POSTER
#PND100

THE HUMANISTIC AND ECONOMIC BURDEN OF MYASTHENIA GRAVIS (MG) - A DEBILITATING & COSTLY DISEASE

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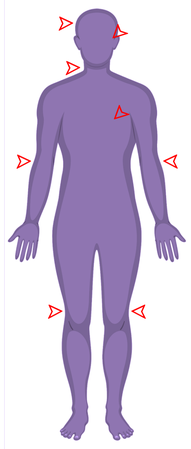
PURPLE SQUIRREL ECONOMICS

BACKGROUND

- Myasthenia gravis (MG) is a rare, neuromuscular, autoimmune disease characterized by fluctuating skeletal muscle weakness (Grob, et al. 2008; Gilhus, et al. 2015).
- Patients with gMG experience a range of debilitating symptoms relating to weakness of affected muscles, including blurred vision, difficulty swallowing, fatigue, impaired speech, and dyspnea (Grob, et al. 2008; Gilhus, et al. 2015)
- Given the debilitating nature of disease, gMG is associated with a high economic and humanistic burden (Hoffmann, et al. 2016; Omorodion, et al. 2017).

VARIOUS MUSCLES CAN BE AFFECTED

- Patients typically present with weakness of the eye (ocular MG), which progresses to generalized weakness involving various muscles of the body in the majority of patients within 2 years (gMG) (Grob, et al. 1987; Grob, et al. 2008).
- Fifteen to 20% of patients experience myasthenic crises, which are a serious and potentially life-threatening complication of disease requiring mechanical ventilation (Wendell, et al. 2011).



OBJECTIVE

- We conducted a QOL and economic systematic literature review (SLR) to further quantify the humanistic and economic burden of gMG by reviewing published evidence.

SYSTEMATIC LITERATURE REVIEW

- Two SLRs (QOL and economic) following PRISMA guidelines were conducted, with the scope defined in terms of PICOS criteria (Population, Intervention, Comparators, Outcomes and Study Design).

Table 1: PICOS used in the selection process

PICOS	Inclusion
Patient population	• The population included in both SLRs were adult patients with gMG. Studies of non-human subjects, pediatric patients, and patients with ocular MG (non-generalized) were excluded.
Intervention and Comparators	• The interventions and comparators were any systemic treatment or surgery.
Outcomes measures	• Outcome measures assessed were health-related quality of life (HRQOL) outcomes in the QOL SLR and economic outcomes in the economic SLR. Utilities, disutilitites, quality-adjusted life years (QALYs) for health states or adverse events (AEs) were included in both SLRs.
Study design	• The QOL SLR considered HRQOL and utility studies, including both interventional and non-interventional studies. The economic SLR considered economic evaluation studies. Systematic reviews and meta-analyses were included in both SLRs to cross-check references.

- The methodology of both SLRs followed the principles outlined by the Cochrane Collaboration and the UK's National Institute for Health and Care Excellence (NICE) (Higgins & Green, 2011; CRD 2009; NICE, 2012).
- MEDLINE® and Embase® were searched through the Ovid platform from January 2009 to April 2019. Publications from the AAN and ISPOR conferences were screened manually from 2017 to 2019.
- Publications identified through the two systematic reviews were evaluated to assess whether they should be included for data extraction. The inclusion/exclusion criteria used against the publications were developed using the PICOS format. Data from included studies were extracted into an Excel-based data extraction template.

Figure 1: QOL SLR PRISMA

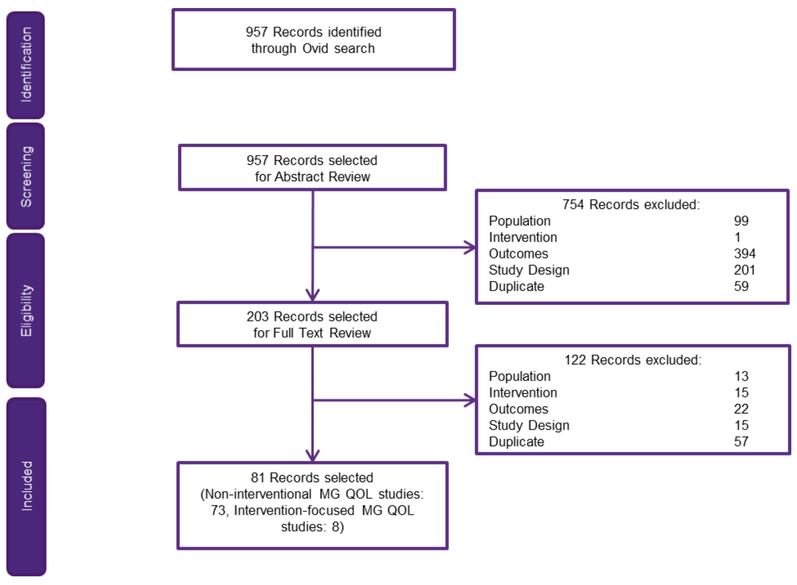
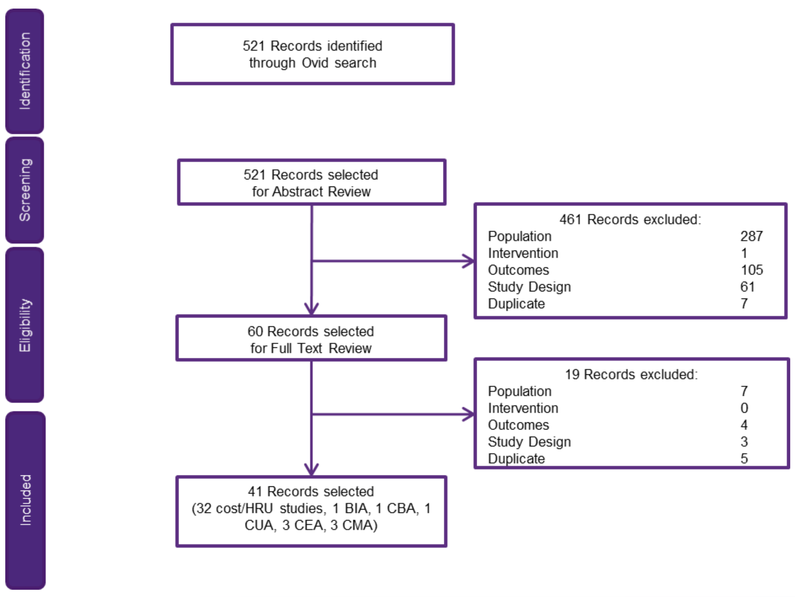


Figure 2: Economic SLR PRISMA



QUALITY OF LIFE RESULTS

- Across the QOL studies, various QOL measures were used, including SF-36, EQ-5D, HADS, MG-ADL, MG-QOL15, Neuro-QOL-Fatigue, QMG, and MGC scales. Only one study mapping utility values by MFGA classification was identified by Barnett et al., 2019.
- Findings showed a considerable decline in EQ-5D utility values with higher MGFA class, indicating worsening QOL with greater disease severity (Figure 3) (Barnett, et al. 2019). These were supported by two Italian studies, which likewise reported a relationship between disease severity and HRQOL and disability in MG patients (Raggi, et al. 2010; Leonardi, et al. 2010).
- MG had a negative impact on patients' physical and mental QOL across various PRO measures, including the SF-36, MG-ADL, MG-QOL15 (Boscoe, et al. 2019; Boldingh, et al. 2015). MG patients reported high levels of fatigue, sleep disturbances, anxiety, and depression (Hoffmann, et al. 2016; Martinez, et al. 2012; Braz, et al. 2018).

ECONOMIC RESULTS

- Thirty-two economic studies reported on the cost burden/healthcare resource use (HCRU) in MG, and 9 described economic models; results reported here focus on cost studies.
- A US cost study found that the average hospitalization cost per MG patient nearly doubled from $48,024 in 2003 to $98,795 in 2013, (USD, cost year not reported), which can be attributed to increases in the incidence of disease and rising treatment costs (Omorodion, et al. 2017).
- Gross inpatient costs increased 13-fold from $41.8m to $546.8m across the 10-year period (Omorodion, et al. 2017).
- The rise in hospitalization costs was considerably higher for MG compared with multiple sclerosis as a comparable neurologic disease (Figure 4) (Omorodion, et al. 2017).
- Compared with matched controls, total annual per patient healthcare costs were significantly higher in MG patients in a retrospective analysis of a US insurance claims database (Table 1) (Guptill, et al. 2012).

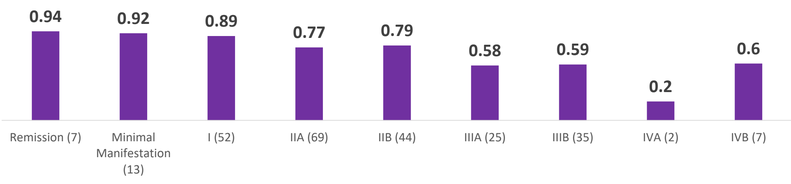
Table 1: Annualized claims-paid costs for MG and non-MG patients (calendar year 2009, cost year not reported)*

Costs	MG (n = 113)	Non-MG matched controls (n = 339)
Mean annual total cost (±SEM)**	$20,190 ($4,763)	$4,515 ($457)
Mean annual pharmacy cost (±SEM)**	$9,012 ($3,723)	$608 ($66)
Mean annual non-pharmacy cost (±SEM)**	$11,178 ($2,751)	$3,958 ($457)

*IVIg infusion costs were included in mean annual non-pharmacy costs.
**In the control group, the sum of pharmacy and non-pharmacy costs exceeds the total costs, which were capped at the 99th percentile.

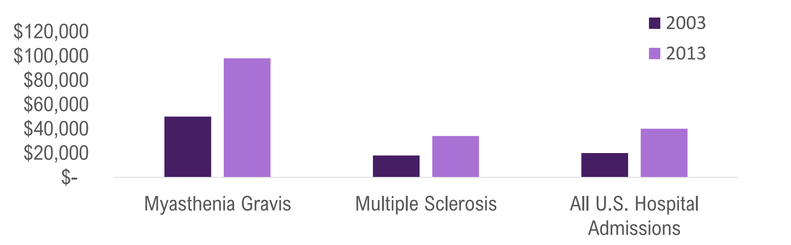
- Inpatient, outpatient, and home costs (including IVig infusions) were key cost drivers, accounting for 27%, 23%, and 23% of annual MG healthcare costs (Guptill, et al. 2012).

Figure 3: EQ-5D-5L utility by MGFA classification



- Being able to maintain employment and medication adherence were also negatively affected by MG symptoms and side effects associated with treatment (Blum, et al. 2015; Bacci, et al. 2018 [abstract]).
- In one US survey study (N=773), MG patients with refractory disease had higher total scores on the MG-QOL (31.4 vs 20.8; p<0.0001) and MG-ADL (9.4 vs 5.7; p<0.0001) than non-refractory patients, indicating poorer function and QOL (Boscoe, et al. 2019)
- Myasthenic crises are life-threatening events requiring hospitalization and mechanical ventilation due to respiratory failure, leading to deteriorations in patient QOL (Masuda, et al. 2014; Kalita, et al. 2014).
- In another retrospective study of commercially insured MG patients (N= 677), total healthcare costs increased significantly within the 6 months following diagnosis (6 months pre- vs post-diagnosis: US$17,293 vs $24,611; p=0.01), which was likewise seen for inpatient costs ($12,868 vs $20,601), clinic visits ($3,161 vs $4,336), and pharmacy costs ($2,294 vs $3,138, p=0.01 for all comparisons) (Gordon, et al. 2016 [abstract]).

Figure 4: Cost per discharge from 2003 to 2013 for MG, MS and all US hospital admissions



- Other studies reporting costs and HCRU in MG identified in the economic SLR are summarized in Table 2.
- Another US claims database study found annual MG healthcare costs to be ~4 times higher in refractory (n=403) versus non-refractory patients (n=3,811; $109,004 vs $24,196, p<0.001), likely driven by an increase in myasthenic crises/exacerbations (Engel-Nitz, et al. 2016).
- In addition to increased costs, refractory patients had greater HCRU, with significantly more hospitalizations (1.0 vs 0.4; p<0.001) and longer inpatient stay (10.7 vs 3.7 days; p<0.001) after 1-year (Engel-Nitz, et al. 2016).
- Other studies identified in the economic SLR assessing refractory versus non-refractory disease likewise reported higher costs and HCRU with refractory disease (Table 3) (Xin, et al. 2018; Harris, et al. 2019; Murai, et al. 2019).

Table 2: Summary of other cost/HCRU studies in MG

Reference	Study design	Country	N (patients)	Patient population	Key results
Vellipuram et al., 2018 (abstract)	HRU, cost	US	2,330	MG crisis patients requiring mechanical ventilation	-hospital charges for MG patients: $232,160 +/- $222,881
Gordon et al., 2016 (abstract)	Retrospective, database, cost, HRU	US	677	Commercially insured MG patients	Cost and HRU, 6 months pre-diagnosis vs 6 months post-diagnosis -total cost: $17,293 vs $24,611, p=0.01; -inpatient cost: $12,868 vs $20,601, p=0.01 -pharmacy cost: $2,294 vs $3,138, p=0.01
Gordon et al., 2015 (abstract)	Retrospective, database, HRU	US	2,047	MG patients with at least 2 diagnoses	Male vs female MG patients -inpatient stays: 9.1% vs 12.9%, p=0.03 -ER visits: 31.8% vs 36.8%, p=0.01
He et al., 2014 (abstract)	Retrospective, database, cost, HRU	US	NR	MG patients	-average length of hospitalization (days per year), min vs max: 6.96 (2008) vs 10.72 (1992), p<0.0001 -mean hospital charges (per year per patient), min vs max: $29,577 (1997) vs $67,382 (2009), p<0.0001
Ji et al., 2014 (abstract)	Retrospective, database, cost, HRU	US	NR	Elderly MG patients	-average length of hospitalization (days per year), min vs max: 7.98 (2008) vs 11.62 (1993), p<0.0001 -mean hospital charges (per year per patient), min vs max: $29,176 (1995) vs $68,403 (2009), p<0.0001
Elmoursi et al., 2014 (abstract)	Retrospective, database, cost, HRU	US	NR	Elderly MG patients hospitalized and treated with plasmapheresis	-average length of hospitalization (days per year), min vs max: 5.30 (2002) vs 11.16 (1992), p=0.001 -mean hospital charges (per year per patient), min vs max: $21,213 (1993) vs $86,431 (2007), p<0.0001
Wang et al., 2014 (abstract)	Retrospective, database, cost, HRU	US	NR	Adult mechanically ventilated MG patients	-average length of hospitalization (days per year), min vs max: 10.30 (1998) vs 17.13 (2001), p=0.935 -mean hospital charges (per year per patient), min vs max: $49,173 (1995) vs $139,896 (2009), p<0.0001
Guptill et al., 2011	Retrospective, claims, database, HRU, cost	US	1,288	MG patients	-total annual claims-based cost: $24,988 (median $9,023) -total pharmacy costs for the cohort (1,288 patients): $9.4 million (43% of total) -IVig administration accounted for 85% of pharmacy costs with a single infusion mean cost of $4,663
Strens et al., 2016 (abstract)	Retrospective, chart review, single center, cost, HRU	Belgium	62	Adult MG patients treated at least once with plasma exchange	Cost per person year (PY) from perspective of the Belgian public payer (RIZIV/INAMI) and patient's perspective (PP) -Length of hospitalization per PY: 7.9 days -Overall cost per PY for RIZIV/INAMI vs PP: €5,466 vs €260 -Cost of hospitalization per PY for RIZIV/INAMI vs PP: €4,092 vs €138
Athanasakis et al., 2011 (abstract)	Retrospective, chart review, cost	Greece (societal perspective)	32	MG patients that visited the MG clinic	-total annual cost per patient: €4,125 (€614 direct, €3,512 indirect) -major cost drivers: early retirement (49%), home help (31%), medications (8%)
Ogino et al., 2017	Retrospective, claims database, cost	Japan (private payer)	NR	MG patients	-Per patient per month MG costs (PPPM): ¥82,944

Table 3: Costs and HCRU in refractory vs non-refractory MG

Reference	Study design	Country	N (patients)	Population	Summary points
Xin et al., 2018 (abstract)	Registry, HRU	US	825	Refractory and non-refractory MG patients	HRU over 6 months, refractory vs non-refractory MG patients -at least one exacerbation: 67.1% vs 50.2%, p=0.01 -at least one ER visit: 43.4% vs 26.7%, p<0.01 -at least one overnight hospitalization: 32.9% vs 20.3%, p=0.03 -been in an ICU: 61.8% vs 32.4%, p<0.01
Engel-Nitz et al., 2016 (abstract)	Retrospective, database, cost, HRU	US	4,617	Refractory MG vs non-refractory MG vs non-MG controls	Costs and HRU over 1 year - refractory MG vs non-refractory MG vs control -hospitalization admissions: 1.0 vs 0.4 vs 0.2, p<0.001 for both -length of hospitalization: 10.7 vs 3.7 vs 1.7 days, p<0.001 for both -healthcare costs: $109,004 vs $24,196 vs $11,582, p<0.001 for both
Engel-Nitz et al., 2018	Retrospective, claims database, HRU	US	4,617	Adult MG patients (refractory and non-refractory) who has at least 2 medical claims on separate dates and non-MG controls	HRU over 1 year, refractory MG vs non-refractory MG (adjusted OR, 95% CI) -ER visit: 1.9 (1.6, 2.4), p<0.001 -inpatient hospitalization: 3.5 (2.8, 4.3), p<0.001
Harris et al., 2019	Retrospective, cohort, HRU	England	1,398	Non-refractory MG, refractory MG and non-MG controls	HRU per person-year, refractory MG vs non-refractory MG (all p<0.001) -GP visits: 13.6 vs 9.5 -outpatient hospital visits: 7.1 vs 4.8 -Inpatient visits: 1.5 vs 0.8 -time spent in hospital during follow-up: 33 vs 16
Murai et al., 2019	Retrospective, observational, database, multicenter	Japan (commercial)	3,302	Adult MG patients with at least 2 claims on separate dates	HRU, refractory MG vs non-refractory MG (over 12 months) -prescribed corticosteroids (%): 98.8% vs 51.3% -hospitalizations: 0.7 vs 0.09, p<0.001 -ER visits: 0.07 vs 0.03, p=0.002 -hospital outpatient visits: 16.8 vs 11.9, p<0.001 -days of hospitalization: 22.2 vs 2.8, p<0.001

LIMITATIONS

- One limitation was the heterogeneity of study design across studies as they were conducted in different countries, settings and with different payers (e.g. Medicare and commercial in the US) which made cross-study comparisons challenging, particularly for economic findings.
- Additionally, as the majority of studies were conducted using real-world data from various sources, it is likely there is a degree of heterogeneity across MG patient populations of different studies, such as age and proportion of females, among other baseline characteristics, which could limit cross-study comparison without further adjustment.
- Another limitation is that both the economic and QOL studies were not assessed for the quality of their design via validated measures.

CONCLUSIONS

- MG is associated with a substantial humanistic burden; patients suffer from impaired QOL, which worsens with increasing disease severity.
- Patients experience a range of debilitating symptoms including loss of function, weakness, fatigue, depression, anxiety, and sleep disturbances.
- Patients with refractory disease have poorer QOL than those with non-refractory disease.
- MG is associated with a high economic burden to payers and healthcare systems, with a substantial rise in total healthcare costs across 2003 to 2013 in the US.
- Inpatient, outpatient, and home health costs are important costs drivers, and patients with uncontrolled, refractory MG incur higher HCRU and healthcare costs than those with controlled disease (p<0.001).

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ISPOR US 2020
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