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Effect of adherence to the first-generation injectable immunomodulatory drugs on disability accumulation in multiple sclerosis

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ABSTRACT

Objective: To examine the association between optimal adherence to the first-generation injectable immunomodulatory drugs (IMDs) for multiple sclerosis (MS) and subsequent disability accumulation.

Methods: We accessed prospectively collected linked clinical and administrative health data from British Columbia, Canada. MS subjects treated with a first-generation injectable IMD at a MS Clinic (1996-2004) were followed until their last clinic visit before 2009. Adherence was estimated using the proportion of days covered (PDC). The primary outcome was disability accumulation, defined as an increase in the Expanded Disability Status Scale (EDSS) score as recorded during each year of follow-up. Generalized estimating equation models, adjusted for baseline sex, age, EDSS and time between scores, were used to measure associations between optimal adherence (≥80% PDC) during the first year of treatment and subsequent disability accumulation. The relationship between early IMD adherence and the secondary outcome, time to sustained EDSS 6, was examined using Cox proportional hazards regression.

Results: Among 801 subjects, 598 (74.7%) had optimal adherence over the first year of IMD treatment and 487 (39.0%) demonstrated one or more instances of disability accumulation. Early optimal adherence was not associated with disability accumulation [adjusted odds ratio (adjOR) 0.94;95%CI:0.78-1.15], nor with time to sustained EDSS 6 (adjOR 0.91;95%CI:0.57-1.44).

Conclusions: Almost three-quarters of MS subjects had optimal early adherence to their first-line injectable IMD. There was no evidence that this was associated with disability accumulation in the following years.

KEYWORDS: Multiple sclerosis; adherence, immunomodulatory drugs, disease progression, longitudinal analysis, observational study

STRENGTHS AND LIMITATIONS OF THIS STUDY

- One of the first population-based studies to examine the association between drug adherence and subsequent disability accumulation in multiple sclerosis
- Real world setting which increases the generalizability of the study results
- Observational studies cannot adjust or assess all potential (unknown) confounders

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system and is considered one of the most common reasons for non-trauma related disability in young adults.[1] The injectable immunomodulatory therapies (IMDs), beta-interferon and glatiramer acetate, are associated with reduced MS relapse rates in short-term clinical trials,[2] but the evidence regarding the effects of these therapies on longer-term disability progression drawn from observational studies is mixed.[2, 3] These drugs are considered first-line therapies in Canada, and are commonly used to treat MS worldwide.[4]

To maximize the potential benefit of any drug, it should be taken as indicated; however, multiple lifestyle, patient-specific and drug-related factors can affect adherence.[5] Adherence levels early in treatment predict future adherence patterns.[6-8] In general, poor medication adherence is associated with poorer health-related outcomes, including higher risk of morbidity and mortality, increased health services utilization, and increased health care costs.[9-11] In MS, poor adherence to the IMDs is associated with decreased quality of life, higher relapse rates and higher medical costs.[9, 12, 13] However, to date, the effects of IMD adherence on MS progression are unknown. We examined the association between adherence during the initial year of therapy to a first-line injectable IMD and subsequent disability accumulation in people with relapsing-onset MS in British Columbia (BC), Canada.

METHODS

Study design and data sources

This was a retrospective cohort study, involving linkage of prospectively collected clinical and administrative health data in BC. The BC Multiple Sclerosis (BCMS) database was the source of the MS cohort. This database, established in 1980, captures detailed clinical information on patients registered at one of the four original MS clinics in BC. The BCMS cohort had previously been linked to BC administrative data to the end of 2008; linkage was complete in 2010 at which time all personal identifiers were removed. Routinely collected data include date of MS symptom onset, disease course at onset (relapsing or primary progressive), and level of disability at the time of each clinical assessment as measured by the Expanded Disability Status Scale [EDSS].[14]

British Columbia's comprehensive drug database (PharmaNet)[15] captures >99% of prescriptions dispensed at outpatient and community pharmacies, with data available since January 1st, 1996. The Medical Service Plan database contains physician billing records including dates and diagnostic codes for each patient encounter using the International Classification of Disease (ICD), ninth version, and the Discharge Abstracts Database contains hospital admission and discharge dates,[16, 17] and diagnosis codes using ICD ninth version (to 2004) or ICD tenth (from 2005) systems. These databases were used to estimate the comorbidity status of patients. The BC Registration and Premium Billing Files,[18] which include registration dates in the compulsory provincial health care plan, were used to confirm residency during the study period. An estimate of socioeconomic status (SES) was obtained from each individual's postal code and census-derived neighbourhood income data using an algorithm developed by Statistics Canada.[19] A

study-specific dataset was created by linking the data at the individual-level using each person's unique personal heath number (a life-long number assigned to every resident of BC). All personal identifiers were removed before data release and analyses.

Ethical approval for this study was granted by the University of British Columbia's Clinical Research Ethics Board.

Study cohort

The study subjects included all persons with MS diagnosed by a MS specialist neurologist[20, 21] who were registered at a BCMS Clinic before December 31, 2004, and received at least one prescription dispensation for a first-line injectable IMD between January 1, 1996 and December 31, 2008 as recorded in the provincial prescription database. The only first-line IMDs available during the study period were interferon-beta-1b, interferon-beta-1a, and glatiramer acetate.

Subjects were followed from their index date (date of the first IMD dispensation) until the last recorded EDSS score before the study end date which was defined as the earlier of: start of a non–first-line IMD for MS, entry in a MS drug-related clinical trial or December 31, 2008. Subjects were required to have at least one year of residency in BC before the index date (the 'baseline year') and one year of residency between the index date and study end. Subjects were also required to have at least two recorded EDSS scores; one during the baseline year and one after the first year of IMD therapy. Because the first IMD for MS was approved for use in Canada 1995, virtually all of the included subjects were incident (new) users.

Study Exposure and Outcome

In the absence of guidelines for how long an individual should remain on an IMD, or prior studies examining adherence and disability progression, we examined adherence during the first year of therapy. Prior studies have suggested that this first year may be clinically relevant, predicting longer-term response to the IMDs.[22] Adherence was estimated using the proportion of days covered (PDC) measure, calculated as the total number of days of drug dispensed during the one-year period divided by 365 days.[23] All first-line injectable IMDs were considered as one therapeutic group, and switching between these agents was allowed. A PDC of ≥80% indicated 'optimal' adherence, and <80% indicated 'suboptimal' adherence.[24] This threshold was used because it has been associated with health-related outcomes in previous studies, and to allow for comparison with other adherence-related findings.[25, 26]

The outcome of interest was disability accumulation, defined as an increase in the EDSS score of at least:

(1) 1.5 points if the reference (prior) EDSS was 0[27-29]

(2) 1 EDSS point if the reference (prior) EDSS was ≥1 and <5[27, 28]

(3) 0.5 point if the reference (prior) EDSS was ≥5.0[27]

Each subject's follow-up period was divided into one year intervals. EDSS scores were examined for each one-year interval (starting during the 2nd year after the index date) to determine if disability accumulation had occurred (categorized as 'yes or no') relative to the previous year. The date the EDSS score was recorded within each yearly interval was the 'outcome date' for that interval. If multiple EDSS scores were recorded in a single interval, the

highest (and earliest in the case of identical scores) was used. If no EDSS score was recorded in the reference interval, the score from most recent one year interval with an available EDSS score was used as the reference (*Figure S1*).

Statistical analyses and model adjustment

The association between IMD adherence and subsequent disability accumulation was examined using logistic regression models fitted via generalized estimating equations with an exchangeable working correlation structure.[30] IMD adherence was modeled as a binary variable (optimal vs. suboptimal). Potential confounders were selected for inclusion in the final models based either on clinical relevance (baseline sex, age, and EDSS) or association with the outcome ($p \leq 0.1$ from univariate analyses).[31] These potential confounders (measured during the baseline year) included: all prescriptions dispensed (excluding the MS IMDs), grouped according to the Anatomical Therapeutic Chemical (ATC) Classification System at the fourth level (i.e. pharmacological subgroup)[32] and categorized as 0-2; 3-4; 5-6 or ≥7, comorbidity status measured using Deyo's adaptation of the Charlson comorbidity index[33] (categorized as 0 or ≥1), and estimated neighbourhood SES (expressed as quintiles). All models were adjusted for the time between the reference and outcome EDSS score.

Sensitivity and secondary analyses

To fully explore the association between IMD adherence and disability accumulation we performed three sensitivity analyses and assessed one secondary outcome. For the sensitivity analyses we first measured disability only over the time period that the subject was 'on drug', ending follow-up at the last EDSS assessment before the earliest of: IMD discontinuation

(defined as the first day of >180 days with no exposure to a first-line IMD), initiation of a non-first-line IMD, MS drug clinical trial registration, or December 31, 2008. Second, if multiple EDSS scores were recorded in a single one-year interval, the lowest, rather than highest, score was used as the outcome EDSS. Finally, we examined the association between early adherence and disability accumulation in only those subjects with both reference and outcome EDSS scores recorded for every year between the index date and study end date (i.e. no EDSS scores were carried forward as reference values).

Our secondary study outcome was time to a confirmed and sustained EDSS score of 6.0. This outcome, considered as irreversible disability, was achieved when all subsequent EDSS scores were 6.0 or higher, with at least two records of EDSS 6.0 separated by ≥180 days, as used previously.[3] Multivariable Cox proportional hazards models were used to examine the association between IMD adherence and time to sustained EDSS 6.0, adjusted for potential confounders (see supplementary methods and Figure S1 for additional details).

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), Version 21.0., IBM Corp. Armonk, NY,[34] and R (Version 3.1.2).[35]

RESULTS

A total of 801 subjects were included in the primary analyses with a mean age of 41.5 years, a mean disease duration of 9.9 years and a median EDSS of 3.0 at the index date. There were a total of 6,305 person-years of follow-up (mean of 7.9 (SD:2.4) years) (Table 1). Overall, 598

subjects (74.7%) had optimal adherence during the first year of therapy, and 487 (39.0%) met the disability accumulation criterion at least once during follow-up.

Socioeconomic status, prescription drug exposure and comorbidity index measures during the baseline year were not significantly associated with subsequent disability accumulation in the univariate analyses and were not included in the multivariable models. After adjustment for baseline sex, age and EDSS, and the amount of time between reference and outcome EDSS scores, there was no evidence of an association between optimal adherence to a first-line injectable IMD during the first year of therapy and subsequent disability accumulation [adjusted odds ratio (adjOR) 0.94; 95% CI 0.78 – 1.15] (Table 2). Compared to women, men were at greater risk of disability accumulation over the study period (adjOR 1.28 (1.07 – 1.53) (Table 2).

Findings from the sensitivity and secondary analyses were consistent with those from the primary analyses; optimal adherence was not associated with disability accumulation or time to sustained EDSS 6.0 (adjusted hazard ratio (adjHR) 0.91; 95% CI 0.57 – 1.44) (Tables S1 and S2).

DISCUSSION

In this MS cohort, nearly three-quarters of the subjects demonstrated optimal adherence during the first year of using a first-line injectable IMD therapy. We did not observe a difference in the odds of disability accumulation for those with optimal IMD adherence in the first year of therapy compared to those with suboptimal adherence. Similarly, no difference was observed when disability was assessed as the time to the sustained milestone, EDSS 6.0.

Most individuals in our cohort were found to have optimal adherence, which is similar to adherence levels reported in previous studies.[12, 36] For instance, a study that examined adherence during the first year of IMD therapy in 2,446 MS patients covered by commercial health plans in the United States reported that 60% of the cohort had optimal (≥80%) adherence.[9] Another recent study examined adherence in 4,830 individuals with MS using health administrative data from three provinces in Canada (which included BC). Optimal adherence (≥80%) was achieved in 76% of subjects during the first year of therapy.[36]

Previous studies have reported on the effects of IMD adherence on MS patients' quality of life,[10] medical care costs,[9] and relapse risk,[37] but to our knowledge, no study has examined the association between IMD adherence and disability accumulation. We did not observe positive effects of IMD adherence on disability. As it is known that not all individuals respond to beta-interferon or glatiramer acetate therapy, one potential explanation for this null finding could be that, optimal adherence is only associated with beneficial effects within certain subgroups of people with MS. Alternatively, while the first-line injectable IMDs have demonstrated modest effects on disability accumulation over the short term in clinical trials,[2, 38] it is possible that this effect does not translate into long-term benefits in real world clinical practice. Although it is not known how long a person should be on an IMD before gaining benefit, assessment of adherence over the first year may be insufficient. We specifically assessed adherence in the first year for a number of reasons. First, others have shown that this initial window may be of clinical relevance, predicting future response.[22] Second, this method facilitated a degree of separation between the exposure (adherence) and outcome (disability accumulation). Finally, previous studies have

shown that early adherence after drug initiation is predictive of later adherence in some chronic conditions, including MS.[6-8] One recent study from an American managed care program database found that adherence over the one year period immediately following IMD initiation predicted adherence over the subsequent year.[6] Similarly, adherence to statins during the first 4 months after therapy initiation was shown to predict adherence over the subsequent year in a large North American population.[7]

A major strength of this study is the use of a representative sample of individuals with MS in the 'real-world' setting. Although findings from the short-term clinical trials of the first-generation IMDs demonstrated modest effects on disability accumulation, clinical trials tend to enrol participants who are highly selected in terms of age, comorbidities and motivation, and employ strict protocols for clinical monitoring to prevent or mitigate severe adverse events. Thus, trial participants may not be fully representative of those treated in clinical practice, such that data on effectiveness and adherence derived from clinical trial participants may not be generalizable to the wider MS population. Further strengths include study outcomes (EDSS scores) that were assigned by the treating MS neurologists during clinic visits, and captured prospectively. Also, our use of prescription dispensations from administrative data to estimate adherence eliminated the potential for recall bias. Finally, to test the robustness of our main findings, we examined the association between IMD adherence and disability accumulation using a variety of approaches, including a secondary (alternative) outcome. All of the findings from these sensitivity analyses confirmed that there was no evidence of an association between optimal IMD adherence during the first treatment year and subsequent disability accumulation.

There are limitations that should be noted. We cannot be certain that a patient who received a dispensation for an IMD actually administered the drug. However, given the high cost of IMDs, the number of patients who actively filled repeated prescriptions for their medications but did not use them is assumed to be negligible. As with all observational studies, we were not able to assess all potential confounders; our data did not include information on lifestyle, such as smoking status or diet, both of which could be associated with IMD adherence and disability accumulation.[39, 40] However, we were able to account for disability level and comorbidity burden at baseline, both of which have been linked to IMD adherence and subsequent MS disability accumulation in previous studies.[40] Finally, we used the EDSS to measure disability accumulation. While this is a routine clinical measure and the most widely used and internationally recognized disability assessment tool in MS, it is heavily influenced by ambulation, and does not adequately capture other common MS symptoms such as cognitive deficits and fatigue.

This is the first study to examine the impact of adherence to the first-line injectable IMDs on disability accumulation in MS. Among a cohort of incident users of first-line injectable IMDs, we were unable to find evidence that individuals with MS with optimal adherence during the first year of therapy were at lower odds of disability accumulation compared to those with suboptimal adherence. However, it remains possible that optimal adherence to IMDs positively affect other important outcomes for people with MS that were not considered here, such as quality of life and employment status. Further research examining other relevant MS related outcomes is needed to fully understand the impact of IMD adherence in MS.

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Contributorship Statement: The corresponding author (CE) and the first author (TZ) had access to the data in the study and take responsibility for the integrity of the data and accuracy of the data analyses. CE, EK, HT and TZ designed the study and CE, HT and RAM obtained funding. TZ drafted the manuscript. All authors were involved with the interpretation of the data, critically revising the manuscript, and have approved the final version to be published.

Competing Interests: Dr. Zhang, Dr. Kingwell and Mr Zhu declare no conflicts. Dr. Petkau holds research funding from the Natural Sciences and Engineering Research Council of Canada (NSERC), and over the past three years has received consulting fees or fees for service on Data Safety Monitoring Boards from the Canadian Study Group on CCSVI, EMD Serono, Novartis, and Teva Pharmaceuticals Europe. Dr. Kastrukoff has received honoraria or consultation fees from Bayer Healthcare, Biogen Idec, EMD Canada, Genzyme, Merck Serono, Novartis, Hoffmann La-Roche, Teva Canada, and unrestricted travel grants to attend scientific meetings including: the American Academy of Neurology, American Neurological Association, Neuroscience, ECTRIMS, ISNI, and IHW from Bayer Healthcare, BiogenIdec, EMD Serono, Hoffmann La-Roche, Novartis, and Teva Canada. Dr Marrie receives research funding from:

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Table 1. Characteristics of subjects included in the primary analysis (n=801)

Characteristics	**Descriptive Summaries**
At the index date (baseline)	
Sex, n (%):	
Males	192 (24.0)
Females	609 (76.0)
Age in years, mean (SD)	41.5 (9.5)
[a]Disease duration in years, mean (SD)	9.9 (8.3)
Initial (index) IMD, n (%):	
Beta-interferon	713 (89.0)
Glatiramer acetate	88 (11.0)
During the baseline year	
EDSS, median (IQR)	3.0 (2.0 - 4.0)
EDSS, n (%):	
≤3	472 (58.9)
>3 and ≤5.5	201 (25.1)
≥6	128 (16.0)
Concurrent prescription drug classes, n (%):	
0-2	252 (31.5)
3-4	194 (24.2)
5-≤6	185 (23.1)
≥7	170 (21.2)

[b]Socioeconomic status, n (%):	
1 (lowest)	130 (16.2)
2	136 (17.0)
3	179 (22.3)
4	164 (20.5)
5 (highest)	168 (21.0)
Charlson's comorbidity index score, n (%):	
0	729 (91.0)
≥1	72 (9.0)

Abbreviations: EDSS, Expanded Disability Status Scale; IQR, interquartile range.

[a]Disease duration measured from MS symptom onset (recorded in the BCMS database) to the index date (missing for 5 subjects).

[b]Based on neighbourhood income at index (missing for 19 subjects).

Table 2. Association between IMD adherence and disability accumulation: results from the GEE models (n=801)

Factors	Odds Ratios[a] (95% Confidence Intervals)	
	Univariate Analysis	**Multivariable Analysis**
Level of adherence (PDC)		
Suboptimal (<80%)	1	1
Optimal (≥80%)	0.94 (0.78 – 1.13)	0.94 (0.78 – 1.15)
Sex		
Female	1	1
Male	1.28 (1.07 – 1.52)	1.28 (1.07 – 1.53)
Baseline age, years	1.07 (0.99 – 1.01)	1.00 (0.99 - 1.01)
Baseline EDSS	1.03 (0.98 – 1.08)	1.03 (0.98 – 1.08)
Time (years) between reference and outcome EDSS	1.41 (1.30 – 1.55)	1.42 (1.30 - 1.56)

Abbreviations: EDSS, Expanded Disability Status Scale; PDC, proportion of days covered

[a]Odds ratio >1 indicates an increased likelihood of disability accumulation.

SUPPLEMENTARY MATERIAL

Additional Methodological Details – Secondary Analysis

For the secondary outcome of time to a confirmed and sustained EDSS score of 6.0, subjects were required to have at least one year of residency in BC following initiation of treatment ('Year 1'). There were additional residency and EDSS related requirements. Subjects were required to have at least two EDSS scores; one recorded during Year 1 (the baseline EDSS) and one after Year 1. For this time-to-event analysis, subjects were followed from the start of Year 2 until either the outcome was reached or the study end (Figure S1b). Adherence was estimated using the proportion of days covered (PDC) during Year 1. If the outcome was not reached, subjects were censored at their last recorded EDSS score, or at the preceding EDSS measurement if the last score was ≥6.0 and could not be confirmed as sustained.

Potential confounders for the multivariable Cox proportional hazards models included sex, age, EDSS, SES quintile, number of distinct prescription drug classes (fourth level of ATC classification), and Deyo's adaption of the Charlson comorbidity index, all measured during Year 1. Covariates were categorized, and selected for inclusion in the adjusted model, using the same approach as for the primary analyses.

Results from the secondary analysis

The secondary analysis, examining the association between IMD adherence and time to sustained EDSS 6.0, included 673 MS subjects. Similar to results from the primary analysis,

SES, prescription drug exposure and the comorbidity index were not significantly associated with time to sustained EDSS 6. After adjustment for sex, age, and baseline EDSS, optimal adherence was not found to be associated with the hazard of reaching sustained EDSS 6.0 (adjusted hazard ratio (adjHR) 0.91; 95% CI 0.57 – 1.44) (Table S1). A shorter time to the disability outcome was associated with increased age [adjHR 1.02; 95% CI 1.00 – 1.05] and with higher baseline EDSS [adjHR 1.49; 95% CI 1.33 – 1.68].

Results from the sensitivity analyses

A total of 634 subjects were included in the sensitivity analysis, in which the effects of IMD adherence on disability accumulation were examined only over the period that the subject was still 'on drug'. Optimal adherence was not associated with disability accumulation (adjusted odds ratio (adjOR) 1.06; 95% CI 0.81 – 1.39) (Table S2).

A total of 801 subjects were included in the sensitivity analysis where the lowest, rather than highest, score was used as the outcome EDSS when multiple EDSS scores were recorded in a single one-year interval. Consistent with the primary analysis, optimal adherence was not associated with disability accumulation (adjOR 1.03; 95% CI 0.84 – 1.26), (Table S2).

When we examined the association between first year adherence and disability accumulation in only those subjects with both reference and outcome EDSS scores available for every year between the index date and study end date, a total of 703 were included in this analysis.

Consistent with previous findings, optimal adherence was not associated with disability accumulation (adjOR 1.12; 95% CI 0.87 – 1.44).

Table S1. Association between IMD adherence anD disability accumulation: findings based on Cox Proportional Regression analysis of time to sustained EDSS 6 (n=673)

Factors	Hazard Ratios [a] (95% Confidence Intervals)	
	Univariate Analysis	Multivariable Analysis[b]
Level of adherence (PDC)		
'Suboptimal' (<80%)	1	1
'Optimal' (≥80%)	0.84 (0.53 – 1.33)	0.91 (0.57 – 1.44)
Sex		
Female	1	1
Male	1.49 (0.97 – 2.31)	1.20 (0.77 – 1.88)
Baseline age, years	1.03 (1.01 – 1.06)	1.02 (1.00 – 1.05)
Baseline EDSS	1.53 (1.37 – 1.71)	1.49 (1.33 – 1.68)

Abbreviations: EDSS, Expanded Disability Status Scale; PDC, proportion of days covered.

[a]Hazard ratio > 1 indicated an increased hazard of disability accumulation.

[b]Model adjusted for age, sex, and baseline EDSS

Table S2. Association between IMD adherence and disability accumulation: findings from the three sensitivity analyses

Factors	Odds Ratios [a] (95% Confidence Intervals)	
	Univariate Analysis	**Multivariable Analysis**
[b]*Analysis 1: Follow-up continued only during exposure to first-line injectable IMDs (n=634)*		
Level of adherence (PDC)		
'Suboptimal' (<80%)	1	1
'Optimal' (≥80%)	1.04 (0.80 – 1.34)	1.06 (0.81 – 1.39)
Analysis 2: When multiple EDSS scores were available in a given year, the lowest (rather than highest) was selected (n=801)		
Level of adherence (PDC)		
'Suboptimal' (<80%)	1	1
'Optimal' (≥80%)	1.02 (0.84 – 1.23)	1.03 (0.84 – 1.26)
[c]*Analysis 3: EDSS scores were not carried forward (only patients with both reference and outcome EDSS scores for every year between the index date and study end were included, n= 703)*		
Level of adherence (PDC)		
Suboptimal (<80%)	1	1
Optimal (≥80%)	1.16 (0.91 - 1.48)	1.12 (0.87 – 1.44)

Abbreviations: EDSS, Expanded Disability Status Scale; PDC, proportion of days covered; IMD, immunomodulatory drug.

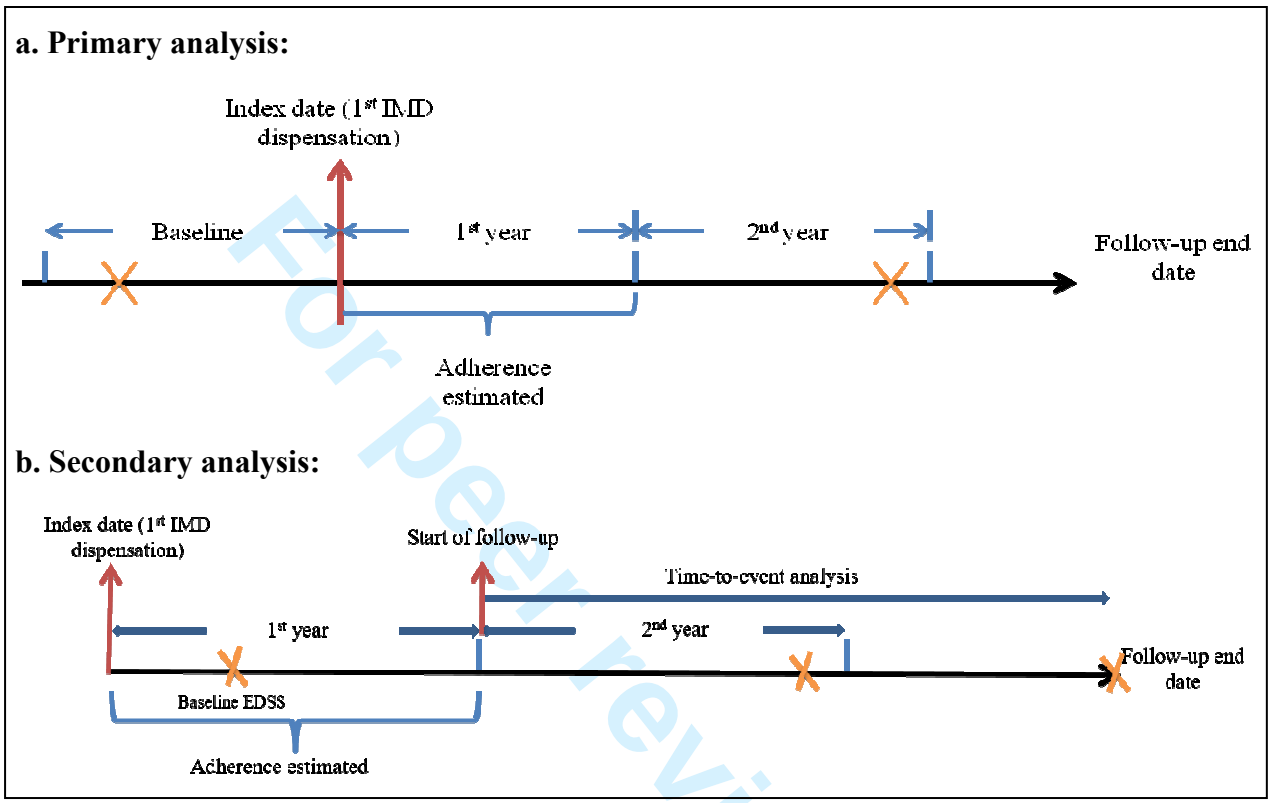
Each model was adjusted for sex, baseline age, baseline EDSS, and time between the reference and outcome EDSS.

[a]OR>1 indicated an increased likelihood of disability accumulation; hazard ratio >1 indicated an increased hazard of disability accumulation.

[b]Analysis 1: Subjects were followed until the last available EDSS before: first-line IMD discontinuation, initiation of a non-first line IMD, MS drug clinical trial registration, or December 31, 2008. There were 167 fewer subjects included in this sensitivity analysis compared to the primary analysis because these individuals discontinued their first-line injectable IMD before the start of Year 2 (i.e. no follow-up EDSS assessments were available prior to drug discontinuation).

[c]Analysis 3: There were 98 fewer subjects included compared to the primary analysis because these individuals did not have at least one EDSS score available in each one year interval between the index date and the study end date.

Figure S1. Measurement of the study exposure (adherence) and outcomes (disability accumulation and the sustained disability milestone, EDSS 6.0)



Notes:

X indicates a recorded EDSS score.

Subjects were followed from their index date (date of the first IMD dispensation) until the last available EDSS score recorded prior to the study end.

a. For the primary analysis, adherence was measured during Year 1. EDSS scores were examined during each one-year interval from Year 2 onwards to determine if disability accumulation had occurred (yes/no) relative to the previous year (the reference interval). The effects of IMD adherence on subsequent disability accumulation were examined using generalized estimating equations.

If no EDSS score was available during the reference interval, the EDSS score from the most recent interval (including the baseline year) with a recorded EDSS score was used as the reference. In Figure 1a, for example, as an EDSS score was not available during Year 1, the baseline EDSS served as the reference for the EDSS score during Year 2.

b. For the secondary analysis, adherence was measured during Year 1. Time from the beginning of Year 2 (start of follow-up) to a confirmed and sustained EDSS score of 6.0 was modeled using multivariable Cox proportional hazards regression models, which were adjusted for sex and age at the start of Year 2, and Year 1 (baseline) EDSS. In the situation where a patient reached EDSS 6.0 at their last assessment, but this was not confirmed by another score of EDSS >= 6.0 after at least 180 days, the patient was censored at the preceding EDSS assessment.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	Pg 1,3	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	Pg 5	Explain the scientific background and rationale for the investigation being reported
Objectives	Pg 5	State specific objectives, including any prespecified hypotheses
Methods		
Study design	Pg 6	Present key elements of study design early in the paper
Setting	Pg 6-7	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	Pg 7-8	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	Pg 7-10	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	Pg 7-10	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	Pg 13	Describe any efforts to address potential sources of bias
Study size	Pg 7	Explain how the study size was arrived at We were limited to the number of subjects registered in the MS clinics who met the eligibility criteria
Quantitative variables	Pg 9 Supp Materials	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Also see Supplementary Materials
Statistical methods	Pg 9	(*a*) Describe all statistical methods, including those used to control for confounding
	Supp Materials	(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed

	Case-control study—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy Also see Supplementary Materials
	(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	Pg 10-11	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	Pg 10-11 Table 1	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	Pg 11 Supp Materials	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	Pg 11 Table 2 Supp Materials	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	Supp Materials	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	Pg 11-12	Summarise key results with reference to study objectives
Limitations	Pg 14	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	Pg 14	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	Pg 13	Discuss the generalisability (external validity) of the study results
Other information		
Funding	Pg 16	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Effect of adherence to the first-generation injectable immunomodulatory drugs on disability accumulation in multiple sclerosis: a longitudinal cohort study

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Effect of adherence to the first-generation injectable immunomodulatory drugs on disability accumulation in multiple sclerosis: a longitudinal cohort study

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ABSTRACT

Objective: To examine the association between optimal adherence to the first-generation injectable immunomodulatory drugs (IMDs) for multiple sclerosis (MS) and subsequent disability accumulation.

Methods: We accessed prospectively collected linked clinical and administrative health data from British Columbia, Canada. MS subjects treated with a first-generation injectable IMD at a MS Clinic (1996-2004) were followed until their last clinic visit before 2009. Adherence was estimated using the proportion of days covered (PDC). The primary outcome was disability accumulation, defined as an increase in the Expanded Disability Status Scale (EDSS) score as recorded during each year of follow-up. Generalized estimating equation models, adjusted for baseline sex, age, EDSS and time between scores, were used to measure associations between optimal adherence (≥80% PDC) during the first year of treatment and subsequent disability accumulation. The relationship between early IMD adherence and the secondary outcome, time to sustained EDSS 6, was examined using Cox proportional hazards regression.

Results: Among 801 subjects, 598 (74.7%) had optimal adherence over the first year of IMD treatment and 487 (39.0%) demonstrated one or more instances of disability accumulation. Early optimal adherence was not associated with disability accumulation (adjusted odds ratio 0.94;95%CI:0.78-1.15), nor with time to sustained EDSS 6 (adjusted hazard ratio 0.91;95%CI:0.57-1.44).

Conclusions: Almost three-quarters of MS subjects had optimal early adherence to their first-line injectable IMD. There was no evidence that this was associated with disability accumulation in the following years.

KEYWORDS: Multiple sclerosis; adherence, immunomodulatory drugs, disease progression, longitudinal analysis, observational study

STRENGTHS AND LIMITATIONS OF THIS STUDY

- One of the first population-based studies to examine the association between drug adherence and subsequent disability accumulation in multiple sclerosis
- Real world setting which increases the generalizability of the study results
- Observational studies cannot adjust or assess all potential (unknown) confounders

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system and is considered one of the most common reasons for non-trauma related disability in young adults.[1] The injectable immunomodulatory therapies (IMDs), beta-interferon and glatiramer acetate, are associated with reduced MS relapse rates in short-term clinical trials,[2] but the evidence regarding the effects of these therapies on longer-term disability progression drawn from observational studies is mixed.[2, 3] These drugs are considered first-line therapies in Canada, and are commonly used to treat MS worldwide.[4]

To maximize the potential benefit of any drug, it should be taken as indicated; however, multiple lifestyle, patient-specific and drug-related factors can affect adherence.[5] Adherence levels early in treatment predict future adherence patterns.[6-8] In general, poor medication adherence is associated with poorer health-related outcomes, including higher risk of morbidity and mortality, increased health services utilization, and increased health care costs.[9-11] In MS, poor adherence to the IMDs is associated with decreased quality of life, higher relapse rates and higher medical costs.[9, 12, 13] However, to date, the effects of IMD adherence on MS progression are unknown. We examined the association between adherence during the initial year of therapy to a first-line injectable IMD and subsequent disability accumulation in people with relapsing-onset MS in British Columbia (BC), Canada.

METHODS

Study design and data sources

This was a retrospective cohort study, involving linkage of prospectively collected clinical and administrative health data in BC. The BC Multiple Sclerosis (BCMS) database was the source of the MS cohort. This database, established in 1980, captures detailed clinical information on patients registered at one of the four original MS clinics in BC. The BCMS cohort had previously been linked to BC administrative data to the end of 2008; linkage was complete in 2010 at which time all personal identifiers were removed. Routinely collected data include date of MS symptom onset, disease course at onset (relapsing or primary progressive), and level of disability at the time of each clinical assessment as measured by the Expanded Disability Status Scale [EDSS].[14]

British Columbia's comprehensive drug database (PharmaNet)[15] captures >99% of prescriptions dispensed at outpatient and community pharmacies, with data available since January 1st, 1996. The Medical Service Plan database contains physician billing records including dates and diagnostic codes for each patient encounter using the International Classification of Disease (ICD), ninth version, and the Discharge Abstracts Database contains hospital admission and discharge dates,[16, 17] and diagnosis codes using ICD ninth version (to 2004) or ICD tenth (from 2005) systems. These databases were used to estimate the comorbidity status of patients. The BC Registration and Premium Billing Files,[18] which include registration dates in the compulsory provincial health care plan, were used to confirm residency during the study period. An estimate of socioeconomic status (SES) was obtained from each individual's postal code and census-derived neighbourhood income data using an algorithm developed by Statistics Canada.[19] A

study-specific dataset was created by linking the data at the individual-level using each person's unique personal heath number (a life-long number assigned to every resident of BC). All personal identifiers were removed before data release and analyses.

Ethical approval for this study was granted by the University of British Columbia's Clinical Research Ethics Board.

Study cohort

The study subjects included all persons with MS diagnosed by a MS specialist neurologist[20, 21] who were registered at a BCMS Clinic before December 31, 2004, and received at least one prescription dispensation for a first-line injectable IMD between January 1, 1996 and December 31, 2008 as recorded in the provincial prescription database. The only first-line IMDs available during the study period were interferon-beta-1b, interferon-beta-1a, and glatiramer acetate.

Subjects were followed from their index date (date of the first IMD dispensation) until the last recorded EDSS score before the study end date which was defined as the earlier of: start of a non–first-line IMD for MS, entry in a MS drug-related clinical trial or December 31, 2008. Subjects were required to have at least one year of residency in BC before the index date (the 'baseline year') and one year of residency between the index date and study end. Subjects were also required to have at least two recorded EDSS scores; one during the baseline year and one after the first year of IMD therapy. Because the first IMD for MS was approved for use in Canada 1995, virtually all of the included subjects were incident (new) users.

Study Exposure and Outcome

In the absence of guidelines for how long an individual should remain on an IMD, or prior studies examining adherence and disability progression, we examined adherence during the first year of therapy. Prior studies have suggested that this first year may be clinically relevant, predicting longer-term response to the IMDs.[22] Adherence was estimated using the proportion of days covered (PDC) measure, calculated as the total number of days of drug dispensed during the one-year period divided by 365 days.[23] All first-line injectable IMDs were considered as one therapeutic group, and switching between these agents was allowed. A PDC of ≥80% indicated 'optimal' adherence, and <80% indicated 'suboptimal' adherence.[24] This threshold was used because it has been associated with health-related outcomes in previous studies, and to allow for comparison with other adherence-related findings.[25, 26]

The outcome of interest was disability accumulation, defined as an increase in the EDSS score of at least:

(1) 1.5 points if the reference (prior) EDSS was 0[27-29]

(2) 1 EDSS point if the reference (prior) EDSS was ≥1 and <5[27, 28]

(3) 0.5 point if the reference (prior) EDSS was ≥5.0[27]

Each subject's follow-up period was divided into one year intervals. EDSS scores were examined for each one-year interval (starting during the 2nd year after the index date) to determine if disability accumulation had occurred (categorized as 'yes or no') relative to the previous year. The date the EDSS score was recorded within each yearly interval was the 'outcome date' for that interval. If multiple EDSS scores were recorded in a single interval, the

highest (and earliest in the case of identical scores) was used. If no EDSS score was recorded in the reference interval, the score from most recent one year interval with an available EDSS score was used as the reference (*Figure S1*).

Statistical analyses and model adjustment

The association between IMD adherence and subsequent disability accumulation was examined using logistic regression models fitted via generalized estimating equations with an exchangeable working correlation structure.[30] IMD adherence was modeled as a binary variable (optimal vs. suboptimal). Potential confounders were selected for inclusion in the final models based either on clinical relevance (baseline sex, age, and EDSS) or association with the outcome ($p \leq 0.1$ from univariate analyses).[31] These potential confounders (measured during the baseline year) included: all prescriptions dispensed (excluding the MS IMDs), grouped according to the Anatomical Therapeutic Chemical (ATC) Classification System at the fourth level (i.e. pharmacological subgroup)[32] and categorized as 0-2; 3-4; 5-6 or ≥7, comorbidity status measured using Deyo's adaptation of the Charlson comorbidity index[33] (categorized as 0 or ≥1), and estimated neighbourhood SES (expressed as quintiles). All models were adjusted for the time between the reference and outcome EDSS score.

Sensitivity and secondary analyses

To fully explore the association between IMD adherence and disability accumulation we performed several sensitivity analyses and assessed one secondary outcome. For the sensitivity analyses we first measured disability only over the time period that the subject was 'on drug', ending follow-up at the last EDSS assessment before the earliest of: IMD discontinuation

(defined as the first day of >180 days with no exposure to a first-line IMD), initiation of a non-first-line IMD, MS drug clinical trial registration, or December 31, 2008. Second, if multiple EDSS scores were recorded in a single one-year interval, the lowest, rather than highest, score was used as the outcome EDSS. Third, we examined the association between early adherence and disability accumulation in only those subjects with both reference and outcome EDSS scores recorded for every year between the index date and study end date (i.e. no EDSS scores were carried forward as reference values). Finally, we examined the association between disability accumulation and adherence with adherence treated as a continuous variable, categorized into quartiles, and using a 90% (instead of 80%) threshold for optimal adherence.

Our secondary study outcome was time to a confirmed and sustained EDSS score of 6.0. This outcome, considered as irreversible disability, was achieved when all subsequent EDSS scores were 6.0 or higher, with at least two records of EDSS 6.0 separated by ≥180 days, as used previously.[3] Multivariable Cox proportional hazards models were used to examine the association between IMD adherence and time to sustained EDSS 6.0, adjusted for potential confounders (see supplementary methods and Figure S1 for additional details).

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), Version 21.0., IBM Corp. Armonk, NY,[34] and R (Version 3.1.2).[35]

RESULTS

A total of 801 subjects were included in the primary analyses with a mean age of 41.5 years, a mean disease duration of 9.9 years and a median EDSS of 3.0 at the index date. There were a

total of 6,305 person-years of follow-up (mean of 7.9 (SD:2.4) years) (Table 1). Overall, 598 subjects (74.7%) had optimal adherence during the first year of therapy (Figure 1), and 487 (39.0%) met the disability accumulation criterion at least once during follow-up.

Socioeconomic status, prescription drug exposure and comorbidity index measures during the baseline year were not significantly associated with subsequent disability accumulation in the univariate analyses and were not included in the multivariable models. After adjustment for baseline sex, age and EDSS, and the amount of time between reference and outcome EDSS scores, there was no evidence of an association between optimal adherence to a first-line injectable IMD during the first year of therapy and subsequent disability accumulation [adjusted odds ratio (adjOR) 0.94; 95% CI 0.78 – 1.15] (Table 2). Compared to women, men were at greater risk of disability accumulation over the study period (adjOR 1.28 (1.07 – 1.53) (Table 2).

Findings from the sensitivity and secondary analyses were consistent with those from the primary analyses; optimal adherence was not associated with disability accumulation or time to sustained EDSS 6.0 (adjusted hazard ratio (adjHR) 0.91; 95% CI 0.57 – 1.44) (Tables S1 and S2). There was also no evidence of an association between optimal adherence and disability accumulation when adherence was included in the models as a continuous variable, categorized into quartiles, or with a 90% threshold for optimal adherence (results not shown).

DISCUSSION

In this MS cohort, nearly three-quarters of the subjects demonstrated optimal adherence during the first year of using a first-line injectable IMD therapy. We did not observe a difference in the

odds of disability accumulation for those with optimal IMD adherence in the first year of therapy compared to those with suboptimal adherence. Similarly, no difference was observed when disability was assessed as the time to the sustained milestone, EDSS 6.0.

Most individuals in our cohort were found to have optimal adherence, which is similar to adherence levels reported in previous studies.[12, 36] For instance, a study that examined adherence during the first year of IMD therapy in 2,446 MS patients covered by commercial health plans in the United States reported that 60% of the cohort had optimal (≥80%) adherence.[9] Another recent study examined adherence in 4,830 individuals with MS using health administrative data from three provinces in Canada (which included BC). Optimal adherence (≥80%) was achieved in 76% of subjects during the first year of therapy.[36]

Previous studies have reported on the effects of IMD adherence on MS patients' quality of life,[10] medical care costs,[9] and relapse risk,[37] but to our knowledge, no study has examined the association between IMD adherence and disability accumulation. We did not observe positive effects of IMD adherence on disability. As it is known that not all individuals respond to beta-interferon or glatiramer acetate therapy, one potential explanation for this null finding could be that, optimal adherence is only associated with beneficial effects within certain subgroups of people with MS. Alternatively, while the first-line injectable IMDs have demonstrated modest effects on disability accumulation over the short term in clinical trials,[2, 38] it is possible that this effect does not translate into long-term benefits in real world clinical practice. Although it is not known how long a person should be on an IMD before gaining benefit, assessment of adherence over the first year may be insufficient, and may miss non-adherence that occurs after the first

year, due to needle fatigue for example.[39] We specifically assessed adherence in the first year for a number of reasons. First, others have shown that this initial window may be of clinical relevance, predicting future response.[22] Second, this method facilitated a degree of separation between the exposure (adherence) and outcome (disability accumulation). Finally, previous studies have shown that early adherence after drug initiation is predictive of later adherence in some chronic conditions, including MS.[6-8] One recent study from an American managed care program database found that adherence over the one year period immediately following IMD initiation predicted adherence over the subsequent year.[6] Similarly, adherence to statins during the first 4 months after therapy initiation was shown to predict adherence over the subsequent year in a large North American population.[7]

A major strength of this study is the use of a representative sample of individuals with MS in the 'real-world' setting. Although findings from the short-term clinical trials of the first-generation IMDs demonstrated modest effects on disability accumulation, clinical trials tend to enrol participants who are highly selected in terms of age, comorbidities and motivation, and employ strict protocols for clinical monitoring to prevent or mitigate severe adverse events. Thus, trial participants may not be fully representative of those treated in clinical practice, such that data on effectiveness and adherence derived from clinical trial participants may not be generalizable to the wider MS population. Further strengths include study outcomes (EDSS scores) that were assigned by the treating MS neurologists during clinic visits, and captured prospectively. Also, our use of prescription dispensations from administrative data to estimate adherence eliminated the potential for recall bias. Finally, to test the robustness of our main findings, we examined the association between IMD adherence and disability accumulation using a variety of approaches,

including a secondary (alternative) outcome and different methods of categorizing adherence. All of the findings from these sensitivity analyses confirmed that there was no evidence of an association between optimal IMD adherence during the first treatment year and subsequent disability accumulation.

There are limitations that should be noted. We cannot be certain that a patient who received a dispensation for an IMD actually administered the drug. However, given the high cost of IMDs, the number of patients who actively filled repeated prescriptions for their medications but did not use them is assumed to be negligible. As with all observational studies, we were not able to assess all potential confounders; our data did not include information on lifestyle, such as smoking status or diet, both of which could be associated with IMD adherence and disability accumulation.[40, 41] However, we were able to account for disability level and comorbidity burden at baseline, both of which have been linked to IMD adherence and subsequent MS disability accumulation in previous studies.[41] Finally, we used the EDSS to measure disability accumulation. While this is a routine clinical measure and the most widely used and internationally recognized disability assessment tool in MS, it is heavily influenced by ambulation, and does not adequately capture other common MS symptoms such as cognitive deficits and fatigue.

This is the first study to examine the impact of adherence to the first-line injectable IMDs on disability accumulation in MS. Among a cohort of incident users of first-line injectable IMDs, we were unable to find evidence that individuals with MS with optimal adherence during the first year of therapy were at lower odds of disability accumulation compared to those with suboptimal

adherence. However, it remains possible that optimal adherence to IMDs positively affect other important outcomes for people with MS that were not considered here, such as quality of life and employment status. Further research examining other relevant MS related outcomes is needed to fully understand the impact of IMD adherence in MS.

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Disclaimer: All inferences, opinions, and conclusions drawn in this study are those of the authors, and do not reflect the opinions or policies of the Data Steward(s).

Contributorship Statement: The corresponding author (CE) and the first author (TZ) had access to the data in the study and take responsibility for the integrity of the data and accuracy of the data analyses. CE, EK, HT and TZ designed the study and CE, HT and RAM obtained funding. TZ drafted the manuscript. All authors were involved with the interpretation of the data, critically revising the manuscript, and have approved the final version to be published.

Competing Interests: Dr. Zhang, Dr. Kingwell and Mr Zhu declare no conflicts. Dr. Petkau holds research funding from the Natural Sciences and Engineering Research Council of Canada (NSERC), and over the past three years has received consulting fees or fees for service on Data Safety Monitoring Boards from the Canadian Study Group on CCSVI, EMD Serono, Novartis, and Teva Pharmaceuticals Europe. Dr. Kastrukoff has received honoraria or consultation fees from Bayer Healthcare, Biogen Idec, EMD Canada, Genzyme, Merck Serono, Novartis, Hoffmann La-Roche, Teva Canada, and unrestricted travel grants to attend scientific meetings including: the American Academy of Neurology, American Neurological Association, Neuroscience, ECTRIMS, ISNI, and IHW from Bayer Healthcare, BiogenIdec, EMD Serono, Hoffmann La-Roche, Novartis, and Teva Canada. Dr Marrie receives research funding from:

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Data Sharing Statement: Privacy legislation and policies of the British Columbia Ministry of Health prevent the sharing of data.

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Table 1. Characteristics of subjects included in the primary analysis (n=801)

Characteristics	**Descriptive Summaries**
At the index date (baseline)	
Sex, n (%):	
Males	192 (24.0)
Females	609 (76.0)
Age in years, mean (SD)	41.5 (9.5)
[a]Disease duration in years, mean (SD)	9.9 (8.3)
Initial (index) IMD, n (%):	
Beta-interferon	713 (89.0)
Glatiramer acetate	88 (11.0)
During the baseline year	
EDSS, median (IQR)	3.0 (2.0 - 4.0)
EDSS, n (%):	
≤3	472 (58.9)
>3 and ≤5.5	201 (25.1)
≥6	128 (16.0)
Concurrent prescription drug classes, n (%):	
0-2	252 (31.5)
3-4	194 (24.2)
5-≤6	185 (23.1)
≥7	170 (21.2)

[b]Socioeconomic status, n (%):	
1 (lowest)	130 (16.2)
2	136 (17.0)
3	179 (22.3)
4	164 (20.5)
5 (highest)	168 (21.0)
Charlson's comorbidity index score, n (%):	
0	729 (91.0)
≥1	72 (9.0)

Abbreviations: EDSS, Expanded Disability Status Scale; IQR, interquartile range.

[a]Disease duration measured from MS symptom onset (recorded in the BCMS database) to the index date (missing for 5 subjects).

[b]Based on neighbourhood income at index (missing for 19 subjects).

Table 2. Association between IMD adherence and disability accumulation: results from the GEE models (n=801)

Factors	Odds Ratios[a] (95% Confidence Intervals)	
	Univariate Analysis	**Multivariable Analysis**
Level of adherence (PDC)		
Suboptimal (<80%)	1	1
Optimal (≥80%)	0.94 (0.78 – 1.13)	0.94 (0.78 – 1.15)
Sex		
Female	1	1
Male	1.28 (1.07 – 1.52)	1.28 (1.07 – 1.53)
Baseline age, years	1.07 (0.99 – 1.01)	1.00 (0.99 - 1.01)
Baseline EDSS	1.03 (0.98 – 1.08)	1.03 (0.98 – 1.08)
Time (years) between reference and outcome EDSS	1.41 (1.30 – 1.55)	1.42 (1.30 - 1.56)

Abbreviations: EDSS, Expanded Disability Status Scale; PDC, proportion of days covered

[a]Odds ratio >1 indicates an increased likelihood of disability accumulation.

Figure Legend

Figure 1. Distribution of Adherence

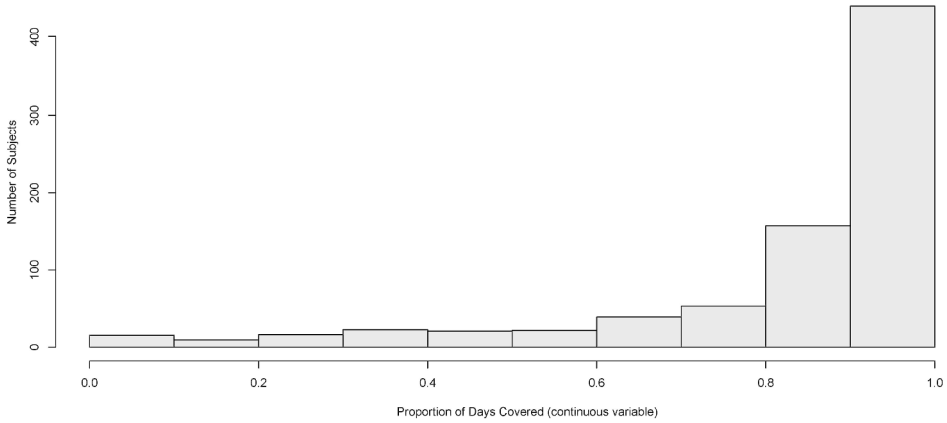


Figure 1. Distribution of Adherence

355x177mm (300 x 300 DPI)

SUPPLEMENTARY MATERIAL

Additional Methodological Details – Secondary Analysis

For the secondary outcome of time to a confirmed and sustained EDSS score of 6.0, subjects were required to have at least one year of residency in BC following initiation of treatment ('Year 1'). There were additional residency and EDSS related requirements. Subjects were required to have at least two EDSS scores; one recorded during Year 1 (the baseline EDSS) and one after Year 1. For this time-to-event analysis, subjects were followed from the start of Year 2 until either the outcome was reached or the study end (Figure S1b). Adherence was estimated using the proportion of days covered (PDC) during Year 1. If the outcome was not reached, subjects were censored at their last recorded EDSS score, or at the preceding EDSS measurement if the last score was ≥6.0 and could not be confirmed as sustained.

Potential confounders for the multivariable Cox proportional hazards models included sex, age, EDSS, SES quintile, number of distinct prescription drug classes (fourth level of ATC classification), and Deyo's adaption of the Charlson comorbidity index, all measured during Year 1. Covariates were categorized, and selected for inclusion in the adjusted model, using the same approach as for the primary analyses.

Results from the secondary analysis

The secondary analysis, examining the association between IMD adherence and time to sustained EDSS 6.0, included 673 MS subjects. Similar to results from the primary analysis,

SES, prescription drug exposure and the comorbidity index were not significantly associated with time to sustained EDSS 6. After adjustment for sex, age, and baseline EDSS, optimal adherence was not found to be associated with the hazard of reaching sustained EDSS 6.0 (adjusted hazard ratio (adjHR) 0.91; 95% CI 0.57 – 1.44) (Table S1). A shorter time to the disability outcome was associated with increased age [adjHR 1.02; 95% CI 1.00 – 1.05] and with higher baseline EDSS [adjHR 1.49; 95% CI 1.33 – 1.68].

Results from the sensitivity analyses

A total of 634 subjects were included in the sensitivity analysis, in which the effects of IMD adherence on disability accumulation were examined only over the period that the subject was still 'on drug'. Optimal adherence was not associated with disability accumulation (adjusted odds ratio (adjOR) 1.06; 95% CI 0.81 – 1.39) (Table S2).

A total of 801 subjects were included in the sensitivity analysis where the lowest, rather than highest, score was used as the outcome EDSS when multiple EDSS scores were recorded in a single one-year interval. Consistent with the primary analysis, optimal adherence was not associated with disability accumulation (adjOR 1.03; 95% CI 0.84 – 1.26), (Table S2).

When we examined the association between first year adherence and disability accumulation in only those subjects with both reference and outcome EDSS scores available for every year between the index date and study end date, a total of 703 were included in this analysis.

Consistent with previous findings, optimal adherence was not associated with disability accumulation (adjOR 1.12; 95% CI 0.87 – 1.44).

Table S1. Association between IMD adherence anD disability accumulation: findings based on Cox Proportional Regression analysis of time to sustained EDSS 6 (n=673)

Factors	Hazard Ratios [a] (95% Confidence Intervals)	
	Univariate Analysis	Multivariable Analysis[b]
Level of adherence (PDC)		
'Suboptimal' (<80%)	1	1
'Optimal' (≥80%)	0.84 (0.53 – 1.33)	0.91 (0.57 – 1.44)
Sex		
Female	1	1
Male	1.49 (0.97 – 2.31)	1.20 (0.77 – 1.88)
Baseline age, years	1.03 (1.01 – 1.06)	1.02 (1.00 – 1.05)
Baseline EDSS	1.53 (1.37 – 1.71)	1.49 (1.33 – 1.68)

Abbreviations: EDSS, Expanded Disability Status Scale; PDC, proportion of days covered.

[a]Hazard ratio > 1 indicated an increased hazard of disability accumulation.

[b]Model adjusted for age, sex, and baseline EDSS

Table S2. Association between IMD adherence and disability accumulation: findings from the three sensitivity analyses

Factors	Odds Ratios [a] (95% Confidence Intervals)	
	Univariate Analysis	**Multivariable Analysis**
[b]*Analysis 1: Follow-up continued only during exposure to first-line injectable IMDs (n=634)*		
Level of adherence (PDC)		
'Suboptimal' (<80%)	1	1
'Optimal' (≥80%)	1.04 (0.80 – 1.34)	1.06 (0.81 – 1.39)
Analysis 2: When multiple EDSS scores were available in a given year, the lowest (rather than highest) was selected (n=801)		
Level of adherence (PDC)		
'Suboptimal' (<80%)	1	1
'Optimal' (≥80%)	1.02 (0.84 – 1.23)	1.03 (0.84 – 1.26)
[c]*Analysis 3: EDSS scores were not carried forward (only patients with both reference and outcome EDSS scores for every year between the index date and study end were included, n= 703)*		
Level of adherence (PDC)		
Suboptimal (<80%)	1	1
Optimal (≥80%)	1.16 (0.91 - 1.48)	1.12 (0.87 – 1.44)

Abbreviations: EDSS, Expanded Disability Status Scale; PDC, proportion of days covered; IMD, immunomodulatory drug.

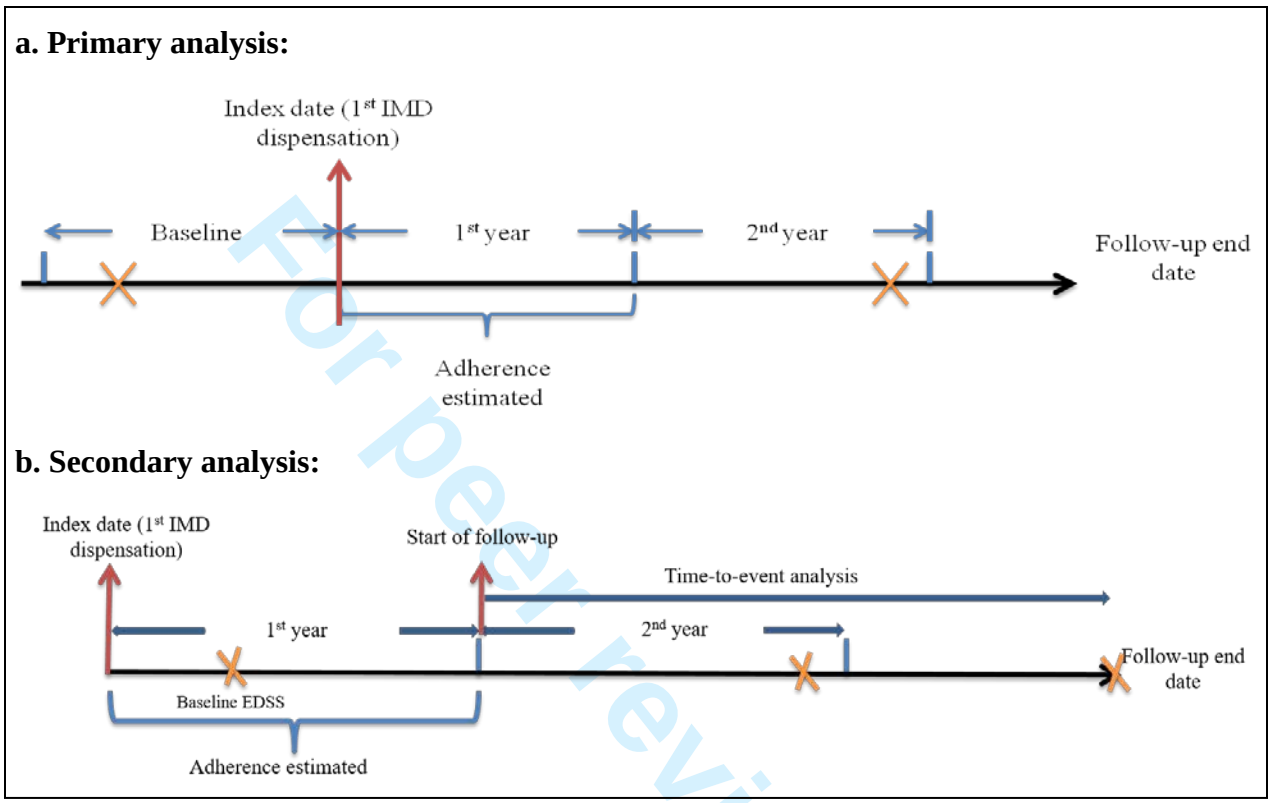
Each model was adjusted for sex, baseline age, baseline EDSS, and time between the reference and outcome EDSS.

[a]OR>1 indicated an increased likelihood of disability accumulation; hazard ratio >1 indicated an increased hazard of disability accumulation.

[b]Analysis 1: Subjects were followed until the last available EDSS before: first-line IMD discontinuation, initiation of a non-first line IMD, MS drug clinical trial registration, or December 31, 2008. There were 167 fewer subjects included in this sensitivity analysis compared to the primary analysis because these individuals discontinued their first-line injectable IMD before the start of Year 2 (i.e. no follow-up EDSS assessments were available prior to drug discontinuation).

[c]Analysis 3: There were 98 fewer subjects included compared to the primary analysis because these individuals did not have at least one EDSS score available in each one year interval between the index date and the study end date.

Figure S1. Measurement of the study exposure (adherence) and outcomes (disability accumulation and the sustained disability milestone, EDSS 6.0)



Notes:

X indicates a recorded EDSS score.

Subjects were followed from their index date (date of the first IMD dispensation) until the last available EDSS score recorded prior to the study end.

a. For the primary analysis, adherence was measured during Year 1. EDSS scores were examined during each one-year interval from Year 2 onwards to determine if disability accumulation had occurred (yes/no) relative to the previous year (the reference interval). The effects of IMD adherence on subsequent disability accumulation were examined using generalized estimating equations.

If no EDSS score was available during the reference interval, the EDSS score from the most recent interval (including the baseline year) with a recorded EDSS score was used as the reference. In Figure 1a, for example, as an EDSS score was not available during Year 1, the baseline EDSS served as the reference for the EDSS score during Year 2.

b. For the secondary analysis, adherence was measured during Year 1. Time from the beginning of Year 2 (start of follow-up) to a confirmed and sustained EDSS score of 6.0 was modeled using multivariable Cox proportional hazards regression models, which were adjusted for sex and age at the start of Year 2, and Year 1 (baseline) EDSS. In the situation where a patient reached EDSS 6.0 at their last assessment, but this was not confirmed by another score of EDSS >= 6.0 after at least 180 days, the patient was censored at the preceding EDSS assessment.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	Pg 1,3	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	Pg 5	Explain the scientific background and rationale for the investigation being reported
Objectives	Pg 5	State specific objectives, including any prespecified hypotheses
Methods		
Study design	Pg 6	Present key elements of study design early in the paper
Setting	Pg 6-7	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	Pg 7-8	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	Pg 7-10	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	Pg 7-10	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	Pg 13	Describe any efforts to address potential sources of bias
Study size	Pg 7	Explain how the study size was arrived at We were limited to the number of subjects registered in the MS clinics who met the eligibility criteria
Quantitative variables	Pg 9 Supp Materials	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Also see Supplementary Materials
Statistical methods	Pg 9	(*a*) Describe all statistical methods, including those used to control for confounding
	Supp Materials	(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed

	Case-control study—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy Also see Supplementary Materials
(*e*) Describe any sensitivity analyses	

Continued on next page

Results		
Participants	Pg 10-11	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	Pg 10-11	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
	Table 1	(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	Pg 11 Supp Materials	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	Pg 11 Table 2 Supp Materials	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	Supp Materials	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	Pg 11-12	Summarise key results with reference to study objectives
Limitations	Pg 14	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	Pg 14	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	Pg 13	Discuss the generalisability (external validity) of the study results
Other information		
Funding	Pg 16	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.