SciMedCentral

International Journal of Rare Diseases & Orphan Drugs

Research Article

Myotonic Dystrophy Patient Journey: Increased Use of Healthcare Resources in the Year Prior to Diagnosis as Evidenced by Insurance Claims

John W. Day[1], Kathryn A. Munoz[2+], Chao- Yin Chen[2+], Richard A. Brook[3], Nathan L. Kleinman[3], Brad McEvoy[2], Mark Stahl[2], and Li-Jung Tai[1,2]*

[1]*Department of Stanford Neuroscience Health Center, USA*
[2]*Department of Avidity Biosciences, USA*
[3]*Department of Better Health Worldwide, USA*
[+]*Former Employee of Avidity Biosciences*

***Corresponding author**
Li-Jung Tai, Executive Director, Department of Clinical Development, Avidity Biosciences, Inc., California, USA

Submitted: 04 November 2023
Accepted: 06 December 2023
Published: 08 December 2023

ISSN: 2576-0092

Keywords
- Healthcare costs
- Healthcare resource utilization
- Insurance claims database
- Rare disease
- Myotonic dystrophy
- Patient journey

Abstract

Myotonic dystrophy (DM) is an inherited autosomal dominant disease with progressive myopathy and comorbidities involving multiple organ systems. There is no cure, but a deeper understanding of the patient journey, the use of healthcare resources, and the cost of care before and after diagnosis would assist in managing supportive care. This longitudinal analysis of medical and pharmacy insurance claims between January 2010 and March 2021 included 1,694 patients with two or more DM diagnostic claims compared with 8,470 matched control (MC) patients who were propensity-score matched by index date (i.e., month of diagnosis), age, region, sex, plan, and payer type. Eligible patients had a minimum of 12 months of continuous data. Comorbidities consistent with the clinical profile of DM were more prevalent in patients with DM than in the MC cohort. The aggregate per-member-per-year medical costs were $18,239 for a patient with DM and $5,609 for a MC. The corresponding pharmacy costs were $3,029 and $1,478. Overall, resource utilization – including emergency departments, inpatient facilities, outpatient facilities, office practices, pharmacies, laboratories, procedures (Healthcare Common Procedure Coding System or Current Procedural Terminology codes), prescription medications, and clinician-administered drugs (J-codes) – and their associated costs were higher for patients with DM than MCs. Until a diagnosis of DM is established, the varied presentations of this multisystemic disorder complicates diagnostic testing and medical care. During the pre-diagnosis period, patients, caregivers, and families experience the stress and additional cost burden associated with the uncertainty of an undiagnosed condition. To further elucidate the impact of DM, additional analyses are ongoing to assess changes in comorbidities, use of healthcare resources, and costs.

ABBREVIATIONS

AHRQ: Agency for Healthcare Research and Quality; ATC: Anatomical Therapeutic Chemical; DM: Myotonic Dystrophy; CCI: Charlson Comorbidity Index; CPI: Consumer Price Index; CTP: Current Procedural Terminology; DMPK: Dystrophica Myotonica Protein Kinase; ED: Emergency Department; HCPCS: Healthcare Common Procedure Coding System; ICD-9: International Classification of Disease Ninth Revision; ICD-10: International Classification of Disease Tenth Revision; MC: Matched Control; PMPY: Per Member Per Year; SD: Standard Deviation.

INTRODUCTION

Myotonic dystrophy (DM) is the most common form of muscular dystrophy in adults. It is a rare, inherited autosomal dominant disease with progressive myopathy, myotonia, and multiorgan involvement. Comorbidities may involve the respiratory, gastrointestinal, cardiac, and central nervous systems, among others, resulting in a disease burden that has significant impact on patient and family quality of life [1-3]. Two distinct forms of DM have been identified: DM1, or Steinert's disease, and DM2. They have clinical and pathophysiologic similarities that appear at various ages and times during the disease continuum, but they are different disorders that require genetic diagnostic testing for confirmation. Genetic screening is possible but has not been performed in large populations [4]. The most frequently cited estimate of the prevalence of DM1 is 1 in 8,000 people worldwide [5], while a more recent systematic review estimated the worldwide prevalence of DM as 0.5–18.1 per 100,000 people, without differentiating between types [6]. The prevalence of DM2 appears to be lower than that of DM1, except for populations originating from Northern Europe [7]. The

epidemiology of DM has not been systematically studied in the USA, but clinical experience suggests that DM2 is approximately 5-fold less prevalent than DM1 [4]. Rarity, variable presentation, and neuromuscular features that are shared with other diseases complicate diagnosis after the onset of the initial symptoms and result in a long patient journey. There is no cure or disease-modifying treatment, but establishing a focused, comprehensive approach to clinical care can extend patient lifespan and help maintain mobility and quality of life. Longitudinal data on the use of medical resources by patients with DM prior to diagnosis would add to what is known about the use of available resources, clinical experience, and the cost of medical care. This study analyzed healthcare claims paid during the 12 months before diagnosis (pre-index period). Identifiable claim codes were analyzed to allow in-depth views of the prevalence and costs of comorbid conditions, product use, and procedures prior to patients' diagnosis of DM and in a matched control (MC) group.

METHODS

Study design

This study was a longitudinal analysis of medical and pharmacy claims made by insured patients between January 2010 and March 2021 and retrieved from the IQVIA US PharMetrics® Plus database [Figure 1]. The claims data were de-identified, and the study did not influence patient care; consequently, the study was exempt from institutional review board approval. The analysis compared a cohort of patients with DM who were identified by claims including International Classification of Disease Ninth Revision (ICD-9) code 359.21 and Tenth Revision (ICD-10) code G71.11 diagnosis codes for myotonic muscular dystrophy without distinguishing type 1 and type 2 DM. Eligible patients had ≥ 2 DM diagnosis claims filed ≥ 30 days apart. The index date was used as a proxy for initial diagnosis of DM, and eligible patients had a minimum of 12 months of continuous data prior to their index date. The patients with DM were compared with a 5% random sample of patients remaining in the PharMetrics® Plus database records after excluding the DM cohort. Patients with ICD-9 359.xx (muscular dystrophies and other myopathies), ICD-10 G71.xxx (primary disorders of muscles), ICD-10 M62.5xx (muscular wasting and disuse atrophy), or ICD-10 M63.8xx (other muscle disorders in disease classified elsewhere) claims were excluded from the MC cohort. Each patient with DM was matched by index month, baseline age, region, sex, plan, and payer type to five MCs using a propensity-score-matching algorithm and nearest-neighbor matching (R MatchIt) [8]. Resource utilization was reported in each cohort as the percentage of patients with relevant claims during the pre-index period. For analysis, plan costs plus member-paid costs and days or number of billed services were aggregated for each patient over the 12 months preceding the index date and reported as per-member-per-year (PMPY) values. Costs were inflation-adjusted to December 2020 dollars using the US Bureau of Labor Statistics Consumer Price Index (CPI); medical claims used the medical-cost CPI, and prescription claims used the prescription-cost CPI. The ICD-9 and ICD-10 claims included in the database were assigned and aggregated into 283 specific US Agency for Healthcare Research and Quality (AHRQ) categories (https://hcup-us.ahrq.gov/toolssoftware/ccsr/DXCCSR-User-Guide-v2019-1.pdf). The categories were used to compare the prevalence of comorbid conditions, reasons for inpatient admissions and emergency department (ED) visits, and related costs and services. As general measures of comorbidity, Charlson Comorbidity Index (CCI) scores [9] were also calculated, along with the number of patients with CCIs >1, the per-patient number of diagnoses (ICD-9s and ICD-10s), and the per-patient number of AHRQ condition categories. The utilization, PMPY cost, and number of prescription fills in each cohort were compared using the Anatomical Therapeutic Chemical (ATC) drug hierarchy classification of the World Health Organization (https://www.who.int/tools/atc-ddd-toolkit/atc-classification). Injectable drugs that are not ordinarily self-administered (i.e., are clinician-administered) were identified by their J-codes in the medical claims. Medical procedures were identified by Healthcare Common Procedure Coding System (HCPCS) and Current Procedural Terminology (CPT) codes.

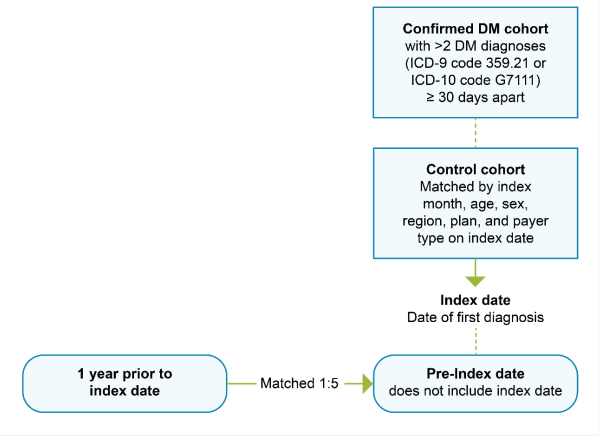


Figure 1 Study plan and patient selection. The analysis included medical and pharmacy claims made by insured patients between January 2010 and March 2021. **Abbreviations:** DM: myotonic dystrophy; ICD-9: International Classification of Disease Ninth Revision; ICD-10: International Classification of Disease Tenth Revision

Statistical analysis

The statistical analysis was descriptive. Results were reported as means ± standard deviation or numbers and percentage. Comparisons of utilization, cost, number of services, and number of days of service in the 12 months prior to the index date were made with two-sample *t*-tests for continuous variables and chi-square tests for discrete variables. Differences were considered significant at $p \leq 0.01$.

RESULTS

Descriptive characteristics of patients with DM

We identified 1,694 patients with DM in the claims database and matched them to 8,470 MCs. The age, region, sex, insurance

plan, and payer type of the patients with DM and MCs are shown in Table 1. There were no significant differences in the descriptive characteristics between cohorts.

Comorbid conditions

Overall, there were observed differences ($p < 0.0001$) in the CCI mean scores (DM cohort 0.82 ± 1.51 vs MC cohort 0.44 ± 1.19), the percentages of patients with CCI scores ≥ 1 (19.1% vs 9.7%), the number of ICD-9/-10 diagnoses (11.87 ± 10.28 vs 6.26 ± 7.11), and the number of prevalent AHRQ categories (8.66 ± 6.42 vs 4.88 ± 4.90).

The prevalence of pre-index healthcare conditions and associated PMPY costs and services used were higher in patients with DM compared with MCs. The largest differences in prevalence included the AHRQ categories "other nervous system disorders" (54.4% vs 10.2%), "other connective tissue disease" (49.4% vs 20.1%), and "other lower respiratory disease" (29.8% vs 14.6%). The 20 comorbid conditions with the largest cohort differences are shown in [Figure 2A]. Pre-index prevalence was greater in patients with DM than in MCs in 143 of the 283 AHRQ categories. Pre-index PMPY costs differed in 22 AHRQ categories, 18 of which were higher in patients with DM. The 20 categories with the greatest PMPY cost differences are shown in [Figure 2B]. The number of billed pre-index services differed in 50 AHRQ categories, 49 of which were higher in patients with DM. The 20 categories with the greatest differences in number of services are shown in [Figure 2C]. Comparisons between the DM cohort and MCs of the 283 AHRQ categories are shown in [Supplementary Table 1].

Table 1: Age, sex, US region, insurance plan, and payer types of patients with DM and MCs on the index date

	Patients with DM (n = 1,694)	MCs (n = 8,470)		
Characteristic	**Mean ± SD or %**	**Mean ± SD or %**	**Difference, %**	***P*-value**
Age, years	43.4 ± 18.1	43.5 ± 18.2	−0.1	0.7823
< 18	10.8	10.9	−0.1	0.8980
18 to ≤ 35	19.3	19.0	0.3	0.7603
35 to ≤ 45	18.2	18.2	0.0	0.9908
45 to ≤ 55	20.1	19.9	0.2	0.8591
55 to ≤ 65	23.0	23.1	−0.1	0.9078
> 65	8.6	8.9	−0.3	0.7078
Sex, female	50.5	50.7	−0.2	0.8731
US region				
South	30.5	30.4	0.1	0.9155
Midwest	28.5	28.5	0.0	0.9686
Northeast	20.8	21.1	−0.3	0.8024
West	18.5	18.3	0.2	0.8274
Unknown	1.7	1.7	0.0	0.9190
Insurance				
Preferred provider organization	66.0	65.9	0.1	0.9329
Health maintenance organization	23.0	22.8	0.2	0.8657
Point of service plan	5.4	5.7	−0.3	0.6725
Consumer-directed healthcare	2.8	2.9	−0.1	0.7706
Indemnity/traditional plan	1.6	1.6	0.0	0.9146
Unknown	1.2	1.2	0.1	0.8380
Payer				
Commercial	60.3	60.7	−0.4	0.7784
Self-insured	21.5	21.6	−0.1	0.9227
Medicaid	9.0	9.0	0.0	0.9506
Medicare advantage	5.5	5.0	0.5	0.3619
Medicare supplemental	2.8	2.9	−0.1	0.8945
Unknown line of business	0.9	0.8	0.0	0.8464

Abbreviations: DM: myotonic dystrophy; MC: matched control; SD: standard deviation

Prescription medications

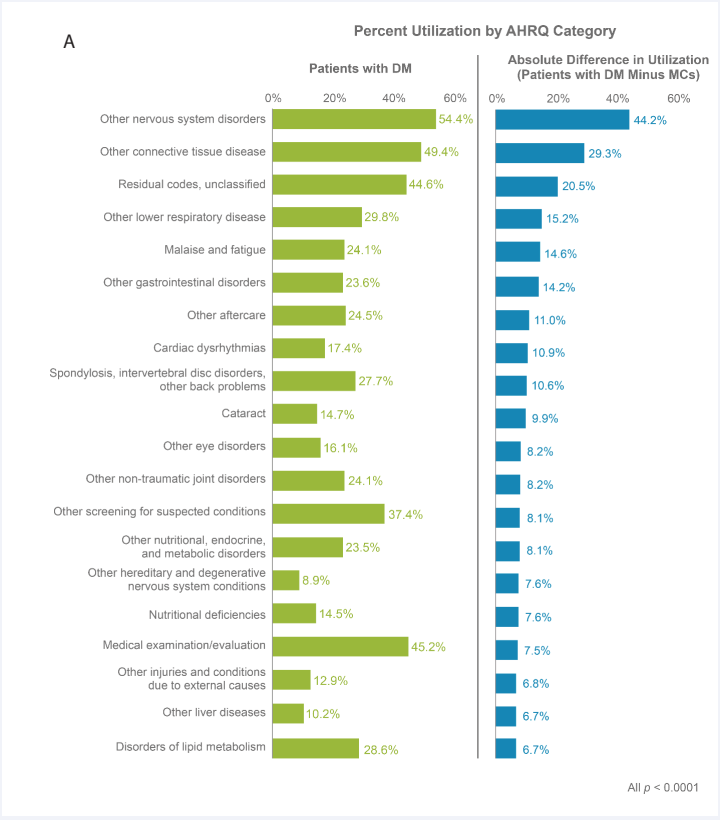
Comparison of claims for 88 ATC category 2 drugs, which are classified by the organ or system on which they act and their therapeutic properties, found 49 that had significantly higher use in the DM cohort. The 20 classes with the greatest differences are shown in [Figure 3A], and are led by systemic antibacterials (46.1% vs 35.5%), ophthalmologicals (36.3% vs 27.4%), and intestinal anti-inflammatory drugs (20.9% vs 13.4%). Twenty categories had significant cost differences between cohorts, and the PMPY costs of 18 drug classes were higher in the DM cohort than in the MC cohort. The greatest differences [Figure 3B], were seen in diabetes drugs ($357 vs $227, $p = 0.0169$), antiepileptics ($122 vs $32, $p = 0.0054$), and drugs for obstructive-airway diseases ($219 vs $150, $p = 0.0441$). Differences in prescription fills [Figure 3C], were significant in 42 of the 88 drug classes, and patients with DM had significantly more fills than MCs in 40 of the classes. The greatest PMPY differences in number of fills were for ophthalmologicals (1.35 vs 0.82), systemic antibacterials (1.39 vs 0.87), and psychoanaleptics (1.49 vs 1.04). Differences in all three metrics in ATC class 2 drugs are in line with those found in class 3 and 4 drugs, which are shown in [Supplementary Tables 2] [Supplementary Table 3].

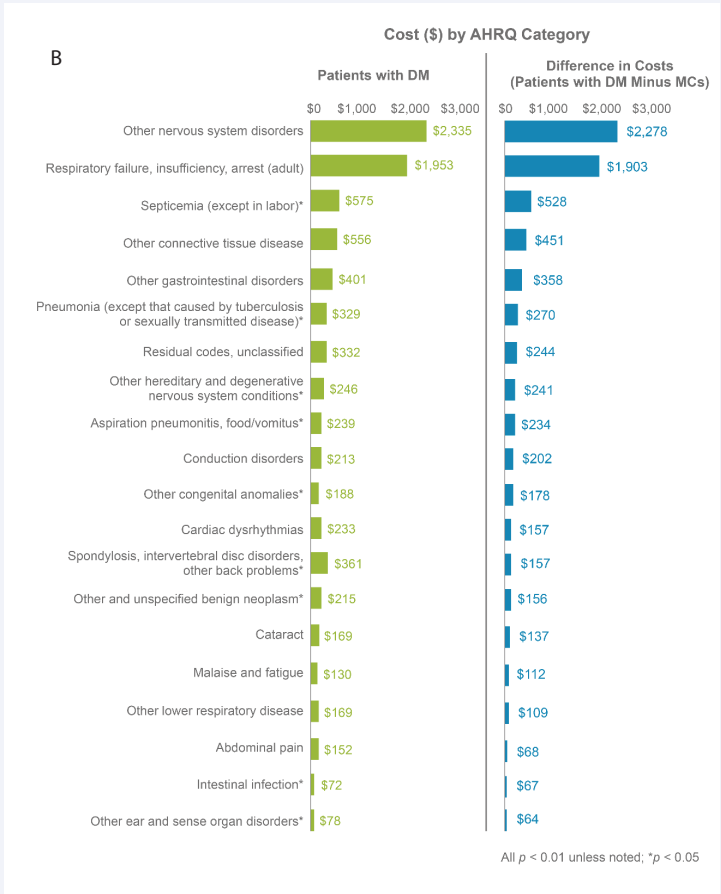
Clinician-administered medications

The use of 34 of the 290 clinician-administered drugs identified as being used by either cohort and included in the analysis differed significantly between patients with DM and MCs at $p < 0.01$. For each of the drugs, the percentage of claims was greater in the DM cohort. The PMPY costs of 57 drugs were significantly different, with 17 being higher for DM. The number of administrations was significantly different for 79 drugs, with 38 drugs having more administrations in the DM cohort. Widely used injectable agents with significantly greater prevalence, PMPY costs, and administrations in the DM population are shown in Table 2. The prevalence, PMPY costs, and number of administrations of the 290 administered drugs are shown in [Supplementary Table 4].

Location of care

The percentages of patients with DM who received care at EDs, inpatient facilities, outpatient facilities, office practices, laboratories, pharmacies (i.e., outpatient-dispensed and -filled prescription drugs), and "other" locations were all significantly


A
Percent Utilization by AHRQ Category
Patients with DM
Absolute Difference in Utilization (Patients with DM Minus MCs)
0% 20% 40% 60%
Other nervous system disorders 54.4% 44.2%
Other connective tissue disease 49.4% 29.3%
Residual codes, unclassified 44.6% 20.5%
Other lower respiratory disease 29.8% 15.2%
Malaise and fatigue 24.1% 14.6%
Other gastrointestinal disorders 23.6% 14.2%
Other aftercare 24.5% 11.0%
Cardiac dysrhythmias 17.4% 10.9%
Spondylosis, intervertebral disc disorders, other back problems 27.7% 10.6%
Cataract 14.7% 9.9%
Other eye disorders 16.1% 8.2%
Other non-traumatic joint disorders 24.1% 8.2%
Other screening for suspected conditions 37.4% 8.1%
Other nutritional, endocrine, and metabolic disorders 23.5% 8.1%
Other hereditary and degenerative nervous system conditions 8.9% 7.6%
Nutritional deficiencies 14.5% 7.6%
Medical examination/evaluation 45.2% 7.5%
Other injuries and conditions due to external causes 12.9% 6.8%
Other liver diseases 10.2% 6.7%
Disorders of lipid metabolism 28.6% 6.7%
All p < 0.0001


B
Cost ($) by AHRQ Category
Patients with DM
Difference in Costs (Patients with DM Minus MCs)
$0 $1,000 $2,000 $3,000
Other nervous system disorders $2,335 $2,278
Respiratory failure, insufficiency, arrest (adult) $1,953 $1,903
Septicemia (except in labor)* $575 $528
Other connective tissue disease $556 $451
Other gastrointestinal disorders $401 $358
Pneumonia (except that caused by tuberculosis or sexually transmitted disease)* $329 $270
Residual codes, unclassified $332 $244
Other hereditary and degenerative nervous system conditions* $246 $241
Aspiration pneumonitis, food/vomitus* $239 $234
Conduction disorders $213 $202
Other congenital anomalies* $188 $178
Cardiac dysrhythmias $233 $157
Spondylosis, intervertebral disc disorders, other back problems* $361 $157
Other and unspecified benign neoplasm* $215 $156
Cataract $169 $137
Malaise and fatigue $130 $112
Other lower respiratory disease $169 $109
Abdominal pain $152 $68
Intestinal infection* $72 $67
Other ear and sense organ disorders* $78 $64
All p < 0.01 unless noted; *p < 0.05

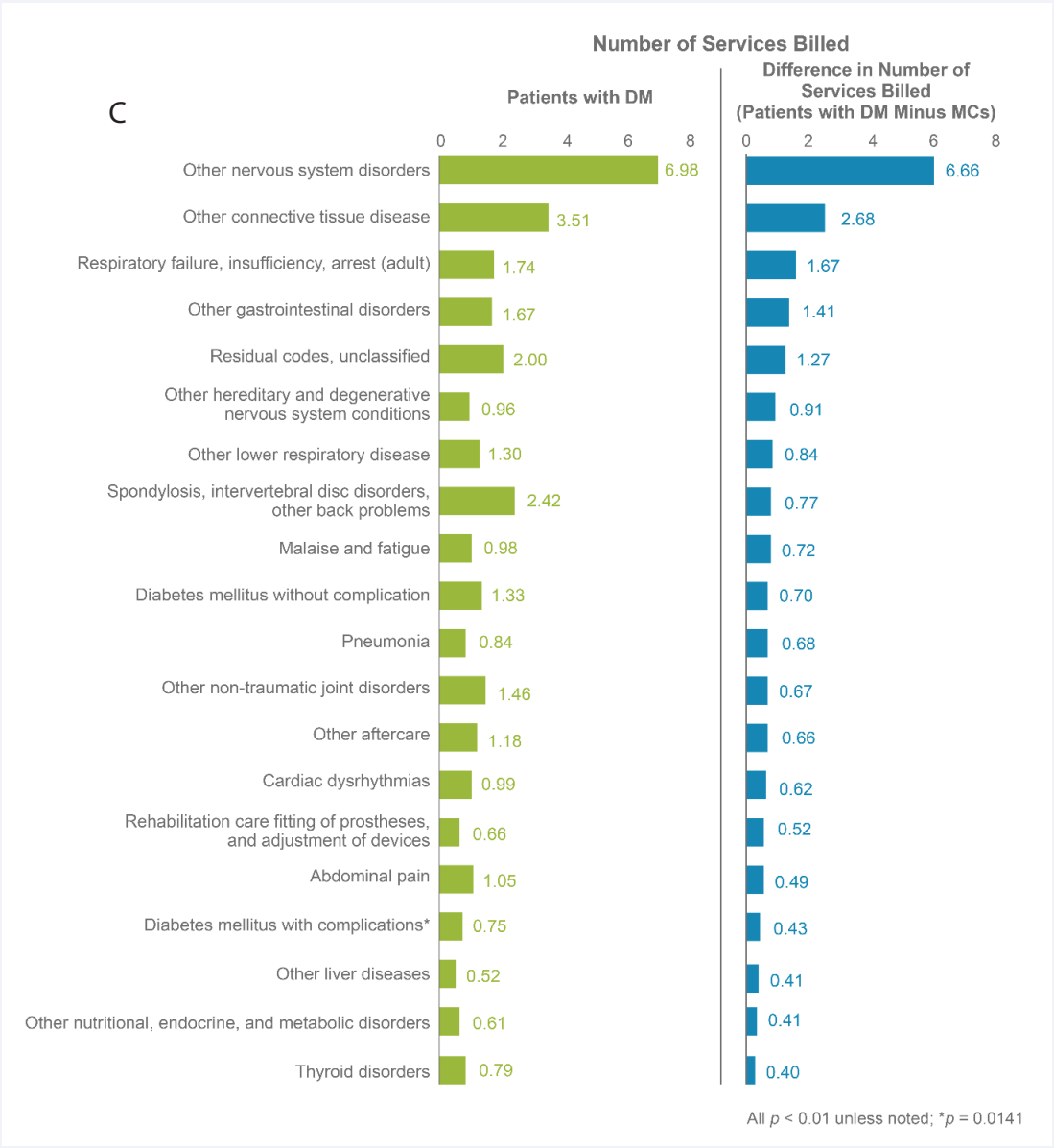
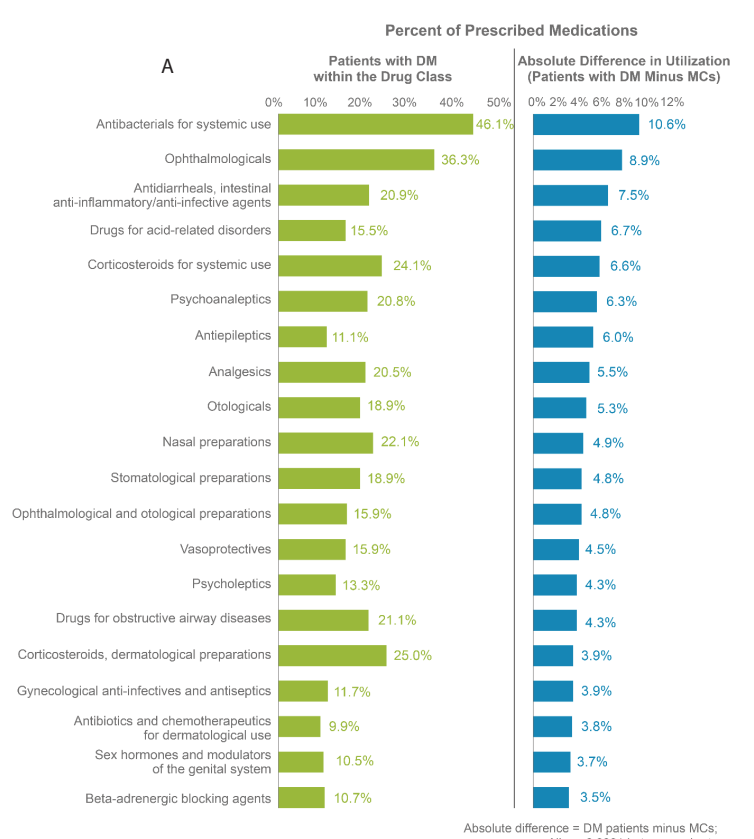


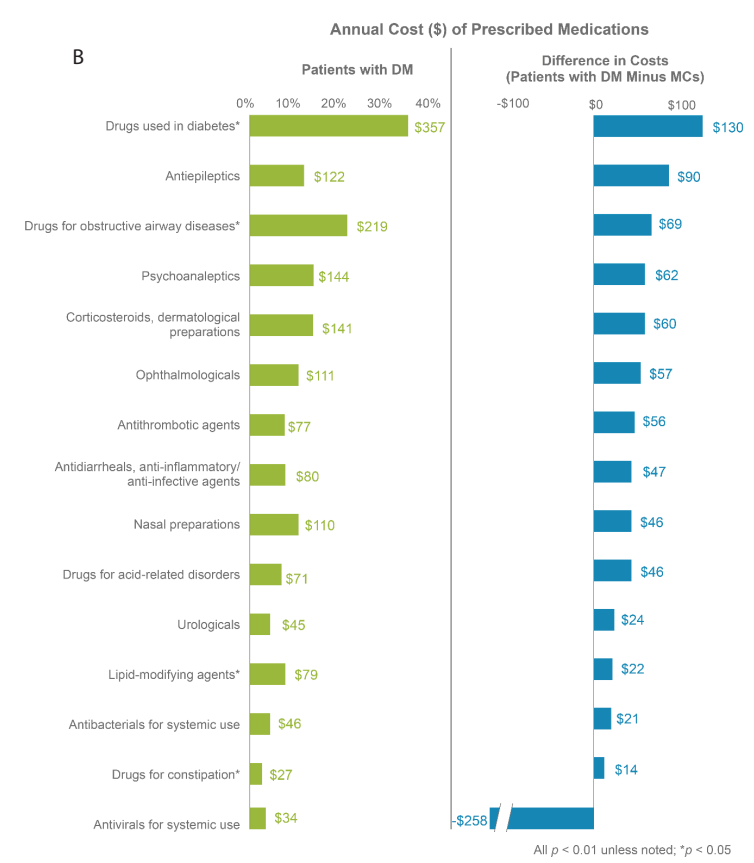
Figure 2 AHRQ categories with the largest between-group differences in (A) utilization, (B) PMPY per member per year costs, and (C) number of billed services
Abbreviations: AHRQ: Agency for Healthcare Research and Quality; DM: myotonic dystrophy; MC: matched control; PMPY: per-member-per-year

higher than those of the MCs. The overall use of medical and pharmacy locations of care was 97.7% vs 85.9%. The PMPY number of services were 88.4 ± 115.35 vs 44.1 ± 70.3, and the PMPY days of service were 30.8 ± 33. 4 vs 16. 25 ± 21.5 for patients with DM and MCs, respectively. The aggregate PMPY medical costs associated with locations of care were $18,239 for patients with DM and $5,609 for MCs, a difference of 225.2%. The corresponding pharmacy costs were $3,029 and $1,478, a difference of 105%. The location of care comparisons are shown in [Table 3].

Inpatient admissions and ED visits

Inpatient admissions and ED visits were identified by ICD-9 and ICD-10 codes corresponding to the 283 AHRQ-specific diagnostic categories. The percentage of inpatient admissions was 17.0% for patients with DM and 7.0% for MCs. The corresponding percentages of ED visits were 22.1% and 13.7%, respectively. Inpatient admissions were significantly higher ($p < 0.01$) in patients with DM than in MCs in 71 AHRQ categories. ED visits were higher in patients with DM in 28 categories. Patients with DM had higher prevalence for all categories compared with the MCs. Clinically and economically relevant differences in inpatient admissions and ED visits included nervous system disorders, lower respiratory disease, adult respiratory failure


Percent of Prescribed Medications
A
Patients with DM within the Drug Class
Absolute Difference in Utilization (Patients with DM Minus MCs)
0% 10% 20% 30% 40% 50%
0% 2% 4% 6% 8% 10% 12%
Antibacterials for systemic use 46.1% 10.6%
Ophthalmologicals 36.3% 8.9%
Antidiarrheals, intestinal anti-inflammatory/anti-infective agents 20.9% 7.5%
Drugs for acid-related disorders 15.5% 6.7%
Corticosteroids for systemic use 24.1% 6.6%
Psychoanaleptics 20.8% 6.3%
Antiepileptics 11.1% 6.0%
Analgesics 20.5% 5.5%
Otologicals 18.9% 5.3%
Nasal preparations 22.1% 4.9%
Stomatological preparations 18.9% 4.8%
Ophthalmological and otological preparations 15.9% 4.8%
Vasoprotectives 15.9% 4.5%
Psycholeptics 13.3% 4.3%
Drugs for obstructive airway diseases 21.1% 4.3%
Corticosteroids, dermatological preparations 25.0% 3.9%
Gynecological anti-infectives and antiseptics 11.7% 3.9%
Antibiotics and chemotherapeutics for dermatological use 9.9% 3.8%
Sex hormones and modulators of the genital system 10.5% 3.7%
Beta-adrenergic blocking agents 10.7% 3.5%
Absolute difference = DM patients minus MCs;


Annual Cost ($) of Prescribed Medications
B
Patients with DM
Difference in Costs (Patients with DM Minus MCs)
0% 10% 20% 30% 40%
-$100 $0 $100
Drugs used in diabetes* $357 $130
Antiepileptics $122 $90
Drugs for obstructive airway diseases* $219 $69
Psychoanaleptics $144 $62
Corticosteroids, dermatological preparations $141 $60
Ophthalmologicals $111 $57
Antithrombotic agents $77 $56
Antidiarrheals, anti-inflammatory/ anti-infective agents $80 $47
Nasal preparations $110 $46
Drugs for acid-related disorders $71 $46
Urologicals $45 $24
Lipid-modifying agents* $79 $22
Antibacterials for systemic use $46 $21
Drugs for constipation* $27 $14
Antivirals for systemic use $34 -$258
All p < 0.01 unless noted; *p < 0.05

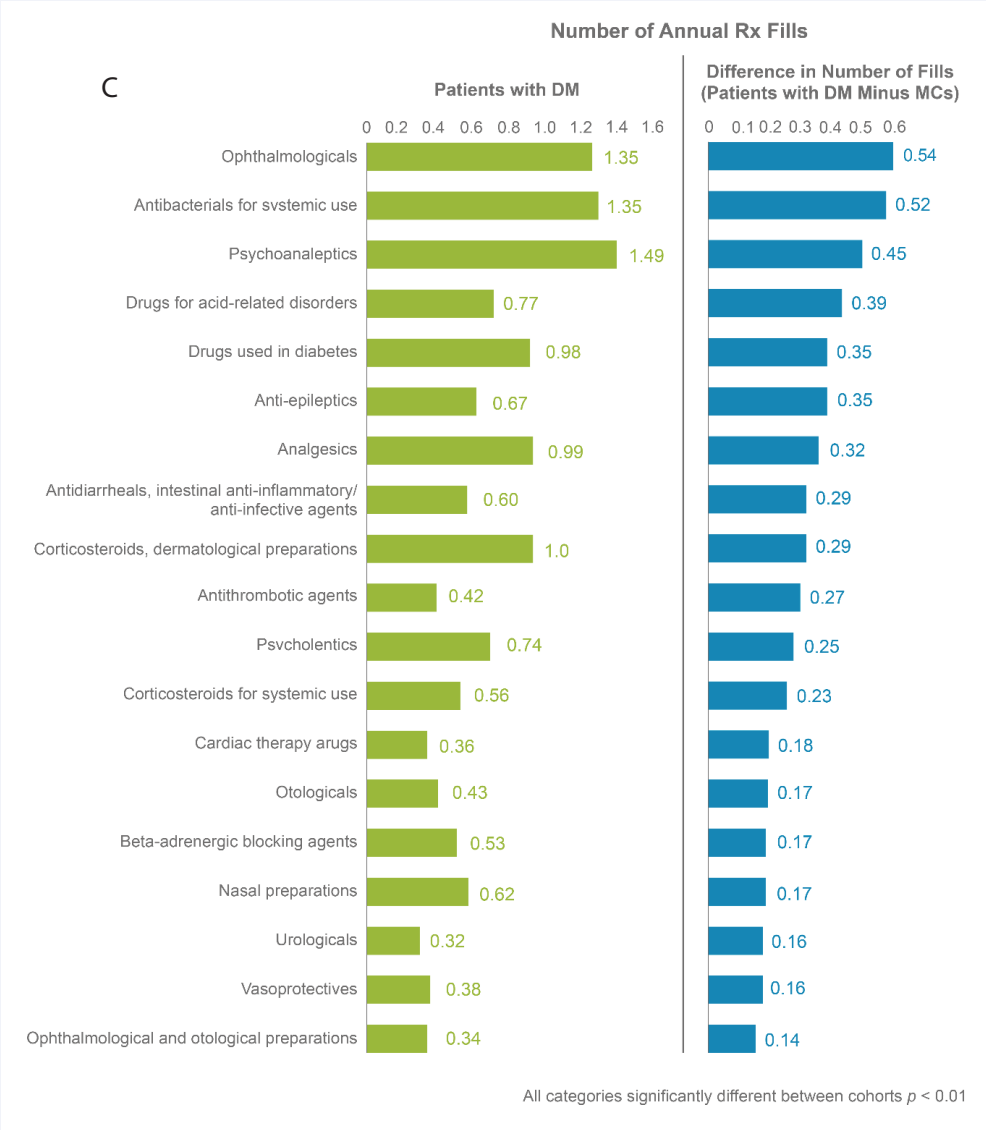


Figure 3 Anatomical Therapeutic Chemical category 2 drugs with the largest between-group differences in (A) utilization, (B) per member per year costs, and (C) number of fills.
Abbreviations: DM: myotonic dystrophy; Rx: prescription

Table 2: Injectable drugs with significantly greater prevalence, PMPY costs, or administrations in patients with DM than in MCs

Drug	Prevalence, %	PMPY cost, $	Administration, *n*
Ondansetron HCl, 1 mg	7.4 vs 4.2	2.6 vs 1.7*	0.11 vs 0.06
Midazolam HCl, 1 mg	6.7 vs 3.3	1.1 vs 0.5†	0.09 vs 0.04
Fentanyl citrate, 0.1 mg	6.5 vs 3.3	1.5 vs 0.7*	0.09 vs 0.04
Ketorolac tromethamine, 15 mg	5.0 vs 3.5	0.9 vs 0.6*	0.07 vs 0.05
Cefazolin sodium, 500 mg	3.0 vs 1.5	3.0 vs 1.5*	0.04 vs 0.02

$p < 0.0001$ unless noted
*Not significant ($p > 0.01$)
†$p = 0.0065$
Abbreviations: DM, myotonic dystrophy; MC, matched control; PMPY, per member per year

and insufficiency, and gastrointestinal disorders. The AHRQ categories with the greatest differences in prevalence are shown in [Figure 4A,Figure 4B], and the results of all categories are shown in [Supplementary Table 5].

PROCEDURES

HCPCS or CPT procedure codes identified 158 procedure categories, which were then divided into ten groups for analysis [Supplementary Table 6]. The between-cohort differences in utilization were significant in 91 procedure categories with higher utilization for patients with DM. PMPY costs were significantly different in 52 procedures, with the cost of 50 procedures higher in patients with DM. PMPY number of services was different in

Table 3: Utilization by patients with DM and MCs in the year prior to DM diagnosis by location of care

	Claims			PMPY cost			PMPY services			Days of service		
Location of care	DM, %	MC, %	DM – MC, %†	DM Mean ± SD, $	MC Mean ± SD, $	DM – MC, $	DM Mean ± SD, n	MC Mean ± SD, n	DM – MC, n	DM Mean ± SD, n	MC Mean ± SD, n	DM – MC, n
Emergency department	22.1	13.67	62	437 ± 1,901	237 ± 1,855	201	3.0 ± 13.1	1.4 ± 8.0	1.6	0.5 ± 1.4	0.3 ± 1.2	0.2
Inpatient	17.0	7.02	142	7,741 ± 46,605	1,570 ± 11,774	6,170	8.2 ± 32.6	2.4 ± 16.4	5.8	2.0 ± 9.5	0.5 ± 4.1	1.4
Outpatient	69.7	46.20	51	4,036 ± 11,670	1,877 ± 11,898	2,159	18.5 ± 46.2	7.8 ± 25.0	10.7	4.2 ± 8.4	1.9 ± 6.9	2.3
Office practice	93.0	79.16	18	2,868 ± 12,137	1,263 ± 4,667	1,605	23.8 ± 31.7	13.5 ± 23.8	10.3	11.4 ± 13.2	6.4 ± 9.9	5.0
Laboratory	40.7	30.83	32	195 ± 806	73 ± 382	122	5.2 ± 12.1	2.9 ± 9.1	2.3	1.2 ± 2.6	0.7 ± 1.8	0.5
Pharmacy	85.0	71.65	19	3,039 ± 13,883	1,478 ± 6,490	1,561	20.1 ± 28.0	13.3 ± 22.1	6.7	13.7 ± 16.0	8.8 ± 12.5	4.9
Other	36.0	17.65	104	2,963 32,521	589 ± 13,143	2,374	9.7 ± 42.3	2.8 ± 18.7	6.9	4.1 ± 18.9	1.0 ± 5.1	3.2
Total (medical + pharmacy)*	97.7	85.89	14	21,278 ± 6,102	7,087 ± 25,977	14,191	88.4 ± 115.4	44.1 ± 70.3	44.3	30.8 ± 33.4	16.3 ± 21.5	14.5

*Sums may not add to numbers because of rounding

†Relative difference = (DM % – MC %) / MC. DM versus MC utilization differences (chi-square) and PMPY cost, services, and days of service (*t*-test) by location of care are all $p < 0.0001$

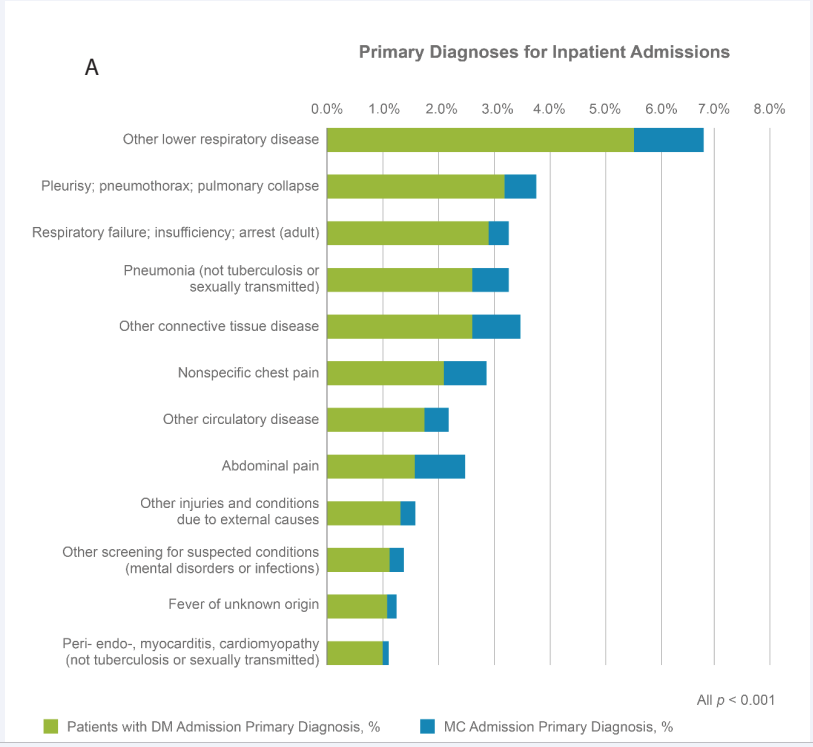
Abbreviations: DM: myotonic dystrophy; MC: matched control; PMPY: per member per year; SD: standard deviation

Table 4: Procedures identified by HCPCS or CPT procedure codes in patients with DM and MCs in the year prior to the DM diagnosis

		Prevalence			PMPY cost		
Group	Category	DM, %	MC, %	% ↑	DM, $ mean ± SD,	MC, $ mean ± SD	DM – MC, $
Anesthesia	Anesthesia, head	3.96	1.17	238	38 ± 264	9 ± 107	30
Other	Walking aids and wheelchairs	5.84	1.07	444	113 ± 1,013	2 ± 56	111
	Genetic tests	4.37	0.19	2,213	88 ± 760	1 ± 32	87
	Muscle biopsy	2.30	0.00	–	48 ± 468	0 ± 0	48
	Electrocardiogram	33.06	16.86	96	35 ± 138	14 ± 74	21
	Echocardiogram	17.06	5.17	230	148 ± 871	33 ± 234	115
	Lung function	10.45	4.64	125	39 ± 268	8 ± 67	31
	Electromyography	14.99	0.91	1,549	55 ± 250	2 ± 39	53
	Muscle enzyme	21.72	3.05	613	5 ± 19	1 ± 10	5
Evaluation/management	Office/other outpatient services	90.02	72.46	24	819 ± 994	398 ± 612	421
	Hospital inpatient services	12.69	4.77	166	243 ± 1,411	66 ± 627	178
	Consultations	26.15	7.80	235	117 ± 308	23 ± 105	94
	Emergency department services	27.04	16.04	69	280 ± 820	153 ± 761	127
HCPCS code	Transportation, medical and surgical supplies, miscellaneous, experimental	26.74	11.20	139	365 ± 2,107	91 ± 914	274
	Enteral and parenteral therapy	1.77	0.06	2,900	71 ± 749	0 ± 14	70
	Other durable medical equipment	12.22	3.13	291	400 ± 2,475	32 ± 449	368
	Temporary codes for durable medical equipment regional carriers	4.84	0.31	1,477	74 ± 692	2 ± 92	72
	Orthotic/prosthetic procedures	8.91	4.24	110	95 ± 628	19 ± 371	76
Medicine	Special otorhinolaryngologic services	8.91	4.17	114	46 ± 367	8 ± 123	38
	Other pulmonary	6.55	2.67	146	6 ± 47	1 ± 23	5
	Other neurology and neuromuscular procedures	20.13	2.72	641	245 ± 1,447	29 ± 323	216
	Physical medicine and rehabilitation	21.07	10.01	110	332 ± 1,228	106 ± 710	227
	Ophthalmology	26.33	13.96	89	64 ± 189	30 ± 127	33
Pathology and laboratory	Organ or disease-oriented panels	59.62	41.77	43	72 ± 161	41 ± 144	31
	Other genetic analysis/testing	6.43	0.85	657	50 ± 316	7 ± 124	43
	Other chemistry	61.75	41.10	50	209 ± 649	72 ± 338	137
	Hematology and coagulation	50.83	31.45	62	38 ± 133	19 ± 96	20
	Immunology	27.15	13.67	99	47 ± 258	13 ± 111	34
	Other surgical pathology	20.60	12.36	67	165 ± 796	50 ± 268	115
Radiology	Diagnostic radiology	54.60	31.61	73	694 ± 1,779	254 ± 1,115	440
	Diagnostic ultrasound	21.37	14.05	52	96 ± 403	54 ± 252	42

DM versus MC prevalence (chi-square) and differences in PMPY costs and services (*t*-test) are all $p < 0.0003$. Items of particular clinical or economic relevance are shaded

Abbreviations: CPT: Current Procedural Terminology; DM: myotonic dystrophy; HCPCS: Healthcare Common Procedure Coding System; MC: matched control; PMPY: per member per year; SD: standard deviation



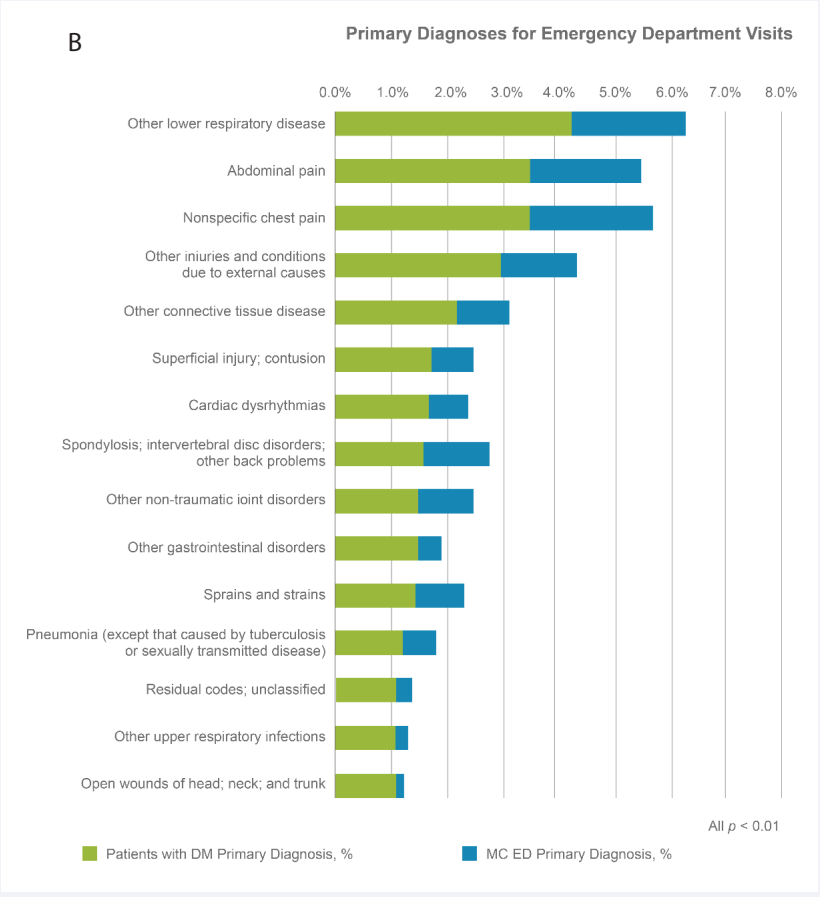


Figure 4 Primary diagnoses with a prevalence 1% more in patients with DM than in MCs on (A) inpatient admission and (B) emergency department visit in the year prior to the index date. **Abbreviations:** DM: myotonic dystrophy; ED: emergency department; MC: matched control.

64 procedures, with 63 procedures having more services for patients with DM. All three metrics were significantly different in the 31 categories listed in [Table 4].

DISCUSSION

In this study, insurance claims data were analyzed to portray the medical management experienced by patients with DM versus MCs in the year before the DM diagnosis. We found that patients with DM had more healthcare utilization needs than MCs, as profiled by their higher need for prescription medications, medical procedures, and healthcare encounters, as well as a higher prevalence of comorbid conditions, which might reflect the multisystemic involvement of DM. The comorbidities underlying DM were also reflected by differences in the prevalence of reasons for inpatient admissions and ED visits (e.g., respiratory and cardiovascular disorders) and the prevalence of procedure claims (e.g., genetic testing, electrocardiography, electromyography, or consultations). Differences in location-of-care utilization in the year before diagnosis highlight a greater need for healthcare encounters in patients with DM compared with MCs. Differences in the percentage of patients with prescriptions, number of prescription fills, and PMPY costs of numerous drugs were observed. The ATC 2 anatomical and therapeutic subgroup results confirm the increased overall use of pharmacy resources by the DM cohort. Differences between the DM and MC cohorts in the use of ATC level 3, 4, and 5 drugs after diagnosis provided more disease-specific information about drug use. The increased use of medical and drug resources was consistently associated with higher PMPY costs and increased use of services in many categories prior to the DM diagnosis index date compared with the MCs. The study results are a "snapshot" of data in both patients with DM and MCs in the year before the index date, and the "bottom line" aggregate PMPY medical and pharmacy costs of $21,278 for patients with DM was three times higher than the $7,087 for MCs. Differences in study design and data sources do not allow for reliable comparison with the results of previous studies. Our results are in line with previously reported claims-derived costs of $15,852 for patients with DM, which was 2.37 times higher than the $6,688 for controls without DM [10]. The MC results are also consistent with a 2020 US Bureau of Labor Statistics estimate of $5,177 as the average individual healthcare cost in the US (https://www.bls.gov/opub/reports/consumer-expenditures/2020/home.htm). Between-group differences were seen in AHRQ categories [Figure 2] including nervous system disorders, lower respiratory disease, malaise and fatigue, gastrointestinal disorders, cardiac dysrhythmias, and cataracts, all of which are known clinical presentations of DM [2, 4, 11, 12]. A small study of 80 patients with genealogy data and a DM diagnosis (ICD-9 359.21), which included both DM1 and DM2, reported that having the conditions was significantly associated with an increased risk of cardiac arrhythmias, central and obstructive sleep apnea, cataracts, intellectual disabilities, and hypothyroidism [13]. In this analysis, differences in the prevalence of comorbidities, as shown by AHRQ category claims, between the DM and MC cohorts were in line with those reported in the group of 80 patients diagnosed with DM. Between-group differences in claims associated with the diagnosis of comorbidities at inpatient admission and ED visits [Figure 4] were consistent with differences in the AHRQ categories. Differences between patients with DM and controls in the HCPCS or CPT procedure codes [Table 4] were consistent with the use of resources that might be required for patient evaluation or support before a DM diagnosis, i.e., before the index date. In addition to genetic testing, they included electrocardiograms and echocardiograms, electromyography, muscle enzymes, pulmonary testing, neurology procedures, and organ- or disease-oriented panels. Differences in location-of-care utilization [Table 3] may reflect the burden of undiagnosed disease, including comorbidities and diagnostic procedures and difficulties involved in establishing a diagnosis of DM. The clinical characteristics of DM that are useful for early recognition and differential diagnosis of DM1 and DM2, including muscle signs and symptoms and manifestations indicative of multiorgan involvement, along with recommendations for disease management, have been reviewed recently [12,14,15]. A 2018 review of the clinical phenotypes of DM suggested that patients experienced diagnostic delay leading to increased morbidity and treatment burden in the year prior to diagnosis compared with MCs [12]. This could not be confirmed here because it could not be determined when, in their patient journey, the patients with DM were diagnosed, only that paid claims with a DM diagnosis were in the database. Although DM1 is a dominantly inherited, progressive neuromuscular disease, only 10.8% of the patients identified in this study were <18 years old. This along with the mean age of 43.4 years in patients included in this study potentially signifies nearly 3 decades of delay in diagnosis. Identifying DM as the underlying condition may be delayed until the patient experiences muscle weakness and receives care from a clinician who recognizes the hallmark features. It would be interesting to investigate the changes in use of healthcare resources associated with a decrease in the interval between the initial symptoms and the diagnosis of DM. Results of this study support published recommendations for care that include multidisciplinary management of DM. Care may be coordinated by a neuromuscular specialist or general neurologist, or a physician with related training (such as physical medicine and rehabilitation), along with several other specialties. Management often requires the involvement of physical, speech, and occupational therapists, pulmonologists, cardiologists, gastroenterologists, ophthalmologists, and others. There are no disease-specific treatments for DM, but diagnosis-focused symptom management and treatment of comorbidities might decrease the cost and burden to patients and society. If analysis of insurance claims can help identify comorbidities that are associated with an increased risk of a DM diagnosis, then it would facilitate early selection of patients who would benefit from a formal diagnosis of DM and appropriate multidisciplinary care. The strengths of this study include a relatively large sample of insured people in the US, matched DM and control cohorts, and comparison of objective outcomes that describe the use of healthcare resources. The study highlights specific drugs, procedures, comorbid conditions, and locations of care where the

DM and MC cohorts differ. The index date marks the end of a patient journey to a diagnosis. The inability to differentiate patients diagnosed with DM1 from those with DM2 was a study limitation, since ICD-9/ICD-10 codes do not distinguish between the two diseases, and the insurance claims database lacks electronic medical records data that would allow differentiation between DM types. Significant differences in pre-index healthcare claims between the DM and MC cohorts were observed, and cohorts were matched by payer type. Research comparing patients with DM with MCs on the changes before and after the index date is under way and focuses on healthcare resource use, costs, comorbidities, and clinical characteristics that precede hospitalizations and ED visits. Comorbid conditions reported in the literature as associated with DM, such as sleep apnea, that are not uniquely defined as AHRQ categories should be investigated in future research. There is an unmet need for targeted therapeutic interventions [2], because these would change the post-diagnosis care required by patients with DM and might result in earlier genetic testing. Some DM1 interventions in development involve the activity of small RNAs that target RNA-encoding dystrophica myotonica protein kinase (DMPK) for degradation [16,17]; an example is AOC 1001, which is currently under clinical evaluation for the potential treatment of DM1 (ClinicalTrials.gov identifiers: NCT05027269 and NCT05479981).

CONCLUSION

DM is a complex neuromuscular condition and commonly causes disparate symptoms that confuse the medical care team until diagnosis of this genetic disorder is established. During the pre-diagnosis period, patients, caregivers, and families may experience the stress and additional cost burden associated with the uncertainty of an undiagnosed condition. Characterization of the patient journey, determination of healthcare resources utilized, and documenting cost of care before establishing the diagnosis will help define appropriate and efficient supportive and diagnostic care. Given the complex course and involvement of multiple systems, multidisciplinary patient-centered care is necessary for this multifaceted monogenic disorder. To further elucidate the impact of DM, additional analyses are ongoing to assess changes in comorbidities, use of healthcare resources, and costs that occur after diagnosis.

Funding: This manuscript was funded by Avidity Biosciences, Inc.

ACKNOWLEDGMENTS

The authors would like to thank Clement Weinberger, PhD from Stylus Edits Medical Communications, Kinnelon, NJ, USA, for providing medical writing support and Han Cho PharmD, MS from Avidity Biosciences for editorial and administrate support.

REFERENCES

1. Gourdon G, Meola G. Myotonic dystrophies: state of the art of new therapeutic developments for the CNS. Front Cell Neurosci. 2017; 11: 101.
2. LoRusso S, Weiner B, Arnold WD. Myotonic dystrophies: targeting therapies for multisystem disease. Neurotherapeutics. 2018; 15: 872-884.
3. Udd B, Krahe R. The myotonic dystrophies: molecular, clinical, and therapeutic challenges. Lancet Neurol. 2012; 11: 891-905.
4. Thornton CA. Myotonic dystrophy. Neurol Clin. 2014; 32: 705-719.
5. Harper P. Myotonic dystrophy. 3rd edn. London: Saunders. 2001.
6. Mah JK, Korngut L, Fiest KM, Dykeman J, Day LJ, Pringsheim T, et al. A systematic review and meta-analysis on the epidemiology of the muscular dystrophies. Can J Neurol Sci. 2016; 43: 163-177.
7. Bachinski LL, Udd B, Meola G, Sansone V, Bassez G, Eymard B, et al. Confirmation of the type 2 myotonic dystrophy (CCTG)n expansion mutation in patients with proximal myotonic myopathy/proximal myotonic dystrophy of different European origins: a single shared haplotype indicates an ancestral founder effect. Am J Hum Genet. 2003; 73: 835-848.
8. Greifer N, Stuart EA. Matching methods for confounder adjustment: an addition to the epidemiologist's toolbox. Epidemiol Rev. 2022; 43: 118-129.
9. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987; 40: 373-383.
10. Howe SJ, Ladipus D, Hull M, Yeaw J, Stevenson T, Sampson JB. Healthcare resource utilization, total costs, and comorbidities among patients with myotonic dystrophy using U.S. insurance claims data from 2012 to 2019. Orphanet J Rare Dis. 2022; 17: 79.
11. Meola G, Cardani R. Myotonic dystrophy type 2: an update on clinical aspects, genetic and pathomolecular mechanism. J Neuromuscul Dis. 2015; 2: S59-S71.
12. Wenninger S, Montagnese F, Schoser B. Core clinical phenotypes in myotonic dystrophies. Front Neurol. 2018; 9: 303.
13. Johnson NE, Abbott D, Cannon-Albright LA. Relative risks for comorbidities associated with myotonic dystrophy: a population-based analysis. Muscle Nerve. 2015; 52: 659-661.
14. Bird TD. Myotonic dystrophy type 1. 1999 Sep 17 [Updated 2021 Mar 25]. In: Adam MP, Ghayda MM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993.
15. Schoser B, Montagnese F, Bassez G, Fossati B, Gamez J, Heatwole C, et al. Consensus-based care recommendations for adults with myotonic dystrophy type 2. Neurol Clin Pract. 2019; 9: 343-353.
16. Kakouri AC, Koutalianos D, Koutsoulidou A, Oulas A, Tomazou M, Nikolenko N, et al. Circulating small RNA signatures differentiate accurately the subtypes of muscular dystrophies: small-RNA next-generation sequencing analytics and functional insights. RNA Biol. 2022; 19: 507-518.
17. Levin AA. Treating disease at the RNA level with oligonucleotides. N Engl J Med. 2019; 380: 57-70.