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Trends in the use of disease-modifying therapies among reproductive-aged women with multiple sclerosis in the United States from 2010 to 2019

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Abstract

Purpose: Multiple sclerosis (MS) is a chronic disease of the central nervous system that disproportionately affects women, with typical onset during reproductive age. Several disease-modifying therapies (DMTs) are FDA-approved to slow disease progression, but are not indicated for use during pregnancy. Our objective was to describe trends over time (2010–2019) in monthly point prevalence of DMT use among reproductive-age women, overall and by generic name.

Methods: This study used administrative claims data from the US during 2009–2019 to identify women age 15–44 with MS and continuous insurance coverage for ≥12 months. DMTs were identified using prescription fills and procedural claims for alemtuzumab, daclizumab, dimethyl fumarate, fingolimod, glatiramer acetate, interferon beta, mitoxantrone, natalizumab, ocrelizumab, and teriflunomide. Monthly prevalent use was defined as ≥1 days' supply of a DMT in the month. Age- and region-standardized monthly prevalence was estimated nonparametrically.

Results: Among 42 281 reproductive-aged women over 818 179 person-months, DMT use increased from a minimum monthly prevalence of 49.3% (February, 2011) to a maximum of 58.7% (April, 2019). In 2010, prevalence of injectable DMTs was 43.1% compared to 2.5% for oral DMTs; by 2014, however, oral DMTs (26.5%) surpassed injectable DMTs (23.7%) as the most common route of administration. In the most recent data available (December, 2019), the most common DMTs were dimethyl fumarate, glatiramer acetate, and fingolimod.

Conclusions: DMT use among reproductive-aged women has rapidly evolved during the past decade. Collaborative treatment decision making between women with MS and clinicians may help optimize MS care and improve DMT uptake during reproductive years.

KEYWORDS
dimethyl fumarate, disease-modifying therapies, drug utilization, fingolimod, glatiramer acetate, multiple sclerosis, women's health

Key Points

- Among a cohort of commercially insured women aged 15–44 years with multiple sclerosis in the US, the monthly point prevalence of disease-modifying therapy (DMT) use varied between 49.3% and 58.7% between 2010 and 2019.

- Treatment patterns have rapidly evolved during this period with oral DMTs overtaking injectable DMTs as the most common formulation after 2014.
- Dimethyl fumarate, glatiramer acetate, and fingolimod were the most common DMTs by the end of the study period (December, 2019).
- DMT use increased with increasing age, but utilization of specific DMTs was proportional across age groups.

1 | INTRODUCTION

Multiple sclerosis (MS) is a chronic disease of the central nervous system. MS is more common in women than men and disease onset typically occurs during reproductive years.[1] Relapsing–remitting MS, which constitutes 80%–90% of new MS cases, is characterized by exacerbations of neurologic symptoms and worsening of neurologic function, followed by periods of symptom improvement.[2] Approximately 10%–15% of MS cases have a primary progressive onset, characterized by progressive worsening of neurologic function without periods of exacerbations.[2]

There is no cure for MS, and disease-modifying therapies (DMTs) are indicated to reduce the accumulation of brain lesions, slow disability, and prevent relapses. Several DMTs have been approved by the Food and Drug Administration (FDA) during the past decade. DMTs are currently available in injectable, infused, and oral forms. Guidelines advise starting DMTs early following the initial diagnosis of MS and continuous adherence and persistence to medications are associated with better outcomes.[3] Choice of which treatment to initiate is generally made based on patient and provider preferences and considers efficacy, adherence, tolerability, costs, and potential drug interactions.[3]

No DMTs are approved for the treatment of MS during pregnancy and the safety profiles of DMTs during pregnancy remain largely unknown.[4] Treatment guidelines advise women to discontinue DMTs prior to pregnancy unless there is high risk of relapse or disease progression.[3] However, there are safety concerns related to withdrawing DMTs during pregnancy, including a potential for rebound in disease activity.[4] Between one-fifth and one-third of women with MS deliver a child after disease onset.[5]

Recent studies on treatment utilization in patients with MS[6–8] have not reported utilization in reproductive-aged women who have complex health concerns related to family planning. The objective of our study was to describe trends in the monthly prevalence of DMT use, overall and by type of DMT, among commercially-insured, reproductive-aged women with MS from 2010–2019.

2 | METHODS

2.1 | Data source and study population

Our study utilized the IBM Watson Health MarketScan Commercial Claims and Encounters database from 2009 to 2019. For each calendar month between 2010 and 2019, we identified reproductive-aged women (15–44 years) who were continuously enrolled during the 12 months prior (baseline period; Supplemental Figure S1, Supplemental Figure S2). Women were required to have at least one inpatient or two outpatient diagnosis codes for MS (International Classification of Disease, Ninth Revision, Clinical Modification [ICD-9-CM]: 340; ICD-10-CM: G35) during the baseline period. Women contributed to all months where they met eligibility criteria.

2.2 | Study variables

DMTs were identified using generic names in outpatient prescription claims and Healthcare Common Procedural Coding System codes in inpatient and outpatient services files (Supplemental Table S1). Fills with overlapping days' supply were assumed to be taken sequentially. Days covered by DMTs identified using procedure codes were based on prescribing information (Supplemental Table S2, Supplemental Figure S3). The injectable DMTs considered included interferon beta (IFNβ-1a, IFNβ-1b, peginterferon beta 1a) and glatiramer acetate; infused DMTs included alemtuzumab, daclizumab, mitoxantrone, natalizumab, and ocrelizumab; and oral DMTs were dimethyl fumarate, fingolimod, and teriflunomide.

Baseline comorbidities, symptoms, medications, and healthcare utilization were assessed using diagnosis and procedure codes during the baseline period (Supplemental Table S1). Baseline MS relapses were identified using a validated claims-based algorithm.[9,10] The algorithm defines relapses as either a hospitalization with a primary diagnosis of MS or an outpatient visit with a diagnosis of MS followed by a claim for corticosteroids within 7 days.

2.3 | Statistical analysis

Baseline characteristics were summarized using descriptive statistics stratified by time period (2010–2013, 2014–2016, 2017–2019). The time periods were chosen based on FDA approvals for dimethyl fumarate (2013) and ocrelizumab (2017). We computed the monthly point prevalence as the number of women with at least 1 days' supply of a DMT in the month, divided by the number of women meeting inclusion criteria in that month. We estimated 95% confidence intervals (CIs) using generalized estimating equations with an independent correlation structure to account for repeated observations within women. Prevalence estimates were standardized by age and region

TABLE 1 Demographic and clinical characteristics of reproductive-aged women with multiple sclerosis in the IBM Watson Health MarketScan Commercial Claims and Encounters database from 2010 to 2019, by time period

Characteristic	2010–2013		2014–2016		2017–2019	
	358 817 PMs (23 672 women)		251 589 PMs (17 567 women)		207 773 PMs (13 725 women)	
Demographics						
Age, mean ± SD	36.4	(6.1)	36.4	(6.2)	36.4	(6.2)
Median (IQR)	38	(33, 41)	38	(33, 42)	38	(33, 41)
Age categories, n (%)						
15–24	18 081	(5.0)	15 243	(6.1)	12 207	(5.9)
25–34	101 177	(28.2)	66 752	(26.5)	55 376	(26.7)
35–44	239 559	(66.8)	169 594	(67.4)	140 190	(67.5)
Region, n (%)						
South	135 498	(38.2)	103 478	(41.5)	93 358	(45.0)
North Central	97 332	(27.4)	54 278	(21.8)	43 261	(20.8)
Northeast	66 874	(18.8)	51 719	(20.8)	42 646	(20.5)
West	55 335	(15.6)	39 667	(15.9)	28 311	(13.6)
Unknown	3778		2447		197	
Baseline relapses						
Any baseline relapse, n (%)	88 849	(24.8)	65 722	(26.1)	67 817	(32.6)
Number of baseline relapses, mean (SD)	0.4	(0.8)	0.4	(0.8)	0.5	(0.9)
Median (IQR)	0	(0, 0)	0	(0, 1)	0	(0, 1)
Baseline comorbidities and symptoms						
Pain, n (%)	161 435	(45.0)	120 400	(47.9)	98 716	(47.5)
Prior mental illness or substance use disorder, n (%)	108 051	(30.1)	92 839	(36.9)	87 931	(42.3)
Fatigue, n (%)	88 597	(24.7)	73 583	(29.2)	64 707	(31.1)
Thyroid disorder, n (%)	45 217	(12.6)	35 273	(14.0)	31 068	(15.0)
Hypertension, n (%)	42 637	(11.9)	33 961	(13.5)	29 947	(14.4)
Hyperlipidemia, n (%)	38 181	(10.6)	26 725	(10.6)	21 796	(10.5)
CCI, n (%)						
0	284 081	(79.2)	197 191	(78.4)	163 020	(78.5)
1	51 444	(14.3)	37 046	(14.7)	28 397	(13.7)
2	16 157	(4.5)	11 711	(4.7)	10 707	(5.2)
3+	7135	(2.0)	5641	(2.2)	5649	(2.7)
Conditions of the CCI, n (%)						
COPD	30 194	(8.4)	23 951	(9.5)	21 128	(10.2)
Uncomplicated diabetes mellitus	15 559	(4.3)	11 850	(4.7)	8823	(4.2)
Cerebrovascular disease	17 256	(4.8)	10 839	(4.3)	6936	(3.3)
Cancer without metastases	7062	(2.0)	4368	(1.7)	4095	(2.0)
Rheumatic disease	6692	(1.9)	4762	(1.9)	3961	(1.9)
Hemiplegia	4503	(1.3)	3522	(1.4)	3227	(1.6)
Diabetes mellitus with chronic complications	2462	(0.7)	2676	(1.1)	4146	(2.0)
Peripheral vascular disease	2595	(0.7)	1927	(0.8)	1856	(0.9)
Moderate to severe renal disease	1693	(0.5)	1438	(0.6)	1281	(0.6)
Peptic ulcer disease	1531	(0.4)	993	(0.4)	989	(0.5)
Congestive heart failure	1225	(0.3)	927	(0.4)	723	(0.3)
Metastatic solid tumor	769	(0.2)	580	(0.2)	610	(0.3)
Prior myocardial infarction	688	(0.2)	542	(0.2)	480	(0.2)

(Continues)

TABLE 1 (Continued)

Characteristic	2010–2013		2014–2016		2017–2019	
	358 817 PMs (23 672 women)		251 589 PMs (17 567 women)		207 773 PMs (13 725 women)	
Mild liver disease	571	(0.2)	561	(0.2)	382	(0.2)
Dementia	331	(0.1)	266	(0.1)	296	(0.1)
HIV/AIDS	406	(0.1)	148	(0.1)	188	(0.1)
Moderate to severe liver disease	174	(0.0)	113	(0.0)	91	(0.0)
Baseline drug use						
Antidepressants	153 586	(42.8)	104 754	(41.6)	85 671	(41.2)
Muscle spasm and anticholinergic	144 172	(40.2)	103 233	(41.0)	83 970	(40.4)
Corticosteroid	119 452	(33.3)	87 115	(34.6)	81 496	(39.2)
Fatigue medication	59 628	(16.6)	35 517	(14.1)	26 256	(12.6)
Anti-hypertensives	51 265	(14.3)	37 764	(15.0)	31 049	(14.9)
Urinary continence treatment	33 136	(9.2)	21 862	(8.7)	16 684	(8.0)
Anti-hyperlipidemia	15 071	(4.2)	10 262	(4.1)	6603	(3.2)
Dalfampridine	11 845	(3.3)	8152	(3.2)	6516	(3.1)
Baseline healthcare utilization						
Any inpatient admission, n (%)	53 356	(14.9)	33 263	(13.2)	27 279	(13.1)
Any outpatient visit, n (%)	356 845	(99.5)	250 346	(99.5)	206 558	(99.4)
Number of outpatient visits, mean (SD)	8.1	(5.9)	8.1	(6.5)	8.1	(6.1)
Median (IQR)	7	(4, 10)	7	(4, 10)	7	(4, 11)
Any ER visit, n (%)	108 433	(30.2)	72 640	(28.9)	60 007	(28.9)
Number of ER visits, mean (SD)	0.6	(1.6)	0.6	(1.6)	0.6	(1.6)
Median (IQR)	0	(0, 1)	0	(0, 1)	0	(0, 1)

Abbreviations: AIDS, acquired immunodeficiency syndrome; CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; ER, emergency room; HIV, human immunodeficiency virus; IQR, interquartile range; PMs, person-months; SD, standard deviation.

using direct standardization.[11] The proportion of women in groups defined by age (15–24, 25–34, and 35–44 years) and region (South, North Central, Northeast, West) in December 2019 served as the standard population. We also assessed differences in monthly point prevalence of DMT use by age group during the period from 2017–2019. All analyses were performed using SAS Version 9.4 (SAS Institute, Cary, NC).

3 | RESULTS

Our study included 42 281 reproductive-aged women with MS who contributed 818 179 person-months to the study. The number of women in the study population in each month ranged from 5356 to 9126. Median age was stable over time at 38 years (Table 1). Twenty-five to thirty-three percent of women experienced at least one relapse during the baseline period, and the mean number of baseline relapses ranged from 0.4 to 0.5. Pain, mental illness or substance abuse, and fatigue were common. Baseline use of antidepressants, muscle spasm and anticholinergic medications, and corticosteroids was also high.

The age- and region-standardized prevalence of any DMT use increased steadily over time, with a minimum prevalence of 49.3% (95% CI, 48.2–50.5%) in February 2011 and a maximum prevalence of 58.7% (95% CI, 57.6–60.1%) in April 2019 (Figure 1, Panel A). Oral DMTs were the most common type in later years, surpassing injectable DMTs in 2014 (Figure 1, Panel A). In the most recent years of data (2017–2019), utilization of DMTs increased with increasing age (Figure 1, Panel B), although the distribution of type of DMT was proportional across age groups. Utilization of DMTs by age for earlier years is provided in Supplemental Figure S4 and Supplemental Figure S5.

Interferon beta was the most common DMT in 2010, with a peak monthly point prevalence of 25.7% in April 2010 that declined thereafter (Figure 1, Panel C). Prevalence of glatiramer acetate use declined steadily over time from a peak prevalence of 19.6% in December 2010 to a minimum of 9.8% in February 2019, but remained the second-most common DMT during later years. Dimethyl fumarate became the most common DMT in 2014, with a monthly prevalence of use after 2014 ranging from 11.8% to 17.1%. Use of fingolimod increased drastically after its approval in 2010, with a peak prevalence of 10.7% in April 2017. Fingolimod remained

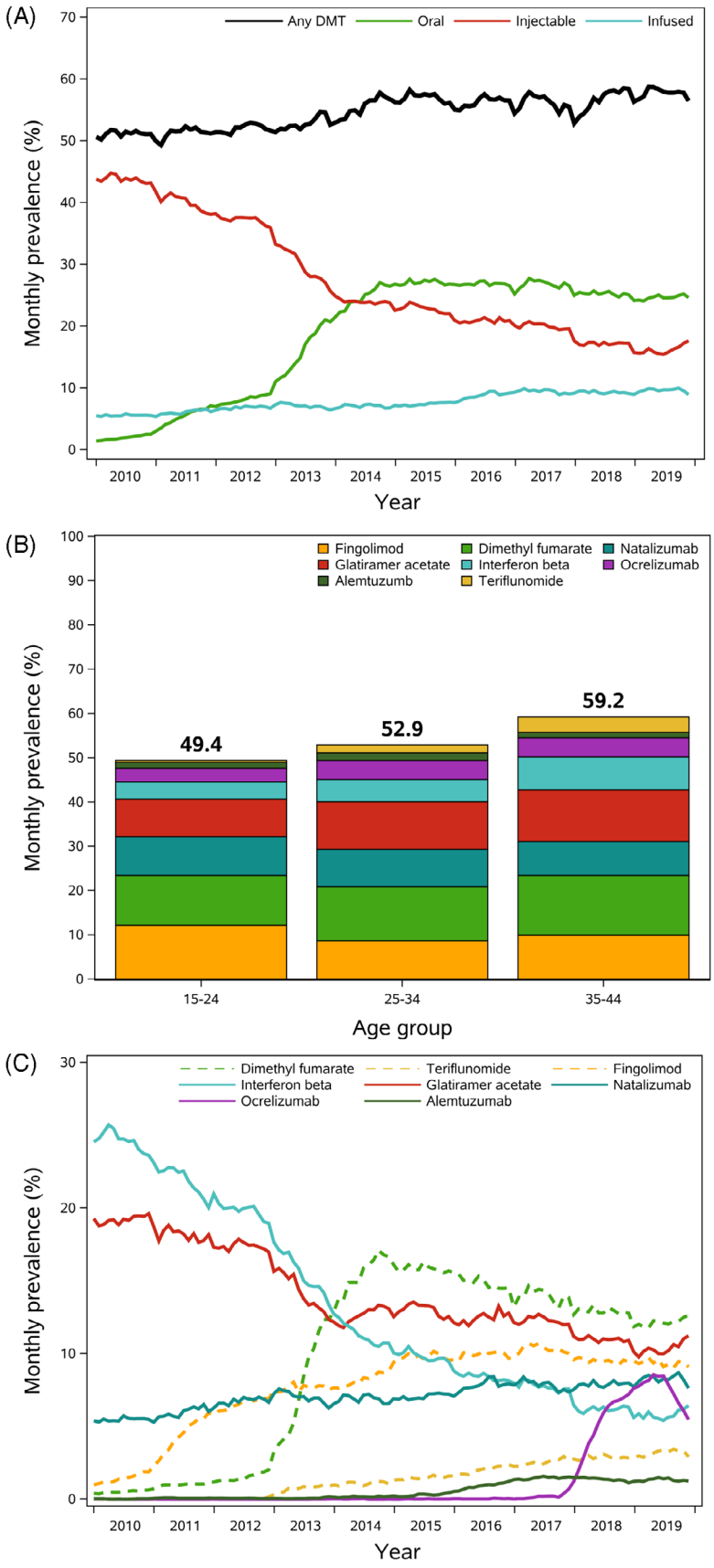

FIGURE 1 Prevalence of disease-modifying therapies from 2010–2019. DMT, disease modifying therapy. (A) Age- and region-standardized monthly prevalence of DMT use over time, overall and by route of administration. (B) Average monthly prevalence of DMT use during the period from 2017–2019 by age category. Daclizumab and mitoxantrone are not presented since prevalence was low across the entire study follow-up. (C) Age- and region-standardized monthly prevalence of DMT use over time, by generic name. Dashed lines represent oral DMTs, and solid lines represent infused or injected DMTs. Daclizumab and mitoxantrone are not presented since prevalence was low across the entire study follow-up (max monthly prevalence mitoxantrone: 0.1% in May 2010; daclizumab: 0.2% in September 2017)

the third most common DMT in 2019. The prevalence of natalizumab use was stable across years, ranging from 5.3% in January 2011 to 8.7% in October 2019. Prevalence of ocrelizumab use increased sharply after its approval in 2017, peaking at 8.5% in May 2019. Use of alemtuzumab, teriflunomide, mitoxantrone, and daclizumab were low across all years.

4 | DISCUSSION

Our study is the first to describe trends in DMT use among reproductive-aged women with MS using contemporary US data. We found that during the past decade the prevalence of DMT use has ranged from 49.3–58.7% and that treatment patterns have rapidly changed. In recent years, dimethyl fumarate, glatiramer acetate, and fingolimod were the most common DMTs. Prevalence of ocrelizumab has seen the sharpest increase since its approval in 2017. Daclizumab use was low in all years, even prior to its withdrawal from the global market in March 2018.

There is strong evidence that DMTs are effective for reducing relapses and slowing the accumulation of brain lesions.[3] Earlier initiation can improve outcomes and DMTs are recommended to be continued indefinitely once disease is controlled if no adverse events occur.[3] Despite this, our study found that between 40–50% of women did not receive DMTs during each month. Some of this may be due to decisions to avoid DMTs during family planning. However, low utilization may also reflect suboptimal adherence and persistence, which have been reported in previous studies.[3,7,12] We also found that the prevalence of DMT use was lower in younger age groups. Although evidence for the safety and effectiveness of certain DMTs for pediatric patients remains uncertain, patients <18 years of age are recommended to initiate treatment with a beta interferon or glatiramer acetate shortly after diagnosis.[13]

Reproductive-aged women have the highest incidence of MS and there remains a paucity of information on the safety of DMTs during pregnancy. In addition, due to the chronic nature of MS, treatment patterns in older populations differ than younger populations due to disease progression and subsequent discontinuations and treatment switches.[14] Prior studies have reported high frequencies of DMT exposure during pregnancy for women with MS, particularly during the first trimester. In an analysis of the MarketScan database, 35% of women were exposed to DMTs during the 90 days prior to pregnancy and approximately a quarter were exposed during the first trimester.[15] In the MSBase Registry, 42% of reported pregnancies were conceived while on a DMT.[16] While minimal risks have been reported for the older injectable DMTs, evidence on newer agents remains limited.[4,17] Future research on the safety of DMTs during pregnancy is vital, particularly for the DMTs that were found to have the highest utilization in our study.

Results of this study should be interpreted considering several limitations. First, our study was conducted in an employer-sponsored insurance claims database and women who are uninsured or covered by publicly-funded insurance are not represented. This population is not negligible, since many women with MS may be covered under federal insurance programs and 43% of births are covered under Medicaid.[18] In addition, the high and variable costs of DMTs may drive utilization patterns in this study population of commercially-insured women, and may lead to different patterns in uninsured or publicly-insured women. The median annual wholesale acquisition costs for DMTs was $91 835 in 2020 and patients often face high out-of-pocket costs.[19] Second, several new DMTs, such as ofatumumab, diroximel fumarate, siponimod, cladribine, ozanimod, and monomethyl fumarate have been approved for treatment of MS since 2019 and we were not able to capture them in our study. Third, outpatient prescription claims only capture fills and may not reflect actual consumption of medications. Alternatively, DMT use captured using procedure codes are likely very accurate. Finally, in order to evaluate monthly point prevalence, eligibility criteria for our cohort were applied at the person-month level to provide a set of serial snapshots of DMT use. In turn, this study cannot be used to evaluate duration of therapy, treatment discontinuation, and treatment switches at the individual level. The requirements for MS diagnosis codes during baseline may also have led to excluding some less severe cases of MS from our month-level denominator. However, women with MS tend to have high healthcare resource utilization,[20] so we anticipate the number of women excluded based on these criteria to be small.

Our study summarized trends in utilization of DMTs among reproductive-aged women in a rapidly changing treatment landscape. Collaborative treatment discussions and decision making between women with MS and clinicians may help optimize MS care and improve DMT uptake during reproductive years. Finally, a greater understanding is needed about the safety of DMTs during pregnancy.

CONFLICT OF INTEREST

Emilie D Duchesneau and Jennifer L Lund have received salary support from AbbVie, Inc. for unrelated work. GlaxoSmithKline (GSK), AbbVie, Boehringer Ingelheim, Takeda and UCB have collaborative agreements with the Center for Pharmacoepidemiology, Department of Epidemiology, University of North Carolina at Chapel Hill. Michele Jonsson Funk receives salary support as Director of the Center. Michele Jonsson Funk is a member of the Scientific Steering Committee (SSC) for a post-approval safety study funded by GSK. All compensation for services provided on the SSC is invoiced by and paid to UNC Chapel Hill. These companies do not review any research nor provide any input into the analysis of the drug classes being studied.

ETHICS STATEMENT

This study was determined to be exempt by the Office of Human Research Ethics of the University of North Carolina at Chapel Hill (#19-1801).

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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