Evidence Gap Analysis of the Burden of Disease and Treatment of Myasthenia Gravis

RWD138

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BACKGROUND

- Myasthenia Gravis (MG) is a chronic autoimmune neurological disorder characterized by defective transmission at the neuromuscular junction and manifested by fatigable muscle weakness[1]
- Patients with MG experience unpredictable and fluctuating clinical symptoms of muscle weakness and fatigue that may impose a considerable disease burden,[2] which has not been fully characterized

OBJECTIVES

- To characterize current evidence related to MG burden of disease, including epidemiologic, clinical, humanistic, economic, and treatment-related aspects
- To identify evidence gaps that could be addressed by future research and to improve the clinical management of MG patients

METHODS

- This analysis included a structured review of scientific literature published from May 4, 2013, to May 4, 2023
  - Literature searches were conducted in PubMed, Embase, and the Cochrane Library using predefined Boolean search strings to identify papers focused on epidemiology, burden of disease (clinical, humanistic, and economic), treatments, practice patterns, and guidelines associated with MG
- Supplemental online searches were performed to obtain information on regulatory reports, ongoing clinical trials, and primary sources for review papers included from the literature searches

RESULTS

Characterization of source material

- A total of 251 unique records were identified (**Figure 1**), and primarily included real-world evidence studies and clinical studies (**Figure 2**)
- Data on burden of disease were available in US, European, and Asian populations (**Figure 3**)

Figure 1. Attrition of source materials

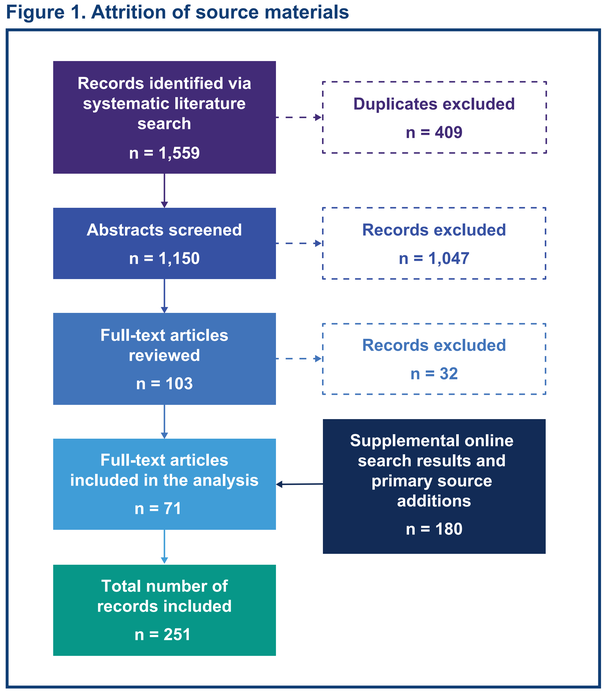
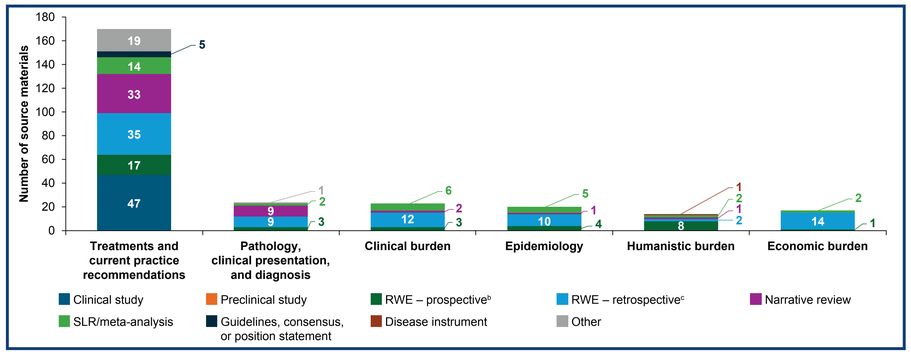
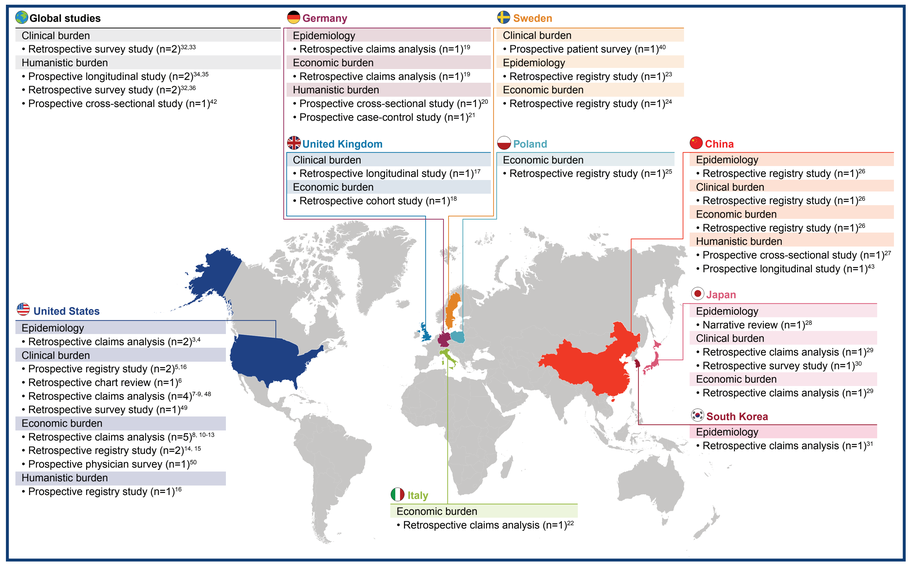


Figure 2. Characterization of sources included by topic[a] and type



[a]Individual source materials may have covered >1 topic; [b]Includes prospective cross-sectional, longitudinal, registry, survey, case report, health state utilities, and genetic studies; [c]Includes retrospective chart reviews, registry, claims, and survey studies. RWE, real-world evidence; SLR, systematic literature review.

Figure 3. Availability of burden of disease data for MG[a]



[a]Includes RWE studies. RWE, real-world evidence.

Summary of current evidence and key evidence gaps

Table 1. Epidemiologic burden

CURRENT EVIDENCE	EVIDENCE GAPS
• Globally, reported epidemiologic rates of MG vary substantially, with prevalence rates ranging from 2 to 37 per 100,000 persons[37,38] and incidence rates ranging from 0.17 to 3.0 per 100,000 person-years[38,39] • Great variability exists across epidemiologic studies conducted in different countries, but it is unclear whether such variability reflects true regional disparities or whether it could be attributed to methodological differences[37-39] – No studies were identified for South America, Australia, or New Zealand • Epidemiologic data are available by sex and age of onset; however, autoantibody subtype data are limited, which may reflect differences in access to antibody testing[37-39]	• **Updated studies using consistent methodology and definitions to assess epidemiology across geographic regions, including autoantibody subtype assessment** • **Epidemiology estimates specifically in South American and Australasian populations**

MG, myasthenia gravis.

Table 2. Humanistic burden

CURRENT EVIDENCE	EVIDENCE GAPS
• The humanistic burden of MG has been studied using a wide variety of instruments specific to MG or neurological disorders, as well as generic instruments[20,21,27,32,35,36] – Overall, MG patients experience worse HRQOL compared with the general population, and greater MG severity correlates with worse HRQOL and with greater impairment of daily activities, severity of depression and anxiety	• **Updated studies with wider geographic coverage evaluating differences in HRQOL among patient subgroups defined by autoantibody subtype, age of onset, or type of treatment (including emerging biologic therapies targeting terminal complement or neonatal fragment crystallizable receptor)**
• Factors associated with worse HRQOL in patients with MG include: higher number of comorbidities[27]; unemployment[27]; greater disease severity[20,32,35] or exacerbations[27,35]; inactive lifestyle[27]; female sex[21,27,35]; older age[21]; lower income[21]; and depression and/or anxiety[20,21]	• **Additional studies and analyses to assess how different comorbidities may contribute to worse humanistic outcomes in MG patients**
• One study evaluated the burden of MG for caregivers and found a significant impact on their HRQOL, with patient symptom severity and depression having a particularly negative impact on caregivers[20]	• **Additional studies assessing the caregiver burden associated with MG and evaluating potential mitigation strategies**
• The majority of RWE studies related to humanistic burden were cross-sectional in nature,[16,20,21,27,32,36,42] with limited longitudinal data[35,43]	• **Robust longitudinal studies investigating the long-term impact of MG on patient HRQOL**

HRQOL, health-related quality of life; MG, myasthenia gravis; RWE, real-world evidence.

Table 3. Clinical burden

CURRENT EVIDENCE	EVIDENCE GAPS
• Diagnosis of MG is a complex multistep process that often results in diagnostic delays[5] and corresponding higher disease activity[40] • Muscle fatigability (peripheral fatigue) is the hallmark of MG, although many patients also report symptoms of central or general fatigue, defined as a lack of energy and feeling of tiredness not related to muscle weakness or pain, that interferes with mental or physical activities[41] – The most commonly reported symptoms include general fatigue (67%), weakness of eye muscles (59%), and drooping eyelids (55%), followed by weakness in the arms (53%), weakness in the legs (42%), and blurred or double vision (36%)[32] • Myasthenic crisis occurs in up to 20% of patients with MG and is characterized by neuromuscular respiratory failure[7]	• **Consistent implementation of objective diagnostic criteria, and studies evaluating the factors contributing to misdiagnosis or delays in diagnosis of MG**
• MG is associated with several comorbidities including cardiovascular and mental health conditions[33] – In a real-world study using data from the Adelphi MG Disease Specific Programme, comorbidities were present in 69.0% of patients and most commonly included hypertension (28.1%), anxiety (17.8%), dyslipidemia (17.3%), depression (16.0%), diabetes (10.5%), obesity (8.0%), chronic pulmonary disease (5.9%), osteoporosis (5.1%), peripheral vascular disease (4.5%) and rheumatologic disease (4.1%), with similar results found in a separate US-based retrospective study[8,33]	• **Risk analyses to evaluate the association of autoantibody subtype, age of onset, or geographic region with MG comorbidities**
• We identified a single study conducted in a Chinese hospital database that evaluated mortality in MG, with an admission mortality rate of 14.7% (16.5% in men, 12.9% in women), and an overall mortality rate of 1.5%[26]	• **Additional studies evaluating mortality rates and risk factors for mortality across globally diverse patient populations**

MG, myasthenia gravis; OR, odds ratio.

Table 4. Economic burden

CURRENT EVIDENCE	EVIDENCE GAPS
• Healthcare resource utilization is increased for patients with MG[8] – In the US, rates of hospitalization and intensive care unit admissions were reported to be 2.6- and 4.5-fold higher, respectively, for patients with MG versus matched controls[8] • Healthcare resource utilization over 5–10 years for patients with MG has been reported for several countries – In Poland, from 2013 to 2018, 0.8–1.0% of MG patients were hospitalized in intensive care units annually, with an average length of stay of 10.8–14.0 days/patient[25] – In Germany, the mean hospitalization rate from 2010 to 2020 was 10.7% for all patients with prevalent MG[19] – In Japan, the length of hospital stay from 2008 to 2016 ranged from 2.81 (nonrefractory MG) to 22.19 (refractory MG) days per year[29]	• **Studies or analyses to identify factors that drive healthcare resource utilization (eg, MG severity or subtype, country, treatment)**
• Healthcare costs vary substantially across countries, as reported in a systematic literature review that analyzed 16 economic studies and reported costs in 2018 $US[44] – Global annual direct costs of MG ranged from $730 (India) to $28,780 (US) per patient – Global annual indirect costs of MG ranged from $80 (India) to $3,550 (Germany) per patient – Cost per hospitalization for MG ranged from $2,550 (Thailand) to $164,730 (US patients requiring mechanical ventilation)	• **Given the evolving treatment landscape, additional economic studies to evaluate the impact of recent drug approvals** • **Studies assessing the long-term economic burden of MG**
• Exacerbations and myasthenic crises are associated with high healthcare costs (eg, due to hospitalization and rescue therapy)[11,12,18] – One US study reported mean total MG-related costs during initial exacerbation of $43,043,[11] with additional costs during the following 12 weeks totaling $24,417 for patients with multiple exacerbations[11] – In another US study, the mean yearly cost of IVIg ranged from $73,970 to $164,223 for patients with prior exacerbations or crises[12] – In the UK, the cumulative cost of admission was £907,071 for patients receiving IVIg (drug costs excluded)[18]	• **Studies examining the impact of current vs emerging MG treatments on the costs associated with exacerbations and crises** • **Characterization of non-US country- or region-specific costs of admission and drug treatment for exacerbations or crises**
• Employment rates among patients with MG varied from 28% to 82% and the overall pooled proportion of workers was 50% in an SLR and meta-analysis of 19 publications[45] – Subgroup analyses suggested a lower proportion of workers among those with generalized, bulbar, and respiratory symptoms; however, the relatively low proportion of studies (<2%) containing information on employment status in patient subgroups limits interpretation of these results	• **Studies exploring the effects of MG on employment status (or routine reporting of employment status in studies of MG) to better understand the effects of health interventions on productivity**

IVIg, intravenous immunoglobulin; MG, myasthenia gravis; SLR, systematic literature review.

Table 5. Treatment patterns

CURRENT EVIDENCE	EVIDENCE GAPS
• Treatment patterns have been evaluated in the US, Asia, and Europe • In a retrospective analysis of health claims data, a substantial proportion of patients received multiple therapies within 2 years after diagnosis[46]: – 72% received any treatment during the 730 days following diagnosis – Among those receiving >1 treatment, 54% received 2 therapies, 32% received 3, and 17% received ≥4 in their combination regimen – In the US, AChEIs and steroids were the most frequently prescribed chronic first-line treatments among patients with moderate to severe symptoms, followed by non-steroidal immunosuppressive therapy[13] – More than a third of patients in the US required acute treatment, with the most prescribed acute treatments being high-dose steroids and IVIg[6] – In one analysis of US claims from 2014–2019, 43% of patients who initiated IVIg required chronic treatment (≥6 courses of IVIg) during the first year[12] • In South Korea, the use of IVIg has remained stable from 2010–2018, whereas thymectomy is performed earlier than before, and the distribution of immunosuppressant therapies has changed over the years[31] • In Japan, treatment patterns are changing following the publication/release of Japanese guidelines recommending a goal of minimal manifestations or better with an oral prednisolone dose of 5 mg per day or less (termed MM-5 mg)[47] • In Germany, most patients with MG are treated with AChEIs, glucocorticosteroids, immunosuppressive monotherapy, or combination therapy[19] – However, crisis intervention is necessary for 2% to 5% of patients, and therapeutic monoclonal antibodies are increasingly used[19]	• **Studies to assess the real-world effectiveness of emerging therapies such as recently available biologics (eg, eculizumab, ravulizumab, efgartigimod, rozanolixizumab, zilucoplan)**

AChEIs, acetylcholinesterase inhibitors; IVIg, intravenous immunoglobulin; MG, myasthenia gravis.

CONCLUSIONS

- **Considerable variability exists among epidemiologic studies of MG in different country cohorts, and it is unclear whether this variability reflects true regional disparities or whether it is the result of methodological differences**
- **Despite available treatments, patients continue to experience a high burden of disease and high rates of healthcare resource utilization, including management of exacerbations and myasthenic crises**
- **Patients with MG experience substantial clinical, humanistic, and economic burden as evidenced by decreased HRQOL, low employment rate, and high healthcare resource utilization**
- **We identified several gaps in the literature, including the need for consistent implementation of objective diagnostic criteria; longitudinal studies of HRQOL burden; studies assessing long-term economic burden; and real-world studies of clinical practice patterns, treatment effectiveness, and economic impact in the context of emerging biologic therapies**

References, acknowledgments, and disclosures are accessible via QR code.

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DISCLOSURES

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