



Physician-Reported Perspectives on Myasthenia Gravis in the United States: A Real-World Survey

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ABSTRACT

Introduction: Myasthenia gravis (MG) is a rare, debilitating, chronic disorder caused by the production of pathogenic immunoglobulin G autoantibodies against the neuromuscular junction. A lack of real-world studies in rare diseases reflects a relatively limited understanding of the significant unmet needs and burden of disease for patients. We aimed to provide comprehensive real-world insights into the management and burden of MG from treating physicians in the United States (US).

Methods: Data were collected using the Adelphi Real World MG Disease Specific Programme™, a point-in-time survey of physicians and their patients with MG, in the US between March and July 2020. Physician-reported

clinical data, including demographics, comorbidities, symptoms, disease history, treatments, and healthcare resource utilization, were collected.

Results: In total, 456 patient record forms were completed by 78 physicians based in the US. At time of survey completion, patient mean age was 54.5 years. Mean time from symptom onset to diagnosis was 9.0 months ($n = 357$). Ocular symptoms were reported in 71.7% of patients. General fatigue affected 47.1% of patients and over half of those reported the severity as moderate or severe (59.5%, $n = 128$). Acetylcholinesterase inhibitors and/or steroids were the most frequently prescribed first-line treatment type among patients receiving treatment at time of survey completion and with moderate-to-severe symptoms (77.9%, $n = 159/204$). High-dose steroids ($n = 14$) and intravenous immunoglobulin ($n = 13$) were the most prescribed acute treatments among those receiving an acute treatment at time of survey completion ($n = 36$), with symptom exacerbations or myasthenic crises being the most common reasons for acute treatment. On average, 2.5 healthcare professionals were involved in patient management and 5.0 consultations were made per patient over the last 12 months.

Conclusions: Our findings indicated that, despite treatment, there is a proportion of patients with MG in the US who had a significant need for improved disease management.

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Key Summary Points

Why carry out this study?

There is a lack of real-world evidence in myasthenia gravis (MG), reflecting a limited understanding of patients' unmet needs and burden of disease.

What did the study ask?

Using data collected from physician-completed patient record forms as part of the Adelphi Real World MG Disease Specific Programme™ in MG, this study aimed to provide comprehensive real-world insights into the clinical presentation and management of MG from treating physicians in the United States.

What was learned from the study?

The mean number of symptoms per patient was the same (five) after treatment as it was at diagnosis, suggesting that many patients were still impacted by disease, despite treatment.

Over one-third of the patients in this cohort required acute treatment at some point, predominantly for the treatment of exacerbations or myasthenic crisis.

On average, 2.5 healthcare professionals were involved in patient management and 5.0 consultations were made per patient over the last 12 months.

Our findings showed that current maintenance treatment does not fully control the disease, as patients continued to experience a high burden of disease and healthcare resource utilization despite treatment, highlighting the need for improved treatment options in MG.

INTRODUCTION

Myasthenia gravis (MG) is a debilitating, chronic, autoimmune, neuromuscular disease with most patients experiencing fluctuating muscle weakness and fatigue [1, 2]. MG is caused by pathogenic immunoglobulin G autoantibodies, which can inhibit signal transmission at the neuromuscular junction (NMJ) by binding to various proteins including receptors [3–5]. Approximately 74–88% of patients have acetylcholine receptor (AChR) autoantibody-positive MG. Synaptic transmission to muscle fibers is impacted by these pathogenic autoantibodies that, by binding to receptors, block acetylcholine and increase receptor degradation. Additionally, AChR autoantibodies trigger the classical complement cascade, which converges at complement C5, leading to damage of the NMJ, and ultimately impairment to muscle contraction [6].

MG is a rare disease, with an estimated 60,000 cases of MG in the United States (US) [7, 8]. As with many rare diseases, because of the relatively low prevalence compared with more common diseases, there is a lack of real-world studies in MG to understand and address patients' unmet needs and the burden of disease [9]. While randomized clinical trials are necessary to obtain robust efficacy and safety data on a treatment, observational real-world studies are also important as they can provide information on larger, more representative populations compared with clinical trials, and an understanding of the true progression and management of the disease [9]. An analysis of insurance claims between 2010 and 2019 from the IBM® MarketScan® database showed that 91% of patients living with MG in the US received drug therapy, and 40% of those received non-steroidal immunosuppressive treatment (IST) or biologics [10]. However, some survey research has suggested that as many as 50% of patients with MG fail to reach minimal symptom expression (Myasthenia Gravis Activities of Daily Living score 0 or 1) [11], while more stringent criteria for refractory disease has been estimated at 10–20% of the MG population [12, 13]. Inadequately controlled disease is more

likely to have significant impact on prognosis, health-related quality of life, and use of healthcare resources compared with the nonrefractory MG population [3, 13–15]. Hospitalizations, myasthenic crises, and use of acute treatments for MG worsening such as IVIg and PLEX are key drivers of increased MG-related healthcare costs [16]. Despite these insights, comprehensive data are still lacking on real-world clinical experiences and perspectives from a large sample.

Adelphi Real World Disease Specific Programmes™ (DSPs) are an established methodology for investigating treatment practices across a large range of diseases using point-in-time surveys [17]. They collect real-world data from clinical practice, including patient demographics, treatment practices and physician-reported healthcare resource utilization (HCRU) [9].

Here, using data from the MG DSP, we aimed to provide comprehensive real-world insights and evidence into the HCRU, management and disease burden of MG in the US.

METHODS

Study Design and Data Source

Data were obtained via the Adelphi Real World MG DSP, a point-in-time survey of MG-treating physicians in the US and their patients between March and July 2020. A complete description of the methods of the survey has been previously published and validated [17–19], and further information on the phases of a DSP can be found in Supplementary Material (Fig. 1). This survey obtained ethics approval from the Western Institutional Review Board, sponsor protocol number: AG8768. The DSP is Health Insurance Portability and Accountability Act compliant, and all data was aggregated and de-identified. Patients and physicians provided informed consent to take part in the Adelphi Myasthenia Gravis Disease Specific Programme™ market research survey, on which this secondary data analysis is based. Data were collected in such a way that patients and physicians could not be identified directly.

Study Population

Physicians were recruited to participate in the DSP by local fieldwork agents and were eligible to participate in the survey following a short screening questionnaire. Physicians and healthcare professionals (HCPs) were eligible for inclusion if their primary specialty was identified as neurology, geriatrics, or primary care medicine. All those included were required to be treating at least one patient with a confirmed diagnosis of MG, based on the judgement and diagnostic skills of the respondent physician. Physician participation was financially incentivized, with reimbursement upon survey completion according to fair market research rates. No formal patient selection procedures were in place. However, physicians and HCPs were asked to provide data for a consecutive series of patients to avoid selection bias and to generate a patient sample reflective of real-world practice, with data collected at the time of each patient's appointment to reduce the likelihood of recall bias. Furthermore, by not only collecting data from specialist centers, it was more likely that data would be collected for a more general MG population than severe patients only. Due to the consecutive nature of patient recruitment to mitigate against selection bias, and the diversity within the physician cohort, it is extremely unlikely that a patient would be counted twice in this analysis.

Study Outcomes

Physician-completed patient record forms (PRFs) were completed online after a consultation. Data collected from the PRFs included patient demographics, comorbid conditions and medications. Clinical profiles, including Myasthenia Gravis Foundation of America (MGFA) classification, and symptom type and severity, were reported at diagnosis and at time of survey completion. Symptoms were checked from a pre-selected list. "Ocular myasthenia", "ptosis" and "diplopia" were all separate options during data collection. Ocular myasthenia was defined as "general weakness of the eye muscles", ptosis was defined as "drooping of one or

Table 1 Patient demographics and comorbidities

Enrolled physicians, <i>N</i>	78
Completed patient record forms, <i>N</i>	456 ^a
Mean (SD) age at MG diagnosis, years	(<i>n</i> = 357) 50.5 (15.79)
Mean (SD) time since MG diagnosis, months	(<i>n</i> = 419) 42.8 (48.72)
Mean (SD) age at survey completion, years	54.5 (16.09)
Sex, %	
Male	53.1
Female	46.9
Ethnicity, <i>n</i> (%)	
White/Caucasian	347 (76.1)
African American	63 (13.8)
Native American	0
Asian-Indian subcontinent	4 (0.9)
Asian other	6 (1.3)
Hispanic/Latinx	15 (3.3)
Middle Eastern	3 (0.7)
Mixed race	6 (1.3)
South-East Asian	12 (2.6)
Other	0
BMI	
Mean (SD), kg/m ²	26.4 (4.30)
< 18.5 kg/m ² , <i>n</i> (%)	6 (1.3)
18.5–24.9 kg/m ² , <i>n</i> (%)	165 (36.2)
24.91–30.0 kg/m ² , <i>n</i> (%)	215 (47.1)
≥ 30.0 kg/m ² , <i>n</i> (%)	70 (15.4)
Weight, lbs, mean (SD)	170.1 (34.3)
Weight distribution, lbs, <i>n</i> (%)	
< 120	19 (4.2)
120–149	101 (22.1)
150–179	176 (38.6)

Table 1 continued

180–209	102 (22.4)
210–240	41 (9.0)
> 240	17 (3.7)
Employment status, <i>n</i> (%)	(<i>n</i> = 455)
Working full time	154 (33.8)
Working part time	80 (17.6)
On long-term sick leave	26 (5.7)
Homemaker	31 (6.8)
Student	4 (0.9)
Retired	130 (28.6)
Unemployed	18 (4.0)
Don't know	12 (2.6)
Patients with ≥ 1 comorbidity, <i>n</i> (%)	334 (73.2)
Top five most reported comorbidities (%)	
1 Hypertension	(34.4)
2 Dyslipidemia	(21.7)
3 Anxiety	(18.6)
4 Depression	(18.6)
5 Diabetes without chronic complications	(10.5)
Patients with ≥ 1 comorbid condition taking co-medications, <i>n</i> (%)	295 (88.3)
Number of co-medications per patient with ≥ 1 comorbid condition, mean	2.7

Table 1 continued

Top five most reported co-mediations in patients with ≥ 1 comorbid condition (%)	1	Statins (38.3)
	2	Antidepressants (31.1)
	3	ARBs (24.3)
	4	ACE inhibitors (18.3)
	5	Diuretics (16.5)

ACE angiotensin-converting enzyme, *ARB* angiotensin II receptor blocker, *BMI* body mass index, *MG* myasthenia gravis, *PRF* physician-completed patient record form, *SD* standard deviation

^aUnless otherwise stated. Not all questions were completed in all PRFs due to logic routing, and as a result there was variation in the total number of patients per variable

both eyelids” and diplopia was defined as “blurred or double vision”. Treatment, defined as “ever treated” or “current treatment” at time of survey completion, included both acute and chronic treatments. Acute treatment was described in the PRF as “rescue or acute treatments”, and options were intravenous immunoglobulin (IVIg), subcutaneous immunoglobulin (SCIg), high-dose steroids, plasmapheresis, and a free text option for “other”. The PRF also collected data on duration of treatment, reasons for treatment choice, physician management and involvement, and hospitalizations. “Don’t know” was a valid response to questions on symptom onset, diagnosis, and number and type of consultations.

Statistical Analysis

Data were analyzed using UNICOM® Intelligence Reporter version 7.5 (UNICOM Systems, Inc., Mission Hills, CA, USA). Categorical values are reported as frequencies and percentages. Continuous values are reported as mean and standard deviation (SD).

RESULTS

Patient Demographics and Comorbidities

Between March and July 2020, 456 PRFs were completed by 78 physicians based in the US. Most of these physicians were neurologists (63%, $n = 49$) and the remainder were general physicians (37%, $n = 29$), with a mean (SD) proportion of 13.8% (18.11) of their professional time spent managing patients with MG.

Not all questions were completed in all PRFs due to logic routing, and as a result there was variation in the total number of patients per variable. Physician-reported patient demographics are shown in Table 1. The overall mean age at the time of survey completion was 54.5 years and 53.1% ($n = 242$) of patients were male. Nearly three-quarters of patients had one or more comorbidities (73.2%, $n = 334$) and, of these, over one-third (34.4%, $n = 157$) listed hypertension as a comorbidity, followed by dyslipidemia (21.7%, $n = 99$) and anxiety (18.6%, $n = 85$). Among patients who had one or more comorbidities ($n = 334$), 88.3% ($n = 295$) took medication for their concomitant condition(s). Additionally, 9.4% ($n = 43$) of patients also took over-the-counter medications or herbal supplements alongside their MG or concomitant treatment. There was a mean total of 2.9 prescribed and non-prescribed medications taken per person for all conditions. Statins (38.3%, $n = 128$) were the most commonly prescribed medications for comorbidities, followed by antidepressants (31.1%, $n = 104$) and angiotensin II receptor blockers (24.3%, $n = 81$).

Clinical Profile

The mean age at MG symptom onset was 50.1 years ($n = 362$), with a mean time from symptom onset to diagnosis of 9.0 months (274.0 days, $n = 357$) and a mean time since MG diagnosis of 42.8 months (1297.6 days, $n = 419$). Mean time from symptom onset to first consultation was 4.8 months (146.5 days, $n = 341$) and mean time from symptom-related consultation to diagnosis was 3.9 months (118.7 days, $n = 361$; Table 2). Diagnosing

Table 2 Symptoms at diagnosis and symptoms at time of survey completion, most reported symptoms, and most “troublesome” symptoms

		<i>N</i> = 456 ^a		
Mean (SD) age at symptom onset, years		50.1 (15.71)		
		(<i>n</i> = 362)		
Mean time from symptom onset to first consultation ^b , months		4.8		
		(<i>n</i> = 341)		
Mean time from symptom-related consultation to diagnosis ^b , months		3.9		
		(<i>n</i> = 361)		
Mean time from symptom onset to diagnosis ^b , months		9.0		
		(<i>n</i> = 357)		
Mean number of symptoms per patient at diagnosis		5		
Mean number of symptoms per patient at time of survey completion		5		
		Symptom	%	Severity, %
Top five most reported current ^c symptoms and severity	1	Ocular myasthenia	53.3	Mild: 68.7 Moderate: 30.5 Severe: 0.8
	2	Ptosis	49.3	Mild: 65.8 Moderate: 33.3 Severe: 0.9
	3	General fatigue	47.1	Mild: 40.5 Moderate: 52.6 Severe: 7.0
	4	Weakness in the arms	36.6	Mild: 57.5 Moderate: 39.5 Severe: 3.0
	5	Diplopia	31.1	Mild: 64.1 Moderate: 33.1 Severe: 2.8
Top five most “troublesome” current symptoms (%) <i>n</i> = 375	1	General fatigue (25.1)		
	2	Diplopia (16.6)		
	3	Ocular myasthenia (15.1)		
	4	Ptosis (14.9)		
	5	Weakness in the legs (13.2)		

Symptoms were checked from a pre-selected list. “Ocular myasthenia”, “ptosis”, and “diplopia” were all separate options during data collection. Ocular myasthenia was defined as “general weakness of the eye muscles”, ptosis was defined as “drooping of one or both eyelids” and diplopia was defined as “blurred or double vision”

PRF physician-completed patient record form, SD standard deviation

^aUnless otherwise stated. Not all questions were completed in all PRFs due to logic routing, and as a result there was variation in the total number of patients per variable

^b“Don’t know” was a valid response to this question

^cCurrent at time of survey completion

physicians were predominantly neurologists (76.1%, $n = 347$), after initial consultation by a primary care physician (53.9%, $n = 246$). Almost one-fifth of patients (19.3%, $n = 88$) were initially misdiagnosed with another condition, most commonly chronic fatigue syndrome, which accounted for over one-third (37.5%, $n = 33$) of misdiagnoses (Table 3).

At time of survey completion, the mean number of symptoms experienced by each patient was five, with the top five current symptoms reported as ocular myasthenia (53.3%, $n = 243$), ptosis (49.3%, $n = 225$), general fatigue (47.1%, $n = 215$), weakness in the arms (36.6%, $n = 167$) and diplopia (31.1%, $n = 142$; Table 2). Nearly half of patients (49.7%, $n = 222$) were experiencing weakness in their arms, legs, hands or fingers and, of these 222 patients, just over half (52.3%, $n = 116$) had moderate-to-severe symptoms. General fatigue was also experienced by around half of patients (47.1%, $n = 215$), of whom 59.5% ($n = 128$) were moderately or severely affected.

At diagnosis, 66.7% ($n = 304$) of patients had more than just ocular symptoms (MGFA Class II–V) indicating generalized MG, and at time of survey completion this proportion was 80.8% ($n = 367$) of patients. At any point from a confirmed MG diagnosis until time of survey completion, 41.0% ($n = 187$) of patients were classified with MGFA Class III or above, meaning that they had experienced moderate-to-severe weakness of limb, axial, oropharyngeal and/or respiratory muscles (Fig. 1).

Treatment

Most patients had been prescribed treatment over the course of their disease; 4.8% ($n = 22$) of patients had never received any prescribed treatment for their MG. Of patients who had one or more moderate-to-severe symptom at time of survey completion ($n = 233$), 51.5% ($n = 120$) had received chronic (maintenance) therapy only, 2.6% ($n = 6$) had received acute treatment only, 42.1% ($n = 98$) had received both chronic and acute therapy, whilst 3.8% ($n = 9$) had received neither. Of the nine patients untreated and experiencing a

Table 3 Patient disease history

		$N = 456$
Physician first consulted, n (%)		
PCP/GP		246 (53.9)
Neurologist		90 (19.7)
Internist		51 (11.2)
Ophthalmologist		15 (3.3)
Another physician		28 (6.1)
Don't know		26 (5.7)
Diagnosing physician, n (%)		
Neurologist		347 (76.1)
PCP/GP		82 (18.0)
Ophthalmologist		11 (2.4)
Internist		8 (1.8)
Another physician		3 (0.7)
Don't know		5 (1.1)
Patients with misdiagnosis, n (%)		88 (19.3)
Top five common misdiagnoses in patients who were initially misdiagnosed with another condition (%)		
1	Chronic fatigue syndrome (37.5)	
2	Multiple sclerosis (34.1)	
3	Guillain–Barré syndrome (12.5)	
4	Connective tissue disease (11.4)	
5	Other (11.4)	

GP general practitioner, PCP primary care physician

moderate-to-severe symptom, eight patients were classified as MGFA Class IIa or higher. At time of survey completion, 92.5% of patients were receiving treatment.

Of the 233 patients who were still experiencing moderate-to-severe symptoms, 87.6% ($n = 204$) were receiving chronic treatment, 12.4% ($n = 29$) were receiving acute treatment

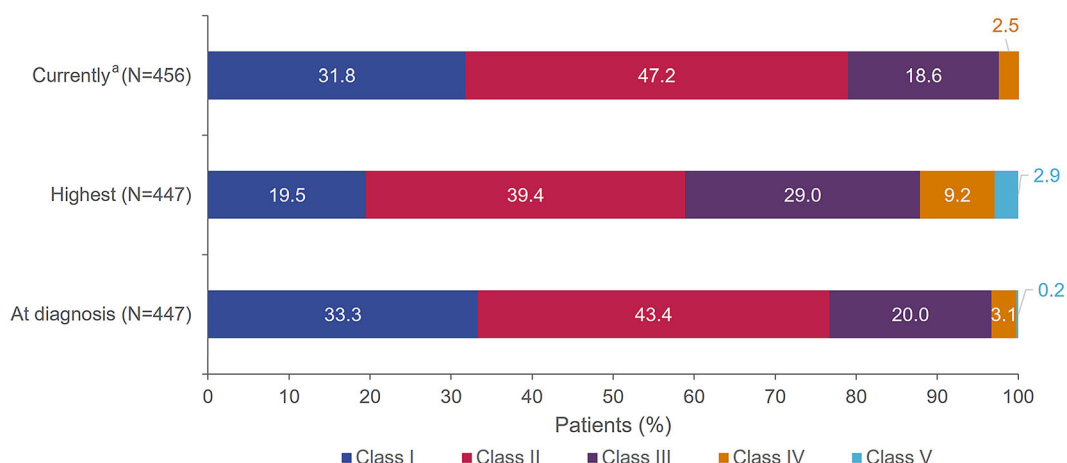


Fig. 1 MGFA classifications at diagnosis, currently^a, and the highest. ^aAt time of survey completion. *MGFA* Myasthenia Gravis Foundation of America

Table 4 Proportion of patients receiving chronic or acute treatment with ≥ 1 moderate-to-severe symptom at time of survey completion

	<i>N</i> = 456
Never received prescribed treatment, <i>n</i> (%)	22 (4.8)
Patients who had never received prescribed treatment (<i>n</i> = 22) and had ≥ 1 moderate-to-severe symptom, <i>n</i> (%)	9 (41.0)
Patients who had received prescribed treatment (<i>n</i> = 434) and had ≥ 1 moderate-to-severe symptom, <i>n</i> (%)	233 (53.7)
Patients with ≥ 1 moderate-to-severe symptom (<i>n</i> = 233), <i>n</i> (%)	
Receiving chronic treatment	204 (87.6)
Receiving acute treatment	29 (12.4)
Not receiving either chronic or acute treatment	24 (10.3)
Never prescribed acute treatment	113 (48.5)

(alongside chronic or alone) and 10.3% (*n* = 24) were not receiving any treatment (Table 4).

Chronic Treatment

The acetylcholinesterase inhibitor (AChEI) pyridostigmine was the most prescribed current chronic treatment (67.6%, *n* = 254; Fig. 2a), mostly chosen for the known symptomatic improvements in mobility (51.3%, *n* = 182). AChEIs and/or steroids were the most frequently prescribed first-line treatment type among patients with moderate-to-severe symptoms at time of survey completion (77.9%, *n* = 159), followed by second-line non-steroidal IST alone (47.1%, *n* = 96). In general, patients with higher MGFA classifications were receiving later-line treatments: Patients with moderate-to-severe symptoms and MGFA Class I–IIb (*n* = 129) were mostly prescribed AChEIs and/or steroids (47.3%), while for MGFA Class IIIa and above (*n* = 75), the most prescribed treatment was non-steroidal IST (62.7%; Fig. 2b). Patients with a higher MGFA class had a greater number of maintenance treatments prescribed at time of survey completion, although patient numbers were much lower in the higher MGFA classes (Supplementary Material [Fig. 2]).

On average, patients received their previous treatment for 25.6 months (775.7 days) before switching or stopping (*n* = 46). The most common reason for switching or stopping therapy was diminished effect over time (45.1%, *n* = 55); other reasons included risk factors and side effects (Fig. 3a). Physicians reported

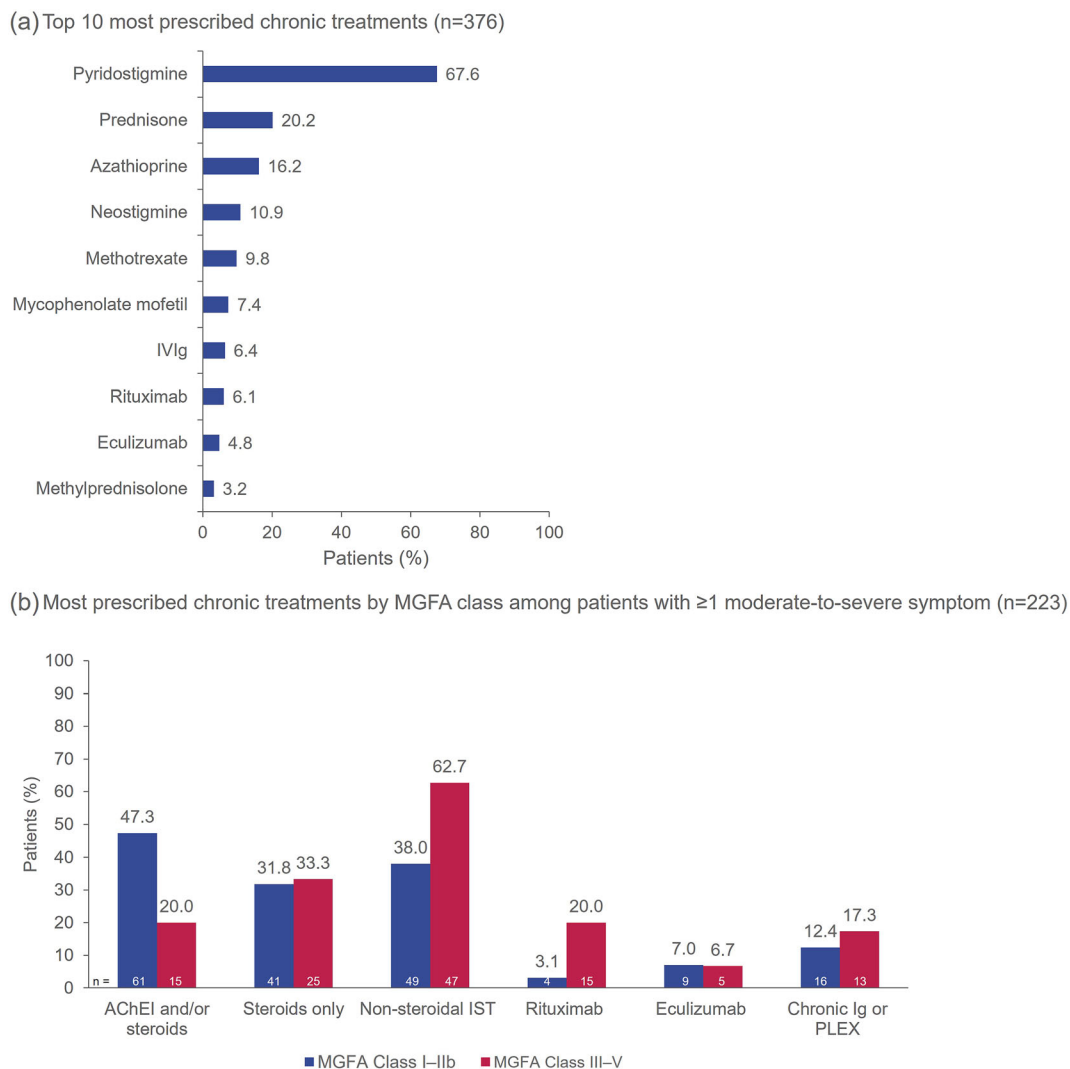


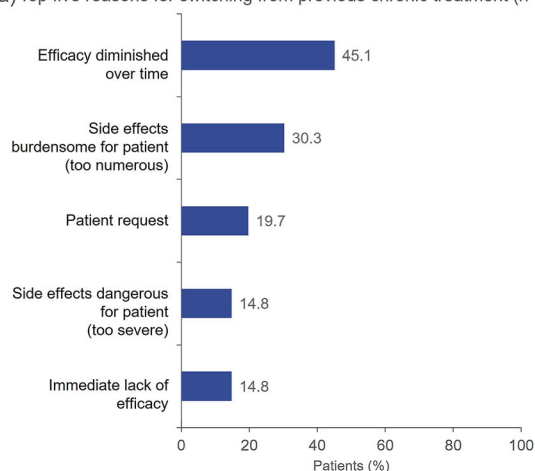
Fig. 2 Most prescribed chronic treatments (current^a). **a** Top 10 most prescribed chronic treatments ($n = 376$). **b** Most prescribed chronic treatments by MGFA class among patients with ≥ 1 moderate-to-severe symptom ($n = 223$). ^aAt time of survey completion. *AChEI*

acetylcholinesterase inhibitor, *Ig* immunoglobulin, *IST* immunosuppressive treatment, *IVIg* intravenous immunoglobulin, *MGFA* Myasthenia Gravis Foundation of America, *PLEX* plasma exchange

diminishing efficacy as the biggest driver of patient dissatisfaction with treatment overall (42.0%, $n = 66$; Fig. 3b). Physicians reported that 72.1% ($n = 285$) of patients were fully adherent to their medication; however, of the 26.6% ($n = 105$) who were not entirely adherent, some patients had issues remembering (29.5%, $n = 31$) or believed that they only needed to take medication when their symptoms worsened (27.6%, $n = 29$). Considering this, physicians perceived 89.8% ($n = 335$) of

patients to be at least somewhat satisfied with their current maintenance treatment, which corroborated with 80.2% of patients self-reporting to be at least somewhat satisfied with their current treatment ($n = 243$ of 303 patients on current treatment with a confirmed patient self-completion form).

(a) Top five reasons for switching from previous chronic treatment (n=122)



(b) Top five factors driving lack of satisfaction (n=157)

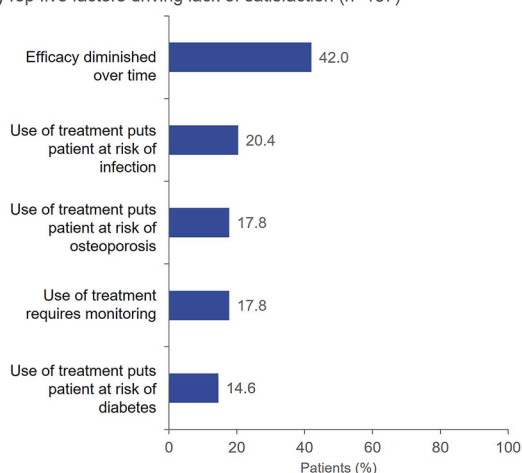


Fig. 3 Treatment perceptions in MG patients. **a** Top five reasons for switching from previous chronic treatment ($n = 122$). **b** Top five factors driving lack of satisfaction ($n = 157$). *MG* myasthenia gravis

Acute Treatment

In total, 7.9% ($n = 36$) of patients were receiving acute treatment at time of survey completion, while 36.0% ($n = 164$) of patients had previously received acute treatment (Table 5). On average, among patients who received IVIg and SCIG courses as acute treatment, the average number of courses in the last 12 months from time of survey completion were 1.9 ($n = 68$) and 1.5 ($n = 13$), respectively. High-dose steroids (38.9%, $n = 14$) and IVIg (36.1%, $n = 13$) were the most prescribed acute treatments. The most

Table 5 Number of patients receiving current^a or previous acute treatment, most frequently prescribed current^a acute treatments and main reasons for acute treatment

$N = 456$	
Previous acute treatment, n (%)	164 (36.0)
Current ^a acute treatment, n (%)	36 (7.9)
IVIg	13 (36.1)
High-dose steroids	14 (38.9)
Other	7 (19.4)
SCIG	4 (11.1)
Plasmapheresis	1 (2.8)
Reasons for current ^a acute treatment ($n = 36$), n (%)	
Exacerbation	24 (66.7)
Myasthenic crisis	5 (13.9)
Patient needs fast onset of action until maintenance therapy	4 (11.1)
Patient not responding to maintenance/chronic therapy	3 (8.3)
Prior to an unrelated surgery	2 (5.6)
Prior to thymectomy surgery	0
Don't know	0
Total (mean) number of courses of acute treatment in the last 12 months	
IVIg and SCIG combined	77 (2.0)
IVIg	68 (1.9)
SCIG	13 (1.5)
Steroids	111 (1.5)
Plasmapheresis	30 (1.4)

IVIg intravenous immunoglobulin, *SCIG* subcutaneous immunoglobulin

^aAt time of survey completion

common reasons for prescribing acute treatment were exacerbations or myasthenic crises, but some patients received acute treatment as

Table 6 Most frequently involved HCPs in patient management^a, total number of HCPs involved in patient management, and number of consultations in the last 12 months by MGFA class

	All (<i>N</i> = 456)	Current ^b MGFA classification							
		Class I (<i>n</i> = 145)	Class IIa (<i>n</i> = 160)	Class IIb (<i>n</i> = 55)	Class IIIa (<i>n</i> = 67)	Class IIIb (<i>n</i> = 18)	Class IVa (<i>n</i> = 8)	Class IVb (<i>n</i> = 3)	Class V (<i>n</i> = 0)
Total HCPs, mean	2.5	2.4	2.3	2.6	2.8	2.9	3.3	3.0	–
Number of consultations in the last 12 months, mean	5.0	4.2	4.8	5.4	6.0	6.0	6.4	20.0	–
Primary care physician, %	53.9	51.0	56.3	49.1	56.7	66.7	50.0	33.3	–
Neurologist, %	33.3	35.9	28.8	20.0	44.8	38.9	50.0	66.7	–
Ophthalmologist, %	16.7	27.6	9.4	10.9	13.4	27.8	12.5	–	–
Internist, %	15.4	7.6	11.9	25.5	25.4	33.3	25.0	33.3	–
Pulmonologist, %	10.3	7.6	7.5	12.7	19.4	5.6	37.5	0.0	–
Neuromuscular specialist nurse, %	3.5	4.1	3.1	5.5	3.0	–	–	–	–
Dietician, %	2.9	2.1	2.5	–	3.0	5.6	12.5	33.3	–
Pain specialist, %	2.6	–	1.9	–	7.5	5.6	–	33.3	–
Rheumatologist, %	2.2	1.4	3.1	3.6	–	5.6	–	–	–
Gastroenterologist, %	–	–	–	5.5	–	–	–	–	–
Cardiologist, %	–	–	–	–	–	5.6	–	–	–
Psychiatrist, %	–	–	–	–	3.0	–	12.5	–	–
Other, %	–	1.4	–	3.6	–	–	25.0	–	–

HCP healthcare professional, MGFA, Myasthenia Gravis Foundation of America

^aLimited to the nine most frequently involved HCPs

^bAt time of survey completion

bridging therapy while waiting for slow-onset maintenance or chronic therapy to work, or because they did not respond to maintenance or chronic therapy. At time of survey completion, only one patient was using IVIg or SCIG as bridging therapy. In total, 62.5% (*n* = 285) of patients had never received an acute treatment.

HCRU

On average, 2.5 HCPs were involved in patient management and 5.0 consultations were made per patient, across all HCPs, over the previous 12 months (Table 6, *n* = 456). Patients in higher MGFA classes consulted more frequently with HCPs of different specialties in the last 12 months.

Table 7 Hospital admissions by MGFA class

	Total (<i>N</i> = 456)	Current ^a MGFA classification							
		Class I (<i>n</i> = 145)	Class IIa (<i>n</i> = 160)	Class IIb (<i>n</i> = 55)	Class IIIa (<i>n</i> = 67)	Class IIIb (<i>n</i> = 18)	Class IVa (<i>n</i> = 8)	Class IVb (<i>n</i> = 3)	Class V (<i>n</i> = 0)
Patients with at least one hospitalization in the last 12 months, <i>n</i> (%)	69 (15.1)	15 (10.3)	20 (12.5)	9 (16.4)	13 (19.4)	6 (33.3)	3 (37.5)	3 (100.0)	–
Patients hospitalized at least once in the last 12 months									
	<i>n</i> = 69	<i>n</i> = 15	<i>n</i> = 20	<i>n</i> = 9	<i>n</i> = 13	<i>n</i> = 6	<i>n</i> = 3	<i>n</i> = 3	<i>n</i> = 0
Events at any point across all admissions, %									–
Admitted through an ER	60.9	73.3	65.0	66.7	53.8	50.0	0	66.7	
Spent time in the ICU	23.2	13.3	20.0	44.4	15.4	16.7	33.3	66.7	
Had a feeding tube fitted or required intubation	20.3	6.7	15.0	22.2	23.1	33.3	33.3	66.7	
Reasons for admission, %									–
To treat a complication ^b	37.7	40.0	40.0	55.6	23.1	50.0	0	33.3	
To receive IVIg	21.7	26.7	30.0	0	23.1	16.7	0	33.3	
Other	18.8	20.0	5.0	33.3	23.1	0	66.7	33.3	
For surgery	17.4	13.3	20.0	11.1	15.4	16.7	33.3	33.3	
To receive plasmapheresis	13.0	6.7	20.0	0	15.4	16.7	0	33.3	
Don't know	1.4	0	5.0	0	0	0	0	0	
Patients requiring overnight hospital stay									
	<i>n</i> = 41	<i>n</i> = 12	<i>n</i> = 8	<i>n</i> = 6	<i>n</i> = 7	<i>n</i> = 5	<i>n</i> = 0	<i>n</i> = 3	<i>n</i> = 0
Mean length of stay in the last 12 months, nights	6.8	5.7	4.0	3.0	10.3	6.0	–	19.0	–

ER emergency room, ICU intensive care unit, IVIg intravenous immunoglobulin, MGFA Myasthenia Gravis Foundation of America

^aAt time of survey completion

^bA "complication" was open to the physician's interpretation and was not defined within the survey

In the 12 months prior to survey, 15.1% (*n* = 69) of all patients were hospitalized at least once. Of those patients, 60.9% (*n* = 42) were admitted, at least once, through the emergency room and 23.2% (*n* = 16) spent time in an intensive care unit. Across these patients' admissions, the most common reason was to treat a complication (undefined; 37.7%, *n* = 26), followed by receiving IVIg (21.7%, *n* = 15). Among the 69 patients admitted to hospital, 59.4% (*n* = 41) required at least one stay overnight, with a mean hospital length of stay of 6.8 nights (Table 7). Patients with a current MGFA classification of Class IVb had the longest

average stay in hospital in the previous 12 months with a mean of 19 nights (*n* = 3, Table 7).

DISCUSSION

Drawing on a real-world sample of consulting physicians and presenting patient populations, these data obtained from the Adelphi Real World MG DSP provided valuable insights into the management of MG in the US.

Our data show that, on average, patients waited approximately 9 months for a diagnosis

from their onset of symptoms, which could have left them untreated and thus at risk of acute deterioration of symptoms and development of myasthenic crisis [20, 21]. Delays in diagnosis can be due to the fluctuating nature of MG symptoms, making MG difficult to diagnose on clinical examination. Diagnoses may also be missed in primary and non-neurology specialist care as patients can have normal serology and electrophysiology results, particularly in ocular MG, suggesting there is a need for education in primary care and of non-neurology specialists, and more reliable methods of detection [20, 21]. Some patients also experienced unnecessary, non-specific investigations, leading to a mean delay of approximately 5 months from first symptom to consultation with a specialist consultant. MG is also under-recognized in elderly patients due to symptoms such as fatigue and slurred speech falling under broader illness symptoms and thus patients only being referred to non-specialist clinicians [21]. Our study found that approximately 1 in 5 patients were initially misdiagnosed, which may have increased the burden of disease for patients [20].

The number of symptoms reported at diagnosis and after treatment was used as a measure of impact of treatment on disease burden, and as the mean number of symptoms per patient was the same after treatment as it was at diagnosis, many patients may still have been impacted by various aspects of the disease, despite treatment. This suggests that treatment does not necessarily reduce patient burden, even though some of these symptoms will be different than at diagnosis. This is supported by several studies highlighting the fact that many people with generalized MG still report a negative impact of disease or treatment and report fatigue [22, 23], muscle weakness, anxiety and depression, despite receiving treatment [24–30]. However, whilst many of the symptoms were MG-specific, some such as general fatigue could also be attributed to other comorbidities. Ocular myasthenia was found to be the most frequently reported symptom and general fatigue was the most “troublesome” symptom, with 60% of symptoms at time of survey completion reported as moderate or severe. The

burdensome nature of general fatigue may be common, as observational studies report a similar correlation between the increase in disease severity and an increase in fatigue score [31, 32]. The proportion of patients with more than just ocular symptoms (MGFA Class II–V) increased following diagnosis and throughout the course of disease, demonstrating progression from ocular MG to generalized MG, which is likely to negatively impact patients’ quality of life [2].

Among patients with moderate-to-severe MG (MGFA Class III and above) nonsteroidal ISTs were the most prescribed treatment class, while one-third of patients in these classes required chronic steroids. In addition, over one-third of the patients in our survey required acute treatment at some point, predominantly for the treatment of exacerbations or myasthenic crisis, highlighting the lack of disease control with current maintenance treatments or regimens. About 10% of patients have also used acute treatment as bridging therapy due to slow onset of action of some available maintenance or chronic therapies. This finding supports data from the US medical claims database (IBM® MarketScan® Commercial Claims and Encounters) showing that, while receiving AChEI and/or steroids, 27% of patients experienced exacerbations and, of these, 38% of patients required IVIg rescue therapy [10]. Patients with more severe disease require more consultations and have more hospital admissions, placing additional burden on patients and healthcare resources, while disease burden is further exacerbated by limitations of current treatment, such as toxicity and delayed onset of action [32].

The development of new agents with selective immunological targets and rapid onset of action, such as complement inhibitors (eculizumab, ravulizumab, zilucoplan) and neonatal Fc receptor blockers (efgartigimod, rozanolixizumab, nipocalimab) that, while real-world clinical experience is needed to understand whether these drugs will fulfil their potential, may help to resolve these limitations of current treatments and, ultimately, have a positive impact on the burden of disease in patients with MG [32]. In addition, increased use of SCIG in

place of IVIg may be beneficial to reducing hospital admissions for IVIg. In our survey, the second most common reason (21.7%) for hospital admissions was for receiving IVIg, thus self-administered treatment at home may help to reduce this burden for both patients and the healthcare system. Continued disease burden and high healthcare cost is, unfortunately, a familiar issue in the US. Real world data on treatment patterns and HCRU show high burden and high cost for a wide range of diseases [33–35], and while the development of new MG treatment options is therefore of benefit, they are unlikely to fully resolve the issues identified in our study.

Inherent limitations to data collection via questionnaires apply to this study, including missing fields and answers dependent on either physicians' perception or patients' memory. As a result, there was some variation in the total number of patients per variable. Data capture was dependent on patients presenting within the fieldwork time frame, in which, while generating data for a range of patients across treatment types and disease stage, some patients may have consulted or presented more frequently than others. In addition, not all physicians in this survey were neurologists, and, therefore, the practices of primary care physicians or geriatricians may have not been fully representative of how MG is treated by specialists, especially in more complex cases. However, minimal inclusion criteria and the inclusion of non-neurologists aim to ensure that a broad population of physicians, other HCPs and patients, and therefore perspectives, is captured. Physician and patient participation is influenced by willingness to participate in the research and practical considerations of geographic location. In addition, our aim was to give a broad picture of MG patients in general, not only those treated at specialized centers. Follow-up studies of this nature that dive deeper into specialist providers and patient subpopulations will be even more beneficial. Patient-reported outcomes are a useful measure to assess the impact of treatment, however, due to the nature of this point-in-time study, patient-reported outcomes were only collected at the time of the survey and were not captured at diagnosis

for a comparison to before MG treatment initiation. The majority of the patients included in our survey were reported to have at least one comorbidity, a small proportion of whom were using over-the-counter medication or supplements in addition to their MG treatment. Some of these over-the-counter medications, such as quinine and magnesium, have been shown in some instances to exacerbate MG [36]. In addition, the mean age at diagnosis was relatively high compared with the expected age of MG onset, [37, 38]. Thus, it is possible that a subgroup analysis of a younger population with fewer comorbidities may have yielded different results. Furthermore, with the data collection occurring during the 2020 coronavirus pandemic, face-to-face consultations may have been restricted and healthcare resources reduced. Finally, as MGFA classification is used predominantly in clinical trials and not routinely in clinical practice, the applicability of the disease severity data may be limited.

Despite these limitations, real-world studies in MG are vital for the understanding of the impact of disease burden on patients living with MG.

CONCLUSIONS

Overall, these real-world data suggest that a proportion of patients with MG in the US had a significant need for improved disease management. This is consistent with additional real-world evidence from US claims databases that has identified an unmet need for improved treatment options in MG to reduce the disease burden placed upon patients and healthcare resources.

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Data Availability. All data, including methodology, materials, data, and data analysis, that support the findings of this survey are the intellectual property of Adelphi Real World. All requests for access should be addressed directly to Jonathan DeCourcy (jonathan.decourcy@adelphigroup.com).

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