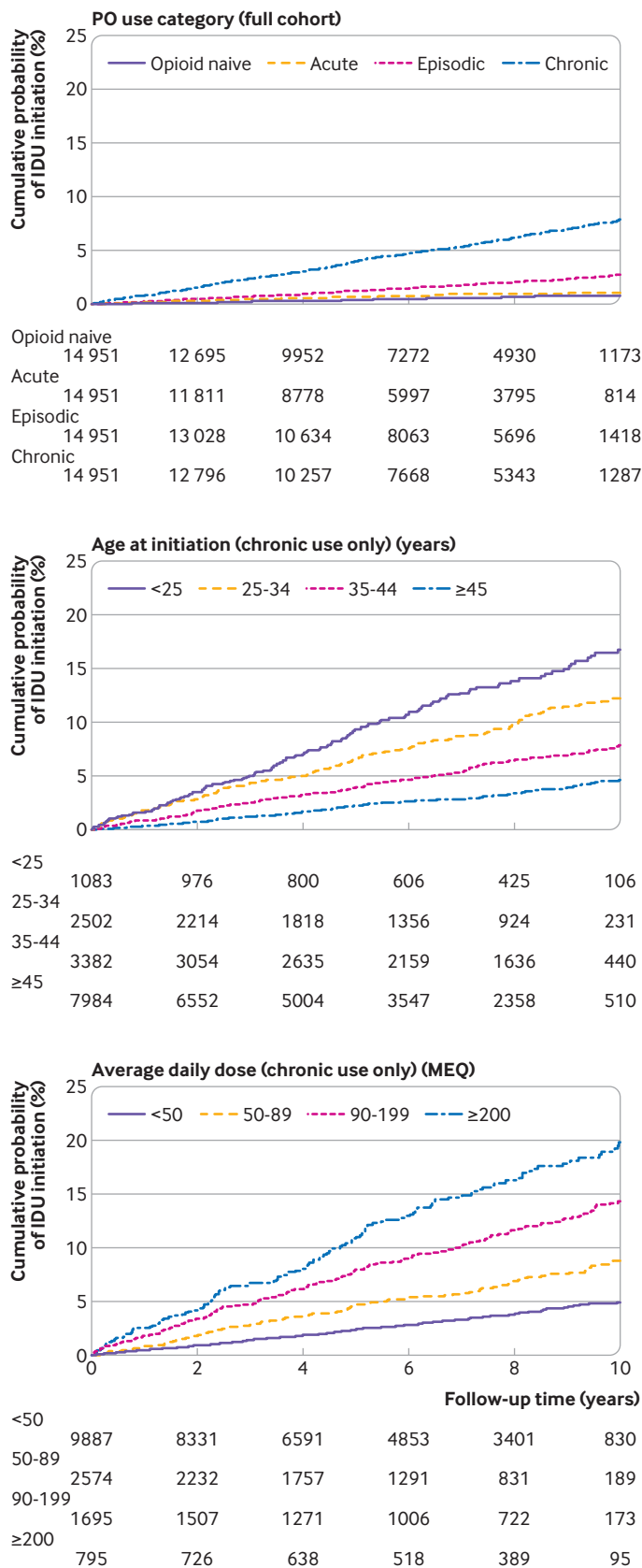
PO use category (full cohort)

Opioid naive	14 951	12 695	9952	7272	4930	1173
Acute	14 951	11 811	8778	5997	3795	814
Episodic	14 951	13 028	10 634	8063	5696	1418
Chronic	14 951	12 796	10 257	7668	5343	1287

Age at initiation (chronic use only) (years)

<25	1083	976	800	606	425	106
25-34	2502	2214	1818	1356	924	231
35-44	3382	3054	2635	2159	1636	440
≥45	7984	6552	5004	3547	2358	510

Average daily dose (chronic use only) (MEQ)

<50	9887	8331	6591	4853	3401	830
50-89	2574	2232	1757	1291	831	189
90-199	1695	1507	1271	1006	722	173
≥200	795	726	638	518	389	95

Fig 2 | Cumulative incidence of injection drug use initiation by prescription opioid use category, age at initiation of chronic episode (chronic use category only), and average daily dose of chronic episode (chronic use category only). PO=prescription opioid; MEQ=morphine equivalents; IDU=injection drug use. See methods for more details on opioid use categories. Average daily dose calculated as the cumulative morphine equivalents dispensed during episode divided by number of episode days covered by drug supply

Table 3 | Association between prescription opioid use category and initiation of injection drug use in Cox models

Prescription opioid use category*	Full matched cohort (primary analysis; n=59 804)					Matched cohort of individuals with history of chronic pain (sensitivity analysis; n=33 564)				
	No of individuals	5 year cumulative probability of IDU initiation (%)	Bivariable (unweighted; HR (95% CI))	Bivariable (IPTW; HR (95% CI))	Multivariable (IPTW; aHR (95% CI))	No of individuals	5 year cumulative probability of IDU initiation (%)	Bivariable (unweighted; HR (95% CI))	Bivariable (IPTW; HR (95% CI))	Multivariable (IPTW; aHR (95% CI))
Opioid naive	14 951	0.4	Reference	Reference	Reference	8391	0.3	Reference	Reference	Reference
Acute	14 951	0.7	1.5 (1.1 to 2.1)	1.5 (1.0 to 2.0)	1.4 (1.0 to 2.0)	8391	0.5	1.8 (1.1 to 2.9)	1.6 (1.0 to 2.7)	1.6 (1.0 to 2.6)
Episodic	14 951	1.3	3.2 (2.4 to 4.1)	2.8 (2.1 to 3.7)	2.7 (2.1 to 3.6)	8391	1.0	4.2 (2.7 to 6.3)	3.3 (2.2 to 5.1)	3.3 (2.1 to 5.0)
Chronic	14 951	4.0	9.7 (7.6 to 12.4)	8.4 (6.5 to 11.0)	8.4 (6.4 to 10.9)	8391	3.4	12.6 (8.5 to 18.6)	9.9 (6.7 to 14.8)	9.7 (6.5 to 14.5)

HR=hazard ratio; aHR=adjusted hazard ratio; IPTW=inverse probability treatment weighting; IDU=injection drug use.
The multinomial logistic regression model used to calculate the generalised propensity scores for IPTW included the following variables: sex, age, ethnic origin, health authority, material deprivation, chronic pain (full cohort only), major mental illness, and alcohol use problems. The multivariable IPTW models were adjusted for the same variables as the multinomial logistic regression model used to generate propensity scores. All models used a robust sandwich covariate matrix to account for intracluster correlation within each matched group of four.
*See methods on more details on opioid use categories.

Implications for clinicians and policy makers

Our findings could have implications for strategies to prevent the initiation of injection drug use (eg, more judicious opioid prescribing), but should not be used as a reason to support involuntary tapering or discontinuation of prescription opioid treatment. Abrupt discontinuation could lead to some individuals to access the increasingly dangerous illicit drug market,[23][27][28][43] and could explain some of the initiations of injection drug use in our analysis. Inadequately managed pain and denial of pain drug treatments have been identified as risk factors for illicit drug use, particularly among people with history of substance use.[29][43][44] The Canadian Pain Task Force has identified a need to foster shared decision making between providers and individuals living with chronic pain and "support opioid prescribing that balances the benefits and harms of these medications based on the needs of the individual."[45] Improved access to multidisciplinary approaches to treat pain is also needed.[14][45] Regarding non-opioid interventions, evidence suggests that some non-invasive (eg, exercise therapy, multidisciplinary rehabilitation, cognitive behavioural therapy) and invasive (eg, nerve blocks) treatments can improve function and/or reduce pain for specific conditions.[46][47]

The dose-response relation suggests that interventions aimed at preventing and treating prescription opioid dependence, appropriately tapering or discontinuing opioid use, and adequately treating pain (because dose might be a proxy for pain severity) could reduce the risk of injection drug use initiation. Guidelines generally recommend the avoidance of escalation to high doses, slow and voluntary tapering to the lowest effective dose (and potentially discontinuation) for people receiving high doses, and a multidisciplinary programme for individuals experiencing challenges in tapering.[12][13] Best practices for treating opioid dependence include provision of opioid agonist treatment in conjunction with psychosocial interventions and supports. Harm reduction interventions (eg, sterile drug use equipment, safer injection sites, and use of prescription opioids as a pharmaceutical alternative to illicit drugs) could reduce the risk of downstream harms from illicit or injection drug use.

We also found male sex, younger age, higher material deprivation, and history of mental illness and alcohol use problems to be associated with the initiation of injection drug use. These populations might also benefit from enhanced efforts to prevent initiation of injection.

Comparison to other findings

Our large longitudinal analysis supports findings from several surveys and smaller longitudinal studies demonstrating an association between self-reported NMPOU and initiation of heroin use.[20] While many of these studies enrolled specific populations and might not be widely generalisable, two large analyses of pooled data from a nationally representative survey in

Table 4 | Characteristics associated with initiation of injection drug use in the multivariable IPTW Cox model, full matched cohort (n=59 804)

	Adjusted hazard ratio (95% CI)
Prescription opioid use category (v opioid naive)*	
Acute	1.4 (1.0 to 2.0)
Episodic	2.7 (2.1 to 3.6)
Chronic	8.4 (6.4 to 10.9)
Male sex (v female)	1.6 (1.4 to 1.8)
Age (v 55-65 years)	
‹25	4.8 (3.7 to 6.2)
25-34	3.3 (2.6 to 4.2)
35-44	2.0 (1.6 to 2.6)
45-54	1.1 (0.9 to 1.5)
Ethnic origin (v other residents of British Columbia)	
South Asian	0.5 (0.3 to 0.7)
East Asian	0.4 (0.2 to 0.9)
Material deprivation (v 1 (least))	
2	1.3 (1.0 to 1.6)
3	1.4 (1.1 to 1.8)
4	1.4 (1.1 to 1.8)
5 (most)	1.6 (1.3 to 2.0)
Missing†	2.1 (1.2 to 3.7)
Chronic pain	0.8 (0.7 to 0.9)
Alcohol use problem	2.7 (2.2 to 3.3)
Major mental illness	1.6 (1.3 to 1.8)

IPTW=inverse probability of treatment weighting.
Model also adjusted for health authority (no statistically significant associations). The multinomial logistic regression model used to calculate the generalised propensity scores for IPTW included all the variables included in the multivariable Cox model. The Cox model used a robust sandwich covariate matrix to account for intracluster correlation within each matched group.
*See methods on more details on opioid use categories.
†Missing material deprivation was retained in the model because it could be a proxy for homelessness.

the US (National Survey on Drug Use and Health) found that incidence of heroin use initiation was 19 times higher among participants reporting previous NMPOU (unadjusted analysis),[48] and that young individuals (aged 12-21 years) with a history of NMPOU were at 13 times higher risk of initiating heroin use.[49] In one of the only studies to assess medically dispensed opioids for pain, high dose treatment was associated with a 2.5-fold higher risk of heroin use among military veterans in the US with a high prevalence of HIV (51%) and hepatitis C virus (33%).[50]

Our overall five year cumulative rate of injection drug use initiation after chronic prescription opioid use (3.4-4.0%) is similar to the widely cited transition rate from NMPOU to heroin use (3.6% within five years) from the National Survey on Drug Use and Health.[48] While any comparisons require caution, a common motivation for NMPOU is the relief of pain,[29] perhaps explaining the similarity. Higher rates of transition to heroin use have been observed in studies of specific populations.[51-54] The overall rate of injection drug use initiation in our analysis is also supported by estimated rates of misuse and addiction after prescription opioid treatment for chronic pain (21-29% and 8-12%, respectively),[11] because only a proportion of misuse or addiction would be expected to progress to injection. Initiation rates in our analysis were subject to several potential sources of over-estimation (eg, study limited to individuals tested for HIV or hepatitis C virus, exclusion of individuals older than 65 years of age, possible inclusion of people accessing prescription opioids for non-pain purposes, potential low positive predictive value) and under-estimation (eg, low sensitivity of the injection drug use algorithm, exclusion of people with a history of substance use), and should therefore be interpreted with caution.

Strengths and weaknesses of the study
Confounding could partly explain the association between prescription opioids and initiation of injection drug use, and could limit the extent to which firm conclusions can be drawn. We noted an increasing prevalence of potential risk factors for injection drug use across the gradient of increasing length and intensity of prescription opioid use (that is, from opioid naive to chronic use), including chronic pain, higher social or material deprivation, major mental illness, and alcohol use problems. To adjust for this potential source of bias, we matched on sociodemographic variables, used IPTW to balance further differences, and performed a sensitivity analysis limited to individuals with chronic pain (a key confounder by indication because individuals might transition to injection drug use to manage uncontrolled chronic pain, independent of their current or previous prescription opioid use). Among people with chronic opioid use in this sensitivity analysis, the cumulative probability of initiation decreased but the relative strength of association (hazard ratio) did not. Possible sources of residual confounding include the use of administrative databases to identify confounders (a source of misclassification bias), potential inclusion of individuals accessing prescription opioids for non-pain purposes (eg, euphoric effects, dependence, off-label opioid agonist treatment), and the inability to adjust for severity of pain.

Several strengths and weaknesses were related to the use of our administrative algorithm to identify injection drug use. Strengths include the high specificity of the algorithm, advantages compared to the use of self-report, and contribution to a relatively new field of research exploring the use of such algorithms (which is inherently challenged by the lack of diagnostic codes specific to injection drug use). Limitations include low sensitivity and low potential positive predictive value (owing to expected low prevalence of the outcome), validation of our algorithm via self-report (although self-report is generally considered the gold standard), inability to identify exact date of injection initiation, and delays between actual initiation and algorithm identification.

Our analysis had several other limitations, including challenges using pharmacy dispensation data to determine how drug treatments were actually taken and possible inclusion of people with undetected injection drug use at baseline (owing to the imperfect sensitivity of the algorithm). Furthermore, the dose-response analysis was based on the average daily dose across the full chronic episode and could include dispensations after initiation of injection drug use. We did not compare prescription opioids to alternative pain treatments, and this requires further research. Also, our analysis did not take into account the time varying nature of potential confounders; instead, covariates

were measured as binary variables at study start. Although the study end date was 2015, our analysis captures an important period in British Columbia when prescription opioid use increased and could have contributed to the illicit opioid overdose epidemic that started in 2015-16 (by facilitating transitions to illicit or injection drug use). Finally, our study population was primarily limited to people tested for HIV or hepatitis C virus, potentially limiting generalisability of study findings. In particular, the absolute rates of injection drug use initiation could be higher in our study sample than the general population. However, HIV and hepatitis C virus testing is broadly offered to some populations in British Columbia (eg, pregnant people, baby boomers, sexually active individuals).

Conclusion

The rate of injection drug use initiation among individuals who received chronic prescription opioid treatment for non-cancer pain was infrequent overall (3-4% within five years), but 8-10 times higher than opioid naive individuals. Rate of initiation was more frequent with greater doses and at younger ages. Our findings could help inform strategies and policies to prevent further transitions to injection drug use and related harms secondary to such use, but should not be used as a reason to inappropriately taper or discontinue long term prescription opioid treatment.

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1   Mathers BM, Degenhardt L, Bucello C, Lemon J, Wiessing L, Hickman M. Mortality among people who inject drugs: a systematic review and meta-analysis. *Bull World Health Organ* 2013;91:102-23. doi:10.2471/BLT.12.108282

2   Zibbell JE, Asher AK, Patel RC, et al. Increases in Acute Hepatitis C Virus Infection Related to a Growing Opioid Epidemic and Associated Injection Drug Use, United States, 2004 to 2014. *Am J Public Health* 2018;108:175-81. doi:10.2105/AJPH.2017.304132

3   Jacka B, Larney S, Degenhardt L, et al. Prevalence of Injecting Drug Use and Coverage of Interventions to Prevent HIV and Hepatitis C Virus Infection Among People Who Inject Drugs in Canada. *Am J Public Health* 2020;110:45-50. doi:10.2105/AJPH.2019.305379

4   Degenhardt L, Grebely J, Stone J, et al. Global patterns of opioid use and dependence: harms to populations, interventions, and future action. *Lancet* 2019;394:1560-79. doi:10.1016/S0140-6736(19)32229-9

5   Larney S, Peacock A, Mathers BM, Hickman M, Degenhardt L. A systematic review of injecting-related injury and disease among people who inject drugs. *Drug Alcohol Depend* 2017;171:39-49. doi:10.1016/j.drugalcdep.2016.11.029

6   Bradley H, Rosenthal EM, Barranco MA, Udo T, Sullivan PS, Rosenberg ES. Use of Population-Based Surveys for Estimating the Population Size of Persons Who Inject Drugs in the United States. *J Infect Dis* 2020;222(Suppl 5):S218-29. doi:10.1093/infdis/jiaa318

7   Werb D, Buxton J, Shoveller J, Richardson C, Rowell G, Wood E. Interventions to prevent the initiation of injection drug use: a systematic review. *Drug Alcohol Depend* 2013;133:669-76. doi:10.1016/j.drugalcdep.2013.08.017

8   Knaul FM, Farmer PE, Krakauer EL, et al, Lancet Commission on Palliative Care and Pain Relief Study Group. Alleviating the access abyss in palliative care and pain relief-an imperative of universal health coverage: the Lancet Commission report. *Lancet* 2018;391:1391-454. doi:10.1016/S0140-6736(17)32513-8

9   Busse JW, Wang L, Kamaleldin M, et al. Opioids for Chronic Noncancer Pain: A Systematic Review and Meta-analysis. *JAMA* 2018;320:2448-60. doi:10.1001/jama.2018.18472

10 Chou R, Turner JA, Devine EB, et al. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. *Ann Intern Med* 2015;162:276-86. doi:10.7326/M14-2559

11 Vowles KE, McEntee ML, Julnes PS, Frohe T, Ney JP, van der Goes DN. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. *Pain* 2015;156:569-76. doi:10.1097/01.j.pain.0000460357.01998.f1

12 Busse JW, Craigie S, Juurlink DN, et al. Guideline for opioid therapy and chronic noncancer pain. *CMAJ* 2017;189:E659-66. doi:10.1503/cmaj.170363

13 Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain - United States, 2016. *MMWR Recomm Rep* 2016;65:1-49. doi:10.15585/mmwr.rr6501e1

14 Lynch ME. The need for a Canadian pain strategy. *Pain Res Manag* 2011;16:77-80. doi:10.1155/2011/654651

15 King NB, Fraser V, Boikos C, Richardson R, Harper S. Determinants of increased opioid-related mortality in the United States and Canada, 1990-2013: a systematic review. *Am J Public Health* 2014;104:e32-42. doi:10.2105/AJPH.2014.301966

16 DeWeerdt S. Tracing the US opioid crisis to its roots. *Nature* 2019;573:S10-2. doi:10.1038/d41586-019-02686-2

17 Campbell G, Nielsen S, Bruno R, et al. The Pain and Opioids IN Treatment study: characteristics of a cohort using opioids to manage chronic non-cancer pain. *Pain* 2015;156:231-42. doi:10.1097/01.j.pain.0000460303.63948.8e

18 Wilton J, Chong M, Abdia Y, et al. Cohort profile: development and characteristics of a retrospective cohort of individuals dispensed prescription opioids for non-cancer pain in British Columbia, Canada. *BMJ Open* 2021;11:e043586. doi:10.1136/bmjopen-2020-043586

19 Ray GT, Bahorik AL, VanVeldhuisen PC, Weisner CM, Rubinstein AL, Campbell CI. Prescription opioid registry protocol in an integrated health system. *Am J Manag Care* 2017;23:e146-55.

20 Compton WM, Jones CM, Baldwin GT. Relationship between Nonmedical Prescription-Opioid Use and Heroin Use. *N Engl J Med* 2016;374:154-63. doi:10.1056/NEJMra1508490

21 Mars SG, Bourgois P, Karandinos G, Montero F, Ciccarone D. "Every 'never' I ever said came true": transitions from opioid pills to heroin injecting. *Int J Drug Policy* 2014;25:257-66. doi:10.1016/j.drugpo.2013.10.004

22 Lankenau SE, Teti M, Silva K, Jackson Bloom J, Harocopos A, Treese M. Initiation into prescription opioid misuse amongst young injection drug users. *Int J Drug Policy* 2012;23:37-44. doi:10.1016/j.drugpo.2011.05.014

23 Nolte K, Drew AL, Friedmann PD, Romo E, Kinney LM, Stopka TJ. Opioid initiation and injection transition in rural northern New England: A mixed-methods approach. *Drug Alcohol Depend* 2020;217:108256. doi:10.1016/j.drugalcdep.2020.108256

24 Syvertsen JL, Paquette CE, Pollini RA. Down in the valley: Trajectories of injection initiation among young injectors in California's Central Valley. *Int J Drug Policy* 2017;44:41-9. doi:10.1016/j.drugpo.2017.03.003

25 Cicero TJ, Ellis MS. Oral and non-oral routes of administration among prescription opioid users: Pathways, decision-making and directionality. *Addict Behav* 2018;86:11-6. doi:10.1016/j.addbeh.2018.05.015

26 Darnall BD, Juurlink D, Kerns RD, et al. International Stakeholder Community of Pain Experts and Leaders Call for an Urgent Action on Forced Opioid Tapering. *Pain Med* 2019;20:429-33. doi:10.1093/pm/pny228

27 Oliva EM, Bowe T, Manhapra A, et al. Associations between stopping prescriptions for opioids, length of opioid treatment, and overdose or suicide deaths in US veterans: observational evaluation. *BMJ* 2020;368:m283. doi:10.1136/bmj.m283

28 Mark TL, Parish W. Opioid medication discontinuation and risk of adverse opioid-related health care events. *J Subst Abuse Treat* 2019;103:58-63. doi:10.1016/j.jsat.2019.05.001

29 Lynch M. Nonmedical use of prescription opioids: what is the real problem? *Pain Res Manag* 2013;18:67-8. doi:10.1155/2013/824914

30 Janjua NZ, Islam N, Kuo M, et al, BC Hepatitis Testers Cohort Team. Identifying injection drug use and estimating population size of people who inject drugs using healthcare administrative datasets. *Int J Drug Policy* 2018;55:31-9. doi:10.1016/j.drugpo.2018.02.001

31 McGrew KM, Homco JB, Garwe T, et al. Validity of International Classification of Diseases codes in identifying illicit drug use target conditions using medical record data as a reference standard: A systematic review. *Drug Alcohol Depend* 2020;208:107825. doi:10.1016/j.drugalcdep.2019.107825

32 Janjua NZ, Kuo M, Chong M, et al. Assessing Hepatitis C Burden and Treatment Effectiveness through the British Columbia Hepatitis Testers Cohort (BC-HTC): Design and Characteristics of Linked and Unlinked Participants. *PLoS One* 2016;11:e0150176. doi:10.1371/journal.pone.0150176

33 Von Korff M, Saunders K, Thomas Ray G, et al. De facto long-term opioid therapy for noncancer pain. *Clin J Pain* 2008;24:521-7. doi:10.1097/AJP.0b013e318169d03b

34 Smolina K, Crabtree A, Chong M, et al. Patterns and history of prescription drug use among opioid-related drug overdose cases in British Columbia, Canada, 2015-2016. *Drug Alcohol Depend* 2019;194:151-8. doi:10.1016/j.drugalcdep.2018.09.019

35 Mamdani M, Rochon PA, Juurlink DN, et al. Observational study of upper gastrointestinal haemorrhage in elderly patients given selective cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs. *BMJ* 2002;325:624. doi:10.1136/bmj.325.7365.624

36 Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med* 2015;34:3661-79. doi:10.1002/sim.6607

37 Lee EW, Wei LJ, Amato DA, Leurgans S. *Cox-Type Regression Analysis for Large Numbers of Small Groups of Correlated Failure Time Observations. Survival Analysis: State of the Art.* Springer Netherlands, 1992: 237-47.

38 Lin DY, Wei LJ, Ying Z. Checking the Cox model with cumulative sums of martingale-based residuals. *Biometrika* 1993;80:557-72. doi:10.1093/biomet/80.3.557.

39 Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. *J Am Stat Assoc* 1999;94:496-509. doi:10.1080/01621459.1999.10474144.

40 Rimawi M, Hilsenbeck SG. Making sense of clinical trial data: is inverse probability of censoring weighted analysis the answer to crossover bias? *J Clin Oncol* 2012;30:453-8. doi:10.1200/JCO.2010.34.2808

41 Tian TY, Zlateva I, Anderson DR. Using electronic health records data to identify patients with chronic pain in a primary care setting. *J Am Med Inform Assoc* 2013;20(e2):e275-80. doi:10.1136/amiajnl-2013-001856

42 Tonelli M, Wiebe N, Fortin M, et al, Alberta Kidney Disease Network. Methods for identifying 30 chronic conditions: application to administrative data. *BMC Med Inform Decis Mak* 2015;15:31. doi:10.1186/s12911-015-0155-5

43 Behar E, Bagnulo R, Knight K, Santos G-M, Coffin PO. "Chasing the pain relief, not the high": Experiences managing pain after opioid reductions among patients with HIV and a history of substance use. *PLoS One* 2020;15:e0230408. doi:10.1371/journal.pone.0230408

44 Voon P, Callon C, Nguyen P, et al. Denial of prescription analgesia among people who inject drugs in a Canadian setting. *Drug Alcohol Rev* 2015;34:221-8. doi:10.1111/dar.12226

45 Canadian Pain Task Force. Chronic Pain in Canada: Laying a Foundation for Action. 2019. https://www.canada.ca/content/dam/hc-sc/documents/corporate/about-health-canada/public-engagement/external-advisory-bodies/canadian-pain-task-force/report-2019/canadian-pain-task-force-June-2019-report-en.pdf

46 Skelly AC, Chou R, Dettori JR, et al. *Noninvasive Nonpharmacological Treatment for Chronic Pain: A Systematic Review Update.* Agency for Healthcare Research and Quality (US). 2020. doi:10.23970/AHRQEPCCER227.

47 Hong T, Wang H, Li G, Yao P, Ding Y. Systematic Review and Meta-Analysis of 12 Randomized Controlled Trials Evaluating the Efficacy of Invasive Radiofrequency Treatment for Knee Pain and Function. *Biomed Res Int* 2019;2019:9037510. doi:10.1155/2019/9037510

48 Muhuri P, Gfroerer M, Davies C. Associations of Nonmedical Pain Reliever Use and Initiation of Heroin Use in the United States. 2013. https://www.samhsa.gov/data/sites/default/files/DR006/DR006/nonmedical-pain-reliever-use-2013.htm

49 Cerdá M, Santaella J, Marshall BDL, Kim JH, Martins SS. Nonmedical Prescription Opioid Use in Childhood and Early Adolescence Predicts Transitions to Heroin Use in Young Adulthood: A National Study. *J Pediatr* 2015;167:605-12.e1, 2. doi:10.1016/j.jpeds.2015.04.071

50 Banerjee G, Edelman EJ, Barry DT, et al. High-dose prescribed opioids are associated with increased risk of heroin use among United States military veterans. *Pain* 2019;160:2126-35. doi:10.1097/j.pain.0000000000001606

51 Banerjee G, Edelman EJ, Barry DT, et al. Non-medical use of prescription opioids is associated with heroin initiation among US veterans: a prospective cohort study. *Addiction* 2016;111:2021-31. doi:10.1111/add.13491

52 Carlson RG, Nahhas RW, Martins SS, Daniulaityte R. Predictors of transition to heroin use among initially non-opioid dependent illicit pharmaceutical opioid users: A natural history study. *Drug Alcohol Depend* 2016;160:127-34. doi:10.1016/j.drugalcdep.2015.12.026

53 Surratt HL, Kurtz SP, Buttram M, Levi-Minzi MA, Pagano ME, Cicero TJ. Heroin use onset among nonmedical prescription opioid users in the club scene. *Drug Alcohol Depend* 2017;179:131-8. doi:10.1016/j.drugalcdep.2017.06.034

54 Kelley-Quon LI, Cho J, Strong DR, et al. Association of Nonmedical Prescription Opioid Use With Subsequent Heroin Use Initiation in Adolescents. *JAMA Pediatr* 2019;173:e191750. doi:10.1001/jamapediatrics.2019.1750

Web appendix: Supplementary Appendix