

## Prescription opioid use in multiple sclerosis

### INTRODUCTION

Pain can be one of the worst symptoms of multiple sclerosis (MS).<sup>1</sup> Modifiable factors, including depression and anxiety, may influence its severity and impact.<sup>2</sup> Opioids used for chronic non-cancer pain may be prescribed to persons with MS when neuropathic pain therapies are ineffective. Given the potential harms of opioid use and limited data supporting their utility in MS, it is important to understand the extent of opioid prescribing for persons with MS. We estimated incidence, prevalence and patterns of opioid prescription in an MS population and a matched cohort without MS. We assessed whether comorbid mood/anxiety disorders modified the association between MS and prescription opioid use (hereinafter 'opioid use').

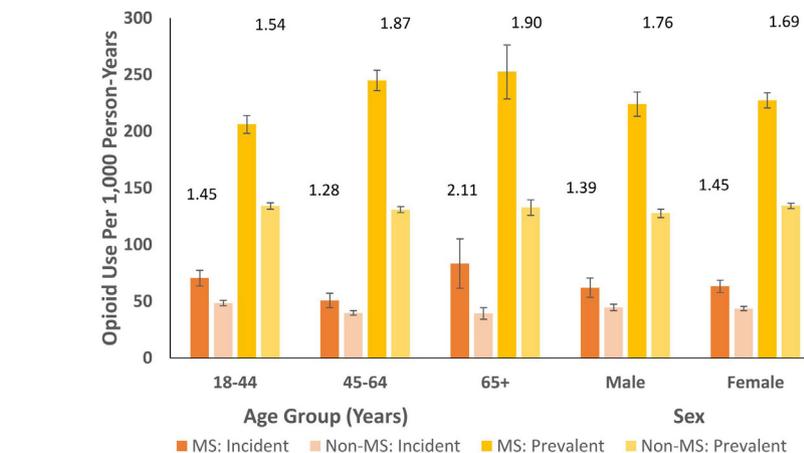
### METHODS

Briefly, this matched retrospective cohort study was conducted in Manitoba, Canada. Online supplemental appendix 1 details methods and references.

We identified Manitobans with MS from 1984 to 2016 using a validated definition relying on health claims; the earliest demyelinating disease claim constituted the index date. A general population cohort was matched 5:1 on sex, year of birth ( $\pm 5$  years) and residence region to the MS cohort, after excluding anyone with diagnosis codes for demyelinating disease or MS disease-modifying therapies. Each control was assigned the index date of their matched case. From these cohorts, we selected incident MS cases and matched controls with an index date  $\geq 1997$ , excluding individuals with cancer/palliative care. We censored anyone who developed cancer or entered palliative care post index when relevant codes first appeared and censored individuals on death or leaving the province.

Using validated definitions, we updated mood/anxiety disorder status annually (active vs inactive/absent). Individuals with schizophrenia were not excluded.

New (incident) users of opioids were those with no dispensation of  $\geq 1$  year before initial dispensation. Prevalent opioid users were individuals with  $\geq 1$  opioid dispensation in the year of interest. We measured time from first opioid dispensation to discontinuation. We described use patterns among cohort



**Figure 1** Average annual age-stratified and sex-stratified incidence and prevalence of opioid use in MS and non-MS cohorts. \*Error bars indicate 95% CIs. Incidence rate ratios and prevalence ratios comparing MS and non-MS cohorts shown above relevant columns. MS, multiple sclerosis.

members with  $\geq 5$  years of follow-up post-index. We noted use of non-steroidal anti-inflammatory drugs, cannabinoids, tricyclic antidepressants, serotonin and norepinephrine reuptake inhibitors and anticonvulsants based on  $\geq 1$  dispensation.

We estimated the crude annual incidence and prevalence of opioid use, overall and stratified by sex and age. We age and sex standardised the estimates. To assess the association between cohort (MS vs non-MS), mood/anxiety disorders (active vs inactive/absent) and opioid use, we employed multivariable generalised linear models. We tested two-way interactions between cohort and mood/anxiety status. Covariates included sex, age, residence region, socioeconomic status, disease duration, index year, number of physical comorbidities and annual number of classes (types) of prescription medications dispensed, after excluding opioids.

### RESULTS

We included 2918 persons with MS and 14539 persons without MS (online supplemental appendix table e1). In 2016, the crude incidence/1000 persons of opioid use was 1.49-fold higher (rate ratio [RR] 1.49, 95% CI 1.35 to 1.64) in the MS cohort (62.94, 95% CI 58.34 to 67.54) than in the non-MS cohort (43.89, 95% CI 42.39 to 45.40). Temporal trends are shown in online supplemental appendix figure e1. Average annual incidence rate of opioid use did not differ by sex in either cohort (figure 1). Opioid use was higher in the MS than in the non-MS cohorts at all ages; this effect was greatest in those aged  $\geq 65$  years (age $\times$ cohort interaction,  $p=0.0081$ ; figure 1). Over the study period, the MS cohort had 1.71-fold

higher crude prevalence/1000 persons of opioid use (226.4, 95% CI 220.7 to 232.2) than the non-MS cohort (132.5, 95% CI 130.6 to 134.4).

Time to discontinuation of opioids by 25% of those initiating treatment was 12 days longer in the MS cohort (see online supplemental appendix 1). Among incident opioid users with  $\geq 5$  years of follow-up who had MS but no mood/anxiety disorder, 30.0% obtained only one opioid dispensation, and 8.4% used opioids continuously for  $\geq 3$  months. In contrast, among individuals with MS and a mood/anxiety disorder, few had only one dispensation (11.4%), and 11.4% used opioids continuously for  $\geq 3$  months (11.4%) (online supplemental appendix figure e2).

After adjusting for covariates, the MS cohort had an increased incidence (RR 1.18, 95% CI 1.08 to 1.29) and prevalence of opioid use (RR 1.49, 95% CI 1.41 to 1.57) than the non-MS cohort (online supplemental appendix table e2). Having an active mood/anxiety disorder was associated with an increased prevalence of opioid use (RR 1.22, 95% CI 1.17 to 1.27), but there were no statistically significant interactions between cohort and mood/anxiety disorders on opioid use (all  $p>0.05$ ).

### DISCUSSION

We examined opioid use in people with and without MS over two decades. On average, the annual prevalence of opioid use was 226/1000 persons with MS, but only 132/1000 persons without MS, an adjusted relative increase of 49% in the MS cohort. This higher use of opioids was irrespective of the presence of a mood/

anxiety disorder, similar to prior findings for benzodiazepines.<sup>3</sup> Notably, average incidence of opioid use in those with MS aged  $\geq 65$  years was quite high, at 83/1000 persons, and prevalent use affected one in four persons. Although incident opioid use was only slightly higher in the MS cohort, higher prevalent use indicated longer duration of use, which was corroborated by our examination of patterns of use. In both cohorts, mood/anxiety disorders were associated with longer duration of opioid use.

One American survey of individuals with MS found that 37.7% currently used opioids.<sup>4</sup> Our finding that approximately 10% of our MS cohort used opioids long-term highlights the need for further pain management research in MS as guidelines state that opioids should not be first-line therapies, given the uncertainty regarding long-term benefits.<sup>5</sup>

Study limitations included inability to assess use of over-the-counter acetaminophen–codeine combinations or to exclude non-MS-related pain syndromes in the MS cohort. We applied validated definitions to identify individuals affected by mood/anxiety disorders, but these only capture individuals receiving care from insured (i.e., physician) providers.

Prescription opioid use is more common in people with MS than those without MS. Both MS and mood/anxiety disorders are associated with longer durations of chronic opioid use. Given the limited evidence supporting opioid use for pain management in MS, the high prevalence of opioid use in persons with MS is concerning and indicates a pressing need for alternative pain management strategies.

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#### REFERENCES

- 1 Stenager E, Knudsen L, Jensen K. Acute and chronic pain syndromes in multiple sclerosis. *Acta Neurol Scand* 1991;**84**:197–200.
- 2 Harrison AM, McCracken LM, Bogosian A, *et al.* Towards a better understanding of MS pain: a systematic review of potentially modifiable psychosocial factors. *J Psychosom Res* 2015;**78**:12–24.
- 3 Marrie RA, Fisk JD, Walld R, *et al.* Use of benzodiazepines and Z-Drugs in multiple sclerosis. *Front Neurol* 2022;**13**:874724.
- 4 Ehde DM, Alschuler KN, Osborne TL, *et al.* Utilization and patients' perceptions of the effectiveness of pain treatments in multiple sclerosis: a cross-sectional survey. *Disabil Health J* 2015;**8**:452–6.
- 5 Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain - United States, 2016. *Morbidity and Mortality Recommendations and Reports* 2016;**65**:1–50 <https://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm>