Inpatient Admissions and Costs Associated with Persistent Use of Dalfampridine Extended-Release in Multiple Sclerosis: A Claims Database Analysis

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ABSTRACT

BACKGROUND: While the clinical benefits of dalfampridine extended-release (D-ER) have been established in patients with multiple sclerosis (MS) through multiple clinical trials, there is limited real-world data on D-ER use, in particular the persistent use of D-ER, and associated acute care resource utilization and costs.

OBJECTIVE: To examine the real-world association of D-ER use and inpatient admissions and costs among patients with MS.

METHODS: This study was a retrospective observational claims analysis of the MarketScan database (April 2009–March 2014). Eligible patients consisted of adult enrollees aged 18–64 years who had (a) 12 months of continuous private plan enrollment preceding (baseline) and following (follow-up) the first D-ER claim; (b) ≥ 2 MS diagnosis codes with ≥ 1 during the baseline period; (c) ≥ 2 consecutive D-ER claims; and (d) no alternate gait-impairing etiologies during the baseline and follow-up periods. Patients were separated into 2 D-ER cohorts in the main analysis: persistent (≥ 360 days of D-ER supply) and nonpersistent (< 360 days of supply) users. Sensitivity analyses were conducted, examining additional breakdowns of days of supply within the nonpersistent cohort. Inpatient admissions (all-cause and MS-related) and health care expenditures were calculated and compared between the cohorts during follow-up using Wilcoxon rank-sum and chi-square tests. Regression models were conducted, controlling for age, sex, MS relapses, comorbidities, disease-modifying therapy use, and other baseline factors, including inpatient admissions and costs.

RESULTS: Of 1,598 eligible patients, 719 (45.0%) were persistent D-ER users, and 879 (55.0%) were nonpersistent D-ER users. The 2 cohorts had similar demographic and clinical characteristics, with mean (SD) ages of 51.0 (8.4) and 50.6 (8.6) years and were 71.3% and 66.6% female, respectively. Compared with nonpersistent D-ER use, persistent D-ER use was associated with lower odds of all-cause inpatient admissions (OR = 0.58, $P = 0.010$) and MS-related inpatient admissions (OR = 0.50, $P = 0.004$). Persistent use was also associated with lower inpatient expenditures for all-cause admissions (\$669 vs. \$1,515, $P = 0.002$) and MS-related admissions (\$388 vs. \$891, $P = 0.008$).

CONCLUSIONS: Persistent D-ER use was associated with significantly lower rates of all-cause and MS-related inpatient admissions and costs.

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What is already known about this subject

- Patients with multiple sclerosis (MS) experience substantial medical costs and disability because of the chronic and complex nature of the disease.
- Walking difficulty has been reported by some patients with MS to be the most important bodily function affected by the disease.
- Dalfampridine extended-release (D-ER) is indicated to improve walking in patients with MS as demonstrated by an increase in walking speed.

What this study adds

- This study describes the association between persistent use of D-ER and inpatient admissions and costs in a real-world MS patient population.
- Persistent D-ER use was associated with lower rates of inpatient hospitalization and lower costs, in both unadjusted and baseline-adjusted comparisons.
- The most differences were found between persistent D-ER users and those with less than a 180-day supply of D-ER in a year.

Multiple sclerosis (MS) is a chronic and disabling immune-mediated condition of the central nervous system, with a variable and intermittent disease course in most cases, but eventually leading to progressive neurological and functional decline.¹ MS was estimated to affect around 400,000 people in the United States and approximately 2.3 million worldwide in 2013.² Symptoms typically appear between the ages of 20 and 40 years, with diagnoses being rare after the age of 50.^{3,4}

Walking has been reported to be the most important bodily function affected by MS. In a 2008 survey of MS patients, 70% of the respondents reported that walking difficulty was the most challenging aspect of their condition.^{5,6} In other studies, 85% of patients with MS experienced walking-related mobility challenges.⁷ This functional impairment can have broad implications for patients' daily lives and can result in direct economic consequences.^{8–11} Costs may be even higher when considering indirect costs such as work loss and disability. For example, 79% of patients experienced negative employment effects.¹²

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FIGURE 1 Sample Selection Flowchart

^aContraindications for D-ER consisted of seizure activity and moderate or severe renal impairment.

^bThe list of non-MS conditions that might impair walking/mobility is in Appendix A2 (available in online article).

4-AP=4-aminopyridine; D-ER=dalfampridine-extended release; ICD-9-CM=International Classification of Diseases, Ninth Revision, Clinical Modification; MS=multiple sclerosis.

Dalfampridine extended-release (D-ER; known as prolonged-release fampridine in Europe and as fampridine modified- or sustained-release elsewhere) 10 mg tablets twice daily was the first symptomatic therapy approved by the U.S. Food and Drug Administration (January 2010) to improve walking ability in MS patients.¹³ In phase III trials, MS patients on D-ER showed improved walking ability over a 14-week observational period.¹⁴⁻¹⁶ Currently, however, there is limited real-world

data on the longer-term effects of D-ER on walking ability and patient outcomes. An exception to this is a recent claims database study that found that the majority of patients initiated on D-ER were adherent to treatment and that patients on D-ER experienced fewer physician and other outpatient visits related to walking impairment than patients not treated with D-ER.¹⁷

In our study, we add to the literature on real-world use of D-ER and associated patient outcomes. In particular, we

assessed the association between persistent versus nonpersistent use of D-ER and inpatient admissions and costs across D-ER users from a real-world MS patient population. These acute care outcomes are highly relevant for this population, given the broad and pronounced health implications that walking impairment can have for patients. These implications include increased fall risk, decline in cardiovascular and musculoskeletal health, and poorer mental health, which can precipitate acute medical events. In addition, these outcomes are highly relevant to payers for whom they can be important cost drivers.

Methods

Data Source and Study Design

A retrospective analysis was conducted using the Truven Health Analytics MarketScan Commercial Claims and Encounters (CCAE) Database. The CCAE database captures medical benefits, enrollment history, and claims for medical and pharmacy services for all enrolled employees and their dependents.

All data in this study were de-identified by Truven Health Analytics and comply with the patient confidentiality requirements of the Health Insurance Portability and Accountability Act. The data were exempt from individual institutional review board approval.

Study Sample

The study period was April 2009-March 2014, and over 74.2 million covered lives were included. The start date was selected to maximize capture of patients on D-ER and allowed for a 12-month baseline period before the launch of D-ER in March 2010. Cost information in the data represents actual payments rather than the charged amounts, enabling description of real-world costs experienced across payers.

Patient inclusion criteria were as follows: (a) 12 months of continuous private health plan enrollment preceding (baseline period) and following (follow-up period) their first D-ER claim (index date); (b) ≥ 2 MS diagnosis codes (*International Classification of Diseases, Ninth Revision, Clinical Modification* code 340) with ≥ 1 MS diagnosis occurring during the baseline period; (c) aged 18-64 years at the index date; and (d) ≥ 2 consecutive D-ER claims (i.e., a supply gap ≤ 30 days between the first 2 claims; Figure 1).

Patients were excluded if they exhibited any of the following characteristics during the baseline or follow-up periods: (a) experienced a contraindication for D-ER use per the prescribing information (Appendix A1, available in online article); (b) had a gait-impairing etiology other than MS (i.e., brain neoplasm/abscess, Parkinson's disease, cerebral palsy, muscular dystrophy, stroke, tendonitis/tendon injury, spinal cord injury, and paralysis/hemiplegia); or (c) had a diagnosis code indicating they were wheelchair bound (Appendix A2). Patients were also excluded if they were covered by a capitated health plan,

since their payment amounts may not have accurately reflected usage patterns (by virtue of the capitation system).

Patients were grouped into 2 mutually exclusive cohorts: *persistent D-ER users* (having ≥ 360 days of D-ER supply during the follow-up period) and *nonpersistent D-ER users* (having < 360 days of D-ER supply during the follow-up period). Among the nonpersistent cohort, the mean (standard deviation [SD]) days of D-ER supply was 187 (93), while the median (interquartile range) was 180 (90-270). Sensitivity analyses were also conducted, examining additional breakdowns of days of supply within the nonpersistent cohort to provide greater granularity on the relationship between D-ER persistence and the outcomes.

Patient Characteristics and Study Outcomes

A wide range of patient characteristics were collected and assessed for each study cohort during the 12-month baseline period. These characteristics included demographics; MS disease characteristics (number of inferred MS relapses, walking difficulties, falls and fractures, and MS symptoms); the Charlson Comorbidity Index (CCI),^{18,19} comorbidities; previous treatments for mobility and MS-related issues; health resource utilization (HRU); and expenditures. MS relapses were inferred using a widely used algorithm developed by Ollendorf et al. (2002)²⁰ and modified by Halpern et al. (2011).²¹ The diagnosis and procedure codes and treatments used to identify the baseline characteristics are listed in Appendix A.

The following outcomes were assessed for each study cohort over the 12-month follow-up period: all-cause and MS-related inpatient admissions and all-cause and MS-related inpatient expenditures. For the inpatient admission outcomes, the percentage of patients with any admission was examined, as well as the number of admissions per patient. For the expenditure outcomes, insurer and patient contributions were included in the calculations. Expenditures were converted to 2014 U.S. dollars, using the medical care component of the Consumer Price Index.

Statistical Analyses

Baseline characteristics, including HRU and expenditures, were summarized for the cohorts using descriptive statistics. Differences between the cohorts were assessed using Wilcoxon rank-sum tests for continuous variables and chi-square tests for categorical variables.

The study outcomes were summarized and compared for the cohorts over the follow-up period, using unadjusted and baseline-adjusted analyses. For the unadjusted analyses, comparisons were performed using Wilcoxon rank-sum and chi-square tests for continuous and categorical variables, respectively. For the adjusted analyses, regressions analyses were used that controlled for a comprehensive set of baseline characteristics, which could represent potential confounders.

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TABLE 1 Baseline Characteristics

	Persistent D-ER Users n = 719		Nonpersistent D-ER Users n = 879		P Value ^a
Demographics and insurance					
Age at the index date (years), mean (SD)	51.0	(8.4)	50.6	(8.6)	0.422
Female, n (%)	513	(71.3)	585	(66.6)	0.040 ^b
Region of residence, n (%)					0.086
Northeast	196	(27.3)	228	(25.9)	
North Central	218	(30.3)	273	(31.1)	
South	183	(25.5)	257	(29.2)	
West	122	(17.0)	118	(13.4)	
Unknown	0	(0.0)	3	(0.3)	
Insurance type, n (%)					0.624
Comprehensive	35	(4.9)	47	(5.3)	
Exclusive provider organization	16	(2.2)	12	(1.4)	
Noncapitated point of service	67	(9.3)	76	(8.6)	
Preferred provider organization	470	(65.4)	589	(67.0)	
Consumer-directed health care	46	(6.4)	45	(5.1)	
Other	85	(11.8)	110	(12.5)	
MS characteristics					
Number of MS relapses, mean (SD)	0.77	(2.19)	0.75	(2.07)	0.618
MS symptoms, n (%)					
Muscle weakness	72	(10.0)	78	(8.9)	0.437
Spasms (muscle)	67	(9.3)	78	(8.9)	0.758
Disturbances of skin sensation	48	(6.7)	75	(8.5)	0.166
Malaise and fatigue	122	(17.0)	185	(21.0)	0.040 ^b
Dizziness/giddiness/vertiginous syndromes	33	(4.6)	50	(5.7)	0.325
Vision problems	44	(6.1)	78	(8.9)	0.039 ^b
Visual disturbances (including optic neuritis)	29	(4.0)	56	(6.4)	0.038 ^b
Use of DMTs, n (%)	570	(79.3)	677	(77.0)	0.278
Interferon beta-1a	216	(30.0)	273	(31.1)	0.661
Interferon beta-1b	77	(10.7)	81	(9.2)	0.319
Glatiramer acetate	203	(28.2)	227	(25.8)	0.280
Natalizumab	103	(14.3)	133	(15.1)	0.652
Other DMTs ^c	25	(3.5)	27	(3.1)	0.650
Walking and/or movement difficulties, n (%)	204	(28.4)	262	(29.8)	0.530
Difficulty in walking	42	(5.8)	49	(5.6)	0.819
Abnormal gait	152	(21.1)	195	(22.2)	0.615
Lack of coordination	25	(3.5)	43	(4.9)	0.163
Abnormal involuntary movements	38	(5.3)	39	(4.4)	0.431
Antitremor and/or antispasticity medication use, n (%)	358	(49.8)	428	(48.7)	0.662
Anticonvulsant medication use, n (%)	90	(12.5)	111	(12.6)	0.947
Any falls or fractures resulting in medical visits, n (%)	125	(17.4)	144	(16.4)	0.594
Accidental falls	13	(1.8)	17	(1.9)	0.854
Traumatic fractures	40	(5.6)	44	(5.0)	0.619
Nontraumatic fractures	92	(12.8)	103	(11.7)	0.513
Purchase of a wheelchair or wheelchair accessory, n (%)	47	(6.5)	58	(6.6)	0.961
Comorbidities ^d					
CCI, mean (SD)	0.36	(0.79)	0.32	(0.70)	0.470
Comorbid condititions, n (%)					
Depression	59	(8.2)	123	(14.0)	<0.001 ^e
Dyslipidemia	174	(24.2)	236	(26.8)	0.228
Thyroid disease	87	(12.1)	95	(10.8)	0.418
Hypercholesterolemia	176	(24.5)	239	(27.2)	0.219
Arthritis	338	(47.0)	413	(47.0)	0.992
Mild to moderate diabetes	39	(5.4)	56	(6.4)	0.426
Cardiovascular disease (including hypertension)	184	(25.6)	241	(27.4)	0.411

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TABLE 1 Baseline Characteristics (continued)

	Persistent D-ER Users n = 719		Nonpersistent D-ER Users n = 879		P Value ^a
Resource use and expenditures					
Any medical visit, n (%)					
Any all-cause outpatient visit	719	(100.0)	879	(100.0)	–
Any MS-related outpatient visit	719	(100.0)	879	(100.0)	–
Any physical therapy outpatient visit	297	(41.3)	339	(38.6)	0.265
Any ER visit	106	(14.7)	165	(18.8)	0.033 ^b
Any inpatient admission	49	(6.8)	83	(9.4)	0.058
Medical visits, mean (SD)					
All-cause outpatient visits	23.20	(18.16)	22.40	(18.25)	0.285
MS-related outpatient visits	11.44	(11.19)	10.59	(10.86)	0.101
Physical therapy outpatient visits	4.77	(9.87)	4.34	(10.72)	0.229
ER visits	0.18	(0.49)	0.29	(0.84)	0.019 ^b
Inpatient admissions	0.07	(0.27)	0.11	(0.36)	0.053
Days in inpatient care	0.36	(1.65)	0.62	(2.63)	0.050 ^b
Health care expenditures (2014 USD), mean (SD)					
All-cause outpatient visits	\$44,242	(\$27,305)	\$41,086	(\$25,935)	<0.001 ^c
MS-related outpatient visits	\$10,772	(\$19,538)	\$10,431	(\$19,086)	0.032 ^b
Physical therapy outpatient visits	\$746	(\$1,626)	\$669	(\$1,853)	0.254
ER visits	\$198	(\$2,111)	\$224	(\$829)	0.034 ^b
Inpatient admissions	\$1,294	(\$8,097)	\$1,701	(\$7,304)	0.058
Pharmacy	\$28,079	(\$21,286)	\$24,628	(\$20,051)	<0.001 ^c
Year of index date					
Year, n (%)					0.007 ^d
2010	419	(58.3)	566	(64.4)	
2011	156	(21.7)	193	(22.0)	
2012	122	(17.0)	100	(11.4)	
2013	22	(3.1)	20	(2.3)	

^aP values comparing the persistent and nonpersistent D-ER users were calculated using Wilcoxon rank-sum and chi-square tests for the continuous and categorical variables, respectively.

^bSignificant differences between cohorts at 5%.

^cOther DMTs were teriflunomide, fingolimod, mitoxantrone, and dimethyl fumarate.

^dComorbidities affecting at least 5% of a cohort are included. Other comorbidities were not statistically significantly different between cohorts, including chronic pain, anxiety, chronic diabetes, non-skin cancer, and obesity.

^eSignificant differences between cohorts at 0.1%.

^fSignificant differences between cohorts at 1%.

CCI = Charlson Comorbidity Index; D-ER = dalfampridine-extended release; DMT = disease-modifying therapy; ER = emergency room; MS = multiple sclerosis; SD = standard deviation; USD = U.S. dollars.

These characteristics included age at index date, sex, U.S. region of residence, index year (i.e., the calendar year of the index date), number of MS relapses, malaise and fatigue, vision problems, any use of disease-modifying therapies (DMTs), CCI, depression, any antitremor and/or antispasticity medication use, any anticonvulsant medication use, any walking and/or movement difficulties, any falls or fractures resulting in medical visits, and the number of emergency room (ER) visits during the baseline period. In addition, the adjusted analyses for inpatient admissions controlled for the number of inpatient admissions during the baseline period. Similarly, the adjusted analysis for inpatient expenditures additionally controlled for total all-cause expenditures during the baseline period.

For the adjusted regression analyses, functional forms for the models were selected according to the outcome examined. Logistic regressions were used to examine the binary outcomes (e.g., any inpatient admission), and the odds ratios (ORs) were reported. For the count outcomes (e.g., number of inpatient admissions), analyses were conducted using negative binomial regressions with the incidence rate ratios (IRRs) reported. Inpatient expenditures were analyzed using generalized linear models with a Tweedie distribution (due to their rightward skew),²² and the mean difference between the cohorts was reported. For each model, the predicted value was calculated for the patient with average characteristic levels in the overall sample and compared under 2 scenarios—with and without

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TABLE 2 Health Care Resource Utilization and Expenditures for Persistent Versus Nonpersistent D-ER Users over Follow-up Period

	Persistent D-ER Users ^a n = 719		Nonpersistent D-ER Users ^a n = 879		P Value ^b
Inpatient admissions					
Any all-cause inpatient admission, n (%)	39	(5.4)	82	(9.3)	0.003 ^c
Any MS-related inpatient admission	29	(4.0)	72	(8.2)	<0.001 ^d
All-cause inpatient admissions, mean (SD)	0.06	(0.27)	0.12	(0.41)	0.003 ^c
MS-related inpatient admissions	0.04	(0.22)	0.10	(0.39)	<0.001 ^d
Health care resource expenditures (2014 USD)					
All-cause inpatient expenditures, mean (SD)	\$1,387	(\$8,826)	\$3,019	(\$15,751)	0.003 ^c
MS-related inpatient expenditures	\$937	(\$7,401)	\$1,580	(\$7,442)	<0.001 ^d

^aPersistent D-ER users were defined as patients with at least 360 days of D-ER supply. Nonpersistent D-ER users were defined as patients with less than 360 days of D-ER supply.

^bP values comparing the persistent and nonpersistent D-ER users were calculated using Wilcoxon rank-sum and chi-square tests for the continuous and categorical variables, respectively.

^cSignificant differences between the cohorts at 1%.

^dSignificant differences between the cohorts at 0.1%.

D-ER = dalfampridine-extended release; MS = multiple sclerosis; SD = standard deviation; USD = U.S. dollars.

persistent D-ER use—to assess association of persistent D-ER use with the patient outcomes.

In addition to the main analyses, a sensitivity analysis was conducted comparing inpatient admissions and expenditures of the persistent D-ER cohort with subgroups of the nonpersistent D-ER user cohort to better understand trends associated with varying levels of nonpersistence. Four subgroups were examined consisting of the following: (1) D-ER supply of <90 days; (2) D-ER supply ≥90 and <180 days; (3) D-ER supply ≥180 and <270 days; and (4) D-ER supply ≥270 and <360 days. Comparisons conducted mirrored those of the main analyses, as previously described.

All statistical analyses were performed using SAS software version 9.3 (SAS Institute, Cary, NC).

Results

Patient and Disease Characteristics

A total of 1,598 patients met the inclusion criteria and were included in the study. Of these, 719 were persistent D-ER users, and 879 were nonpersistent D-ER users (Figure 1). The 2 cohorts were similar for many of the baseline characteristics assessed. These characteristics included age, region of residence, and insurance type, along with the following MS-related characteristics: number of MS relapses; MS symptoms (i.e., muscle weakness, spasms, disturbances of skin sensation, and dizziness); use of DMTs; recorded walking and movement difficulties; use of antitremor/antispasticity medications; use of anticonvulsant medications; any falls or fractures; and purchase of a wheelchair or wheelchair accessory. Other similarities between the cohorts included various comorbidities (i.e., dyslipidemia, thyroid disease, hypercholesterolemia, arthritis,

mild to moderate diabetes, and cardiovascular disease), as well as outpatient and physical therapy visits.

Significant differences between the cohorts were observed for the following set of baseline characteristics: sex, malaise and fatigue, visual problems including visual disturbances, depression, ER visits, ER costs, days in inpatient care, and select expenditure variables. For some of these characteristics, such as vision problems and visual disturbances, the numeric difference between the cohorts was quite small (less than 3%). Among the expenditure variables, baseline overall expenditures were significantly higher among the persistent D-ER users compared with the nonpersistent users (\$44,242 vs. \$41,086, $P < 0.001$). A similar trend was observed for MS-related outpatient visit costs (\$10,772 vs. \$10,431 for persistent and nonpersistent D-ER users, respectively, $P = 0.032$) and pharmacy costs (\$28,079 vs. \$24,628, respectively, $P < 0.001$; Table 1).

Inpatient Admissions

During the follow-up period, fewer persistent D-ER users had inpatient admissions than nonpersistent D-ER users (5.4% vs. 9.3%, $P = 0.003$; Table 2). A similar trend was also observed for MS-related inpatient admissions (4.0% vs. 8.2% for persistent vs. nonpersistent D-ER users, respectively, $P < 0.001$). Rates of per-patient inpatient admissions were also consistent with these patterns, with lower rates observed for persistent versus nonpersistent D-ER users (all-cause: 0.06 vs. 0.12 admissions per patient per year, respectively, $P = 0.003$; MS-related: 0.04 vs. 0.10, respectively, $P < 0.001$; Tables 1 and 2). Results of the sensitivity analysis, comparing the persistent D-ER cohort with subgroups of the nonpersistent D-ER cohort, were consistent with the main analysis and showed lower persistence levels

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TABLE 3 Adjusted Comparison of Health Care Resource Utilization and Expenditures for Persistent Versus Nonpersistent D-ER Users^a

	Adjusted Analysis: 12-Month Follow-up			
	Comparative Estimate [A] vs. [B]	P Value	Persistent D-ER Users [A]	Nonpersistent D-ER Users [B]
Any inpatient admission	Odds ratio		Adjusted mean probability (%)	
Any all-cause inpatient admission	0.58	0.010 ^b	4.6	7.6
Any MS-related inpatient admission	0.50	0.004 ^b	3.3	6.4
Number of inpatient admissions	Incidence rate ratio		Adjusted mean incidence rate (12 months)	
Number of all-cause inpatient admissions	0.60	0.012 ^c	0.05	0.09
Number of MS-related inpatient admission	0.48	0.002 ^b	0.04	0.07
Health care resource expenditures (2014 USD)	Mean difference		Adjusted mean expenditures (12 months)	
All-cause inpatient expenditures	-\$846	0.002 ^b	\$669	\$1,515
MS-related inpatient expenditures	-\$503	0.008 ^b	\$388	\$891

^aThe adjusted mean analyses were conducted for the patient with average characteristic levels in the overall sample and evaluated with persistent D-ER use versus without.

^bSignificance for the comparative estimates at 1%.

^cSignificance for the comparative estimates at 5%.

D-ER = dalfampridine-extended release; MS = multiple sclerosis; SD = standard deviation; USD = U.S. dollars.

being associated with higher resource use (Appendix B, available in online article).

After adjusting for baseline characteristics, the previously mentioned trends in inpatient admission outcomes persisted, with the odds of all-cause hospitalization being significantly lower for persistent D-ER users relative to nonpersistent D-ER users (adjusted OR=0.58, $P=0.010$; Table 3). This corresponded to an adjusted probability of having an all-cause inpatient admission during the follow-up year of 4.6% with persistent D-ER use versus 7.6% with nonpersistent use. Similarly, the odds of having an MS-related inpatient admission during the follow-up period for persistent D-ER users were half of those of the nonpersistent D-ER users (adjusted OR=0.50, $P=0.004$); the adjusted probability for persistent versus nonpersistent use was 3.3% versus 6.4%, respectively. In adjusted analyses that compared the cohorts' all-cause and MS-related inpatient admissions, persistent D-ER users had lower rates of admissions than nonpersistent users (IRRs of 0.60, $P=0.012$, and 0.48, $P=0.002$, respectively; Table 3).

The results of the sensitivity analyses were consistent with the main analysis, with lower persistence levels being associated with higher resource use (Table 4). For all-cause inpatient admissions, the adjusted mean probability of having an admission was 9.8%, 8.9%, 6.5%, and 6.4% for the nonpersistent subgroups with D-ER supply of <90 days, ≥ 90 and <180 days, ≥ 180 and <270 days, and ≥ 270 and <360 days, respectively. By contrast, patients in the persistent cohort had an adjusted mean probability of an inpatient admission of 4.5%. The regression results showed a significant difference between the 2 nonpersistent subgroups with lowest persistence (i.e., <90 days D-ER supply and ≥ 90 and <180 days of D-ER supply) compared

with the persistent cohort ($P=0.019$ and $P=0.008$, respectively). Although the other 2 nonpersistent subgroups displayed numerically higher adjusted mean probabilities for an inpatient admission than the persistent cohort (i.e., 6.5% and 6.4% vs. 4.5%), significance was not detected. This may, however, reflect inadequate sample size and power to detect a difference.

Inpatient Expenditures

Inpatient expenditures were significantly lower for the persistent D-ER users relative to the nonpersistent D-ER users in the follow-up period. Specifically, mean all-cause inpatient expenditures were \$1,387 per year for persistent users versus \$3,019 per year for nonpersistent users ($P=0.003$; Table 2). For MS-related inpatient admissions, these expenditures were \$937 per year versus \$1,580, respectively ($P<0.001$). In the sensitivity analysis comparing inpatient expenditures of the persistent D-ER cohort with subgroups of the nonpersistent D-ER cohort, the greatest differences again appeared between the persistent D-ER cohort and nonpersistent patients in the lowest persistence subgroups (Appendix B).

Significant differences in inpatient expenditures remained for the 2 cohorts after adjusting for baseline characteristics. For all-cause inpatient admissions, the adjusted mean expenditure per patient was \$669 for persistent users versus \$1,515 for nonpersistent users, a difference of \$846 ($P=0.002$; Table 3). Similar results were observed for MS-related inpatient expenditures (Table 3). In the sensitivity analysis with adjustments for baseline characteristics, greater persistence was again associated with lower expenditures (Table 4). The subgroups with <90 days and ≥ 90 and <180 days D-ER supply had significantly higher all-cause (mean differences of \$1,415, $P=0.012$, and \$1,120, $P=0.004$, respectively) and MS-related (mean

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TABLE 4 Sensitivity Analysis: Adjusted Comparison of Health Care Resource Utilization and Expenditures for Persistent Users Versus Subgroups of Nonpersistent D-ER Users^a

	Adjusted Analysis: 12-Month Follow-up		
	Comparative Estimate	P Value	D-ER Users
Any inpatient admission	Odds ratio		Adjusted mean probability (%)
Any all-cause inpatient admission			
D-ER supply <90 days	2.28	0.019 ^b	9.8
90 days ≤ D-ER supply < 180 days	2.05	0.008 ^c	8.9
180 days ≤ D-ER supply < 270 days	1.45	0.243	6.5
270 days ≤ D-ER supply < 360 days	1.44	0.208	6.4
Persistent D-ER users	Reference	—	4.5
Any MS-related inpatient admission			
D-ER supply <90 days	2.57	0.014 ^b	8.1
90 days ≤ D-ER supply < 180 days	2.26	0.006 ^c	7.2
180 days ≤ D-ER supply < 270 days	1.70	0.126	5.5
270 days ≤ D-ER supply < 360 days	1.71	0.086	5.5
Persistent D-ER users	Reference	—	3.3
Number of inpatient admissions	Incidence rate ratio		Adjusted mean incidence rate (12 months)
Number of all-cause inpatient admissions			
D-ER supply <90 days	2.45	0.005 ^c	0.13
90 days ≤ D-ER supply < 180 days	1.88	0.015 ^b	0.10
180 days ≤ D-ER supply < 270 days	1.35	0.321	0.07
270 days ≤ D-ER supply < 360 days	1.40	0.219	0.07
Persistent D-ER users	Reference	—	0.05
Number of MS-related inpatient admissions			
D-ER supply <90 days	2.82	0.004 ^c	0.10
90 days ≤ D-ER supply < 180 days	2.29	0.004 ^c	0.08
180 days ≤ D-ER supply < 270 days	1.75	0.091	0.06
270 days ≤ D-ER supply < 360 days	1.80	0.048 ^b	0.06
Persistent D-ER users	Reference	—	0.04
Health care resource expenditures	Mean difference		Adjusted mean expenditures (12 months)
All-cause inpatient expenditures (2014 USD)			
D-ER supply <90 days	1,415	0.012 ^b	\$2,087
90 days ≤ D-ER supply < 180 days	1,120	0.004 ^c	\$1,792
180 days ≤ D-ER supply < 270 days	451	0.209	\$1,123
270 days ≤ D-ER supply < 360 days	623	0.068	\$1,295
Persistent D-ER users	Reference	—	\$672
MS-related inpatient expenditures (2014 USD)			
D-ER supply <90 days	\$741	0.045 ^b	\$1,131
90 days ≤ D-ER supply < 180 days	\$598	0.025 ^b	\$988
180 days ≤ D-ER supply < 270 days	\$416	0.128	\$806
270 days ≤ D-ER supply < 360 days	\$362	0.129	\$752
Persistent D-ER users	Reference	—	\$390

^aThe adjusted analyses of the health care resource utilization and expenditure outcomes were conducted based on the mean D-ER user with or without persistent use in the study sample.

^bSignificance for the comparative estimates at 5%.

^cSignificance for the comparative estimates at 1%.

D-ER=dalfampridine-extended release; ER=emergency room; MS= multiple sclerosis; USD=U.S. dollars.

differences of \$741, $P=0.045$, and \$598, $P=0.025$) inpatient expenditures than persistent users. Although the other nonpersistent subgroups had numerically higher expenditures than

the persistent cohort, significance was not detected. Similar to the inpatient admission analysis, this may reflect inadequate sample size and power to detect a difference.

Discussion

This retrospective claims database analysis evaluated the association between persistent D-ER use and inpatient admissions and expenditures among patients with MS in a real-world setting. The study's findings show that persistent D-ER use is associated with significantly lower inpatient resource utilization and costs, even after controlling for differences in baseline characteristics that could influence these outcomes. These results were further reinforced by sensitivity analyses that revealed a general trend of greater D-ER persistence levels being associated with lower inpatient resource utilization and costs.

These results are consistent with previous literature indicating that impaired walking/abnormal gait in MS patients is associated with higher economic costs.^{8,10,11} One study found that the cost of MS nearly doubled in patients with gait abnormality relative to the overall MS patient population (\$48,361 [\$55,472] vs. \$26,520 [\$38,478], respectively, for mean [SD] annual per patient charges in a 2011 sample of MS patients with private insurance in the United States).¹¹ In a 2009 real-world cross-sectional doctor and patient survey in the European Union, increasing severity of mobility issues was associated with significantly higher frequency of hospitalization due to MS ($P < 0.001$).⁸ In addition, patients with longer walking times during the timed 25-foot walk (indicating greater walking impairment) were significantly more likely to require primary care consultations ($P = 0.004$), urologist visits ($P = 0.006$), and time spent with occupational therapists ($P = 0.010$).⁸ Recent claims database analyses evaluating walking-attributable hospitalizations and outpatient visits (to neurologists and physical/occupational therapy) among D-ER adherent and nonadherent patients with MS found that the D-ER adherent cohort experienced significantly less HRU over a 12-month period than nonadherent users.¹⁷

Although causality cannot be established from these findings, it is possible that walking impairment, with its broad implications for patient health, well-being, and social functioning, may be a direct contributor to, and an indirect marker of, acute care needs. Persistent use of D-ER to improve ambulatory function may have additional real-world consequences beyond the direct effect on mobility as suggested by the decrease in accompanying inpatient admissions and costs.

Limitations

This study is subject to several limitations, some of which are inherent to claims analyses and observational studies. First, claims data may be subject to coding errors and incompleteness and do not directly capture certain clinical assessment.²³⁻²⁵ For example, walking and/or movement difficulties may have been undercoded or miscoded within claims, which could have resulted in underreporting. Second, although claims data capture patients' prescription filling behavior, it is not known

whether patients actually took their medications; use must be inferred from patient prescription fills. Third, as with any observational study, despite efforts to extensively control for differences between the cohorts, unobserved confounders may exist. These confounders may include unobserved differences in disease severity between the cohorts that could affect the outcomes, as well as unobserved differences in responsiveness or resistance to D-ER treatment that could influence patient persistence.

Despite the limitations, claims data remain a valuable resource for examining real-world treatment trends and outcomes, with their findings strongly representative of clinical practice.^{26,27} In addition, they provide important and relevant information on real-world clinical and economic outcomes for MS patients, their families, and employers.

Conclusions

This study showed that persistent use of D-ER is associated with lower inpatient admissions and costs. This association remains even after controlling for differences in patient baseline characteristics.

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DISCLOSURES

Funding for this research and medical writing assistance was provided by Acorda Therapeutics. The study sponsor was involved in all stages of the study research and manuscript preparation. Guo and Niyazov were employees of Acorda Therapeutics at the time of this study and may own stock/stock options. Wu, Macaulay, Terasawa, and Schmerold are employees of Analysis Group, which received consultancy fees from Acorda Therapeutics for this project. Krieger was a consultant for Acorda Therapeutics for this project and has the following additional financial interests to report: consulting/advisory board work with Bayer, Biogen, EMD Serono, Novartis, Genentech, Genzyme, and Teva.

Study concept and design were contributed by Guo, Niyazov, Macaulay, and Wu. Macaulay, Terasawa, Schmerold, and Wu helped prepare the data, and data interpretation was performed by Krieger, Guo, Niyazov, and Macaulay, along with Terasawa and Wu. The manuscript was written by Terasawa and Schmerold, along with Macaulay, and revised by all the authors.

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Inpatient Admissions and Costs Associated with Persistent Use of Dalfampridine Extended-Release in Multiple Sclerosis: A Claims Database Analysis

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APPENDIX A Diagnostic and Drug Codes Used in Study Selection and Design

Type	Condition	Codes
1. Contraindications for Dalfampridine		
ICD-9-CM	History of seizures	345.xx, 780.3x
	Moderate or severe renal impairment	580.81, 584.xx-588.xx, 590.0-590.3, 590.8, 590.9, 599.7, 791.0, 794.4, 39.95, 54.98, 55.69, V45.1, V56.0-V56.2, V56.31, V56.32, V56.8
2. Non-MS Conditions that Impair Mobility		
ICD-9-CM	Brain neoplasm/abscess	191.xx, 198.3, 225.0, 237.5, 239.6, 324.0, 324.9, V12.41
	Parkinson's disease	332.x
	Cerebral palsy	333.7, 343.xx
	Muscular dystrophy	359.0, 359.1, V46.3
	Stroke	430.x-432.x, 433.x1, 434.x1, 436, 438.xx
	Tendonitis/tendon injury	726.6-726.9, 727.xx, 891.2x, 893.2x, 894.2x
	Spinal cord injury	806.x, 952.x
	Paralysis/hemiplegia	342.x, 344.0x, 344.1x, 344.3x
	Long-term wheelchair use	V46.3
3. MS Symptoms		
ICD-9-CM	Muscular weakness	728.87
	Spasms (muscle)	781.0, 728.85
	Disturbances of skin sensation	782.0
	Visual disturbances (including optic neuritis)	341.0, 377.3x
	Vision loss	369.xx
	Blurred vision	368.8
	Diplopia	368.2
	Nystagmus	379.5x
	Internuclear ophthalmoplegia	378.86
	Dizziness/giddiness/vertiginous syndromes	386.xx, 780.4
	Malaise and fatigue	780.7
4. MS Comorbidities		
ICD-9-CM	Depression	296.2, 296.3, 311
	Chronic pain	338.0, 338.29, 338.4, 780.96
	Anxiety	293.84, 300.0x, 309.24
	Urinary incontinence	788.3
	Urinary tract infection	590.xx, 595.xx, 597.xx, 599.xx
	Dyslipidemia	272.0-272.5
	Hypercholesterolemia	272.0
	Thyroid disease	193.xx, 240.xx-246.xx
	Arthritis	274.x, 710.xx-716.xx, 719.xx-721.xx, 725.xx-729.xx
	Diabetes mellitus	250.xx
	Non-skin cancer	140.xx-209.xx (excluding 172.x, 173.x)
	History of cardiovascular disease (including hypertension)	389.91, 401.xx-405.xx, 414.0, 414.2, 414.3, 428.0, 428.3, 428.4, 440.xx-449.xx, V17.49
	Hypertension	401.xx-404.xx, 642.0x-642.2x, 642.7x
	Obesity	278.xx, V85.35-V85.39, V85.4
5. Walking/Movement Impairment		
ICD-9-CM	Walking/movement difficulties	
	Difficulty in walking	719.7
	Abnormal gait	781.2
	Lack of coordination	781.3
	Abnormal involuntary movements	781.0
	Falls or fractures resulting in medical visits	
	Accidental falls	E880.x-E888.x
	Traumatic fractures	800.xx-829.x
	Non-traumatic fractures	733.xx

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**Inpatient Admissions and Costs Associated with Persistent Use of Dalfampridine
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APPENDIX A Diagnostic and Drug Codes Used in Study Selection and Design *(continued)*

Type and Purpose	Drug Name
6. Medications Used in Study	
Corticosteroids for inferred MS relapses	Intravenous methylprednisolone, corticotrophin, oral methylprednisolone, prednisone, prednisolone, dexamethasone, and betamethasone
Noncorticosteroid therapies for inferred MS relapses	Adrenocorticotrophic hormone (ACTH), plasmapheresis
Antispasticity and antitremor medications	Baclofen, intrathecal baclofen, tizanidine, gabapentin, dantrolene, Sativex (oromucosal spray), botulinum toxin, isoniazid, hydroxyzine, propranolol, primidone, acetazolamide, buspirone, and clonazepam
Anticonvulsants	Gabapentin, carbamazepine, oxcarbazepine, lamotrigine, pregabalin, phenytoin
DMTs	Teriflunomide, interferon beta-1a, interferon beta-1b, glatiramer acetate, fingolimod, mitoxantrone, dimethyl fumarate, natalizumab
Type	Codes
7. Physical Therapy Outpatient Visits Codes	
CPT-4	97001, 97002, 97003, 97004, 97110, 97112, 97113, 97116, 97124, 97139, 97140, 97504, 97760, 97530, 97799
Revenue codes	0420, 0421, 0422, 0423, 0424, 0429, 0977
Provider type	850

CPT-4 = Current Procedural Terminology, 4th edition; DMTs = disease-modifying therapies; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

**Inpatient Admissions and Costs Associated with Persistent Use of Dalfampridine
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APPENDIX B Sensitivity Analysis: Health Care Resource Utilization and Expenditures for Persistent Versus Nonpersistent D-ER Users over Follow-up Period

	Persistent D-ER Users ^a		Nonpersistent D-ER Users ^a											
	Overall [A] n = 719		D-ER Supply < 90 Days [B] n = 125		P Value ^b [A] vs. [B]	90 Days ≤ D-ER Supply < 180 Days [C] n = 268		P Value ^b [A] vs. [C]	180 Days ≤ D-ER Supply < 270 Days [D] n = 211		P Value ^b [A] vs. [D]	270 Days ≤ D-ER Supply < 360 Days [E] n = 275		P Value ^b [A] vs. [E]
Inpatient admissions														
Any all-cause inpatient admission, n (%)	39	(5.4)	14	(11.2)	0.014 ^c	29	(10.8)	0.003 ^d	16	(7.6)	0.242	23	(8.4)	0.086
Any MS-related inpatient admission, n (%)	29	(4.0)	12	(9.6)	0.008 ^d	25	(9.3)	0.001 ^d	14	(6.6)	0.114	21	(7.6)	0.020 ^c
All-cause inpatient admissions, mean (SD)	0.06	(0.27)	0.17	(0.55)	0.012 ^c	0.13	(0.40)	0.003 ^d	0.09	(0.35)	0.245	0.11	(0.39)	0.085
MS-related inpatient admissions, mean (SD)	0.04	(0.22)	0.14	(0.52)	0.007 ^d	0.11	(0.37)	0.001 ^d	0.08	(0.34)	0.111	0.09	(0.37)	0.019 ^c
Health care resource expenditures (2014 USD)														
All-cause inpatient expenditures, mean (SD)	1,387	(8,826)	4,951	(28,898)	0.012 ^c	3,088	(12,909)	0.002 ^d	2,990	(15,467)	0.227	2,097	(8,294)	0.077
MS-related inpatient expenditures, mean (SD)	937	(7,401)	1,762	(6,729)	0.007 ^d	1,742	(7,099)	0.001 ^d	1,699	(9,741)	0.113	1,249	(5,914)	0.020 ^c

^aPersistent D-ER users were defined as patients with at least 360 days of D-ER supply. Nonpersistent D-ER users were defined as patients with less than 360 days of D-ER supply.

^bP values comparing the persistent and nonpersistent D-ER users were calculated using Wilcoxon rank-sum and chi-square tests for the continuous and categorical variables, respectively.

^cSignificance at 5%.

^dSignificance at 1%.

D-ER = dalfampridine-extended release; MS = multiple sclerosis; SD = standard deviation; USD = U.S. dollars.