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Medication adherence in multiple sclerosis as a potential model for other chronic diseases: a population-based cohort study

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ABSTRACT

Objective To determine whether better medication adherence in multiple sclerosis (MS) might be due to specialised disease-modifying drug (DMD) support programmes by: (1) establishing higher adherence in MS than in other chronic diseases and (2) determining if higher adherence is associated with patient-specific or treatment-specific factors.

Design Retrospective cohort study with data from 1 January 1996 to 31 December 2015.

Setting Population-based health administrative data from three Canadian provinces.

Participants Individual cohorts were created using validated case definitions for MS, epilepsy, Parkinson's disease (PD) and rheumatoid arthritis (RA). Subjects were included if they received ≥1 dispensation for a disease-related drug between 1 January 1997 and 31 December 2014.

Main outcome measure(s) Proportion of subjects with optimal adherence (≥80%) measured by the medication possession ratio 1 year after the index date (first dispensation of disease-related drug).

Results 126 478 subjects were included in the primary analysis (MS, n=6271; epilepsy, n=55 739; PD, n=21 304; RA, n=43 164). Subjects with epilepsy (adjusted OR, aOR 0.29; 95% CI 0.19 to 0.45), PD (aOR 0.42; 95% CI 0.29 to 0.63) or RA (aOR 0.26; 95% CI 0.19 to 0.35) were less likely to have optimal 1-year adherence compared with subjects with MS. Within the MS cohort, adherence was higher for DMD than for chronic-use non-MS medications, and no consistent patient-related predictors of adherence were observed across all four non-MS medication classes, including having optimal adherence to DMD.

Conclusions Subjects with MS were significantly more likely to have optimal 1-year adherence than subjects with epilepsy, RA and PD, and optimal adherence appears related to treatment-specific factors rather than patient-related factors. This supports the hypothesis that higher adherence to the MS DMDs could be due to the specialised support programmes; these programmes may serve as a model for use in other chronic conditions.

Strengths and limitations of this study

- ► One of the first studies to compare adherence in different chronic diseases using the same population-based data sources and methodologies.
- ► Established that adherence is better in multiple sclerosis (MS) than other comparable chronic diseases; higher adherence appears to be related to drug-specific, rather than patient-related factors.
- ► The strategies used for supporting patients prescribed disease-modifying drugs for MS may serve as a model for improving adherence to other chronic medications.
- ► Observational studies contain potential unknown confounders.
- ► Some clinical information is not available in administrative data.

INTRODUCTION

Almost two decades ago, WHO released their Adherence to Long Term Therapies: Evidence for Action report estimating that only 50% of individuals were adherent to their chronic medications.[1] Since that time, a multitude of research has demonstrated the impact of medication non-adherence on health outcomes and healthcare systems,[2–5] including increased healthcare utilisation, morbidity and mortality.[4–7] Annual costs of medication non-adherence are estimated to be between US$100–US$290 billion in the USA, €1.25 billion in Europe and $C7–$C9 billion in Canada.[3 8]

Reasons for non-adherence are complex and few predictors have been consistently associated with levels of adherence across diseases.[2 9] Further complicating, this is the lack of consistency and standardisation in how medication adherence is studied.[10] While numerous studies have examined adherence in many diseases and for various medications, results are often conflicting and comparisons are difficult due to differences in study design, data sources, outcome measures and adherence definitions. It has been suggested

that improving medication adherence will have more beneficial impact on health outcomes than the development of new therapies.[1] Despite this, there has been little success to date in identifying effective interventions to improve medication adherence.[4 5 11 12]

In previous work, we have shown that adherence to disease-modifying drugs (DMDs) in multiple sclerosis (MS) is higher than what has been reported for many chronic-use medications in other diseases.[13 14] We hypothesised that this higher adherence in MS is due to the specialised management and support provided to individuals who are prescribed DMDs in Canada. However, to test this hypothesise, we first needed to firmly establish that adherence was actually higher in MS than in other populations, and that the findings were not explained by differences in methodology between studies. To do this, we compared adherence to DMDs in MS with adherence to disease-specific medications in three other chronic conditions using similar population-based cohorts, methodology and outcomes from three Canadian provinces. Second, as adherence can be influenced by many different factors,[1 4] we examined adherence to chronic-use non-DMD medications in the MS cohort to determine if the higher adherence was associated with patient-related or treatment-specific factors.

METHODS

Data source

This retrospective cohort study used population-based health administrative data from three Canadian provinces, Manitoba (MB), Saskatchewan (SK) and British Columbia (BC) from 1 January 1996 to 31 December 2014 (BC) or 31 December 2015 (MB, SK). Each provincial government maintains linkable health administrative databases that capture information on virtually all (>99%) residents. We accessed databases that contained registration (ie, residency) and demographic information, hospital separations, physician services and prescription drug dispensations. International Classification of Diseases (ICD) codes (ICD-9 or ICD-10-CA) are used to record diagnoses in the hospital and physician databases, and the prescription drug databases provide information on all prescribed medications dispensed in an outpatient setting, including the unique drug identification number that is linkable to the Anatomical Therapeutic Chemical (ATC) classification system.[15–19]

MB data were accessed through the MB Population Research Data Repository at the MB Centre for Health Policy, SK data was accessed at the SK Health Quality Council under data sharing agreements with the SK Ministry of Health and eHealth SK, and BC data were accessed through Population Data BC.[20] As per individual provincial data agreements, no additional data are available.

Study cohorts

We used validated administrative case definitions involving combinations of hospital, physician and prescription claims, to create individual cohorts for each of the following four diseases: MS,[21] rheumatoid arthritis (RA),[22] epilepsy[23] and Parkinson's disease (PD)[24] (online supplemental eAppendix). We then identified subjects within each disease cohort who had at least one dispensation for a specific disease-related drug (as listed in online supplemental eAppendix) between 1 January 1997 and 31 December 2014 for use in the primary analyses. If a subject received a disease-related drug from more than one disease group during the study period, the first of the disease-related drugs dispensed was used to assign the disease cohort. We selected these three diseases as they allowed for comparability on non-demographic factors that might affect adherence, such as type of disease course (relapsing remitting with underlying progression (MS and RA) vs gradual progression only (PD)), the length of time until the consequence of non-adherence are realised (immediate (epilepsy, PD) vs delayed (MS)), potential adverse effects, route of drug administration (oral vs injection/infusion) and drug costs. Each of these diseases also has a significant impact on the healthcare system, and patient-related outcomes, including quality of life.[25 26] Disease-specific medications for inclusion in the adherence calculations were selected based on their ATC classifications (eg, antiepileptics),[15] previous inclusion in adherence studies[27–30] and availability in Canada during the study period.

The date of the first dispensation after 1 January 1997 for a disease-related drug was defined as the index date. Because many of the study drugs are contraindicated or discouraged in pregnancy, we identified all subjects with a claim for a delivery (ICD-9: V27, ICD-10: Z37) and censored their data 365 days prior to their delivery date. Subjects with less than 1 year of residency in their respective province before or after the index date were excluded. To ensure only incident users were included in the analyses, subjects with a dispensation for any study drug associated with their disease cohort (online supplemental eAppendix) in the 1 year before the index date were excluded.

Patient and public involvement

Patients and/or the public were not involved in the design or conduct of this study.

Study outcomes

The primary outcome was the proportion of subjects with optimal adherence measured 1 year after the index date. The first year of therapy was purposefully selected for the primary outcome, as it has been recognised as the most critical time for non-adherence.[2 31] Adherence was estimated using the medication possession ratio (MPR), calculated as the sum of the days' supply for all study drug dispensations during the observation period divided by the number of days in the observation period. In SK, a days' supply variable was not available. As most prescriptions in SK are dispensed in 1-month quantities, we made the assumption that each dispensation of a disease-specific

drug contained a 30-day supply. An MPR ≥80% was considered optimal.[2] Secondary outcomes included the proportion of subjects with optimal adherence at years 2, 3, 4 and 5 after the index date, in those subjects with adequate follow-up available. We also examined non-persistence to the disease-related medications, measured as the proportion of subjects who discontinued the medication after only one dispensation, within the first 6 months, and within the first year of therapy; these three outcomes were mutually exclusive. A discontinuation was defined as a continuous gap with no disease-related medication >90 days. As a sensitivity analyses, we estimated adherence over the same time periods using the proportion of days covered (PDC), which can provide a more conservative estimate of adherence, especially when switches within a medication class can occur.[32] The PDC was calculated as the number of days covered by drug dispensations during the observation period divided by the number of days in the observation period.[33] All study outcomes were estimated by class effect (eg, all antiepileptic drugs) and switching between medications was allowed.

Within the MS disease cohort only, we identified those subjects who had at least one dispensation for one of the following medication classes, categorised using the ATC[15] classifications: HMG-CoA reductase inhibitors (statins; ATC: C01AA), ACE inhibitors (ACEI; ATC: C09AA), angiotensin receptor blockers (ARB; ATC: C09CA), and thyroid hormone replacement therapies (ATC: H03AA). These medication classes were selected based on their frequency of use in MS.[34 35] We estimated adherence and persistence for incident users of each of these four medication classes using the same methods as described above, except we used the quantity dispensed to determine the days' supply in SK, as these medications are primarily prescribed as once daily dosing.

Statistical analysis

We described baseline characteristics of the subjects using frequencies, means and SD. To identify potential predictors of optimal adherence among the disease cohorts at 1 year, we used multivariable logistic regression with the following covariates measured at the index date (date of first drug dispensation): age (continuous), sex, location (urban vs rural), median household income estimated by linking the first three digits of postal ('zip') code to Canadian census data (reported as quintiles), and calendar year (1997–1998, 1999–2000, 2001–2002, 2003–2005, 2006–2008, 2009-study end). We also adjusted for the number of physician visits (0–3, 4–11, ≥12), hospitalisations (0,≥1) and non-study prescription medication classes dispensed (0, 1–2, 3–4, ≥5) in the year before the index date as a measure of prior healthcare utilisation. Logistic regression models, with the same covariates described above were used to identify predictors of 1 year persistence for the disease cohorts. Models were checked for multicollinearity (variance inflation factor >2.5) and goodness of fit (Hosmer-Lemshow, p>0.05).[36] Results were reported as adjusted OR (aOR) with 95% CIs.

In the MS cohort, potential predictors of 1-year adherence for each of the chronic-use medication classes were assessed for subjects who received at least one dispensation for a DMD, using logistic regression models with the following covariates measured at the index date: age (continuous), sex, location (urban vs rural), median household income estimated by linking the first three digits of postal code to Canadian census data (reported as quintiles) and calendar year (continuous). Calendar year was included as a continuous variable in these models because the smaller cohort size. We also adjusted for the mean number of physician visits, hospitalisations and prescription medication classes dispensed in the year before the index date as a measure of prior healthcare utilisation, and whether or not the subject had optimal 1-year adherence (MPR ≥80%) to their DMDs.

As per provincial data regulations, analyses were performed separately in each province and combined using random effects meta-analysis. Random effects models were chosen because tests for heterogeneity (I^2 indicated moderate (25%–50%) to high (>75%) levels of heterogeneity between outcomes from the three provinces.[13 37] Statistical analyses were generated using SAS software, V.9.4 of the SAS System for Windows (SAS Institute), and R software V.3.6.1 (R Foundation for Statistical Computing, Vienna, Austria, 2019).

RESULTS

A total of 126 478 subjects were included in the primary analysis (MS, n=6271; epilepsy, n=55 739; PD, n=21 304; RA, n=43 164) (figure 1A). There were no notable differences in the characteristics of each disease cohort between provinces (table 1). Within the overall MS cohort (ie, with or without a DMD dispensation during the study period, n=28 176), 13 780 subjects were identified as receiving at least one dispensation for a statin (n=4628), ACEI (n=4569), ARB (n=1971) or thyroid replacement (n=2612) medication, and were included in the analyses (figure 1B, online supplemental eTable 1).

The proportion of subjects with optimal adherence (MPR) at 1 year was highest for the MS cohort (77.2%, 95% CI 72.4% to 81.3%), followed by PD (61.0%, 95% CI 54.9% to 66.8%), epilepsy (50.9%, 95% CI 42.5% to 59.3%) and RA (47.0%, 95% CI 45.4% to 48.8%) (table 2). The proportion of subjects with optimal adherence consistently decreased over the 5-year period for all diseases. Similar results were observed for the sensitivity analyses where the PDC adherence measure was used (table 2). Non-persistence was lowest in the MS cohort, with approximately 17% of subjects discontinuing all DMD within the first year of therapy. Levels of non-persistence varied between diseases, although most non-persistent subjects in each cohort discontinued their

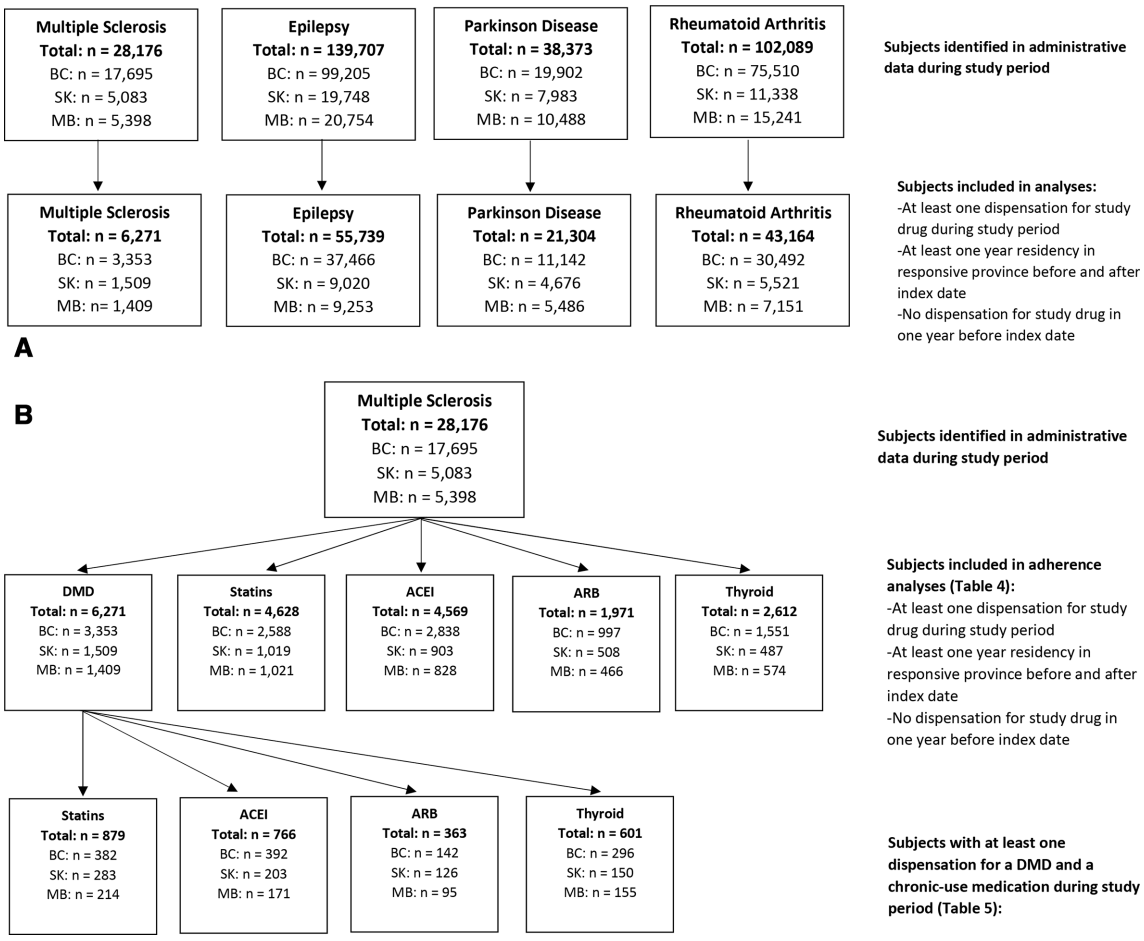

Figure 1 Flow diagram of subjects for study cohorts. ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; BC, British Columbia; DMD, disease-modifying drug; MB, Manitoba; SK, Saskatchewan.

disease-related medications within the first 6 months of starting therapy (table 2).

After adjustment for potential confounders, subjects with MS were statistically significantly more likely to have optimal adherence than subjects with PD (aOR 0.42; 95% CI 0.29 to 0.63), epilepsy (aOR 0.29; 95% CI 0.19 to 0.45) or RA (aOR 0.26; 95% CI 0.19 to 0.35) at 1 year. Optimal adherence decreased as the time since initiation (index date) increased, and was associated with increased healthcare (physician and hospital) contact in the year before the index date and a higher median household income level (table 3). A higher number of prescription medications in the year before the index date was associated with lower adherence levels; age and sex were not associated with adherence. Similar associations were observed for persistence at 1 year (table 3).

Within the MS cohort, 1-year adherence was highest for the DMDs (77.2%; 95% CI 72.4% to 81.3%), followed by thyroid replacement (72.3%; 95% CI 68.1% to 76%.1), ARB (60.3%; 95% CI 56.7% to 63.8%), statins (55.3%; 95% CI 51.0% to 59.4%) and ACEI (54.7%; 95% CI 53.3% to 56.2%). As indicated by non-overlapping confidence intervals, the difference in adherence was statistically significant for ARB, statins and ACEI. Persistence levels varied among the medication classes, but the majority of subjects who discontinued within the first year of therapy did so in the first 6 months (table 4).

Within the MS cohort, no consistent predictors of adherence were observed across all four non-MS medication classes (table 5). Optimal 1-year adherence to DMDs was associated with increased odds of optimal 1-year adherence to a non-MS medication class, but only reached statistical significance for ACEI (aOR 1.83; 95% CI 1.23 to 2.71).

DISCUSSION

For this retrospective cohort study, we used population-based health administrative data, and found that 1-year adherence to disease-specific therapy was highest in MS when compared with epilepsy, PD and RA. Early discontinuations appeared to be a major reason for non-adherence, as up to 30% of subjects discontinued all antiepileptics or RA medications within the first 6 months of therapy. This impact of early discontinuations is consistent with evidence from other disease cohorts.[38–40] Adherence levels decreased with increased time since initiation in all disease cohorts. We also found that, within the MS cohort, adherence was higher to the DMDs than to other chronic-use non-MS medications.

Table 1 Disease cohort characteristics at index date*

	Multiple sclerosis				Epilepsy			
Characteristic	BC n=3353	SK n=1509	MB n=1409	All provinces Combined (95% CI)†	BC n=37 466	SK n=9020	MB n=9253	All provinces Combined (95% CI)*
Age (years), mean (SD)	39.9 (9.8)	39.0 (9.9)	39.8 (10.6)	39.5 (5.8)	42.9 (23.9)	40.1 (24.1)	39.8 (24.0)	40.9 (13.9)
Female, n (%)	2475 (73.8)	1084 (71.8)	1049 (74.4)	73.4 (72.0 to 74.8)	18 039 (48.1)	4176 (46.3)	4533 (49.0)	47.8 (46.5 to 49.1)
Median household income (quintiles), n (%)‡								
1 (lowest)	620 (18.5)	214 (14.2)	195 (13.8)	15.5 (12.5 to 19.0)	8664 (23.1)	2262 (25.1)	2677 (28.9)	25.6 (22.3 to 29.3)
2	597 (17.8)	294 (19.5)	260 (18.5)	18.4 (17.4 to 19.3)	7456 (19.9)	1806 (20.0)	1879 (20.3)	20.0 (19.7 to 20.3)
3	703 (21.0)	266 (17.6)	317 (22.5)	20.3 (17.9 to 23.0)	7156 (19.1)	1527 (16.9)	1770 (19.1)	18.4 (17.1 to 19.7)
4	704 (21.0)	329 (21.8)	275 (19.5)	20.9 (19.8 to 22.0)	6749 (18.0)	1677 (18.6)	1542 (16.7)	17.8 (16.8 to 18.7)
5 (highest)	676 (20.2)	303 (20.1)	362 (25.7)	21.8 (18.6 to 25.4)	6337 (16.9)	1281 (14.2)	1385 (15.0)	15.4 (13.7 to 17.2)
Location, n (%)								
Urband	2939 (87.7)	1058 (70.1)	926 (65.7)	76.0 (58.4 to 87.8)	32 256 (86.1)	5925 (65.7)	5641 (61.0)	72.6 (51.2 to 87.0)
Rural	414 (12.3)	451 (29.9)	483 (34.3)	24.0 (12.2 to 41.6)	5210 (13.9)	3071 (34.0)	3612 (39.0)	27.4 (13.0 to 48.7)
Index year, n (%)								
1997	107 (3.2)	23 (1.5)	6 (0.4)	1.4 (0.5 to 3.5)	2567 (6.9)	546 (6.1)	680 (7.3)	6.7 (6.2 to 7.4)
1998	171 (5.1)	162 (10.7)	76 (5.4)	6.7 (4.0 to 11.0)	2316 (6.2)	518 (5.7)	572 (6.2)	6.1 (5.9 to 6.3)
1999	224 (6.7)	112 (7.4)	108 (7.7)	7.1 (6.5 to 7.8)	2362 (6.3)	529 (5.9)	539 (5.8)	6.1 (5.7 to 6.4)
2000	311 (9.3)	126 (8.3)	145 (10.3)	9.3 (8.4 to 10.3)	2151 (5.7)	532 (5.9)	574 (6.2)	5.9 (5.6 to 6.2)
2001	267 (8.0)	105 (7.0)	121 (8.6)	7.9 (7.1 to 8.7)	2269 (6.1)	493 (5.5)	580 (6.3)	5.9 (5.6 to 6.4)
2002	231 (6.9)	88 (5.8)	100 (7.1)	6.7 (6.0 to 7.4)	2143 (5.7)	445 (4.9)	563 (6.1)	5.6 (5.1 to 6.2)
2003	222 (6.6)	86 (5.7)	134 (9.5)	7.1 (5.4 to 9.4)	2196 (5.9)	444 (4.9)	526 (5.7)	5.5 (5.0 to 6.1)
2004	180 (5.4)	71 (4.7)	95 (6.7)	5.6 (4.6 to 6.7)	1996 (5.3)	419 (4.6)	490 (5.3)	5.1 (4.7 to 5.5)
2005	148 (4.4)	76 (5.0)	60 (4.3)	4.5 (4.0 to 5.1)	2046 (5.5)	418 (4.6)	551 (6.0)	5.3 (4.8 to 6.0)
2006	167 (5.0)	66 (4.4)	80 (5.7)	5.0 (4.4 to 5.7)	1972 (5.3)	345 (3.8)	552 (6.0)	5.0 (4.0 to 6.1)
2007	139 (4.1)	54 (3.6)	57 (4.0)	4.0 (3.5 to 4.5)	2012 (5.4)	308 (3.4)	481 (5.2)	4.6 (3.6 to 5.8)
2008	171 (5.1)	64 (4.2)	52 (3.7)	4.4 (3.6 to 5.4)	1994 (5.3)	1229 (13.6)	475 (5.1)	7.3 (3.7 to 13.8)
2009	182 (5.4)	73 (4.8)	60 (4.3)	5.0 (4.3 to 5.7)	1973 (5.3)	483 (5.4)	463 (5.0)	5.2 (5.1 to 5.4)
2010	142 (4.2)	48 (3.2)	45 (3.2)	3.6 (2.9 to 4.4)	1894 (5.1)	447 (5.0)	463 (5.0)	5.0 (4.9 to 5.2)
2011	167 (5.0)	54 (3.6)	58 (4.1)	4.3 (3.5 to 5.2)	1965 (5.2)	417 (4.6)	425 (4.6)	4.8 (4.4 to 5.4)
2012	160 (4.8)	62 (4.1)	68 (4.8)	4.6 (4.1 to 5.2)	1913 (5.1)	373 (4.1)	460 (5.0)	4.7 (4.2 to 5.3)
2013	152 (4.5)	75 (5.0)	86 (6.1)	5.1 (4.3 to 6.1)	1886 (5.0)	377 (4.2)	456 (4.9)	4.7 (4.3 to 5.3)
2014	212 (6.3)	80 (5.3)	58 (4.1)	5.3 (4.1 to 6.7)	1811 (4.8)	352 (3.9)	403 (4.4)	4.4 (3.8 to 5.0)
Physician visits in year before index date, n (%)								
0–3	45 (1.3)	38 (2.5)	69 (4.9)	2.6 (1.2 to 5.5)	1873 (5.0)	1121 (12.4)	812 (8.8)	8.2 (4.6 to 14.3)
4–11	618 (18.4)	524 (34.7)	525 (37.3)	29.3 (18.0 to 43.9)	9002 (24.0)	3234 (35.9)	3078 (33.3)	30.8 (23.2 to 39.6)

Continued

Table 1 Continued

Characteristic	Multiple sclerosis				Epilepsy			
	BC	SK	MB	All provinces Combined (95% CI)†	BC	SK	MB	All provinces Combined (95% CI)*
	n=3353	n=1509	n=1409		n=37 466	n=9020	n=9253	
≥12	2690 (80.2)	947 (62.8)	815 (57.8)	67.8 (51.4 to 80.8)	26 591 (71.0)	4665 (51.7)	5363 (58.0)	60.5 (47.3 to 72.4)
Hospitalisations in year before index date, n (%)								
0	2706 (80.7)	1045 (69.3)	1089 (77.3)	76.1 (68.6 to 82.2)	19 210 (51.3)	4420 (49.0)	5804 (62.7)	54.4 (47.1 to 61.5)
≥1	647 (19.3)	464 (30.7)	320 (22.7)	23.9 (17.8 to 31.4)	18 256 (48.7)	4600 (51.0)	3449 (37.3)	45.6 (38.5 to 52.9)
Prescription medicationse in year before index date, n (%)								
0	273 (8.1)	162 (10.7)	117 (8.3)	9.0 (7.5 to 10.7)	5170 (13.8)	1942 (21.5)	1613 (17.4)	17.4 (13.1 to 22.7)
1–2	835 (24.9)	423 (28.0)	377 (26.8)	26.4 (24.5 to 28.4)	8366 (22.3)	2344 (26.0)	2260 (24.4)	24.2 (22.0 to 26.6)
3–4	800 (23.9)	360 (23.9)	369 (26.2)	24.5 (23.1 to 25.9)	6513 (17.4)	1599 (17.7)	1649 (17.8)	17.5 (17.2 to 17.8)
≥5	1445 (43.1)	564 (37.4)	546 (38.8)	39.8 (36.1 to 43.6)	17 417 (46.5)	3135 (34.8)	3731 (40.3)	40.4 (33.5 to 47.8)
Age (years), mean (SD)	73.1 (10.3)	73.1 (10.5)	73.8 (11.1)	73.5 (6.1)	54.9 (15.8)	54.5 (15.9)	52.2 (16.3)	53.9 (9.2)
Female, n (%)	4643 (41.7)	1948 (41.7)	2435 (44.4)	42.5 (40.8 to 44.3)	21 986 (72.1)	3940 (71.4)	5236 (73.2)	72.2 (71.4 to 73.1)
Median household income (quintiles), n (%)§								
1 (lowest)	2396 (21.5)	889 (19.0)	1286 (23.4)	21.3 (19.2 to 23.6)	6291 (20.6)	1164 (21.1)	1587 (22.2)	21.2 (20.3 to 22.2)
2	2222 (19.9)	880 (18.8)	1163 (21.2)	20.0 (18.8 to 21.2)	6005 (19.7)	1102 (20.0)	1447 (20.2)	19.8 (19.4 to 20.2)
3	2076 (18.6)	897 (19.2)	1181 (21.5)	19.7 (18.0 to 21.6)	5954 (19.5)	963 (17.4)	1391 (19.5)	18.9 (17.7 to 20.0)
4	2021 (18.1)	895 (19.1)	952 (17.4)	18.2 (17.3 to 19.1)	5847 (19.2)	1072 (19.4)	1431 (20.0)	19.4 (18.9 to 19.9)
5 (highest)	2205 (19.8)	851 (18.2)	904 (16.5)	18.1 (16.2 to 20.2)	5655 (18.5)	926 (16.8)	1295 (18.1)	17.9(16.9 to 18.9)
Location, n (%)								
Urbanc	9710 (87.1)	2938 (62.8)	3411 (62.2)	72.7 (51.3 to 87.0)	25 366 (83.2)	3415 (61.9)	4292 (60.0)	69.6 (49.3 to 84.4)
Rural	1432 (12.9)	1729 (37.0)	2075 (37.8)	27.3 (13.0 to 48.5)	5126 (16.8)	2092 (37.9)	2859 (40.0)	30.3 (15.6 to 50.5)
Index year, n (%)								
1997	737 (6.6)	312 (6.7)	353 (6.4)	6.6 (6.3 to 6.9)	1724 (5.7)	196 (3.6)	486 (6.8)	5.2 (4.0 to 6.8)
1998	735 (6.6)	337 (7.2)	350 (6.4)	6.7 (6.3 to 7.1)	1744 (5.7)	260 (4.7)	466 (6.5)	5.6 (4.9 to 6.5)
1999	729 (6.5)	275 (5.9)	322 (5.9)	6.2 (5.7 to 6.7)	1511 (5.0)	209 (3.8)	378 (5.3)	4.7 (4.0 to 5.4)
2000	666 (6.0)	260 (5.6)	321 (5.9)	5.9 (5.5 to 6.2)	237 (4.3)	237 (4.3)	363 (5.1)	4.9 (4.4 to 5.3)
2001	664 (6.0)	243 (5.2)	348 (6.3)	5.9 (5.3 to 6.5)	256 (4.6)	256 (4.6)	406 (5.7)	5.3 (4.8 to 5.8)
2002	676 (6.1)	227 (4.9)	310 (5.7)	5.5 (4.9 to 6.3)	264 (4.8)	264 (4.8)	419 (5.9)	5.4 (4.9 to 5.9)
2003	673 (6.0)	249 (5.3)	300 (5.5)	5.7 (5.2 to 6.1)	211 (3.8)	211 (3.8)	398 (5.6)	4.9 (4.1 to 5.9)
2004	654 (5.9)	229 (4.9)	288 (5.2)	5.4 (4.8 to 6.0)	250 (4.5)	250 (4.5)	386 (5.4)5.3 (4.6 to 6.1)	5.3 (4.6 to 6.1)
2005	640 (5.7)	215 (4.6)	318 (5.8)	5.4 (4.7 to 6.1)	220 (4.0)	220 (4.0)	402 (5.6)	5.1 (4.2 to 6.2)
2006	598 (5.4)	241 (5.2)	282 (5.1)	5.3 (5.0 to 5.6)	225 (4.1)	225 (4.1)	397 (5.6)	5.2 (4.2 to 6.4)
2007	614 (5.5)	202 (4.3)	309 (5.6)	5.2 (4.5 to 5.9)	279 (5.1)	279 (5.1)	397 (5.6)	5.6 (5.1 to 6.1)

Continued

Table 1 Continued

	Multiple sclerosis				Epilepsy			
	BC	SK	MB	All provinces Combined (95% CI)†	BC	SK	MB	All provinces Combined (95% CI)*
Characteristic	n=3353	n=1509	n=1409		n=37 466	n=9020	n=9253	
2008	617 (5.5)	305 (6.5)	283 (5.2)	5.7 (5.0 to 6.5)	578 (10.5)	578 (10.5)	417 (5.8)	6.9 (4.6 to 10.4)
2009	606 (5.4)	253 (5.4)	286 (5.2)	5.4 (5.1 to 5.7)	342 (6.2)	342 (6.2)	459 (6.4)	6.1 (5.6 to 6.5)
2010	557 (5.0)	244 (5.2)	332 (6.1)	5.4 (4.8 to 6.1)	310 (5.6)	310 (5.6)	4.5 (5.7)	5.6 (5.4 to 5.8)
2011	570 (5.1)	235 (5.0)	268 (4.9)	5.0 (4.8 to 5.3)	324 (5.9)	324 (5.9)	344 (4.8)	5.4 (4.9 to 5.9)
2012	511 (4.6)	224 (4.8)	304 (5.5)	4.9 (4.4 to 5.6)	328 (5.9)	328 (5.9)	338 (4.7)	5.4 (4.8 to 6.0)
2013	483 (4.3)	190 (4.1)	262 (4.8)	4.4 (4.0 to 4.8)	296 (5.4)	296 (5.4)	344 (4.8)	5.2 (4.9 to 5.5)
2014	412 (3.7)	209 (4.5)	250 (4.6)	4.2 (3.6 to 4.8)	347 (6.3)	347 (6.3)	346 (4.8)	5.5 (4.8 to 6.2)
Physician visits in year before index date, n (%)								
0–3	258 (2.3)	321 (6.9)	256 (4.7)	4.2 (2.2 to 7.8)	197 (3.6)	197 (3.6)	252 (3.5)	2.0 (0.7 to 5.9)
4–11	1752 (15.7)	1510 (32.3)	1607 (29.3)	25.0 (15.5 to 37.7)	1847 (33.5)	1847 (33.5)	2126 (29.7)	23.4 (11.0 to 42.9)
≥12	9132 (82.0)	2845 (60.8)	3623 (66.0)	70.5 (55.1 to 82.4)	3477 (63.0)	3477 (63.0)	4773 (66.7)	74.3 (52.3 to 88.4)
Hospitalisations in year before index date, n (%)								
0	7042 (63.2)	2772 (59.3)	3707 (67.6)	63.4 (59.2 to 67.5)	3889 (70.4)	3889 (70.4)	5253 (73.5)	72.8 (70.6 to 75.0)
≥1	4100 (36.8)	1904 (40.7)	1779 (32.4)	36.6 (32.5 to 40.8)	1632 (29.6)	1632 (29.6)	1898 (26.5)	27.2 (25.0 to 29.4)
Prescription medicationse in year before index date, n (%)¶								
0	620 (5.6)	328 (7.0)	366 (6.7)	6.4 (5.5 to 7.4)	214 (3.9)	214 (3.9)	153 (2.1)	2.5 (1.7 to 3.6)
1–2	1542 (13.8)	713 (15.2)	867 (15.8)	14.9 (13.7 to 16.2)	599 (10.8)	599 (10.8)	957 (13.4)	11.7(10.5 to 13.0)
3–4	1951 (17.5)	801 (17.1)	1042 (19.0)	17.9 (16.9 to 18.9)	5524 (18.1)	997 (18.1)	1472 (20.6)	18.9 (19.6 to 20.2)
≥5	7029 (63.1)	2834 (60.6)	3211 (58.5)	60.8 (57.9 to 63.6)	21 040 (69.0)	3711 (67.2)	4569 (63.9)	66.8 (64.3 to 69.1)

*Subjects with disease and at least one dispensation for a disease-specific drug.
†Only combined proportions reported.
‡Percentage may not total 100, due to missing values.
§Definitions for urban vary between provinces: BC, determined by forward sortation area (non-zero digit as the second character of the postal code) (https://www.ic.gc.ca/eic/site/bsf-osb.nsf/eng/br03396.html); SK, population >1000 (https://www150.statcan.gc.ca/n1/pub/11-630-x/11-630-x2015004-eng.htm); MB, population >50 000 (only two cities in Manitoba are classified as urban).
¶Number of non-study medication classes based on Anatomical Therapeutic Chemical Classification (https://www.whocc.no/atc_ddd_index/).
BC, British Columbia; MB, Manitoba; SK, Saskatchewan.

Table 2 Disease-specific adherence and persistence (all provinces combined)

Measure	Multiple sclerosis n=6271	Epilepsy n=55 739	Parkinson disease n=21 304	Rheumatoid arthritis n=43 164
Medication possession ratio ≥80%, n (%, 95% CI)				
Year 1	4757/6271 (77.2, 72.4 to 81.3)	28247/55739 (50.9, 42.5 to 59.3)	13173/21304 (61.0, 54.9 to 66.8)	20605/43164 (47.0, 45.4 to 48.8)
Year 2	3854/5769 (68.3, 62.7 to 73.3)	23330/50615 (45.7, 37.5 to 54.2)	11837/19388 (59.6, 53.5 to 65.4)	16183/39809 (40.1, 38.9 to 41.4)
Year 3	3238/5332 (62.1, 56.7 to 67.2)	19875/46047 (42.4, 34.9 to 50.3)	10539/17351 (59.0, 51.4 to 66.1)	13574/36656 (36.4, 34.7 to 38.0)
Year 4	2815/4953 (58.1, 53.0 to 63.1)	17301/41863 (40.5, 33.6 to 47.8)	9273/15309 (58.9, 48.8 to 68.3)	11726/33608 (34.4, 32.8 to 36.1)
Year 5	2461/4606 (54.5, 50.1 to 58.8)	15096/37977 (38.7, 32.1 to 45.8)	8044/13380 (58.7, 45.9 to 70.4)	10198/30695 (32.8, 30.9 to 34.8)
Proportion Days Covered ≥80%, n (%, 95% CI)				
Year 1	4698/6271 (75.9, 73.0 to 78.5)	27339/55739 (48.7, 41.5 to 56.0)	12706/21304 (58.5, 52.9 to 63.9)	19953/43164 (44.8, 41.8 to 47.8)
Year 2	3818/5769 (67.4, 62.6 to 71.9)	22442/50615 (43.6, 35.8 to 51.7)	11406/19388 (57.2, 50.9 to 63.3)	15696/39809 (38.5, 36.3 to 40.7)
Year 3	3209/5332 (61.4, 56.5 to 66.1)	19055/46047 (40.4, 33.1 to 48.2)	10117/17351 (56.5, 48.9 to 63.8)	13119/36656 (34.7, 32.1 to 37.3)
Year 4	2788/4953 (57.4, 53.8 to 60.9)	16502/41863 (38.4, 31.6 to 45.7)	8861/15309 (56.2, 46.6 to 65.4)	11311/33608 (32.8, 30.5 to 35.2)
Year 5	2452/4606 (54.2, 50.1 to 58.3)	14341/37977 (36.6, 30.0 to 43.7)	7641/13380 (55.6, 43.7 to 67.0)	9806/30695 (31.2, 28.7 to 33.8)
Discontinued within the first 365 days, n (%, 95% CI)	1113 (17.7, 16.8 to 18.7)	24 162 (43.3, 42.9 to 43.8)	6629 (31.1, 30.5 to 31.7)	19 132 (44.3, 43.9 to 44.8)
Discontinued after only one dispensation, n (%, 95% CI)	168 (2.6, 2.0 to 3.3)	9434 (15.6. 12.5 to 19.2)	2458 (11.9, 10.3 to 13.8)	4968 (13.1, 9.5 to 18.0)
Discontinued within first 180 days,* n (%, 95% CI)	411 (5.9, 4.3 to 8.2)	9897 (16.0, 12.7 to 19.9)	2881 (13.4, 12.6 to 14.2)	8746 (18.2, 14.5 to 22.4)
Discontinued between day 181 and 365, n (%, 95% CI)	534 (8.2, 6.9 to 9.7)	4831 (8.8, 7.7 to 9.9)	1290 (6.1, 5.7 to 6.4)	5418 (12.1, 11.2 to 13.2)

Numerators include number of subjects with sufficient follow-up available for each time period.
*Excluding those who discontinued after only one dispensation.

It is often assumed that individuals with a chronic, potentially disabling disease will be fully motivated to adhere to drug treatment; in reality this can be quite different. Reviews of the literature estimate 33%–88% of individuals with MS,[41] 20%–75% with epilepsy,[29] 30%–80% with RA[27] and 10%–67% with PD[28] have good adherence to their disease-specific medications. This wide variability is due to differences in data sources and study methodologies, and makes comparisons within and between diseases difficult. Our study addressed this limitation by using identical data sources, time periods, methodology and outcomes. Our finding that subjects with MS were significantly more likely to have optimal 1-year adherence to their disease-specific medications compared with subjects with epilepsy, RA and PD, establishes that adherence to disease-specific therapies is better in MS than in other chronic diseases.

Although adherence decreased over the first 5 years of therapy in all disease cohorts, the decrease was greatest in the MS cohort. As therapy-related and disease-related factors such treatment regimen and disease duration have not been consistently associated with adherence,[42 43] we hypothesise this may be due to the lack of consensus on how long individuals living with MS should be treated with DMDs. While other chronic conditions, including those in this study, require indefinite treatment, this is not the case with MS. As MS progresses, inflammation becomes less prominent and the current DMDs become less effective. In many cases, healthcare payers and insurance plans discontinue coverage of the DMDs once a certain level of progression or disability has been reached.[13] Because of this, it is difficult to assess long-term adherence in MS, which is another reason we chose to focus our primary analyses on the first year of treatment.

When we examined the MS cohort specifically, we found that adherence was higher, in some cases significantly, to DMD compared with other non-MS chronic medications. This suggests that the high level of DMD adherence is likely related to DMD-specific factors, rather than patient-level factors. This is further supported by the observation that no consistent predictors of adherence

Table 3 Predictors of adherence and persistence at 1 year (all provinces combined)

Covariate	Adherence ≥80% at Year 1 OR (95% CI)		Persistence at year 1 OR (95% CI)
	Medication possession ratio	Proportion days covered	
Age (years), n=1 26 478	**1.00 (1.00 to 1.00)**	**1.00 (1.00 to 1.00)**	**1.01 (1.00 to 1.01)**
Sex			
Male, n=54 537	Reference	Reference	Reference
Female, n=71 941	0.98 (0.90 to 1.06)	0.98 (0.90 to 1.06)	0.99 (0.94 to 1.04)
Median household income (quintiles)			
1 (lowest), n=28 245	Reference	Reference	Reference
2, n=25 111	**1.10 (1.03 to 1.17)**	**1.10 (1.04 to 1.17)**	1.06 (0.95 to 1.20)
3, n=24 201	**1.18 (1.09 to 1.29)**	**1.19 (1.09 to 1.29)**	1.11 (0.93 to 1.32)
4, n=23 494	**1.22 (1.09 to 1.37)**	**1.22 (1.09 to 1.38)**	1.12 (0.97 to 1.31)
5 (highest), n=22 180	**1.29 (1.07 to 1.54)**	**1.29 (1.09 to 1.52)**	1.15 (0.94 to 1.42)
Location			
Urban,* n=97 877	Reference	Reference	Reference
Rural, n=28 554	**0.95 (0.91 to 0.98)**	**0.94 (0.91 to 0.98)**	0.97 (0.92 to 1.03)
Index year			
1997–1998, n=15 444	Reference	Reference	Reference
1999–2000, n=14 521	**1.13 (1.04 to 1.21)**	**1.11 (1.04 to 1.20)**	**1.11 (1.05 to 1.19)**
2001–2002, n=14 540	**1.23 (1.09 to 1.38)**	**1.20 (1.08 to 1.34)**	**1.14 (1.07 to 1.21)**
2003–2005, n=20 853	**1.31 (1.16 to 1.47)**	**1.31 (1.17 to 1.47)**	**1.25 (1.06 to 1.46)**
2006–2008, n=21 284	**1.47 (1.19 to 1.82)**	**1.46 (1.18 to 1.81)**	**1.22 (1.11 to 1.33)**
2009-study end,† n=39 836	**1.55 (1.31 to 1.82)**	**1.52 (1.31 to 1.75)**	**1.31 (1.13 to 1.53)**
Physician visits in year before index date			
0–3, n=5442	Reference	Reference	Reference
4–11, n=29 405	**1.35 (1.07 to 1.70)**	**1.35 (1.07 to 1.70)**	**1.11 (1.02 to 1.20)**
≥12, n=91 631	**1.52 (1.22 to 1.88)**	**1.50 (1.21 to 1.86)**	**1.24 (1.14 to 1.34)**
HospitaliSations in year before index date			
0, n=79 625	Reference	Reference	Reference
≥1, n=46 853	**1.14 (1.06 to 1.23)**	**1.14 (1.06 to 1.23)**	**1.12 (1.03 to 1.21)**
Prescription medications‡ in year before index date			
0, n=11 513	Reference	Reference	Reference
1–2, n=22 656	**0.80 (0.69 to 0.93)**	**0.81 (0.69 to 0.94)**	**0.87 (0.82 to 0.93)**
3–4, n=23 077	**0.70 (0.59 to 0.83)**	**0.70 (0.59 to 0.83)**	0.87 (0.75 to 1.00)
≥5, n=69 232	**0.66 (0.49 to 0.90)**	**0.67 (0.49 to 0.90)**	0.91 (0.73 to 1.13)
Disease cohort			
Multiple sclerosis, n=6271	Reference	Reference	Reference
Epilepsy, n=55 739	**0.29 (0.19 to 0.45)**	**0.29 (0.18 to 0.45)**	0.68 (0.36 to 1.31)
Parkinson disease, n=21 304	**0.42 (0.29 to 0.63)**	**0.41 (0.28 to 0.60)**	**0.67 (0.46 to 0.95)**
Rheumatoid arthritis, n=43 164	**0.26 (0.19 to 0.35)**	**0.25 (0.18 to0.35)**	**0.48 (0.32 to 0.71)**

Bold values indicate statistical significance.
*Definitions for urban vary between provinces: British Columbia, determined by forward sortation area (non-zero digit as the second character of the postal code) (https://www.ic.gc.ca/eic/site/bsf-osb.nsf/eng/br03396.html); Saskatchewan, population >1000 (https://www150.statcan.gc.ca/n1/pub/11-630-x/11-630-x2015004-eng.htm); Manitoba, population >50 000 (only two cities in Manitoba are classified as urban).
†Study end was 31 December 2014 for British Columbia, and 31 December 2015 for Saskatchewan and Manitoba.
‡Number of non-study medication classes based on Anatomical Therapeutic Chemical Classification (https://www.whocc.no/atc_ddd_index/).

were observed across all four non-MS medication classes, including having optimal adherence to DMD.

During the study period, DMDs were prescribed by MS-specialist neurologists through MS centres in BC and MB. In SK, most individuals with MS were managed by community-based neurologists, none of whom had a practice dedicated to MS, and the one provincial MS centre at the time was focused on rehabilitative care. Despite this, adherence did not differ across provinces, and was actually found to be highest in SK in both the current (data not shown), and previous study.[13] Combined, our findings suggest there is something unique about the DMDs themselves that is resulting in higher adherence, and support our hypothesis that the higher adherence seen in MS may

Table 4 Adherence and persistence to the MS specific and non-MS chronic medications within the MS Cohort* (all provinces combined)

	DMD	Statins	ACEI	ARB	Thyroid replacement
Measure	**n=6271**	**n=4628**	**n=4569**	**n=1971**	**n=2612**
Medication Possession Ratio (MPR) ≥80%, n (%, 95% CI)					
Year 1	4757/6271 (77.2, 72.4 to 81.3)	2571/4628 (55.3, 51.0 to 59.4)	2500/4569 (54.7, 53.3 to 56.2)	1188/1971 (60.3, 56.7 to 63.8)	1847/2612 (72.3, 68.1 to 76.1)
Year 2	3854/5769 (68.3, 62.7 to 73.3)	2148/4347 (49.1, 45.7 to 52.5)	1991/4261 (46.7, 45.2 to 48.2)	968/1849 (52.4, 50.1 to 54.6)	1593/2407 (67.4, 63.5 to 71.0)
Year 3	3238/5332 (62.1, 56.7 to 67.2)	1870/4060 (45.7, 43.1 to 48.3)	1694/3937 (43.0, 41.5 to 44.6)	855/1727 (49.1, 45.9 to 52.4)	1428/2208 (65.9, 62.0 to 69.5)
Year 4	2815/4953 (58.1, 53.0 to 63.1)	1642/3780 (43.1, 40.6 to 45.6)	1443/3607 (39.3, 36.6 to 42.1)	738/1582 (46.1, 42.5 to 49.8)	1265/1992 (65.0, 60.6 to 69.2)
Year 5	2461/4606 (54.5, 50.1 to 58.8)	1459/3464 (42.1, 40.5 to 43.8)	1253/3295 (37.4, 34.7 to 40.2)	641/1421 (44.9, 41.7 to 48.1)	1115/1791 (63.3, 59.3 to 67.2)
Proportion Days Covered (PDC) ≥80%, n (%, 95% CI)					
Year 1	4698/6271 (75.9, 73.0 to 78.5)	2518/4628 (53.8, 50.4 to 57.2)	2465/4569 (54.0, 52.5 to 55.4)	1161/1971 (58.9, 56.5 to 61.2)	1822/2612 (70.7, 67.5 to 73.7)
Year 2	3818/5769 (67.4, 62.6 to 71.9)	2116/4347 (48.3, 45.5 to 51.0)	1974/4261 (46.3, 44.8 to 47.8)	962/1849 (52.0, 49.7 to 54.3)	1569/2407 (66.1, 62.7 to 69.3)
Year 3	3209/5332 (61.4, 56.5 to 66.1)	1846/4060 (45.1, 42.8 to 47.4)	1672/3937 (42.5, 40.9 to 44.0)	841/1727 (48.3, 44.9 to 51.6)	1413/2208 (64.9, 61.5 to 68.1)
Year 4	2788/4953 (57.4, 53.8 to 60.9)	1621/3780 (42.4, 39.9 to 45.0)	1430/3607 (38.9, 36.1 to 41.7)	734/1582 (45.8, 42.1 to 49.6)	1247/1992 (63.5, 59.9 to 66.9)
Year 5	2452/4606 (54.2, 50.1 to 58.3)	1445/3464 (41.7, 39.7 to 43.7)	1236/3295 (36.7, 33.8 to 39.7)	638/1421 (44.6, 41.2 to 48.0)	1103/1791 (62.4, 58.7 to 65.8)
Discontinued within the first 365 days, n (%, 95% CI)	1113 (17.7, 16.8 to 18.7)	1827 (39.5, 38.1 to 40.9)	1991 (43.6, 42.1 to 45.0)	712 (36.1, 34.0 to 38.3)	742 (28.4, 26.7 to 30.2)
Discontinued after only one dispensation, n (%, 95% CI)	168 (2.6, 2.0 to 3.3)	423 (8.9, 5.8 to 13.4)	470 (9.8, 5.9 to 15.9)	169 (8.3, 5.9 to 11.6)	138 (5.1, 3.0 to 8.6)
Discontinued within first 180 days,† n (%, 95% CI)	411 (5.9, 4.3 to 8.2)	909 (18.6, 13.8 to 24.7)	984 (20.9, 16.3 to 26.5)	348 (17.4, 13.8 to 21.6)	392 (12.1, 7.0 to 20.1)
Discontinued between day 181 and 365, n (%, 95% CI)	534 (8.2, 6.9 to 9.7)	495 (10.7, 9.8 to 11.6)	537 (11.5, 10.1 to 13.0)	195 (9.9, 8.7 to 11.3)	212 (8.1, 7.1 to 9.2)

Numerators include number of subjects with sufficient follow-up available for each time period.
*MS cohort includes all subjects diagnosed with MS, with or without a dispensation for a DMD during the study period (n=28 176).
†Excluding those who discontinued after only one dispensation.
ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; DMD, disease-modifying drug; MS, multiple sclerosis.

Table 5 Predictors of adherence to chronic-use medications within the MS cohort* at 1 year (all provinces combined)

	Medication possession ratio (MPR) at tear 1 OR (95% CI)			
Covariate	**Statins n=879**	**ACEI n=766**	**ARB n=363**	**Thyroid n=601**
Age (years)	**1.03 (1.01 to 1.05)**	**1.02 (1.00 to 1.03)**	0.99 (0.94 to 1.05)	**1.02 (1.00 to 1.04)**
Sex				
Male	Reference	Reference	Reference	Reference
Female	0.79 (0.50 to 1.26)	**0.51 (0.36 to 0.72)**	**0.53 (0.29 to 0.96)**	1.33 (0.66 to 2.65)
Median household income (quintiles)				
1 (lowest)	Reference	Reference	Reference	Reference
2	**1.70 (1.04 to 2.77)**	0.95 (0.29 to 3.14)	1.04 (0.47 to 2.31)	1.13 (0.60 to 2.12)
3	1.26 (0.50 to 2.86)	0.79 (0.39 to 1.59)	1.05 (0.27 to 4.08)	1.32 (0.68 to 2.53)
4	0.99 (0.63 to 1.57)	0.76 (0.20 to 2.82)	1.04 (0.15 to 7.37)	1.02 (0.50 to 2.09)
5 (highest)	1.31 (0.82 to 2.11)	0.80 (0.30 to 2.15)	1.27 (0.31 to 5.12)	0.90 (0.47 to 1.69)
Location				
Urban†	Reference	Reference	Reference	Reference
Rural	**0.64 (0.42 to 0.97)**	0.83 (0.58 to 1.21)	0.84 (0.47 to 1.53)	1.01 (0.62 to 1.65)
Index year	1.02 (0.97 to 1.07)	1.02 (0.95 to 1.08)	1.00 (0.90 to 1.11)	1.01 (0.98 to 1.05)
Mean no of physician visits in year before index date	1.01 (0.99 to 1.03)	0.99 (0.98 to 1.00)	1.01 (0.99 to 1.03)	1.00 (0.99 to 1.02)
Mean no of hospitalisations in year before index date	0.99 (0.80 to 1.22)	1.15 (0.90 to 1.47)	0.88 (0.64 to 1.22)	1.40 (0.97 to 2.01)
Mean no of prescription medications‡ in year before index date	**1.04 (1.00 to 1.08)**	**1.05 (1.00 to 1.09)**	1.04 (0.98 to 1.11)	0.98 (0.93 to 1.03)
Adherence (MPR) to DMD at year 1 ≥80%				
No	Reference	Reference	Reference	Reference
Yes	1.35 (0.94 to 1.95)	**1.83 (1.23 to 2.71)**	1.18 (0.66 to 2.13)	1.33 (0.85 to 2.07)

Bold values indicate statistical significance.
*Only includes subject who received at least one dispensation for a DMD and a chronic-used medication during the study period.
†Definitions for urban vary between provinces: BC, determined by forward sortation area (non-zero digit as the second character of the postal code) (https://www.ic.gc.ca/eic/site/bsf-osb.nsf/eng/br03396.html); SK, population >1000 (https://www150.statcan.gc.ca/n1/pub/11-630-x/11-630-x2015004-eng.htm); MB, population >50 000 (only two cities in Manitoba are classified as urban).
‡Number of non-study medication classes based on Anatomical Therapeutic Chemical Classification (https://www.whocc.no/atc_ddd_index/).
ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; DMD, disease-modifying drug; MB, Saskatchewan; SK, Saskatchewan.

be due to the specialised DMD management and support programmes provided to individuals.

In Canada, each individual pharmaceutical company with a marketed DMD for MS has an established patient support programme.[44] These programmes are often led by nurse educators, and provide individualised training, and ongoing support and follow-up at no-cost to individuals. Although the literature is full of examples of interventions aimed at improving adherence, few methods have proven effective or sustainable.[4 5 11] These DMD support programmes differ from most existing adherence interventions in that they provide comprehensive and continuous support, and may serve as an example for future interventions.

Our study is not without limitations. As with all observational studies, we were not able to control for all potential confounders. With administrative data, we lacked information on disease severity, and potential adverse effects, which may affect adherence and persistence. Although we excluded subjects who were pregnant, we were not able to determine the reason(s) for discontinuations or non-adherence. We did not include a variable specifically measuring comorbidity, as there is no optimal method for estimating comorbidity burden in administrative data.[45] However, we included prior healthcare utilisation and medication use, which have previously been used as proxy measures for comorbidity, and which predict important outcomes such as mortality.[13 45 46] Although there is always a potential for lack of efficacy with any drug, we are not concerned that it affected our results. All study outcomes were estimated using a class effect, so switching between drugs was allowed. Therefore, if one agent was not effective, a subjectl was not 'penalised' for switching to another drug. In all of the study diseases it is highly unlikely that a lack of efficacy of one agent would results in a complete withdrawal of all drugs, especially within the first year of therapy. We had to make an assumption of the days' supply for the adherence calculations using SK data. This assumption may have resulted in lower adherence levels; however, the assumption was applied consistently across all cohorts, and therefore, would not affect the adherence comparisons. Finally, we arbitrarily chose a threshold

of 80% to define optimal adherence. This threshold is widely used in the adherence literature and has been associated with fewer hospitalisations and deaths, and allowed for comparability of our findings.[2 47 48] Nevertheless, this large cohort study included over 126 000 subjects from 3 Canadian provinces that provide universal healthcare coverage. Because all data were population based, and only incident users were included in our analyses, we minimised several biases often noted in adherence studies.[49 50] The use of identical data sources, definitions, outcomes and time periods ensured our findings were robust and not due to variability between study methodologies.

To date, there has been little success in identifying effective interventions to improve medication adherence.[4 5 11 12] Reasons for non-adherence are complex and few predictors have been consistently associated with levels of adherence across diseases.[2 9] As such, disease-specific adherence evaluations and comparisons such as ours are imperative. Given the impact of non-adherence on increased mortality, morbidity and healthcare costs,[2 47] further examination of DMD adherence and the effects of access to, and quality of, these support programmes in other regions is warranted to better understand their potential as a model for improving adherence to medications for other chronic conditions.

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REFERENCES

1 World Health Organization. Adherence to long-term therapies - evidence for action, 2003. Available: http://www.who.int/chp/knowledge/publications/adherence_introduction.pdf [Accessed 1 Sep 2009].
2 Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med* 2005;353:487–97.
3 Cutler RL, Fernandez-Llimos F, Frommer M, *et al*. Economic impact of medication non-adherence by disease groups: a systematic review. *BMJ Open* 2018;8:e0169982.
4 Costa E, Giardini A, Savin M, *et al*. Interventional tools to improve medication adherence: review of literature. *Patient Prefer Adherence* 2015;9:1303–14.
5 Kini V, Ho PM. Interventions to improve medication adherence: a review. *JAMA* 2018;320:2461–73.
6 Mongkhon P, Ashcroft DM, Scholfield CN, *et al*. Hospital admissions associated with medication non-adherence: a systematic review of prospective observational studies. *BMJ Qual Saf* 2018;27:902–14.
7 Cutler DM, Long G, Berndt ER, *et al*. The value of antihypertensive drugs: a perspective on medical innovation. *Health Aff* 2007;26:97–110.
8 Dutt M. Affordable Access to Medicines - A Prescription for Canada, 2014. Available: https://www.policyalternatives.ca/affordable-access-medicines [Accessed 29 Jun 2020].
9 Haynes RB. Improving patient adherence: state of the art, with a special focus on medication taking for cardiovascular disorders. In: Burke L, Ockene I, eds. *Compliance in healthcare and research*. Armonk, New York: Futura Publishing Company, Inc, 2001: 3–24.
10 Raebel MA, Schmittdiel J, Karter AJ, *et al*. Standardizing terminology and definitions of medication adherence and persistence in research employing electronic databases. *Med Care* 2013;51:S11–21.
11 McDonald HP, Garg AX, Haynes RB. Interventions to enhance patient adherence to medication prescriptions: scientific review. *JAMA* 2002;288:2868–79.
12 Haynes RB, McDonald H, Garg AX, *et al*. Interventions for helping patients to follow prescriptions for medications. *Cochrane Database Syst Rev* 2002:CD000011.

13 Evans C, Marrie RA, Zhu F, *et al*. Adherence and persistence to drug therapies for multiple sclerosis: a population-based study. *Mult Scler Relat Disord* 2016;8:78–85.
14 Melesse DY, Marrie RA, Blanchard JF, *et al*. Persistence to disease-modifying therapies for multiple sclerosis in a Canadian cohort. *Patient Prefer Adherence* 2017;11:1093–101.
15 World Health Organization Collaborating Centre for Drug Statistics Methodology. ATC/DDD index 2020, 2020. Available: https://www.whocc.no/atc_ddd_index/ [Accessed 5 May 2020].
16 British Columbia Ministry of Health [creator] (2016). Medical Services (MSP) Payment Information File. V2. Population Data BC [publisher]. Data Extract. MOH, 2016. Available: http://www.popdata.bc.ca/data
17 British Columbia Ministry of Health [creator]. PharmaNet (Data Extract). BC Ministry of Health [publisher]. Data Extract. Data Stewardship Committee, 2016. Available: http://www.popdata.bc/data
18 British Columbia Vital Statistics Agency [creator]. Vital Statistics Deaths. Population Data BC [publisher]. Data Extract BC Vital Statistics Agency, 2016. Available: http://www.popdata.bc.ca/data
19 Canadian Institute for Health Information [creator]. Discharge Abstract Database (Hospital Separations). Population Data BC [publisher]. Data Extract. MOH, 2016. Available: http://www.popdata.bc.ca/data
20 British Columbia Ministry of Health [creator]. Consolidation File (MSP Registration & Premium Billing). Population Data BC [publisher]. Data Extract. MOH, 2016. Available: http://www.popdata.bc.ca/data
21 Marrie RA, Yu N, Blanchard J, *et al*. The rising prevalence and changing age distribution of multiple sclerosis in Manitoba. *Neurology* 2010;74:465–71.
22 Peschken CA, Hitchon CA, Garland A, *et al*. A population-based study of intensive care unit admissions in rheumatoid arthritis. *J Rheumatol* 2016;43:43.
23 Reid AY, St Germaine-Smith C, Liu M, *et al*. Development and validation of a case definition for epilepsy for use with administrative health data. *Epilepsy Res* 2012;102:173–9.
24 Butt DA, Tu K, Young J, *et al*. A validation study of administrative data algorithms to identify patients with parkinsonism with prevalence and incidence trends. *Neuroepidemiology* 2014;43:28–37.
25 Canadian Institute of Health Information. *The burden of neurological diseases, disorders and injuries in Canada*. Ottawa, 2007.
26 Lagace C, O'Donnell S, McRae L. Life with arthritis in Canada. A personal and public health challenge, 2010. Available: http://www.phac-aspc.gc.ca/cd-mc/arthritis-arthrite/lwaic-vaaac-10/pdf/arthritis-2010-eng.pdf [Accessed 14 Feb 2016].
27 van den Bemt BJF, Zwikker HE, van den Ende CHM. Medication adherence in patients with rheumatoid arthritis: a critical appraisal of the existing literature. *Expert Rev Clin Immunol* 2012;8:337–51.
28 Malek N, Grosset DG. Medication adherence in patients with Parkinson's disease. *CNS Drugs* 2015;29:47–53.
29 Malek N, Heath CA, Greene J. A review of medication adherence in people with epilepsy. *Acta Neurol Scand* 2017;135:507–15.
30 Hamer HM, Dodel R, Strzelczyk A, *et al*. Prevalence, utilization, and costs of antiepileptic drugs for epilepsy in Germany--a nationwide population-based study in children and adults. *J Neurol* 2012;259:2376–84.
31 Alfian SD, Denig P, Coelho A, *et al*. Pharmacy-based predictors of non-adherence, non-persistence and reinitiation of antihypertensive drugs among patients on oral diabetes drugs in the Netherlands. *PLoS One* 2019;14:14.
32 Pharmacy Quality Alliance. PQA adherence measures, 2018. Available: https://www.pqaalliance.org/adherence-measures [Accessed 5 May 2020].
33 Leslie S. Using arrays to calculate medication utilization SAS global forum 2007 web site, 2007. Available: https://support.sas.com/resources/papers/proceedings/proceedings/forum2007/043-2007.pdf [Accessed 7 Jul 2020].
34 Marrie RA, Cohen J, Stuve O, *et al*. A systematic review of the incidence and prevalence of comorbidity in multiple sclerosis: overview. *Mult Scler* 2015;21:263–81.
35 Marrie RA, Yu BN, Leung S, *et al*. Rising prevalence of vascular comorbidities in multiple sclerosis: validation of administrative definitions for diabetes, hypertension, and hyperlipidemia. *Mult Scler* 2012;18:1310–9.
36 Allison P. *Logistic Regression Using SAS: Theory and Application*. 2nd edn. Cary, NC: SAS Institute Inc, 2012.
37 Higgins JPT, Thompson SG, Deeks JJ, *et al*. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.
38 Pasma A, Schenk CV, Timman R, *et al*. Non-adherence to disease-modifying antirheumatic drugs is associated with higher disease activity in early arthritis patients in the first year of the disease. *Arthritis Res Ther* 2015;17:281.
39 Evans CD, Eurich DT, Remillard AJ, *et al*. First-Fill medication Discontinuations and nonadherence to antihypertensive therapy: an observational study. *Am J Hypertens* 2012;25:195–203.
40 Blackburn DF, Dobson RT, Blackburn JL, *et al*. Adherence to statins, beta-blockers and angiotensin-converting enzyme inhibitors following a first cardiovascular event: a retrospective cohort study. *Can J Cardiol* 2005;21:485–8.
41 Menzin J, Caon C, Nichols C, *et al*. Narrative review of the literature on adherence to disease-modifying therapies among patients with multiple sclerosis. *J Manag Care Pharm* 2013;19:S24–40.
42 Mathes T, Jaschinski T, Pieper D. Adherence influencing factors - a systematic review of systematic reviews. *Arch Public Health* 2014;72:37.
43 Gast A, Mathes T. Medication adherence influencing factors-an (updated) overview of systematic reviews. *Syst Rev* 2019;8:112.
44 Multiple Sclerosis Society of Canada. Program and Services - Pharmaceutical Company Support Programs, 2020. Available: https://mssociety.ca/support-services/programs-and-services/1051/pharmaceutical-company-support-programs [Accessed 26 Jun 2020].
45 Quail JM, Lix LM, Osman BA, *et al*. Comparing comorbidity measures for predicting mortality and hospitalization in three population-based cohorts. *BMC Health Serv Res* 2011;11:146.
46 Schneeweiss S, Seeger JD, Maclure M, *et al*. Performance of comorbidity scores to control for confounding in epidemiologic studies using claims data. *Am J Epidemiol* 2001;154:854–64.
47 Simpson SH, Eurich DT, Majumdar SR, *et al*. A meta-analysis of the association between adherence to drug therapy and mortality. *BMJ* 2006;333:15.
48 Karve S, Cleves MA, Helm M, *et al*. Good and poor adherence: optimal cut-point for adherence measures using administrative claims data. *Curr Med Res Opin* 2009;25:2303–10.
49 Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. *Am J Epidemiol* 2003;158:915–20.
50 Li X, Cole SR, Westreich D, *et al*. Primary non-adherence and the new-user design. *Pharmacoepidemiol Drug Saf* 2018;27:361–4.