Acetylcholinesterase inhibitor treatment for myasthenia gravis (Review)

Mehndiratta MM, Pandey S, Kuntzer T

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# Table of Contents

- **Header** .................................................. 1
- **Abstract** .................................................. 1
- **Plain Language Summary** ................................. 2
- **Summary of Findings for the Main Comparison** .......... 2
- **Background** ................................................. 5
- **Objectives** ................................................. 6
- **Methods** .................................................... 6
- **Results** ..................................................... 7
  - Figure 1. ..................................................... 8
  - Figure 2. ..................................................... 8
- **Discussion** .................................................. 9
- **Authors' Conclusions** ..................................... 10
- **Acknowledgements** ......................................... 10
- **References** ................................................. 10
- **Characteristics of Studies** ............................... 12
- **Data and Analyses** ........................................ 15
  - Analysis 1.1. Comparison 1 Intranasal neostigmine versus placebo, Outcome 1 Improved muscle function. .......... 15
- **Appendices** ................................................ 15
- **History** ..................................................... 17
- **Contributions of Authors** ................................ 17
- **declarations of interest** .................................. 17
- **Sources of Support** ........................................ 17
- **Differences between Protocol and Review** ............... 18
Acetylcholinesterase inhibitor treatment for myasthenia gravis

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ABSTRACT

Background
In myasthenia gravis, antibody-mediated blockade of acetylcholine receptors at the neuromuscular junction abolishes the naturally occurring 'safety factor' of synaptic transmission. Acetylcholinesterase inhibitors provide temporary symptomatic treatment of muscle weakness, but there is controversy about their long-term efficacy, dosage and side effects.

Objectives
To evaluate the efficacy of acetylcholinesterase inhibitors in all forms of myasthenia gravis.

Search strategy
We searched The Cochrane Neuromuscular Disease Group Specialized Register (5 October 2009), The Cochrane Central Register of Controlled Trials CENTRAL (The Cochrane Library Issue 3, 2009), MEDLINE (January 1966 to September 2009), EMBASE (January 1980 to September 2009) for randomised controlled trials and quasi-randomised controlled trials regarding usage of acetylcholinesterase inhibitors in myasthenia gravis. Two authors scanned the articles for any study eligible for inclusion. We also contacted the authors and known experts in the field to identify additional published or unpublished data.

Selection criteria
Types of studies: all randomised or quasi-randomised trials.
Types of participants: all myasthenia gravis patients diagnosed by an internationally accepted definition.
Types of interventions: treatment with any form of acetylcholinesterase inhibitor.
Types of outcome measures
Primary outcome measure
Improvement in the presenting symptoms within 1 to 14 days of the start of treatment.
Secondary outcome measures
(1) Improvement in the presenting symptoms more than 14 days after the start of treatment.
(2) Change in impairment measured by a recognised and preferably validated scale, such as the quantitative myasthenia gravis score within 1 to 14 days and more than 14 days after the start of treatment.

(3) Myasthenia Gravis Association of America post-intervention status more than 14 days after start of treatment.

(4) Adverse events: muscarinic side effects.

Data collection and analysis
One author (MM) extracted the data, which were checked by a second author. We contacted study authors for extra information and collected data on adverse effects from the trials.

Main results
We did not find any large randomised or quasi-randomised trials of acetylcholinesterase inhibitors in generalised myasthenia gravis. One cross-over randomised trial using intranasal neostigmine in a total of 10 subjects was only available as an abstract.

Authors’ conclusions
Except for one small and inconclusive trial of intranasal neostigmine, no randomised controlled trial has been conducted on the use of acetylcholinesterase inhibitors in myasthenia gravis. Response to acetylcholinesterase inhibitors in observational studies is so clear that a randomised controlled trial depriving participants in the placebo arm of treatment would be difficult to justify.

PLAIN LANGUAGE SUMMARY
Acetylcholinesterase inhibitor treatment for myasthenia gravis
Myasthenia gravis is a disease in which antibodies directed against acetylcholine receptors block the transmission of nerve impulses to muscles, causing fluctuating muscle weakness and fatigability. Acetylcholinesterase inhibitors, including pyridostigmine, inhibit the breakdown of acetylcholine, the neurotransmitter at the neuromuscular junction. The inhibition produced by these drugs increases the availability of acetylcholine to stimulate the acetylcholine receptors and so facilitates muscle activation and contraction. This can be beneficial in disorders affecting the neuromuscular junction, particularly myasthenia gravis.

The acetylcholinesterase inhibitors are therefore used as symptomatic treatment and have been considered helpful as initial therapy when a person is newly diagnosed with myasthenia gravis. Other treatments proposed for myasthenia gravis include drugs that suppress the immune system, including corticosteroids and azathioprine, and thymectomy (surgical removal of the thymus gland).

Only one small randomised controlled cross-over trial relevant to the treatment of myasthenia gravis was identified. It included three participants with ocular myasthenia gravis and seven with generalised myasthenia gravis who received intranasal neostigmine (an acetylcholinesterase inhibitor) or placebo. This trial did not enable us to draw firm conclusions regarding how effective acetylcholinesterase inhibitors were in preventing progression to more severe myasthenia gravis or in improving muscle weakness for sustained periods. Several observational studies, case reports, case series and daily clinical experience favour the use of acetylcholinesterase inhibitors. Consequently, placebo controlled trials to confirm the effectiveness of the drug are probably not ethical and are unlikely to be performed. At present, the optimal dose and duration of treatment with acetylcholinesterase inhibitors is determined by the balance between clinical improvement and adverse effects. This varies over time and depends on other types of treatment given at the same time to inhibit the underlying autoimmune response.
<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of Participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved muscle function</td>
<td>Placebo</td>
<td>RR 19 (1.25 to 287.92)</td>
<td>20 (1 study)</td>
<td>+OOO very low&lt;sup&gt;3,4,5&lt;/sup&gt;</td>
<td>Abstract only. See text for details</td>
</tr>
<tr>
<td></td>
<td>Intranasal neostigmine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>Placebo</td>
<td>Not estimable</td>
<td>20 (1 study)</td>
<td>+OOO very low</td>
<td>One participant developed borborygmi and fasciculations after using intranasal neostigmine</td>
</tr>
<tr>
<td></td>
<td>Intranasal neostigmine</td>
<td></td>
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</tr>
<tr>
<td>Change in impairment 1 to 14 days after the start of treatment - not reported</td>
<td>Placebo</td>
<td>Not estimable</td>
<td>_</td>
<td>See comment</td>
<td>No data available</td>
</tr>
<tr>
<td></td>
<td>Intranasal neostigmine</td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; RR: risk ratio
<table>
<thead>
<tr>
<th>GRADE Working Group grades of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High quality:</strong> Further research is very unlikely to change our confidence in the estimate of effect.</td>
</tr>
<tr>
<td><strong>Moderate quality:</strong> Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.</td>
</tr>
<tr>
<td><strong>Low quality:</strong> Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.</td>
</tr>
<tr>
<td><strong>Very low quality:</strong> We are very uncertain about the estimate.</td>
</tr>
</tbody>
</table>

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1. Primary outcome not stated but 9 of the 10 participants improved in either ocular, bulbar, breathing or strength symptoms on intranasal neostigmine and 0 of the 10 participants improved on placebo.
2. Number of participants refers to 10 participants in a cross-over trial.
3. Abstract only available so that it is difficult to assess quality.
4. Small sample size reduces confidence in result.
5. Large effect size: 9 of 10 participants improved in at least one muscle function with neostigmine and 0 of 10 with placebo.
Myasthenia gravis (MG) is caused by antibody-mediated autoimmunity against the nicotinic ACh receptor (AChR) at the neuromuscular junction (NMJ) (Drachman 1994; Vincent 2001). MG has a reported annual incidence of about three to four cases per million, and the prevalence is about 60 cases per million (Punga 2009). Treatments for MG include acetylcholinesterase (AChE) inhibitors (AChEIs), corticosteroids, immunosuppressants, intravenous immunoglobulin, plasma exchange and thymectomy. In the literature the terms anticholinesterase / acetylcholinesterase inhibitor have been used interchangeably. We shall use acetylcholinesterase inhibitor in this review. Immunosuppressive agents used for generalised MG, and medical and surgical treatment for ocular myasthenia have been the subjects of five Cochrane reviews (Gajdos 2002; Benatar 2006a; Gajdos 2006; Schneider-Gold 2005; Hart 2007).

Antibody-mediated blockade of NMJ receptors abolishes the naturally occurring ‘safety factor’ of synaptic transmission. The antibodies bind to AChR molecules and speed up breakdown of acetylcholine possibly through a complement mediated effect on the membrane. These mechanisms in turn lead to reduced activation of voltage-gated sodium channels. These channels normally help in the process of depolarization and facilitate the end plate potential to create the muscle action potential (Conti-Fine 2006). Approximately 85% of people with MG have measurable antibody levels against AChRs (Vincent 1985). A significant proportion of people with MG who are ‘seronegative’ for AChR antibodies have antibodies directed against muscle specific kinase (MuSK). MuSK is a NMJ protein that is associated with the AChR and helps in its assembly (Vincent 2003; Conti-Fine 2006; Newsom-Davis 2007).

Jolly noted that symptoms of MG were similar to those of curare poisoning in animals, and suggested that physostigmine might be of therapeutic value, but did not use it (Taylor 1996). Mary B Walker was the first physician to report a MG patient with a rapid response to the AChEI physostigmine (Walker 1934; Walker 1935).

Edrophonium chloride (Tensilon) is a short-acting AChEI used for diagnostic purposes in the Tensilon test. In a positive test, edrophonium improves the function of a weak muscle group (Osserman 1952; Nicholson 1983; Daroff 1986; Benatar 2006). The longer acting AChEIs neostigmine and pyridostigmine are used for symptomatic treatment (Drachman 1994; Engel 2004; Conti-Fine 2006; Skeie 2006).

In patients with MG, the required dose of AChEI and the interval between doses may vary from day to day because the natural history of MG is characterised by exacerbations and remissions (Richman 2003). The most disabling phase may occur years after onset (Grob 1981). About 10% of people with MG experience spontaneous remissions in the 10 years after disease onset, but these are often temporary (Oosterhuis 1981). MG patients rarely experience complete amelioration of weakness when treated with AChEIs, but in some instances it may improve enough for normal activity to be regained. However, corticosteroids appear more effective, particularly in ocular MG (Benatar 2006; Bhanushali 2008). Bhanushali et al recruited 35 participants with ocular myasthenia gravis from a database of 83 people. Eight participants received AChEI only, while six were initially treated with AChEI followed by steroids, and 21 received steroids alone. Improvement was seen in 70% in the steroid treatment group and 29% in the AChEI treatment group. When people with MG require more than the recommended dose of AChEI to achieve adequate relief of their symptoms, they are often judged to be candidates for other modalities of treatment.

Treatment advances over the past 50 years have reduced MG mortality and morbidity markedly (Oosterhuis 1988). The current management of ocular and generalised MG includes AChEIs for temporary improvement, removal of anti-AChR antibodies and nonspecific immunomodulation or immunosuppression (Drachman 1994; Drachman 1994a; Richman 2003). Thymoma is an indication for thymectomy.

The side effects of AChEIs include muscarinic overactivity symptoms such as nausea, vomiting, abdominal cramping, diarrhoea, diaphoresis, increased lacrimation, salivation, tearing and bronchial secretions, bradycardia and atroventricular block. Bradycardia may cause light-headedness or syncope (Gehi 2008). Some nicotinic side effects have also been reported such as muscle cramps and fasciculations. Higher than recommended doses of AChEIs desensitise AChRs and increase weakness resulting in ‘cholinergic crisis’ (Munsat 1984; Richman 2003).

Rarely, patients with a polymorphism in the promoter region of the gene that encodes the catalytic subunit of AChE show acutely exaggerated sensitivity to conventional doses of AChEI (Shapira 2003). Punja et al reported cholinergic adverse effects in the majority of people with MG examined after oral pyridostigmine treatment (Punga 2008). In addition, experimentally, long-term high-dose exposure to AChEIs causes degeneration of the junctional folds, loss of postsynaptic AChRs, and decreased motor end plate potential amplitudes (Engel 1973).

The immediate effects of AChEIs can be so dramatic in MG that some authors consider a therapeutic response part of the definition of the disease. For instance, Simpson et al (Simpson 1966) excluded patients from their study of 295 patients with MG when there was failure of symptoms to respond to therapeutic doses of neostigmine or pyridostigmine. Rowland et al (Rowland 1980) stated that “There is no need for a controlled trial when ptosis disappears before your very eyes or ophthalmoplegia melts into normal motion.” However, some MG patients, such as those with MuSK-antibodies, may show poor tolerance to AChEI agents or lack of improvement (Sanders 2003).
In clinical practice, these AChEI agents are often prescribed for people with MG and the impression is that their usefulness has been adequately established. However, therapeutic studies have been low in methodological quality (Benatar 2006), and so far have failed to establish, for example, the optimal dosage and duration of treatment for these drugs (Rowland 1980).

**OBJECTIVES**

The objective was to evaluate the efficacy of AChEI therapy in all forms of MG.

**METHODS**

Criteria for considering studies for this review

**Types of studies**

We searched for randomised controlled trials (RCTs) or quasi-RCTs of any form of AChEI for generalised MG compared with placebo, no treatment or any other form of treatment. Quasi-RCTs are studies in which treatment allocation is organised in a way which is intended to have the effect of randomisation but which might nevertheless be biased (eg. alternate allocation).

**Types of participants**

Participants of any age with any type and severity of MG, regardless of concomitant use of glucocorticosteroids or immunomodulatory therapies or thymectomy.

**Types of interventions**

We included studies which compared AChEIs with no treatment, placebo or another treatment. We considered any AChEI agent used in the treatment of MG. We examined any randomised or quasi-RCT or branch of a trial evaluating the efficacy of one of these AChEI drugs versus placebo or glucocorticosteroids or both. We did not include studies of AChEI treatment in congenital myasthenic syndromes because the response to AChEIs can vary greatly, being beneficial in one type but harmful in another, such as in congenital myasthenic syndromes with endplate AChE deficiency (Engel 2007).

**Types of outcome measures**

**Primary outcomes**

Improvement in the presenting symptoms within 1 to 14 days of the start of treatment.

**Secondary outcomes**

1. Improvement in the presenting symptoms more than 14 days after the start of treatment.
2. Change in impairment measured by a recognised and preferably validated scale, such as the quantitative myasthenia gravis score within 1 to 14 days and more than 14 days after the start of treatment (Bedlack 2005).
3. Myasthenia Gravis Association of America post-intervention status (Jaretzki 2000) more than 14 days after the start of treatment.
4. Adverse events: we planned to record muscarinic side effects such as abdominal pain, diarrhoea, bronchorrhoea, excessive sweating, bradycardia and cholinergic crisis.

Search methods for identification of studies

We searched the Cochrane Neuromuscular Disease Group Specialized Register (5 October 2009), The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, Issue 3, 2009), MEDLINE (January 1966 to September 2009) and EMBASE (January 1980 to September 2009) for RCTs and quasi-RCTs regarding usage of AChEIs in myasthenia gravis. This review also identified observational (case-control or cohort) studies that report use of AChEI agents for symptomatic treatment of MG. We only used case-control/cohort studies found using the RCT filters. We did not specifically search for these.

We scanned the references of all manuscripts included in the review to identify additional articles of relevance and contacted experts in the field to identify published and unpublished data. We contacted three authors and received a reply from one.

Electronic searches

See Appendix 1, Appendix 2 and Appendix 3.

Data collection and analysis

Selection of studies

Two authors (MMM and SP) read the titles and abstracts of all articles accessed and reviewed the full text of all articles that were of possible relevance. They independently decided which trials fitted the inclusion criteria and graded their methodological quality. The authors resolved disagreements about inclusion criteria by discussion.

Data extraction and management

One author (MMM) extracted the data, which were checked by a second author. We extracted data on study type, interventions, methodological quality, participants, outcomes and adverse events
in a tabular form. We attempted to obtain missing data by contacting authors. In the discussion, we supplemented evidence concerning adverse events obtained from RCTs with information on adverse events reported in the non-randomised studies. At a minimum we took into consideration side effects reported in Meyle’s Side Effects of Drugs (Dukes 2006). In the absence of formal studies of cost-effectiveness, we planned to collect evidence from non-randomised studies.

Assessment of risk of bias in included studies
We completed an assessment of risk of bias on the included study (to the extent it was possible) according to the guidelines in the Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.0 (Higgins 2008). Two authors (MMM and SP) independently assessed randomisation, sequence generation, allocation concealment, blinding (participants, personnel and outcome assessors), incomplete outcome data, selective outcome reporting and other sources of bias.

We made a judgement on each of these criteria relating to the risk of bias, such that a judgement of ‘yes’ indicated a low risk of bias, ‘no’ a high risk of bias and ‘unclear’ an unknown risk of bias.

Measures of treatment effect
With only one included study no meta-analysis was possible. If in the future we identify further studies we will use risk ratios and mean differences to assess outcomes.

Unit of analysis issues
Meta-analysis could not be performed as only a single RCT was identified.

Dealing with missing data
Attempts were made to obtain missing data by contacting authors.

Assessment of heterogeneity
We planned to note whether the meta-analyses showed evidence of heterogeneity. If they did, we planned to investigate its source by repeating the analysis after elimination of trials with a high risk of bias, paying particular attention to allocation concealment.

If there was still heterogeneity, we planned to repeat the analysis using a random-effects model.

Assessment of reporting biases
Since only one trial was found, further assessment of bias than that described above was not possible. Had sufficient studies been available we would have looked for evidence of reporting bias by inspecting forest plots and producing funnel plots.

Data synthesis
Not possible.

Subgroup analysis and investigation of heterogeneity
Not possible.

Sensitivity analysis
Not possible.

R E S U L T S

Description of studies
See: Characteristics of included studies; Characteristics of excluded studies.

Our search revealed only one eligible randomised placebo-controlled double-blind cross-over trial (Badrising 1996). Ten participants, seven with generalised MG and three with ocular MG received 4.5 mg intranasal neostigmine or placebo three times a day for two consecutive weeks preceded by a baseline observation week. All participants scored their ocular, bulbar and global muscle function separately by comparing symptoms with those of the baseline week.

Risk of bias in included studies
The risk of bias was ‘unclear’ for all categories (Figure 1).
Effects of interventions

See: Summary of findings for the main comparison Intranasal neostigmine compared with placebo for myasthenia gravis

Primary outcome

Improvement in generalised MG occurred with intranasal neostigmine in two of five participants with ocular symptoms, four of four with bulbar symptoms and four of seven participants with impaired muscle power. Dyspnoea improved in both the participants with this symptom. One participant experienced no effect. One of three participants with ocular MG had less ptosis with neostigmine. None of the participants showed improvement on placebo (Figure 2, Analysis 1.1).

Figure 1. Risk of bias summary: review authors’ judgements about each risk of bias item for each included study.

Figure 2. Forest plot of comparison: Intranasal neostigmine versus placebo, outcome: 1.1 Improved muscle function.
Secondary outcomes
The secondary outcomes 1–4 could not be assessed as there was no information available.
One participant developed borborygmi and fasciculations after intranasal neostigmine.
No data on cost effectiveness were available.

DISCUSSION
We only identified one RCT. This compared the effect of intranasal neostigmine and placebo in MG. Its sample size was too small to permit robust conclusions regarding the efficacy of AChEI in MG.

See Summary of findings for the main comparison. There is no large randomised trial of AChEI in MG to determine whether or not these drugs are effective.

Overall completeness and applicability of evidence
This study is not of much clinical relevance as the intranasal route is not a commonly used method of treatment and the study duration was only two weeks. However, the results suggested efficacy of the drug over placebo. All relevant types of participants, interventions and outcomes were not investigated. The efficacy of AChEIs by the oral route in the treatment of MG has not yet been evaluated in a RCT.

Quality of the evidence
The risk of bias in the included study was unclear (Figure 1). We have considered observational studies discussed below but the evidence is necessarily of very low quality.

Potential biases in the review process
It is impossible to perform a comprehensive review of observational studies.

Agreements and disagreements with other studies or reviews
This review also identified observational (case-control or cohort) studies that report use of AChEI agents for symptomatic treatment of MG. Herbert Schwarz (Schwarz 1956) was the first to use pyridostigmine, comparing pyridostigmine with neostigmine in 14 participants and concluding that pyridostigmine was more effective over a follow-up period of one year “because of its superior ability to control myasthenic phenomena and the absence of side-effects after prolonged use”. In three participants, the combination of pyridostigmine with neostigmine was more effective than either drug alone. In two participants, no difference was noted between the two drugs and in another two, pyridostigmine was found to be inferior to neostigmine. The author concluded that pyridostigmine alone or in combination with neostigmine is the drug of choice in MG because of the excellent response and lower toxicity. Similar conclusions came from an analysis of 295 participants with MG by Simpson et al (Simpson 1966) who wrote “the drug of choice was determined for those participants who have used more than one of the acetylcholinesterase inhibitor preparations. Of 69 participants who compared neostigmine with pyridostigmine, only 12 preferred neostigmine”. In 1993, 95 participants with MG were followed for 10 years to evaluate the long term effects of prednisolone, thymectomy, or both, and they were compared with a group on AChEI (Seto 1993). Only 15% of the participants on AChEI alone (40 participants, most treated before 1975) had shown improvement 10 years after the onset of MG, but more than 60% of those treated with prednisolone, thymectomy, or both showed improvement. The study was retrospective, and no statistical analysis was performed. In a study of 100 people with MG, epidemiological characteristics, evolution of early signs, delay in diagnosis, yield of diagnostic tests and effects of treatment were reported (Beekman 1997). At the end of the follow-up period, 55% were using an AChEI, 22% prednisolone, 19% azathioprine and 1% cyclosporine. However, more had received these drugs during the course of their disease: 99% AChEI, 49% prednisolone, 28% azathioprine and 4% cyclosporine. Overall, 51% were treated with immunosuppressants at some time. No comparison between groups was performed, but it was reported that 34% of the participants who received pyridostigmine had one or more side effects, which were mostly mild. In another study on late onset MG, which included 113 people, the proportion treated with AChEIs was 41% at treatment onset, and 16% five years later. Surprisingly, the authors assumed that participants on AChEIs “probably had a more benign course and hence were often lost to follow-up” (Slesak 1998).

Zhou Shui-Zhen et al (Zhou 2004) reported that in 77 children, aged from 3 months to 16 years, the prognosis of MG was “good following treatment with acetylcholinesterase inhibitor drugs and steroid treatment”, but no statistical analysis was available to assess the efficacy of AChEI agents.

In a study of 102 participants with generalized MG, 73 were found to be AChR-antibody positive and out of the remaining 29, 14 were MuSK-Ab positive and 22 MuSK-Ab negative (Hatanaka 2005). In comparison to MuSK-Ab-negative or seropositive groups, the proportion of positive edrophonium tests in the MuSK-Ab-positive group was significantly lower. The edrophonium test was positive in only 5 of 10 tested MuSK-Ab positive participants. AChEI nonresponsiveness was noted in 10 of 14 MuSK-Ab-positive participants (71%) which was very high.
in comparison to MuSK-Ab-negative participants (4 of 22 non-responsive (18%)) and seropositive generalised MG participants (13 of 73 non-responsive (18%)). Benefit with pyridostigmine on long-term treatment was also significantly higher in MuSK-Ab-negative and seropositive groups in comparison to participants in the MuSK-Ab-positive group.

In 2006, a Task force of the European Federation of Neurological Societies (EFNS) (Skeie 2006) reported that "there are no placebo controlled randomised studies of these drugs, but case reports, case series and daily clinical experience demonstrate an objective and marked clinical effect. Although there is inadequate evidence for a formal recommendation, the Task force agreed that acetylcholinesterase inhibitor drug should be the first-line treatment of all forms of MG (class IV evidence, good practice point”).

However, it appears that some patients may not respond to AChEIs, and this may be a feature of MuSK-Ab-positive MG patients.

Acetylcholinesterase inhibitors used in people with myasthenia gravis may cause general and systemic side effects. General side effects include bradycardia, colicky pain, hypersalivation and headache. If administered as bromide salts, bromide rash may occur. Systemic adverse effects may be related to cardiovascular, nervous system, gastrointestinal, musculoskeletal or immunological systems (Dukes 2006). The most common systemic side effects are sweating, hypersalivation, lacrimation, bronchial constriction and nightmares. In a study of 100 people with MG, the most common side effects reported were gastrointestinal disorders (30%); and infrequent side effects were hypersalivation (6%), increased perspiration (4%), urgency (3%), increased bronchial secretion (2%), rash (1%) and blurred vision (1%). Four per cent developed tingling sensations in fingers and toes. Only one patient had to stop taking pyridostigmine; this was because of stomach complaints (Beekman 1997).

**AUTHORS’ CONCLUSIONS**

**Implications for practice**

There is no evidence from RCTs to support the common practice of using AChEIs to treat myasthenia gravis.

**Implications for research**

No adequate RCT has been performed but the evidence from observational studies is so strong that none is needed to establish that AChEIs are efficacious.

**ACKNOWLEDGEMENTS**

None.

**REFERENCES**

References to studies included in this review

Badrising 1996  *(published data only)*


References to studies excluded from this review

Beekman 1997  *(published data only)*


Hatanaka 2005  *(published data only)*


Schwarz 1956  *(published data only)*


Seto 1993  *(published data only)*


Slesak 1998  *(published data only)*


Zhou 2004  *(published data only)*


Additional references

Bedlack 2005


Benatar 2006


Acetylcholinesterase inhibitor treatment for myasthenia gravis (Review)
Benatar 2006a
Benatar M, Kaminski H. Medical and surgical treatment for ocular myasthenia. Cochrane Database of Systematic Reviews 2006, Issue 2. [Art. No.: CD005081. DOI: 10.1002/14651858.CD005081.pub2]

Bhanushali 2008

Conti-Fine 2006

Daroff 1986

Drachman 1994

Drachman 1994a

Dukes 2006

Engel 1973

Engel 2004

Engel 2007

Gajdos 2002

Gajdos 2006

Gehi 2008

Grob 1981

Hart 2007

Higgins 2008

Jaretzki 2000

Munsat 1984

Newsum-Davis 2007

Nicholson 1983

Oosterhuis 1981

Oosterhuis 1988

Osserman 1952

Punga 2008

Punga 2009

Richman 2003

Rowland 1980
Sanders 2003

Schneider-Gold 2005

Shapira 2003

Simpson 1966

Skeie 2006

Taylor 1996

Vincent 1985

Vincent 2001

Vincent 2003

Walker 1934

Walker 1935

* Indicates the major publication for the study
**CHARACTERISTICS OF STUDIES**

Characteristics of included studies  *(ordered by study ID)*

**Badrising 1996**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>RCT single centre, cross-over trial</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>10 participants, 7 with generalised MG and 3 with ocular MG were treated</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>4.5 mg neostigmine intranasal or placebo three times a day for two consecutive weeks preceded by a baseline observation week</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Improvement in generalised MG occurred in 2 of 5 participants with ocular symptoms, 4 of 4 with bulbar symptoms and 4 of 7 participants with impaired muscle power. Dyspnoea improved in both participants with this symptom. One participant experienced no effect. 1 of 3 participants with ocular MG had less ptosis with neostigmine. None of the participants showed improvement on placebo</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>One participant developed borborygmi and fasciculations after using intranasal neostigmine. The study could provide data for the primary outcome but only one of the secondary outcomes</td>
</tr>
</tbody>
</table>

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Unclear risk</td>
<td>Study in abstract form. No information regarding sequence generation available</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Unclear risk</td>
<td>Study in abstract form. No information regarding allocation concealment available</td>
</tr>
<tr>
<td>Blinding? All outcomes</td>
<td>Unclear risk</td>
<td>Study in abstract form. Author mentions that the study was blinded but does not describe the method</td>
</tr>
<tr>
<td>Incomplete outcome data addressed? All outcomes</td>
<td>Unclear risk</td>
<td>Study in abstract form. No information regarding outcome data available</td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>Unclear risk</td>
<td>Study in abstract form. No information regarding selective reporting available</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>Unclear risk</td>
<td>Study in abstract form. No information available whether the study was free of other bias</td>
</tr>
</tbody>
</table>

RCT: randomised controlled trial  
MG: myasthenia gravis
### Characteristics of excluded studies  [ordered by study ID]

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beekman 1997</td>
<td>Retrospective study. Thymectomy and immunosuppressive drugs mainly considered over and above AChEIs</td>
</tr>
<tr>
<td>Hatanaka 2005</td>
<td>Differential response to AChEIs in MuSK-Ab participants</td>
</tr>
<tr>
<td>Schwarz 1956</td>
<td>Comparative study of prostigmine and neostigmine in different groups</td>
</tr>
<tr>
<td>Seto 1993</td>
<td>Comparative study of prednisolone, thymectomy and combination</td>
</tr>
<tr>
<td>Slesak 1998</td>
<td>Different immunosuppressive agents compared</td>
</tr>
<tr>
<td>Zhou 2004</td>
<td>Clinical progression and outcome analysed rather than effect of treatment</td>
</tr>
</tbody>
</table>

MG: myasthenia gravis.
AChE: acetylcholinesterase inhibitor.
MuSK-Ab: muscle specific kinase antibodies.
**DATA AND ANALYSES**

Comparison 1. Intranasal neostigmine versus placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Improved muscle function</td>
<td>1</td>
<td>20</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>19.0 [1.25, 287.92]</td>
</tr>
</tbody>
</table>

**Analysis 1.1. Comparison 1 Intranasal neostigmine versus placebo, Outcome 1 Improved muscle function.**

Review: Acetylcholinesterase inhibitor treatment for myasthenia gravis

Comparison: 1 Intranasal neostigmine versus placebo

Outcome: 1 Improved muscle function

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Neostigmine (intranasal) n/N</th>
<th>Placebo n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight %</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Badrising 1996</td>
<td>9/10</td>
<td>0/10</td>
<td>19.00 [1.25, 287.92]</td>
<td>100.0</td>
<td>19.00 [1.25, 287.92]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>10</td>
<td>10</td>
<td>100.0 %</td>
<td>19.00 [1.25, 287.92]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 9 (Neostigmine (intranasal)), 0 (Placebo)

Heterogeneity: not applicable

Test for overall effect: \( Z = 2.12 \) (\( P = 0.034 \))
APPENDICES

Appendix 1. MEDLINE (OvidSP) search strategy

1 randomized controlled trial.pt.
2 controlled clinical trial.pt.
3 randomized.ab.
4 placebo.ab.
5 drug therapy.fs.
6 randomly.ab.
7 trial.ab.
8 groups.ab.
9 or/1-8
10 (animals not (animals and humans)).sh.
11 9 not 10
12 myastheni$.tw.
13 exp myasthenia gravis/
14 Myasthenic Syndromes, Congenital/
15 or/12-14
16 Cholinesterase Inhibitors/
17 Cholinesterase inhibitor$.tw.
18 (anticholinesterase$ or anti-cholinesterase$ or AChE).tw.
19 (AChE1 or AChE inhibitor$1).tw.
20 (Acetylcholine-esterase Inhibitor$1 or acetylcholineesterase inhibitor$1 or acetylcholinesterase inhibitor$1).tw.
21 neostigmine/
22 pyridostigmine bromide/
23 (pyridostigmine or mestinon or neostigmine).tw.
24 or/16-23
25 11 and 15 and 24

Appendix 2. EMBASE (OvidSP) search strategy

1 crossover-procedure/
2 double-blind procedure/
3 randomized controlled trial/
4 single-blind procedure/ (8566)
5 (random$ or factorial$ or crossover$ or cross over$ or cross-over$ or placebo$ or (doubl$ adj blind$) or (singl$ adj blind$) or assign$ or allocat$ or volunteer$).tw.
6 or/1-5
7 human/
8 6 and 7
9 nonhuman/ or human/
10 6 not 9
11 8 or 10
12 myastheni$.tw.
13 exp myasthenia gravis/
14 Myasthenic Syndromes, Congenital/
15 or/12-14
16 Cholinesterase Inhibitor/
17 cholinesterase inhibitor$.tw.
18 (anticholinesterase$ or anti-cholinesterase$ or AChE).tw.
19 (AChE1 or AChE inhibitor$1).tw.
20 (acetylcholine-esterase inhibitor$1 or acetylcholineesterase inhibitor$1 or acetylcholinesterase inhibitor$1).tw.
21 neostigmine/
Appendix 3. The Cochrane Central Register of Controlled Trials search strategy

#1 MeSH descriptor Myasthenia Gravis, this term only
#2 MeSH descriptor Myasthenic Syndromes, Congenital, this term only
#3 (myastheni*)
#4 (#1 OR #2 OR #3)
#5 MeSH descriptor Cholinesterase Inhibitors, this term only
#6 (cholinesterase inhibitor*)
#7 (anticholinesterase* or anti-cholinesterase* or AChE)
#8 AChEI or (ACHE inhibitor*)
#9 (acetylcholinesterase inhibitor*)
#10 (acetylcholine-esterase inhibitor*)
#11 MeSH descriptor Neostigmine, this term only
#12 MeSH descriptor Pyridostigmine Bromide, this term only
#13 pyridostigmine or mestinon or neostigmine
#14 (#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13)
#15 (#4 AND #14)

HISTORY
Protocol first published: Issue 1, 2008
Review first published: Issue 2, 2011

CONTRIBUTIONS OF AUTHORS
First (Man Mohan Mehndiratta) and second (Sanjay Pandey) authors evaluated each paper. Man Mohan Mehndiratta extracted the data and Sanjay Pandey checked it. Both wrote the first draft of the review and sent it to third author (Thierry Kuntzer) who read and incorporated important changes. All the disagreements were resolved by mutual discussion.

DECLARATIONS OF INTEREST
None.

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**Internal sources**

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- Sanjay Pandey, India.
  No financial grant received from any source for this review
- Thierry Kuntzer, Switzerland.
  No financial grant received from any source for this review

**External sources**

- No sources of support supplied

**Differences between protocol and review**

In protocol we stated that ocular myasthenia will not be included. Since the only randomised controlled trial available regarding AChEI included participants with ocular myasthenia, we included those cases of ocular myasthenia recruited in the review.

The sequence of authors has changed.