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Practice parameter: The medical treatment of ocular myasthenia (an evidence-based review)

Report of the Quality Standards Subcommittee of the American Academy of Neurology

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ABSTRACT Objective: To perform a systematic review of the relevant literature and to provide evidence-based guidelines for the medical treatment of ocular myasthenia. **Methods:** Medline, EMBASE, and the Cochrane Neuromuscular Disease Group Register were searched for articles of possible relevance to the medical treatment of ocular myasthenia. The titles and abstracts of all articles, as well as the full texts of all potentially relevant manuscripts, were read by both reviewers. Experts in the field were also contacted to identify other published or unpublished literature. All articles were evaluated using predefined criteria to evaluate their methodologic quality. Data from these articles were extracted to address two questions: 1) Are there any effective treatments for symptoms of ocular myasthenia? 2) Are there any treatments that reduce the risk of progression from ocular to generalized myasthenia gravis (MG)? **Results:** A single randomized controlled trial compared the efficacy of intranasal neostigmine to placebo for the treatment of ocular symptoms. Methodologic limitations of this study preclude any firm conclusions. A second randomized controlled trial compared the efficacy of corticotropin with placebo, but outcome was reported in terms of a quantification of the range of eye movements. For this reason, the results of the second study could not be used to address the issues of improvement in ocular symptoms or the risk of progression to generalized MG. This review did not identify any randomized controlled trials addressing the risk of progression to generalized MG but did identify five observational studies reporting the effects of corticosteroids on progression to generalized MG, two of which also reported the effects of azathioprine. **Recommendations:** The absence of high-quality evidence means that it is not possible to make any evidence-based recommendations regarding the effects of cholinesterase inhibitors, corticosteroids, or other immunosuppressive agents with respect to improvement of ocular symptoms. There is similarly an absence of evidence regarding the effects of cholinesterase inhibitors on the risk of progression to generalized myasthenia gravis (MG). Based on data from several observational studies, corticosteroids and azathioprine are of uncertain benefit in terms of their effect on the risk of progression to generalized MG.

INTRODUCTION Background and justification. Myasthenia gravis (MG) is an uncommon neurologic disorder with an estimated prevalence of approximately 5 to 15 per 100,000.¹⁻⁷ Approximately 50% of patients present with purely ocular symptoms (ptosis, diplopia), so-called ocular myasthenia.^{7,8} Between 50% and 60% of those who present with purely ocular symptoms will progress to develop generalized disease,^{7,8} and the vast majority will do so within the first 1 to 2 years.^{7,8}

The treatment of ocular myasthenia, with the goals of alleviating symptoms and preventing progression to generalized MG, is a subject of debate.⁹⁻¹¹ Options for treatment include cholinesterase inhibitors, blepharoplasty, and lid crutches for relief of symptoms as well as immunosuppressive

therapy with corticosteroids and/or a range of corticosteroid-sparing immunosuppressive agents to prevent progression to generalized MG. Opponents of immunosuppressive therapy argue that ocular myasthenia is not life-threatening and, therefore, that symptoms may not justify the potential for significant adverse effects associated with immunosuppressive drugs, that symptoms may be alleviated via other means such as a lid crutches or eye patching, and that there is little evidence to support the use of immunosuppressive therapy either in terms of permanent relief of ocular symptoms or with regard to the risk of progression to generalized disease.⁹ The proponents of immunosuppressive therapy, on the other hand, argue that the symptoms of ocular myasthenia (diplopia and ptosis)

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may impair vision sufficiently to interfere with work and quality of life and that such treatment often eliminates symptoms. Further, the initial presentation with ocular myasthenia affords the opportunity to intervene therapeutically to reduce the likelihood of progression to generalized MG.¹⁰

Clinical questions. Because the primary goals of treatment for ocular myasthenia are 1) to alleviate the symptoms of ocular myasthenia and 2) to prevent or limit the severity of the generalization of the disease, this review was performed to address these two specific questions:

1. Does pharmacologic treatment lead to an improvement in ocular symptoms (diplopia and ptosis)?
2. Is pharmacologic treatment associated with a reduced risk of progression from ocular to generalized MG?

The question of the role of thymectomy in the treatment of ocular myasthenia was not addressed by this review given that the general issue of the benefits of thymectomy in MG has been the subject of a previous practice parameter.¹²

Description of the analytical process. Panel selection and literature review process. Two neurologists with experience in the evaluation and treatment of patients with MG were appointed by the American Academy of Neurology Quality Standards Subcommittee to prepare this review. The Cochrane Neuromuscular Disease Group Register was searched for randomized controlled trials; Medline (1966 to 2004) and EMBASE (1980 to 2004) were also searched for randomized controlled trials, case-control studies, and cohort studies. Search terms included *myasthenia gravis*, *eye*, *ocular*, and *vision*, as well as a series of terms describing specific therapies and specific types of clinical studies. To be included in the review, studies had to meet three criteria: 1) randomized (or quasi-randomized) controlled trial or observational (cohort or case-control) study design; 2) active treatment compared with placebo, no treatment, or some other treatment; and 3) results reported separately for patients with ocular myasthenia (Grade 1) as defined by the Myasthenia Gravis Foundation of America.¹³ Studies reporting outcome in children and adults were considered.

The quality of randomized controlled trials was evaluated in six domains—method of randomization, allocation concealment, patient blinding, observer blinding, explicit inclusion/exclusion criteria, and completeness of follow-up—using a set of predefined criteria. The quality of observational studies was similarly evaluated in three domains—

control for confounding, completeness of follow-up, and observer blinding—using predefined criteria. The method of randomization was graded as adequate (computer-generated random numbers, tables of random numbers, coin toss), unclear (statement made that trial is randomized but method not described), or inadequate (quasi-randomized). Allocation concealment was graded as adequate (identical prenumbered containers prepared by an independent pharmacy of central randomization unit or sequentially numbered opaque sealed envelopes), unclear (no details given of how the next assignment in the sequence was concealed), inadequate (open allocation schedule, unsealed or nonopaque envelopes, alternation, days of week, etc.), or not done. Patient and observer blinding were graded as adequate (method of blinding described and thought to be sufficient to ensure that the investigator was unaware of the treatment received at the time outcome evaluation was performed), unclear (authors state that study was blinded, but details not provided), inadequate (some method used to blind investigators, but technique was unreliable), or not done. Completeness of follow-up was graded as adequate (analysis performed with >80% of patients), unclear (insufficient details provided on withdrawals, dropouts, etc.), inadequate (<80% of patients included in the analysis), or not done. Finally, control for confounding was graded as adequate (multivariate analysis that included at least two factors—age, duration of ocular symptoms before initiation period of follow-up, concomitant immunosuppressive therapy, duration of follow-up after entry into the study, antibody status, presence of abnormalities on repetitive nerve stimulation or single fiber electromyography—or data presented showing that the treatment groups were comparable at baseline with respect to this same set of factors), unclear (authors state that they controlled for confounding, but details not given), inadequate (some effort made to control for confounding, but insufficient number of relevant factors were considered in the analysis), or not done.

ANALYSIS OF EVIDENCE Are cholinesterase inhibitors, corticosteroids, or other immunosuppressive agents effective in improving visual symptoms in ocular myasthenia? **Evidence.** Two randomized controlled trials that included patients with ocular myasthenia were identified.^{14,15} The methodological quality and results of these studies are summarized in table 1 and table E-1 (at www.neurology.org). The first study included 43 patients with ocular myasthenia who were randomly assigned to receive either an 8-day course of corticotropin or placebo in a parallel group design (Class II).¹⁴ The range of ocu-

Table 1 Design characteristics and outcome of randomized controlled trials in ocular myasthenia

Author (year)	Class	n	Participants	Treatment modality	Treatment schedule	Method of randomization	Allocation concealment	Patient blinding	Observer blinding	Follow-up duration (proportion)	RR* (95% CI)
Mount (1964)	II	43	Age and sex not reported	ACTH	290 U over 8 days	Unclear	Adequate	Adequate	Adequate	12 months (72%)	No data for symptomatic improvement
Badrising (1996)	III	3	Age not reported; 60% male	Intranasal neostigmine	4.5 mg TID	Unclear	Unclear	Unclear	Unclear	2 weeks (100%)	3 (0.17-53.7)

*Risk ratio (RR) comparing improvement in ocular symptoms amongst those receiving active treatment compared with those receiving control treatment. ACTH = corticotropin.

lar movement was determined from projections of photographic negatives of each eye in different positions of gaze. By marking the midpoint of the pupil with the eye deviated to the left, to the right, upward, and downward and then connecting these four points with an elliptical curved line, the investigators estimated the area of eye movement. The effectiveness of therapy was determined by comparing the area of eye movement between baseline and post-treatment time points (10 days, 1 month, and 3 months). Results were reported separately for each eye. There was improvement in the area of movement of 10 of 15 right eyes and 14 of 17 left eyes among subjects who received corticotropin. In the placebo-treated patients, there was improvement in 8 of 14 right eyes and 11 of 16 left eyes. There was no evaluation of ocular symptoms or the risk of progression to generalized disease. Because this study did not report outcome in terms of either of the two clinical questions this evidence-based report aimed to answer, it was not possible to include the results in this evidence-based report.

The second study included only three patients with ocular myasthenia (and seven patients with generalized myasthenia) who were randomly assigned to receive a 2-week course of either intranasal neostigmine or placebo in a crossover study design without a washout period (Class III).¹⁵ No primary outcome measure was specified, but the authors reported that ptosis was improved in one of the patients during treatment with neostigmine. The review did not identify any observational studies that reported outcome in terms of improvement in ocular symptoms.

Conclusions. There is only a single randomized controlled trial that has examined the question of whether pharmacotherapy improves symptoms in ocular myasthenia. This study compared the efficacy of intranasal neostigmine to placebo (Class III).¹⁵ No firm conclusions can be drawn from this study given the extremely small sample size ($n = 3$) and other methodologic limitations of the study. There are no studies that examined the efficacy of

pyridostigmine (Mestinon), corticosteroids, or other immunosuppressive agents in improving the symptoms of ocular myasthenia.

Recommendations. Given the absence of evidence, it is not possible to make any evidence-based recommendations regarding the effects of cholinesterase inhibitors, corticosteroids, or other immunosuppressive agents in improving the symptoms of ocular myasthenia.

Are cholinesterase inhibitors, corticosteroids, or other immunosuppressive agents effective in reducing the risk of progression from ocular to generalized MG?

Evidence. Neither of the two randomized controlled trials identified by this review reported outcome in terms of the risk of progression to generalized MG. The review did identify five observational studies that reported the impact of corticosteroids on the risk of progression from ocular to generalized MG,¹⁶⁻²⁰ two of which also examined the effect of azathioprine on the risk of developing generalized MG.^{17,20} The methodologic quality of these studies (table 2) was fairly uniform with adequate follow-up in most, and adequate control for confounding but lack of independent assessment of outcome (Class IV). The point estimates of the risk ratios and odds ratios in the studies that examined the effects of oral corticosteroids showed a benefit in terms of reducing the risk of progression to generalized MG in three studies^{17,18,20} (Class IV), with the confidence interval (CI) spanning unity in two studies,^{16,19} only one of which did not show a benefit (Class IV)¹⁶ (table 2). The two studies that examined the effects of azathioprine similarly showed a beneficial effect on the risk of progression to generalized MG with CIs that did not span unity (Class IV)^{17,20} (table 2).

Conclusions. There are no randomized controlled trials that have examined the efficacy of cholinesterase inhibitors, corticosteroids, or other immunosuppressive agents in reducing the risk of progression to generalized MG. The available studies that have examined this question are all observational and of

Table 2 Design characteristics and outcome of observational studies in ocular myasthenia

Author (year)	Class	n	Participants	Treatment modality	Treatment schedule	Control for confounding	Completeness of follow-up	Patient blinding*	OR†/RR‡ (95% CI)
Papapetropoulos (2003), case-control	IV	28	Mean age 49 y (range 15-80); 61% male	Corticosteroids	Gradual titration to 60 mg QOD and then tapered to lowest dose required (5-10 mg QOD)	Adequate	Adequate; 100%; ≥8 y	Not done	4.3 (0.7-25.9)
Mee (2003), case-control	IV	34	Mean age 55 y (range 18-87); 56% male	Corticosteroids	25 mg QD (mean duration of therapy 33.5 months)	Adequate	Adequate; 100%; mean 4.2 y	Not done	0.02 (0.001-0.16)
Kupersmith (2003), cohort	IV	147	Mean age 50 y (range 2-80); 57% male	Corticosteroids	10 mg QD for 2 days, 20 mg QD for 2 days, dose increased to 50-60 mg QD for 4-5 days, 40 mg QD for 1 week, 30 mg QD for 1 week, 20 mg QD for 1 week, 10 mg/20 mg alternating QD for 1 week, dose further reduced by 2.5 mg QD each week	Adequate	Inadequate; 64%; mean 3.6 y; range ½-16 y	Not done	0.19 (0.07-0.54)
Monsul (2004), cohort	IV	56	Mean age 53 y; sex not reported	Corticosteroids	40-60 mg QD tapered to 2.5-10 mg QD over 3-6 months	Adequate	Adequate; 100% ≥2 y	Not done	0.32 (0.1-1.05)
Sommer (1997), cohort	IV	78	Mean age 51 y (range 10-84); 49% male	Corticosteroids	Maximum dose 52 mg QD (mean duration of therapy 32 months)	Inadequate	Adequate; 100%	Not done	0.19 (0.08-0.46)
Mee (2003), case-control	IV	34	Mean age 55 y (range 18-87); 56% male	Azathioprine	Dose not specified (mean duration of therapy 24 months)	Adequate	Adequate; 100%; mean 3.6 y	Not done	0.04 (0.002-0.72)
Sommer (1997), cohort	IV	78	Mean age 51 y (range 10-84); 49% male	Azathioprine	Maximum dose 145 mg QD (mean duration of therapy 44 months)	Inadequate	Adequate; 100%	Not done	0.27 (0.09-0.82)

*Blinding was not the only factor used to determine whether outcome assessment was regarded as independent (see Appendix 1, Classification of Evidence)

†Exposure odds ratio (OR) comparing those progressing to generalized myasthenia gravis (MG) with those who do not progress, where exposure represents treatment with corticosteroids or azathioprine (OR reported for case-control studies).

‡Risk ratio (RR) comparing risk of progression to generalized MG amongst those on active rather than control therapy (RR reported for cohort studies).

limited quality (Class IV). Three of the five observational studies that examined the efficacy of corticosteroids and both observational studies that examined the efficacy of azathioprine suggest that these agents may be effective in reducing the risk of progression from ocular to generalized MG (Class IV).

Recommendations. For patients with ocular myasthenia, the evidence does not support or refute the use of corticosteroids and/or azathioprine to reduce the risk of progression to generalized MG (Level U). The decision to use such agents should be weighed against the potential for harmful side effects of these medications. Furthermore, it is not possible to make any evidence-based recommendations with regard to the question of whether cholinesterase inhibitors have any effect in reducing the risk of progression to generalized MG. Recommendations cannot be made because of an absence of evidence.

RECOMMENDATIONS FOR FUTURE RESEARCH

There is a need for well-designed, randomized, placebo-controlled studies of the efficacy of cholinesterase inhibitors, corticosteroids, and other immunosuppressive agents. These studies should use clinically relevant outcome measures such as improvement or resolution of ocular symptoms and the risk of progression to generalized MG. These studies should carefully document the frequency and severity of treatment-related side effects because this information will be critical to any cost-benefit analysis of immunosuppressive treatment in ocular myasthenia.

In the absence of randomized controlled trials, well-designed observational studies may shed light on the efficacy of cholinesterase inhibitors, corticosteroids, and other immunosuppressive agents. These studies should adequately control for potentially confounding factors (age, the use of concomi-

tant therapy, the duration of ocular symptoms before entry into the study, the duration of follow-up following entry into the study, antibody status, and the presence of systemic abnormalities of repetitive nerve stimulation or single fiber electromyography), should assess adverse effects, and should ensure that the outcome measure is ascertained in a blinded fashion to minimize bias.

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MISSION STATEMENT OF QSS

The Quality Standards Subcommittee (QSS) of the AAN seeks to develop scientifically sound, clinically relevant Practice Parameters for the practice of neurology. Practice Parameters are strategies for patient management that assist physicians in clinical decision making. A Practice Parameter is one or more specific recommendations based on analysis of evidence of a specific clinical problem. These might include diagnosis, symptoms, treatment, or procedure evaluation.

DISCLAIMER

This statement is provided as an educational service of the American Academy of Neurology (AAN). It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved.

CONFLICT OF INTEREST STATEMENT

The American Academy of Neurology is committed to producing independent, critical and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline projects. Drafts of the guideline have been reviewed by at least three AAN committees, a network of neurologists, *Neurology* peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com. With regards to this specific report, all authors have stated that they have nothing to disclose.

APPENDIX 1

Quality Standards Subcommittee members: Jacqueline French, MD, FAAN (Co-chair); Gary S. Gronseth, MD (Co-chair); Charles E. Argoff, MD; Stephen Ashwal, MD, FAAN (ex-officio); Christopher Bever Jr., MD, MBA, FAAN (facilitator); John D. England, MD, FAAN; Gary M. Franklin, MD, MPH (ex-officio); Gary H. Friday, MD, MPH, FAAN; Larry B. Goldstein, MD, FAAN; Deborah Hirtz, MD (ex-officio); Robert G. Holloway, MD, MPH, FAAN; Donald J. Iverson, MD, FAAN;

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APPENDIX 2

AAN classification of therapeutic evidence

Class I: Prospective, randomized, controlled clinical trial with masked outcome assessment, in a representative population. The following are required:

a) primary outcome(s) clearly defined; b) exclusion/inclusion criteria clearly defined; c) adequate accounting for drop-outs and cross-overs with numbers sufficiently low to have minimal potential for bias; d) relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class II: Prospective matched group cohort study in a representative population with masked outcome assessment that meets a–d above OR a RCT in a representative population that lacks one criteria a–d.

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.*

Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion.

*Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

APPENDIX 3

Classification of recommendations

A = Established as effective, ineffective, or harmful for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)

B = Probably effective, ineffective, or harmful for the given condition in the specified population. (Level B rating requires at least one Class I study or at least two consistent Class II studies.)

C = Possibly effective, ineffective, or harmful for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

U = Data inadequate or conflicting; given current knowledge, treatment is unproven.

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