Supplemental Appendix

METHODS

This matched retrospective cohort study was conducted in Manitoba, a Canadian province with a population of ~1.4 million, and universal health care. Medically necessary services are publicly funded, and the provincial governmental captures health service use by nearly all residents.

Data Sources

We accessed administrative databases held by The Population Research Data Repository at the Manitoba Centre for Health Policy. The databases (and variables used) included the population registry (dates of birth, death and health care coverage; sex; and postal code which provided region of residence), medical services/physician claims (one physician-assigned diagnosis and date of service), the Discharge Abstract Database (DAD; hospitalizations, including admission and separation dates, and diagnoses), and Drug Program Information Network (DPIN; outpatient prescription dispensations, including the date, drug name, and Health Canada drug identification number [DIN]). Physician claims use the International Classification of Diseases (ICD), 9th revision, Clinical Modification (ICD-9-CM) to document diagnoses. Up to 2004, diagnosed in the DAD are also documented using (ICD)-9-CM, and ICD 10th revision, Canadian version (ICD-10-CA) codes are used thereafter. All databases were linked at the individual level using an encrypted unique identifier. We obtained approval to conduct this population-based cohort study from Manitoba’s Health Information Privacy Committee and the University of Manitoba Health Research Ethics Board.

Study populations

We identified all Manitobans with MS over the period 1984 to 2016 by applying a validated case definition that required ≥3 health care encounters for MS, as identified based on diagnostic codes for MS in hospitalizations or physician visits, or the use of MS-specific disease-modifying therapies in any combination. We assigned the index date for each person with MS based on the earliest demyelinating disease claim. Next, we chose a general population cohort matched 5:1 on sex, year of birth (± 5 years), and forward sortation area (first 3 digits of postal code) to the MS cohort. The matched (non-MS) cohort excluded anyone with any ICD-9-CM and ICD-10-CA diagnosis codes for demyelinating disease or use of any MS-specific disease-modifying therapies. The non-MS cohort also excluded individuals with codes
for inflammatory bowel disease and rheumatoid arthritis because we conducted parallel studies for these diseases. The index date for each control was the index date of their matched case. Collectively, these comprised the prevalent cohorts.

From these cohorts, we subsequently selected incident (newly diagnosed) MS cases and matched controls with an index date of 1997 or later. DPIN data began in the fiscal year 1995/96 so this index date coupled with identification of incident MS cases provided a one year run-in period to determine whether opioid use was truly new post-index. Opioids are indicated for the management of acute pain, and cancer pain. Therefore, we also excluded individuals in the MS and non-MS cohorts with cancer (based on ≥1 ICD-9 140-208 or ICD-10-CA C00-C97 code) or in palliative care (based on hospital ICD-9/ICD-10-CA V66.7/Z51.5 or DPIN claims indicating palliative care). To preserve the matching balance, the corresponding matched cases or controls were also excluded. Anyone who developed cancer or entered palliative care following the index date was censored when the relevant diagnostic code first appeared. We also censored individuals on death or leaving the province.

**Psychiatric comorbidity**

To identify persons with any diagnosed mood/anxiety disorder (including ≥1 of depression, anxiety, or bipolar disorders) we used validated case definitions. We assigned the date of the first claim for each condition as the diagnosis date. Mood/anxiety disorder status was updated annually to account for the relapsing and remitting nature of these disorders. The affected person was deemed to be an ‘active’ case if there were ≥2 physician claims or one hospital claim with a diagnosis code for the mood/anxiety disorder in that year; for hospital claims the mood/anxiety disorder was required to be the most responsible diagnosis. Prescription claims alone were not considered a marker of ‘active’ disease.

**Outcomes**

The DIN recorded in DPIN can be linked to the World Health Organization’s Anatomical Therapeutic Chemical (ATC) Classification System. Based on DINs and ATC codes we identified opioids (N02AA03, N02AA01, N02AA05, N02AB03, N02AB02) available in Canada. We defined new (incident) users of opioids as those with no dispensation for any opioid for ≥1 year before initial dispensation. Prevalent opioid users were individuals with ≥1 opioid dispensation in the year of interest.

We measured time from the first dispensation of an opioid to discontinuation of therapy (gap ≥ 90 days between dispensations) based on dispensation dates and number of days supplied at dispensation. We
also described patterns based on the duration and frequency of use. To ensure similar follow-up, these analyses were restricted to cohort members who had ≥5 years of follow-up post-index date. We aimed to describe short-term use (<3 months) and chronic use (≥3 months) within that five year period. A prior systematic review had identified 3 months’ use as the most common definition of long-term opioid use. We report the percentage (95% confidence interval [95%CI]) for (i) single dispensation; (ii) continuous use for ≥3 months; (iii) cumulative use for ≥3 months in any one year period; (iv) continuous use for ≥6 months; (v) cumulative use of ≥6 months in a one year period; and (vi) intermittent use, defined as prescriptions in two or more years, with a gap of ≥1 year between dispensations. Because of the five-year period, discontinuation of opioids could be followed by re-initiation of therapy, and the total percentages could exceed 100%.

To provide additional context for our findings we also report the frequency of use of other classes of medications that may be used for chronic pain management, in the year before the first opioid dispensation. These included non-steroidal anti-inflammatory drugs (NSAIDs), cannabinoids (A04AD11, A04AD10, N02BG10), tricyclic antidepressants (N06AA), serotonin and norepinephrine reuptake inhibitors (SNRIs, N06AB), SSRIs (N06AB) and anticonvulsants (N03AX12, N03AX16, N03AF01, N03AF02, N03AB02), identified based on at least one dispensation.

Covariates

Covariates in the analyses included demographic, health service use and clinical characteristics. Sociodemographic covariates included sex (male as reference group), current age (18-44 [reference group], 45-64, ≥65), region of residence (urban, rural [reference]), and socioeconomic status (SES, continuous). We measured SES in the index year by linking postal code to dissemination-area level census data, then calculating the Socioeconomic Factor Index version 2 (SEFI-2) which integrates average household income, high school education rates, unemployment rates and percent of single parent households into a single score. Score <0 indicate higher SES. Health service use covariates, to account for general differences in health care use between cohorts, included annual numbers of physician visits, annual number of classes (types) of prescription medications dispensed, at the 4th level of the ATC system (e.g. by chemical subgroup) after excluding opioids (0-1, 2-3, ≥4). Clinical characteristics included index year (continuous), disease duration from the index date (continuous), and number of physical comorbidities (0 [reference group], 1, ≥2). The number of comorbidities were obtained using the John Hopkins Adjusted Clinical Group System Aggregated Diagnosis Groups (ADGs™), a case-mix system known to predict health care use in Canadian populations. We used chronic (not...
time-limited) major physical ADGs, for consistency with our prior work. For analyses of incident opioid use we assessed physical comorbidity, number of physician visits, and number of medication classes used in the year before the first dispensation, but we updated these variables annually for the prevalent use analyses.

Analysis
We used descriptive statistics to characterize the MS and non-MS cohorts including frequency (percent), mean (standard deviation [SD]), and median (interquartile range [IQR]). For each year in the study period, we estimated the crude incidence rate (new users) and prevalence of any opioid use, overall as well as stratified by sex, and age (18-44, 45-64, ≥65 years). We also report incidence rates and prevalence estimates age- and sex-standardized to the 2010 Canadian population (from the Statistics Canada census) and 95%CI based on a negative binomial distribution. We report rate ratios and 95%CI comparing incidence rates and prevalence between the MS and non-MS cohorts.

To further assess the association between cohort (MS vs. non-MS), mood/anxiety disorders (active vs. inactive/absent) and use of opioids we employed multivariable generalized linear models. These models used a binomial distribution and the log of person-time as the model offset. We used generalized estimating equations with an exchangeable correlation structure to account for repeated observations in individuals in the prevalence analyses. We also tested for the presence of a two-way interaction between cohort and MAD status for each outcome. Covariates in these models included demographic, health service use and clinical characteristics as delineated above.

Statistical analyses were conducted using SAS V9.4 (SAS Institute Inc., Cary, NC).
RESULTS

Table e1. Characteristics of incident disease cohorts at the time of diagnosis, and matched cohorts at the matched index date.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Matches (n = 14539)</th>
<th>MS (n = 2918)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>10232 (70.4)</td>
<td>2051 (70.3)</td>
</tr>
<tr>
<td>Age at diagnosis, mean (SD)</td>
<td>40.30 (12.34)</td>
<td>40.36 (12.38)</td>
</tr>
<tr>
<td>Duration of follow-up from the index date (years), median (IQR)</td>
<td>9.78 (6.09)</td>
<td>9.12 (5.93)</td>
</tr>
<tr>
<td>Urban region of residence, n (%)</td>
<td>9542 (65.6)</td>
<td>1917 (65.7)</td>
</tr>
<tr>
<td>Socioeconomic status</td>
<td>-0.16 (0.83)</td>
<td>-0.20 (0.84)</td>
</tr>
<tr>
<td>No. physician visits in year pre-index, mean (SD)</td>
<td>4.18 (4.99)</td>
<td>6.54 (6.83)</td>
</tr>
<tr>
<td>Cohort sample sizes (%) for ranges of study index yearsa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1997-2001</td>
<td>4101 (28.2)</td>
<td>823 (28.2)</td>
</tr>
<tr>
<td>2002-2006</td>
<td>3632 (25.0)</td>
<td>729 (25.0)</td>
</tr>
<tr>
<td>2007-2011</td>
<td>3262 (22.4)</td>
<td>655 (22.4)</td>
</tr>
<tr>
<td>2012-2017</td>
<td>3544 (24.4)</td>
<td>711 (24.4)</td>
</tr>
</tbody>
</table>

MS = multiple sclerosis; Socioeconomic status = Socioeconomic Factor Index scores; values less than zero indicate higher socioeconomic status; a- earliest index year was 1997 to allow one year lookback period as of first availability of prescription claims data

Other medications used prior to opioids

In the year before the initial opioid dispensation, of 719 people with MS, 201 (28.1%) had ≥1 prescription dispensation for ≥1 of the following categories of medication: NSAIDS, tricyclic antidepressants, SNRIs, SSRIs, anticonvulsants or cannabinoids; 106 (14.7%) had a dispensation from at least two of those categories. In contrast, among the 3255 people in the non-MS cohort, 669 (20.6%) had received ≥1 prescription dispensation from any of those categories and only 127 (3.9%) had received prescriptions for ≥2 of those categories. Among the MS cohort, NSAIDs were the most commonly used of these medications (20.9%) followed by SSRIs (14.5%) and anticonvulsants (11.5%).

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Supplemental material

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NSAIDs were also the most commonly dispensed medication in the year prior to first opioid use among the non-MS cohort (16.1%), followed by SSRIs (6.7%).

**Figure e1.** Age and sex-standardized annual incidence of opioid use in multiple sclerosis (MS) and non-MS cohorts. After age-standardization, the incidence rate of opioid use declined faster in the MS cohort ($\beta = -4.69$/year) than in the non-MS cohort ($\beta = -2.89$/year) over the study period.

Patterns of opioid use

Time to discontinuation of opioids by 25% of those initiating treatment was 22 days (95%CI: 15-30) in the MS cohort, and 10 days (95%CI: 10-10) in the non-MS cohort. Among incident opioid users with $\geq$5 years of follow-up who had MS but no mood/anxiety disorder, 30.0% (95%CI: 25.6-35.0%) obtained only one opioid dispensation, 8.4% (95%CI: 6.0-11.8%) used opioids continuously $\geq$3 months, and 34.9% used them intermittently (95%CI: 30.3-40.1%). Among individuals with MS and a mood/anxiety disorder, a lower proportion obtained only one dispensation (11.4%; 6.2-21.1%), and a higher proportion used opioids continuously $\geq$3 months (11.4%; 6.2-21.1%). We observed a similar pattern of differences between those with, versus without, mood/anxiety disorders among individuals without MS, although the proportions with single opioid dispensation was higher, and the proportions with continuous use $\geq$3 months was lower (Figure e2).
**Figure e2.** Patterns of opioid use in multiple sclerosis (MS) and non-MS cohorts stratified by mood/anxiety disorder (MAD) status*

![Graph showing patterns of opioid use](image)

*Error bars indicate 95% confidence intervals.

**Table e2.** Rate Ratios (95% confidence interval) for the association of multiple sclerosis (MS), active mood/anxiety disorder (MAD) and incidence and prevalence of opioid use.

|                  | Incidence | | | | Prevalence | | | |
|------------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
|                  | Unadjusted| Adjusted* | Adjusted**| Unadjusted| Adjusted* | Adjusted**|
| MS vs. not       | 1.40      | 1.18      | 1.13      | 1.66      | 1.49      | 1.43      |
|                  | (1.29, 1.52)| (1.08, 1.29)| (1.03, 1.23)| (1.57, 1.75)| (1.41, 1.57)| (1.35, 1.51)|
| Active MAD vs. not| 1.31      | 1.12      | 1.04      | 1.35      | 1.22      | 1.16      |
|                  | (1.19, 1.45)| (1.01, 1.25)| (0.93, 1.16)| (1.30, 1.41)| (1.17, 1.27)| (1.11, 1.21)|

*Adjusted for age (18-44, 45-64, 65+), sex, region, ADG (0, 1, 2+), number of prescription drug classes (0-1, 2-3, 4+), disease duration, index year

**Adjusted for age (18-44, 45-64, 65+), sex, region, ADG (0, 1, 2+), number of prescription drug classes (0-1, 2-3, 4+), number of physician visits (0-3, 4-7, 7+), disease duration, index year
REFERENCES

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