

Treatment patterns and health care resource utilization associated with dalfampridine extended release in multiple sclerosis: a retrospective claims database analysis

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Background: Although previous studies have demonstrated the clinical benefits of dalfampridine extended release (D-ER) tablets in patients with multiple sclerosis (MS), there are limited real-world data on D-ER utilization and associated outcomes in patients with MS.

Purpose: The objective of this study was to evaluate treatment patterns, budget impact, and health care resource utilization (HRU) associated with D-ER use in a real-world setting.

Methods: A retrospective claims database analysis was conducted using the HealthCore Integrated Research DatabaseSM. Adherence (measured by medication possession ratio, or [MPR]) and persistence (measured by days between initial D-ER claim and discontinuation or end of follow-up) were evaluated over 1-year follow-up. Budget impact was calculated as cost per member per month (PMPM) over the available follow-up period. D-ER and control cohorts were propensity-score matched on baseline demographics, comorbidities, and MS-related resource utilization to compare walking-impairment-related HRU over follow-up.

Results: Of the 2,138 MS patients identified, 1,200 were not treated with D-ER (control) and 938 were treated with D-ER. Patients were aged 51 years on average and 74% female. Approximately 82.6% of D-ER patients were adherent (MPR >80%). The estimated budget impact range of D-ER was \$0.014–\$0.026 PMPM. Propensity-score-matched D-ER and controls yielded 479 patients in each cohort. Postmatching comparison showed that the D-ER cohort was associated with fewer physician (21.5% vs 62.4%, $P<0.0001$) and other outpatient visits (22.8% vs 51.4%, $P<0.0001$) over the 12-month follow-up. Changes in HRU from follow-up to baseline were lower in the D-ER cohort for metrics including walking-impairment-related hospitalizations and emergency department visits.

Conclusion: The majority of D-ER patients were adherent to treatment. D-ER utilization was associated with fewer walking-impairment-related physician and outpatient visits, with lower HRU increase over time. The budget impact of D-ER was low.

Keywords: budget impact, costs, real-world, health outcomes, walking impairment

Introduction

Multiple sclerosis (MS) is a complex, progressive, immune-mediated disease affecting more than 2.3 million people worldwide, including an estimated 400,000 in the United States.¹ It is the third most common neurological cause of disability.² Although symptoms vary widely and may fluctuate over time, the most common symptoms include fatigue, pain, weakness, spasticity, and gait disturbances.¹ Most people with

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MS are diagnosed between 20 and 50 years of age and face considerable physical, emotional, and economic burdens.³ Direct medical costs were found to be nearly fivefold higher among those with newly diagnosed MS compared with healthy people.³ These costs become even higher when indirect costs, such as time lost from work, are considered.⁴

A significant portion of the burden of MS arises from the considerable disability caused by the disease over time, driven primarily by gait and motor disturbances.^{2,5} Approximately 75% of MS patients experience clinically significant walking disturbances.⁶ Regardless of the level of disability and disease duration, MS patients consider lower-limb function as their highest priority and a key component affecting their quality of life,⁷ independence, and perception of their ability to perform activities of daily living.⁸ MS patients with moderate and severe walking impairment face costs up to four and eight times higher, respectively, when compared with patients who are less disabled.⁹ Gait dysfunction is also associated with substantial social burden in terms of reduced productivity or inability to continue employment, disability, caregiver burden, and the need for physical and occupational therapy services, home modifications, and assistive devices.¹⁰

Based on consistent changes in walking speed demonstrated in clinical studies,^{11–14} dalfampridine extended-release (D-ER; known as prolonged-release fampridine in Europe and as fampridine modified- or sustained-release elsewhere) tablets, 10 mg twice-daily, were approved by the US Food and Drug Administration in January 2010 to improve walking in MS patients.¹³

Although D-ER has been on the market for 5 years and has been prescribed to more than 200,000 MS patients,¹⁵ there is limited information on its utilization and associated outcomes in a real-world environment. This study intends to fill the gap by investigating D-ER treatment patterns and budget impact as well as associated walking-impairment-related health care resource utilization (HRU).

Methods

Data source

This retrospective observational study used data from the HealthCore Integrated Research Database (HIRDSM, Wilmington, DE, USA). The HIRD consists of longitudinal pharmacy and medical-claims data associated with a large US commercial health insurer including, but not limited to, patient demographics, clinical characteristics, and treatment information such as medication use, laboratory tests, physician office visits, and hospital and emergency department (ED) visits.

This study was exempt from Institutional Review Board review and was fully compliant with applicable provisions of the Health Insurance Portability and Accountability Act. Patient confidentiality was maintained throughout the study, and all data remained anonymous as researchers had access to relevant datasets only after all individual patient identifiers were removed.

Study cohorts

For this study, claims connected to 20.3 million lives from a geographically diverse US population between January 1, 2009, and February 29, 2013, were extracted from the HIRD. The earliest D-ER claim was set as index date, and the index period was defined as January 1, 2010, to February 29, 2012. Patients were required to have at least two preindex MS-related claims (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] diagnosis code 340.xx) or pharmacy claims for disease-modifying therapies (DMTs) and have at least 12 months of preindex and postindex continuous enrollment. Patients were excluded from the analysis if they were <18 years old or had other etiologies of gait/movement dysfunction as indicated by medical claims for stroke, Parkinson's disease, neoplasm of the brain, brain abscess, tendonitis or tendon injury, and/or cerebral palsy during the 12-month preindex period.

Patient baseline demographic and clinical characteristics were evaluated during the 12-month baseline period. Comorbidity burden was assessed via the Quan–Charlson comorbidity index (QCI).¹⁶ Individual comorbid conditions and symptoms commonly associated with MS were assessed based on ICD-9-CM codes. DMTs and other pharmacotherapeutic agents were identified based on generic product identifier and current procedure terminology codes.

A control cohort of patients was constructed for comparison of HRU and cost differences to the D-ER cohort. The control cohort contained patients with similar inclusion criteria to the D-ER cohort, except for requiring ≥ 1 claim for a walking-related disorder (ICD-9-CM 781.0x, 781.2x, 781.3x, or 719.7x; earliest claim was set as index date) and with no D-ER use.

Data analyses

D-ER treatment patterns and budget impact

Treatment patterns

D-ER treatment patterns were evaluated during the 12-month postindex period (inclusive of index date) and included

D-ER prescription-fill dose, number of D-ER prescription fills, D-ER daily pill count, and the time between prescription fills for patients with at least two D-ER prescriptions. Discontinuation was defined as a prescription-fill gap of >30 days past the expected refill date, which was defined as the last refill date plus days' supply as noted on the D-ER refill claim.¹⁷ Patients were considered persistent until discontinuation occurred. Persistence was measured as the time (days) between the index date and the date of discontinuation. For patients who did not discontinue, the number of days from index date to the end of the 12-month follow-up period was considered as the duration of persistence. A medication restart was defined as a refill of D-ER following discontinuation. Adherence to D-ER treatment was defined as the proportion of patients with a medication possession ratio (MPR) of $\geq 80\%$.¹⁷ MPR was calculated as the percentage of total number of days with D-ER pharmacy claims during the follow-up period divided by the number of days between the index date and the last refill date plus days' supply of the last refill.

Budget impact

Propensity-score matching was performed to balance the cohorts on baseline demographics and disease severity (see "Statistical Analysis" section). Estimates of cost offset by D-ER use were derived from the walking-impairment-associated medical cost difference between the propensity-score-matched D-ER and control cohorts. Walking-impairment-associated medical costs included inpatient hospitalization, ED, physician office visits, and other outpatient visits (laboratory tests, outpatient procedures, and other miscellaneous items involving ≥ 1 ICD-9-CM diagnosis for gait/movement dysfunction or walking-associated events). Budget impact was calculated as the cost of D-ER per member per month (PMPM) over the available follow-up period. Costs of D-ER were based on the cost of prescription fills for D-ER patients.

Health care resource utilization

HRU was compared between the propensity-score-matched D-ER and control cohorts. To control for potential confounding factors between cohorts due to the observational nature of the study, D-ER and control cohorts were propensity-score matched on baseline demographics, comorbidities, and MS-related resource utilization (see "Statistical Analysis" section).

Walking-impairment-related HRU was reported by place of service (inpatient hospitalization, ED, physician

office visits, and other outpatient visits, which included laboratory tests, outpatient procedures, and other miscellaneous items) and was based on medical claims using the same ICD-9-CM codes as were used for control cohort identification (ICD-9-CM 781.0x, 781.2x, 781.3x, or 719.7x). Physical or occupational therapy visits were identified based on current procedure terminology codes. Differences over time in these HRU metrics (change scores, defined as follow-up minus baseline) were also calculated within each cohort.

Statistical analysis

Descriptive analysis included means (standard deviation [SD]) and frequencies for baseline continuous and categorical variables, respectively. Comparisons between D-ER and control cohorts used two-sample *t*-tests or Wilcoxon rank-sum tests for the normal or nonnormally distributed continuous variables, and χ^2 -tests or Fisher's exact tests for the categorical variables. Change scores were compared across cohorts using two-sample *t*-tests. A *P*-value <0.05 was prespecified to indicate statistical significance.

The propensity-score matching was developed using a logistic regression that determined the likelihood (ie, propensity) of each patient initiating D-ER compared with those not initiating D-ER.^{18–20} A 1:1 D-ER-to-control match was conducted using each patient's propensity score. Balance across cohorts after matching was assessed using statistical testing as well as standardized differences. Standardized differences of >10 were considered to have potential clinical significance.²¹

Sensitivity analysis

To adjust for the difference in walking-impairment-related events at baseline between the D-ER and control cohorts, a subgroup analysis was conducted including only those patients with no medical claims for walking-related disorders prior to the index date in both the D-ER and control cohorts. HRU was compared across the two subgroups. This allowed balancing of D-ER and control cohorts with regard to walking-impairment-related claims prior to index date (in the main analysis patients with medical claims for walking-related disorders prior to the index date were excluded only in the control cohort). The aim of this sensitivity analysis was to assess if the difference in walking-impairment-related claims prior to index date in the D-ER and control cohorts had biased the HRU comparison between the two.

Results

Patient demographics and clinical characteristics at baseline

A total of 2,138 patients (938 D-ER; 1,200 control) met all study inclusion criteria (Figure 1). Patients were aged 51 years on average, with more than 73% female (Table 1). A large proportion of patients were treated by a neurologist (42.2%). The comorbidity burden, as measured by the Quan-Charlson comorbidity index, was low, suggesting a low overall prevalence of mortality-predictive complications (mean 0.74; Table 1). Muscular weakness or spasticity was the most frequently reported MS symptom (18.1%), followed by disturbances of skin sensation (16.1%) and dizziness (giddiness or vertiginous symptoms; 9.7%). The

most commonly prescribed DMT at baseline was interferon- β -1a (23.3%), followed by glatiramer acetate (21.5%). Pain medications were the most frequently prescribed medication class at baseline (48.3%), followed by antidepressants (46.5%).

D-ER treatment patterns and budget impact

Median dose on the index date prescription fill was 20 mg, and average daily pill count was 1.98 (SD, 0.2), suggesting that it is likely that D-ER was prescribed in a manner consistent with its recommended daily dose of 20 mg taken as two 10 mg tablets. During the 12-month follow-up period, 78.3% (n=734) filled their D-ER prescription two or more

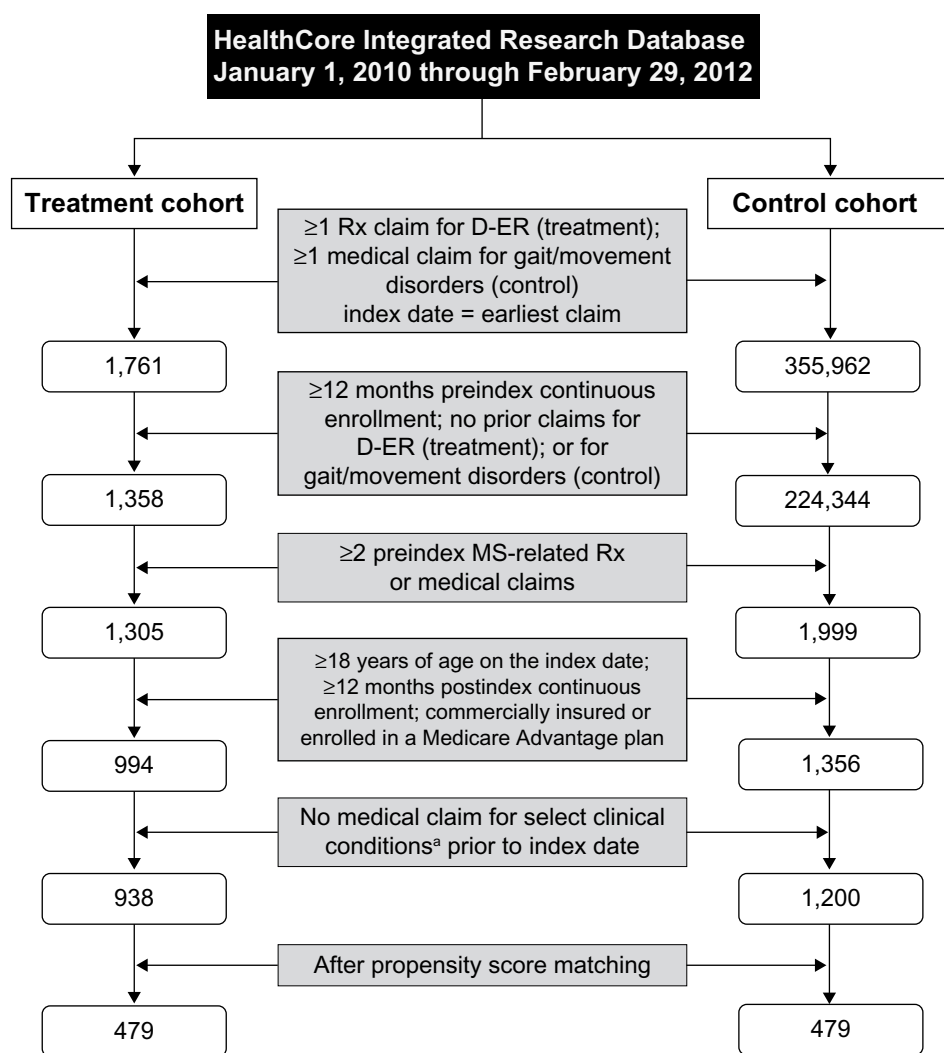


Figure 1 Attrition flow diagram.

Notes: ^aNo medical claims for stroke, Parkinson's disease, neoplasm of brain, brain abscess, tendonitis/tendon injury, and/or cerebral palsy during the 12-month baseline period.

Abbreviations: D-ER, dalfampridine extended release; MS, multiple sclerosis; Rx, prescription.

Table 1 Baseline demographics and clinical characteristics

	All patients (n=2,138), n (%)
Receiving D-ER	938 (43.9)
Female	1,575 (73.7)
Age, mean (SD)	51.2 (11.1)
Geographic region	
Northeast	485 (22.7)
South	516 (24.1)
Midwest	633 (29.6)
West	439 (20.5)
Medicare Advantage	292 (13.7)
Treating/prescribing physician specialty	
Neurologist	903 (42.2)
PCP	295 (13.8)
Rehabilitation	39 (1.8)
Others	482 (22.5)
Missing/unknown	419 (19.6)
Quan–Charlson comorbidity index score, mean (SD)	0.74 (1.26)
MS symptoms ^a	
Muscular weakness/spasticity	387 (18.1)
Disturbances of skin sensation	345 (16.1)
Dizziness/giddiness/vertiginous syndromes	207 (9.7)
Visual disturbances (including optic neuritis)	151 (7.1)
Comorbidities ^a	
Hypertension	911 (42.6)
Urinary tract infections	456 (21.3)
Depression	506 (23.7)
Thyroid disease	296 (13.8)
Arthritis (rheumatoid and osteoarthritis)	277 (12.9)
Hypercholesterolemia	272 (12.7)
Diabetes mellitus (type I or II)	202 (9.5)
Anxiety	157 (7.3)
Nonskin cancer	134 (6.3)
Baseline pharmacotherapies ^a	
Pain medications	1,033 (48.3)
Antidepressants	994 (46.5)
Corticosteroids	884 (41.4)
Anticonvulsants	713 (33.4)
Adrenals	572 (26.8)
Urinary antibiotics	210 (9.8)
Preindex MS-associated DMTs ^a	
Glatiramer acetate	460 (21.5)
Interferon- β -1a	498 (23.3)
Interferon- β -1b	165 (7.7)
Natalizumab	234 (10.9)

Notes: ^aOnly those with prevalence $\geq 5\%$ are listed. All values are n (%) unless stated otherwise.

Abbreviations: D-ER, dalfampridine extended release; DMT, disease-modifying therapy; MS, multiple sclerosis; PCP, primary care physician, including family/general and internal medicine; SD, standard deviation.

times (including the index date prescription fill), with a mean of 4.9 (SD, 4.3) prescription fills (Table 2). The mean MPR was 0.8 (SD, 0.3), with 82.6% (n=775) having an MPR of 80% or higher.

The gross budget impact of D-ER was calculated as total cost of D-ER (mean monthly cost per patient multiplied by number of D-ER patients) divided by total number of health

Table 2 D-ER treatment patterns

	D-ER Patients (n=938)
Index fill dose (mg)	
Mean (SD)	19.6 (2.3)
Median (Q1–Q3)	20 (20–20)
Daily pill count	
Mean (SD)	2.0 (0.2)
Median (Q1–Q3)	2 (2–2)
Number of patients with ≥ 2 fills, n (%)	734 (78.3)
Number of prescription refills	
Mean (SD)	4.9 (4.3)
Median (Q1–Q3)	4 (1–9)
Time between each fill in days, (SD)	
Mean (SD)	0.8 (0.4)
Patients who discontinued (allowed gap of 30 days), n (%)	697 (74.3)
Persistence in days, mean (SD)	181.1 (137.4)
Patients who restarted (allowed gap of 30 days)	185 (26.5)
MPR	
Mean (SD)	0.8 (0.3)
MPR $\geq 80\%$, n (%)	775 (82.6)

Abbreviations: MPR, medication possession ratio; SD, standard deviation; Q, quartile; D-ER, dalfampridine extended release.

plan members (\$0.026 PMPM). Similarly, the budget impact of non-D-ER walking-related medical treatments was calculated as the total cost of medical treatments for non-D-ER patients divided by total number of health plan members. Non-D-ER walking-related budget impact was \$0.013 PMPM vs \$0.018 PMPM for the propensity-score-matched D-ER vs control cohort and was \$0.013 PMPM vs \$0.025 PMPM for the unmatched cohorts. The budget impact difference between D-ER and control cohorts was potentially due to cost offset when treated by D-ER. The differences were estimated to be \$0.005 and \$0.012 PMPM for propensity-score-matched and unmatched cohorts. Therefore, the estimated net budget impact of D-ER was \$0.021 and \$0.014 PMPM for the propensity-score-matched and unmatched cohorts, respectively. The range of D-ER budget impact was thus estimated to be between \$0.014 and \$0.026 PMPM.

Health care utilization

A total of 958 patients remained after the matching, with 479 patients in each cohort. The baseline demographic and clinical characteristics post-matching are reported in Table S1. Compared with the D-ER cohort, the control cohort had significantly more physician office visits (62.4% vs 21.5%, $P < 0.0001$), particularly neurologist visits (45.5% vs 13.8% $P < 0.0001$). Table 3 shows a comparison of mean number of visits per patient. Other outpatient office visits were also higher in the control cohort than in the

Table 3 Walking impairment-related health care resource utilization over 12-month follow-up for treatment vs control cohorts post-matching

	Treatment cohort (n=479)	Control cohort (n=479)	P-value
Inpatient hospitalizations			
Number of hospitalizations per patient, mean (SD)	0.04 (0.2)	0.1 (0.3)	0.2297
Total number of hospitalizations, n	21	31	
ED visits			
Number of ED visits per patient, mean (SD)	0 (0.1)	0.0 (0.1)	0.2049
Total number of ED visits, n	2	6	
Physician office visits			
Number of physician office visits per patient, mean (SD)	0.4 (1.0)	1.0 (1.3)	<0.0001
Total number of physician office visits, n	206	496	
Neurologist visits			
Number of neurologist visits per patient, mean (SD)	0.3 (0.7)	0.7 (1.1)	<0.0001
Total number of neurologist visits, n	118	354	
Other outpatient visits			
Number of outpatient visits per patient, mean (SD)	1.9 (5.3)	3.5 (7.5)	0.0001
Total number of outpatient visits, n	894	1,673	
PT/OT visits			
Number of PT/OT visits per patient, mean (SD)	1.5 (4.5)	3.0 (7.3)	0.0001
Total number of PT/OT visits, n	728	1,455	

Notes: P-values are from two-sample t-tests or Wilcoxon rank-sum tests. A P-value <0.05 was prespecified to indicate statistical significance.

Abbreviations: ED, emergency department; PT/OT, physical therapy and/or occupational therapy; SD, standard deviation.

treatment cohort (51.4% vs 22.8%, $P<0.0001$). Changes in walking-impairment-related HRU from follow-up to baseline (Table 4) showed that HRU metrics, including inpatient hospitalizations, ED visits, physician office visits, and other outpatient visits increased significantly

more in the control cohort compared with the D-ER cohort.

To adjust for the differences in walking-impairment-related events at baseline between D-ER and control cohorts, a sensitivity analysis was performed on a subgroup of patients

Table 4 Change in scores in walking impairment-related health care resource utilization from baseline to follow-up period for treatment vs control cohorts post-matching

Change scores	D-ER cohort (n=479)	Control cohort (n=479)	P-value
Inpatient hospitalizations			
Mean number of hospitalizations per patient	0.02	0.06	0.0089
Total number of hospitalizations	8	31	
ED visits			
Mean number of ED visits per patient	-0.01	0.01	0.029
Total number of ED visits	-3	6	
Physician office visits			
Mean number of physician office visits per patient	-0.13	1.04	<0.0001
Total number of physician office visits	-63	496	
Neurologist visits			
Mean number of neurologist visits per patient	-0.11	0.74	<0.0001
Total number of neurologist visits	-52	354	
Other outpatient visits			
Mean number of outpatient visits per patient	0.30	3.49	<0.0001
Total number of outpatient visits	144	1,673	
Physical and/or occupational therapy			
Mean number of PT/OT visits per patient	0.19	3.04	<0.0001
Total number of PT/OT visits	92	1,455	

Notes: Numbers represent change scores, calculated as value at follow-up minus value at baseline for each metric. Change score units reflect units of the underlying metric. For example, the change score of 0.02 for inpatient hospitalizations in the D-ER cohort reflects an increase from a mean number of hospitalizations per person of 0.03 at baseline to 0.04 at follow-up (rounded). P-values are from two-sample t-tests. A P-value <0.05 was prespecified to indicate statistical significance.

Abbreviations: D-ER, dalfampridine extended release; ED, emergency department; PT/OT, physical therapy and/or occupational therapy.

from both cohorts with no medical claims for walking-related disorders prior to the index date. Comparison of HRU between the two subgroups showed that the findings were broadly consistent with that from the main analysis (Table S2).

Discussion

This analysis is one of the first to evaluate D-ER treatment patterns, budget impact, and HRU of MS patients in a large, real-world US population. The D-ER treatment patterns observed in our analysis appeared to be consistent with the recommendations from the D-ER prescribing information with respect to dosage and frequency of medication intake. The majority of patients who initiated D-ER were adherent to therapy.

We used propensity-score matching to select a control cohort of non-D-ER users. The use of propensity-score matching reduced selection bias by including subjects who are comparable on a broad range of baseline demographic, clinical, and economic characteristics. A comparison of propensity-score-matched D-ER and control cohorts showed that walking-impairment-related physician visits and other outpatient visits were significantly higher in the control cohort during the follow-up period. Additionally, metrics of walking-impairment-related HRU increased at a higher rate from baseline to follow-up in the control cohort, suggesting a faster increase in HRU over time in the control cohort. One possible explanation is that improvement in walking in the D-ER cohort may have resulted in less HRU. In this regard, a recent claims study that examined the treatment patterns and medical costs of MS patients treated with prolonged-release fampridine in Germany showed that treatment was associated with significant reductions in the number of MS-related inpatient hospitalizations, length of stay, and costs when compared before and after treatment.²²

The budget impact of D-ER in this study population was estimated at \$0.014–\$0.026 PMPM, with and without taking into consideration the potential cost offset due to D-ER treatment. This budget impact of D-ER is minimal in comparison to that of MS specialty drugs, as reported in a study that benchmarked specialty drug costs by therapeutic class. The budget impact for MS specialty drugs in 2010 was \$2.54 PMPM.²³

Our analysis suggests that a significantly greater number of patients receiving D-ER were taking DMTs at baseline compared with the control cohort, which may reflect higher levels of disease severity, or more thorough care management. A relatively high proportion of patients did not persist on

D-ER treatment throughout the 12-month follow-up period. Further studies assessing association of persistence and outcomes are warranted.

Limitations

Although this study was based on a large and geographically diverse patient population, several limitations exist. As with any claims database analysis, the presence of a diagnosis code on a medical claim is not a confirmation of the presence of a disease, as the diagnosis code may have been incorrectly entered or included as a rule-out criterion. Specifically, walking-related disorders may have been under-coded or miscoded within claims, potentially resulting in the underestimation of walking-impairment-related health care burden. Similarly, the absence of a code does not necessarily indicate that the disease or condition was not present. In addition, a claim for a filled prescription does not indicate that the medication was consumed or that it was taken as prescribed. Furthermore, the effect of some patient demographics as well as clinical and disease-specific parameters, such as race, education, body mass index, disease severity, or types of MS, could not be assessed in the claims data and could have affected outcomes.

Propensity-score matching was used to generate cohorts balanced on observable characteristics to reduce the bias. However, it is possible that some bias remains due to unobservable characteristics. Finally, the study sample was taken from one large US commercial health plan, and the results may not be generalizable to patients enrolled in different plans, uninsured patients, or people with MS living outside of the United States.

Conclusion

This analysis is one of the first to evaluate treatment patterns, resource utilization, and the budget impact of D-ER in a large, real-world population of MS patients. Treatment patterns of patients initiating D-ER seemed to be consistent with prescribing recommendations. The use of D-ER was associated with a lower number of walking-impairment-related physician and other outpatient office visits among patients with MS over 12-month follow-up, while inpatient hospitalization and ED utilization were directionally lower in the treatment group. Changes from follow-up to baseline in HRU metrics (inpatient hospitalization, ED, physician office visits, and other outpatient visits) were found to be lower in the treatment cohort, indicating a trend of lower HRU over time in the treatment cohort. Results of this real-world analysis suggest D-ER may lead to cost offsets through reductions in

HRU. Future research should examine the robustness of our results in different and larger real-world populations as well as the effect of D-ER adherence on clinical and economic outcomes.

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Disclosure

Amy Guo, Matthew Sidovar, and Peter Aupperle are employees and stockholders of Acorda Therapeutics Inc. Stephen Krieger is a consultant for Acorda Therapeutics Inc., Biogen Idec, Genentech Inc., Genzyme Corporation, Questcor Pharmaceuticals Inc., Teva Pharmaceutical Industries Ltd., and is a member of the Scientific Advisory Board for Acorda Therapeutics Inc., Bayer, Biogen Idec, Questcor Pharmaceuticals Inc. and Teva Pharmaceutical Industries Ltd. Michael Grabner is an employee of HealthCore, Inc., an independent research organization that received funding from Acorda Therapeutics Inc. for the conduct of the study. Swetha Palli was an employee of HealthCore Inc. at the time the study was conducted. Jessica Elder was a contractor to Acorda Therapeutics Inc. at the time the study was conducted. The authors report no other conflicts of interest in this work.

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Supplementary materials

Table S1 Baseline demographics and clinical characteristics in the matched cohorts

	D-ER cohort (n=479)	Control cohort (n=479)	P-value	Standardized difference
Sex				
Female	356 (74.32)	352 (73.49)	0.7685	2
Age				
Mean (\pm SD)	51.81 (\pm 9.76)	49.13 (\pm 10.41)	<0.0001	27
Median	53.00	52.00	<0.0001	
Treating or prescribing physician specialty				
Neurologist	210 (43.84)	209 (43.63)	0.9481	0
All other specialties	269 (56.16)	270 (56.37)		0
PCP	151 (31.52)	41 (8.56)	<0.0001	60
Rehabilitation	2 (0.42)	11 (2.3)		-16
Others	31 (6.47)	121 (25.26)		-53
Missing/unknown	85 (17.75)	97 (20.25)		-6
Quan-Charlson comorbidity index				
Mean (\pm SD)	0.58 (\pm 1.14)	0.62 (\pm 1.1)	0.6454	-3
MS symptoms				
Muscular weakness/spasticity	75 (15.66)	75 (15.66)	1.0000	0
Disturbances of skin sensation	71 (14.82)	69 (14.41)	0.8549	1
Visual disturbances (including optic neuritis)	38 (7.93)	34 (7.1)	0.6240	3
Dizziness/giddiness/vertiginous syndromes	36 (7.52)	41 (8.56)	0.5524	-4
Migraine	20 (4.18)	29 (6.05)	0.1869	-9
Preindex MS-associated DMTs				
Glatiramer acetate	100 (20.88)	114 (23.8)	0.2775	-7
Interferon- β -1a	122 (25.47)	133 (27.77)	0.4213	-5
Natalizumab	61 (12.73)	54 (11.27)	0.4865	4
Interferon- β -1b	43 (8.98)	41 (8.56)	0.8193	1

Notes: P-values are from two-sample t-tests/Wilcoxon rank-sum tests (for continuous variables) and χ^2 -tests or Fisher exact tests (for categorical variables). A P-value <0.05 was prespecified to indicate statistical significance. All values are n (%) unless stated otherwise.

Abbreviations: D-ER, dalfampridine extended release; DMTs, disease-modifying therapies; MS, multiple sclerosis; PCP, primary care physician, including family/general and internal medicine; SD, standard deviation.

Table S2 Sensitivity analysis: walking-impairment-related HRU over 12-month follow-up in a subgroup of matched patients without claims for walking-related disorders at baseline

	Treatment cohort (n=300)	Control cohort (n=300)	P-value
Inpatient hospitalizations			
Number of hospitalizations per patient, mean (SD)	0.0 (0.2)	0.1 (0.3)	0.0799
Total number of hospitalizations, n	10	21	
ED visits			
Number of ED visits per patient, mean (SD)	0 (0.1)	0.01 (0.1)	0.3165
Total number of ED visits, n	1	3	
Physician office visits			
Number of physician office visits per patient, mean (SD)	0.1 (0.4)	1.1 (1.4)	<0.0001
Total number of physician office visits, n	28	326	
Neurologist visits			
Number of neurologist visits per patient, mean (SD)	0.1 (0.3)	0.7 (1.2)	<0.0001
Total number of neurologist visits, n	14	220	
Other outpatient visits			
Number of outpatient visits per patient, mean (SD)	1.3 (4.7)	3.5 (7.8)	<0.0001
Total number of outpatient visits, n	396	1,043	
PT/OT visits			
Number of PT/OT visits per patient, mean (SD)	1.1 (3.7)	3.1 (7.6)	<0.0001
Total number of PT/OT visits, n	317	919	

Notes: P-values are from two-sample t-tests or Wilcoxon rank-sum tests. A P-value <0.05 was prespecified to indicate statistical significance.

Abbreviations: ED, emergency department; HRU, health care resource utilization; PT/OT, physical therapy and/or occupational therapy; SD, standard deviation.

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