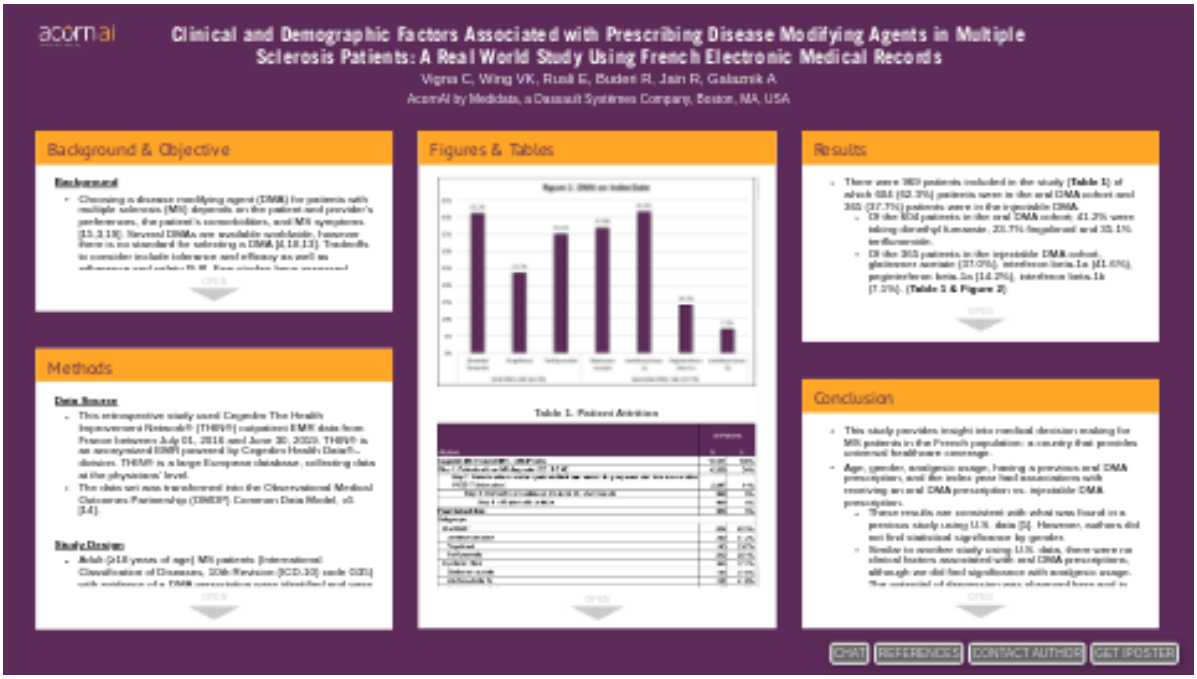
Clinical and Demographic Factors Associated with Prescribing Disease Modifying Agents in Multiple Sclerosis Patients: A Real World Study Using French Electronic Medical Records



Vigna C, Wing VK, Rusli E, Buderi R, Jain R, Galaznik A

AcornAI by Medidata, a Dassault Systèmes Company, Boston, MA, USA

PRESENTED AT:

BACKGROUND & OBJECTIVE

Background

- Choosing a disease modifying agent (DMA) for patients with multiple sclerosis (MS) depends on the patient and provider's preferences, the patient's comorbidities, and MS symptoms [15,3,19]. Several DMAs are available worldwide, however there is no standard for selecting a DMA [4,18,13]. Tradeoffs to consider include tolerance and efficacy as well as adherence and safety [9,8]. Few studies have assessed factors associated with prescribed DMAs for patients with MS [5,3].
- One in one thousand people are estimated to suffer from MS in France, causing France to have one of the highest prevalences of MS in the world [1]. In France, all healthcare costs associated with the treatment of MS are covered as it is classified as one of the thirty long-term illnesses [6].

Objective

- The aim of this study was to identify factors associated with prescribing oral DMAs for MS patients in France using electronic medical record (EMR) data.

METHODS

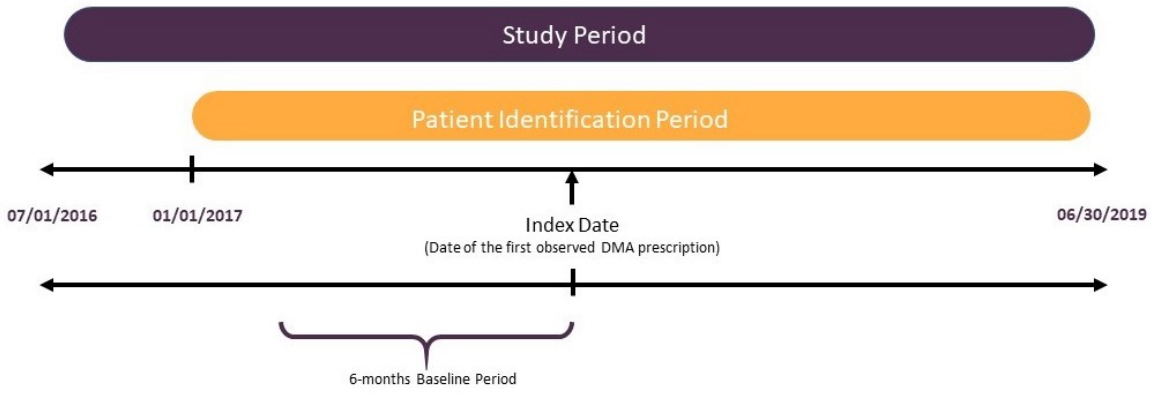
Data Source

- This retrospective study used Cegedim The Health Improvement Network® (THIN®) outpatient EMR data from France between July 01, 2016 and June 30, 2019. THIN® is an anonymized EMR powered by Cegedim Health Data®–division. THIN® is a large European database, collecting data at the physicians' level.
- The data set was transformed into the Observational Medical Outcomes Partnership (OMOP) Common Data Model, v5 [14].

Study Design

- Adult (≥18 years of age) MS patients (International Classification of Diseases, 10th Revision (ICD-10) code G35) with evidence of a DMA prescription were identified and were classified into an oral or injectable cohort based on the first prescription ***(index exposure)*** between January 01, 2017 and June 30, 2019. The date of the first prescription was assigned as the ***index date***.
- Patients were required to have ≥ 6 months of data prior to the index date, defined as the ***baseline period*** (**Figure 1**).

Figure 1. Study Design



- The index exposures were defined as oral or injectable and included the following:
  - Orals: dimethyl fumarate, fingolimod, teriflunomide
  - Injectables: glatiramer acetate, interferon beta-1a, peginterferon beta-1a, interferon beta-1b
- Patient demographics such as age and gender were evaluated on index date.
- The following baseline clinical characteristics were evaluated:
  - Elixhauser score [7,11,12]
  - Comorbidities
  - MS symptoms [5]
  - DMA prescription before but closest to index date
  - Symptomatic medications [5]
- The proportion of patients for each category were described and compared across oral and injectable groups.
- All demographics, baseline clinical characteristics and study measures of interest were described with univariate statistics. Mean and standard deviation for the continuous variables, and relative frequency and percentage for categorical variables were calculated.
- The statistical significance was assessed by using the Welch two sample t-test for continuous variables and 2-sample test for equality of proportions without continuity correction for categorical variables. A

conventional alpha of 0.05 and a two-tailed level of significance was used. All statistical analyses were performed using R v1.1.456.

- A logistic regression model was used to measure the relationship between prescribing an oral DMA and patients' baseline demographic and clinical characteristics.
  - Marginal effects were estimated [16,17]
  - The goodness-of-fit was assessed using Hosmer-Lemeshow goodness of fit test

FIGURES & TABLES

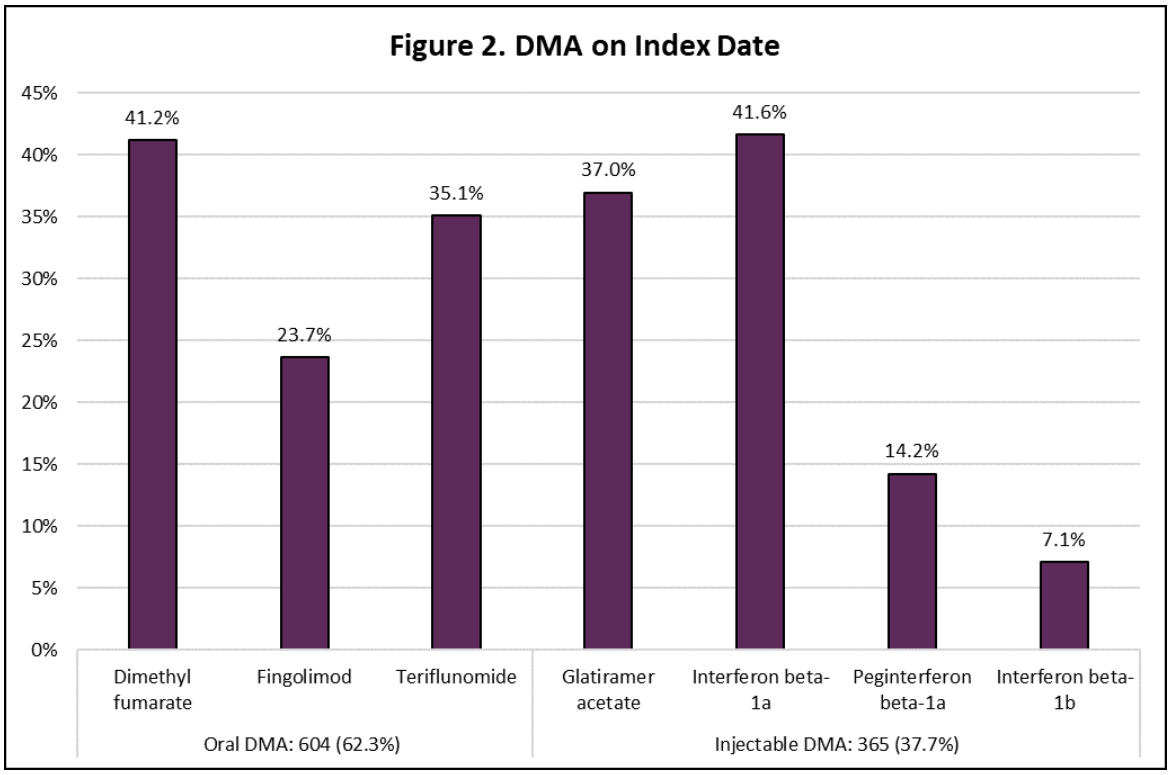


Table 1. Patient Attrition

Attrition	All Patients N	All Patients %
Cegedim MS French EMR - OMOP Data	18,551	100%
Step 1: Patients with an MS diagnosis (ICD10 G35)	10,038	54%
Step 2: Patients with an oral or injectable DMA and earliest drug exposure start date is on or after 1/1/2017 (index date)	2,047	11%
Step 3: ≥6 months of continuous pre-index observation data	969	5%
Step 4: ≥18 years old on index	969	5%
Final Cohort Size	969	5%
Subgroups		
Oral DMA[1]	604	62.3%
Dimethyl fumarate	249	41.2%
Fingolimod	143	23.7%
Teriflunomide	212	35.1%
Injectable DMA	365	37.7%
Glatiramer acetate	135	37.0%
Interferon beta-1a	152	41.6%
Peginterferon beta-1a	52	14.2%
Interferon beta-1b	26	7.1%
[1]Disease modifying agent		

Table 2. Baseline Patient Characteristics

Characteristics at Index and Within 6 Months Prior to index	All Patients N= 969 N/Mean	%/SD	Patients who indexed on oral DMA N= 604 N/Mean	%/SD	Patients who indexed on injectable DMA N= 365 N/Mean	%/SD	p-value
Age*							
At index date (Mean, SD)[1]	46.6	11.4	45.5	10.9	48.5	12.0	*<0.001*
Gender* (n, %)							
Male	273	28.2%	197	32.6%	76	20.8%	*<0.001*
Female	696	71.8%	407	67.4%	289	79.2%	
Index Year (n, %)							
2017*	639	65.9%	374	61.9%	265	72.6%	*<0.001*
2018*	244	25.2%	168	27.8%	76	20.8%	*0.015*
2019 [2]	86	8.9%	62	10.3%	24	6.6%	0.050
Elixhauser Score during baseline							
Score (Mean, SD)	4.2	2.2	4.2	2.2	4.2	2.3	0.225
Score categories (n, %)							
<0	12	1.2%	8	1.3%	4	1.1%	0.755
0	499	51.5%	298	49.3%	201	55.1%	0.084
1-4	11	1.1%	6	1.0%	5	1.4%	0.592
≥5	447	46.1%	292	48.3%	155	42.5%	0.075
Comorbidities during baseline (n, %)							
Cardiac arrhythmias	5	0.5%	4	0.7%	1	0.3%	0.414
Hypertension, uncomplicated	17	1.8%	9	1.5%	8	2.2%	0.420
Hypertension, complicated	1	0.1%	0	0.0%	1	0.3%	0.198
Paralysis	6	0.6%	4	0.7%	2	0.5%	0.826
Other neurological disorders	466	48.1%	299	49.5%	167	45.8%	0.258
Chronic pulmonary disease	9	0.9%	4	0.7%	5	1.4%	0.266
Diabetes, uncomplicated	5	0.5%	2	0.3%	3	0.8%	0.302
Hypothyroidism	5	0.5%	3	0.5%	2	0.5%	0.914
Liver disease	3	0.3%	1	0.2%	2	0.5%	0.299
Solid tumor, without metastasis	2	0.2%	0	0.0%	2	0.5%	0.069
Rheumatoid arthritis/collagen vascular disease	1	0.1%	0	0.0%	1	0.3%	0.198
Weight loss	2	0.2%	1	0.2%	1	0.3%	0.719
Psychoses	1	0.1%	1	0.2%	0	0.0%	0.437
Depression*	19	2.0%	7	1.2%	12	3.3%	*0.021*
MS Symptoms during baseline (n, %)							
Brainstem symptoms (facial neuralgia, vertigo, dizziness)	8	0.8%	6	1.0%	2	0.5%	0.458
Visual symptoms (visual loss, visual disturbances)	1	0.1%	0	0.0%	1	0.3%	0.198
Pyramidal symptoms (weakness, paralysis, spasticity/muscle symptoms)	5	0.5%	3	0.5%	2	0.5%	0.914
Bladder/bowel symptoms (incontinence/constipation) or sexual dysfunction	6	0.6%	3	0.5%	3	0.8%	0.532
Sensory symptoms (disturbances of skin sensation)	15	1.5%	9	1.5%	6	1.6%	0.851
Cerebellar symptoms (movement disorders, ataxia, tremor)	4	0.4%	4	0.7%	0	0.0%	0.119

[1]Calculated from year of birth

[2]January through June

*P-value is statistically significant (<0.05)

Table 3. Baseline Medication Use

Medications Within 6 Months Prior to index	All Patients N= 969 N	%	Patients who indexed on oral DMA N= 604 N	%	Patients who indexed on injectable DMA N= 365 N	%	p-value
DMA prescription during the baseline period and closest to index date (n, %)[1]							
Oral	83	8.6%	82	13.6%	1	0.3%	
Dimethyl fumarate	37	3.8%	36	6.0%	1	0.3%	
Fingolimod	20	2.1%	20	3.3%	0	0.0%	
Teriflunomide	26	2.7%	26	4.3%	0	0.0%	
Injectable	60	6.2%	1	0.2%	59	16.2%	
Glatiramer acetate	16	1.7%	0	0.0%	16	4.4%	0.054
Interferon beta-1a	29	3.0%	0	0.0%	29	7.9%	
Peginterferon beta-1a	9	0.9%	0	0.0%	9	2.5%	
Interferon beta-1b	6	0.6%	1	0.2%	5	1.4%	
None	826	85.2%	521	86.3%	305	83.6%	
Prior medication is same as index medication	141	14.6%	82	13.6%	59	16.2%	
Symptomatic Medications (n, %)							
Analgesics*	139	14.3%	71	11.8%	68	18.6%	*0.003*
Antidepressants	54	5.6%	30	5.0%	24	6.6%	0.290
Bladder dysfunction	33	3.4%	23	3.8%	10	2.7%	0.374
Fatigue	10	1.0%	6	1.0%	4	1.1%	0.878
Anticonvulsants	30	3.1%	23	3.8%	7	1.9%	0.100
Spasticity	44	4.5%	27	4.5%	17	4.7%	0.892
Other	9	0.9%	5	0.8%	4	1.1%	0.673

[1]P-value is for oral vs. injectable

*P-value is statistically significant (<0.05)

Table 4. Logistic Regression Modeling: Oral Prescription Likelihood

Characteristics Associated with Initiating an Oral DMA vs. an Injectable DMA				
Predictor	**Categories**	**Beta**	**Marginal Effects**	**p-value**
Age*	NA	-0.02	-0.005	*<0.001*
Gender*	Male (vs. Female)	0.62	0.124	*<0.001*
Elixhauser Score	NA	-0.03	-0.006	0.828
Comorbidities	Cardiac arrhythmias	0.27	0.055	0.819
	Hypertension, uncomplicated	-0.01	-0.002	0.988
	Other neurological disorders	0.06	0.013	0.931
	Chronic pulmonary disease	-0.67	-0.135	0.429
	Diabetes, uncomplicated	-0.14	-0.029	0.900
	Hypothyroidism	-0.48	-0.098	0.610
	Liver disease	-2.36	-0.475	0.235
	Weight loss	-0.76	-0.155	0.786
	Depression	-1.34	-0.272	0.186
MS Symptoms	Brainstem symptoms	1.32	0.272	0.124
	Bladder/bowel symptoms or sexual dysfunction	-0.99	-0.200	0.403
	Sensory symptoms	-0.42	-0.085	0.500
Prior DMA Prescription*	Oral	4.85	0.411	*<0.001*
Symptomatic Medications*	Analgesics	-0.51	-0.104	*0.026*
	Antidepressants	-0.03	-0.006	0.939
	Bladder dysfunction	0.63	0.127	0.245
	Fatigue	-0.32	-0.064	0.694
	Anticonvulsants	0.67	0.135	0.176
	Spasticity	-0.16	-0.032	0.683
	Other	0.04	0.007	0.964
Index Year*	2018 (vs. 2017)	0.67	0.136	*<0.001*
	2019 (vs. 2017)	0.94	0.185	*<0.001*

[1]Hosmer-Lemeshow (GOF): p-value = 0.268

[2]AIC = 1179.8

*P-value is statistically significant (<0.05)

RESULTS

- There were 969 patients included in the study (**Table 1**) of which 604 (62.3%) patients were in the oral DMA cohort and 365 (37.7%) patients were in the injectable DMA.
  - Of the 604 patients in the oral DMA cohort; 41.2% were taking dimethyl fumarate, 23.7% fingolimod and 35.1% teriflunomide.
  - Of the 365 patients in the injectable DMA cohort, glatiramer acetate (37.0%), interferon beta-1a (41.6%), peginterferon beta-1a (14.2%), interferon beta-1b (7.1%). (**Table 1 & Figure 2**)
- The average age of all the patients was 46.6±11.4 years (oral vs injectable: 45.5±10.9 vs 48.5±12.0; p<0.001). Nearly three-fourths (71.8%) of the patients were females (67.4% vs 79.2%; p<0.001). (**Table 2**)
- The average Elixhauser scores for all the patients was 4.2±2.2 and was statistically similar between the oral and the injectable cohorts (4.2±2.2 vs 4.2±2.3; p=0.225) (**Table 2**).
- Nearly half (48.1%) had a history of other neurological disorders (49.5% vs 45.8%; p=0.258). All other comorbidities were similar across the two cohorts (**Table 2**).
- Majority (85.2%) of the patients had no evidence of DMA prescription in the six months prior to the baseline period. A small proportion (14.6%) of patients had evidence of DMA use in the baseline period.
  - Among the patients in the oral cohort, 13.6% had prior DMA use and among the injectable cohort, 16.2% had prior DMA use.
    - Among patients with prior DMA use, nearly all patients had the same route of administration (**Table 3**).
- Adjusted results: Modeling likelihood of being prescribed an oral DMA.
  - Each additional year of age ***decreased*** the likelihood of being prescribed an oral DMA by 0.5 percentage points (p<0.001).
  - Relative to women, men had a 12.4 percentage point (p<0.001) ***higher*** likelihood of being prescribed an oral DMA.
  - Patients that received an oral DMA during the baseline period had a 41.1 percentage point (p<0.001) ***higher*** likelihood of being prescribed an oral DMA at index.
  - Patients taking analgesics during the baseline period had a ***lower*** likelihood of being prescribed an oral DMA by 10.4 percentage points (p=0.026)
  - Over the calendar years, the likelihood of being prescribed an oral DMA increased 13.6 percentage points [p<0.001] in 2018 relative to 2017; 18.5 percentage points [p<0.001] in 2019 relative to 2017) (**Table 4**)

CONCLUSION

- This study provides insight into medical decision making for MS patients in the French population: a country that provides universal healthcare coverage.
- Age, gender, analgesic usage, having a previous oral DMA prescription, and the index year had associations with receiving an oral DMA prescription vs. injectable DMA prescription.
  - These results are consistent with what was found in a previous study using U.S. data [5]. However, authors did not find statistical significance by gender.
  - Similar to another study using U.S. data, there were no clinical factors associated with oral DMA prescriptions, although we did find significance with analgesic usage. The potential of depression was observed here and in Desai, et al. (2019) which did not have statistical significance in the model [3]. Authors did observe an increase in oral DMA use over increasing years as we found when comparing prescription index dates to 2017.
- Understanding factors associated with oral vs. injectable use can guide physicians in better tailoring treatment approaches to specific patient needs and support personalized medicine approaches.

Limitations

- Due to the nature of EMR data, it is unknown whether prescriptions that were prescribed to patients were filled.
- The database does not include information on the inpatient setting, therefore the use of infusions was not captured.

Future Considerations

- Expand study to include additional countries and reimbursement models
- Include infusible data and functional status data to account for variation in patient severity

AUTHOR INFORMATION

Vigna C, Wing VK, Rusli E, Buderi R, Jain R, Galaznik A

Medidata, a Dassault Systèmes company, Boston, MA, USA

REFERENCES

1. Chevalier, J., Chamoux, C., Hammes, F., & Chicoye, A. Cost-effectiveness of treatments for relapsing remitting multiple sclerosis: a French societal perspective. PloS one. 2016;11(3). doi:10.1371/journal.pone.0150703
2. Condé S, Moisset X, Pereira B, et al. Dimethyl fumarate and teriflunomide for multiple sclerosis in a real-life setting: a French retrospective cohort study. Eur J Neurol. 2019;26(3):460-467. doi:10.1111/ene.13839
3. Desai, R.J., Mahesri, M., Gagne, J.J., et al. Utilization patterns of oral disease-modifying drugs in commercially insured patients with multiple sclerosis. J Manag Care Spec Pharm. 2019;25(1):113-21.
4. Dorr, J., Paul, F. The transition from first-line to second-line therapy in multiple sclerosis. Curr Treat Options Neurol. 2015;17(6):354.
5. Earla, J.R., Hutton, G.J., Thornton, J.D. & Aparasu, R.R. Factors associated with prescribing oral disease modifying agents in multiple sclerosis: a real-world analysis of electronic medical records. Multiple Sclerosis and Related Disorders. 2020;45. doi: https://doi.org/10.1016/j.msard.2020.102334
6. Fromont, A., Binquet, C., Sauleau, E.A., et al. Geographic variations of multiple sclerosis in France. Brain. 2010;133(7):1889-99. https://doi.org/10.1093/brain/awq134
7. Gasparini, A. Comorbidity: An R package for computing comorbidity scores. Journal of Open Source Software. 2018;3(23), 648, https://doi.org/10.21105/joss.00648
8. Kim, W., Zandoná, M.E., Kim, S.H., Kim, H.J. Oral disease-modifying therapies for multiple sclerosis. J Clin Neurol. 2015;11(1):9-19. doi:10.3988/jcn.2015.11.1.9
9. Longbrake, E.E., Cross, A.H. & Salter, A. Efficacy and tolerability of oral versus injectable disease-modifying therapies for multiple sclerosis in clinical practice. Mult Scler J Exp Transl Clin. 2016;2. doi:10.1177/2055217316677868
10. Mantia, L.L., Tramacere, I., Firwana, B., et al. Fingolimod for relapsing-remitting multiple sclerosis. Cochrane Database of Systematic Reviews. 2016;4 doi: 10.1002/14651858.CD009371.pub2.
11. Menendez, M.E., Neuhaus, V., van Dijk, C.N., Ring, D. The Elixhauser comorbidity method outperforms the Charlson index in predicting inpatient death after orthopaedic surgery. Clinical Orthopaedics and Related Research. 2014;472(9):2878-2886. doi: 10.1007/s11999-014-3686-7
12. Moore, B.J., White, S., Washington, R., et al. Identifying increased risk of readmission and in-hospital mortality using hospital administrative data: the AHRQ Elixhauser comorbidity index. Medical Care. 2017;55(7):698-705. doi: 10.1097/MLR.0000000000000735
13. Multiple Sclerosis Coalition. The Use of Disease Modifying Therapies In Multiple Sclerosis: Principles and Current Evidence. 2019. Accessed July 20, 2020. https://ms-coalition.org/the-use-of-disease-modifying-therapies-in-multiple-sclerosis-updated/
14. Observational Health Data Sciences and Informatics. OMOP Common Data Model. Accessed April 29, 2020. https://www.ohdsi.org/data-standardization/the-common-data-model/
15. Ontaneda, D., Tallantyre, E., Kalincik, T., et al. Early highly effective versus escalation treatment approaches in relapsing multiple sclerosis. Lancet Neurol. 2019;18(10):973-80.
16. Onukwugha E, Bergtold J, Jain R. (2015) A Primer on Marginal Effects—Part I: Theory and Formulae. PharmacoEconomics; 33(1):25-30.
17. Onukwugha E, Bergtold J, Jain R. (2015) A Primer on Marginal Effects—Part II: Health Services Research Applications. PharmacoEconomics; 33(2):97-103
18. Rae-Grant, A., Day, G.S., Marrie, R.A., et al. Practice guideline recommendations summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology. 2018;90(17):777-88.
19. Saylor, D. Comorbidities Are Associated with Treatment Intolerance in Multiple Sclerosis. NEJM. 2018. Accessed July 20, 2020. https://www.jwatch.org/na45621/2018/01/02/comorbidities-are-associated-with-treatment-intolerance