

OPEN

Neurology®

The most widely read and highly cited peer-reviewed neurology journal
The Official Journal of the American Academy of Neurology



Neurology Publish Ahead of Print
DOI: 10.1212/WNL.0000000000011124

International Consensus Guidance for Management of Myasthenia Gravis: 2020 Update

Pushpa Narayanaswami, MBBS, DM; Donald B. Sanders, MD; Gil Wolfe, MD; Michael Benatar, MD; Gabriel Cea, MD; Amelia Evoli, MD; Nils Erik Gilhus, MD; Isabel Illa, MD; Nancy L Kuntz, MD; Janice Massey, MD; Arthur Melms, MD; Hiroyuki Murai, MD; Michael Nicolle, MD; Jacqueline Palace, MD; David Richman, MD; Jan Verschuuren, MD

The Article Processing Charge was funded by The Myasthenia Gravis Foundation of America.

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND), which permits downloading and sharing the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Neurology® Published Ahead of Print articles have been peer reviewed and accepted for publication. This manuscript will be published in its final form after copyediting, page composition, and review of proofs. Errors that could affect the content may be corrected during these processes.

Equal Author Contributions:

These authors contributed equally to this work: Pushpa Narayanaswami MBBS, DM, Donald B Sanders MD, Gil I Wolfe MD

Corresponding Author:

Pushpa Narayanaswami

pnarayan@bidmc.harvard.edu

Affiliation Information for All Authors:

Pushpa Narayanaswami, Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA, USA

Donald Sanders, Department of Neurology, Duke University Medical Center, Durham, NC, USA; Gil Wolfe, Department of Neurology, Univ. at Buffalo Jacobs School of Medicine and Biomedical Sciences, State University of New York, Buffalo, NY, USA

Michael Benatar, Department of Neurology, University of Miami, Miller School of Medicine, Miami, FL, USA

Gabriel Cea, Departamento de Ciencias Neurologicas, Facultad de Medicina, Universidad de Chile, Santiago, Chile

Amelia Evoli, Dipartimento di Neuroscienze, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Roma, Italy

Nils Erik Gilhus, Department of Clinical Medicine, University of Bergen, Norway; Isabel Illa, Department of Neurology, Hospital Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, ERN EURO-NMD and CIBERER U762, Spain; Nancy Kuntz, Departments of Pediatrics and Neurology, Northwestern Feinberg School of Medicine, Chicago, IL, USA

Janice Massey, Department of Neurology, Duke University Medical Center, Durham, NC, USA

Arthur Melms, Neurology, University of Tübingen Medical Centre, Tübingen, Germany

Hiroyuki Murai, Department of Neurology, International University of Health and Welfare, Narita, Japan

Michael Nicolle, Department of Clinical Neurological Sciences, Western University, London, ON, Canada; Jacqueline Palace, Department of Clinical Neurology, John Radcliffe Hospital, Oxford University Hospitals Trust, Oxford, UK

David Richman, Department of Neurology, University of California, Davis, Davis, CA 95616 USA

Jan Verschuuren, Department of Neurology, Leiden University Medical Centre, Leiden, the Netherlands

Contributions:

Pushpa Narayanaswami: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data; Additional contributions: Statistical analysis, study supervision

Donald B. Sanders: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Additional contributions: Study supervision

Gil Wolfe: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Additional contributions: study supervision

Michael Benatar: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Gabriel Cea: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Amelia Evoli: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Nils Erik Gilhus: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Isabel Illa: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Nancy L Kuntz: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Janice Massey: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Arthur Melms: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Hiroyuki Murai: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Michael Nicolle: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Jacqueline Palace: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

David Richman: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Jan Verschuuren: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Number of characters in title: 81

Abstract Word count: 218

Word count of main text: 4284

References: 55

Figures: 0

Tables: 1

Supplemental data: doi:10.5061/dryad.6hdr7sqxx

Statistical Analysis performed by: Pushpa Narayanaswami, MD Beth Israel deaconess Medical Center/Harvard Medical School, Boston, MA

Search Terms: [179] Myasthenia

Acknowledgements: We acknowledge the support of the Myasthenia Gravis Foundation of America

Study funding: No targeted funding reported.

Disclosures:

Narayanaswami P: Research support: Momenta Pharmaceuticals, PCORI, Advisory board: Argenx, Alexion, Member, Medical and Scientific Advisory Board, Myasthenia Gravis Foundation of America (MGFA)

Sanders DB: Research support from PCORI, Consultant for Accordant Health Services, Alexion, Cabaletta, Janssen RnD, Kashiv Biosciences and Momenta Pharmaceuticals; Wolfe GI: Advisory board for Grifols, Alexion, Takeda, BPL, UCB, ArgenX, Ra. Research support from ArgenX, Ra, Immunovant, MGFA

Benatar M: Advisory Boards: Immunovant, Viela Bio; Site-PI on industry trials: UCB; Federal funding: Site-PI for MGNet (U54115054)

Cea G: No relevant disclosures

Evoli A: Scientific award jury member for Grifols and a safety data monitor for UCB

Gilhus NE: Consultant for Ra Pharma, Argenx, and UCB. Speakers honoraria from Octapharma, Alexion, and MerckSerono

Illa I: Consultant and Scientific award jury member for Grifols; Kuntz NL: Medical advisory boards for Argenx, Audentes, AveXis, Biogen, Cytokinetics, Roche and Sarepta; Massey JM: Site PI, Revance Therapeutics

Melms A: Advisory board, UCB; Murai H: Consultant for Alexion, Argenx and Ra, Speaker honoraria from the Japan Blood Products Organization, Research support from the Ministry of Health, Labour and Welfare, Japan

Palace J: partly funded by highly specialised services to run a national congenital myasthenia service and a neuromyelitis service, support for scientific meetings and honorariums for advisory work from Merck Serono, Biogen Idec, Novartis, Teva, Chugai Pharma and Bayer Schering, Alexion, Roche, Genzyme, MedImmune, EuroImmune, MedDay, Abide ARGENX, UCB and Viela Bio and grants from Merck Serono, Novartis, Biogen Idec, Teva, Abide, MedImmune, Bayer Schering, Genzyme, Chugai and Alexion. She has received grants from the MS society, Guthrie Jackson Foundation, NIHR, Oxford Health Services Research Committee, EDEN, MRC, GMSI, John Fell and Myaware for research studies

Richman DP: Research funding from NINDS (1R21NS104516), Myasthenia Gravis Foundation of America, and Cabaletta Bio Inc. Member of the Advisory Board of Cabaletta Bio Inc.

Verschuuren J: receives financial support from Target to B consortium, Prinses Beatrix Spierfonds, and has been involved in trials or consultancies for Argenx, Alexion, or Ra pharma.

Member of the European Reference Network for Rare Neuromuscular Diseases [ERN EURO-NMD]

Abstract:

OBJECTIVE: To update the 2016 formal consensus-based guidance for the management of myasthenia gravis (MG) based on the latest evidence in the literature.

METHODS: In October 2013, the Myasthenia Gravis Foundation of America appointed a Task Force to develop treatment guidance for MG, and a panel of 15 international experts was convened. The RAND/UCLA appropriateness method was used to develop consensus recommendations pertaining to seven treatment topics. In February 2019, the international panel was reconvened with the addition of one member to represent South America. All prior recommendations were reviewed for currency, and new consensus recommendations were developed on topics that required inclusion or updates based on recent literature. Up to three rounds of anonymous e-mail votes were used to reach consensus, with modifications to recommendations between rounds based on panel input. A simple majority vote (80% of panel members voting 'yes') was used to approve minor changes in grammar and syntax to improve clarity.

RESULTS: The previous recommendations for thymectomy were updated. New recommendations were developed for the use of rituximab, eculizumab and methotrexate as well as for the following topics: early immunosuppression in ocular MG and MG associated with immune checkpoint inhibitor treatment.

CONCLUSION: This updated formal consensus guidance of international MG experts, based on new evidence, provides recommendations to clinicians caring for MG patients worldwide.

Introduction:

Evidence-based recommendations for the treatment of myasthenia gravis (MG) have historically been difficult to develop because of limited evidence from studies with a low risk of bias such as large, well-designed randomized controlled studies (RCTs). To address the lack of uniform, globally accepted standards for the care of people with MG, the Myasthenia Gravis Foundation of America (MGFA) appointed a Task Force in 2013 to develop treatment recommendations for MG. A panel of 15 international experts in the treatment of MG was convened, and in 2016, published an international consensus guidance for management of MG.¹

Results of several new trials of MG treatment have been published since that guidance statement was published, and in 2019, the panel reviewed the previous recommendations for currency and identified new topics that may affect practice. All members of the previous MGFA Task Force participated in this update; one new member (GC) was added to the international panel, which now consists of experts from Canada (MN), Chile (GC), Germany (AM), Italy (AE), Japan (HM), Norway (NEG), the Netherlands (JV), Spain (II), UK (JP) and USA (PN, DS, GW, MB, NK, JMM and DPR). All except PN were voting members; PN served as the methodologist.

Methods:

Topics informing new recommendations were selected based on a review of studies of treatment of MG published since 2013. Panel members disclosed any conflicts of interest (COI) using the Neurology® COI disclosure form; all conflicts were reviewed by the panel co-chairs (DS, GW). One or two panel members prepared narrative reviews of recent literature and proposed initial recommendations for each topic. Conflicted panel members abstained from participating in the literature review and from developing initial recommendation statements for the conflicted topic(s), but participated in the group discussions and voting to obtain expert consensus for all topics.

Topics Identified for Development of Recommendations:

Based on the availability of new clinical trial data that the panel co-chairs determined may affect previous recommendations or lend themselves to new recommendations, the following interventions were selected: thymectomy, rituximab in MG with antibodies to acetylcholine receptors (AChR) and muscle specific kinase (MuSK), eculizumab, and methotrexate. Recommendations were also developed to inform early immunosuppression in ocular MG, the role of physical training/exercise in MG, and management of MG associated with immune checkpoint inhibitor treatment. Physical training/exercise was excluded after review because of the low quality of evidence informing recommendations.

The RAND UCLA appropriateness method for formal consensus was used to obtain consensus, with the same *a priori* assumptions regarding treatment availability and costs, etc. as in the initial guidance document.^{1,2} All voting was conducted by e-mail and the responses returned only to

the methodologist to avoid the potential for panel members' opinions and votes being influenced by others. Topics were voted on sequentially, although rounds of voting for different topics frequently overlapped for efficiency. All recommendation statements were edited after the first round of voting by the co-chairs and methodologist in response to the panel's suggestions for changes and depending on whether consensus was reached or not. The edited recommendations were sent by e-mail to the panel along with collated panel comments from the previous round for voting. The process was repeated for up to three rounds of voting, as needed. Recommendations that did not achieve consensus after three rounds of voting were discarded. The panel rated each recommendation for appropriateness on a nine point scale (1-3: inappropriate, 4-6: uncertain, and 7-9: appropriate). Median and range were calculated for each recommendation to assess appropriateness and agreement per the RAM method. Tables e1- e10 summarize all the recommendations of the original guideline that are still current plus those from the present update. Table 1 provides an update of drugs to avoid or use with caution in MG.

Results:

All recommendations below achieved panel consensus agreement as being appropriate, and these recommendations should be considered extensions or additions to recommendations made in the initial international consensus guidance.¹ The range outside of the "appropriate" category (7-9) indicates the breadth of opinions (dispersion) within the panel.

Thymectomy

The multicenter, randomized, rater-blinded MGTX trial enrolled patients < 65 years of age with acetylcholine receptor antibody positive (AChR-Ab+) generalized non-thymomatous MG of < 5

years duration.³ Sixty-six subjects underwent extended transsternal thymectomy and received prednisone using a standard dosing schedule, while 60 subjects received the standardized prednisone dosing schedule alone. An effect favoring thymectomy was seen in both of the co-primary outcome measures: reductions in the time-weighted average Quantitative MG (QMG) score and the time-weighted average alternate-day prednisone dose. Secondary outcome measures including azathioprine use, intravenous immunoglobulin (IVIg) use and hospitalizations for MG exacerbations, also favored thymectomy plus prednisone. Benefits were seen within the first year and were sustained through year 3. In a post-hoc analysis, neither the prednisone dose nor QMG scores were significantly different between the two treatment groups in patients 50 years or older.³ An extension of the MGTX trial followed 68 (61%) participants from the original trial for two additional years. At 60 months, lower time-weighted average QMG scores and a reduction in average time-weighted prednisone dose favored thymectomy plus prednisone.⁴ A recent AAN Practice Advisory recommended that clinicians should discuss thymectomy with patients with AChR Ab+ generalized MG and should counsel patients considering minimally invasive thymectomy techniques that it is uncertain whether the benefit attained by extended transsternal thymectomy will also be attained by minimally invasive approaches (Level B).⁵

Recommendations:

1a. In non-thymomatous, generalized MG patients with AChR-Ab, aged 18-50 years, thymectomy should be considered early in the disease to improve clinical outcomes and to minimize immunotherapy requirements and need for hospitalizations for disease exacerbations. (Median 9, range 2-9)

1b. Thymectomy should be strongly considered in patients with AChR-Ab+ generalized MG if they fail to respond to an initial adequate trial of immunotherapy or have intolerable side effects from that therapy. (Median 9, range 5-9)

2. Thymectomy for MG is an elective procedure and should be performed when the patient is stable and deemed safe to undergo a procedure where postoperative pain and mechanical factors can limit respiratory function. (Median 9, range 9)

Recommendations 4 and 5 below are unchanged from the 2016 consensus guidance.¹

3. *Endoscopic and robotic approaches to thymectomy are increasingly performed and have a good track record for safety in experienced centers. Data from randomized, controlled comparison studies are not available. Based on comparisons across studies, less invasive thymectomy approaches appear to yield similar results to more aggressive approaches.*(Median 9, range 4-9)

4. *Thymectomy may be considered in generalized MG patients without detectable AChR-Ab if they fail to respond adequately to immunosuppressive (IS) therapy, or to avoid/minimize intolerable adverse effects from IS therapy. Current evidence does not support an indication for thymectomy in patients with MuSK, low-density lipoprotein receptor-related protein 4 (LRP4) or agrin antibodies.* (Median 9, range 6-9)

Ocular MG:

A small RCT comparing prednisone to placebo in 11 ocular MG patients who had previously failed to achieve minimal manifestation (MM) status after 4-6 weeks of pyridostigmine, found that five of six participants (83%) in the prednisone group achieved the primary end-point of sustained MM status at a median of 14 weeks on prednisone (median dose 15mg/day), compared to none of 5 in the placebo group.⁶ Three of the five placebo participants switched to prednisone

(60 mg/day) with rapid taper; two attained sustained MM status. A prospective cohort study of 13 consecutive ocular and 76 generalized MG patients evaluated the effect of immunosuppressive (IS) agents on ophthalmoparesis.⁷ Fifty-nine percent of patients had complete resolution of ophthalmoparesis within 12±2 months of initiation of IS agents. Patients with milder ophthalmoparesis had greater odds of symptom resolution in the first year of treatment. Median time to resolution was 7 months after IS agents were started.

Evidence for the efficacy of thymectomy in ocular MG is limited by the retrospective design of most published studies. In a case control study of 47 patients with non-thymomatous ocular MG who underwent thymectomy matched to 67 patients who refused surgery, there was no difference in the proportion of patients achieving stable remission at a median follow-up of 100-116 months.⁸ A retrospective analysis of 236 patients with thymomatous and non-thymomatous MG reported no improvement after thymectomy in 25 patients, of whom 17 (68%) were ocular or predominantly ocular, over 12 months of follow-up.⁹ In another retrospective case series of 52 patients with MG, only 2 of 11 patients with ocular MG (18%) achieved remission post thymectomy, in contrast to 28%-50% of generalized MG patients.¹⁰

A retrospective case series of 110 patients with ocular MG who underwent extended transsternal thymectomy reported that at a median follow up of 33.5 months, 26% achieved complete remission (defined as asymptomatic without medications for 12 months).¹¹ Five patients had a thymoma.¹¹ A retrospective case series of 49 non-thymomatous ocular MG and 12 ocular MG with thymoma undergoing thymectomy followed for a mean duration of 9 years reported a cure defined as asymptomatic without need for medications in 51%.¹² In yet another retrospective

case series of transcervical thymectomy in MG, 57% of 12 patients with ocular MG achieved MGFA post-intervention status (PIS) of complete stable remission (CSR)¹³ at 5 years.¹⁴ A subsequent case series of 151 patients with MG who underwent transcervical thymectomy followed for 5 years showed a higher odds ratio for remission in ocular MG compared to generalized MG without controlling for other variables (analysis performed by PN).¹⁵ In 12 patients with ocular MG undergoing thymectomy because of an abnormal chest CT scan, all but one required additional immunosuppression after thymectomy; 6 achieved remission at mean follow-up of 81 months.¹⁶ In a retrospective analysis of 50 juvenile MG patients undergoing thymectomy, of whom 46% were ocular, 50% showed improved PIS at a mean of 3.5 years follow-up.¹⁷ There was no difference between ocular and generalized MG. In a meta-analysis of 26 studies of thymectomy in non-thymomatous MG, the pooled CSR rate was 0.51.¹⁸ There was high heterogeneity in the meta-analysis model, indicating substantial differences among the included studies.

Recommendations: (Table e-10)

1. Ophthalmoparesis or ptosis in ocular MG that is not responding to anti-cholinesterase agents should be treated with immunosuppressant agents if symptoms are functionally limiting or troublesome to the patient. (Median 9, range 7-9)
2. Corticosteroids should be used as the initial IS agent in ocular MG. Steroid-sparing IS agents may be needed when corticosteroids alone are ineffective, contraindicated or not tolerated. (Median 9, range 6-9)
3. Data from a single small RCT suggest that low-dose corticosteroids may be effective for ocular MG and may avoid side effects associated with high-dose corticosteroids. (Median 9, range 4-9)

4. AChR Ab+ patients with ocular MG who do not respond adequately to acetylcholinesterases and who either prefer not to take IS therapy or have contraindications to or are refractory to IS agents may be offered thymectomy. (Median 8, range 5-9)

Rituximab:

Most studies of rituximab (RTX) are retrospective and some combine patients with AChR-Ab, MuSK-Ab and seronegative MG. A multicenter blinded prospective review of MuSK-Ab+ MG patients demonstrated that 14 of 24 (58%) of patients treated with RTX achieved MM status and required only low dose IS therapy, compared to 5 of 31 (16%) of the non-RTX group.¹⁹

In a prospective open label study of 22 refractory AChR-Ab+, MuSK-Ab+, and seronegative MG, MG Manual Muscle testing (MMT) scores revealed significant improvement from baseline at mean follow-up of 29± 19 months in the AChR-Ab+ and MuSK-Ab+ groups.²⁰ Another prospective open label study of 14 patients with refractory AChR-Ab+, MuSK-Ab+ and seronegative MG reported improvement in MMT scores at mean follow-up of 22 months.²¹ The time to peak response after a single cycle of RTX was 4.5± 1 months. A retrospective multicenter study of MuSK-Ab+ MG reported that RTX given in the dose of 375 mg/m² weekly for 4 weeks and then monthly for the next 2 months was associated with lower relapse rates (18%) compared to a regimen of two 1 gm infusions separated by 2 weeks (80%).²² A retrospective Austrian nationwide study of 56 patients with AChR-Ab+ and MuSK-Ab+ MG reported that 26% of patients were in remission 3 months after treatment with varying dosing protocols of RTX. At a median of 20 months, 43% were in remission and 25% achieved MM status.²³ A single center retrospective study of 21 AChR-Ab+, 3 MuSK-Ab+ and 4 double seronegative MG patients found that muscle strength improved significantly from baseline at 6 months, and then stabilized up to 36 months, and PIS was improved in 43% at 6 months.²⁴ A

retrospective combined analysis of previously published case reports of 169 patients between January 2000 and August 2015 reported that 72% of MuSK-Ab+ MG and 30% of AChR-Ab+ MG patients treated with RTX achieved MM status or better.²⁵ The number of cycles of RTX varied but did not have an effect on the response. A recent systematic review of previous studies of 165 patients with AChR-Ab+ MG treated with RTX concluded that despite heterogeneous outcome measures, significant clinical improvement was seen in 113 patients (68%), with 36% achieving remission.²⁶ A Phase II RCT of RTX (Beat-MG) enrolled 52 patients with generalized non-thymomatous AChR-Ab+ MG on a stable regimen of prednisone for 4 weeks or prednisone plus another IS agent for 6 months.²⁷ Two cycles of RTX 6 months apart were compared to placebo with the primary outcome being a steroid-sparing effect ($\geq 75\%$ reduction in mean daily prednisone requirements in the 4 weeks prior to week 52 compared to the 4-week period prior to randomization). The study was designed to assess futility (non-superiority). Preliminary results reported that the area under the curve for prednisone was not significantly different between RTX and placebo groups, with 60% on RTX and 56% on placebo achieving the primary outcome. There were no significant differences in mean QMG or MG-composite (MGC) changes between the groups. The study suggests that in mildly to moderately symptomatic generalized AChR-Ab+ MG, RTX is unlikely to have a clinically meaningful steroid-sparing effect over 12 months.

Three cases of progressive multifocal leukoencephalopathy (PML) have been reported in MG. One was RTX related, although the patient had previously received other IS agents,²⁸ another

patient was on azathioprine and prednisone²⁹ and the third patient was on prednisolone, IVIg and azathioprine.³⁰

Recommendations:

Recommendation 1 is unchanged from the 2016 consensus guidance.¹

1. *Rituximab should be considered as an early therapeutic option in patients with MuSK-Ab+ MG who have an unsatisfactory response to initial immunotherapy. (Median 9, range 4-9)*
2. The efficacy of rituximab in refractory AChR-Ab+ MG is uncertain. It is an option if patients fail or do not tolerate other IS agents. (Median 8, range 4-9)

Methotrexate:

Studies on the use of methotrexate (MTX) in MG are limited and the available data do not provide convincing evidence of efficacy. In a retrospective case series of 16 patients with MG treated with MTX, (abstract only) 8 patients reduced pyridostigmine doses and 6 showed “clinical improvement.”³¹ A prospective open-label case series published only as an abstract reported that 14 of 16 MG patients treated with MTX had an improved PIS on mean follow-up of 20.6 months.³² In a single-blinded trial, 24 patients with generalized MG on prednisone were randomized to MTX (11) or azathioprine (13).³³ At 24 months the average prednisone dose required to achieve and maintain MM status was lower in both MTX and azathioprine treated patients but was not different between the groups. At months 10 and 12, the prednisone dose was lower in the MTX group but the confidence interval includes clinically meaningful and non-meaningful effects. Similar proportions of both groups achieved MM status, and there were no differences in QMG or MG-activity of daily living (MG-ADL) scores between the groups.³³ An RCT enrolled 50 patients with AChR-Ab+ MG taking prednisone at a dose of ≥ 10 mg/day.³⁴

Patients were randomized 1:1 to MTX 20 mg/week or placebo. There was no difference in the primary outcome measure, the area under the prednisone dose-time curve between months 4 and 12, and the mean 12-month change in QMG, MMT, MG-Quality of life (MG-QoL), MG-ADL and MGC were no different between treatment groups.

Recommendation:

1. While evidence from RCTs is lacking, oral methotrexate may be considered as a steroid-sparing agent in patients with generalized MG who have not tolerated or responded to steroid-sparing agents that are better supported by RCT data. (Median 9, range 5-9)

Eculizumab:

Eculizumab is a humanized monoclonal antibody against the terminal C5 complement molecule.³⁵ Eculizumab prevents the formation of the membrane attack complex (MAC) and reduces damage caused by complement-fixing AChR antibodies.³⁶ In a Phase II crossover RCT of 14 patients with refractory generalized AChR-Ab+ MG, at the end of the first treatment period, 6/7 (86%) of eculizumab-treated patients achieved the primary endpoint of a 2-point reduction in the QMG score, compared to 57% with placebo.³⁷ A repeated measures mixed model of data from all visits revealed significant differences in QMG score favoring eculizumab. Eculizumab was well tolerated. In a phase III international multicenter RCT of 125 patients with refractory generalized non-thymomatous AChR-Ab+ MG (REGAIN), the primary outcome measure of change in MG-ADL score from baseline to week 26, measured by worst-rank ANCOVA, was not significantly different ($p=0.0698$) between eculizumab and placebo arms.³⁸ However, QMG score change on worst-rank ANCOVA, all pre-specified secondary endpoints (changes in QMG, MGC and MG-QOL15 scores and responder analyses of QMG and MG-ADL

scores) and multiple sensitivity analyses showed a significant benefit for eculizumab.

Participants who completed the 26-week REGAIN study were followed in an open label extension (OLE) within 2 weeks of completing REGAIN.³⁹ A pre-planned interim analysis of the OLE at 22.7 months median follow-up found a reduction in MG exacerbations by 75% compared to the year before REGAIN. In addition, 56% (65/116) of patients achieved MM status or pharmacologic remission. The magnitude of response on all clinical measures for the placebo patients in REGAIN who crossed over to receive eculizumab in the OLE was similar to the eculizumab treated patients in REGAIN. A clinically meaningful response in MG-ADL and QMG scores was seen in 55% and 39.7% of patients, respectively. Eculizumab was well tolerated. One case of meningococcal meningitis occurred despite vaccination in the OLE and the patient was successfully treated.

Vaccination against *Neisseria meningitidis* (both meningococcal conjugate MenACWY and serogroup B or MenB) is required at least 2 weeks prior to starting treatment with eculizumab. The conjugate ACWY vaccines available in the USA include Menveo® (1 dose, GlaxoSmithKline Biologicals, Inc.) and Menactra® (1 dose, single booster 4 years after initial dose if needed, Sanofi Pasteur, Inc.). The two brands of MenB vaccine are Bexsero® (2 dose series, GlaxoSmithKline Biologicals, Inc.) and Trumenba® (3 dose series, Pfizer, Inc.). The brands are not interchangeable, and a course should be completed with the same brand of the vaccine for all doses. The vaccine does not confer absolute protection against meningococcal meningitis. Antibiotic coverage, for at least 4 weeks after immunization is recommended if eculizumab is started prior to the two-week period post-vaccination. The recommendations for antibiotic coverage vary. Penicillin VK 250-500 mg every 12 hours is usually the first line

chemoprophylaxis.^{40,41} Erythromycin 500 mg twice daily, Azithromycin 500 mg daily or Ciprofloxacin 500 mg daily are alternatives for penicillin allergic patients.⁴⁰⁻⁴² However, both fluoroquinolones and macrolides can worsen MG. Chemoprophylaxis of meningococcal infections in penicillin allergic patients can therefore be challenging, and infectious disease consultation may be required.

Recommendations

1. Eculizumab should be considered in the treatment of severe, refractory, AChR-Ab+ generalized MG. (Median 9, range 2-9)
2. The role of eculizumab in the treatment of MG is likely to evolve over time. Until further data become available to allow comparisons of cost and efficacy with other treatments, eculizumab should be considered after trials of other immunotherapies have been unsuccessful in meeting treatment goals. (Median 9, range 5-9)
3. Recommendations of the Advisory Committee on Immunization Practice (ACIP) or other local guidelines regarding immunization against meningococcal meningitis should be followed prior to treatment with eculizumab. (Median 9, range 8-9)
4. Future research should include assessment of the duration of eculizumab therapy necessary to achieve and maintain treatment goals, its efficacy in other MG populations (MG with thymoma, seronegative MG), and in other stages of disease (MG crises, exacerbations, early therapy in non-refractory AChR-Ab+ MG). (Median 8, range 4-9)

Immune Checkpoint Inhibitors (ICIs):

Immune checkpoints (ICPs) are most often inhibitory molecules expressed on the surface of T-cells, which modulate the immune response and prevent host tissue damage due to uncontrolled responses to foreign or self-antigens. The immune inhibitory cytotoxic T-lymphocyte-associated

protein 4 (CTLA-4), programmed cell death protein 1 (PD-1) and programmed cell death ligand 1 (PDL1) are the best-characterized ICPs and are targeted in cancer immunotherapy. CTLA-4 reduces T-cell activation, competing with CD28 in binding B7 molecules (CD80 and CD86) on antigen-presenting cells. PD-1 binds its ligands (PD-L1 and PD-L2) and reduces activated T-cell proliferation through the inhibition of specific phosphorylation pathways.^{43, 44} Monoclonal antibodies against CTLA-4, PD-1 and PD-L1 act by blocking these inhibitory ICP molecules in order to stimulate antitumor immunity (immune checkpoint inhibitors, ICIs). These include the CTLA-4 inhibitor ipilimumab, PD-1 inhibitors pembrolizumab, nivolumab and cemiplimab, and the PDL-1 inhibitors atezolizumab, durvalumab, and avelumab. Because of the up-regulation of the immune response, multisystem immune-related adverse events (irAEs) such as skin rash, thyroid dysfunction, pneumonitis, colitis, hepatitis, nephritis, hypophysitis, and neurologic disorders including MG have been reported in patients receiving checkpoint inhibitors. The literature on irAEs of these drugs is rapidly evolving. *De novo* MG has been reported in patients treated with anti-CTLA-4 agents (ipilimumab),⁴⁵ PD1 inhibitors (nivolumab or pembrolizumab)⁴⁵⁻⁴⁷ and with combined (anti-CTLA-4 plus anti-PD-1 or PD-L1) therapy.⁴⁵ The estimated frequency of MG among patients treated with PD-1 inhibitors ranges from 0.12% to 0.2%.⁴⁸⁻⁵² Exacerbation of pre-existing MG and subclinical AChR-Ab+ MG has been reported in patients treated with PD-1 inhibitors.^{45, 53, 54}

MG onset or exacerbation varies in severity and generally occurs in the early phase of treatment. MG can overlap with other immune-mediated peripheral and central neurological syndromes.^{48,}
⁵⁵ In a review of the literature combined with a single center experience, of 63 patients with MG due to ICIs, 52 had new onset MG and 11 had a flare of preexisting MG. Most received PD1

therapy. Concurrent myositis was diagnosed in 24 patients (37%), and myocarditis in five (8%); two had the triad of MG/myositis/myocarditis. Median time from ICI initiation to developing MG was 4 weeks (6 days- 16 weeks). Respiratory failure requiring mechanical ventilation occurred in 29 patients (45%). Patients with MG/myositis/myocarditis developed respiratory failure more frequently than those with MG alone (54% vs. 42%). AChR-Ab titers were elevated in 37/56 (66%) of tested patients. Three patients had AChR-Ab when tested before ICI initiation and antibody titers increased at least 2-fold after ICI initiation. Intravenous corticosteroids were used in 59/63 patients. Thirty-eight patients received steroids as first line therapy and 24 (63%) improved. Four patients with ocular MG developed respiratory insufficiency after corticosteroid treatment. MG symptoms completely resolved in 12 patients (19%), improved in 34 (55%), and worsened in 16 (26%).⁵¹ In a review of 1834 patients receiving ICIs, four had MG, of whom one was AChR- Ab+. Three were associated with myositis. Three MG patients received combined CTLA-4 and PD1 ICIs and one received a CTLA4 ICI. Concurrent occurrence of MG with myocarditis and thyroiditis was also noted.⁵⁰ The diagnosis of ICI related MG can be challenging. Many cancer patients have fatigue or generalized weakness. The recognition of underlying neuromuscular disease may be delayed by the focus on the oncologic illness. Concurrent myositis may make MG difficult to diagnose especially when associated with ocular and bulbar weakness. Seronegative MG appears to be more frequent in these patients, making the diagnosis even more challenging.⁵⁰ The severity of the illness may be the result of multiple concurrent conditions including MG, myositis and myocarditis. Central nervous system involvement may occur in conjunction with MG or MG-myositis overlap.⁵⁰ Corticosteroid therapy appears to result in favorable outcomes.⁵⁰

Recommendations:

1. The risk of MG and other immune-mediated neurologic illnesses should be discussed with patients who are candidates for ICIs. (Median 9, range 5-9)
2. At this time, there is no evidence to either support or refute the utility of AChR antibody testing in patients without MG prior to starting ICIs. (Median 8, range 7-9)
3. MG associated with ICIs is generally severe, with a high rate of respiratory crises. (Median 8, range 5-9)
4. Pre-existing MG does not constitute an absolute contraindication to the use of ICIs, at least in patients with well-controlled disease (MM status or better). However, in these patients:
 - a. It may be prudent to avoid combined therapy (anti-CTLA-4 plus anti-PD1/PD-L1 monoclonal antibodies), given the higher potential for severe irAEs.
 - b. Close clinical monitoring, particularly of respiratory and bulbar function, is mandatory.
 - c. Although the therapeutic response to ICIs seems to be less satisfactory in patients receiving immunosuppressants, MG treatment should be maintained and may even be restarted in patients whose MG is in remission prior to treatment with ICIs. (Median 8, range 5-9)
5. Early aggressive treatment with high-dose steroids in combination with plasma exchange or IVIg may be required in patients who develop overt MG while on ICIs. The decision to withdraw ICIs is determined by the oncologic status. (Median 8, range 7-9)

Discussion:

This is an updated formal international consensus guidance of MG experts, based on new evidence that has become available since the initial guidance was published in 2016.¹ As before, these statements are intended as a guide for clinicians worldwide and are not absolute

recommendations for management. They are also not intended for establishing payment policies or drug tiering by payers. This continues to be a living document, which will require periodic review and updates to reflect new information relevant to the management of MG.

ACCEPTED

Appendix 1: Authors

Name	Location	Contribution
Pushpa Narayanaswami, MBBS, DM*	Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA, USA	study concept and design, acquisition of data, analysis of data, drafting/revising the manuscript, study supervision.
Donald B Sanders, MD*	Duke University Medical Center, Durham, NC, USA	study concept and design, acquisition of data, drafting/revising the manuscript, study supervision.
Gil Wolfe, MD*	Univ. at Buffalo Jacobs School of Medicine and Biomedical Sciences, State University of New York, Buffalo, NY, USA	study concept and design, acquisition of data, drafting/revising the manuscript, study supervision.
Michael Benatar MD, PhD	University of Miami, Miller School of Medicine. Miami, FL, USA	acquisition of data, drafting/revising the manuscript for intellectual content
Gabriel Cea MD	Facultad de Medicina, Universidad de Chile, Santiago, Chile	acquisition of data, drafting/revising the manuscript for intellectual content

Amelia Evoli MD	Fondazione Policlinico Universitario “A. Gemelli” IRCCS, Università Cattolica del Sacro Cuore, Roma, Italy	acquisition of data, drafting/revising the manuscript for intellectual content
Nils Erik Gilhus MD	University of Bergen, Norway	acquisition of data, drafting/revising the manuscript for intellectual content
Isabel Illa MD	Hospital Santa Creu i Sant Pau. Universitat Autònoma de Barcelona, Barcelona, ERN EURO-NMD and CIBERER U762, Spain	acquisition of data, drafting/revising the manuscript for intellectual content
Nancy L Kuntz MD	Northwestern Feinberg School of Medicine, Chicago, IL, USA	acquisition of data, drafting/revising the manuscript for intellectual content
Janice M Massey MD	Duke University Medical Center, Durham, NC, USA	acquisition of data, drafting/revising the manuscript for intellectual content
Arthur Melms MD	University of Tübingen Medical Centre, Tübingen, Germany.	acquisition of data, drafting/revising the manuscript for intellectual content
Hiroyuki Murai MD	International University of Health and Welfare, Narita,	acquisition of data, drafting/revising the manuscript

	Japan	for intellectual content
Michael Nicolle MD	Western University, London, ON, Canada	acquisition of data, drafting/revising the manuscript for intellectual content
Jacqueline Palace BM, DM	John Radcliffe Hospital, Oxford University Hospitals Trust, Oxford, UK	acquisition of data, drafting/revising the manuscript for intellectual content
David P Richman MD	University of California, Davis, Davis, CA, USA	acquisition of data, drafting/revising the manuscript for intellectual content
Jan Verschuuren MD	Leiden University Medical Centre, Leiden, the Netherlands	acquisition of data, drafting/revising the manuscript for intellectual content

* These authors contributed equally

References:

1. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis: Executive summary. *Neurology* 2016;87:419-425.
2. Fitch K, Bernstein SJ, Aguilar MD, et al. The RAND/UCLA Appropriateness Method User's Manual. [online]. Available at: https://www.rand.org/pubs/monograph_reports/MR1269.html. Accessed July 10, 2020.
3. Wolfe GI, Kaminski HJ, Aban IB, et al. Randomized trial of thymectomy in myasthenia gravis. *N Engl J Med* 2016;375:511-522.
4. Wolfe GI, Kaminski HJ, Aban IB, et al. Long-term effect of thymectomy plus prednisone versus prednisone alone in patients with non-thymomatous myasthenia gravis: 2-year extension of the MGTX randomised trial. *Lancet Neurol* 2019;18:259-268.
5. Gronseth GS, Barohn R, Narayanaswami P. Practice advisory: Thymectomy for myasthenia gravis (practice parameter update): Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology* 2020;94:705-709.
6. Benatar M, McDermott MP, Sanders DB, et al. Efficacy of prednisone for the treatment of ocular myasthenia (EPITOME): A randomized, controlled trial. *Muscle Nerve* 2016;53:363-369.
7. Europa TA, Nel M, Heckmann JM. Myasthenic ophthalmoparesis: Time to resolution after initiating immune therapies. *Muscle Nerve* 2018;58:542-549.
8. Mineo TC, Ambrogio V. Outcomes after thymectomy in class I myasthenia gravis. *J Thorac Cardiovasc Surg* 2013;145:1319-1324.
9. Evoli A, Batocchi AP, Provenzano C, Ricci E, Tonali P. Thymectomy in the treatment of myasthenia gravis: report of 247 patients. *J Neurol* 1988;235:272-276.
10. Hatton PD, Diehl JT, Daly BDT, et al. Transsternal radical thymectomy for myasthenia gravis: A 15-year review. *Ann Thorac Surg* 1989;47:838-840.
11. Liu Z, Feng H, Yeung S-CJ, et al. Extended transsternal thymectomy for the treatment of ocular myasthenia gravis. *Ann Thorac Surg* 2011;92:1993-1999.
12. Roberts PF, Venuta F, Rendina E, et al. Thymectomy in the treatment of ocular myasthenia gravis. *J Thorac Cardiovasc Surg* 2001;122:562-568.

13. Jaretzki A, 3rd, Barohn RJ, Ernstoff RM, et al. Myasthenia gravis: recommendations for clinical research standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America. *Neurology* 2000;55:16-23.
14. Shrager JB, Deeb ME, Mick R, et al. Transcervical thymectomy for myasthenia gravis achieves results comparable to thymectomy by sternotomy. *Ann Thorac Surg* 2002;74:320-326; discussion 326-327.
15. Shrager JB, Nathan D, Brinster CJ, et al. Outcomes after 151 extended transcervical thymectomies for myasthenia gravis. *Ann Thorac Surg* 2006;82:1863-1869.
16. Sommer N, Sigg B, Melms A, et al. Ocular myasthenia gravis: response to long-term immunosuppressive treatment. *Journal of Neurology, Neurosurgery & Psychiatry* 1997;62:156-162.
17. Kim AG, Upah SA, Brandsema JF, Yum SW, Blinman TA. Thoracoscopic thymectomy for juvenile myasthenia gravis. *Pediatric Surgery International* 2019;35:603-610.
18. Zhu K, Li J, Huang X, et al. Thymectomy is a beneficial therapy for patients with non-thymomatous ocular myasthenia gravis: a systematic review and meta-analysis. *Neurological Sciences* 2017;38:1753-1760.
19. Hehir MK, Hobson-Webb LD, Benatar M, et al. Rituximab as treatment for anti-MuSK myasthenia gravis: Multicenter blinded prospective review. *Neurology* 2017;89:1069-1077.
20. Beecher G, Anderson D, Siddiqi ZA. Rituximab in refractory myasthenia gravis: Extended prospective study results. *Muscle & Nerve* 2018;58:452-455.
21. Anderson D, Phan C, Johnston WS, Siddiqi ZA. Rituximab in refractory myasthenia gravis: a prospective, open-label study with long-term follow-up. *Annals of Clinical and Translational Neurology* 2016;3:552-555.
22. Cortés-Vicente E, Rojas-García R, Díaz-Manera J, et al. The impact of rituximab infusion protocol on the long-term outcome in anti-MuSK myasthenia gravis. *Annals of Clinical and Translational Neurology* 2018;5:710-716.
23. Topakian R, Zimprich F, Iglseder S, et al. High efficacy of rituximab for myasthenia gravis: a comprehensive nationwide study in Austria. *J Neurol* 2019;266:699-706.
24. Afanasiev V, Demeret S, Bolgert F, Eymard B, Laforet P, Benveniste O. Resistant myasthenia gravis and rituximab: A monocentric retrospective study of 28 patients. *Neuromuscular Disorders* 2017;27:251-258.

25. Tandan R, Hehir MK, Waheed W, Howard DB. Rituximab treatment of myasthenia gravis: A systematic review. *Muscle Nerve* 2017;56:185-196.
26. Di Stefano V, Lupica A, Rispoli MG, Di Muzio A, Brighina F, Rodolico C. Rituximab in AChR subtype of myasthenia gravis: systematic review. *Journal of Neurology, Neurosurgery & Psychiatry* 2020;91:392-395.
27. Nowak RJ, Coffey C, Goldstein J. AAN 2018 Emerging science abstracts: B - cell targeted treatment in myasthenia gravis (BeatMG) - a phase 2 trial of rituximab in myasthenia gravis: topline results. *Neurology* 2018;90:e2182 - e2194.
28. Kanth KM, Solorzano GE, Goldman MD. PML in a patient with myasthenia gravis treated with multiple immunosuppressing agents. *Neurology: Clinical Practice* 2016;6:e17-e19.
29. Dawson DM. Progressive multifocal leukoencephalopathy in myasthenia gravis. *Ann Neurol* 1982;11:218-219.
30. Gedizlioglu M, Coban P, Ce P, Sivasli IE. An unusual complication of immunosuppression in myasthenia gravis: progressive multifocal leukoencephalopathy. *Neuromuscul Disord* 2009;19:155-157.
31. Hartman J, Rivner MH. Methotrexate in myasthenia gravis. *Clin Neurophysiol* 2009;120:e123-e124.
32. Abdou A. Methotrexate for treatment of myasthenia gravis. *Neurology* 2007;68:A300.
33. Heckmann JM, Rawoot A, Bateman K, Renison R, Badri M. A single-blinded trial of methotrexate versus azathioprine as steroid-sparing agents in generalized myasthenia gravis. *BMC Neurology* 2011;11:97.
34. Pasnoor M, He J, Herbelin L, et al. A randomized controlled trial of methotrexate for patients with generalized myasthenia gravis. *Neurology* 2016;87:57-64.
35. Dhillon S. Eculizumab: A review in generalized myasthenia gravis. *Drugs* 2018;78:367-376.
36. Rother RP, Rollins SA, Mojcik CF, Brodsky RA, Bell L. Discovery and development of the complement inhibitor eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria. *Nat Biotechnol* 2007;25:1256-1264.
37. Howard JF, Jr., Barohn RJ, Cutter GR, et al. A randomized, double-blind, placebo-controlled phase II study of eculizumab in patients with refractory generalized myasthenia gravis. *Muscle Nerve* 2013;48:76-84.

38. Howard JF, Jr., Utsugisawa K, Benatar M, et al. Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicentre study. *Lancet Neurol* 2017;16:976-986.
39. Muppidi S, Utsugisawa K, Benatar M, et al. Long-term safety and efficacy of eculizumab in generalized myasthenia gravis. *Muscle Nerve* 2019;60:14-24.
40. Meningococcal infection and eculizumab/complement inhibitors [online]. Available at: <https://www.pnhleeds.co.uk/professionals/meningococcal-infection-and-eculizumab-complement-inhibitors/>. Accessed July 10, 2020.
41. Benamu E, Montoya JG. Infections associated with the use of eculizumab: recommendations for prevention and prophylaxis. *Curr Opin Infect Dis* 2016;29:319-329.
42. Girgis N, Sultan Y, Frenck RW, Jr., El-Gendy A, Farid Z, Mateczun A. Azithromycin compared with rifampin for eradication of nasopharyngeal colonization by *Neisseria meningitidis*. *Pediatr Infect Dis J* 1998;17:816-819.
43. Postow MA, Callahan MK, Wolchok JD. Immune checkpoint blockade in cancer therapy. *J Clin Oncol* 2015;33:1974-1982.
44. Topalian SL. Targeting immune checkpoints in cancer therapy. *JAMA* 2017;318:1647-1648.
45. Makarios D, Horwood K, Coward JIG. Myasthenia gravis: An emerging toxicity of immune checkpoint inhibitors. *Eur J Cancer* 2017;82:128-136.
46. Mohn N, Beutel G, Gutzmer R, Ivanyi P, Satzger I, Skripuletz T. Neurological immune related adverse events associated with nivolumab, ipilimumab, and pembrolizumab therapy- review of the literature and future outlook. *J Clin Med* 2019;8.
47. Moreira A, Loquai C, Pfohler C, et al. Myositis and neuromuscular side-effects induced by immune checkpoint inhibitors. *Eur J Cancer* 2019;106:12-23.
48. Kao JC, Brickshawana A, Liewluck T. Neuromuscular complications of programmed cell death-1 (PD-1) Inhibitors. *Curr Neurol Neurosci Rep* 2018;18:63.
49. Suzuki S, Ishikawa N, Konoeda F, et al. Nivolumab-related myasthenia gravis with myositis and myocarditis in Japan. *Neurology* 2017;89:1127-1134.
50. Dubey D, David WS, Reynolds KL, et al. Severe neurological toxicity of immune checkpoint inhibitors: growing spectrum. *Annals of Neurology* 2020;87:659-669.

51. Safa H, Johnson DH, Trinh VA, et al. Immune checkpoint inhibitor related myasthenia gravis: single center experience and systematic review of the literature. *J Immunother Cancer* 2019;7:319.
52. Xu M, Nie Y, Yang Y, Lu YT, Su Q. Risk of neurological toxicities following the use of different immune checkpoint inhibitor regimens in solid tumors: A systematic review and meta-analysis. *Neurologist* 2019;24:75-83.
53. Abdel-Wahab N, Shah M, Lopez-Olivo MA, Suarez-Almazor ME. Use of immune checkpoint Inhibitors in the treatment of patients with cancer and preexisting autoimmune disease. *Ann Intern Med* 2018;169:133-134.
54. Cooper DS, Meriggioli MN, Bonomi PD, Malik R. Severe exacerbation of myasthenia gravis associated with checkpoint inhibitor immunotherapy. *J Neuromuscul Dis* 2017;4:169-173.
55. Puwanant A, Isfort M, Lacomis D, Zivkovic SA. Clinical spectrum of neuromuscular complications after immune checkpoint inhibition. *Neuromuscul Disord* 2019;29:127-133.

Table 1. Drugs to avoid or use with caution in MG*

Drug	Comment
Aminoglycoside antibiotics (e.g., gentamycin, neomycin, tobramycin)	Used for gram-negative bacterial infections. May worsen MG. Use cautiously if no alternative treatment available.
Beta- blockers	Commonly prescribed for hypertension, heart disease and migraine but potentially dangerous in MG. May worsen MG. Use cautiously.
Botulinum toxin	Pre-synaptic neuromuscular junction blocker. Avoid
Chloroquine and hydroxychloroquine	Used to treat/prevent malaria and for certain autoimmune diseases. May precipitate <i>de novo</i> MG or worsen preexisting MG. Use only if necessary and observe for worsening.
Corticosteroids	A standard treatment for MG, but may cause transient worsening within the first two weeks. Monitor carefully for this possibility.
Desferrioxamine (deferoxamine)	Chelating agent used for hemochromatosis. May worsen MG.
D-penicillamine	Used for Wilson disease and rarely for rheumatoid arthritis. Strongly associated with causing MG. Avoid
Fluoroquinolone antibiotics (e.g., ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin)	Commonly prescribed broad-spectrum antibiotics that are associated with worsening MG. The US FDA has designated a “black box” warning for these agents in MG. Use cautiously, if at all.
Immune checkpoint inhibitors (e.g., ipilimumab, pembrolizumab, atezolizumab,	Used for certain cancers. Can precipitate <i>de novo</i> MG or worsen preexisting MG. Use with caution as determined by oncologic status.

nivolumab)	
Iodinated radiologic contrast agents	Older reports document increased MG weakness, but modern contrast agents appear safer. Use cautiously and observe for worsening.
Macrolide antibiotics (e.g., erythromycin, azithromycin, clarithromycin)	Commonly prescribed antibiotics for gram-positive bacterial infections. May worsen MG. Use cautiously, if at all.
Magnesium	Potentially dangerous if given intravenously, i.e. for eclampsia during late pregnancy or for hypomagnesemia. Use only if absolutely necessary and observe for worsening.
Procainamide	Used for irregular heart rhythm. May worsen MG. Use with caution.
Quinine	Occasionally used for leg cramps. Use prohibited except in malaria in US.
Statins(e.g., atorvastatin, pravastatin, rosuvastatin, simvastatin)	Used to reduce serum cholesterol. May rarely worsen or precipitate MG. Evaluate closely for worsening MG when statin treatment is commenced.
Teletromycin	Antibiotic for community acquired pneumonia. Associated with hepatotoxicity and risk of prolonged QTc interval. Causes severe, often fatal worsening in MG. Had been given a “black box” warning by the US FDA contraindicating use in MG. Drug withdrawn from most markets internationally. Should not be used in MG.
Live Attenuated Vaccines (Measles, Mumps, Rubella, Varicella Zoster, intranasal	Do not affect MG but are contraindicated in patients on immunosuppressive treatments because of the risk for adverse reactions due to uninhibited growth of the attenuated live virus or

Influenza, oral Polio, Adenovirus Type 4 and 7, Zostavax (Herpes Zoster), Rotavirus, oral Typhoid, Smallpox, Yellow fever),	bacteria.
---	-----------

*Many drugs are associated with worsening of MG. However, reported associations do not necessarily mean these medications should never be prescribed in MG. Reports are often rare or represent a coincidental association. Clinical judgment and the risk-to-benefit ratio of the drug should be considered when it is deemed important for a patient's treatment. Listed above are medications that have the strongest evidence for worsening MG.

Neurology®

International consensus guidance for management of myasthenia gravis: 2020 update

Pushpa Narayanaswami, Donald B. Sanders, Gil Wolfe, et al.

Neurology published online November 3, 2020

DOI 10.1212/WNL.0000000000011124

This information is current as of November 3, 2020

Updated Information & Services	including high resolution figures, can be found at: http://n.neurology.org/content/early/2020/11/03/WNL.0000000000011124.full
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): Myasthenia http://n.neurology.org/cgi/collection/myasthenia
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.neurology.org/about/about_the_journal#permissions
Reprints	Information about ordering reprints can be found online: http://n.neurology.org/subscribers/advertise

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2020 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.

