Characteristics of a population-based multiple sclerosis cohort treated with disease-modifying drugs in a universal healthcare setting

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Abstract

Background: Relatively little is known about the use of disease-modifying drugs (DMDs) for multiple sclerosis (MS) in the population-based universal healthcare setting. This study aimed to describe the characteristics of a population-based cohort with MS and their DMD exposure in four Canadian provinces.

Methods: We identified all adults (aged ≥18 years) with MS using linked population-based health administrative data. Individuals were followed from the most recent of their first MS or demyelinating event or 01/January/1996(study entry), to the earliest of death, emigration, or 31/March/2018(study end). Cohort characteristics examined included sex, age, socioeconomic status, and comorbidity burden.

Results: Overall, 10,418/35,894 (29%) of MS cases filled a DMD prescription during the 22-year study period. Most were women (n=7,683/10,418;74%), and 17% (n=1,745/10,418) had some comorbidity (Charlson Comorbidity Index≥1) at study entry. Nearly 20% (n=1,745/10,418) were aged ≥50 when filling their first DMD; the mean age was 39.6 years.

Conclusions: Almost 1 in 6 people with MS had at least some comorbidity, and nearly 1 in 6 were ≥50 years old at the time of their first DMD. As these individuals are typically excluded from clinical trials, findings illustrate the need to understand the harms and benefits of DMD use in these understudied groups.

Keywords: Canada, cohort studies, disease-modifying drugs, health administrative data, multiple sclerosis, population-based

1. Introduction

Multiple sclerosis (MS) is a chronic demyelinating and degenerative disease affecting the central nervous system. It is estimated that more than 2.2 million people are living with MS globally,[1] and the prevalence in Canada is among the world's highest.[2-5] Approximately 90,000 Canadians live with MS; this is expected to rise to >130,000 by 2030.[6] The incidence of MS is projected to increase from 4,051 cases in 2011 to 4,794 cases per 100,000 Canadian population in 2031.[6] In the last two decades, the management of MS has shifted from no MS-specific disease-modifying drugs (DMDs) to more than 15 drugs.[7] Many DMD-related studies are based on select groups of patients, such as those who are actively seeking care at MS specialist centres or are enrolled in a specific health insurance plan.[8-13] However, such individuals may not be representative of the wider MS population. Remarkably, few regions worldwide capture individual-level primary and secondary health-related data for the entire population which can be linked to demographic and prescription medication use.[14]

Canada has some of the world's most comprehensive administrative health data as a result of universal health care funding.[15] Administrative health data are created as a byproduct of health services provision, and include hospital admissions, visits to physicians, and filled prescriptions at outpatient pharmacies. These routinely collected administrative health data have been increasingly used by health care researchers to conduct population-based observational studies.[16] These health data, for example, can be used to understand patterns of DMD use which can guide efforts to identify potential barriers to DMD use or inappropriate DMD use, and to assess gaps and generalizability of findings from clinical trials to clinical practice.

By use of linked administrative health data from multiple Canadian provinces collected over 20 years, this study aimed to describe the characteristics of a population with MS and their DMD exposure patterns in the real-world setting.

2. Methods

2.1 Data sources

We conducted a cohort study using prospectively collected and linked administrative health data in four Canadian provinces spanning the west to east coast: British Columbia (population 4.65 million [2016]), Saskatchewan (population 1.10 million [2016]), Manitoba (population 1.28 million [2016]) and Nova Scotia (population 924,000 [2016]).[17] Residents combined from these four provinces made up nearly one-quarter of the Canadian population.

The administrative health data in each province consisted of five datasets, which we accessed to identify and characterize the MS populations and to establish each individual's DMD exposure. The physician services and hospital (Discharge Abstract Database) data enabled capture of all diagnoses, coded using the International Classification of Diseases (ICD) system.[18, 19] The prescription databases in British Columbia,[20] Manitoba and Saskatchewan provided details of all prescriptions filled at outpatient pharmacies, and for Nova Scotia only, the Dalhousie MS Research Unit Database captured dispensing records of the MS DMDs (including out-of-province or clinical trial DMD use). The provincial health insurance registries[21] provided information on provincial residency status and demographics, including sex, date of birth and socioeconomic status. Socioeconomic status was estimated from mean neighbourhood income via an extensively used Statistics Canada algorithm and expressed as quintiles).[22] The vital

statistics/registry files[23] provided mortality data. Within each province, these five datasets were linked using encrypted unique personal health care numbers for each individual, and de-identified data were analyzed. As part of the data access requirements, aggregated data could be released from each province provided that all reported groups contained at least 6 individuals.

2.2 Study population: identification, follow-up and description

We identified individuals with ≥3 MS-specific diagnosis codes (ICD-9 code 340 or ICD-10-CA code G35) in the hospital and physician data, or ≥1 MS-specific DMD (beta-interferon, glatiramer acetate, natalizumab, fingolimod, dimethyl fumarate, teriflunomide, alemtuzumab, daclizumab or ocrelizumab) in the prescription data. This algorithm has been validated in Canada, and used in other observational studies, to identify cases of MS.[2, 4, 5, 24] The study entry date was the most recent of: the first MS-specific or other central nervous system demyelinating code recorded in any of the physician, hospital or prescription data (Supplementary Tables 1 and 2); a person's 18th birthday; or the first date of prescription data availability (January 1st 1996 [British Columbia], April 1st 1996 [Manitoba], January 1st 1997 [Saskatchewan] or January 1st 1998 [Nova Scotia]). For all provinces, these calendar years represent the first full year that the DMDs were available and financially covered by the respective provincial governments.

All individuals required at least one-year of residency in the province before the study entry date to allow a comprehensive description of the study population's epidemiological characteristics at their study entry, specifically: sex, age, socioeconomic status, comorbidity burden (measured using the Charlson Comorbidity Index, based on hospital and physician derived ICD codes in the one-year before the study entry and modified to exclude hemiplegia/paraplegia to avoid misclassifying MS complications as comorbidity).[25-27] Briefly, the Charlson Comorbidity Index

combined 16 different comorbid conditions (with an associated weight for each comorbid condition) into one score which can range from 0 (no comorbidity) through to 27.[27]

The study populations were followed from their study entry until the earliest of death, emigration from the province or the study end date (December 31st 2017 [British Columbia, Manitoba, Nova Scotia] or March 31st 2018 [Saskatchewan]).

We described exposure to any MS DMD and then by the individual type of DMD (DMD class), over the entire study period. In addition, the sex, age and DMD class at the date of the first prescription filled was described, and by calendar period (grouped as 1996-2012 (when <5 individual DMD classes were available) and 2013-2017/18 (when ≥5 individual DMD classes were available; see Supplementary Table 2). In British Columbia only (the largest province), patterns of switching between the DMDs (from first to the second DMD) were described by calendar period (1996-2012 versus 2013-2017/18). The first generation of DMDs available in Canada were the beta-interferons (all beta-interferon products were grouped into one class; see Supplementary Table 2), followed by glatiramer acetate. The second generation of DMDs entered the market in 2006 (natalizumab), followed by fingolimod, dimethyl fumarate, teriflunomide, alemtuzumab, daclizumab and ocrelizumab. Three of the DMDs, natalizumab, fingolimod or alemtuzumab, are typically used for individuals who have had an inadequate response to, or are unable to tolerate another DMD.

2.3 Statistical analyses

Descriptive statistics including the count and proportion for categorical variables, and the mean and standard deviation for continuous variables, were conducted separately in each province using a common analytical plan. The aggregated results were released from each of the four

provinces and were then combined by one author (HSN) to produce the descriptive summary for the overall study cohort by DMD exposure status (people who had at least one dispensation for a DMD during the study period [DMD-treated] versus non-treated groups). Chi-square (for categorical variables) and t-tests (for continuous variables) were performed to assess the differences between the overall cohort of people who were treated with a DMD and those not treated. All analyses were conducted using SAS software version 9.4 (SAS Institute, Cary, NC, USA).

2.4 Ethics approval

This study was approved by the Research Ethics Boards at the: University of British Columbia and University of Saskatchewan (harmonized ethics: #H18-00407), University of Manitoba (HS21764), and Nova Scotia Health Authority (#1023555).

3. Results

3.1 Overall study cohort

A total of 35,894 people with MS were identified in the four Canadian provinces; 10,418 (29%) filled a DMD prescription during the 22-year study period (Table 1). The overall mean follow-up was 12 years and almost half of the study population (16,498/35,894; 46%) entered the study between the calendar years of 1996 and 1999, rising to 28,049/35,894 (78% of the study population) by 2009.

Most of the individuals were women (72%); 74% of those filling, and 71% of those not filling a prescription were women. At study entry, people who were subsequently treated with a DMD

were approximately 10 years younger than those not treated (p <0.001). Generally, the number of individuals were evenly distributed across neighbourhood income-based quintiles (a marker of socioeconomic status) regardless of whether they were, or were not, treated with a DMD during follow-up. The burden of comorbidity measured using the Charlson Comorbidity Index (which encompasses 16 comorbid conditions) at study entry was lower in the DMD-treated group than the non-treated group (p <0.001); 1,745/10,418 (17%) had a comorbidity in the DMD-treated group, compared to 6,176/25,476 (24%) of the non-treated group. Although the overall proportions of individuals with multiple comorbidities was relatively modest, the relative difference was sizable – 91 (0.9%) and 729 (2.9%) of the treated and non-treated groups respectively had a Charlson Comorbidity score of 3 and above.

3.2 Demographic characteristics at first DMD prescription

The mean (SD) age at first DMD prescription was 39.6 (10.1) years (Table 2). Nearly 20% (1,745/10,418) of the individuals were aged ≥50 years when they filled their first DMD prescription, and 3% (270/10,418) were ≥60 years old. The mean age at first DMD fill ranged from 35.9 (10.0) years for alemtuzumab (n=43) to 43.6 (10.9) years for teriflunomide (n=338). The majority of the people with MS who initiated a DMD were women, ranging from 65% for alemtuzumab to 77% for glatiramer acetate. Almost three-quarter (7,736/10,418) of people filled their first DMD prescription between 1996 and 2012.

3.3 Patterns of DMD use

Among those who filled a DMD prescription during follow-up, almost two-thirds (6,649/10,418) were exposed to only one DMD, while over one-third (3,769/10,418) were exposed to ≥2 different DMDs (Table 1). Nearly 90% (9,204/10,418) of people filled a prescription for a first-

generation DMD (beta-interferon or glatiramer acetate), and over one-third (3,668/10,418) filled a prescription for a second-generation DMD. There were consistent patterns of type of DMD across the four provinces. Specifically, the most commonly used DMD during the entire study period was beta-interferon (n=6,753; 65% of people), followed by glatiramer acetate (n=4,249; 41% of people), while dimethyl fumarate (n=1,829; 18% of people) and teriflunomide (n=1,060; 10% of people) were the two most frequently prescribed second generation DMDs.

From 1996-2012, the most common first DMD prescription filled was for either beta-interferon (n=5,569, 72% of people) or glatiramer acetate (n=2,084, 27% of people) (Table 2). From 2013-2017/18, as more DMDs became available, this pattern shifted. While glatiramer acetate remained relatively common, being the first DMD prescription filled for 33% (n=883) of people, this was followed by dimethyl fumarate (n=711, 27%), beta-interferon (n=602, 22%), and teriflunomide (n=332, 12%) with 6% first exposed to natalizumab, fingolimod or alemtuzumab.

When sufficient data were available to explore the patterns of switching between the DMDs by calendar period (i.e. in British Columbia, the largest province), we found 1337 people who initiated a DMD between 1996 and 2012 and were exposed to ≥2 different DMDs during the entire study follow-up (Supplementary Table 3). For these individuals, a common first DMD switch was from a beta-interferon to glatiramer acetate (38% of people) or from beta-interferon to dimethyl fumarate (14% of people). For 359 individuals who initiated a DMD in more recent years (between 2013 and 2017) and were exposed to ≥2 different DMDs, the most common first switch was from a beta-interferon or glatiramer acetate to dimethyl fumarate (22% of people) or fingolimod (15% of people) or teriflunomide (13% of people). Other switches included from dimethyl fumarate to teriflunomide (6% of people) or fingolimod (5% of people).

4. Discussion

This is one of only a few large, population-based studies to describe the demographic-related characteristics of people with MS and their exposure to DMDs in a universal healthcare setting. In this multi-site study of 35,894 people with MS residing in Canada, nearly one-third were treated with a DMD during the 22-year study period (1996-2017/18). People who were not treated with a DMD during follow-up were older and had a higher comorbidity burden than people who were treated. Nonetheless, among people with MS filling a DMD prescription, nearly 1 in 6 had at least some comorbidity, and almost 1 in 6 were 50 years or older.

The pivotal clinical trials of the DMDs for MS have typically excluded persons over 50, or 60, years of age,[28] or individuals with comorbidity.[29] However, we observed that nearly 20% of people were 50 years or older when filling their first DMD prescription and almost 20% had comorbidity, as measured by the Charlson Comorbidity Index (which includes 16 different comorbid conditions) at study entry. Nonetheless, the burden of comorbidity at study entry was lower in the DMD-treated group than the non-treated group which was consistent with prior work showing that a higher comorbidity burden was associated with a lower likelihood of starting a DMD (specifically a first generation, injectable DMD).[30] Together, these findings illustrate the need to understand the harms and benefits of DMD use in these understudied and perhaps undertreated groups – individuals with MS living with comorbidities.

We also observed variations in the average age at first prescription fill across the different DMDs, ranging from 35.9 years for alemtuzumab to 43.6 years for teriflunomide. The mean age among people enrolled in the pivotal clinical trials was often younger, for example, averaging over 5 years younger (37.7 years; eligibility range: 18-55 years) for teriflunomide.[31, 32] Although, for alemtuzumab, the mean age of people enrolled in the pivotal clinical trials (mean range: 32.1

to 35.1 years)[33-35] was closer to what observed in clinical practice. A meta-analysis of 38 randomized controlled trials showed that the efficacy of DMDs on MS disability decreased with increasing age; the therapeutic benefit of receiving DMDs was limited after the age of 53 years.[36] In addition, for the average patient aged 40 years or older, there may be limited benefit of a higher efficacy DMDs (such as alemtuzumab, natalizumab or ocrelizumab) relative to a lower efficacy DMDs.[36] Interestingly, we observed that in three of the four provinces, at the first DMD prescription fill, the mean age of those filling a prescription for natalizumab was 40 years or older.

In terms of the sex distribution, while as expected the majority of the people with MS in our study were women, this differed by DMD, ranging from 65% for alemtuzumab to 77% for glatiramer acetate. The proportion of women enrolled in the pivotal clinical trials for alemtuzumab (range: 64% to 66%)[33-35] was comparable to what we observed in our study. However, for glatiramer acetate, the proportion of women participating in the pivotal clinical trials was slightly lower (range: 68% to 72%).[37-39] While a recent systematic review found no significant differences in demographic characteristics, including mean age and sex distribution, between MS patients in randomized controlled trials and clinical practice across several types of DMDs, the authors combined all DMDs together and did not report specific comparisons for individual DMDs.[40]

The overall proportion of MS patients exposed to a DMD has varied substantially across observational studies,[8, 13, 41-43] and will, in part, depend on the era and health care setting. We found in our study that over the 22-year study period (1996-2017/18), nearly 30% of all people with MS were treated with a DMD in a universal health care setting. Few comparable studies exist; however, our estimate does fall within the ranges reported in Denmark, where there is also

population-based data within a universal healthcare setting. Although it is challenging to make direct comparisons as the rates in Denmark were reported by year of MS symptom onset, the overall DMD exposure rate was 18.5% for individuals with MS symptom onset between 1950-1999, with a large increase in the more recent years, rising from 10.6% to 50.6% for those with MS symptom onset between 1980-1989 and 1990-1999, respectively.[43] In contrast, one observational cohort study conducted using the MSBase Registry that included 1,113 MS patients with remitting-relapsing disease recruited from seven Australian MS specialist clinics at academic centres found as much as 80% of the study population were exposed to a DMD during follow-up between 1998 and mid-2010.[8] Another cohort study conducted in the United States in 2012 found that, while half of MS patients enrolled in a private health insurance program received a DMD, only about one-third of those enrolled in the public health insurance program (Medicaid) received such treatment.[41] The differences in the proportions of people receiving DMDs between studies likely reflects differences in observation periods, study settings and the selection of subjects from the source population. For example, across studies, the proportions of people being treated were generally higher in the more recent study periods which likely reflects the increased choice of DMDs. Patients included in the MSBase Registry were probably actively seeking care at tertiary MS treatment centres, while people with private health insurance are more likely to be able to afford the out-of-pocket fee associated with a DMD. Studies including select groups of patients that are subject to selection bias may not be representative of the wider MS population. Our source population comprised all MS cases resident in one of four Canadian provinces during the study period, regardless of socioeconomic status or ability, or willingness, to travel to access a specialist MS clinic or tertiary care, thus the proportion of MS cases exposed to a DMD is likely to be a realistic population estimate. Interestingly, in this universal healthcare

setting, we did not observe a large difference in socioeconomic status between the DMD-treated and non-treated groups which may be a direct result of the provincial governments drug plans which provide financial reimbursement for the MS DMDs. Another Canadian study has shown that access to (and use of) a specific health care resource – an MRI – was not affected by socioeconomic status among people with MS.[44]

The patterns of treatment changed considerably between 1996 to 2012 and 2013 to 2017/18 as more DMDs became available to treat MS. Beta-interferon and glatiramer acetate were the only two DMDs available in Canada between 1996 and 2006 and both required regular injections. The first oral DMDs – fingolimod, dimethyl fumarate and teriflunomide – were approved by Health Canada in 2011, 2013 and 2014, respectively. Thus, while beta-interferon and glatiramer acetate were the two most commonly used DMDs between 1996 and 2012, with >98% of individual's first DMD fill being for one of these drugs, this dropped to 55% between 2013 and 2017/18. Instead, about 40% of individual's first fill was for an oral DMD (with dimethyl fumarate being the most common). Other studies have reported increased uptake of the oral DMDs as the initial therapy internationally.[45, 46] Oral formulations are preferred by MS patients over injectable medications, as reported from studies funded by the manufacturers of the oral DMDs[47-49] and also by independently funded studies.[50, 51] Treatment with an infused DMD (alemtuzumab or natalizumab) was relatively low, representing <5% of people first DMD prescription fill (from 2013 to 2017/18), which likely reflects that, in Canada, initiation of these higher efficacy DMDs typically requires failure to respond to, or tolerate, another DMD.

Over the whole study period, over one-third of our MS study population were exposed to multiple different DMDs. This proportion is similar to those described in other observational studies.[8, 13] A common DMD switch, as observed in our study, was from beta-interferon to

glatiramer acetate or from an injectable medication (beta-interferon or glatiramer acetate) to an oral DMD (dimethyl fumarate or fingolimod). A change to an oral DMD could be an option for patients who experience injection fatigue or discomfort with injections over time.[52] Other common reasons for switching therapy, as reported in the literature, included perceived lack of effectiveness, inability to tolerate a DMD, or lack of adherence to a DMD.[53-56]

Our study has several limitations. We did not have access to DMD use that may have occurred out-of-province or as part of a clinical trial in three of the four provinces. Thus, for a minority of individuals it is possible that we may have slightly overestimated the mean age at first DMD, but this is unlikely to have a substantially effect. For example, we observed only six individuals in Nova Scotia who were exposed to teriflunomide before regulatory approval in Canada. In addition, movement in or out of a province in people with chronic disease is relative low, and was estimated to affect prevalence estimates by as little as 1% for people with MS or Parkinson's disease in a previous Canadian study.[57] We used the Charlson comorbidity index to assess the overall comorbidity burden; it would be of value for future studies to assess the contribution of individual comorbidities, such as depression, hypertension, hyperlipidemia, and thyroid diseases which are common in the MS population and may influence treatment decisions. Nonetheless, the Charlson comorbidity index can be a useful population metric and is, for example, associated with important health outcomes such as mortality.[27, 58] We were not able to stratify the study population by disease course (i.e. relapsing-remitting and progressive) as this clinical information was not available in the population-based administrative health data. It would be of value for future studies to assess the patterns of DMD use in pregnant women as DMD discontinuation is common during pregnancy.[52, 59] Nonetheless, this study provides an important overview on the demographic-related characteristics of the entire population with MS

(minimizing selection bias) and their DMD exposure in a defined geographical region within the universal healthcare setting over a 22-year period. There are few regions worldwide where access to these types of individual-level data is possible. Our study provides valuable insights into the 'real-world' use of the DMDs to treat MS. Our findings can help identify key gaps in knowledge surrounding DMD safety and effectiveness, and the current challenges in applying evidence derived from clinical trials to the demographically broader populations treated in clinical practice.

5. Conclusion

We found that almost 1 in 6 people with MS had at least some burden of comorbidity, and nearly 1 in 6 were ≥50 years old at the time of their first DMD in a population-based cohort within a universal health care setting. As older individuals or individuals with comorbidity are often excluded from clinical trials, our data illustrate the need to understand the harms and benefits of DMD use in these understudied groups, and how these might differ from those observed in clinical trial populations.

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Table 1 Characteristics of the multiple sclerosis study population by exposure to a disease-modifying drug during the study follow-up in four Canadian provinces

Characteristics	British Columbia, Total n= 19,360		Manitoba, Total n= 5,825		Nova Scotia, Total n=5,352		Saskatchewan, Total n= 5,357		Overall cohort, Total n= 35,894		DMD-treated vs not treated P-value[b]
	DMD treated[a], n=4,732	Not treated[a], n=14,628	DMD treated[a], n=1,762	Not treated[a], n=4,063	DMD treated[a], n=2,036	Not treated[a], n=3,316	DMD treated[a], n=1,888	Not treated[a], n=3,469	DMD treated[a], n= 10,418	Not treated[a], n=25,476	
Sex, n (%)											
Women	3,469 (73.3)	10,471 (71.6)	1,304 (74.0)	2,827 (69.6)	1,553 (76.3)	2,436 (73.5)	1,367 (72.4)	2,350 (67.7)	7,693 (73.8)	18,084 (71.0)	<0.0001
Men	1,263 (26.7)	4,157 (28.4)	4,58 (26.0)	1,236 (30.4)	483 (23.7)	880 (26.5)	521 (27.6)	1,119 (32.3)	2,725 (26.2)	7,392 (29.0)	
Age at study entry in years,											
mean (SD)	37.1 (9.8)	46.9 (13.7)	36.5 (9.6)	47.9 (13.7)	38.1 (9.7)	48.5 (13.4)	37.3 (9.6)	49.6 (14.2)	37.2 (9.7)	47.6 (13.7)	<0.0001
Age group at study entry, n (%)											
< 30 years	1,145 (24.2)	1,441 (9.9)	456 (25.9)	305 (7.5)	408 (20.0)	224 (6.8)	464 (24.6)	260 (7.5)	2,473 (23.7)	2,230 (8.8)	<0.0001
30 to 39 years	1,721 (36.4)	3,040 (20.8)	642 (36.4)	866 (21.3)	737 (36.2)	638 (19.2)	691 (36.6)	642 (18.5)	3,791 (36.4)	5,186 (20.4)	
40 to 49 years	1,351 (28.6)	4,373 (29.9)	506 (28.7)	1,208 (29.7)	626 (30.7)	1,006 (30.3)	555 (29.4)	987 (28.5)	3,038 (29.2)	7,574 (29.7)	
50 to 59 years	449 (9.5)	3,159 (21.6)	139 (7.9)	881 (21.7)	236 (11.6)	785 (23.7)	164 (8.7)	796 (22.9)	988 (9.5)	5,621 (22.1)	
≥ 60 years	66 (1.4)	2,615 (17.9)	19 (1.1)	803 (19.8)	29 (1.4)	663 (20.0)	14 (0.7)	784 (22.6)	128 (1.2)	4,865 (19.1)	
Socioeconomic status[c], n (%)											
1 (lowest income quintile)	914 (19.3)	2,849 (19.5)	259 (14.7)	626 (15.4)	364 (17.9)	545 (16.4)	263 (13.9)	609 (17.6)	1,800 (17.3)	4,629 (18.2)	<0.0001
2	870 (18.4)	2,825 (19.3)	339 (19.2)	749 (18.4)	386 (19.0)	644 (19.4)	367 (19.4)	736 (21.2)	1,962 (18.8)	4,954 (19.4)	
3	992 (21.0)	2,939 (20.1)	392 (22.2)	863 (21.2)	429 (21.1)	614 (18.5)	362 (19.2)	642 (18.5)	2,175 (20.9)	5,058 (19.9)	
4	1,006 (21.3)	3,088 (21.1)	321 (18.2)	781 (19.2)	414 (20.3)	620 (18.7)	438 (23.2)	716 (20.6)	2,179 (20.9)	5,205 (20.4)	
5 (highest income quintile)	938 (19.8)	2,841 (19.4)	443 (25.1)	867 (21.3)	381 (18.7)	633 (19.1)	367 (19.4)	621 (17.9)	2,129 (20.4)	4,962 (19.5)	
Unavailable	12 (0.3)	86 (0.6)	8 (0.5)	177 (4.4)	62 (3.0)	260 (7.8)	91 (4.8)	145 (4.2)	173 (1.7)	668 (2.6)	
Comorbidity score[d], n (%)											
0	3,960 (83.7)	11,042 (75.5)	1,454 (82.5)	3,071 (75.6)	1,673 (82.2)	2,476 (74.7)	1,586 (84.0)	2,711 (78.1)	8,673 (83.3)	19,300 (75.8)	<0.0001
1	584 (12.3)	2,381 (16.3)	255 (14.5)	708 (17.4)	275 (13.5)	575 (17.3)	255 (13.5)	541 (15.6)	1,369 (13.1)	4,205 (16.5)	
2	146 (3.1)	757 (5.2)	44 (2.5)	191 (4.7)	56 (2.8)	159 (4.8)	39 (2.1)	135 (3.9)	285 (2.7)	1,242 (4.9)	
≥ 3	42 (0.9)	448 (3.1)	9 (0.5)	93 (2.3)	32 (1.6)	106 (3.2)	8 (0.4)	82 (2.4)	91 (0.9)	729 (2.9)	
Calendar year at study entry, n (%)											
1996-1999	1,529 (32.3)	7,004 (47.9)	628 (35.6)	2,492 (61.3)	713 (35.0)	1,935 (58.4)	555 (29.4)	1,642 (47.3)	3,425 (32.9)	13,073 (51.3)	<0.0001
2000-2004	958 (20.2)	2,298 (15.7)	382 (21.7)	484 (11.9)	374 (18.4)	429 (12.9)	422 (22.4)	644 (18.6)	2,136 (20.5)	3,855 (15.1)	
2005-2009	933 (19.7)	2,228 (15.2)	297 (16.9)	427 (10.5)	396 (19.4)	406 (12.2)	331 (17.5)	542 (15.6)	1,957 (18.8)	3,603 (14.1)	
2010-2014	863 (18.2)	2,079 (14.2)	328 (18.6)	439 (10.8)	385 (18.9)	380 (11.5)	356 (18.9)	416 (12.0)	1,932 (18.5)	3,314 (13.0)	
2015-2017/2018	449 (9.5)	1,019 (7.0)	127 (7.2)	221 (5.4)	168 (8.3)	166 (5.0)	224 (11.9)	225 (6.5)	968 (9.3)	1,631 (6.4)	

Follow-up[a] time in years, median (Q1, Q3) mean (SD)	11.9 (5.8, 18.6) 12.0 (7.0)	10.9 (4.9, 18.8) 11.6 (7.3)	13.3 (6.3, 19.4) 12.8 (6.9)	13.5 (6.2, 21.8) 13.1 (7.4)	12.5 (6.6, 19.5) 12.2 (6.4)	14.5 (6.5, 20.0) 13.0 (6.9)	11.8 (5.3, 18.0) 11.6 (6.9)	11.1 (5.2, 17.7) 11.4 (7.0)	NA 12.1 (6.8)	NA 12.0 (7.2)	 0.0490
Number of DMDs exposed during the follow-up[a]											
1	3,036 (64.2)	NA	1,210 (68.7)	NA	1,234 (60.6)	NA	1,169 (61.9)	NA	6,649 (63.8)	NA	NA
2	1,224 (25.9)		419 (23.8)		554 (27.2)		524 (27.8)		2,721 (26.1)		
≥ 3	472 (10.0)		133 (7.5)		248 (12.2)		195 (10.3)		1,048 (10.1)		
Type of DMD exposure during follow-up, n (%)[a]											
First generation DMDs – any[e]	4,124 (87.2)	NA	1,694 (96.1)	NA	1,763 (86.6)	NA	1,623 (86.0)	NA	9,204 (88.3)	NA	NA
Beta-interferon	*3,140 (66.4)*		*1,294 (73.4)*		*1,300 (63.9)*		*1,019 (54.0)*		*6,753 (64.8)*		
Glatiramer acetate	*1,719 (36.3)*		*782 (44.4)*		*778 (38.2)*		*970 (51.4)*		*4,249 (40.8)*		
Second generation DMDs – any[e]	1,756 (37.1)		340 (19.3)		870 (42.7)		702 (37.2)		3,668 (35.2)		
Natalizumab	*286 (6.0)*		*52 (3.0)*		*207 (10.2)*		*49 (2.6)*		*594 (5.7)*		
Fingolimod	*421 (8.9)*		*69 (3.9)*		*201 (9.9)*		*42 (2.2)*		*733 (7.0)*		
Dimethyl fumarate	*758 (16.0)*		*193 (11.0)*		*360 (17.7)*		*518 (27.4)*		*1,829 (17.6)*		
Teriflunomide	*520 (11.0)*		*86 (4.9)*		*260 (12.8)*		*194 (10.3)*		*1,060 (10.2)*		
Alemtuzumab	*179 (3.8)*		*6 (0.3)*		*39 (1.9)*		*71 (3.8)*		*295 (2.8)*		
Daclizumab	*6 (0.1)*		*0*		*0*		*0*		*6 (<0.1)*		
Ocrelizumab	*<6*		*0*		*7 (0.3)*		*0*		*~7 (<0.1)[f]*		

Key: DMD, disease-modifying drugs; NA, not applicable; SD, standard deviation.
The study entry was the most recent of: the first MS-specific or other demyelinating code recorded in any of the physician, hospital or prescription data, or a person's 18th birthday, or January 1st 1996 (British Columbia), April 1st 1996 (Manitoba), January 1st 1997 (Saskatchewan), January 1st 1998 (Nova Scotia).
As per data privacy and access agreements, small cell size (<6 individuals within any group) are suppressed.

[a]Follow-up was from study entry until the earliest of: death; emigration from the province; or study end (December 31st 2017 [British Columbia, Manitoba, Nova Scotia] or March 31st 2018 [Saskatchewan]).
[b]Chi-square (for categorical variables) and t-tests (for continuous variables) were performed to assess the differences between the overall cohort of people with MS who were treated with a DMD and those not treated.
[c]Socioeconomic status is represented by neighborhood income quintiles, based on the closest available measurement to the study entry date.
[d]Comorbidity is measured using the Charlson Comorbidity Index (modified to exclude hemiplegia/paraplegia to avoid misclassifying MS complications as comorbidity) during the one-year period prior to the study entry date.
[e]Some people were exposed to >1 DMD; hence the sum of the individual first or second generation DMDs exceeds the sum of any first or second generation DMD.
[f]As per data privacy and access agreements, small cell size (<6 individuals within any group) are suppressed and were not included in the total count (the denominator remains the same).

Table 2 Characteristics of the multiple sclerosis population at their first disease-modifying drug prescription filled during study follow-up in four Canadian provinces

Characteristics at the first DMD[a]	**British Columbia, Total n= 4,732**	**Manitoba, Total n= 1,762**	**Nova Scotia, Total n= 2,036**	**Saskatchewan, Total n= 1,888**	**Overall cohort, Total n= 10,418**
First DMD prescription, n (%)					
Beta-interferon	2,955 (62.5)	1,188 (67.4)	1,189 (58.4)	839 (44.4)	6,171 (59.2)
Glatiramer acetate	1,128 (23.8)	501 (28.4)	563 (27.7)	775 (41.0)	2,967 (28.5)
Natalizumab	68 (1.4)	<6	48 (2.4)	<6	~116 (~1.2)[f]
Fingolimod	33 (0.7)	<6	23 (1.1)	<6	~56 (~0.6)[f]
Dimethyl fumarate	313 (6.6)	52 (3.0)	137 (6.7)	209 (11.1)	711 (6.8)
Teriflunomide	196 (4.1)	17 (1.0)	72 (3.5)	53 (2.8)	338 (3.2)
Alemtuzumab	37 (0.8)	0	<6	<6	~37 (~0.4)[f]
Daclizumab	<6	0	0	0	<6
Ocrelizumab	<6	0	<6	0	<6
Sex [female], n (%)[b]					
Overall	3,469 (73.3)	1,304 (74.0)	1,553 (76.3)	1,367 (72.4)	7,693 (73.8)
By individual DMD class					
Beta-interferon	*2,169 (73.4)*	*901 (75.8)*	*891 (74.9)*	*570 (67.9)*	*4,531 (73.4)*
Glatiramer acetate	*869 (77.0)*	*359 (71.7)*	*460 (81.7)*	*601 (77.5)*	*2,289 (77.1)*
Natalizumab	*45 (66.2)*	*<6*	*32 (66.7)*	*<6*	*77 (66.4)[g]*
Fingolimod	*27 (81.8)*	*<6*	*15 (65.2)*	*<6*	*42 (75.0)[g]*
Dimethyl fumarate	*202 (64.5)*	*29 (55.8)*	*95 (69.3)*	*151 (72.2)*	*477 (67.1)*
Teriflunomide	*132 (67.4)*	*12 (70.6)*	*57 (79.2)*	*37 (69.8)*	*238 (70.4)*
Alemtuzumab	*24 (64.9)*	*NA*	*<6*	*<6*	*24 (64.9)[g]*
Daclizumab	*<6*	*NA*	*NA*	*NA*	*<6*
Ocrelizumab	*<6*	*NA*	*<6*	*NA*	*<6*
Age at first DMD in years, mean (SD)					
Overall	39.7 (10.1)	39.1 (10.3)	40.4 (10.1)	39.2 (9.9)	39.6 (10.1)
By individual DMD class					
Beta-interferon	*39.7 (10.0)*	*39.5 (10.5)*	*39.8 (9.6)*	*39.5 (10.0)*	*39.7 (10.0)*
Glatiramer acetate	*39.2 (10.1)*	*38.2 (9.9)*	*41.0 (10.3)*	*39.0 (9.6)*	*39.3 (10.0)*
Natalizumab	*40.0 (12.3)*	*45.0 (2.8)*	*38.5 (12.1)*	*41.9 (6.4)*	*39.6 (12.0)*
Fingolimod	*39.0 (11.5)*	*37.0 (2.8)*	*44.3 (10.2)*	*40.6 (11.5)*	*41.0 (10.9)*
Dimethyl fumarate	*39.7 (10.2)*	*37.7 (9.4)*	*39.9 (11.4)*	*38.0 (10.2)*	*39.1 (10.4)*
Teriflunomide	*43.1 (10.8)*	*42.5 (12.0)*	*45.8 (10.7)*	*43.0 (11.1)*	*43.6 (10.9)*
Alemtuzumab	*35.9 (10.3)*	*NA*	*36.7 (5.5)*	*35.2 (8.1)*	*35.9 (10.0)*
Age group at first DMD, n (%)					
< 30 years	815 (17.2)	359 (20.4)	312 (15.3)	374 (19.8)	1,860 (17.9)
30 to 39 years	1,547 (32.7)	550 (31.2)	637 (31.3)	625 (33.1)	3,359 (32.2)
40 to 49 years	1,560 (33.0)	576 (32.7)	688 (33.8)	630 (33.4)	3,454 (33.2)
50 to 59 years	686 (14.5)	227 (12.9)	340 (16.7)	222 (11.8)	1,475 (14.2)
≥ 60 years	124 (2.6)	50 (2.8)	59 (2.9)	37 (2.0)	270 (2.6)
Calendar period at first DMD, n (%)					
1996-2012	3,477 (73.5)	1,309 (74.3)	1,577 (77.5)	1,373 (72.7)	7,736 (74.3)
2013-2017/18	1,255 (26.5)	453 (25.7)	459 (22.5)	515 (27.3)	2,682 (25.7)
First DMD filled 1996-2012, n (%)[c]					
Beta-interferon	2,740 (78.8)	1,037 (79.2)	1,068 (67.7)	724 (52.7)	5,569 (72.0)
Glatiramer acetate	697 (20.1)	270 (20.6)	473 (30.0)	644 (46.9)	2,084 (26.9)
Natalizumab	31 (0.9)	<6	18 (1.1)	<6	~49 (~0.7)[f]
Fingolimod	9 (0.3)	0	12 (0.8)	0	21 (0.3)
Teriflunomide	0	0	6 (0.4)[e]	0	6 (0.1)

Total, n (%)	3,477 (100)	1,309 (100)	1,577 (100)	1,373 (100)	7,736 (100)
First DMD filled 2013-2017/18, n (%)[d]					
Beta-interferon	215 (17.1)	151 (33.3)	121 (26.4)	115 (22.3)	602 (22.4)
Glatiramer acetate	431 (34.3)	231 (51.0)	90 (19.6)	131 (25.4)	883 (32.9)
Natalizumab	37 (3.0)	0	30 (6.5)	<6	~67 (~2.5)[f]
Fingolimod	24 (1.9)	<6	11 (2.4)	<6	~35 (~1.4)[f]
Dimethyl fumarate	313 (24.9)	52 (11.5)	137 (29.8)	209 (40.6)	711 (26.5)
Teriflunomide	196 (15.6)	17 (3.8)	66 (14.4)	53 (10.3)	332 (12.4)
Alemtuzumab	37 (3.0)	0	<6	<6	~37 (~1.4)[f]
Daclizumab	<6	0	0	0	<6
Ocrelizumab	<6	0	<6	0	<6
Total, n (%)	1,255 (100)	453 (100)	459 (100)	515 (100)	2,682 (100)

Key: DMD, disease-modifying drugs; NA, not applicable; SD, standard deviation.
As per data privacy and access agreements, small cell size (<6 individuals within any group) are suppressed.

[a]DMD exposure information was captured as dispensed/filled prescriptions in the provincial drug databases, except for Nova Scotia where all issued prescriptions were captured. An estimated <1% (14/2036) of patients in Nova Scotia had their first DMD dispensed out-of-province or as part of a clinical trial; such data were unavailable in the other provinces.
[b]The denominator used to estimate the proportions was the total number of people with that type (class) of first DMD.
[c]The denominator used to estimate the proportions was the total number of people filling their first DMD prescription between 1996-2012.
[d]The denominator used to estimate the proportions was the total number of people filling their first DMD prescription between 2013-2017/18.
[e]The six cases in Nova Scotia who were exposed to teriflunomide prior to regulatory approval in Canada were clinical trial participation (before Health Canada approval).
[f]As per data privacy and access agreements, small cell size (<6 individuals within any group) are suppressed and were not included in the total count (the denominator remains the same).
[g]As per data privacy and access agreements, small cell size (<6 individuals within any group) are suppressed and were not included in the total count (either the numerator or denominator).

Supplementary Materials

Supplementary Table 1 Diagnostic codes for MS and other central nervous system demyelinating diseases

Diseases	**ICD-9 code**	**ICD-10 code**
Multiple sclerosis	340	G35
Optic neuritis	377.3	H46
Acute transverse myelitis	323.82, 341.2	G37.3
Acute disseminated encephalomyelitis	323	G36.9
Demyelinating disease of central nervous system (CNS) unspecified	341.9	G37.8
Other acute disseminated demyelination	NA	G36
Neuromyelitis optica	341.0	G36.0

Supplementary Table 2 MS-specific disease-modifying drugs approved by Health Canada from 1995 to 2017

Individual DMD	**Brand name & related details**	**Health Canada approval date**	**First or second generation drugs**
Beta-interferon	Interferon beta-1b [Betaseron®] (0.3 mg/vial)	July 1995	1st generation
	Interferon beta-1b [Extavia®] (0.3mg/vial)	November 2009	
	Peginterferon beta-1a [Plegridy®] (125mcg/0.5ml); (94mcg/0.5ml); (63 mcg/0.5ml); (starter pack; 63 µg/0.5ml & 94 µg/0.5ml)	August 2015	
	Interferon beta-1a [Avonex®] (30 µG/kit); (30 µG/0.5 ml)	April 1998	
	Interferon beta-1a [Rebif®] (initiation pack); (8.8 µG); (11 µG); (22 µG); (44 µG); (66µG); (132µG)	February 1998	
Glatiramer acetate	Copaxone® (20mg/1 vial); (20mg/1 ml); (40mg/1ml) Glatect® (20mg/1 ml)	October 1997, August 2017	1st generation
Natalizumab	Tysabri® (300mg/15ml)	September 2006	2nd generation
Fingolimod	Gilenya® (0.5mg capsule)	March 2011	2nd generation
Dimethyl fumarate	Tecfidera® (120 mg capsule) Tecfidera® (240 mg capsule)	April 2013	2nd generation
Teriflunomide	Aubagio® (14 mg tablet)	November 2013	2nd generation
Alemtuzumab	Lemtrada® (12 mg/1.2ml)	December 2013	2nd generation
Daclizumab[a]	Zinbryta® (150mg/ml pre-filled syringe); (150mg/ml pre-filled pen)	December 2016	2nd generation
Ocrelizumab	Ocrevus® (300mg/ml)	August 2017	2nd generation

[a]Daclizumab was withdrawn from the market in March 2018 due to safety concerns.

Rituximab is currently not approved for the treatment of MS in Canada.

Supplementary Table 3 Patterns of DMD switches by calendar period (1996-2012 versus 2013-2017/18) in the largest province (British Columbia)

Characteristics	British Columbia
Initiated first DMD between 1996 and 2012 and had ≥2 different DMDs[a] during entire study period, n (%)[b]	
From beta-interferon to	
Glatiramer acetate	505 (37.8)
Dimethyl fumarate	187 (14.0)
Fingolimod	122 (9.1)
Teriflunomide	110 (8.2)
Natalizumab	98 (7.3)
Alemtuzumab	14 (1.0)
From glatiramer acetate to	
Beta-interferon	156 (11.7)
Dimethyl fumarate	51 (3.8)
Fingolimod	30 (2.2)
Teriflunomide	30 (2.2)
Natalizumab	9 (0.7)
Alemtuzumab	<6
Other DMD switch (first DMD was neither beta-interferon nor glatiramer acetate)	
From fingolimod to other DMD	<6
From natalizumab to other DMD	18 (1.3)
Total, n (%)	1,337 (100)
Initiated first DMD between 2013 and 2017/18 and had ≥2 different DMDs[a] during this time, n (%)[c]	
From beta-interferon to	
Dimethyl fumarate	34 (9.5)
Glatiramer acetate	32 (8.9)
Teriflunomide	20 (5.6)
Fingolimod	16 (4.5)
Natalizumab	<6
Alemtuzumab	<6

From glatiramer acetate to	
Dimethyl fumarate	44 (12.3)
Fingolimod	38 (10.6)
Teriflunomide	25 (7.0)
Alemtuzumab	15 (4.2)
Beta-interferon	10 (2.8)
Other DMD switch (first DMD was neither beta-interferon nor glatiramer acetate)	
From dimethyl fumarate to	
Teriflunomide	21 (5.9)
Fingolimod	18 (5.0)
Glatiramer acetate	14 (3.9)
Alemtuzumab	9 (2.5)
Beta-interferon	8 (2.2)
Natalizumab	<6
Ocrelizumab	<6
From fingolimod to other DMD	<6
From natalizumab to other DMD	7 (1.9)
From teriflunomide to other DMD	32 (8.9)
Total, n (%)	359 (100)

Key: DMD, disease-modifying drugs.

As per data privacy and access agreements, small cell size (<6 individuals within any group) are suppressed.

[a]All switches represent a switch from the first prescription filled for a DMD to the second (by DMD class).

[b]The denominator used to estimate the proportions was the total number of people filling their first DMD prescription between 1996-2012 and had ≥2 different DMDs.

[c]The denominator used to estimate the proportions was the total number of people filling their first DMD prescription between 2013-2017/18 and had ≥2 different DMDs.