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Adverse Events Associated With Disease-Modifying Drugs for Multiple Sclerosis

A Multiregional Population-Based Study

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Abstract

Background and Objectives

It is not possible to fully establish the safety of a disease-modifying drug (DMD) for multiple sclerosis (MS) from randomized controlled trials as only very common adverse events occurring over the short-term can be captured, and the quality of reporting has been variable. We examined the relationship between the DMDs for MS and potential adverse events in a multiregion population-based study.

Methods

We identified people with MS using linked administrative health data from 4 Canadian provinces. MS cases were followed from the most recent of first MS or related demyelinating disease event on January 1, 1996, until the earliest of emigration, death, or December 31, 2017. DMD exposure primarily comprised β-interferon, glatiramer acetate, natalizumab, fingolimod, dimethyl fumarate, teriflunomide, and alemtuzumab. We examined associations between DMD exposure and infection-related hospitalizations and physician visits using recurrent events proportional means models and between DMD exposure and 15 broad categories of incident adverse events using stratified multivariate Cox proportional hazard models.

Results

We identified 35,894 people with MS. While virtually all DMDs were associated with a 42%–61% lower risk of infection-related hospitalizations, there was a modest increase in infection-related physician visits by 10%–33% for select DMDs. For incident adverse events, most elevated risks involved a second-generation DMD, with alemtuzumab's hazard of thyroid disorders being 19.42 (95% CI 9.29–36.51), hypertension 4.96 (95% CI 1.78–13.84), and cardiovascular disease 3.72 (95% CI 2.12–6.53). Natalizumab's highest risk was for cardiovascular disease (adjusted hazard ratio [aHR] 1.61; 95% CI 1.24–2.10). For the oral DMDs, fingolimod was associated with higher hazards of cerebrovascular (aHR 2.04; 95% CI 1.27–3.30) and ischemic heart diseases (aHR 1.64; 95% CI 1.10–2.44) and hypertension (aHR 1.73; 95% CI 1.30–2.31); teriflunomide with higher hazards of thyroid disorders (aHR 2.30; 95% CI 1.11–4.74), chronic liver disease (aHR 1.94; 95% CI 1.19–3.18), hypertension (aHR 1.76; 95% CI 1.32–2.37), and hyperlipidemia (aHR 1.61; 95% CI 1.07–2.44); and from complementary analyses (in 1 province), dimethyl fumarate with acute liver injury (aHR 6.55; 95% CI 1.96–21.87).

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Glossary

aHR = adjusted hazard ratio; **CCI** = Charlson Comorbidity Index; **CR** = crude rate per 1,000 person-years; **DMD** = disease-modifying drug; **FDA** = US Food and Drug Administration; ***ICD-9/10*** = *International Classification of Diseases, Ninth/Tenth Revision*; **MS** = multiple sclerosis; **RCT** = randomized controlled trial; **SARS-CoV-2** = severe acute respiratory syndrome coronavirus 2; **SES** = socioeconomic status.

Discussion

Our study provides an extensive safety profile of several different DMDs used to treat MS in the real-world setting. Our findings not only complement those observed in short-term clinical trials but also provide new insights that help inform the risk-benefit profile of the DMDs used to treat MS in clinical practice. The results of this study highlight the continued need for long-term, independent safety studies of the DMDs used to treat MS.

Classification of Evidence

This study provides Class III evidence that for patients with MS, while DMD exposure reduces the risk of infection-related hospitalizations, there are increased risks of infection-related physician visits and incident adverse events for select DMDs.

Introduction

Disease-modifying drugs (DMDs) for multiple sclerosis (MS) are typically approved after short-term randomized controlled trials (RCTs) conducted over 2–3 years in a limited number of carefully selected individuals and are designed and powered to examine efficacy, not safety. It is not possible to fully establish DMD safety from such studies as only very common adverse events occurring over the short-term are captured, and the quality of reporting has been variable.[1-4] Individuals treated in routine clinical practice, such as older persons or those with comorbidities, are often excluded from RCTs, limiting the generalizability of findings.[5]

Adverse drug reactions have been reported as one of the top 10 leading causes of death in the United States (pre-severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]/coronavirus disease 2019 pandemic), resulting in >100,000 deaths each year.[6] While the first-generation MS DMDs (β-interferon and glatiramer acetate) have been considered relatively safe, to date, surprisingly, few population-based safety studies have been conducted for those or indeed for any of the DMDs.[7-11] Although cancer risk is a concern for all DMDs,[12] just a few population-based studies have examined this and for a limited number of DMDs.[13-15] Very few safety-related studies are independent of the pharmaceutical companies that sell these products, a recognized conflict of interest and a problem in the MS field.[4]

Our primary research question was "what is the relationship between the MS DMDs and risk of adverse events?" We examined this in an MS population using linked administrative data from 4 Canadian provinces collected over 22 years within a universal health care setting.

Methods

Data Sources and Study Population

Canada has a universal, publicly funded health care system; health services are delivered to >98% of the population provincially.[16] We used linked administrative data from British Columbia, Manitoba, Saskatchewan, and Nova Scotia. Combined, these regions covered >8 million residents, representing ∼25% of Canada's population (2016).[17] Linked data included the Discharge Abstract Database (hospital admissions/discharges and International Classification of Diseases [ICD] codes),[e1] physician claims (medical services, including laboratory-related visits, and ICD codes),[e2] provincial health insurance data (demographics and residency confirmation [through enrollment in the mandatory provincial health program],[e3] and for Manitoba/Saskatchewan, death dates), and Vital Statistics (capturing death dates in British Columbia/Nova Scotia).[e4] Prescription data from British Columbia/Manitoba/Saskatchewan[e5] and the Dalhousie MS Research database, Nova Scotia, provided DMD-related information. Together, data captured all medically necessary hospitalizations, physician services, and MS DMD prescriptions filled, unaffected by ability to pay.

We identified all MS cases (described previously), as any individual with ≥3 MS diagnostic codes (*ICD-9/10*:340/G35) or ≥1 DMD record.[17,18] The index date was the most recent of the first MS or related demyelinating disease code recorded in the hospital/physician claims data or first DMD prescription filled; a person's 18th birthday; or the first availability of the DMD prescription data in each province (January 1, 1996/1997/1998 [British Columbia/Saskatchewan/Nova Scotia] and April 1, 1996 [Manitoba]).

MS cases had ≥1 year of provincial residency to allow for baseline characterization at the index date (sex, age, calendar

year, socioeconomic status [SES], and comorbidity). SES was based on neighborhood-level income, using Statistics Canada's algorithm linking census-derived family income with each individual's residential postcode.[17] Comorbidity was measured by the Charlson Comorbidity Index (CCI), using diagnostic codes in hospital/physician (primary/secondary care) claims data in the year pre-index date, excluding hemiplegia/paraplegia.[19] This index has been widely used in MS and other populations, including the examination of long-term mortality,[16] other DMD-related outcomes,[20,21] and adverse drug events.[22,23] The index also captures several common comorbidities, including those most relevant to specific contraindications/cautions for DMD use, such as cardiovascular, cerebrovascular, chronic lung and liver diseases, diabetes, and malignancy. We followed MS cases from their index date until the earliest of emigration, death, or study end (December 31, 2017 [British Columbia/Manitoba/Nova Scotia], and March 31, 2018 [Saskatchewan]).

DMD Exposure

The DMDs approved for MS in Canada during the study period included the first-generation DMDs (β-interferons [all products combined] and glatiramer acetate) and second-generation DMDs (natalizumab, fingolimod, dimethyl fumarate, teriflunomide, alemtuzumab, daclizumab [withdrawn March 2018], and ocrelizumab). DMDs were assessed individually (except for daclizumab and ocrelizumab due to insufficient exposure in our cohorts).

We examined DMD exposure grouped as any DMD, then by generation, and by individual DMD. DMD exposure was defined using 2 approaches ("current" and minimum cumulative exposure) and was updated over time (treated as a time-varying variable). Exposure periods were calculated based on the numbers of days/quantity dispensed or start/stop dates for each DMD. A person could be exposed to 1 or more individual DMDs during the follow-up period, and exposures to different DMDs (e.g., due to switching) were accounted for in the analysis by separate DMD exposure indicators.

"Current" exposure was based on the duration of each DMD used during follow-up. Discontinuation occurred if no dispensations for that DMD for ≥90 consecutive days, plus a 30-day grace period.[20] For alemtuzumab, exposure was "current" for 12 months from the first prescription filled. We used a similar approach for ocrelizumab, except with a 6-month period. Each of these DMDs was then considered discontinued if no further prescriptions were filled for that DMD (plus a 30-day grace period). Individuals could only be exposed to 1 DMD at a time (i.e., once a subsequent DMD prescription was filled, then the previous DMD was considered discontinued).

For the minimum cumulative approach, exposure was based on contiguous use of a DMD, defined as ≥6 months for β-interferon and glatiramer acetate; ≥3 months for natalizumab, fingolimod, dimethyl fumarate, and teriflunomide; and after 3 months following the first prescription filled for alemtuzumab or ocrelizumab.[16] These definitions were based on the minimum time needed for a DMD to yield a clinical response.[16] Once the definition of minimum cumulative exposure for a DMD was reached, a person was considered exposed to that DMD for the remainder of their study follow-up. If the minimum cumulative exposure was not reached for any individual DMD, then that person was considered not exposed to that DMD.

Adverse Event-Related Outcomes

All adverse safety signals (adverse event-related outcomes) were identified using diagnostic codes (*ICD-9/10*).

First, infection-related outcomes captured in the physician and hospital data were assessed as recurrent events (eTable 1, links.lww.com/WNL/D339). As serious infections are of particular concern and hospitalizations can serve as a proxy for severity, the hospital and physician visit data were examined separately (this was performed for infections only, not for other outcomes). To minimize double counting, any overlapping hospital stays or stays beginning ≤1 day of the previous hospitalization were considered as 1 event.[20,24] Similarly, multiple infection-related physician visits falling within a 30-day period were considered as 1 event.[24] The duration of an infection-related hospitalization was excluded from follow-up as someone could not be at risk of another infection-related hospitalization during the existing event, by definition. A 29-day period after an infection-related physician claim was excluded, based on the same reasoning.

Second, incident adverse events were defined as the presence of ≥1 ICD code for each event of interest captured in physician/hospital data (eTable 2, links.lww.com/WNL/D339). These were identified a priori based on the literature and relevant product monographs[7,24-30] and guided by their occurrence and potential importance in MS. They included autoimmune diseases, cancer, cerebrovascular diseases, chronic liver diseases, chronic kidney diseases, diabetes, hyperlipidemia, hypertension, any mental condition (anxiety, depression, or bipolar disorders), migraine, and thyroid disorders. Cardiovascular disorders were assessed as either ischemic heart disease or "other" forms of heart diseases (e.g., pericarditis, cardiac arrhythmias). Incident was defined as not present in the year pre-index date. For each adverse event, persons with evidence of that event in the year pre-index date were not included such that the cohorts could naturally vary for each event examined.

Statistical Analyses

We examined the association between "current" DMD exposure and recurrent infection-related events using a proportional means model with robust sandwich variance estimates. This allowed each individual to have repeated events while accounting for dependence of events. The models were adjusted for sex, SES (quintiles), and age (continuous) at the index date and Charlson comorbidity score (categorized as 0, 1, 2, or ≥3

and updated over time). The index year was also included as a continuous variable to account for secular changes in health care use over time.[20,24]

For all other adverse events (i.e., not infection-related), the association between minimum cumulative DMD exposure and the incident event was examined using a stratified multivariate Cox proportional hazard model. The proportional hazards assumptions were examined by an interaction term between covariates and log (follow-up). Follow-up was defined as time from the index date to the adverse event date of interest or study end. The same model adjustments were applied, except for the index year where models were stratified (grouped as calendar years: 1996–1999, 2000–2005, 2006–2011, or 2012–2017/18) to account for potential differences in health care use over time, baseline risk, and unequal follow-up across each stratum.

As per data access/privacy requirements, analyses were performed within each province, and the results were combined using random-effects meta-analyses[16,20] and reported as adjusted hazard ratios (aHRs) and 95% CIs.

We conducted 3 complementary analyses in the largest province, British Columbia, including (1) 2 additional incident adverse events—acute liver injury and abnormal hematologic findings (eTable 2, links.lww.com/WNL/D339),[7] using the "current" exposure approach; (2) an "intention-to-treat" analysis, by defining the minimum cumulative DMD exposure as at least 1 day; and (3) an assessment of potential incident adverse events by using previously published or validated case definitions (9 were found; eTable 3). Sensitivity analyses included (1) computing E-values to assess how likely the findings were due to unobserved confounding,[31] (2) computing summary measures to assess the susceptibility of findings to selection bias,[32] (3) comparing the results

Table 1 Characteristics of Persons With Multiple Sclerosis Included in the Analysis for Each Potential Adverse Event of Interest From a Total Source Cohort of 35,894 Persons[a]

	Excluded (event present in the year pre-index date)	Characteristics of persons with MS included in the analysis		
Adverse event of interest	Total no. of persons	Total no. of persons	Age at index date, y, mean (SD)	Follow-up from index to study end, y, mean (SD)
Infection-related hospitalizations	NA	35,894	44.6 (13.6)	12.0 (7.2)
Infection-related physician visits	NA	35,894	44.6 (13.6)	12.0 (7.2)
Autoimmune diseases	3,388	32,506	44.4 (13.5)	8.2 (6.6)
Cancer	994	34,900	44.4 (13.5)	10.8 (7.0)
Cardiovascular disorders (ischemic heart diseases)	1,074	34,820	44.2 (13.4)	10.7 (7.1)
Cardiovascular disorders (other forms of heart diseases)	1,257	34,637	44.2 (13.3)	10.4 (7.0)
Cerebrovascular diseases	1,508	34,386	44.3 (13.4)	11.5 (7.2)
Chronic liver diseases	312	35,582	44.5 (13.6)	11.5 (7.1)
Chronic kidney diseases	185	35,709	44.5 (13.5)	11.7 (7.1)
Diabetes	1,411	34,483	44.2 (13.4)	11.0 (7.1)
Hyperlipidemia	1,116	34,778	44.3 (13.6)	10.1 (6.9)
Hypertension	3,495	32,399	43.5 (13.2)	9.2 (6.8)
Mental conditions (anxiety, depression, bipolar disorder)	9,381	26,513	44.9 (14.0)	6.3 (6.2)
Migraine	1,867	34,027	44.8 (13.7)	10.7 (7.3)
Thyroid disorders (autoimmune hypothyroidism and hyperthyroidism)	211	35,683	44.5 (13.6)	11.7 (7.2)
Acute liver injury[a]	*8*	*19,352*	*45.0 (13.5)*	*11.7 (7.3)*
Abnormal hematologic findings[a]	*765*	*18,595*	*44.8 (13.4)*	*11.8 (7.3)*

Abbreviation: NA = not applicable (as per the methods, a person was permitted to have an infection in the prior year; thus, no person was excluded).
Except for infections, all potential adverse events were identified as present in either the in-patient and out-patient information (hospitalization and/or physician visit data).
[a] Total source cohort size was 35,894 from all 4 provinces, except for 2 adverse event of interest, acute liver injury, and abnormal hematologic findings (shown in italics), which was performed in British Columbia only where the total source cohort was 19,360.

of unadjusted and adjusted models to examine the effects of selected confounders,[33] (4) using each individual comorbidity (captured in the CCI) as separate covariates, and (5) using propensity score as a covariate adjustment whereby propensity scores for DMD exposure status (never vs ever) for each outcome were generated separately using logistic regression and included sex, SES (quintiles), individual comorbidity (captured in the CCI), calendar year, and age (modeled with a cubic spline) at index date. The latter 2 sensitivity analyses were conducted in the largest province. These are recognized approaches to assess the impact of biases, including unobserved confounders, in observational studies.[31-33] Statistical analyses were performed using SAS version 9.4 and R version 4.0.2.

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by Research Ethics Boards at the Universities of British Columbia/Saskatchewan/Manitoba (H18-00407/HS21764) and Nova Scotia Health (1023555) and registered with ClinicalTrials.gov (NCT04472975).

Data Availability

With the appropriate approvals, data may be accessed through Population Data British Columbia, Saskatchewan Health Quality Council, Manitoba Centre for Health Policy, and Health Data Nova Scotia of Dalhousie University.

Results

Cohort Characteristics

We identified 35,894 people with MS (Table 1, described previously[17]). These individuals formed the total source population for analyses. In brief, the mean (SD) age at the index date was 44.6 (13.6) years, and the mean (SD) follow-up from index to study end was 12.0 (7.2) years. Everyone from the source population was included in the infection-related analyses. For the incident adverse events, the total number of persons ranged from 26,513 for any mental condition to 35,709 for chronic kidney diseases, with the mean follow-up ranging from 6.3 (SD 6.2) years to 11.7 (SD 7.1) years.

Infection-Related Outcomes

Current exposure to any DMD (vs no current exposure) was associated with a 47% lower hazard of infection-related hospitalizations (95% CI 37%–56%) (Figure, Table 2). This lower hazard was observed for the first-generation and second-generation DMDs (examined as 2 separate groups) and for each individual DMD but was not significant for alemtuzumab. For the individual DMDs, this lower hazard ranged from 42% (aHR 0.58; 95% CI 0.50–0.67) to 61% (aHR 0.39; 95% CI 0.16–0.94). By contrast, there was a modest increase in infection-related physician visits for any

Figure Risk Hazard[a] of Potential Adverse Events Associated With Disease-Modifying Drugs Used to Treat Multiple Sclerosis in Canada (1996–2017/18)

Color coding: Lower hazard — Higher hazard

	Infections (recurrent events)[b]		Incident adverse events[c]												
	Hospitalizations	Physician visits	Autoimmune diseases	Cancer	Ischemic heart disease	Other cardio vascular disorders	Cerebrovascular diseases	Chronic liver diseases	Chronic renal diseases	Diabetes	Hyperlipidemia	Hypertension	Mental conditions	Migraine	Thyroid disorders
No DMD	Reference		Reference												
Any DMD	**0.53**	0.98	1.00	0.99	0.94	1.00	**0.83**	1.00	1.02	0.96	0.93	1.03	1.05	0.97	0.97
First-generation DMD	**0.54**	0.96	0.99	0.98	0.94	0.99	**0.84**	0.98	0.98	0.96	0.95	1.03	1.04	0.87	0.92
Second-generation DMD	**0.45**	**1.11**	1.03	1.16	1.08	1.09	0.94	1.28	1.34	0.83	0.85	1.10	1.04	1.00	1.42
Beta-interferon	**0.58**	**0.94**	1.00	0.97	0.94	1.03	0.92	0.98	1.03	0.98	0.95	**1.11**	1.01	0.99	0.98
Glatiramer acetate	**0.47**	0.99	1.02	1.01	1.03	1.02	**0.78**	1.05	0.97	0.93	0.95	**0.87**	**1.16**	0.95	0.90
Natalizumab	**0.53**	**1.11**	1.05	1.34	1.08	**1.61**	1.46	1.07	1.14	0.77	0.74	0.79	**1.36**	1.37	1.05
Fingolimod	**0.39**	**1.13**	1.17	1.22	**1.64**	0.78	**2.04**	1.58	1.69	1.42	1.30	**1.73**	**0.87**	1.38	1.02
Dimethyl fumarate	**0.40**	**1.10**	1.03	1.22	0.97	1.17	**0.43**	1.07	1.20	0.94	0.73	0.85	1.02	0.89	1.18
Teriflunomide	**0.57**	1.00	0.95	0.87	1.04	0.74	1.24	**1.94**	1.26	0.72	**1.61**	**1.76**	0.77	1.04	**2.30**
Alemtuzumab	0.20	**1.33**	1.37	1.49	1.09	**3.72**	0.53	1.28	**6.43**	**0.51**	0.36	**4.96**	1.24	0.57	**19.42**

DMD = disease-modifying drug. Bold indicates $p < 0.05$. Except for infections, all potential adverse events were identified as presence in either in-patient or out-patient information (hospitalizations or physician visits). [a]Findings from 4 Canadian provinces combined (British Columbia, Saskatchewan, Manitoba, Nova Scotia). The results were adjusted for sex, socioeconomic status (quintiles), and age (continuous) at the index date and Charlson comorbidity score (categorized as 0, 1, 2, or ≥3 and updated overtime). [b]Recurrent events using the "current" DMD exposure approach. [c]Incident adverse events using the "minimum" cumulative DMD approach. See Table 2 for full results, including the hazard ratios with 95% CI and the crude rate for each event.

Table 2 Risk of Potential Adverse Events Associated With Disease-Modifying Drugs Used to Treat Multiple Sclerosis in Canada (1996–2017/18)

Potential adverse event	No. of cases	Py of follow-up	Crude rate per 1,000 py	Crude hazard ratio (95% CI)	Adjusted hazard ratio[a] (95% CI)
Recurrent events using the "current" DMD exposure approach[b]					
Infection-related hospitalizations					
No DMD	21,346	366,061	58.31	Reference	Reference
Any DMD	**1,362**	**63,194**	**21.55**	**0.36 (0.32–0.41)**	**0.53 (0.44–0.63)**
First-generation DMD	**1,208**	**54,514**	**22.16**	**0.37 (0.33–0.43)**	**0.54 (0.45–0.64)**
Second-generation DMD	**154**	**8,680**	**17.74**	**0.27 (0.20–0.36)**	**0.45 (0.33–0.62)**
β-Interferon	**861**	**36,444**	**23.63**	**0.41 (0.36–0.46)**	**0.58 (0.50–0.67)**
Glatiramer acetate	**347**	**18,071**	**19.20**	**0.32 (0.27–0.38)**	**0.47 (0.37–0.59)**
Natalizumab	**29**	**1,747**	**16.60**	**0.30 (0.21–0.45)**	**0.53 (0.36–0.78)**
Fingolimod	**22**	**1,726**	**12.75**	**0.20 (0.07–0.54)**	**0.39 (0.16–0.94)**
Dimethyl fumarate	**48**	**3,347**	**14.34**	**0.24 (0.17–0.34)**	**0.40 (0.29–0.56)**
Teriflunomide	**36**	**1,536**	**23.44**	**0.38 (0.26–0.56)**	**0.57 (0.39–0.84)**
Alemtuzumab	9	317	28.38	0.10 (0.01–1.44)	0.20 (0.01–2.84)
Infection-related physician visits					
No DMD	281,468	338,404	831.75	Reference	Reference
Any DMD	45,214	58,390	774.34	**0.94 (0.92–0.96)**	0.98 (0.92–1.03)
First-generation DMD	38,618	50,276	768.12	**0.93 (0.90–0.95)**	0.96 (0.91–1.01)
Second-generation DMD	**6,596**	**8,115**	**812.85**	1.02 (0.98–1.07)	**1.11 (1.04–1.17)**
β-Interferon	**25,265**	**33,569**	**752.63**	**0.91 (0.88–0.94)**	**0.94 (0.90–0.99)**
Glatiramer acetate	13,353	16,707	799.26	0.96 (0.91–1.01)	0.99 (0.90–1.08)
Natalizumab	1,377	1,630	845.03	1.05 (0.91–1.20)	1.11 (0.95–1.31)
Fingolimod	**1,309**	**1,614**	**810.94**	1.03 (0.92–1.16)	**1.13 (1.03–1.25)**
Dimethyl fumarate	**2,561**	**3,123**	**819.98**	1.03 (0.96–1.09)	**1.10 (1.04–1.18)**
Teriflunomide	1,069	1,446	739.51	0.94 (0.84–1.06)	1.00 (0.91–1.10)
Alemtuzumab	**274**	**296**	**927.06**	1.16 (0.97–1.38)	**1.33 (1.13–1.58)**
Incident adverse event using the "minimum" cumulative DMD approach[b]					
Autoimmune diseases					
No DMD	11,557	214,409	53.90	Reference	Reference
Any DMD	2,493	52,554	47.44	**0.95 (0.91–0.99)**	1.00 (0.95–1.04)
First-generation DMD	2,374	50,412	47.09	0.95 (0.91–1.00)	0.99 (0.95–1.04)
Second-generation DMD	272	5,472	49.71	0.99 (0.87–1.12)	1.03 (0.91–1.17)
β-Interferon	1,812	38,355	47.24	0.96 (0.91–1.01)	1.00 (0.95–1.06)
Glatiramer acetate	800	16,353	48.92	1.00 (0.93–1.08)	1.02 (0.95–1.10)
Natalizumab	71	1,479	48.00	1.00 (0.78–1.26)	1.05 (0.83–1.33)
Fingolimod	60	1,118	53.65	1.11 (0.86–1.44)	1.17 (0.90–1.51)
Dimethyl fumarate	118	2,328	50.70	1.01 (0.78–1.30)	1.03 (0.81–1.31)

Continued

Table 2 Risk of Potential Adverse Events Associated With Disease-Modifying Drugs Used to Treat Multiple Sclerosis in Canada (1996–2017/18) *(continued)*

Potential adverse event	No. of cases	Py of follow-up	Crude rate per 1,000 py	Crude hazard ratio (95% CI)	Adjusted hazard ratio[a] (95% CI)
Teriflunomide	43	945	45.51	0.94 (0.63–1.41)	0.95 (0.64–1.43)
Alemtuzumab	11	158	69.43	1.33 (0.73–2.42)	1.37 (0.76–2.50)
Cancer					
No DMD	5,801	297,917	19.47	Reference	Reference
Any DMD	1,183	78,421	15.09	**0.77 (0.70–0.84)**	0.99 (0.92–1.06)
First-generation DMD	1,132	75,493	14.99	**0.77 (0.70–0.84)**	0.98 (0.91–1.05)
Second-generation DMD	146	8,277	17.64	0.97 (0.81–1.15)	1.16 (0.97–1.38)
β-Interferon	878	57,652	15.23	**0.78 (0.71–0.87)**	0.97 (0.89–1.05)
Glatiramer acetate	370	25,362	14.59	**0.84 (0.75–0.93)**	1.01 (0.90–1.12)
Natalizumab	50	2,355	21.23	1.21 (0.91–1.62)	1.34 (1.00–1.78)
Fingolimod	35	1,717	20.38	1.03 (0.73–1.45)	1.22 (0.87–1.72)
Dimethyl fumarate	59	3,473	16.99	1.04 (0.73–1.47)	1.22 (0.85–1.75)
Teriflunomide	20	1,382	14.48	0.79 (0.50–1.22)	0.87 (0.56–1.35)
Alemtuzumab	6	259	23.21	1.18 (0.53–2.66)	1.49 (0.66–3.35)
Cardiovascular disorders (ischemic heart disease)					
No DMD	5,329	291,350	18.29	Reference	Reference
Any DMD	875	80,290	10.90	**0.60 (0.48–0.74)**	0.94 (0.83–1.07)
First-generation DMD	839	77,369	10.84	**0.61 (0.50–0.75)**	0.94 (0.84–1.05)
Second-generation DMD	100	8,574	11.66	0.84 (0.57–1.24)	1.08 (0.71–1.65)
β-Interferon	655	59,116	11.08	**0.64 (0.52–0.80)**	0.94 (0.82–1.07)
Glatiramer acetate	276	26,046	10.60	**0.74 (0.63–0.86)**	1.03 (0.91–1.17)
Natalizumab	29	2,519	11.51	0.94 (0.65–1.36)	1.08 (0.75–1.58)
Fingolimod	**27**	**1,731**	**15.60**	1.24 (0.84–1.84)	**1.64 (1.10–2.44)**
Dimethyl fumarate	33	3,564	9.26	0.77 (0.54–1.09)	0.97 (0.68–1.38)
Teriflunomide	16	1,425	11.23	0.88 (0.54–1.44)	1.04 (0.64–1.71)
Alemtuzumab	<6	252	NR	0.83 (0.27–2.59)	1.09 (0.35–3.41)
Cardiovascular disorders (other forms of heart disease)					
No DMD	7,267	284,470	25.55	Reference	Reference
Any DMD	1,342	76,835	17.47	**0.65 (0.54–0.80)**	1.00 (0.89–1.12)
First-generation DMD	1,278	74,045	17.26	**0.66 (0.56–0.79)**	0.99 (0.91–1.09)
Second-generation DMD	167	7,955	20.99	0.82 (0.54–1.24)	1.09 (0.73–1.61)
β-Interferon	1,004	56,682	17.71	**0.72 (0.60–0.88)**	1.03 (0.90–1.18)
Glatiramer acetate	431	24,600	17.52	**0.76 (0.66–0.87)**	1.02 (0.90–1.16)
Natalizumab	**59**	**2,233**	**26.42**	**1.38 (1.06–1.80)**	**1.61 (1.24–2.10)**
Fingolimod	21	1,681	12.49	**0.64 (0.41–0.99)**	0.78 (0.50–1.21)
Dimethyl fumarate	64	3,321	19.27	0.93 (0.72–1.19)	1.17 (0.91–1.51)

Continued

Table 2 Risk of Potential Adverse Events Associated With Disease-Modifying Drugs Used to Treat Multiple Sclerosis in Canada (1996–2017/18) *(continued)*

Potential adverse event	No. of cases	Py of follow-up	Crude rate per 1,000 py	Crude hazard ratio (95% CI)	Adjusted hazard ratio[a] (95% CI)
Teriflunomide	27	1,358	19.88	0.65 (0.22–1.89)	0.74 (0.24–2.28)
Alemtuzumab	**13**	**221**	**58.92**	**2.77 (1.59–4.83)**	**3.72 (2.12–6.53)**
Cerebrovascular diseases					
No DMD	3,398	311,339	10.91	Reference	Reference
Any DMD	**448**	**82,897**	**5.40**	**0.53 (0.46–0.61)**	**0.83 (0.75–0.92)**
First-generation DMD	**433**	**80,008**	**5.41**	**0.55 (0.47–0.64)**	**0.84 (0.76–0.94)**
Second-generation DMD	48	8,674	5.53	**0.70 (0.52–0.94)**	0.94 (0.68–1.30)
β-Interferon	357	61,576	5.80	**0.60 (0.44–0.80)**	0.92 (0.73–1.16)
Glatiramer acetate	**123**	**26,665**	**4.61**	**0.55 (0.46–0.66)**	**0.78 (0.65–0.94)**
Natalizumab	17	2,543	6.68	1.18 (0.38–3.68)	1.46 (0.45–4.71)
Fingolimod	**18**	**1,799**	**10.01**	1.45 (0.90–2.33)	**2.04 (1.27–3.30)**
Dimethyl fumarate	**9**	**3,592**	**2.51**	**0.34 (0.17–0.65)**	**0.43 (0.22–0.84)**
Teriflunomide	11	1,431	7.69	0.98 (0.54–1.79)	1.24 (0.68–2.27)
Alemtuzumab	<6	264	NR	0.38 (0.05–2.71)	0.53 (0.07–3.82)
Chronic liver diseases					
No DMD	2,015	325,606	6.19	Reference	Reference
Any DMD	475	84,455	5.62	0.93 (0.84–1.04)	1.00 (0.90–1.11)
First-generation DMD	452	81,406	5.55	0.92 (0.83–1.02)	0.98 (0.88–1.10)
Second-generation DMD	64	8,988	7.12	1.26 (0.84–1.89)	1.28 (0.87–1.90)
β-Interferon	350	62,674	5.58	0.93 (0.83–1.04)	0.98 (0.87–1.11)
Glatiramer acetate	159	26,874	5.92	1.01 (0.85–1.19)	1.05 (0.89–1.25)
Natalizumab	15	2,639	5.68	1.09 (0.53–2.21)	1.07 (0.52–2.17)
Fingolimod	19	1,838	10.34	1.47 (0.73–2.97)	1.58 (0.80–3.12)
Dimethyl fumarate	25	3,748	6.67	1.05 (0.63–1.72)	1.07 (0.65–1.75)
Teriflunomide	**17**	**1,477**	**11.51**	**1.88 (1.15–3.07)**	**1.94 (1.19–3.18)**
Alemtuzumab	<6	272	NR	1.22 (0.30–4.93)	1.28 (0.32–5.19)
Chronic kidney diseases					
No DMD	2,073	330,693	6.27	Reference	Reference
Any DMD	393	86,849	4.53	**0.64 (0.57–0.71)**	1.02 (0.88–1.19)
First-generation DMD	374	83,762	4.47	**0.64 (0.57–0.71)**	0.98 (0.97–1.10)
Second-generation DMD	54	9,188	5.88	0.99 (0.52–1.87)	1.34 (0.71–2.54)
β-Interferon	300	64,406	4.66	**0.70 (0.62–0.79)**	1.03 (0.90–1.17)
Glatiramer acetate	123	27,949	4.40	**0.70 (0.58–0.84)**	0.97 (0.80–1.17)
Natalizumab	12	2,652	4.52	0.94 (0.37–2.37)	1.14 (0.42–3.07)
Fingolimod	9	1,919	4.69	1.15 (0.38–3.55)	1.69 (0.49–5.87)
Dimethyl fumarate	25	3,818	6.55	0.94 (0.35–2.54)	1.20 (0.44–3.26)
Teriflunomide	10	1,537	6.51	1.02 (0.54–1.91)	1.26 (0.67–2.37)

Continued

Table 2 Risk of Potential Adverse Events Associated With Disease-Modifying Drugs Used to Treat Multiple Sclerosis in Canada (1996–2017/18) *(continued)*

Potential adverse event	No. of cases	Py of follow-up	Crude rate per 1,000 py	Crude hazard ratio (95% CI)	Adjusted hazard ratio[a] (95% CI)
Alemtuzumab	**<6**	**270**	**NR**	**3.87 (1.58–9.46)**	**6.43 (2.60–15.95)**
Diabetes					
No DMD	4,260	300,513	14.18	Reference	Reference
Any DMD	827	79,823	10.36	**0.72 (0.66–0.79)**	0.96 (0.88–1.04)
First-generation DMD	796	76,922	10.35	**0.73 (0.67–0.80)**	0.96 (0.88–1.04)
Second-generation DMD	68	8,549	7.95	**0.72 (0.55–0.93)**	0.83 (0.62–1.12)
β-Interferon	632	58,980	10.72	**0.78 (0.72–0.85)**	0.98 (0.90–1.07)
Glatiramer acetate	249	25,709	9.69	**0.76 (0.64–0.90)**	0.93 (0.80–1.09)
Natalizumab	16	2,473	6.47	0.69 (0.42–1.13)	0.77 (0.47–1.27)
Fingolimod	19	1,797	10.57	1.14 (0.72–1.81)	1.42 (0.89–2.25)
Dimethyl fumarate	29	3,534	8.21	0.81 (0.55–1.17)	0.94 (0.65–1.37)
Teriflunomide	9	1,419	6.34	0.65 (0.34–1.26)	0.72 (0.37–1.40)
Alemtuzumab	<6	275	NR	0.42 (0.06–3.00)	0.51 (0.07–3.62)
Hyperlipidemia					
No DMD	6,353	276,919	22.94	Reference	Reference
Any DMD	1,329	73,420	18.10	**0.77 (0.72–0.81)**	0.93 (0.88–1.00)
First-generation DMD	1,295	70,625	18.34	**0.79 (0.74–0.84)**	0.95 (0.89–1.02)
Second-generation DMD	109	8,031	13.57	**0.75 (0.61–0.91)**	0.85 (0.70–1.03)
β-Interferon	987	54,195	18.21	**0.80 (0.75–0.86)**	0.95 (0.89–1.02)
Glatiramer acetate	419	23,386	17.92	**0.82 (0.74–0.90)**	0.95 (0.86–1.06)
Natalizumab	25	2,385	10.48	0.68 (0.45–1.01)	0.74 (0.49–1.10)
Fingolimod	26	1,705	15.25	1.11 (0.75–1.65)	1.30 (0.88–1.93)
Dimethyl fumarate	38	3,303	11.50	**0.66 (0.47–0.92)**	0.73 (0.53–1.01)
Teriflunomide	**30**	**1,254**	**23.92**	1.55 (0.98–2.43)	**1.61 (1.07–2.44)**
Alemtuzumab	<6	269	NR	0.29 (0.04–2.06)	0.36 (0.05–2.53)
Hypertension					
No DMD	8,972	233,816	38.37	Reference	Reference
Any DMD	1,872	65,518	28.57	**0.76 (0.70–0.84)**	1.03 (0.98–1.09)
First-generation DMD	1,814	62,876	28.85	**0.77 (0.70–0.85)**	1.03 (0.98–1.09)
Second-generation DMD	183	7,317	25.01	0.90 (0.77–1.05)	1.10 (0.94–1.28)
β-Interferon	**1,451**	**47,748**	**30.39**	**0.85 (0.79–0.92)**	**1.11 (1.04–1.17)**
Glatiramer acetate	**538**	**21,212**	**25.36**	**0.71 (0.65–0.77)**	**0.87 (0.80–0.95)**
Natalizumab	44	2,245	19.60	**0.70 (0.52–0.95)**	0.79 (0.59–1.07)
Fingolimod	**50**	**1,566**	**31.92**	**1.40 (1.05–1.86)**	**1.73 (1.30–2.31)**
Dimethyl fumarate	64	2,983	21.46	**0.72 (0.56–0.93)**	0.85 (0.66–1.11)
Teriflunomide	**47**	**1,106**	**42.50**	**1.61 (1.20–2.16)**	**1.76 (1.32–2.37)**
Alemtuzumab	**<6**	**225**	**NR**	**3.92 (1.41–10.92)**	**4.96 (1.78–13.84)**

Continued

Table 2 Risk of Potential Adverse Events Associated With Disease-Modifying Drugs Used to Treat Multiple Sclerosis in Canada (1996–2017/18) *(continued)*

Potential adverse event	No. of cases	Py of follow-up	Crude rate per 1,000 py	Crude hazard ratio (95% CI)	Adjusted hazard ratio[a] (95% CI)
Mental conditions (anxiety, depression, bipolar disorders)					
No DMD	13,268	139,192	95.32	Reference	Reference
Any DMD	2,132	26,972	79.05	**1.10 (1.05–1.16)**	1.05 (0.99–1.10)
First-generation DMD	1,989	25,580	77.76	**1.10 (1.04–1.16)**	1.04 (0.99–1.10)
Second-generation DMD	237	2,884	82.18	1.08 (0.94–1.23)	1.04 (0.91–1.19)
β-Interferon	1,446	19,258	75.09	1.07 (1.00–1.14)	1.01 (0.96–1.08)
Glatiramer acetate	**680**	**7,925**	**85.81**	**1.22 (1.13–1.33)**	**1.16 (1.07–1.26)**
Natalizumab	**63**	**626**	**100.59**	**1.41 (1.09–1.82)**	**1.36 (1.06–1.76)**
Fingolimod	38	576	66.00	0.90 (0.65–1.24)	0.87 (0.63–1.20)
Dimethyl fumarate	112	1,328	84.36	1.04 (0.85–1.26)	1.02 (0.84–1.24)
Teriflunomide	28	490	57.12	0.79 (0.54–1.15)	0.77 (0.51–1.15)
Alemtuzumab	11	96	114.44	1.29 (0.71–2.34)	1.24 (0.68–2.26)
Migraine					
No DMD	3,879	291,676	13.30	Reference	Reference
Any DMD	872	72,969	11.95	**1.14 (1.02–1.28)**	0.97 (0.90–1.05)
First-generation DMD	825	70,326	11.73	**1.13 (1.02–1.24)**	0.87 (0.89–1.06)
Second-generation DMD	103	7,482	13.77	1.10 (0.85–1.42)	1.00 (0.78–1.28)
β-Interferon	632	54,004	11.70	**1.14 (1.04–1.24)**	0.99 (0.90–1.10)
Glatiramer acetate	271	23,081	11.74	1.09 (0.96–1.24)	0.95 (0.83–1.08)
Natalizumab	30	2,147	13.97	1.36 (0.82–2.26)	1.37 (0.76–2.49)
Fingolimod	27	1,572	17.18	1.54 (0.89–2.65)	1.38 (0.76–2.51)
Dimethyl fumarate	39	3,089	12.63	0.96 (0.69–1.33)	0.89 (0.64–1.23)
Teriflunomide	16	1,245	12.85	1.05 (0.64–1.73)	1.04 (0.63–1.72)
Alemtuzumab	<6	228	NR	0.66 (0.16–2.66)	0.57 (0.14–2.28)
Thyroid disorders (autoimmune hypothyroidism and hyperthyroidism)					
No DMD	1,003	331,520	3.03	Reference	Reference
Any DMD	234	86,309	2.71	0.94 (0.81–1.09)	0.97 (0.83–1.13)
First-generation DMD	221	83,208	2.66	0.90 (0.77–1.05)	0.92 (0.79–1.08)
Second-generation DMD	31	9,252	3.35	1.38 (0.94–2.02)	1.42 (0.96–2.08)
β-Interferon	172	63,912	2.69	0.95 (0.80–1.12)	0.98 (0.83–1.16)
Glatiramer acetate	73	27,800	2.63	0.90 (0.71–1.16)	0.90 (0.70–1.16)
Natalizumab	7	2,708	2.58	1.05 (0.47–2.31)	1.05 (0.48–2.33)
Fingolimod	<6	1,933	NR	0.96 (0.19–4.92)	1.02 (0.19–5.47)
Dimethyl fumarate	12	3,823	3.14	1.14 (0.62–2.09)	1.18 (0.64–2.16)
Teriflunomide	**8**	**1,537**	**5.21**	**2.29 (1.11–4.72)**	**2.30 (1.11–4.74)**
Alemtuzumab	**10**	**272**	**36.72**	**18.77 (9.51–37.05)**	**19.42 (9.29–36.51)**

Continued

Table 2 Risk of Potential Adverse Events Associated With Disease-Modifying Drugs Used to Treat Multiple Sclerosis in Canada (1996–2017/18) *(continued)*

Potential adverse event	No. of cases	Py of follow-up	Crude rate per 1,000 py	Crude hazard ratio (95% CI)	Adjusted hazard ratio[a] (95% CI)
Incident adverse event using the "current" DMD exposure approach[c]					
Acute liver injury					
No DMD	137	200,004	0.68	Reference	Reference
Any DMD	10	24,925	0.40	0.65 (0.34–1.23)	0.81 (0.42–1.56)
First-generation DMD	<6	20,988	NR	**0.37 (0.15–0.92)**	0.47 (0.19–1.15)
Second-generation DMD	**<6**	**3,936**	**NR**	2.48 (0.96–6.37)	**3.32 (1.28–8.62)**
β-Interferon	<6	15,294	NR	**0.20 (0.05–0.80)**	0.25 (0.06–1.00)
Glatiramer acetate	<6	5,694	NR	0.92 (0.29–2.90)	1.14 (0.36–3.63)
Natalizumab	<6	827	NR	NR	NR
Fingolimod	<6	983	NR	1.99 (0.27–14.63)	2.81 (0.38–20.69)
Dimethyl fumarate	**<6**	**1,245**	**NR**	**4.90 (1.47–16.29)**	**6.55 (1.96–21.87)**
Teriflunomide	<6	657	NR	NR	NR
Alemtuzumab	**<6**	**222**	**NR**	**10.83 (1.43–81.85)**	**16.18 (2.11–123.89)**
Abnormal hematologic findings					
No DMD	4,377	163,122	26.87	Reference	Reference
Any DMD	**539**	**20,745**	**26.03**	0.96 (0.88–1.05)	**1.15 (1.05–1.26)**
First-generation DMD	429	17,649	24.36	0.92 (0.83–1.01)	1.09 (0.98–1.20)
Second-generation DMD	**110**	**3,096**	**35.52**	1.18 (0.97–1.43)	**1.50 (1.23–1.83)**
β-Interferon	**323**	**12,951**	**24.94**	0.96 (0.86–1.08)	**1.13 (1.01–1.27)**
Glatiramer acetate	106	4,698	22.78	**0.81 (0.67–0.98)**	0.96 (0.79–1.17)
Natalizumab	**25**	**634**	**39.45**	1.37 (0.92–2.03)	**1.72 (1.16–2.56)**
Fingolimod	23	783	29.38	1.01 (0.67–1.52)	1.33 (0.88–2.01)
Dimethyl fumarate	35	999	35.03	1.11 (0.79–1.55)	1.40 (1.00–1.97)
Teriflunomide	17	509	33.42	1.08 (0.67–1.75)	1.35 (0.84–2.18)
Alemtuzumab	**10**	**169**	**59.01**	1.83 (0.98–3.41)	**2.38 (1.28–4.46)**

Abbreviations: DMD = disease-modifying drug; NR = results are not reported when a small number of events (<6) occurred in a subgroup; py = person-years
Bold indicates $p < 0.05$.
Except for infections, all potential adverse events were identified at present in either the in-patient and out-patient information (hospitalizations and physician visits), as presented in eTable 2 (links.lww.com/WNL/D339). E-values were calculated for statistically significant events according to recommendations,[31] with relatively common events being infection-related physician visits, cardiovascular disorders, hyperlipidemia, hypertension, mental conditions, and abnormal hematologic findings (all others were considered rare). E-value point estimates and lower/upper limits of the CI were >2 for: all DMD groupings and infection-related hospitalizations (specifically: any DMD, any first-generation DMD, any second-generation DMD) and also for individual DMDs as follows: β-interferon, glatiramer acetate, and dimethyl fumarate. Estimates were also >2 for alemtuzumab and other forms of heart disease, chronic kidney disease, hypertension, thyroid disorder, acute liver injury, dimethyl fumarate, and acute liver injury. For all others, estimates were <2. Summary measures for selection bias were calculated for events reaching significance according to recommendations.[32] All the summary measures for selection bias on the hazard ratios and their lower bounds exceeded 1, inferring that selection bias could not explain away our findings.
[a] Results were adjusted for sex, socioeconomic status (quintiles), and age (continuous) at the index date and Charlson comorbidity score (categorized as 0, 1, 2, or ≥3 and updated overtime).
[b] Findings from 4 Canadian provinces combined (British Columbia, Saskatchewan, Manitoba, Nova Scotia).
[c] Complementary analysis was conducted in British Columbia only.

second-generation DMD (by 11%; 95% CI 4%–17%), and for some individual DMDs, ranging from a 33% (95% CI 13%–58%) higher hazard for alemtuzumab to 10%–13% for dimethyl fumarate (95% CI 4%–18%) and fingolimod (95% CI 3%–25%). Only β-interferon was associated with a lower hazard in both health care settings, albeit only modestly for infection-related physician visits (aHR 0.94; 95% CI 0.90–0.99). No other infection-related findings were significant in either

health care setting. Crude rates of infection-related events for DMDs were highest for alemtuzumab in both settings and lowest for fingolimod (for hospitalizations) and teriflunomide (for physician visits) (Table 2).

Incident Adverse Events

For other incident adverse events, when all DMDs were grouped together, "any DMD" exposure (vs none or less than the defined minimum) was not associated with an increased hazard of adverse event (Figure, Table 2). Similarly, when the first-generation or second-generation DMDs were grouped together, there were no significant increases in the hazard ratios. However, significantly elevated hazards were observed for individual DMDs. Fingolimod was the only DMD associated with an increased hazard of ischemic heart disease (aHR 1.64; 95% CI 1.10–2.44; crude rate per 1,000 person-years [CR] 15.60) and cerebrovascular disease (aHR 2.04; 95% CI 1.27–3.30; CR 10.01). Only alemtuzumab was associated with a significantly higher hazard of chronic kidney disease (aHR 6.43; 95% CI 2.60–15.95; <6 cases), while teriflunomide was associated with a significantly higher hazard of chronic liver disease (aHR 1.94; 95% CI 1.19–3.18; CR 11.51) and hyperlipidemia (aHR 1.61; 95% CI 1.07–2.44; CR 23.92). Two DMDs were associated with significantly higher hazards of thyroid disorders, reaching an aHR of 19.42 (95% CI 9.29–36.51; CR 36.72) for alemtuzumab, followed by 2.30 (95% CI 1.11–4.74; CR 5.21) for teriflunomide. Both these DMDs were also associated with a higher hazard of hypertension, being 4.96 (95% CI 1.78–13.84; <6 cases) for alemtuzumab and 1.76 (95% CI 1.32–2.37; CR 42.50) for teriflunomide, followed by 1.73 (95% CI 1.30–2.31; CR 31.92) for fingolimod and 1.11 (95% CI 1.04–1.17; CR 30.39) for β-interferon. For other forms of heart disease, alemtuzumab (aHR 3.72; 95% CI 2.12–6.53; CR 58.92) and natalizumab (aHR 1.61; 95% CI 1.24–2.10; CR 26.42) were each associated with a significantly higher hazard. Both glatiramer acetate and natalizumab increased the hazard of a mental health condition by 1.16 (95% CI 1.07–1.26; CR 85.81) and 1.36 (95% CI 1.06–1.76; CR 100.59), respectively.

A few DMDs were associated with a lower hazard of an incident adverse event: Glatiramer acetate alone was associated with a lower hazard of hypertension (aHR 0.87; 95% CI 0.80–0.95; CR 25.36), while both glatiramer acetate (aHR 0.78; 95% CI 0.65–0.94; CR 4.61) and dimethyl fumarate (aHR 0.43; 95% CI 0.22–0.84; CR 2.51) were associated with lower hazard of cerebrovascular diseases. No significant differences were observed between individual DMDs (vs no DMD) and the hazard of autoimmune diseases, cancer, diabetes, or migraine (Table 2).

Complementary/Sensitivity Analyses

Current exposure to a DMD (vs no current exposure) was associated with a higher hazard of acute liver injury and abnormal hematologic findings, with most of the significant findings being for the second-generation DMDs (Table 2). For acute liver injury, although both alemtuzumab (aHR 16.18; 95% CI 2.11–123.89) and dimethyl fumarate (aHR 6.55; 95% CI 1.96–21.87) were each associated with a significantly higher hazard, only a few such cases occurred (<6 for either DMD) resulting in wide CIs. Abnormal hematologic findings were significant for alemtuzumab (aHR 2.38; 95% CI 1.28–4.46; CR 59.01), natalizumab (aHR 1.72; 95% CI 1.16–2.56; CR 39.45), followed by β-interferon (aHR 1.13; 95% CI 1.01–1.27; CR 24.94). Both the "intention-to-treat" and incident adverse events (assessed by using available case definitions) yielded results that were generally in the same direction as those from the main analyses (Table 3). For the sensitivity analyses, the E-values and summary measures for selection bias were calculated for events reaching significance (summarized in Table 2). The direction and magnitude of findings were similar between the unadjusted and adjusted models (Table 2) and the individual comorbidities as separate covariates and propensity score adjustment (Table 3).

This study provides Class III evidence that for patients with MS, while DMD exposure reduces the risk of infection-related hospitalizations, there are increased risks of infection-related physician visits and incident adverse events for select DMDs.

Discussion

In our population-based study comprising up to 86,894 person-years of DMD exposed follow-up, we examined the association between 7 different DMDs and a range of potential adverse events. Most of the significantly elevated safety signals involved a second-generation DMDs, with some of the largest estimated risks involving alemtuzumab, where the risk (aHR) of thyroid disorder was 19.42, followed by hypertension (4.96) and other forms of cardiovascular diseases (3.72), all relative to no or less than the defined minimum DMD exposure. Natalizumab was associated with an increased risk of cardiovascular diseases (1.61) and mental conditions (1.36). For the oral DMDs, most of the elevated risks were for fingolimod and teriflunomide; fingolimod was associated with a higher hazard of cerebrovascular disease, hypertension, and ischemic heart disease ranging from 1.64 to 2.04, while teriflunomide was associated with a higher hazard of thyroid disorders, chronic liver disease, hypertension, and hyperlipidemia ranging from 1.61 to 2.30. Reassuringly (and unaffected by any SARS-CoV-2 outbreaks), there were no increases in the risk of being hospitalized for an infection for any of the DMDs studied, and instead, a 42%–61% lower risk was observed across virtually all DMDs. By including a range of safety-related events that are not always feasible to examine in modestly sized, short-term clinical trials, our study provides an important comprehensive assessment of the safety profiles of the DMDs in the real-world setting.

Although the risk of an infection-related hospitalization was lower in those exposed to DMDs, findings were also suggestive of a possible general shift in the health care setting where some DMD-related infections were being managed. This was

Table 3 The Risk (Hazard) of Potential Adverse Events Associated With Disease-Modifying Drugs Used to Treat Multiple Sclerosis, British Columbia, Canada: Intention-to-Treat Analysis, Assessment of Incident Adverse Events Identified Using Available Case Definitions,[a] Sensitivity Analysis Using Each Individual Comorbidity (Captured in CCI) as Separate Covariates, and Using a Propensity Score Adjustment

	Adjusted hazard ratios (95% CI)			
Potential adverse event by DMD exposure	**Intention-to-treat analysis (DMD exposure defined as ≥1 d)[b]**	**Assessment of incident adverse events by using available case definitions[b]**	**Using each individual comorbidity (captured in CCI) as separate covariates[c]**	**Using propensity score adjustment[d] (for the any DMD exposure analysis)**
Recurrent events using the "current" DMD exposure approach				
Infection-related hospitalizations				
No DMD	N/A	N/A	Reference	Reference
Any DMD			**0.64 (0.56–0.73)**	**0.60 (0.53–0.69)**
First-generation DMD			**0.65 (0.56–0.75)**	
Second-generation DMD			**0.61 (0.46–0.80)**	
β-Interferon			**0.66 (0.56–0.77)**	
Glatiramer acetate			**0.61 (0.47–0.80)**	
Natalizumab			0.64 (0.40–1.02)	
Fingolimod			0.59 (0.32–1.07)	
Dimethyl fumarate			**0.46 (0.28–0.78)**	
Teriflunomide			0.69 (0.35–1.33)	
Alemtuzumab			1.28 (0.62–2.64)	
Infection-related physician visits				
No DMD	N/A	N/A	Reference	Reference
Any DMD			1.03 (0.99–1.07)	1.01 (0.97–1.05)
First-generation DMD			1.00 (0.97–1.04)	
Second-generation DMD			**1.16 (1.09–1.24)**	
β-Interferon			0.97 (0.93–1.01)	
Glatiramer acetate			**1.10 (1.03–1.18)**	
Natalizumab			**1.34 (1.14–1.56)**	
Fingolimod			1.11 (0.98–1.26)	
Dimethyl fumarate			**1.14 (1.03–1.26)**	
Teriflunomide			0.98 (0.86–1.12)	
Alemtuzumab			**1.40 (1.15–1.70)**	
Incident adverse event using the "minimum" cumulative DMD approach				
Autoimmune diseases				
No DMD	Reference	N/A	Reference	Reference
Any DMD	0.98 (0.92–1.04)		0.99 (0.93–1.06)	0.97 (0.91–1.04)
First-generation DMD	0.97 (0.91–1.04)		1.00 (0.93–1.07)	
Second-generation DMD	1.03 (0.88–1.22)		1.03 (0.86–1.24)	
β-Interferon	0.98 (0.92–1.05)		0.99 (0.92–1.07)	

Continued

Table 3 The Risk (Hazard) of Potential Adverse Events Associated With Disease-Modifying Drugs Used to Treat Multiple Sclerosis, British Columbia, Canada: Intention-to-Treat Analysis, Assessment of Incident Adverse Events Identified Using Available Case Definitions,[a] Sensitivity Analysis Using Each Individual Comorbidity (Captured in CCI) as Separate Covariates, and Using a Propensity Score Adjustment *(continued)*

	Adjusted hazard ratios (95% CI)			
Potential adverse event by DMD exposure	**Intention-to-treat analysis (DMD exposure defined as ≥1 d)[b]**	**Assessment of incident adverse events by using available case definitions[b]**	**Using each individual comorbidity (captured in CCI) as separate covariates[c]**	**Using propensity score adjustment[d] (for the any DMD exposure analysis)**
Glatiramer acetate	1.06 (0.95–1.17)		1.08 (0.96–1.22)	
Natalizumab	1.15 (0.86–1.53)		1.15 (0.84–1.59)	
Fingolimod	1.28 (0.95–1.73)		1.26 (0.92–1.73)	
Dimethyl fumarate	0.90 (0.69–1.16)		0.77 (0.56–1.07)	
Teriflunomide	0.89 (0.61–1.30)		1.04 (0.69–1.57)	
Alemtuzumab	1.12 (0.60–2.09)		1.36 (0.73–2.56)	
Cancer				
No DMD	Reference	**N/A**	Reference	Reference
Any DMD	0.94 (0.87–1.03)		0.95 (0.87–1.04)	0.94 (0.86–1.03)
First-generation DMD	0.92 (0.84–1.01)		0.93 (0.85–1.03)	
Second-generation DMD	1.22 (1.00–1.49)		1.15 (0.92–1.44)	
β-Interferon	0.91 (0.83–1.00)		0.93 (0.84–1.03)	
Glatiramer acetate	1.13 (0.98–1.30)		1.02 (0.87–1.21)	
Natalizumab	1.06 (0.73–1.53)		1.17 (0.79–1.72)	
Fingolimod	1.28 (0.88–1.87)		1.30 (0.87–1.95)	
Dimethyl fumarate	1.17 (0.85–1.59)		1.08 (0.75–1.56)	
Teriflunomide	1.16 (0.76–1.78)		1.00 (0.59–1.69)	
Alemtuzumab	1.41 (0.66–2.99)		1.46 (0.65–3.29)	
Cardiovascular disorders (ischemic heart disease)				
No DMD	Reference	Reference	Reference	Reference
Any DMD	1.03 (0.94–1.14)	1.06 (0.92–1.22)	1.05 (0.95–1.16)	1.03 (0.93–1.14)
First-generation DMD	1.00 (0.90–1.10)	1.04 (0.90–1.21)	1.02 (0.92–1.13)	
Second-generation DMD	**1.47 (1.18–1.83)**	1.32 (0.89–1.95)	**1.33 (1.03–1.70)**	
β-Interferon	0.97 (0.88–1.08)	1.04 (0.89–1.22)	1.02 (0.91–1.14)	
Glatiramer acetate	**1.17 (1.01–1.37)**	1.18 (0.90–1.54)	1.10 (0.92–1.32)	
Natalizumab	1.28 (0.87–1.88)	0.73 (0.32–1.66)	1.01 (0.63–1.61)	
Fingolimod	**1.56 (1.02–2.38)**	1.59 (0.78–3.24)	**1.76 (1.13–2.74)**	
Dimethyl fumarate	1.24 (0.87–1.77)	1.48 (0.81–2.72)	1.03 (0.66–1.61)	
Teriflunomide	1.01 (0.58–1.75)	0.81 (0.26–2.53)	1.19 (0.66–2.17)	
Alemtuzumab	1.13 (0.42–3.04)	1.12 (0.16–8.10)	1.15 (0.37–3.59)	
Cardiovascular disorders (other forms of heart disease)				
No DMD	Reference	N/A	Reference	Reference

Continued

Table 3 The Risk (Hazard) of Potential Adverse Events Associated With Disease-Modifying Drugs Used to Treat Multiple Sclerosis, British Columbia, Canada: Intention-to-Treat Analysis, Assessment of Incident Adverse Events Identified Using Available Case Definitions,[a] Sensitivity Analysis Using Each Individual Comorbidity (Captured in CCI) as Separate Covariates, and Using a Propensity Score Adjustment *(continued)*

	Adjusted hazard ratios (95% CI)			
Potential adverse event by DMD exposure	**Intention-to-treat analysis (DMD exposure defined as ≥1 d)[b]**	**Assessment of incident adverse events by using available case definitions[b]**	**Using each individual comorbidity (captured in CCI) as separate covariates[c]**	**Using propensity score adjustment[d] (for the any DMD exposure analysis)**
Any DMD	1.07 (0.99–1.16)		1.07 (0.99–1.16)	1.02 (0.94–1.11)
First-generation DMD	1.01 (0.93–1.10)		1.01 (0.92–1.10)	
Second-generation DMD	**1.59 (1.33–1.90)**		**1.60 (1.32–1.95)**	
β-Interferon	0.98 (0.90–1.07)		1.01 (0.92–1.11)	
Glatiramer acetate	**1.18 (1.04–1.34)**		1.16 (1.00–1.35)	
Natalizumab	**1.55 (1.14–2.10)**		**1.43 (1.02–2.02)**	
Fingolimod	1.02 (0.68–1.53)		0.84 (0.52–1.36)	
Dimethyl fumarate	1.09 (0.80–1.47)		1.28 (0.92–1.78)	
Teriflunomide	**1.54 (1.06–2.24)**		**1.69 (1.12–2.57)**	
Alemtuzumab	**3.20 (1.88–5.43)**		**3.88 (2.21–6.82)**	
Cerebrovascular diseases				
No DMD	Reference	Reference	Reference	Reference
Any DMD	**0.82 (0.73–0.93)**	**0.62 (0.43–0.89)**	**0.83 (0.73–0.95)**	**0.80 (0.70–0.91)**
First-generation DMD	**0.80 (0.71–0.91)**	**0.61 (0.42–0.88)**	**0.84 (0.73–0.95)**	
Second-generation DMD	1.19 (0.88–1.60)	1.34 (0.54–3.35)	1.08 (0.76–1.51)	
β-Interferon	0.89 (0.78–1.02)	0.72 (0.49–1.04)	0.90 (0.79–1.04)	
Glatiramer acetate	**0.75 (0.60–0.94)**	0.52 (0.23–1.18)	**0.75 (0.58–0.97)**	
Natalizumab	1.04 (0.59–1.82)	2.30 (0.70–7.56)	1.13 (0.63–2.01)	
Fingolimod	**1.94 (1.16–3.22)**	0.86 (0.11–6.60)	**2.22 (1.34–3.68)**	
Dimethyl fumarate	0.63 (0.34–1.15)	1.30 (0.31–5.40)	0.47 (0.21–1.05)	
Teriflunomide	1.62 (0.91–2.89)	1.30 (0.18–9.42)	1.19 (0.56–2.51)	
Alemtuzumab	0.93 (0.23–3.79)	5.45 (0.70–42.41)	0.55 (0.08–3.92)	
Chronic liver diseases				
No DMD	Reference	N/A	Reference	Reference
Any DMD	1.05 (0.91–1.20)		1.00 (0.86–1.16)	0.96 (0.83–1.11)
First-generation DMD	1.07 (0.93–1.22)		1.00 (0.86–1.17)	
Second-generation DMD	0.91 (0.64–1.30)		1.01 (0.69–1.47)	
β-Interferon	1.11 (0.95–1.28)		1.05 (0.89–1.23)	
Glatiramer acetate	1.00 (0.80–1.26)		1.02 (0.78–1.33)	
Natalizumab	0.56 (0.26–1.19)		0.61 (0.27–1.38)	
Fingolimod	**1.98 (1.19–3.31)**		**2.17 (1.28–3.68)**	
Dimethyl fumarate	0.86 (0.49–1.50)		0.82 (0.42–1.60)	
Teriflunomide	1.12 (0.53–2.38)		1.37 (0.61–3.07)	

Continued

Table 3 The Risk (Hazard) of Potential Adverse Events Associated With Disease-Modifying Drugs Used to Treat Multiple Sclerosis, British Columbia, Canada: Intention-to-Treat Analysis, Assessment of Incident Adverse Events Identified Using Available Case Definitions,[a] Sensitivity Analysis Using Each Individual Comorbidity (Captured in CCI) as Separate Covariates, and Using a Propensity Score Adjustment *(continued)*

	Adjusted hazard ratios (95% CI)			
Potential adverse event by DMD exposure	**Intention-to-treat analysis (DMD exposure defined as ≥1 d)[b]**	**Assessment of incident adverse events by using available case definitions[b]**	**Using each individual comorbidity (captured in CCI) as separate covariates[c]**	**Using propensity score adjustment[d] (for the any DMD exposure analysis)**
Alemtuzumab	1.06 (0.26–4.30)		1.31 (0.32–5.30)	
Chronic kidney diseases				
No DMD	Reference	Reference	Reference	Reference
Any DMD	0.93 (0.80–1.08)	0.86 (0.68–1.08)	0.96 (0.82–1.12)	0.93 (0.80–1.09)
First-generation DMD	0.96 (0.82–1.12)	0.89 (0.70–1.13)	0.98 (0.83–1.16)	
Second-generation DMD	0.88 (0.58–1.35)	0.83 (0.41–1.71)	1.00 (0.65–1.55)	
β-Interferon	1.01 (0.85–1.19)	0.91 (0.71–1.17)	1.03 (0.87–1.23)	
Glatiramer acetate	1.07 (0.83–1.38)	1.09 (0.71–1.67)	1.06 (0.80–1.42)	
Natalizumab	0.91 (0.44–1.85)	0.56 (0.14–2.31)	0.82 (0.36–1.87)	
Fingolimod	0.78 (0.32–1.91)	0.38 (0.05–2.79)	0.86 (0.35–2.11)	
Dimethyl fumarate	0.64 (0.30–1.36)	0.28 (0.04–2.00)	0.47 (0.18–1.28)	
Teriflunomide	0.92 (0.38–2.25)	1.85 (0.59–5.84)	1.19 (0.49–2.88)	
Alemtuzumab	**5.54 (2.22–13.81)**	**10.04 (3.10–32.50)**	**6.65 (2.69–16.44)**	
Diabetes				
No DMD	Reference	Reference	Reference	Reference
Any DMD	1.01 (0.90–1.12)	1.04 (0.89–1.20)	1.01 (0.90–1.12)	0.99 (0.88–1.11)
First-generation DMD	1.01 (0.91–1.13)	1.03 (0.89–1.20)	0.99 (0.88–1.11)	
Second-generation DMD	0.90 (0.66–1.23)	1.15 (0.76–1.75)	1.03 (0.74–1.42)	
β-Interferon	0.96 (0.86–1.08)	0.98 (0.83–1.16)	0.98 (0.87–1.11)	
Glatiramer acetate	1.11 (0.93–1.32)	1.22 (0.94–1.59)	1.05 (0.86–1.29)	
Natalizumab	0.98 (0.58–1.64)	0.89 (0.42–1.90)	0.83 (0.46–1.52)	
Fingolimod	1.47 (0.87–2.48)	**2.10 (1.11–3.98)**	1.59 (0.93–2.72)	
Dimethyl fumarate	0.83 (0.49–1.39)	1.12 (0.55–2.28)	0.97 (0.56–1.70)	
Teriflunomide	0.61 (0.25–1.49)	0.58 (0.15–2.36)	0.81 (0.34–1.97)	
Alemtuzumab	0.43 (0.06–3.05)	N/A	0.51 (0.07–3.67)	
Hyperlipidemia				
No DMD	Reference	Reference	Reference	Reference
Any DMD	**0.89 (0.81–0.98)**	0.93 (0.80–1.07)	0.92 (0.84–1.02)	0.96 (0.87–1.05)
First-generation DMD	0.91 (0.83–1.00)	0.93 (0.80–1.09)	0.94 (0.85–1.04)	
Second-generation DMD	0.89 (0.68–1.16)	0.95 (0.59–1.53)	0.87 (0.65–1.16)	
β-Interferon	**0.88 (0.79–0.97)**	0.92 (0.78–1.08)	0.92 (0.83–1.03)	
Glatiramer acetate	1.04 (0.89–1.21)	0.93 (0.70–1.25)	1.01 (0.84–1.20)	
Natalizumab	0.92 (0.58–1.46)	0.70 (0.29–1.71)	0.86 (0.52–1.45)	

Continued

Table 3 The Risk (Hazard) of Potential Adverse Events Associated With Disease-Modifying Drugs Used to Treat Multiple Sclerosis, British Columbia, Canada: Intention-to-Treat Analysis, Assessment of Incident Adverse Events Identified Using Available Case Definitions,[a] Sensitivity Analysis Using Each Individual Comorbidity (Captured in CCI) as Separate Covariates, and Using a Propensity Score Adjustment *(continued)*

	Adjusted hazard ratios (95% CI)			
Potential adverse event by DMD exposure	**Intention-to-treat analysis (DMD exposure defined as ≥1 d)[b]**	**Assessment of incident adverse events by using available case definitions[b]**	**Using each individual comorbidity (captured in CCI) as separate covariates[c]**	**Using propensity score adjustment[d] (for the any DMD exposure analysis)**
Fingolimod	1.11 (0.67–1.83)	1.36 (0.60–3.09)	1.18 (0.70–1.98)	
Dimethyl fumarate	0.80 (0.51–1.24)	1.03 (0.45–2.33)	0.65 (0.38–1.14)	
Teriflunomide	0.99 (0.54–1.81)	0.38 (0.05–2.69)	1.20 (0.64–2.24)	
Alemtuzumab	0.61 (0.15–2.46)	1.35 (0.19–9.76)	0.36 (0.05–2.57)	
Hypertension				
No DMD	Reference	Reference	Reference	Reference
Any DMD	1.01 (0.94–1.09)	1.06 (0.97–1.17)	1.02 (0.94–1.11)	1.04 (0.96–1.13)
First-generation DMD	1.01 (0.93–1.09)	1.06 (0.96–1.18)	1.01 (0.93–1.10)	
Second-generation DMD	1.10 (0.88–1.37)	1.13 (0.84–1.51)	1.20 (0.95–1.52)	
β-Interferon	1.04 (0.96–1.14)	**1.15 (1.04–1.28)**	1.07 (0.98–1.17)	
Glatiramer acetate	0.87 (0.75–1.00)	0.76 (0.61–0.94)	0.88 (0.75–1.04)	
Natalizumab	1.00 (0.69–1.47)	0.72 (0.41–1.29)	0.78 (0.49–1.23)	
Fingolimod	**1.95 (1.35–2.81)**	**2.11 (1.33–3.35)**	**2.01 (1.37–2.94)**	
Dimethyl fumarate	0.63 (0.41–0.99)	0.73 (0.40–1.32)	0.74 (0.46–1.21)	
Teriflunomide	**1.78 (1.18–2.68)**	**2.32 (1.38–3.89)**	**2.03 (1.31–3.14)**	
Alemtuzumab	N/A	N/A	N/A	
Mental conditions (anxiety, depression, bipolar disorders)				
No DMD	Reference	Reference	Reference	Reference
Any DMD	**1.11 (1.04–1.18)**	**1.16 (1.06–1.26)**	1.04 (0.96–1.12)	1.01 (0.93–1.09)
First-generation DMD	**1.10 (1.03–1.18)**	**1.15 (1.05–1.26)**	1.03 (0.95–1.11)	
Second-generation DMD	1.05 (0.88–1.26)	1.03 (0.81–1.30)	1.06 (0.87–1.30)	
β-Interferon	**1.09 (1.02–1.18)**	**1.14 (1.04–1.25)**	1.02 (0.93–1.11)	
Glatiramer acetate	**1.16 (1.03–1.30)**	1.12 (0.95–1.33)	1.14 (0.99–1.32)	
Natalizumab	**1.42 (1.02–1.99)**	**1.52 (1.03–2.24)**	1.39 (0.95–2.03)	
Fingolimod	0.75 (0.50–1.13)	0.60 (0.35–1.04)	0.88 (0.58–1.33)	
Dimethyl fumarate	1.02 (0.78–1.33)	1.05 (0.72–1.54)	0.97 (0.70–1.33)	
Teriflunomide	0.97 (0.63–1.48)	1.17 (0.66–2.08)	1.00 (0.60–1.66)	
Alemtuzumab	1.14 (0.61–2.13)	0.65 (0.21–2.04)	1.04 (0.49–2.20)	
Migraine				
No DMD	Reference	Reference	Reference	Reference
Any DMD	0.98 (0.89–1.08)	1.10 (0.94–1.28)	0.99 (0.89–1.11)	0.96 (0.86–1.07)
First-generation DMD	1.02 (0.92–1.12)	1.10 (0.94–1.29)	1.01 (0.90–1.13)	
Second-generation DMD	0.85 (0.65–1.12)	1.19 (0.82–1.71)	0.93 (0.70–1.25)	

Continued

Table 3 The Risk (Hazard) of Potential Adverse Events Associated With Disease-Modifying Drugs Used to Treat Multiple Sclerosis, British Columbia, Canada: Intention-to-Treat Analysis, Assessment of Incident Adverse Events Identified Using Available Case Definitions,[a] Sensitivity Analysis Using Each Individual Comorbidity (Captured in CCI) as Separate Covariates, and Using a Propensity Score Adjustment *(continued)*

	Adjusted hazard ratios (95% CI)			
Potential adverse event by DMD exposure	**Intention-to-treat analysis (DMD exposure defined as ≥1 d)[b]**	**Assessment of incident adverse events by using available case definitions[b]**	**Using each individual comorbidity (captured in CCI) as separate covariates[c]**	**Using propensity score adjustment[d] (for the any DMD exposure analysis)**
β-Interferon	1.07 (0.96–1.19)	**1.20 (1.02–1.42)**	1.07 (0.95–1.21)	
Glatiramer acetate	1.02 (0.87–1.20)	0.94 (0.71–1.25)	0.93 (0.76–1.14)	
Natalizumab	0.73 (0.43–1.25)	1.17 (0.62–2.22)	0.87 (0.50–1.51)	
Fingolimod	1.14 (0.71–1.83)	**1.83 (1.06–3.17)**	1.12 (0.67–1.88)	
Dimethyl fumarate	0.92 (0.61–1.38)	0.87 (0.44–1.70)	0.89 (0.55–1.45)	
Teriflunomide	0.89 (0.48–1.67)	1.25 (0.51–3.03)	1.04 (0.51–2.09)	
Alemtuzumab	0.95 (0.35–2.56)	0.92 (0.23–3.74)	0.56 (0.14–2.27)	
Thyroid disorders (autoimmune hypothyroidism and hyperthyroidism)				
No DMD	Reference	Reference	Reference	Reference
Any DMD	0.95 (0.77–1.18)	1.11 (0.82–1.49)	1.00 (0.80–1.26)	0.97 (0.77–1.22)
First-generation DMD	0.93 (0.74–1.16)	0.94 (0.68–1.30)	0.92 (0.73–1.17)	
Second-generation DMD	1.13 (0.66–1.96)	**1.91 (1.02–3.57)**	1.39 (0.81–2.40)	
β-Interferon	1.01 (0.80–1.28)	1.02 (0.72–1.43)	0.95 (0.73–1.22)	
Glatiramer acetate	0.82 (0.56–1.20)	0.93 (0.52–1.64)	1.04 (0.69–1.57)	
Natalizumab	0.56 (0.17–1.83)	0.70 (0.16–2.93)	0.67 (0.21–2.17)	
Fingolimod	0.47 (0.11–1.94)	0.73 (0.17–3.09)	0.50 (0.12–2.05)	
Dimethyl fumarate	0.67 (0.24–1.84)	0.71 (0.17–2.95)	0.68 (0.21–2.17)	
Teriflunomide	0.60 (0.14–2.50)	1.57 (0.37–6.57)	0.97 (0.24–4.00)	
Alemtuzumab	**18.47 (8.86–38.51)**	**23.62 (10.10–55.22)**	**19.31 (9.36–39.83)**	
Incident adverse event using the "current" DMD exposure approach				
Acute liver injury				
No DMD	N/A	N/A	Reference	Reference
Any DMD			0.75 (0.39–1.44)	0.80 (0.41–1.54)
First-generation DMD			0.43 (0.17–1.06)	
Second-generation DMD			**3.01 (1.16–7.83)**	
β-Interferon			**0.24 (0.06–0.99)**	
Glatiramer acetate			0.89 (0.28–2.84)	
Natalizumab			NR	
Fingolimod			2.53 (0.34–18.72)	
Dimethyl fumarate			**6.26 (1.86–21.03)**	
Teriflunomide			NR	
Alemtuzumab			**16.59 (2.14–128.48)**	

Continued

Table 3 The Risk (Hazard) of Potential Adverse Events Associated With Disease-Modifying Drugs Used to Treat Multiple Sclerosis, British Columbia, Canada: Intention-to-Treat Analysis, Assessment of Incident Adverse Events Identified Using Available Case Definitions,[a] Sensitivity Analysis Using Each Individual Comorbidity (Captured in CCI) as Separate Covariates, and Using a Propensity Score Adjustment *(continued)*

	Adjusted hazard ratios (95% CI)			
Potential adverse event by DMD exposure	**Intention-to-treat analysis (DMD exposure defined as ≥1 d)[b]**	**Assessment of incident adverse events by using available case definitions[b]**	**Using each individual comorbidity (captured in CCI) as separate covariates[c]**	**Using propensity score adjustment[d] (for the any DMD exposure analysis)**
Abnormal hematologic findings				
No DMD	N/A	N/A	Reference	Reference
Any DMD			**1.14 (1.04–1.25)**	**1.11 (1.01–1.22)**
First-generation DMD			1.08 (0.97–1.19)	
Second-generation DMD			**1.49 (1.22–1.81)**	
β-Interferon			**1.13 (1.01–1.27)**	
Glatiramer acetate			0.95 (0.78–1.15)	
Natalizumab			**1.69 (1.14–2.52)**	
Fingolimod			1.32 (0.87–2.00)	
Dimethyl fumarate			1.40 (1.00–1.97)	
Teriflunomide			1.33 (0.82–2.14)	
Alemtuzumab			**2.41 (1.29–4.50)**	

Abbreviations: CCI = Charlson Comorbidity Index; DMD = disease-modifying drug; N/A = not applicable.
Bold indicates $p < 0.05$.
[a] Case definitions used are presented in eTable 3 (links.lww.com/WNL/D339).
[b] Results were adjusted for sex, socioeconomic status (quintiles), and age (continuous) at the index date and Charlson comorbidity score (categorized as 0, 1, 2, or ≥3 and updated overtime).
[c] Results were adjusted for sex, socioeconomic status (quintiles), age (continuous) at the index date, and individual comorbidity (captured in CCI) as separate covariates and updated over time.
[d] Propensity scores for DMD exposure status (never vs ever) for each outcome were generated separately using logistic regression and included sex, socioeconomic status (quintiles), individual comorbidities (captured in CCI), calendar year, and age (modeled with a cubic spline) at the index date. The generated propensity scores were adjusted in the model as a covariate.

evidenced by a higher hazard of infection-related physician visits for 3 of the DMDs—dimethyl fumarate, fingolimod, and alemtuzumab, ranging from 10% to 33%. It is also possible that infections may be less severe in nature due to prophylactic use of anti-infective agents, screening and vaccination before the initiation of some DMDs,[34] with each health care setting acting as a proxy of severity (hospitalizations representing the most severe). These findings were generally consistent with our prior, smaller single province study which had been limited by the lack of widespread use of the second-generation DMDs in the timeframe examined.[24] By including a much larger multiregional cohort and by accessing more contemporaneous data, we have substantially advanced those findings, including individual assessments of more second-generation DMDs. A nationwide Swedish study of 6,421 patients with MS took a different approach, comparing the risk of first infection-related hospitalization vs the general population. They observed that the risk was highest for rituximab (where unlike Canada, its off-label use for MS was common) and lowest for β-interferon and glatiramer acetate.[35] Of interest, no other comparisons were made and only the first infection was assessed, whereas we were able to examine all infection-related hospitalizations and physician visits.

We found a limited number of studies with which to compare our other findings. One Italian study analyzed 13,880 physician-reported MS DMD-related adverse reactions to the National Pharmacovigilance Database (2002–2020).[36] Although these voluntarily reporting systems can provide important safety signals, a systematic review found that most serious or severe adverse events (95%) are never reported.[37] Nonetheless, although most of the Italian findings were consistent with the literature, we were able to confirm some of the unexpected signals identified, including, for example, the risk of thyroid disorders for teriflunomide which was significantly elevated in our population-based study.[36] Reassuringly, the higher potential risk of dyslipidemia for fingolimod, natalizumab, and β-interferon reported in the Italian study was not observed in our study.[36]

Other adverse events associated with teriflunomide in our study were chronic liver disease, hyperlipidemia, and hypertension. While the former 2 were not reported in the pivotal

RCTs, drug-induced liver injury was identified in the US Food and Drug Administration (FDA)'s Adverse Event Reporting System database (2004–2016; adjusted reporting odds ratios >2).[38] Cases were also found in a prospective observational study of 1,128 MS persons treated with teriflunomide in Germany (7 cases, including 4 discontinuing drug due to elevated transaminases).[11] Hypertension was previously identified, with 4% of persons randomized to teriflunomide and 2% to placebo reported with this adverse event in the product monograph.[29] While our observed increased risk of hyperlipidemia (primarily associated with teriflunomide) may seem unexpected, the crude event rate was similar to that occurring with no DMD use (23.92 vs 22.94/1,000 person-years). Thus, while clinicians should remain aware, there is currently insufficient information to recommend routine screening of lipid profiles in people receiving teriflunomide.[39]

For dimethyl fumarate, our complementary analyses found a higher hazard of acute liver injury (by 6.55), although there were few (<6) cases contributing to this observation resulting in wide CIs. Nonetheless, our findings are consistent with an FDA report aimed at alerting health care professionals of clinically significant drug-induced liver injury (14 cases were identified postmarketing in their Adverse Event Reporting System database [March 2013–February 2016])[40] and the recommendation for regular biochemical test monitoring.[28] Thus our study is among the first to quantify many of these risks in a real-world setting.

For fingolimod, we observed a higher hazard of 3 circulatory system disorders (hypertension, ischemic heart disease, and cerebrovascular disease). These observations are consistent with fingolimod's effect as a sphingosine-1-phosphate receptor modulator; downregulation of this receptor on endothelial cells likely leads to the increase in blood pressure, necessitating first dose-related monitoring.[41] Hypertension is also a risk factor for ischemic heart and cerebrovascular diseases. Although a small number of cerebrovascular events (stroke) were reported in clinical trials and in the postmarketing setting,[27] we were unable to find any population-based studies examining and quantifying these broader or longer-term effects of fingolimod. Our findings, along with others,[42] underscore the ongoing need for regular cardiovascular-related assessments before and after fingolimod initiation.

For the second-generation DMDs administered by intravenous infusion, alemtuzumab was associated with some of the highest hazards. Among those identified (thyroid disorder, hypertension, and other cardiovascular disorders), thyroid disorders are the most widely established as a known risk.[43] Others have reported significant increases in blood pressure during an alemtuzumab infusion in a small group of 31 people with MS,[44] and cases of cardiovascular issues have been reported in the postmarketing setting.[45] Although routine thyroid function testing (before initiation of alemtuzumab and every 3 months thereafter) is recommended,[30] clinicians may wish to consider assessing risk factors for heart diseases, particularly given our observed high crude rate of cardiovascular disorders associated with alemtuzumab (58.92/1,000 person-years) relative to no DMD (25.55). However, the burden of additional testing should also be considered. For natalizumab, although we observed a higher risk (hazard) of mental conditions, a 2018 systematic review of clinical trials and observational studies did not.[46] However, a small percentage (1.1%) of psychiatric disorders were identified as serious adverse events in the manufacturers' postmarketing study of natalizumab comprising 6,148 patients with MS.[8] Finally, in the complementary analysis, both alemtuzumab and natalizumab were each associated with a higher hazard of abnormal hematologic findings which is consistent with their therapeutic effects; alemtuzumab causes rapid depletion of circulating lymphocytes and can induce autoantibodies (increasing the risk of hematologic conditions, including the rare but serious, immune thrombocytopenic purpura),[30,47] and natalizumab can elevate white blood cell counts through inhibition of leukocytes adhesion to endothelial cells.[26] The high alemtuzumab-associated crude rate of abnormal hematologic findings (59.0/1,000 persons-years) vs no DMD (26.87) may also reflect, in part, the intensive (monthly) safety-related laboratory testing required.[30] Although a higher hazard of hematologic findings was also found for the 3 oral DMDs, the results did not reach statistical significance for these smaller subgroups. It is possible that hematologic findings associated with fingolimod, for example, might not be recorded or coded as abnormal as lymphopenia is thought to contribute to its therapeutic effects.[27]

For the first-generation DMDs, a previous smaller study from our group also found a higher risk of abnormal hematologic findings, although that study only evaluated β-interferon and in 1 region (British Columbia).[7] Nonetheless, this elevated risk was also shown in a meta-analysis of 9 RCTs of β-interferon (vs placebo), with leukopenia and lymphopenia explicitly identified.[48] Our prior smaller study found a higher risk of stroke,[7] which we did not observe in the current larger study with longer follow-up, at least when evaluating the more comprehensive, broader group of cerebrovascular diseases. However, in our larger current study, we did find an increased risk of hypertension, a risk factor for stroke. We were also able to examine glatiramer acetate, the other first-generation DMD, in our current study. As with β-interferon, most of the safety signals associated with glatiramer acetate were relatively modest in magnitude, and some events (cerebrovascular disease and hypertension) were actually lower as compared with no or minimal DMD exposure. A modestly higher hazard of mental conditions was found which concurs with the modestly higher prevalence of psychiatric disorders reported across 4 of the pivotal RCTs for glatiramer acetate.[25]

Finally, no significant differences were observed between individual DMDs (vs no DMD) and the hazard of several other events, including cancer. Nonetheless, there remains a need for further study, especially for cancer risk, particularly as newer DMDs are used more frequently, and over extended periods in clinical practice.

The use of ICD codes to identify a range of conditions as a proxy for safety-related events has limitations, including possible underestimation or overestimation. However, the direction of findings from the complementary analyses (using case definitions) was generally consistent with the main findings. It is also possible that persons taking DMDs may visit clinicians more frequently, increasing the detection of adverse events or comorbidities (surveillance bias). Nonetheless, our previous study showed that treatment with DMD (vs no DMD) was not associated with substantial differences in physician visit rates.[20] While a person stopping a DMD due to an adverse event or lack of response before they reached the definition of "exposed" would have been assigned to the "unexposed" group, our intention-to-treat analyses yielded results generally in the same direction as those from the main analyses. Furthermore, the sample size for the newer MS DMDs approved more recently may be insufficient to detect some rare adverse events. Although findings reached significance for some individual DMDs for specific adverse events, only a few such cases occurred (<6) resulting in wide CIs. The direction and magnitude of findings were largely similar between the unadjusted and adjusted models that accounted for several important characteristics including sex, age, SES, and comorbidity using a validated index, by including the individual CCI comorbidities as separate covariates, and by using propensity score adjustment. However, other relevant factors, including MS disease course and duration, are not captured in administrative data. Although no gold standard comorbidity indices exist, others have been developed using primary care, hospital, or prescription data.[49,50] Each may capture a different dimension of comorbidity worthy of future consideration.[49,50] Residual indication bias may remain, for example, if the presence of specific comorbidities precludes the use of some DMDs. The summary measures showed that the magnitude of selection bias was unlikely to explain away findings. Our estimated E-values indicated that the associations between most DMDs and infection-related hospitalizations and alemtuzumab (for most events) and dimethyl fumarate (liver injury) were unlikely to be explained by unobserved confounders (E-values and CI limits >2). However, other results might be less robust. Although the universal health care setting allowed us to capture data on all MS DMD prescriptions filled and medically necessary hospital and physician services, the generalizability of our results to other health care system with different insurance coverage should be explored. Finally, generalizability of our findings would not be affected by any Canada-specific initiatives related to screening for comorbidities or drug-related complications in MS, although naturally, and similar to other regions worldwide, physicians were free to develop local protocols or practices.

Our study provides an extensive safety profile of 7 different MS DMDs in the real-world setting. Adverse events can have major impacts on both patients and the health care system. Our findings not only complement those observed in short-term clinical trials but also provide new insights that help inform the risk-benefit profile of the DMDs used for treating MS in clinical practice. Our study highlights the continued need for long-term, independent safety studies of the MS DMDs.

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Feng Zhu, MSc	University of British Columbia, Vancouver, Canada	Obtained funding, conceptualized and designed the study, performed data analysis, interpreted the results, and revised the manuscript for intellectual content

Continued

Appendix *(continued)*

Name	Location	Contribution
Yinshan Zhao, PhD	University of British Columbia, Vancouver, Canada	Obtained funding, conceptualized and designed the study, interpreted the results, and revised the manuscript for intellectual content
Shenzhen Yao, PhD	University of Saskatchewan, and Saskatchewan Health Quality Council, Saskatoon, Canada	Performed data analysis and revised the manuscript for intellectual content
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Ruth Ann Marrie, MD, PhD	University of Manitoba, Winnipeg, Canada	Obtained funding and data, conceptualized and designed the study, interpreted the results, and revised the manuscript for intellectual content
Helen Tremlett, PhD	University of British Columbia, Vancouver, Canada	Obtained funding and data, conceptualized and designed the study, interpreted the results, and drafted and revised the manuscript for intellectual content

References

1. Lucchetta RC, Leonart LP, Becker J, Pontarolo R, Fernandez-Llimós F, Wiens A. Safety outcomes of disease-modifying therapies for relapsing-remitting multiple sclerosis: a network meta-analysis. *Mult Scler Relat Disord*. 2019;35:7-15. doi:10.1016/j.msard.2019.06.036
2. Ng HS, Rosenbult CL, Tremlett H. Safety profile of ocrelizumab for the treatment of multiple sclerosis: a systematic review. *Expert Opin Drug Saf*. 2020;19(9):1069-1094. doi:10.1080/14740338.2020.1807002
3. Liang G, Chai J, Ng HS, Tremlett H. Safety of dimethyl fumarate for multiple sclerosis: a systematic review and meta-analysis. *Mult Scler Relat Disord*. 2020;46:102566. doi:10.1016/j.msard.2020.102566
4. Tramacere I, Del Giovane C, Salanti G, D'Amico R, Filippini G. Immunomodulators and immunosuppressants for relapsing-remitting multiple sclerosis: a network meta-analysis. *Cochrane Database Syst Rev*. 2015;2015(9):CD011381. doi:10.1002/14651858.CD011381.pub2
5. Marrie RA, Miller A, Sormani MP, et al. The challenge of comorbidity in clinical trials for multiple sclerosis. *Neurology*. 2016;86(15):1437-1445. doi:10.1212/WNL.0000000000002471
6. U.S. Food and Drug Administration. Preventable adverse drug reactions: a focus on drug interactions. 2018. Accessed November 14, 2022. fda.gov/drugs/drug-interactions-labeling/preventable-adverse-drug-reactions-focus-drug-interactions.
7. de Jong HJI, Kingwell E, Shirani A, et al. Evaluating the safety of β-interferons in MS: a series of nested case-control studies. *Neurology*. 2017;88(24):2310-2320. doi:10.1212/WNL.0000000000004037
8. Butzkueven H, Kappos L, Wiendl H, et al. Long-term safety and effectiveness of natalizumab treatment in clinical practice: 10 years of real-world data from the Tysabri Observational Program (TOP). *J Neurol Neurosurg Psychiatry*. 2020;91(6):660-668. doi:10.1136/jnnp-2019-322326
9. Lebrun-Frenay C, Moulignier A, Pierrot-Deseilligny C, et al. Five-year outcome in the copaxone observatory: a nationwide cohort of patients with multiple sclerosis starting treatment with glatiramer acetate in France. *J Neurol*. 2019;266(4):888-901. doi:10.1007/s00415-019-09211-5
10. Biernacki T, Sandi D, Füvesi J, et al. The safety and efficacy of fingolimod: real-world data from a long-term, non-interventional study on the treatment of RRMS patients spanning up to 5 years from Hungary. *PLoS One*. 2022;17(4):e0267346. doi:10.1371/journal.pone.0267346
11. Kallmann BA, Tiel-Wilck K, Kullmann JS, Engelmann U, Chan A. Real-life outcomes of teriflunomide treatment in patients with relapsing multiple sclerosis: TAURUS-MS observational study. *Ther Adv Neurol Disord*. 2019;12:1756286419835077. doi:10.1177/1756286419835077
12. Lebrun C, Rocher F. Cancer risk in patients with multiple sclerosis: potential impact of disease-modifying drugs. *CNS Drugs*. 2018;32(10):939-949. doi:10.1007/s40263-018-0564-y
13. Kingwell E, Evans C, Zhu F, Oger J, Hashimoto S, Tremlett H. Assessment of cancer risk with beta-interferon treatment for multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2014;85(10):1096-1102. doi:10.1136/jnnp-2013-307238
14. Lebrun C, Vermersch P, Brassat D, et al. Cancer and multiple sclerosis in the era of disease-modifying treatments. *J Neurol*. 2011;258(7):1304-1311. doi:10.1007/s00415-011-5929-9
15. Alping P, Askling J, Burman J, et al. Cancer risk for fingolimod, natalizumab, and rituximab in multiple sclerosis patients. *Ann Neurol*. 2020;87(5):688-699. doi:10.1002/ana.25701
16. Ng HS, Zhu F, Kingwell E, et al. Disease-modifying drugs for multiple sclerosis and association with survival. *Neurol Neuroimmunol Neuroinflamm*. 2022;9(5):e200005. doi:10.1212/NXI.0000000000200005
17. Ng HS, Zhu F, Kingwell E, et al. Characteristics of a population-based multiple sclerosis cohort treated with disease-modifying drugs in a universal healthcare setting. *Expert Rev Neurother*. 2021;21(1):131-140. doi:10.1080/14737175.2021.1847085
18. Marrie RA, Yu N, Blanchard J, Leung S, Elliott L. The rising prevalence and changing age distribution of multiple sclerosis in Manitoba. *Neurology*. 2010;74(6):465-471. doi:10.1212/WNL.0b013e3181cf6ec0
19. Marrie RA, Bernstein CN, Peschken CA, et al. Intensive care unit admission in multiple sclerosis: increased incidence and increased mortality. *Neurology*. 2014;82(23):2112-2119. doi:10.1212/WNL.0000000000000495
20. Ng HS, Zhu F, Kingwell E, et al. Disease-modifying drugs for multiple sclerosis and subsequent health service use. *Mult Scler*. 2022;28(4):583-596. doi:10.1177/13524585211063403
21. Ng HS, Kingwell E, Zhu F, et al. Adherence to laboratory monitoring among people taking oral drugs for multiple sclerosis: a Canadian population-based study. *Mult Scler*. 2021;27(2):239-249. doi:10.1177/1352458520910500
22. Choi E, Kim S, Suh HS. Evaluation of factors associated with adverse drug events in South Korea using a population-based database. *J Clin Med*. 2022;11(21):6248. doi:10.3390/jcm11216248
23. Parameswaran Nair N, Chalmers L, Peterson GM, Bereznicki BJ, Castelino RL, Bereznicki LR. Hospitalization in older patients due to adverse drug reactions: the need for a prediction tool. *Clin Interv Aging*. 2016;11:497-505. doi:10.2147/CIA.S99097
24. Wijnands JMA, Zhu F, Kingwell E, et al. Disease-modifying drugs for multiple sclerosis and infection risk: a cohort study. *J Neurol Neurosurg Psychiatry*. 2018;89(10):1050-1056. doi:10.1136/jnnp-2017-317493
25. Teva Canada Limited. COPAXONE (glatiramer acetate injection 20 mg/1 mL and 40 mg/1 mL) product monograph [online]. 2021. Accessed January 20, 2023. canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html.
26. Biogen Canada Inc. TYSABRI (Natalizumab intravenous infusion 300 mg/15 mL) product monograph [online]. 2017. Accessed January 20, 2023. canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html.
27. Novartis Pharmaceuticals Canada Inc. GILENYA (Fingolimod capsules 0.25 mg and 0.5 mg) product monograph [online]. 2021. Accessed January 20, 2023. canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html.
28. Biogen Canada Inc. TECFIDERA (Dimethyl fumarate delayed-release capsules 120 mg and 240 mg) product monograph [online]. 2021. Accessed January 20, 2023. canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html.
29. Sanofi Genzyme A Division of Sanofi-Aventis Canada Inc. AUBAGIO (Teriflunomide tablets 14 mg) product monograph [online]. 2022. Accessed January 20, 2023. canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html.
30. Sanofi Genzyme A Division of Sanofi-Aventis Canada Inc. LEMTRADA (Alemtuzumab 12 mg/1.2 mL) product monograph [online]. 2022. Accessed January 20, 2023. canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html.
31. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. *Ann Intern Med*. 2017;167(4):268-274. doi:10.7326/M16-2607
32. Smith LH, VanderWeele TJ. Bounding bias due to selection. *Epidemiology*. 2019;30(4):509-516. doi:10.1097/EDE.0000000000001032
33. National Institute for Health and Care Excellence (NICE). NICE real-world evidence framework: methods for real-world studies of comparative studies. 2022. Accessed

July 6, 2023. nice.org.uk/corporate/ecd9/chapter/methods-for-real-world-studies-of-comparative-effects.
34. Epstein DJ, Dunn J, Deresinski S. Infectious complications of multiple sclerosis therapies: implications for screening, prophylaxis, and management. *Open Forum Infect Dis*. 2018;5(8):ofy174. doi:10.1093/ofid/ofy174
35. Luna G, Alping P, Burman J, et al. Infection risks among patients with multiple sclerosis treated with fingolimod, natalizumab, rituximab, and injectable therapies. *JAMA Neurol*. 2020;77(2):184-191. doi:10.1001/jamaneurol.2019.3365
36. Barbieri MA, Sorbara EE, Battaglia A, et al. Adverse drug reactions with drugs used in multiple sclerosis: an analysis from the Italian Pharmacovigilance Database. *Front Pharmacol*. 2022;13:808370. doi:10.3389/fphar.2022.808370
37. Hazell L, Shakir SA. Under-reporting of adverse drug reactions: a systematic review. *Drug Saf*. 2006;29(5):385-396. doi:10.2165/00002018-200629050-00003
38. Antonazzo IC, Poluzzi E, Forcesi E, et al. Liver injury with drugs used for multiple sclerosis: a contemporary analysis of the FDA Adverse Event Reporting System. *Mult Scler*. 2019;25(12):1633-1640. doi:10.1177/1352458518799598
39. Camara-Lemarroy CR, Castilló J, Sastre-Garriga J, Tintore M, Montalban X. Severe hypertriglyceridemia associated with teriflunomide in a patient with multiple sclerosis: a case report. *Mult Scler*. 2018;24(10):1383-1385. doi:10.1177/1352458518761185
40. Muñoz MA, Kulick CG, Kortepeter CM, Levin RL, Avigan MI. Liver injury associated with dimethyl fumarate in multiple sclerosis patients. *Mult Scler*. 2017;23(14):1947-1949. doi:10.1177/1352458516688351
41. Camm J, Hla T, Bakshi R, Brinkmann V. Cardiac and vascular effects of fingolimod: mechanistic basis and clinical implications. *Am Heart J*. 2014;168(5):632-644. doi:10.1016/j.ahj.2014.06.028
42. Zhao Z, Lv Y, Gu ZC, Ma CL, Zhong MK. Risk for cardiovascular adverse events associated with sphingosine-1-phosphate receptor modulators in patients with multiple sclerosis: insights from a pooled analysis of 15 randomised controlled trials. *Front Immunol*. 2021;12:795574. doi:10.3389/fimmu.2021.795574
43. Coles AJ, Arnold DL, Bass AD, et al. Efficacy and safety of alemtuzumab over 6 years: final results of the 4-year CARE-MS extension trial. *Ther Adv Neurol Disord*. 2021;14:1756286420982134. doi:10.1177/1756286420982134
44. Shosha E, Casserly C, Tomkinson C, Morrow SA. Blood pressure changes during alemtuzumab infusion for multiple sclerosis patients. *Eur J Neurol*. 2021;28(4):1396-1400. doi:10.1111/ene.14633
45. Killestein J, van Oosten B. Emerging safety issues in alemtuzumab-treated MS patients. *Mult Scler*. 2019;25(9):1206-1208. doi:10.1177/1352458519851219
46. Gasim M, Bernstein CN, Graff LA, et al. Adverse psychiatric effects of disease-modifying therapies in multiple sclerosis: a systematic review. *Mult Scler Relat Disord*. 2018;26:124-156. doi:10.1016/j.msard.2018.09.008
47. Havrdova E, Horakova D, Kovarova I. Alemtuzumab in the treatment of multiple sclerosis: key clinical trial results and considerations for use. *Ther Adv Neurol Disord*. 2015;8(1):31-45. doi:10.1177/1756285614563522
48. Nikfar S, Rahimi R, Abdollahi M. A meta-analysis of the efficacy and tolerability of interferon-β in multiple sclerosis, overall and by drug and disease type. *Clin Ther*. 2010;32(11):1871-1888. doi:10.1016/j.clinthera.2010.10.006
49. Stirland LE, González-Saavedra L, Mullin DS, Ritchie CW, Muniz-Terrera G, Russ TC. Measuring multimorbidity beyond counting diseases: systematic review of community and population studies and guide to index choice. *BMJ*. 2020;368:m160. doi:10.1136/bmj.m160
50. MacRae C, McMinn M, Mercer SW, et al. The impact of varying the number and selection of conditions on estimated multimorbidity prevalence: a cross-sectional study using a large, primary care population dataset. *PLoS Med*. 2023;20(4):e1004208. doi:10.1371/journal.pmed.1004208
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