Journal of Medical Economics

ISSN: 1369-6998 (Print) 1941-837X (Online) Journal homepage: informahealthcare.com/journals/ijme20

Impact of medication adherence to disease-modifying drugs on severe relapse, and direct and indirect costs among employees with multiple sclerosis in the US

J. I. Ivanova, R. E. Bergman, H. G. Birnbaum, A. L. Phillips, M. Stewart & D. M. Meletiche

To cite this article: J. I. Ivanova, R. E. Bergman, H. G. Birnbaum, A. L. Phillips, M. Stewart & D. M. Meletiche (2012) Impact of medication adherence to disease-modifying drugs on severe relapse, and direct and indirect costs among employees with multiple sclerosis in the US, Journal of Medical Economics, 15:3, 601-609, DOI: 10.3111/13696998.2012.667027

To link to this article: https://doi.org/10.3111/13696998.2012.667027

Published online: 01 Mar 2012.

Journal of Medical Economics Vol. 15, No. 3, 2012, 601–609

1369-6998
doi:10.3111/13696998.2012.667027

Article 0150.R1/667027

Original article

Impact of medication adherence to disease-modifying drugs on severe relapse, and direct and indirect costs among employees with multiple sclerosis in the US

J. I. Ivanova
R. E. Bergman
Analysis Group, Inc, New York, NY, USA

H. G. Birnbaum
Analysis Group, Inc, Boston MA, USA

A. L. Phillips
EMD Serono, Inc., Rockland, MA, USA

M. Stewart
Pfizer, Inc., New London, CT, USA

D. M. Meletiche
EMD Serono, Inc., Rockland, MA, USA

Address for correspondence:
Jasmina Ivanova, MA, Manager, Analysis Group, Inc., 10 Rockefeller Plaza, 15th Floor, New York, NY 10020, USA.
Tel.: 212-492-8100; Fax: 212-492-8188;
jivanova@analysisgroup.com

Key words:
Disease-modifying drugs – Multiple sclerosis – Adherence – Costs – Relapse

Abbreviations:
DMD, disease-modifying drug; MS, multiple sclerosis

Accepted: 13 February 2012; published online: 1 March 2012
Citation: J Med Econ 2012; 15:601–9

Abstract

Objective:
To compare rates of severe relapse and total direct and indirect costs over a 2-year period between US-based employees with multiple sclerosis (MS) who were adherent and non-adherent to disease-modifying drugs (DMDs).

Methods:
Employees with ≥1 MS diagnosis (ICD-9-CM: 340.x) and ≥1 DMD pharmacy claim between 1/1/2002–12/31/2007 were identified from a large US administrative claims database. Patients had continuous coverage ≥6 months before (baseline) and ≥24 months after (study period) their index date (first DMD claim). Adherence was measured using medication possession ratio (MPR) over the study period. Patients with MPR ≥80% were considered adherent ($n=448$) and those with MPR <80% as non-adherent ($n=200$). Multivariate analyses were used to compare rates of severe relapse (inpatient or Emergency Department visit with MS diagnosis) and costs in 2007 dollars between DMD adherent and non-adherent patients. Direct costs were calculated as reimbursements to providers for medical services and prescription drugs excluding DMDs. Indirect costs included disability and medically-related absenteeism costs.

Results:
DMD adherent patients were on average older (43.5 vs 41.8 years, $p=0.015$) and more likely to be male (38.6% vs 26.0%, $p=0.002$) compared with non-adherent patients. Adherent patients had lower rates of depression, higher rates of previous DMD use, and higher baseline MS-related costs. After adjusting for differences in baseline characteristics, DMD adherent patients had a lower rate of severe relapse (12.4% vs 19.9%, $p=0.013$) and lower total (direct and indirect) costs ($14,095 vs $16,638, $p=0.048$) over the 2-year study period.

Conclusions:
In this study, DMD adherence was associated with a significantly lower rate of severe relapse and lower total costs over 2 years. Causality cannot be inferred because adherence and outcomes were measured over the same period. The study was subject to limitations associated with use of claims data and the absence of clinical measures.

Introduction

Multiple sclerosis (MS), a progressive degenerative disease of the central nervous system, affects an estimated 400,000 people in the US and 2.1 million worldwide[1,2]. Most people are diagnosed with MS between the ages of 20–50.

MS is 2–3-times more common in women than in men, more common in Caucasians of northern European ancestry and at northern latitudes that are farther from the equator[2]. A study of prevalence of MS in three US communities using medical records from 1998–2000 found that 3-year US age-adjusted prevalence estimates varied substantially from 47.2 per 100,000 population in the southernmost community studied (Texas) to 109.5 per 100,000 population in the northernmost study area (Ohio)[3]. MS is associated with a significant direct and indirect cost burden. Annual medical costs per MS patient have been reported to range from $7,000–$13,000 (costs measured in various years, 1991–1997)[4,5]. Annual MS-related charges (including pharmacotherapy) were reported at ~$13,000 among patients with MS and ~$19,000 among MS patients with at least one disease-modifying drug (DMD) claim (in 2004)[6]. The annual costs of treatment with DMDs estimated based on published 2009 Red Book Wholesale Acquisition Costs were $26,916–$28,932[7]. Other studies have reported annual medical and non-medical costs at over $47,000 per diagnosed MS patient in 2004 dollars[8–10]. Among employed individuals with MS, indirect costs including short- and long-term disability payments and medically-related absenteeism ($5769) were over 4-times higher than those of age- and gender-matched employed individuals without MS[11]. Physical and cognitive effects of MS, including weakness, fatigue, walking, balance and coordination problems, bladder complaints, bowel problems, and cognitive and visual impairment, may become more permanent and progressively disabling over time.

Patients with MS may experience one of four disease courses: relapse-remitting MS characterized by periods of relapse (or exacerbation) followed by remission during which time patients fully or partially recover from the deficits acquired during the relapse; primary-progressive MS characterized by steady worsening of neurological function without distinct relapses or remissions; secondary-progressive MS that begins as relapse remitting and then functioning steadily worsens; progressive-relapsing MS characterized by steadily worsening disease from the beginning, but with clear attacks of worsening neurologic function[12]. Treatment options for relapsing-remitting MS, the most common form of MS affecting ~85% of MS patients[12], include DMDs (i.e., glatiramer acetate, intramuscular interferon beta-1a, subcutaneous interferon beta-1a, interferon beta-1b, natalizumab, mitoxantrone, and fingolimod)[13]. Studies have found that DMDs reduce the frequency of MS attacks and some DMDs slow disability progression, measured by reduction in relapse rate and reduced deterioration in Expanded Disability Status Scale scores[14–23]. Use of DMDs has been associated with medical and indirect cost savings in MS patients compared with no DMD treatment[24]. Lower adherence may be associated with lower efficacy of therapy and thus with higher risk of relapse. Among patients treated with DMD, those with gaps in treatment of more than 90 days had ~2-times higher probability of experiencing a severe MS relapse during the same study period, compared with those without gaps[25]. Adherence to DMD was also associated with lower likelihood of MS-related hospitalization, MS relapse, and lower medical costs[26,27].

The objective of this study was to compare rates of severe MS relapse (an inpatient or Emergency Department (ED) visit with an MS diagnosis) and total direct and indirect costs between US employees with MS who were adherent and non-adherent to DMDs. Direct and indirect costs were evaluated from the employer perspective (i.e., direct costs included third-party reimbursements to providers, without patient co-pays; and indirect costs included employer payments for disability and medically-related absenteeism). This study is the first to examine differences in direct and indirect costs between DMD-adherent and non-adherent patients.

Methods

Data source

The study sample was selected from a privately-insured claims database, Ingenix Employer Solutions, covering over 6 million beneficiaries (including employees, spouses, and dependents) from 23 US-based companies (1999–2007). The companies have operations nationwide in a broad array of job classifications and industries. The database contains de-identified information on patients' demographics, monthly enrollment history, and medical and pharmacy claims. Utilization of medical services was recorded with date of service, up to two associated diagnoses (i.e., ICD-9 diagnosis codes), performed procedures, billed charges, and actual payment amounts. The database also includes pharmacy claims identified by National Drug Code (NDC), date of prescription fill, days of supply, quantity, and actual payment amounts. Short- and long-term disability claims with dates of disability and actual employer payments (but no reason for disability) are available for employees.

Sample selection

The study sample was drawn from employees of companies providing disability data with at least one MS diagnosis (ICD-9-CM: 340.x) between January 1, 1999 and December 31, 2007 ($n = 4347$), who had at least one DMD pharmacy claim (i.e., glatiramer acetate [Copaxone®, FDA approved in 1996], intramuscular interferon beta-1a [Avonex®, 1993], subcutaneous interferon beta-1a [Rebif®, 2002], interferon beta-1b [Betaseron®, 1993], or natalizumab [Tysabri®, 2006])[13] on or after

January 1, 2002 ($n = 1855$). Note that more recently approved medications (interferon beta-1b [Extavia®, 2009] and fingolimod [Gilenya®, 2010]) which were not on the market during the period of available claims data and mitoxantrone were not included in this analysis. Patients who were enrolled in health maintenance organization (HMO) plans were excluded from this analysis, because claims data for these patients may not be complete. MS therapy claims were identified by NDC codes obtained from a pharmacy database [Master Drug Data Base (MDDB; Medi-Span, Indianapolis, IN)]. Analyses excluded employees with DMD administrations in a physician's office because the medical claims had no information about days supply and adherence could not be calculated without assumptions. The first DMD pharmacy claim on or after January 1, 2002 was defined as the study index date. The analysis focused on employees aged 18–62 years at index date and excluded patients with HMO coverage ($n = 1545$ after exclusion). Employees were required to have at least 6 months of continuous eligibility prior to their index DMD claim (baseline period) and 24 months of continuous eligibility after their index DMD (study period) to ensure that complete claims data were available ($n = 714$). Due to the 24-month continuous eligibility requirement after the index date, the index date for the study was no later than 1/1/2006. Because the research objective was to assess the impact of DMD adherence on total costs including indirect costs, employees who were on disability leave or had medically-related absenteeism for the entire duration of the 3-month period before the index date were excluded from the analyses (i.e., the research sample included only 'actively employed' employees who were not on permanent disability at study index date; $n = 648$ after exclusion). DMD adherence was measured using the medication possession ratio (MPR) calculated as the number of days of any available DMD medication over the 24-month study period as a percentage of the duration of the study period (i.e., 730 days)[28]. If patients had more than 730 days supply of DMD medication, it was assumed that they had 730 days of medication supply (i.e., MPR had a maximum of 100%). Patients with MPR $\geq 80\%$ were classified as adherent ($n = 448$) and those with MPR $< 80\%$ as non-adherent ($n = 200$)[29,30].

Study outcomes

The study outcomes were severe MS relapse and total (direct and indirect) costs excluding DMDs during the study period. Severe relapse was defined as an inpatient or ED visit with an MS diagnosis[25–27]. Direct costs included medical costs and pharmaceutical costs excluding the cost of DMDs. Medical costs were calculated during the 24-month study period based on payments from the insurer/managed care plan to healthcare providers for all care, including inpatient, outpatient (e.g., outpatient surgery), physician, and other ancillary services (e.g., physical therapy, laboratory services, etc.). Indirect costs over the study period included disability and medically-related disability costs. Disability costs for each patient were calculated as the product of the actual disability days (for any reason) over the study period and the overall average employer payment per disability day. The actual employer payments per disability day available in disability claims data are based on a percentage of the employee salary per day. The average employer payment per disability day among all DMD adherent and non-adherent employees with MS was used in the disability cost calculation to control for differences in income between DMD adherent and non-adherent patients. Medically-related absenteeism costs were calculated as the product of the overall average daily wage and medically-related absenteeism days (each hospitalization day accounted for a full day of work loss, while an outpatient or an ED visit accounted for half a day of work loss). Medically-related absenteeism days did not include days with medical services occurring during a period of disability.

All costs were inflated to 2007 US dollars (the most recent year of claims data used in this study) using the Consumer Price Index for Medical Care[31].

Patient characteristics

Patient characteristics compared between DMD adherent and non-adherent patients included demographics (i.e., age, gender), baseline comorbidities, and baseline severity indicators assessed using claims over the 6-month baseline period.

Baseline comorbidities included depressive disorders, migraine, chronic pain excluding migraine, Charlson Comorbidity Index including 17 physical conditions predictive of 1-year mortality, and individual physical comorbidities included in the index[32,33].

Baseline severity indicators included baseline use of DMD medications, any inpatient stay, any ED or outpatient/other visit, MS-related direct costs, non-MS related direct costs, and indirect costs (all measured in the 6-month baseline).

Resource use

All-cause direct healthcare resource use, MS-related direct resource use, and indirect resource use during the study period were compared between adherent and non-adherent patients using univariate analysis. Medical resource use was described by place of service (i.e., inpatient, ED, outpatient/other).

MS-related resource use was based on medical services claims with an MS diagnosis or a diagnosis for MS

symptoms, MS-related tests, imaging, or procedures, and prescriptions for DMD or MS symptom relief medications for common symptoms. MS-related tests and imaging included select laboratory tests for monitoring of immunomodulatory therapy (i.e., complete blood counts, platelet counts, and liver function tests), MRI, and lumbar puncture. MS-related medical services also included visits to neurologists as well as other treatments such as plasmapheresis, and IV immunoglobulin administrations. MS symptom relief medications comprised of corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) and salicylates, muscle relaxants, anti-convulsants, central nervous system stimulants, tricyclic anti-depressants, selective serotonin reuptake inhibitors, quarternary anticholinergics, anti-spasmodics, anti-diuretic hormone, and phosphodiesterase-5 inhibitors[5,34,35]. MS symptom relief medications were identified using NDC codes identified from the pharmacy database noted previously (i.e., MDDB).

Indirect resource use included rates of employees with at least one disability day and actual days of disability, and rates of employees with at least one medically-related absenteeism day and work days with medically-related absenteeism.

Statistical analyses

Patient characteristics were compared between DMD adherent and non-adherent employees with MS. Categorical variables were compared using Chi-squared tests; Fisher's exact tests were used for comparing proportions with patient count < 5. Continuous variables were compared using non-parametric Wilcoxon rank-sum tests.

Multivariate analyses were used to compare study outcomes (i.e., severe relapse and total costs excluding DMD) between DMD adherent and non-adherent employees controlling for baseline characteristics. A logistic regression model was used to estimate the risk-adjusted rate of MS relapse. A generalized linear model with log link and gamma distribution for the error term, commonly used in the analysis of skewed healthcare cost data, was used to estimate risk-adjusted total costs[36,37]. Covariates included DMD adherent indicator, age, gender, salaried employee, depression, arthritis, back/neck pain, migraine, Charlson Comorbidity Index, baseline inpatient stay, baseline ED visit, baseline DMD use, log of baseline direct costs, and log of baseline indirect costs. Risk-adjusted outcomes among DMD adherent and non-adherent employees were calculated as the predicted outcomes from the multivariate models assuming that all patients were DMD adherent or assuming all patients were non-adherent, respectively.

As a sensitivity analysis, the multivariate analyses were also conducted excluding 30 women who had a pregnancy diagnosis (ICD-9-CM: 630–679, V22–V23, V72.42) during the study period. Pregnant women are more likely to discontinue DMD therapy during pregnancy, thereby become classified as non-adherent to DMD therapy. Moreover, inpatient or ED visits due to pregnancy might be coded with an additional MS diagnosis and such visits could be misclassified as severe MS relapses.

All analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, NC). *P*-values less than or equal to 0.05 were considered to indicate statistically significant differences.

Results

Baseline characteristics and comorbidities

Employees meeting sample selection criteria had a mean (median) MPR of 81.1% (92.9%). The study sample included 448 patients classified as DMD adherent and 200 patients classified as non-adherent to DMD. DMD adherent employees were on average significantly older (43.5 year old) compared with non-adherent employees with MS (41.8 years old) and significantly more likely to be male (38.6% vs 26.0%). The comorbidity profile was similar between DMD adherent and non-adherent employees with MS with the exception of a significantly lower rate of depression among adherent patients (4.7% vs 9.5%). During the baseline period, a significantly higher proportion of adherent employees had DMD therapy (49.1% vs 40%). DMD adherent employees had a significantly lower rate of ED visits during the baseline period, similar indirect costs and significantly higher direct costs ($6805 vs $6114) due to higher MS-related direct costs compared with non-adherent employees (Table 1).

Two-year study period resource use

During the 24-month study period, DMD adherent employees had a significantly lower rate of severe MS relapse (12.5% vs 19.5%) compared with non-adherent employees as well as significantly lower rates of MS-related inpatient visits (7.6% vs 12.5%) and MS-related ED visits (8.9% vs 15.0%). A higher proportion of DMD adherent employees had MS-related laboratory tests and imaging (83.9% vs 75.5%). MS symptom relief therapy use was similar between DMD adherent and non-adherent employees with the exception of a significantly lower rate of CNS stimulants among the adherent employees (20.5% vs 28.5%). DMD adherent employees also had significantly lower rates of all-cause inpatient visits (11.2% vs 20%) and ED visits (34.6% vs 43.5%) and a similar rate of outpatient/other visits.

Table 1. Baseline characteristics.

	DMD adherent ($n=448$)	Non-adherent ($n=200$)	p-value†
Demographics, % (*n*)			
Age, mean (SD)	43.5 (8.0)	41.8 (8.1)	0.0152*
Male	38.6% (173)	26.0% (52)	0.0018*
Employed	100.0% (448)	100.0% (200)	–
Salaried,	25.4% (114)	18.5% (37)	0.0533
Baseline comorbidities, % (*n*)			
Selected mental health comorbidities			
Depressive disorders	4.7% (21)	9.5% (19)	0.0187*
Bipolar disorders	0.4% (2)	1.0% (2)	0.5910
Anxiety disorders	2.2% (10)	4.0% (8)	0.2059
Chronic pain			
Arthritis	23.2% (104)	18.5% (37)	0.1791
Back or neck pain	29.0% (130)	31.0% (62)	0.6097
Fibromyalgia	2.5% (11)	1.5% (3)	0.5667
Migraine	2.7% (12)	4.0% (8)	0.3689
Charlson Comorbidity Index, mean (SD)	0.2 (0.8)	0.2 (0.5)	0.2758
Baseline resource use, % (*n*)			
DMD medication use	49.1% (220)	40.0% (80)	0.0317*
Inpatient stay	9.2% (41)	12.5% (25)	0.1930
ED visit	17.2% (77)	24.0% (48)	0.0423*
Outpatient/other visit	98.2% (440)	99.5% (199)	0.2874
Non MS-related direct costs, mean (SD)‡	$1709 ($3188)	$1787 ($2951)	0.4257
MS-related direct costs, mean (SD)‡	$5096 ($4352)	$4327 ($6171)	<0.0001*
Total direct costs, mean (SD)‡	$6805 ($5587)	$6114 ($7804)	0.0004*
Indirect costs, mean (SD)‡	$645 ($1461)	$595 ($1053)	0.9456

DMD, disease-modifying drug; ED, Emergency Department; MS, multiple sclerosis; *n,* number of patients; SD, standard deviation.
*Statistically significant difference at 0.05 level.
†Categorical variables were compared using Chi-squared tests; Fisher's exact tests were used for comparing proportions with patient count <5. Continuous variables were compared using non-parametric Wilcoxon rank-sum tests.
‡Costs in 2007 USD.

In regards to indirect resource use, there were no significant differences in the rate of disability and the distribution of disability days between adherent and non-adherent employees. A significantly higher proportion of adherent employees had medically-related absenteeism days, but the distribution of medically-related absenteeism days was not significantly different between adherent and non-adherent employees (Table 2).

Two-year study period direct and indirect costs (unadjusted)

DMD adherent employees had similar MS-related direct healthcare costs excluding DMD costs compared with non-adherent employees ($5636 vs $6010). Medications for relief of MS symptoms accounted for ~25.0% of MS-related direct costs, outpatient/other visits for 63.4% and inpatient visits 10.5%. All-cause direct costs were also lower, although not significantly, among adherent employees compared with non-adherent employees ($10,906 vs $12,044). DMD adherent employees had significantly lower inpatient and ED costs. There were no significant differences in indirect costs ($3518 vs $4114) and unadjusted total costs ($14,424 vs $16,158) between adherent and non-adherent employees (Table 3).

Two-year study period severe relapse and total costs (risk-adjusted)

After controlling for baseline differences, the risk-adjusted rate of severe relapse during the study period was significantly lower for DMD adherent employees compared with non-adherent employees (12.4% vs 19.9%) (Table 4). The total risk-adjusted costs excluding DMD costs were also significantly lower among adherent employees ($14,095 vs $16,638) (Table 4).

The sensitivity analyses excluding 30 women with a pregnancy diagnosis during the study period had similar findings, but differences in rates of severe relapse and costs were not statistically significant, in part due to the smaller sample size. After excluding pregnant women, the average risk-adjusted rate of severe relapse was 12.7% among DMD adherent employees and 18.5% among non-adherent employees, $p=0.060$. Study period risk-adjusted total costs excluding DMD were on average $13,895 among DMD adherent employees and $16,172 among non-adherent employees, $p=0.079$.

Table 2. Two-year study period resource use.

	DMD adherent ($n = 448$)	DMD non-adherent ($n = 200$)	p-value†
Proportion (number) of patients with at least one:			
MS-related direct resource use			
Severe MS relapse	12.5% (56)	19.5% (39)	0.0200*
Inpatient visit	7.6% (34)	12.5% (25)	0.0447*
ED visit	8.9% (40)	15.0% (30)	0.0215*
Outpatient/other visits	99.1% (444)	98.5% (197)	0.6824
Medication used for MS symptom relief			
Anti-convulsant	29.2% (131)	35.5% (71)	0.1121
Anti-cholinergic	0.4% (2)	1.0% (2)	0.5910
Anti-diuretic hormone	1.1% (5)	1.5% (3)	0.7074
Central muscle relaxant	28.8% (129)	30.5% (61)	0.6596
CNS stimulant	20.5% (92)	28.5% (57)	0.0260*
Corticosteroid	52.5% (235)	53.5% (107)	0.8056
NSAID or salicylate	16.1% (72)	20.5% (41)	0.1699
Phosphodiesterase-5 inhibitor	7.6% (34)	5.5% (11)	0.3338
SSRI	27.5% (123)	35.0% (70)	0.0524
Tricyclic	9.2% (41)	9.0% (18)	0.9505
Urinary tract anti-spasmodic	13.4% (60)	16.0% (32)	0.3797
All-cause direct resource use			
Inpatient visits	11.2% (50)	20.0% (40)	0.0027*
ED visits	34.6% (155)	43.5% (87)	0.0305*
Outpatient/other visit	99.6% (446)	99.0% (198)	0.5910
Indirect resource use			
Disability day	13.2% (59)	17.5% (35)	0.1482
Medically-related absenteeism day	96.9% (434)	93.5% (187)	0.0470*
Work-loss day	98.0% (439)	96.0% (192)	0.1430
Mean, [Median], (SD) number of:			
All-cause direct resource use			
Inpatient visits	0.2, [0.0], (0.8)	0.6 [0.0], (3.9)	0.0023*
ED visits	0.6, [0.0], (1.1)	0.9 [0.0], (1.7)	0.0210*
Outpatient/other visits	28.6, 19.0], (27.0)	28.8, [21.0], (28.7)	0.7792
Prescription drug claims	11.9, [10.0], (9.9)	14.0, [11.0], (11.6)	0.0581
Indirect resource use days			
Disability days	18.3, [0.0], (79.6)	23.2, [0.0], (84.3)	0.1315
Medically-related absenteeism days	6.9, [3.5], (14.8)	7.2, [3.0], (15.1)	0.2420
Work-loss days	25.2, [3.5], (80.7)	30.4, [3.5], (84.8)	0.8282

CNS, central nervous system; DMD, disease-modifying drug; ED, Emergency Department; MS, multiple sclerosis; NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation; SSRI, selective serotonin re-uptake inhibitor.
*Statistically significant difference at 0.05 level.
†Categorical variables were compared using Chi-squared tests; Fisher's exact tests were used for comparing proportions with patient count <5. Continuous variables were compared using non-parametric Wilcoxon rank-sum tests.

Discussion

All DMD therapies are associated with reduced risk of MS relapse, while some DMDs also impact disability progression[9,10,12–14]. After adjusting for differences in baseline characteristics, DMD adherent employees with MS compared with non-adherent employees had a 7.5 percentage point lower relapse rate and an average of $2544 lower total costs excluding DMD medication per person over the 2-year study period. Adherence was associated with lower relapse rate and costs after excluding pregnant women, but differences were not statistically significant, in part due to smaller sample size.

The average adherence rate among employees meeting the sample selection criteria was 81.1% and was close to the high end of the range of previously reported adherence rates (28–87%)[38]. The variation in the published estimates of adherence is understandable because different approaches have been used to measure adherence—discontinuation, medication gaps, missing any injections. Another possible explanation for the high rate of adherence observed here could be that the study focused on employees with ongoing DMD therapy (~40–49% of patients were treated with a DMD in the 6-month period before the index date) rather than newly initiated patients. Patients initiating DMD treatment could be more likely to discontinue treatment. A study of 6134 MS patients initiating DMD medications between 1996–2004 found that 13.1% of patients discontinued initial therapy by 6 months after initiation, 26.0% discontinued by 12 months and 33.9% discontinued by 18 months[39]. Patients often discontinue because of perceived lack of efficacy and adverse events[22,40]. Previous studies reported that adherence is affected by factors such as history of adherence and

Table 3. Two-year study period direct and indirect costs (unadjusted)†.

	DMD adherent ($n = 448$) Mean [Median] (SD)	DMD non-adherent ($n = 200$) Mean [Median] (SD)	*p*-value
MS-related direct costs (excluding DMD)	$5636 [$2952] ($8419)	$6010 [$2999] ($9625)	0.4858
MS-related drug costs (excluding DMD)			
Medications for relief of MS symptoms	$1411 [$364] ($2866)	$1506 [$324] ($2872)	0.6173
MS-related medical costs	$4226 [$2085] ($6875)	$4504 [$1761] ($8371)	0.1860
Inpatient	$420 [$0] ($2942)	$1010 [$0] ($4304)	0.0270*
ED	$55 [$0] ($303)	$74 [$0] ($314)	0.0076*
Outpatient/other	$3750 [$1970] ($5831)	$3420 [$1417] ($5826)	0.0159*
All-cause direct cost (excluding DMD)	$10906 [$6630] ($13801)	$12044 [$6641] ($15401)	0.8753
Drug cost (excluding DMD)	$3071 [$1451] ($4973)	$3234 [$1301] ($4876)	0.9179
Medical cost	$7835 [$4163] ($11137)	$8811 [$4258] ($13236)	0.7739
Inpatient	$768 [$0] ($4444)	$2061 [$0] ($7254)	0.0018*
ED	$175 [$0] ($510)	$287 [$0] ($702)	0.0044*
Outpatient/other	$6893 [$3923] ($9296)	$6462 [$3732] ($8339)	0.1943
Indirect costs	$3518 [$799] ($9043)	$4114 [$799] ($9409)	0.9010
Disability	$1942 [$0] ($8441)	$2462 [$0] ($8941)	0.1315
Medically-related absenteeism	$1576 [$799] ($3376)	$1652 [$685] ($3452)	0.2420
Total costs (excluding DMD)	$14424 [$8018] ($19079)	$16158 [$7776] ($21982)	0.7131

DMD, disease-modifying drug; ED, Emergency Department; MS, multiple sclerosis; SD, standard deviation.
*Statistically significant difference at 0.05 level.
†Costs in 2007 USD were compared using nonparametric Wilcoxon rank-sum tests.

Table 4. Two-year study period outcomes (risk-adjusted), $n = 648$.

	DMD adherent			DMD non-adherent			Difference [1] − [4]	*p*-value [1] vs [4]
	Average risk-adjusted estimate [1]	Median [2]	SD [3]	Average risk-adjusted estimate [4]	Median [5]	SD [6]		
Severe MS relapse rate†	12.4%	9.7%	(8.6%)	19.9%	16.5%	(11.6%)	−7.5%	0.0127*
Total costs (excluding DMD)‡$	$14,095	$11,951	($8,693)	$16,638	$14,108	($10262)	−$2544	0.0475*
Direct costs (excluding DMD)‡$	$10,653	$9,276	($5,697)	$12,217	$10,637	($6534)	−$1564	0.0929
Indirect costs‡$	$3411	$2510	($3577)	$4575	$3367	($4797)	−$1164	0.0240*

DMD, disease-modifying drug; MS, multiple sclerosis; SD, standard deviation.
*Statistically significant difference at 0.05 level.
†A logistic regression model was used to estimate the risk-adjusted rate of study period severe MS relapse among DMD adherent and non-adherent patients controlling for baseline characteristics. Risk-adjusted MS relapse rates among DMD adherent and non-adherent employees were calculated as the predicted probability of relapse assuming that everyone in the sample was adherent or non-adherent, respectively.
‡Generalized linear models with a log link and gamma distribution for the error term were used to estimate risk-adjusted costs with DMD adherence and non-adherence, adjusting for baseline characteristics. Risk-adjusted costs among DMD adherent and non-adherent employees were calculated as the predicted costs assuming that everyone in the sample was adherent or non-adherent, respectively.
$Costs in 2007 USD.

mental health comorbidity[41]. Moreover, employees, as opposed to non-employed patients, may have additional incentive to adhere to therapy in an effort to stay healthy enough to continue to work. In this study, DMD adherent patients were on average older, had a lower rate of depression, and had a higher rate of baseline DMD use. Similar findings were reported in a recent internet survey of 708 patients with relapsing forms of MS[42]. DMD adherent patients in our study also had higher baseline MS-related direct costs, suggesting that these patients may have more severe MS than non-adherent patients.

This study confirmed prior findings that DMD adherence is associated with a lower probability of relapse[16,26,27]. No previous studies have evaluated direct and indirect costs associated with DMD adherence. DMD treatment initiation compared with no DMD treatment was associated with average annual savings of $1794 in medical costs (excluding DMD costs) and savings of $801 in indirect disability and medically-related absenteeism costs over 2 years[15].

The sample used in this study consists of employees drawn from a US geographically diverse database of many large employers. The study focuses on MS patients treated with DMD in a relatively recent period 2002–2007. The claims database provides information about real-world MS treatment patterns, adherence, relapses, and costs.

Moreover, the availability of disability claims data allows the estimation of work loss costs differences associated with adherence.

A key limitation involves issues of generalizability. The study results may not be generalizable to the overall population of patients with MS. The sample was limited to employees diagnosed with MS who remained employed for the duration of the study period. To ensure complete capture of medical and disability costs, employees were required to be continuously eligible for health coverage for at least 24 months after the index date. Therefore, employees who died during the follow-up period or left the health plan were excluded from the analyses. We attempted to examine MS patients treated with all available DMDs during the analytic period; however only two patients used natalizumab, mitoxantrone was not used, and fingolimod was not yet on the market; therefore the study findings are relevant only for patients adherent and non-adherent to injectable DMDs. The study is also subject to the usual limitations associated with use of claims data and the absence of clinical measures. The study relied on the accuracy of diagnosis coding in claims data to identify patients with MS as well as on the accuracy of DMD days supply information in pharmacy claims in order to calculate medication possession ratio and assess adherence. Severe MS relapse in this study was defined as an inpatient or ED visit with an MS diagnosis. It is possible that some MS-related ED visits were not due to a relapse and the overall rate of severe MS relapse may be overestimated, however it is unlikely that there were systematic differences of MS-related ED visits with and without relapse between DMD adherent and non-adherent patients. Because no detail on precise MS diagnosis was available, it was not possible to consider differences in disease severity and distinctions between types of multiple sclerosis. Baseline MS-related costs were used as a proxy for disease severity. Furthermore, this study likely underestimated work loss because it did not capture on-the-job productivity or work absences without use of medical services. Finally, the study evaluated the association between adherence and severe relapse and costs. Both adherence and study outcomes of severe relapse and costs were measured over the same 2-year study period, thus causality cannot be inferred. For example, patients experiencing MS relapse may improve their medication adherence in order to prevent future relapse or may be more likely to discontinue treatment believing that the medication is ineffective. Further analyses to understand causality are needed.

Conclusion

In conclusion, DMD therapy has been associated with a reduction of MS severe relapse rate and medical and indirect costs savings. The findings presented here suggest that, over the 2-year study period, DMD adherent employees with MS had a lower severe relapse rate and lower total costs (excluding DMD cost) compared with non-adherent employees.

Transparency

Declaration of funding

Research funding for this study was provided by EMD Serono, Inc., Rockland, MA and Pfizer, Inc., New York, NY to Analysis Group, Inc.

Declaration of financial/other relationships

JI, RB, and HB are employees of Analysis Group, Inc. AP and DM are employees of EMD Serono, Inc., Rockland, MA. MS is an employee of Pfizer, Inc., New London, CT. AP, DM, and MS provided feedback on the development of the analysis plan, reviewed study results and manuscript; provided feedback on manuscript, and approved the final manuscript.

Acknowledgments

The peer reviewers on this manuscript have disclosed any relevant financial relationships.

References

1. Noonan CW, Kathman SJ, White MC. Prevalence estimates for MS in the Unites States and evidence of an increasing trend in women. Neurology 2002;59:136-8
2. National Multiple Sclerosis Society. ''Who gets MS?''. http://www.nationalmssociety.org/index.aspx. Accessed January 27, 2012
3. Noonan CW, Williamson DM, Henry JP, et al. The prevalence of multiple sclerosis in 3 US communities. Prev Chronic Dis 2010;7:A12. http://www.cdc.gov/pcd/issues/2010/jan/08_0241.htm. Accessed January 27, 2012
4. Pope GC, Urato CJ, Kulas ED, et al. Prevalence, expenditures, utilization, and payment for persons with MS in insured populations. Neurology 2002; 58:37-43
5. Ollendorf DA, Jilinskaia E, Oleen-Burkey M. Clinical and economic impact of glatiramer acetate versus beta interferon therapy among patients with multiple sclerosis in a managed care population. J Manag Care Pharm 2002; 8:469-76
6. Prescott JD, Factor S, Pill M, et al. Descriptive analysis of the direct medical costs of multiple sclerosis in 2004 using administrative claims in a large nationwide database. J Manag Care Pharm 2007;13:44-52
7. Goldberg LD, Edwards NC, Fincher C, et al. Comparing the cost-effectiveness of disease-modifying drugs for the first-line treatment of relapsing-remitting multiple sclerosis. J Manag Care Pharm. 2009;15:543-55
8. Bourdette DN, Prochazka AV, Mitchell W, et al. VA Multiple Sclerosis Rehabilitation Study Group. Health care costs of veterans with multiple sclerosis: implications for the rehabilitation of MS. Arch Phys Med Rehabil 1993; 74:26-31
9. Whetten-Goldstein K, Sloan FA, Goldstein LB, et al. A comprehensive assessment of the cost of multiple sclerosis in the United States. Mult Scler 1998; 4:419-25
10. Kobelt G, Berg J, Atherly D, et al. Costs and quality of life in multiple sclerosis: a cross-sectional study in the United States. Neurology 2006;66:1696-702
11. Ivanova JI, Birnbaum HG, Samuels S, et al. The cost of disability and medically related absenteeism among employees with multiple sclerosis in the US. Pharmacoeconomics 2009;27:681-91

12. National Multiple Sclerosis Society. What is MS? http://www.nationalmssociety.org/about–multiple–sclerosis/what–we–know–about–ms/what–is–ms/index.aspx. Accessed February 1, 2012
13. National Multiple Sclerosis Society. The MS Disease-Modifying Medications General Information. http://www.nationalmssociety.org/about–multiple–sclerosis/what–we–know–about–ms/treatments/index.aspx. Accessed February 1, 2012
14. Johnson KP, Brooks BR, Cohen JA, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. Neurology 1995;45:1268-76
15. Johnson KP, Brooks BR, Ford CC, et al. Sustained clinical benefits of glatiramer acetate in relapsing multiple sclerosis patients observed for 6 years. Mult Scler 2000;6:255-66
16. Jacobs LD, Cookfair DL, Rudick RA, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. Ann Neurol 1996; 39:285-94
17. Rudick RA, Goodkin DE, Jacobs LD, et al. Impact of interferon beta-1a on neurologic disability in relapsing multiple sclerosis. Neurology 1997;49:358-63
18. PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group. Randomised doubleblind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. Lancet 1998;352:1498-504
19. PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group and the University of British Columbia MS/MRI Analysis Group. PRISMS-4: long-term efficacy of interferon-beta-1a in relapsing MS. Neurology 2001;56:1628-36
20. The IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. Neurology 1993;43:655-61
21. The IFNB Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis Group. Interferon beta-1b in the treatment of multiple sclerosis: final outcome of the randomized controlled trial. Neurology 1995; 45:1277-85
22. Schwid SR, Panitch HS. Full results of the Evidence of Interferon Dose-Response-European North American Comparative Efficacy (EVIDENCE) study: a multicenter, randomized, assessor-blinded comparison of low-dose weekly versus high-dose, high-frequency interferon beta-1a for relapsing multiple sclerosis. Clin Ther 2007;29:2031-48
23. Polman CH, O'Connor PW, Havrdova E, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med 2006; 354:899-910
24. Birnbaum HG, Ivanova JI, Samuels S, et al. Economic impact of multiple sclerosis disease-modifying drugs in an employed population: direct and indirect costs. Curr Med Res Opin 2009;25:869-77
25. Okuda DT, Kozma CM, Dickson M, et al. Relationship between gaps in drug treatment for multiple sclerosis and incidence of exacerbations: findings from a national managed care database. Poster presented and the International Society for PharmacoEconomics and Outcomes Research 13th Annual International Meeting, Toronto, ON, May 3–7, 2008
26. Tan H, Cai Q, Agarwal S, et al. Impact of adherence to disease-modifying therapies on clinical and economic outcomes among patients with multiple sclerosis. Adv Ther 2011;28:51-61
27. Steinberg SC, Faris RJ, Chang CF, et al. Impact of adherence to interferons in the treatment of multiple sclerosis: a non-experimental, retrospective, cohort study. Clin Drug Investig 2010;30:89-100
28. Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity, and applications. J Clin Epidemiol 1997; 50:105-16
29. Erickson SR, Coombs JH, Kirking DM, et al. Compliance from self-reported versus pharmacy claims data with metered-dose inhalers. Ann Pharmacother 2001;35:997-1003
30. Pharmacy Quality Alliance. PQA Approved Measures. http://www.pqaalliance.org/files/PQA%20approved%20measures.pdf. Accessed June 28, 2010
31. Bureau of Labor Statistics. Consumer Price Index - All Urban Consumers CUSR0000SAM Seasonally Adjusted U.S. City Average Medical Care. http://data.bls.gov/pdq/SurveyOutputServlet;jsessionid=AAC19B5A8C853682CCB5F8CC770065FB.tc_instance4. Accessed February 1, 2012
32. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-83
33. Romano PS, Roos LL, Jollis J. Adapting a clinical comorbidity index for use with ICD-9-CM administrative data. J Clin Epidemiol 1993;46:1075-9
34. National Multiple Sclerosis Society. Symptoms. http://www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/symptoms/index.aspx. Accessed February 1, 2012
35. National Multiple Sclerosis Society. Medications Used in MS. http://www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/treatments/medications/index.aspx. Accessed February 1, 2012
36. Blough DK, Madden CW, Hornbrook MC. Modeling risk using generalized linear models. J Health Econ 1999;18:153-71
37. Blough DK, Ramsey SD. Using generalized linear models to assess medical care costs. Health Serv Outcomes Res Method 2000;1:185-202
38. Brandes DW, Callender T, Lathi E, et al. A review of disease-modifying therapies for MS: maximizing adherence and minimizing adverse events. Curr Med Res Opin 2009;25:77-92
39. Reynolds MW, Stephen R, Seaman C, et al. Persistence and adherence to disease modifying drugs among patients with multiple sclerosis. Curr Med Res Opin 2010;26:663-74
40. Tremlett HL, Oger J. Interrupted therapy. Stopping and switching of the β-interferons prescribed for MS. Neurology 2003;61:551-4
41. Holland N, Wiesel P, Cavallo P, et al. Adherence to disease-modifying therapy in multiple sclerosis: Part I. Rehab Nurs 2001;26:172-6
42. Treadaway K, Cutter G, Salter A, et al. Factors that influence adherence with disease-modifying therapy in MS. J Neurol 2009;256:568-76