Multiple Sclerosis (MS) Prevalence, Disease-Modifying Drug (DMD) Therapy Use and Adherence, and Total Medical and Pharmacy Claims Expense Associated with MS in a 15 Million Commercially Insured Population

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Background

- Multiple Sclerosis (MS) is a chronic autoimmune disease of the central nervous system characterized pathologically by demyelination and axonal damage.[1]
- Despite MS drugs being a leading driver of pharmacy benefit costs, there are few published studies describing both MS prevalence and treatment cost of MS including the disease modifying drugs (DMDs).
- MS is classified based on initial disease course into: Relapsing Remitting (RR) MS — about 85% of patients, and Primary Progressive (PP) MS — about 15% of patients. After 10 to 15 years, about 70% of RRMS patients develop a progressive course, Secondary Progressive (SP) MS.[2]
- Revisions in 2013 of MS clinical course categories (phenotypes) emphasize the similarities between PPMS and SPMS, grouping them together as "progressive MS," and add subcategories (modifiers) to both RRMS and progressive MS based on presence or absence of active disease and progression.[3]
  - Active disease (clinical and/or magnetic resonance imaging [MRI]) is thought to result from inflammatory processes that may respond to treatment with current DMDs.[4]
  - Progression of damage and disability is thought to result primarily from degenerative processes that do not respond to current DMDs.[4]
- There is only one ICD-10 (and one ICD-9) diagnosis code for MS, so diagnosis codes do not provide a means of sub-classifying MS from administrative claims data.
- More than a dozen different medications have been approved by the Food and Drug Administration (FDA) for RRMS. In March 2017, ocrelizumab (Ocrevus®) became the first drug approved by the FDA for treatment of PPMS. Ocrelizumab was also approved for RRMS.
- Poor adherence to, or discontinuation of, DMD therapy may reduce its clinical benefit. A recent systematic review of published studies that reported a measurement of adherence to DMDs found 24 studies that met inclusion criteria.[5] In these studies, adherence ranged from 41% to 88%, using different methods, some of which used variable and some fixed intervals (denominators).
- There is interest in the current, real-world, MS health care costs that are not for DMDs. Understanding the MS medical care costs that are not associated with the DMD drug therapy allows for estimating the potential medical care cost off-set from improved DMD drug adherence.
- It is commonly stated that medical costs will be decreased through improved MS DMD drug adherence. However, it is unclear as to whether the medical cost savings will result in a return on investment (ROI) or added costs, i.e., a negative ROI.

Objective

- In a large commercial population, to determine:
  1) MS prevalence;
  2) Percentage of MS members treated with a DMD and DMD adherence assessed using the proportion of days covered (PDC); and
  3) Annual total pharmacy (Rx) and medical claims expense for MS members compared with a matched sample of members without MS.

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Methods

- From a monthly average of 15 million commercially insured members, we identified all members who were continuously eligible from October 2013 through September 2017 (four years) and younger than 65 years of age as of Sept. 30, 2017.
- Members with MS were defined as those with two or more inpatient or three or more outpatient medical claims with an MS diagnosis code, or a claim for an MS DMD other than natalizumab, since natalizumab is also used for Crohn's disease.[6]
- For each member identified with an MS diagnosis, the number of days covered by any DMD, switching allowed, was determined for the interval between October 2016 and September 2017 using the incurred dates of any DMD claims. All claims with a date incurred October 2015 through September 2017 were evaluated. Days supply was extracted directly from the pharmacy claim and for medical claims an assumed number of days until next treatment, based on dosing specified in product insert, was used to determine days supply.
  - Adherence was calculated as the number of days covered out of the 365 days in the year 3 measurement period, Oct. 1, 2016 through Sept. 30, 2017, allowing for claims prior to Oct. 1, 2016 with day supplies on or after Oct. 1, 2016 to be counted toward the adherence proportion of days covered calculation. By convention, PDC 80% or greater was described as "adherent" and less than 80% as "not adherent."
  - DMD cost per day: The mean cost per covered day, October 2016 to September 2017, was calculated as the sum of allowed amount for all DMD claims divided by the sum of covered days.
- A matched comparison group (notMS) was used to estimate how much in total and which categories of claims expense were associated with MS. The notMS group was randomly selected from all members continuously enrolled for four years who had no medical claims with an MS diagnosis code and no claims for a DMD during these four years. The notMS group was selected by matching to the MS members 5:1 on one-year age group, gender and health plan.
- All pharmacy claims were categorized by National Drug Codes (NDC). All medical outpatient claims were categorized by Healthcare Common Procedure Coding System (HCPCS) codes. All medical inpatient facility claims were categorized by MS-DRGs. Inpatient professional claims were categorized by first line diagnosis codes.
  - Expense is the sum of insurer and member payments ("allowed amount") without adjustment for rebates or coupons.
  - Mean total and by-category expense for the MS members minus that for the matched notMS members is reported as excess expense associated with MS.

Results

- Out of 4.04 million continuously enrolled members, 8,356 (0.21% total, 0.32% of females, 0.10% of males) were categorized as MS. **Table 1** shows prevalence per 100,000 eligible members by age and gender.
  - MS prevalence was a little over three times as high in females as in males, peaked for both genders between 40 and 49 years of age, and included members younger than 18 years. The lower prevalence of MS in the oldest age categories could be explained by disproportionate disenrollment from commercial insurance among older members with MS.
  - This study used the same criteria for identifying members with MS as a published study of MS prevalence in a commercially insured population, except that our study used claims for four years and the published study used claims for only one year.[6]
    - Prevalence in the published study[6] can be back-calculated from one of its tables as 160.2 per 100,000 age 5 to 64 years, which is 78.2% of the prevalence estimated in our study (206.9 per 100,000).
    - In a separate analysis of our study, that limited claims information to the most recent 12 months, the prevalence estimate was 169.1 per 100,000 aged 5 to 64.
- Of the 8,356 study members with MS, 5,514 (66.0%) had a DMD claim in the most recent 12 months and an additional 819 (9.8%) in the preceding 36 months. **Table 1** shows the proportion with any DMD claim by age categories.
  - A substantially higher percentage, 4,404 of 5,592 (78.8%), of MS members age 18 to 54 years had a DMD claim in four years, compared with MS members age 55 to 64 years, 1,915 of 2,740 (69.9%). It is possible that: a) many of the members with no history of DMD therapy have progressive MS, either PPMS or SPMS, without evidence of clinical or MRI activity judged as justifying DMD therapy, and b) the decline with age in percentage using a DMD reflects the expected relative increase of SPMS.
- **Table 2** summarizes DMD pharmacy plus medical claims between October 2016 and September 2017 by drug.
  - Glatiramer acetate, interferon products and dimethyl fumarate together accounted for 3,849 (69.8%) of the 5,514 MS members with a DMD claim. In a recent review, these were the DMDs assessed as safest but not the most effective.
  - Of the 188 members starting therapy with ocrelizumab, at least 152 (80.9%) had previously been treated with an MS DMD approved only for RRMS.
  - The table also quantifies off-label use of rituximab and ofatumumab, defined as claim lines that had an MS diagnosis code and none for any other known on- or off-label use of these drugs.
- **Table 3** compares claims expense per patient per year (PPPY) for the MS members and matched members without MS.
  - $84,712 PPPY total claims cost for MS members with a DMD claim, October 2016 to September 2017, of which $68,544 (80.9%) was for DMDs.
  - $63,175 total claims cost PPPY for all MS members, i.e., those with and without DMD utilization, of which $45,231 (71.6%) was for DMDs and $17,884 (28.4%) was for all other medical and pharmacy claims.
  - $7,642 PPPY total claims cost PPPY for the matched members without MS.
  - Compared with matched group without MS, MS members had $10,301 PPPY excess medical care expense that was not for DMDs. The largest individual categories identified were:
    - MRIs of the brain and spinal cord – periodic MRIs are part of standard management;[8]
    - Dalfampridine (Ampyra®), a specialty drug approved to improve walking in MS;
    - Hospital inpatient stays for MS, presumably to manage acute exacerbations; and
    - Office visits, most commonly problem-based.

ADHERENCE

- 2,053 (37.2%) of the 5,514 MS members with a DMD claim in the most recent 12 months were non-adherent with a PDC less than 80% and mean number of days covered. The 2,053 non-adherent DMD members averaged 154 (42.2%) of covered days out of 365.
- Using the observed mean DMD cost of $234 per covered day, increasing these 2,053 members to PDC 80% would add $7,948 PPPY incremental DMD cost. Moving the 819 members with only previous history of DMD to becoming adherent to DMD therapy would add $6,710 PPPY.
- $14,648 PPPY is the estimated cost to obtain DMD adherence among the non-adherent DMD members and those members who recently discontinued DMD therapy.

Limitations

- This study uses only information from administrative claims to determine which members have MS.
  - Analyzing four years of claims for all study members increased sensitivity, identifying 20% more members with MS, compared with using only one year of claims. However, the possible loss of specificity and increase in false positives could not be determined.
  - In addition, there is published evidence that the diagnosis of MS is erroneous for some patients, perhaps as many as 10% of patients, including some treated with one or more DMDs for years.[6,9]
- The results are representative of a large commercially insured population, but cannot be extrapolated to non-commercial populations. A study of the total United States population using the Medical Expenditure Panel Survey found a highly disproportionate number of individuals with MS have public insurance.[10]
- There are many different adherence assessment methods. This study estimates the incremental cost of increasing DMD use by all MS members with a history of DMD use to at least 80% PDC, using a 365-day denominator for all, rather than using a different denominator for each member that begins with the first DMD claim for that member.
- This study only measures the direct, insurance claim costs associated with MS in a 12-month interval. However, MS is a disease with a course of several decades that also results in large indirect costs.

Table 1. Multiple Sclerosis (MS) Prevalence and MS Disease Modifying Drug (DMD) Therapy by Age and Gender

	Members meeting MS diagnosis criteria			MS members per 100,000 eligible members*			MS members (%) with disease modifying drug (DMD) claim		
Age (Years)	Female	Male	Total	Female	Male	Total	Year 3 DMD claim	DMD claim in years 0 to 2, but none in year 3	Any DMD claim in years 0 to 3
04 – 09	1	1	**2**	0.8	0.8	**0.8**	1 (50.0%)	–	1 (50.0%)
10 – 17	12	10	**22**	4.8	3.9	**4.3**	13 (59.1%)	–	13 (59.1%)
18 – 24	111	40	**151**	48.0	17.0	**32.4**	95 (62.9%)	10 (6.6%)	105 (69.5%)
25 – 29	98	26	**124**	141.2	33.9	**84.8**	87 (70.2%)	13 (10.5%)	100 (80.6%)
30 – 34	338	112	**450**	289.6	93.0	**189.7**	322 (71.6%)	37 (8.2%)	359 (79.8%)
35 – 39	591	209	**800**	373.4	134.3	**254.8**	573 (71.6%)	80 (10.0%)	653 (81.6%)
40 – 44	853	266	**1,119**	488.9	156.3	**324.7**	781 (69.8%)	118 (10.5%)	899 (80.3%)
45 – 49	1,124	309	**1,433**	537.1	151.1	**346.3**	997 (69.6%)	138 (9.6%)	1,135 (79.2%)
50 – 54	1,175	340	**1,515**	509.5	153.4	**335.0**	997 (65.8%)	156 (10.3%)	1,153 (76.1%)
55 – 59	1,189	349	**1,538**	475.2	146.8	**315.2**	976 (63.5%)	160 (10.4%)	1,136 (73.9%)
60 – 64	915	287	**1,202**	421.2	137.5	**282.2**	672 (55.9%)	107 (8.9%)	779 (64.8%)
Total	**6,407**	**1,949**	**8,356**	**316.2**	**96.9**	**206.9**	**5,514 (66.0%)**	**819 (9.8%)**	**6,333 (75.8%)**

Age = age as of Sept. 30, 2017; MS criteria = >= two inpatient or >= three outpatient medical claims with an MS diagnosis code or a claim for an MS DMD other than natalizumab; FDA-approved for MS; claim = pharmacy or medical benefit claim; Year 3 = October 2016 to September 2017; Year 0 to 2 = October 2013 to September 2016

*Study sample included 4.04 million commercially insured members who were continuously enrolled from October 2013 to September 2017 (four years).

Table 2. Multiple Sclerosis Members Using MS Disease Modifying Drugs (DMD) and Cost

			Claims for MS members, October 2016 to September 2017		
Drug	Route of administration	Trade name	MS members (%) N = 8,356	DMD expense (%)	Mean PPPY (all MS members)
FDA-approved for MS (DMDs):					
Glatiramer acetate	SC	Copaxone® or Glatopa®	1,516 (18.1%)	$85,973,570 (22.9%)	$10,289
Interferon	SC or IM	(four trade names*)	1,310 (15.7%)	$87,050,417 (23.2%)	$10,418
Dimethyl fumarate	PO	Tecfidera®	1,124 (13.5%)	$67,442,575 (17.9%)	$8,071
Fingolimod	PO	Gilenya®	653 (7.8%)	$43,645,555 (11.6%)	$5,223
Natalizumab	IV	Tysabri®	596 (7.1%)	$44,840,920 (11.9%)	$5,366
Teriflunomide	PO	Aubagio®	488 (5.8%)	$25,911,198 (6.9%)	$3,101
Ocrelizumab	IV	Ocrevus®	188 (2.2%)	$8,560,615 (2.3%)	$1,024
Alemtuzumab	IV	Lemtrada®	89 (1.1%)	$11,483,161 (3.1%)	$1,374
Daclizumab	SC	Zinbryta®†	18 (0.2%)	$824,574 (0.2%)	$99
Mitoxantrone	IV	Novantrone®	–	$0	$0
Any DMD			**5,514 (66.0%)**	**$375,732,585 (100.0%)**	**$44,966**
Not FDA-approved for MS (off-label use‡):					
Rituximab	IV	Rituxan®	89 (1.1%)	$2,653,919	$318
Ofatumumab	IV	Arzerra®	1 (0.0%)	$22,400	$3

Note: "MS members" does not sum to "Any DMD" because some members used two or more different DMDs.

DMD = disease modifying drug; FDA-approved for MS; PPPY = per patient per year; Mean PPPY (all MS members) = DMD expense divided by total number of MS members in study (8,356); SC = subcutaneous; IM = intramuscular; SC = subcutaneous; IV = intravenous

*Interferon beta-1a, IM (Avonex®), interferon beta-1a, SC (Rebif®), interferon beta-1b, SC (Betaseron® and Extavia®), peginterferon beta-1a, SC (Plegridy®)

†Daclizumab (Zinbryta®) was withdrawn from the market on March 2, 2018, after reports of serious adverse effects.

‡Rituximab and ofatumumab claims shown above were medical claims with a diagnosis code for MS and no diagnosis codes for any other known uses of these drugs; some MS members also had rituximab use (not shown above) that was coded for rheumatoid arthritis, non-Hodgkin's lymphoma, etc.

Conclusions

- Using real world integrated medical and pharmacy commercially insured members claims data, about two per 1,000 members were found to have an MS diagnosis.
- There may be an opportunity to increase MS DMD use in this MS population as 66% used a DMD in the most recent 12 months and an additional 10% appeared to have discontinued their DMD as they had no DMD claims in the most recent 12 months, but did have a DMD claim in the preceding three years.
- MS DMD adherence is poor, with four in 10 members not achieving an 80% DMD PDC in the most recent 12 months.
- MS is a very costly condition. At $63,200 average annual total health care cost, it was 8.3 times higher than matched members without MS. The primary reason for higher cost was DMD therapy, that accounted for over 80% of the excess cost.
- Excluding the cost of DMDs, the mean annual total health care cost for MS members was $17,900; $10,300 higher than for the matched members without MS at $7,600.
- A clinical program that moves all non-adherent DMD members to adherent and members who had discontinued DMD to a DMD adherent state would add an additional $14,700 PPPY in MS DMD costs to the current $63,200 PPPY total MS health care cost, for a new MS PPPY cost of $77,900. Unfortunately, the $14,700 PPPY in new MS DMD costs is more than could be potentially saved in non-DMD medical care costs, therefore it is not possible to obtain a direct medical cost offset return on investment from improving adherence.
- The value of treating more MS members with DMDs or improving adherence needs to be assessed from a societal perspective and with a time horizon of many years. Multiple studies attempting to assess the total value of DMD therapy have concluded that use of MS DMDs greatly exceeds conventional thresholds for cost-effectiveness without large reductions in the prices of these drugs.[11,12]

Table 3. Multiple Sclerosis (MS) Claims Expense Per Patient Per Year (PPPY) by Categories: MS Members Compared with Matched Members without MS

	Mean claims expense PPPY, October 2016 to September 2017						
	MS members by DMD therapy					Excess for MS**	
Expense category	No DMD in years 0 to 3 N = 2,023	No DMD in year 3, DMD in years 0 to 2 N = 819	DMD in year 3 N = 5,514	All MS members N = 8,356	Matched members without MS* N = 41,780	Mean PPPY	% of total excess
MS DMDs, total	**$0**	**$0**	**$68,544**	**$45,231**	**$0**	**$45,231**	**81.4%**
Pharmacy, DMDs	$0	$0	$56,439	$37,244	$0	$37,244	67.1%
Medical outpatient, DMDs	$0	$0	$11,702	$7,722	$0	$7,722	13.9%
Medical outpatient, DMD infusion	$0	$0	$402	$265	$0	$265	0.5%
Pharmacy, excluding DMDs	**$3,431**	**$4,454**	**$4,032**	**$3,928**	**$1,672**	**$2,256**	**4.1%**
Weakness – dalfampridine (Ampyra®)	$369	$937	$1,357	$1,077	$0	$1,077	1.9%
Spasticity & spasms	$371	$362	$345	$353	$55	$298	0.5%
Pain – opioids	$298	$209	$109	$165	$35	$129	0.2%
Bladder dysfunction	$107	$97	$155	$138	$12	$126	0.2%
Fatigue	$83	$109	$142	$125	$7	$117	0.2%
Relapses – corticotropin	$17	$179	$124	$103	$0	$103	0.2%
Depression/pain – antidepressants	$105	$99	$126	$118	$47	$71	0.1%
Erectile dysfunction	$31	$38	$54	$47	$12	$35	0.1%
All other pharmacy claims	$2,050	$2,422	$1,620	$1,803	$1,504	$299	0.5%
Medical outpatient, excluding DMDs	**$12,817**	**$12,815**	**$9,269**	**$10,475**	**$4,559**	**$5,916**	**10.7%**
MRI, brain or spinal cord	$1,057	$1,096	$1,814	$1,561	$64	$1,497	2.7%
Office visits	$1,232	$1,194	$1,186	$1,198	$624	$574	1.0%
Lab tests	$880	$818	$696	$752	$340	$413	0.7%
Rituximab	$720	$1,256	$106	$416	$25	$391	0.7%
Other imaging	$1,200	$1,086	$884	$980	$597	$383	0.7%
Immune globulin	$680	$1,066	$83	$324	$25	$299	0.5%
Physical therapy	$409	$448	$392	$402	$136	$265	0.5%
Durable medical equipment	$524	$390	$318	$375	$136	$239	0.4%
Emergency room visits	$433	$324	$259	$307	$152	$155	0.3%
Botulinum toxin	$82	$49	$72	$72	$11	$61	0.1%
All other medical outpatient claims	$4,838	$3,956	$2,949	$3,505	$2,179	$1,325	2.4%
Medical inpatient	**$5,409**	**$3,459**	**$2,868**	**$3,541**	**$1,411**	**$2,129**	**3.8%**
Multiple sclerosis	$433	$426	$652	$577	$0	$577	1.0%
Sepsis & urinary tract infection	$754	$375	$202	$352	$38	$315	0.6%
Musculoskeletal	$616	$571	$576	$585	$334	$251	0.5%
Other kidney & urinary tract	$117	$112	$18	$51	$2	$49	0.1%
Seizures	$33	$62	$53	$49	$5	$44	0.1%
Mood disorder	$70	$10	$22	$33	$6	$27	0.0%
Headache	$25	$0	$17	$14	$13	$0	0.0%
All other inpatient claims	$3,361	$1,902	$1,328	$1,877	$1,024	$853	1.5%
Total pharmacy + medical	**$21,658**	**$20,728**	**$84,712**	**$63,175**	**$7,643**	**$55,532**	**100.0%**
Pharmacy + medical, excluding DMDs	**$21,658**	**$20,728**	**$16,168**	**$17,944**	**$7,643**	**$10,301**	**18.6%**

MS = multiples sclerosis; DMD = disease modifying drug, FDA-approved for MS; DMD infusion = medical claim line expense for infusion of DMDs; Year 0 to 2 = October 2013 to September 2016; Year 3 = October 2016 to September 2017; PPPY = per patient per year

Spasticity & spasms = muscle relaxants (e.g., baclofen), anticonvulsants (e.g., pregabalin, gabapentin); bladder dysfunction = urinary antispasmodics; fatigue = modafinil, armodafinil, amantadine; durable medical equipment leading (excess) categories included wheelchairs and urinary catheters; emergency room visits = visits without hospital admission (visits with hospital admission were categorized as medical inpatient)

*Matched members without MS were randomly selected to match MS members 51:01 on gender, one-year age group and health plan.

**Excess MS expense as the mean PPPY extra expense per member with MS compared to the matched members without MS.

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