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INVITED REVIEW

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Utilization of MG-ADL in myasthenia gravis clinical research and care

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Abstract

The Myasthenia Gravis Activities of Living (MG-ADL) scale is an 8-item patient-reported scale that measures myasthenia gravis (MG) symptoms and functional status. The objective of the current review is to summarize the psychometric properties of the MG-ADL and published evidence of MG-ADL use. A targeted literature review for published studies of the MG-ADL was conducted using a database and gray literature search. A total of 48 publications and 35 clinical trials were included. Studies indicated that the MG-ADL is a reliable and valid measure that has been used as an outcome in clinical trials and observational studies to measure MG symptoms and response to treatment. While most often used as a secondary endpoint in clinical trials, its use as a primary endpoint has increased in recent years. The most common MG-ADL endpoint is change in MG-ADL score from baseline, although there has been an increase in the analysis of a responder threshold using the MG-ADL. A new concept of minimal symptom expression (MSE) has emerged more recently. Duration of treatment effect is another important construct that is being increasingly evaluated using the MG-ADL. The use of the MG-ADL as a primary endpoint in clinical trials and in responder threshold analyses to indicate treatment improvement has increased in recent years. MSE using the MG-ADL shows promise in helping to determine success of treatment and may be the aspirational goal of MG treatment for the future once validated, particularly given the evolving treatment landscape in MG.

KEYWORDS
MG symptoms, MG-ADL, minimal symptom expression, myasthenia gravis, neuromuscular disorder

Abbreviations: FDA, Food and Drug Administration; HRQoL, health-related quality of life; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Living; MGC, Myasthenia Gravis Composite; MGFA, Myasthenia Gravis Foundation of America; MGII, Myasthenia Gravis Impairment Index; MG-QOL15, Myasthenia Gravis Quality of Life 15-item; MGTX, Thymectomy Trial in Non-Thymomatous Myasthenia Gravis Patients Receiving Prednisone Therapy; MMS, minimal manifestation status; MMT, Manual Muscle Test; MSE, minimal symptom expression; Neuro-QOL, Quality of Life of Neurological Disorders; PASS, Patient Acceptable Symptom State; QMG, Quantitative Myasthenia Gravis; ROC, receiver operating curve; SF-36, 36-item Short-Form Health Survey.

The objectives of this activity are to: 1) Be able to incorporate the Myasthenia Gravis Activities of Daily Living scale (MG-ADL) as an outcome measure in clinical practice; 2) Be able to incorporate the MG-ADL as an outcome measure in research; 3) Understand and be able to apply the concept of minimal symptom expression in the assessment of patients with MG.

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1 | INTRODUCTION

Myasthenia gravis (MG) is an autoimmune neuromuscular disease that causes weakness in the skeletal muscles.[1,2] Most cases of generalized MG result from antibodies that block or destroy nicotinic acetylcholine receptors, which then hinders neuromuscular transmission; a minority have muscle-specific receptor tyrosine kinase or other antibodies, and some are antibody negative.[3] Treatment for MG can help to control immune system activity and manage symptoms that may cause functional impairment, such as limb weakness, double vision, and difficulties with speech, chewing, swallowing, and breathing. Some MG patients go into remission and require no further treatment.

Many outcome measures have been developed to evaluate the clinical status of patients with MG.[4] Of these outcome measures, there is a range of what is measured, how it is measured, who reports and interprets the symptoms and improvements (e.g., patient report vs. physician report), how the measure is administered, and how it is used. One measure that was used as a primary outcome measure in initial MG clinical trials was the Quantitative Myasthenia Gravis (QMG) score, a 13-item, linearly scored, clinician-reported assessment that was developed in 1983 by Besinger, then modified in 1987 by Tindall and later modified again in 1998 by Barohn.[5-9] The QMG takes up to 25 min to complete and requires technician training, a hand-held dynamometer, a spirometer, and a stopwatch.

The Myasthenia Gravis Activities of Daily Living scale (MG-ADL) is a newer outcome measure, developed in 1999 and partially derived from the QMG.[9] The MG-ADL is an 8-item patient-reported scale that measures MG symptoms and functional status and is administered by a physician or trained clinic personnel (Table 1). Items are linearly scored and not weighted, with each item ranging from 0 to 3 for a total score range of 0 to 24. The MG-ADL is easy to administer, requires no additional training, is quick to complete (<10 min), and can be used in routine clinical practice or in clinical trials.

Since the development of the MG-ADL, its psychometric properties have been assessed, and it has it been adapted and validated in several languages beyond English, including Arabic, Italian, Korean, Malay, Polish, and Dutch.[10-15] Furthermore, following its development, the MG-ADL was integrated into research as a primary and secondary study outcome measure. The MG-ADL can be analyzed in different ways, including examining the change in total score from baseline,[16] using a responder threshold to indicate clinical improvement,[17] and using a cutoff to indicate minimal symptoms.[18] In the United States (US), payers frequently require the MG-ADL for approval of the initiation and maintenance of treatment for MG with recently approved eculizumab.[19-21] Thus, it is important for all stakeholders, including clinicians, researchers, and payers, to understand how the MG-ADL should be used in clinical practice, clinical trials, and observational studies. The objective of the current review is to summarize the psychometric properties of the MG-ADL, review the published evidence of the use of the MG-ADL, and provide recommendations on how to use the MG-ADL in both a research and clinical context based on the available evidence.

2 | METHODS

2.1 | Study design and data sources

A targeted literature review was conducted using a database and gray literature search. The database search was conducted in EMBASE® using the search terms "myasthenia gravis" and "MG-ADL," with

TABLE 1 MG-ADL profile[9]

Symptom	0	1	2	3	Score (0, 1, 2, 3)
1. Talking	Normal	Intermittent slurring of nasal speech	Constant slurring or nasal, but can be understood	Difficult to understand speech	
2. Chewing	Normal	Fatigue with solid food	Fatigue with soft food	Gastric tube	
3. Swallowing	Normal	Rare episode of choking	Frequent choking necessitating changes in diet	Gastric tube	
4. Breathing	Normal	Shortness of breath with exertion	Shortness of breath at rest	Ventilator dependence	
5. Impairment of ability to brush teeth or comb hair	None	Extra effort, but no rest periods needed	Rest periods needed	Cannot do one of these functions	
6. Impairment of ability to arise from a chair	None	Mild, sometimes uses arms	Moderate, always uses arms	Severe, request assistance	
7. Double vision	None	Occurs, but not daily	Daily, but not constant	Constant	
8. Eyelid droop	None	Occurs, but not daily	Daily, but not constant	Constant	
MG-ADL total score (items 1–8)					

TABLE 2 Correlations of the MG-ADL and change in MG-ADL to other measures of MG symptoms

Scale (source)	No. of correlations	No. of studies	Range of correlation coefficients	*P*-values	Languages
MGC[10,11,14,20,23]	6	5	0.63–0.96	All < .01	3 English, 1 Arabic, 1 Italian, 1 Polish
ΔMGC[20]	1	1	0.75	< .0001	English
MGFA Classification[14,24]	2	2	0.80–0.84	All < .01	1 Chinese, 1 polish
MGII[15]	1	1	0.83	< .001	1 Dutch
ΔMGII[25]	1	1	0.69	< .0001	English
MMT[10,22]	5	2	0.30–0.61	All < .01	4 English, 1 Arabic
ΔMMT[22]	2	1	0.33–0.34	All < .05	English
MG-QOL15[10,14,20,26-29]	8	7	0.62–0.85	All < .001	3 English, 2 Arabic, 1 Chinese, 1 French, 1 polish
ΔMG-QOL15[20,28]	2	2	0.48–0.67	All < .001	English
Neuro-QOL Fatigue[30]	1	1	0.63	< .0001	English
OBFR[31]	2	1	0.48–0.61	All < .01	English
OBFRa[31]	2	1	0.63–0.73	All < .0001	English
QMG[9,22,24,32]	50	4	0.33–0.85	< .05 except 1	6 English, 1 Chinese
ΔQMG[22,32]	44	2	0.44–0.74	All < .01	2 English

Note: Scale scores were correlated to the MG-ADL and changes in scale scores were correlated to changes in the MG-ADL.
Abbreviations: OBFR, Oculobulbar Facial Respiratory.
[a]OBFR was correlated to the bulbar items of the MG-ADL.

publication dates from database inception to July 1, 2020. There were no geographic restrictions on the search. The EMBASE search included peer-reviewed manuscripts, as well as conference abstracts from relevant congresses, such as American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) until 2018, European Academy of Neurology, International Congress on Neuromuscular Disease, International Society for Pharmacoeconomics and Outcomes Research, and World Congress of Neurology. For the gray literature search, clinicaltrials.gov was searched for phase 2 and phase 3 clinical trials of MG; related publications of phase 2 and phase 3 clinical trials were identified from clinicaltrials.gov or searched for in PubMed, and additional relevant congresses not indexed in EMBASE were searched. As most relevant congresses were already included in the EMBASE search, we searched conference abstracts from AANEM 2019.

2.2 | Study selection

Titles and abstracts from the articles identified in the EMBASE database search were reviewed, and full-text articles were obtained for relevant manuscripts. Studies identified from the gray literature search that used the MG-ADL were identified. Studies were included that were conducted in a population of MG patients and that examined the psychometric properties of the MG-ADL or that used the MG-ADL as a study outcome. When reviewing studies, data were extracted regarding how the MG-ADL was used as an endpoint and whether duration of treatment effect was examined using the MG-ADL.

3 | RESULTS

3.1 | Psychometric properties of the MG-ADL

Studies examining the reliability of the MG-ADL have found a high test–retest reliability rate of 93.7%[22] and an acceptable internal consistency, with a Cronbach's alpha of 0.70.[23]

The MG-ADL has also demonstrated excellent responsiveness to clinical improvement (effect size = 1.21).[22] A receiver operating curve (ROC) analysis conducted to evaluate MG-ADL with improvement in physician global impression of change score plus improvement in MG-QOL15 score suggested that the MG-ADL has high accuracy for clinical improvement (ROC area under the curve = 0.90). Sensitivity and specificity analyses at various cutoff points showed that a 2-point improvement best predicted clinical improvement in MG clinical status in a sample of mild to moderate MG patients. A trial of mycophenolate mofetil comparing the MG-ADL, QMG, and Manual Muscle Test (MMT) found that the MG-ADL and MMT were the most sensitive for detecting change over time (at weeks 12 and 36), and the MG-ADL had the strongest association with physician global assessment of response.[24]

The MG-ADL has demonstrated good convergent validity, as it has statistically significant positive correlations with other outcome

measures used to assess the clinical status of MG, and the change in the MG-ADL also has statistically significant correlations with changes in other measures of MG; these correlations range from 0.3 to 0.96 (Table 2).[9-11,13,14,22,24-34] However, it should be noted that the MG-ADL contains items that overlap with some other MG measures, such as the Myasthenia Gravis Composite (MGC), which may contribute to some of the significant correlations. The initial analysis of 254 MG patients found a significant correlation with the QMG ($r = 0.58$; $P < .001$).[9] Additionally, a multicenter, scale-validation observational study of 87 MG patients showed significant positive correlations with the MGC ($r = 0.85$; $P < .0001$) and Myasthenia Gravis Quality of Life 15-item (MG-QOL15; $r = 0.76$; $P < .0001$), as well as high correlation coefficients between the change in MG-ADL and changes in these measures (MGC: $r = 0.75$; $P < .0001$, MG-QOL15: $r = 0.67$; $P < .0001$).[22] The MG-ADL is also significantly correlated with physician assessment of response (ΔMG-ADL at month 6 and physician impression of change: $r = 0.70$; $P < .0001$).[22] Results from a clinical trial showed that change in MG-ADL was sensitive in detecting changes in MG status, as measured by global assessment of treatment response determined by the site investigator.[24] However, results comparing the QMG and MG-ADL using data from the Thymectomy Trial in Non-Thymomatous Myasthenia Gravis Patients Receiving Prednisone Therapy (MGTX), a randomized controlled trial of treatment with thymectomy and prednisone compared to prednisone alone, showed a possible floor effect of the MG-ADL.[30] Correlations between QMG and MG-ADL raw scores and change from baseline scores were calculated every 3 mo for 6 mo based on treatment groups and clinical assessment of minimal manifestation status (MMS), as defined by Myasthenia Gravis Foundation of America (MGFA) post-intervention status classification. Raw MG-ADL scores were more highly clustered near zero than raw QMG scores. Correlations between QMG and MG-ADL raw scores were weaker in patients with MMS than without MMS, possibly indicating that there was greater variability in QMG scores and that QMG scores may have continued to improve when MG-ADL reached zero.

The MG-ADL has also shown good concurrent validity, as MG-ADL scores are significantly related to outcomes of fatigue and health-related quality of life (HRQoL). There is a strong relationship between MG-ADL and fatigue, as measured by the Quality of Life of Neurological Disorders (Neuro-Qol) Fatigue and Chalder Fatigue scales.[35,36] The MG-ADL is significantly related to both physical and psychosocial aspects of HRQoL, as measured by the 36-item Short-Form Health Survey (SF-36).[33] No studies identified examined the relationship of MG-ADL to economic outcomes.

3.2 | MG-ADL as a study outcome

The MG-ADL has been used as a primary and a secondary endpoint in both clinical trials and observational studies. The majority (74.3%, n = 26) of the 35 identified ongoing and completed phase 2 and phase 3 MG clinical trials used the MG-ADL as a secondary endpoint (Supporting Information Table S1, which is available online)[16,17,22,34,37-57]; however, its use as a primary outcome in clinical trials has increased in recent years. The phase 2 trial of eculizumab showed promising results with the MG-ADL as a secondary endpoint[41]; as a result, the MG-ADL was used as a primary endpoint in the phase 3 trial of eculizumab.[58] Since trial completion and publication of results for the phase 3 trial of eculizumab, the use of the MG-ADL as a primary endpoint in trials has become widespread. Of trials beginning in 2018 or later, 46.7% (n = 7) have used the MG-ADL as a primary outcome compared to 10.0% (n = 2) of trials prior to 2018 (Figure 1). This also aligns with the Food and Drug Administration's (FDA) recent efforts on patient-focused drug development.[59] Of 11 identified observational studies using the MG-ADL as an outcome,

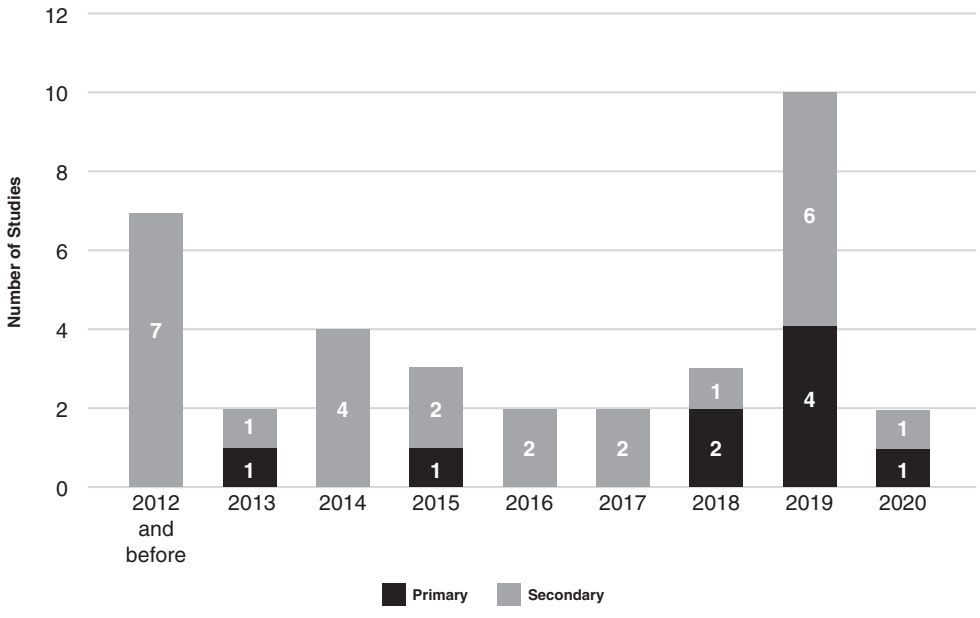

FIGURE 1 MG-ADL as a primary or secondary endpoint in clinical trials by year

81.8% (n = 9) used the MG-ADL as a primary endpoint (Supporting Information Table S1).

3.2.1 | Change in baseline MG-ADL score

The MG-ADL has been analyzed in several different ways as a study endpoint, including change in total score from baseline, responder thresholds, and cutoffs to indicate minimal symptoms. Since the inception of the MG-ADL, most studies using the MG-ADL as an outcome have used the change in total MG-ADL score from baseline, with 94.3% (n = 33) of phase 2 and phase 3 clinical trials, and all of the identified observational studies using change in baseline MG-ADL score as a primary or secondary endpoint.

3.2.2 | MG-ADL responder threshold

Studies have used different thresholds of change in MG-ADL score to indicate clinically meaningful change. In a validation study that aimed to determine the change in MG-ADL value that would best predict improvement in MG clinical status, changes in MG-ADL scores were compared with the presumed gold standard for improvement in MG status, which was based on physician impression of change plus improvement in MG-QOL15 score.[22] In this study, results from sensitivity and specificity analyses indicated that a 1-point change in MG-ADL was highly sensitive (96%) but did not have good specificity (71%), and a 3-point change had good specificity (90%) but was not very sensitive (62%). A 2-point change seemed to provide the best balance between sensitivity (77%) and specificity (82%); thus, this analysis revealed that a 2-point improvement in MG-ADL score best indicated clinical improvement.

MG-ADL responder threshold has been analyzed as an endpoint in 12 phase 2 and phase 3 clinical trials and 1 identified observational study (Table 3). Of these 13 studies, 53.8% (n = 7) used a 2-point improvement only, 30.8% (n = 4) used a 3-point improvement only, 7.6% (n = 1) showed results for improvements ranging from 2 to 8 points, and 7.6% (n = 1) did not report how an MG-ADL responder was defined. The 2 studies that used MG-ADL responder as a primary outcome used a 2-point improvement definition.[39,60] Two studies (REGAIN and REGAIN extension[42,49]) that used a 3-point improvement as a secondary endpoint cited Muppidi 2011[22] and/or Muppidi

TABLE 3 Results of studies using MG-ADL responder as an endpoint

Study/citation	Intervention	Phase	Type of endpoint	MG-ADL responder result
Two-point MG-ADL responder definition				
NCT00727194[36]	Eculizumab	2	Secondary	69.2% (n = 9) of eculizumab patients vs. 23.1% (n = 3) of placebo patients achieved a response
NCT02413580[40]	IVIg	3	Secondary	88.4% (n = 38) achieved a response at day 14; 90.7% (n = 39) achieved a response at day 28
NCT02965573[17]	Efgartigimod	2	Secondary	75% (n = 9) of efgartigimod patients vs. 25% (n = 3) of placebo patients achieved a response for at least 6 consecutive wk ($P = 0.039$)
NCT03669588: ADAPT	Efgartigimod	3	Primary, secondary	No published results
NCT03863080	IMVT-1401	2	Secondary	No published results
Datta 2020[48]	Eculizumab	N/A	Primary	100% (n = 6) of patients achieved a response before or at 5 mo and were maintained to mo 12
Three-point MG-ADL responder definition				
NCT01997229: REGAIN[37]	Eculizumab	3	Secondary	60% (n = 37) of eculizumab patients vs. 40% (n = 25) of placebo patients achieved a response ($P = 0.023$)
NCT02301624a: REGAIN extension[38]	Eculizumab	3	Secondary	71.6% of all open-label eculizumab patients achieved a response; 55.2% achieved a response without use of rescue therapy
NCT03052751[43]	Rozanolixizumab	2	Secondary	47.6% (n = 10) of patients achieved a response with rozanolixizumab vs. 13.6% (n = 3) with placebo ($P = 0.017$) at day 29
NCT03920293	Ravulizumab	3	Secondary	No published results
Number of participants with a 2-, 3-, 4-, 5-, 6-, 7-, or ≥ 8-point improvement in MG-ADL				
NCT03896295[a]	Nipocalimab	2	Secondary	No published results
MG-ADL responder definition not reported				
NCT03971422	Rozanolixizumab	3	Secondary	No published results

Abbreviations: IVIg, intravenous immunoglobulin; N/A, not applicable.
[a]Non-randomized clinical trial.

2012[61] for using a 3-point threshold, although both references support the use of a 2-point change for clinical improvement. Results from the REGAIN trial showed that increasing the stringency of the responder definition at week 26 with higher thresholds revealed a more substantial difference between eculizumab and placebo (3-point MG-ADL improvement: 60% eculizumab responders, 40% placebo responders, $P = .0229$; 5-point MG-ADL improvement: 45% eculizumab responders, 25% placebo responders, $P = .0182$; 7-point MG-ADL improvement: 34% eculizumab responders, 10% placebo responders, $P = .0007$).[42] There were several other studies that referred to the MG-AGL for clinically significant change, although these studies did not use an MG-ADL responder definition in their analyses: 1 clinical trial defined significant disease worsening as a 2-point increase in MG-ADL[62]; 3 other clinical trials and 1 observational study cited a 2-point reduction as a clinically meaningful improvement but did not report results using this MG-ADL responder threshold[51,54,63,64]; 1 open-label trial used a 3-point reduction as clinically meaningful improvement but did not provide a citation for why a 3-point improvement was used[34]; and 1 observational study defined a 4-point reduction to be "therapy responsive."[48] This 4-point reduction was derived by dividing the patients into 2 groups by change in MG-ADL score ("therapy responsive" and "therapy resistant"), and as a result, those who were in the "therapy response" group had a change in MG-ADL score of ≥4 and those who were in the "therapy resistant" group had a change in MG-ADL score of <4.

3.2.3 | Minimal symptoms using the MG-ADL

More recently, several studies have proposed looking at minimal symptoms as an outcome using the MG-ADL. Prior studies have used MMS, which is based on physician evaluation, as an outcome to indicate MG remission. MMS, based on MGFA post-intervention status classification, is defined as "no symptoms or functional limitations from MG but there may be some weakness on examination of some muscles."[65] However, a definition of minimal symptoms based exclusively on a patient's assessments of their symptoms and HRQoL could potentially be more meaningful for patients than physician-based evaluations.[18] Using an absolute score to define minimal symptoms can provide meaningful clinical information in addition to information obtained when using a responder threshold, as patients with significant improvement could still have clinically meaningful disease.

Of the identified studies from the targeted literature search, 3 ways to measure minimal symptoms using the MG-ADL were identified: (1) remission, (2) Patient Acceptable Symptom State (PASS), and (3) minimal symptom expression (MSE).

Remission has been defined as when patients are asymptomatic and do not have manifestations and has been operationalized as an MGC score of 0 and a score of 0 on either the MG-ADL or the MMT (eye closure score of 1 [mild weakness] permitted). This concept of remission has been used in a validation study of the MG-QOL15 that categorized patients into "remission," "ocular," and "generalized" MG.[4] No studies were identified as part of this review that used this definition of remission as a treatment outcome.

PASS has been defined as when patients report feeling "well enough." One study estimated the MG-ADL PASS threshold based on the previously validated Myasthenia Gravis Impairment Index (MGII) PASS threshold.[66] The PASS threshold was determined to be an absolute score of 2 points on the MG-ADL and indicates a global state of well-being, rather than a change in scores or improvement of symptoms. PASS has also not been used in any identified studies as an outcome endpoint to measure treatment change.

MSE occurs when MG symptoms are expressed at a minimal level, defined as an MG-ADL score of 0 or 1.[18] Three clinical trials have reported using MSE as measured by the MG-ADL as an endpoint to assess efficacy (Table 4). In the phase 2 zilucoplan trial, a higher proportion of patients receiving 0.3 mg/kg of zilucoplan (35.7%) achieved MSE than patients receiving 0.1 mg/kg of zilucoplan (26.7%) and placebo (13.3%), but this difference was not statistically significant.[63] A significantly higher proportion of eculizumab patients

TABLE 4 Results of MG-ADL MSE studies

Study	Intervention	Phase	Type of endpoint	Results
NCT03315130[62]	Zilucoplan	2	Secondary	• 35.7% (n = 5) of patients achieved MSE with 0.3 mg/kg of zilucoplan • 26.7% (n = 4) of patients achieved MSE with 0.1 mg/kg of zilucoplan • 13.3% (n = 2) of patients achieved MSE with placebo • The differences in proportions of participants achieving MSE between groups did not reach statistical significance
NCT01997229: REGAIN[18]	Eculizumab	3	Secondary	At REGAIN week 26, 21.5% of eculizumab patients achieved MSE vs. 1.7% of placebo ($P < .001$)
NCT02301624: REGAIN extension[18]	Eculizumab	3	Secondary	At week 130 of the REGAIN open-label extension, 22.9% of patients in the eculizumab/eculizumab group and 27.8% of patients in the placebo/eculizumab group achieved MSE after initiating eculizumab treatment ($P = .786$)

achieved MSE compared to placebo (21.5% vs. 1.7%) at week 26 of the REGAIN study.[18] At week 130 in the open-label extension study of REGAIN, 22.9% of patients in the eculizumab/eculizumab group and 27.8% of patients in the placebo/eculizumab group achieved MSE after initiating eculizumab treatment.[18]

3.2.4 | Duration of treatment effect

Another important consideration when looking at MG treatment outcomes is assessing the duration of treatment effect. When examining duration of treatment effect, this targeted review aimed to identify whether studies measured the duration of treatment effect using the MG-ADL; that is, whether MG-ADL was measured at multiple timepoints rather than a single timepoint. Of the 35 phase 2 and phase 3 clinical trials using change in MG-ADL as an endpoint, 40.0% (n = 14) looked at duration of treatment effect, and of the 10 observational studies using change in MG-ADL as an endpoint, 70.0% (n = 7) looked at duration of treatment effect. Of the 13 studies using MG-ADL responder as an endpoint, 38.5% (n = 5) looked at duration of treatment effect. Of the 3 trials analyzing MSE with MG-ADL as an endpoint, 33.3% (n = 1) looked at duration of treatment effect. Recently published results from trials of eculizumab and efgartigimod showed that these treatments had rapid and durable responses over time when examining change in baseline MG-ADL score,[17,42,49] while trial results of belimumab showed a steady improvement over 24 wk.[40] Using a responder threshold, 75% (n = 9) of patients receiving efgartigimod had at least a 2-point improvement for at least 6 consecutive weeks vs. 25% of patients on placebo ($P < .05$).[17] In a retrospective chart review of data from 6 patients with MG treated for 12 mo with eculizumab, 100% (n = 6) of patients achieved a 2-point improvement before or at 5 mo and were maintained to mo 12.[39] When examining duration of treatment effect with MSE in a phase 3 trial of eculizumab, the proportion of patients achieving MSE increased to 21.3% at wk 26; this proportion remained relatively stable through the open-label extension period up to wk 130.[18]

4 | DISCUSSION

In this targeted literature review, we found evidence that the MG-ADL is a reliable and valid measure with good psychometric properties that has been used in clinical trials and observational studies to measure MG symptoms and response to treatment. The MG-ADL is significantly correlated with other measures of MG, including the MGC, MGII, MG-QOL15, MMT, and QMG, as well as measures of fatigue and HRQoL. Furthermore, changes in the MG-ADL are also significantly related to changes in other measures of MG, as well as physician global assessment of response, although comparisons with the QMG show a possible floor effect.

Historically, the MG-ADL has been used as a secondary outcome; however, its use as a primary outcome has increased in recent years. Although the majority of included observational studies used the MG-ADL as a primary endpoint, this may not be indicative of a true difference in how the MG-ADL has been used in clinical trials and observational studies since studies using the MG-ADL as a secondary or exploratory endpoint without mention of the MG-ADL in the study abstract may not have been identified in our search strategy.

Change from baseline is the most common method of analyzing the MG-ADL in clinical trials and observational studies. Research using sensitivity and specificity analyses has established that a 2-point improvement indicates improved clinical status in patients with mild to moderate MG. Further research is needed to determine whether this change is appropriate to indicate clinical improvement in a severe MG population. Currently, there is no publicly available regulatory guidance from the FDA on an appropriate MG-ADL responder threshold, although the FDA label for eculizumab refers to REGAIN study results using a 3-point improvement. The European public assessment report on eculizumab from the European Medicines Agency notes that a 2-point reduction in MG-ADL score indicates a clinically significant improvement of the patient's condition.[67] Evidence is lacking on the patient perspective of the MG-ADL responder threshold as an indicator of meaningful change. Patient research is needed to help support the interpretation of the MG-ADL responder threshold.

MSE, defined as a score of 0 or 1 on the MG-ADL, is a new concept that has emerged in MG research in the past 2 y. MSE may be a useful tool in measuring therapy effectiveness in MG, particularly as new and promising treatments are developed for MG; however, it is not yet formally validated, so further research is needed to evaluate the optimal range for this construct. Given there is evidence that the MG-ADL has a floor effect and that patients with significant improvement can still have clinically meaningful disease, the proportion of patients achieving MSE may provide an additional meaningful endpoint to change in total score and proportion of patients attaining a responder threshold. While MSE is based on the concept of minimal manifestations, MMS is based on physician evaluation. A definition of minimal symptoms, such as MSE, that incorporates the patient perspective on functioning could provide additional meaning to these physician-based evaluations. More evidence is needed to validate and understand the clinical meaningfulness of MSE in clinical practice.

Duration of treatment effect is a key construct, as it is important to know whether patients maintain improvements in the MG-ADL over time to capture the true benefit of treatment. Less than half of phase 2 and phase 3 trials have assessed or are assessing duration of treatment effect, although this is likely an underestimation, as many recent clinical trials without published results have not provided detailed information on their MG-ADL analysis plans. Future trials and observational studies analyzing the MG-ADL using change in baseline score, a responder threshold, and MSE should measure these endpoints at multiple timepoints to examine duration of treatment effect.

Given that many US payers require the MG-ADL for the approval of initiation and continuation of treatment with eculizumab,[19-21] it is important that insurers requiring the MG-ADL to reimburse for treatment understand the clinical meaningfulness of the MG-ADL. Similarly, treating clinicians should have an understanding of the clinical meaningfulness of the MG-ADL, as well, and stay up to date on

research related to the interpretation of the MG-ADL. In clinical practice, the MG-ADL can be regularly administered to MG patients to measure treatment progress. Incorporating assessment instruments into routine clinical care for MG can improve the quality of care and, potentially, treatment outcomes at the individual patient level by providing important information on trends in symptoms and the functional impact of MG and treatment.[68] In particular, the use of patient-reported assessment may increase the interest and ability of MG patients to become active stakeholders in managing their disease and tracking its progression. As the MG-ADL is easy to administer, requires no additional training, is quick to complete, and can be administered by members of the treatment team other than the treating physician (such as by medical assistants), it is an ideal measure for use in routine clinical practice. Although the QMG is well-validated and often used in clinical trials, the QMG is more time intensive than the MG-ADL, requires training to administer, is physician-derived, and is not practical for routine use in clinical practice. Additionally, the MG-ADL could possibly be implemented via phone or computer, which would allow for more frequent data collection.[68] In addition to examining change in MG-ADL scores over time, analyzing the MG-ADL using a responder threshold may be a valuable way to track progress and significant clinical improvement. A 2-point responder threshold has been established in the mild to moderate MG population, but further research is needed to determine the appropriate responder threshold for a severe MG population. Although MSE has not yet been formally validated, attainment of MSE has the potential to be the most useful endpoint to determine therapy success, as reaching minimal symptoms is the overall aspirational goal of MG treatment.

As the MG-ADL is a measure of MG symptoms and does not directly measure other aspects of disease, such as quality of life or functioning, another recommendation for clinical practice and/or research is to use the MG-ADL in conjunction with other measures so that clinicians and researchers can obtain a more complete picture of their patients and study participants; for example, the MG-ADL can be used in conjunction with disease-specific quality of life measures, such as the MG-QOL15 or other measures that assess functioning, treatment burden, side effects, etc. It is important not only to understand the change in MG symptoms for patients with MG but also to understand the overall impact of those changes on quality of life and functioning, as well as effects of treatment.

There were several limitations of this research. Because this was a targeted literature review, relevant information may have been missed. As MG-ADL was used as a title/abstract search term, studies using this measure as a secondary or exploratory endpoint that did not mention this within their abstract were not captured. Additionally, many clinical trials have recently been initiated and do not have published results yet; as such, the only information on these studies is from clinicaltrials.gov, which does not always list complete study information.

One limitation of the MG-ADL measure is that items are not weighted, and therefore, it assumes equal importance and impact for each item, which likely does not reflect patient experience. For example, grade 1 eyelid droop (occurs but not daily) is not likely to be viewed as the same by patients, caregivers, and clinicians as grade 1 shortness of breath (shortness of breath with exertion). The lack of weighted items when scoring the MG-ADL is a limitation when examining the change in total MG-ADL score or even MSE as measured by the MG-ADL. Despite this limitation, the MG-ADL still provides important information regarding MG symptoms. MG-ADL use should not be limited due to this, but users should be aware of this limitation when using this measure.

The MG-ADL is a useful and versatile measure and can be used in clinical practice or as an outcome in clinical trials or observational studies to measure MG symptoms and response to treatment. The use of the MG-ADL has evolved since its inception; in recent years, it is being used more frequently as a primary endpoint in clinical trials and analyzed using a responder threshold to indicate treatment improvement. MSE using the MG-ADL shows promise in helping to determine success of treatment and may be the aspirational goal of MG treatment for the future once validated, particularly given the evolving treatment landscape in MG.

CONFLICT OF INTEREST

This review was funded by argenx. S. Muppidi has served as a paid consultant for Alexion Pharmaceuticals, argenx, and Ra Pharmaceuticals. N. Silvestri has served as a paid consultant for Alexion Pharmaceuticals, argenx, and UCB. R. Tan and K. Riggs are employees of Xcenda, which was paid by argenx to conduct the literature review upon which this manuscript is based and to help prepare the manuscript. T. Leighton is a former employee of and owns stock in argenx. G. Phillips is a current employee of and owns stock in argenx. The study concept was initiated by T. Leighton. S. Muppidi and N. Silvestri provided guidance during the review process on concepts that should be addressed. R. Tan and K. Riggs conducted the review. S. Muppidi and N. Silvestri provided input on the results and interpretation of the review. G. Phillips provided input on measurement and psychometric concepts in the review. All authors contributed to the writing, review processes, and final approval of the manuscript.

ETHICS STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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