Published in final edited form as:

Cochrane Database Syst Rev. ; 2: CD006539. doi:10.1002/14651858.CD006539.pub3.

Neuroprotection for treatment of glaucoma in adults

Dayse F. Sena¹ and Kristina Lindsley²

¹Massachusetts Eye and Ear Infirmary, Boston, Massachusetts, USA

²Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Contact address: Dayse F Sena, Massachusetts Eye and Ear Infirmary, 243 Charles St, Connecting Building 703, Boston, Massachusetts, 02114, USA. sena.dayse@gmail.com.

CONTRIBUTIONS OF AUTHORS

First publication of review (2010)

Conceiving the review: DS

Designing the review: DS, KR

Coordinating the review: DS

Data collection for the review

- Designing and undertaking electronic search strategies: Cochrane Eyes and Vision Group
- Screening search results: DS, KR
- Organizing retrieval of papers: DS, KL
- Screening retrieved papers against inclusion criteria: DS, KR, KL
- Providing additional data about papers: DS
- Obtaining and screening data on unpublished studies: DS, KL

Data management for the review: DS, KL

Analysis of data: DS, KL

Writing the review: DS, KL

Update of review (2012)

Data collection for the review

- Designing and undertaking electronic search strategies: Cochrane Eyes and Vision Group
- Screening search results: DS, KL
- Organizing retrieval of papers: KL
- Screening retrieved papers against inclusion criteria: DS, KL
- Providing additional data about papers: DS

Data management for the review: DS, KL

Analysis of data: DS, KL

Writing the review: DS, KL

DECLARATIONS OF INTEREST

None known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We stated the minimum follow-up period to be five years for eligible studies in the protocol (Issue 2, 2007) and first published version (Issue 2, 2010) of this review. In updating the review in 2012, we modified the minimum follow-up period to four years.

NOTES

As of Issue 2, 2010 of *The Cochrane Library*:

- This review replaced the published review: Sycha T, Vass C, Findl O, Bauer P, Groke I, Schmetterer L, Eichler HG. Interventions for normal tension glaucoma. *Cochrane Database of Systematic Reviews* 2003, Issue 1.
- The review by Sycha et al. was withdrawn from publication in the *Database of Systematic Reviews*.

Abstract

Background—Glaucoma is a heterogeneous group of conditions involving progressive damage to the optic nerve, deterioration of retinal ganglion cells and ultimately visual field loss. It is a leading cause of blindness worldwide. Open angle glaucoma (OAG), the commonest form of glaucoma, is a chronic condition that may or may not present with increased intraocular pressure (IOP). Neuroprotection for glaucoma refers to any intervention intended to prevent optic nerve damage or cell death.

Objectives—The objective of this review was to systematically examine the evidence regarding the effectiveness of neuroprotective agents for slowing the progression of OAG in adults.

Search methods—We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (*The Cochrane Library* 2012, Issue 9), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE, (January 1950 to October 2012), EMBASE (January 1980 to October 2012), Latin American and Caribbean Literature on Health Sciences (LILACS) (January 1982 to October 2012), the metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictpr/search/en). We did not use any date or language restrictions in the electronic searches for trials. The electronic databases were last searched on 16 October 2012.

Selection criteria—We included randomized controlled trials (RCTs) in which topical or oral treatments were used for neuroprotection in adults with OAG. Minimum follow up time was four years.

Data collection and analysis—Two review authors independently reviewed titles and abstracts from the literature searches. Full-text copies of potentially relevant studies were obtained and re-evaluated for inclusion. Two review authors independently extracted data related study characteristics, risk of bias, and outcome data. One trial was identified for this review, thus we performed no meta-analysis. Two studies comparing memantine to placebo are currently awaiting classification until additional study details are provided. We documented reasons for excluding studies from the review.

Main results—We included one multi-center RCT of adults with low-pressure glaucoma (Low-pressure Glaucoma Treatment Study, LoGTS) conducted in the USA. The primary outcome was visual field progression after four years of treatment with either brimonidine or timolol. Of the 190 adults enrolled in the study, 12 (6.3%) were excluded after randomization and 77 (40.5%) did not complete four years of follow up. The rate of attrition was unbalanced between groups with more participants dropping out of the brimonidine group (55%) than the timolol group (29%). Of those remaining in the study at four years, participants assigned to brimonidine showed less visual field progression than participants assigned to timolol (5/45 participants in the brimonidine group compared with 18/56 participants in the timolol group). Since no information was available for the 12 participants excluded from the study, or the 77 participants who dropped out of the study, we cannot draw any conclusions from these results as the participants for whom data are missing may or may not have progressed. The mean IOP was similar in both groups at the four-year follow up among those for whom data were available: 14.2 mmHg (standard deviation (SD) = 1.9) among the 43 participants in the brimonidine group and 14.0 mmHg (SD = 2.6) among the 48 participants

in the timolol group. Among the participants who developed progressive visual field loss, IOP reduction of 20% or greater was not significantly different between groups: 4/9 participants in the brimonidine group and 12/31 participants in the timolol group. The study authors did not report data for visual acuity or vertical cup-disc ratio. The most frequent adverse event was ocular allergy to study drug, which occurred more frequently in the brimonidine group (20/99 participants) than the timolol group (3/79 participants).

Authors' conclusions—Although neuroprotective agents are intended to act as pharmacological antagonists to prevent cell death, this trial did not provide evidence that they are effective in preventing retinal ganglion cell death, and thus preserving vision in people with OAG. Further clinical research is needed to determine whether neuroprotective agents may be beneficial for individuals with OAG. Such research should focus outcomes important to patients, such as preservation of vision, and how these outcomes relate to cell death and optic nerve damage. Since OAG is a chronic, progressive disease with variability in symptoms, RCTs designed to measure the effectiveness of neuroprotective agents would require long-term follow up (more than four years) in order to detect clinically meaningful effects.

INDEX TERMS: Medical Subject Headings (MeSH)

Administration, Oral; Administration, Topical; Cell Death; Disease Progression; Glaucoma, Open-Angle [*drug therapy]; Neuroprotective Agents [*administration & dosage]; Optic Nerve; Optic Nerve Diseases [etiology, *prevention & control]; Retinal Ganglion Cells [physiology]

Keywords

MeSH check words: Adult; Humans

PLAIN LANGUAGE SUMMARY

Neuroprotection (medicines to protect nerves involved in sight) for treatment of glaucoma in adults

Glaucoma is a leading cause of blindness worldwide. Glaucoma leads to damage of the optic nerve that worsens over time. Furthermore, cells in the retina that send messages to the optic nerve (retinal ganglion cells (RGCs)) become damaged and die off. This affects normal sight by blocking vision in the middle, sides, or top and bottom of a person's view (loss of visual field).

Medicines exist that might protect the optic nerve from damage and prevent the death of RGCs in people who have glaucoma. Treatment aiming to protect nerves is known as neuroprotection. These medicine(s) are prescribed for glaucoma in the hope of preventing or slowing vision loss by protecting the optic nerve. This review investigated whether these treatments really protect the optic nerve and RGCs, and prevent vision loss.

We found one study that compared two different eye drop treatments, given to two groups of adults with low-pressure glaucoma. One group received brimonidine, a neuroprotective drug. The other group received timolol, a drug that lowers fluid pressure in the eyes. The

researchers followed these two groups for four years to see if either treatment really protected the optic nerve and prevented vision loss.

The study began with 99 people in the brimonidine group and 79 people in the timolol group. After four years, many of the people were no longer in the study: only 45 people (45%) remained in the brimonidine group and 56 (70%) people in the timolol group. Since so many people dropped out, and more drop-outs were taking brimonidine than timolol, it is difficult to interpret the results of the study. Bearing this in mind, after four years of treatment, people in the brimonidine group had kept more of their vision (40/45 or 88%) than those in the timolol group (38/56 or 67%). We do not know the results for the people who dropped out of the study.

Neither group showed any significant change in eye pressure (intraocular pressure). Information about visual sharpness (visual acuity) and the vertical cup-disc ratio (a measure of potential optic nerve damage) was not reported. The most common side-effect was an allergic reaction, in the eye, to the medicines that was experienced by 20/99 (20%) people in the brimonidine group and 3/79 (4%) people in the timolol group.

At present, there is not enough evidence to show whether medicines used to protect the optic nerve and optic cells work.

BACKGROUND

Description of the condition

Glaucoma is part of a heterogeneous group of conditions with multiple etiologies (causes). It is characterized by optic neuropathies that involve structural damage of the optic nerve, death of retinal ganglion cells (RGCs) and defects of the visual field. The optic nerve, formed by the clustering of axons from RGCs located in the ganglion cell layer of the retina, carries visual impulses from the eye to the brain (Gupta 1997). When optic nerve damage or deterioration causes the transfer of information to be disrupted, vision loss occurs.

There are two main categories of primary glaucoma: open angle glaucoma and closed angle glaucoma. Open angle glaucoma (OAG), the commonest form of glaucoma, is a chronic and progressive optic nerve disease that is likely to be affected by multiple genetic and environmental factors (Fan 2010; Hauser 2006a; Hauser 2006b). Open angle glaucoma can be accompanied by increased intraocular pressure (IOP; i.e. pressure inside the eye), as with primary open angle glaucoma (POAG), or normal IOP, as with normal tension glaucoma. Closed angle glaucoma tends to occur suddenly and is beyond the scope of this review.

Epidemiology—Glaucoma is the second leading cause of loss of vision in the world (Quigley 2006; Resnikoff 2004), and an increasingly important public health concern due to the aging world population. The World Health Organization (WHO) estimates that 105 million people have glaucoma world wide and around five million are blind as a consequence (Osborne 2003; Quigley 2006).

Open angle glaucoma is the commonest form of glaucoma in white and African populations, whereas closed angle glaucoma is more common in Asian populations (Bonomi 2002;

Tielsch 1991). In the United States, rates of POAG are reported to be four to five times greater in African-American populations compared to European-derived populations, with the rates for Mexican-Americans in between (Quigley 2001; Tielsch 1991). The prevalence of POAG in Chinese populations is reported to be similar to European-derived populations, but is greater in populations from southern India compared to European-derived populations (Foster 2000; Ramakrishnan 2003). According to a 2004 meta-analysis of population-based studies, OAG affects more than two million individuals in the US, and this number is estimated to increase to more than three million by 2020 because of the rapid aging of the US population (Friedman 2004).

Primary open angle glaucoma is inherited as a complex trait, although environmental factors may also contribute to the disease (Hunter 2005). Ocular hypertension, or high IOP, is considered one of the main risk factors for the development of glaucoma, but is neither necessary nor sufficient to induce the neuropathy. Other risk factors for glaucoma include aging, positive family history of glaucoma in a first-degree relative, central corneal thickness less than 555 microns, high myopia (near-sightedness) and migraine headaches (Anderson 2003; Armaly 1980; Heijl 2002).

Presentation and diagnosis—Open angle glaucoma is usually asymptomatic in the early stages. In some cases the disease may go unnoticed until unrecoverable damage to the optic nerve causes peripheral visual field defects. Without treatment there is a gradual loss of vision over time, ultimately leading to irreversible blindness.

In some patients the degeneration of the optic nerve occurs even if the IOP is within the normal range. This is termed as normal or low tension glaucoma, and is thought to represent a subtype of adult onset OAG. The clinical appearance of the optic nerve in normal tension glaucoma and in primary optic neuropathies is very similar. The distinction between high tension glaucoma (HTG) and low tension glaucoma (LTG) is that patients with HTG present with an IOP of 21 mmHg or more (Kamal 1998). In addition to measuring IOP when testing for glaucoma, it is equally important to perform a visual field test and to visualize the optic nerve to establish the diagnosis of glaucoma. Measurements of the vertical cup-disc ratio, especially in relation to the optic disc size, may be useful in identifying potential cases of glaucoma (Garway-Heath 1998). In some patients, RGC death can clinically be detected by specific visual field loss (Schwartz 2000).

Treatment options—Early detection and treatment of glaucoma is critical as progression of the disease will result in permanent blindness (Shields 1996). Once peripheral or central vision is lost due to glaucoma, no form of treatment can ever restore it. Most treatment for glaucoma continues to be directed at reducing IOP and slowing the disease progression, although it is also known that for many patients the reduction of IOP by itself does not prevent optic nerve damage or visual field loss. Furthermore, studies have shown that the loss of RGCs continues despite lowering IOP (Brubaker 1996; Cockburn 1983). Thus, interventions that only focus on reducing IOP may not be beneficial for some glaucoma patients.

Description of the intervention

Treating disease by preventing neuronal death or deterioration has been termed neuroprotection (Levin 1999). Different compounds, natural and synthetic, have been reported to have neuroprotective activity. These include antioxidants, N-methyl-D-aspartate (NMDA) receptor antagonists, inhibitors of glutamate release, calcium channel blockers, polyamine antagonists and nitric synthase inhibitors, as well as cannabinoids, aspirin, melatonin and vitamin B-12 (Neacsu 2003; Neufeld 1998; Weinreb 1999). Neuroprotection for glaucoma refers to any intervention intended to protect the optic nerve or prevent the death of RGCs. The intervention can operate by affecting cellular factors derived from the optic nerve itself, or by eliminating risk factors external to the nerve (for example, reducing IOP). This review will consider oral and topical neuroprotective agents for all patients with OAG regardless of IOP.

Neuroprotection occurs in addition to, and as a separate effect from, lowering IOP. If we consider the lowering of IOP as an indirect approach for neuroprotection, and therefore a treatment for glaucoma, it may be necessary to supplement additional neuroprotective agents (Schwartz 2000; Weinreb 1999). Other neuroprotective interventions include neutralization of the toxicity of risk factors; for example, the use of glutamate receptor antagonists or inhibitors of nitric oxide synthase can be considered as different approaches to neuroprotection (Neufeld 1997).

How the intervention might work

Glaucoma is now recognized as a neurodegenerative disease associated with long-term progressive RGC death (Bathija 1998; Quigley 1999; Schwartz 1996). Some of the cellular processes that result in the death of RGCs, and are consequently targeted by neuroprotective agents, include: (1) the production of external nerve-derived risk factors such as glutamate and nitric oxide (NO); (2) the deprivation of internal trophic (nutritional) factors in the nerve cells; (3) the loss of intracellular self-repair processes; and (4) the generation of intracellular destructive processes (Schwartz 2000). The rationale for treatment is that by acting as pharmacological antagonists, neuroprotective agents can correct the imbalance between cellular death and survival signals, thus preventing RGC death and optic nerve damage. Also, self-repair via neuroprotection may lead to preventing the loss of RGC function by targeting the various processes involved in causing the death of RGCs. Since the loss of RGCs is the terminal process in the pathophysiology of glaucoma, neuroprotection may be helpful in preserving visual function (Chader 2012) however, there is still no consensus on what precisely causes glaucomatous optic neuropathy.

Why it is important to do this review

Glaucoma is a leading cause of permanent blindness worldwide. As a chronic and progressive condition, glaucoma is amenable to treatment in the early stages of disease. As such, many types of interventions have been proposed for the treatment of glaucoma. There is a published Cochrane review of topical treatments for the prevention of progression or onset of glaucomatous optic neuropathy (Vass 2007). This review aims to evaluate the evidence for the effectiveness of neuroprotective agents in treating glaucoma. Consideration

of the results of this review may lead health policy planners to improve access to prevention programs for glaucoma.

OBJECTIVES

The objective of this review was to systematically examine the evidence regarding the effectiveness of neuroprotective agents, either topical or oral, for slowing the progression of OAG in adults.

METHODS

Criteria for considering studies for this review

Types of studies—We included randomized controlled trials (RCTs) in the review.

Types of participants—We included trials of adults (age 30 years and older) who had OAG with: (1) at least two reliable visual fields demonstrating visual field loss compatible with glaucomatous damage (on the basis of mean deviation and corrected pattern standard deviation or corrected loss variance of Humphrey or Octopus perimetry); and (2) glaucomatous optic nerve changes.

Types of interventions—We included trials that used topical and oral treatments to prevent RGC death. Such agents included:

1. pharmacological antagonists like memantine that inhibit excitotoxicity by binding to NMDA receptors and preventing excitatory activity;
2. alpha 2 adrenergic agonists like brimonidine;
3. calcium channel blocking agents;
4. delivery of brain derived neurotrophic factor (BDNF) to RGC;
5. antioxidant and free radical scavengers;
6. *Ginkgo biloba* extract;
7. nitric oxide synthetase inhibitor.

We included trials that compared any of the above interventions with placebo or no intervention. We also included trials in which any of the above interventions were compared to one another or different regimens of the same intervention.

Types of outcome measures

Primary outcomes: The primary outcome for this review was the proportion of participants who developed any progression of visual field loss at follow up five years post intervention. As a result of longer follow up, one is more likely to detect the effect of lowering IOP (AGIS 1994; Nouri-Mahdavi 2004). For this 2012 update of the review, we included a four-year endpoint for visual field loss.

Secondary outcomes

1. Visual acuity: the proportion of participants in each category of visual acuity on the Snellen scale. A 3-line change in visual acuity was considered clinically important. Where visual acuity was measured with a different scale, we planned to convert it to the Snellen scale.
2. Intraocular pressure: differences in mean IOP in the treated group of patients that developed progressive visual field loss and the untreated group of patients that developed progressive visual field loss.
3. Vertical cup-disc ratio: the proportion of participants with asymmetrical vertical cup-disc ratio greater than 0.3.

Adverse effects: We reported adverse effects related to the particular treatment reported in the studies included. These included any ocular and systemic side-effects that occurred during the treatment period, tolerability, any abnormal ocular finding or any adverse event. An adverse event is defined as any undesirable event occurring in a participant, whether considered related to the study treatment, or not.

Quality of life measures: We planned to summarize any quality of life data reported in the included studies.

Economic data: We planned to summarize any economic data including, but not limited to, cost-effectiveness and cost-benefit analyses reported in the included studies. Economic data include direct costs associated with the treatment follow up, estimated and calculated per participant, and indirect costs such as transportation and expenses necessary to the medical follow up.

Follow up: We included trials with at least five years of follow up to allow for adequate assessment of the effect of neuroprotection on progression of visual field loss. Secondary outcomes were assessed at different follow-up times as available from the included studies. For the 2012 update of the review, we revised the minimum follow-up time to include studies with at least four years of follow up.

Search methods for identification of studies

Electronic searches—We searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2012, Issue 9, part of *The Cochrane Library*. www.thecochranelibrary.com (accessed 16 October 2012), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to October 2012), EMBASE (January 1980 to October 2012), Latin American and Caribbean Literature on Health Sciences (LILACS) (January 1982 to October 2012), the *metaRegister* of Controlled Trials (*mRCT*) (www.controlledtrials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictip/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 16 October 2012.

See: Appendices for details of search strategies for CENTRAL (Appendix 1), MEDLINE (Appendix 2), EMBASE (Appendix 3), LILACS (Appendix 4), *mRCT* (Appendix 5), ClinicalTrials.gov (Appendix 6) and the ICTRP (Appendix 7).

Searching other resources—We manually searched the reference lists of publications from the included study to identify additional trials. We also used the Science Citation Index to screen through studies that cited the included study to identify additional trials.

Data collection and analysis

Selection of studies—Two review authors (DS and KL) independently reviewed titles and abstracts resulting from the literature searches according to the inclusion criteria stated above. We classified the abstracts as ‘definitely exclude’, ‘unsure’ or ‘definitely include’. We obtained full text copies of those in the ‘definitely include’ or ‘unsure’ categories and re-assessed for inclusion. We resolved any disagreements through discussion. When necessary, we contacted the authors of studies labeled as ‘unsure’ for further clarification. For all studies excluded after review of the full text, we documented the reasons for exclusion.

Data extraction and management—Two review authors (DS and KL) independently extracted data from the reports of the one included study using data extraction forms developed by the Cochrane Eyes and Vision Group and adapted for this review. We extracted the following data: country of clinical trial; age and sex of participants; trial design; details of the interventions including doses, route of administration and duration of treatment; follow-up schedule and timing of outcome measurements; participant flow charts and the associated numbers. We also recorded details of the methods used to ascertain outcomes. It was anticipated that certain parameters, such as visual field, would be measured by various methods in different trials. We resolved any discrepancies between the two review authors by discussion. One review author (KL) entered data into RevMan 5 (RevMan 2011), and a second review author (DS) verified the data.

Assessment of risk of bias in included studies—Two review authors (DS and KL) independently assessed the included studies for risk of bias according to guidelines set out in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Methods employed to address the following systematic biases were considered to determine the methodological quality of each study:

- a. Selection bias (sequence generation and allocation concealment): any method of allocation concealment such as centralized randomization or use of sequential opaque envelopes, which provide reasonable confidence that the allocation sequence was concealed from participating physicians and patients, was considered to be ‘low risk of bias’. If the allocation was based on unconcealed lists or envelopes, or there was no qualifying statement describing allocation, we assessed it as ‘unclear risk of bias’.
- b. Masking of participants and care providers with regard to treatment allocation to assess for performance bias.
- c. Masking of outcome assessors to assess for detection bias.

- d. Rates of follow up, reasons for loss to follow up and analysis by the principle of intention-to-treat to assess for attrition bias. We considered a trial to have been analyzed by the principle of intention-to-treat if it analyzed patients as randomized, and included patients for whom no outcome measurements were made, and those who received only part or none of the intended treatment.
- e. Selective outcome reporting was examined to assess for reporting bias.

We resolved any disagreement between the review authors through discussion. We did not need to contact the authors of the included study for additional information related to assessing risk of bias.

Measures of treatment effect—As only one study was included in this review, we performed no meta-analysis. If additional studies are included in the future and meta-analysis is appropriate, we will perform data analysis according to the guidelines in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). We will summarize the dichotomous outcomes using risk ratios. We will summarize continuous outcomes as weighted mean differences. We will use the standardized mean difference to summarize outcomes measured on different scales.

Unit of analysis issues—The unit of analysis was the individual.

Dealing with missing data—We did not contact primary investigators from the included study as data were provided in the published reports. If in the future, additional information is needed we will contact primary investigators of trials for missing data.

Assessment of heterogeneity—As only one study was included in this review, we did not assess for heterogeneity across studies. If additional studies are included in the future, we will assess clinical heterogeneity qualitatively before performing statistical tests. If the participants in the included trials differed in any major or obvious way, we will take note and a decision will be made whether or not to perform meta-analysis. We will examine study characteristics and symmetry of the forest plots. We will interpret a poor degree of overlap in the confidence intervals of the studies as the presence of statistical heterogeneity. The effect estimates across studies will be formally tested for inconsistency using the Chi^2 test and I^2 statistic. If the I^2 statistic is greater than 50%, we will consider there to be substantial statistical heterogeneity.

Assessment of reporting biases—We will use a funnel plot to identify publication bias if ten or more studies are included.

Data synthesis—If additional studies are included in the future, and meta-analysis is warranted, we will synthesize data. If the I^2 statistic is less than 50%, we will interpret it to mean there is no significant statistical heterogeneity. If there is no forest plot asymmetry, we will combine the effect estimates in a meta-analysis using a random-effects model. We will use a fixed-effect model if there is no statistical or clinical heterogeneity and if the number of trials is fewer than three. If the I^2 statistic is greater than 50%, and if there is significant

clinical heterogeneity, we will not conduct a meta-analysis. Instead, we will present a tabulated summary, narrative summary or both.

Sensitivity analysis—We will examine the impact of excluding studies of lower methodological quality, unpublished data and industry-funded studies through sensitivity analyses. We will conduct sensitivity analysis to examine whether the summary effect estimate is influenced by any assumptions that have been made during the review.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.

Results of the search—The original electronic searches run in 2010 revealed 1500 records of articles, abstracts and reviews. We obtained full text copies of 24 potentially relevant records and re-evaluated for inclusion. We also reviewed 11 additional articles identified from screening the reference lists of full text articles.

Of the 35 full text articles that we reviewed, which reported 29 total studies, none met the inclusion criteria for this review. From 29 studies excluded at this stage: six were not randomized trials; six did not involve patients with OAG or did not limit the study to patients with OAG; two did not compare the interventions of interest for this review; 15 were short-term trials, between two hours and four years, and thus did not meet the five year follow-up period required for this review.

Through a search of the ClinicalTrials.gov database, we identified two phase III trials investigating the effects of memantine in patients with chronic glaucoma (NCT00141882; NCT00168350). Both studies were conducted by Allergan, Inc. and are described as randomized, double-masked, placebo-controlled, parallel assignment studies. Data for the first trial were not published, but were reported to show potential beneficial effects by two review papers (Cheung 2008; McKinnon 2008). The results of the second trial failed to corroborate the results of the first trial. Reports of the second trial publicly released by Allergan, Inc. indicated that progression of glaucoma was significantly lower in patients receiving high-dose memantine compared to patients receiving low-dose memantine, but that there was no significant effect compared to patients receiving placebo. These trials are awaiting classification for inclusion in this review because the follow-up times for outcome measurements are unclear.

On October 16, 2012, the electronic search was updated, and 655 new records were identified. At this time, we modified the eligibility criteria for this review to include studies with four or more years of follow up. Previously, only studies with a minimum of five years follow up were eligible for this review. One of the studies identified from the original electronic searches in 2010 became eligible based on the change to four years follow up (LoGTS 2011). Of the 655 new records identified, we excluded 638 by screening titles and abstracts and 17 were further reviewed by the full text. Of the 17 full text articles reviewed,

we excluded 14 and included three in the review. These three records included in the review all reported one study, LoGTS 2011.

Included studies—Ultimately, one study was included in this review (LoGTS 2011). LoGTS 2011 was a multi-center, randomized controlled trial (RCT) of people with low-pressure glaucoma conducted in the USA. Brimonidine, an alpha 2 adrenergic agonist and neuroprotective agent, was compared with timolol, a beta-adrenergic receptor blocker and IOP-lowering agent over a four-year treatment period. Participants and study investigators were masked to treatment groups. All study participants discontinued topical ocular hypotensive medications and there was a washout period prior to beginning study interventions.

The 190 LoGTS 2011 study participants included men and women 30 years of age or older with untreated glaucoma of 21 mmHg or less IOP. After randomization, 12/190 (6%) of the study participants were excluded due to the exclusion of a study site (10 participants), withdrawal of consent (one participant), or because the participant did not meet study eligibility criteria (one participant). Of the 178 participants who remained in the study, 99 were randomized to receive brimonidine tartrate 0.2% monotherapy (Alphagan; Allergan, Inc, Irvine, California, USA) and 79 were randomized to receive timolol maleate 0.5% monotherapy (Timoptic; Merck & Co, West Point, Pennsylvania, USA). Both treatment solutions contained benzalkonium chloride (0.005% (50 ppm) in brimonidine, and 0.01% (100 ppm) in timolol) and were applied bilaterally twice a day. After one year of follow up, 36/99 (36%) participants in the brimonidine group and 8/79 (10%) participants in the timolol group had missing data, and after four years of follow up, 54/99 (55%) participants in the brimonidine group and 23/79 (29%) participants in the timolol group had missing data. The primary outcome of the study was visual field progression.

Excluded studies—Forty-one studies were excluded from the review following full text assessment. The reasons for exclusion included: 12 were not randomized trials; six did not involve patients with OAG, or did not limit the study to patients with OAG; two did not compare the interventions of interest for this review; and 21 were short-term trials, between two hours and three years, and thus did not meet the four year follow-up period required for inclusion in the update of this review.

See: ‘Characteristics of excluded studies’ for further details.

Risk of bias in included studies

Allocation—LoGTS 2011 was a randomized controlled trial. The randomization list was computer-generated and maintained during the study by supplying coded study medications to the clinical centers. For these reasons we assessed the study to have low risk of selection bias related to sequence generation and allocation concealment.

Masking (performance bias and detection bias)—“Full masking of patients, physicians, technicians, and the reading center for visual fields and optic disc photographs” was reported in LoGTS 2011. Further, analysis of visual fields, the primary outcome of the

trial, was masked. For these reasons we assessed the study to have low risks of performance bias and detection bias.

Incomplete outcome data—To assess for risk of attrition bias, we considered:

1. exclusion of participants after randomization;
2. rates of loss to follow up;
3. handling of missing data.

The total number of participants stated as enrolled in the study differs between trial reports (LoGTS 2011). The authors of the design and baseline paper, published in 2005, reported that 190 participants were randomized (number assigned to each treatment group was not specified). In the results paper, published in 2011, the study investigators reported that 178 participants were randomized. We considered 12/190 (6%) participants to have been excluded from the study based on the difference between the 2005 and 2011 study reports. Ideally, participants should not be excluded from the study after randomization.

There were differential losses to follow up between the brimonidine and timolol groups at one and four years of follow up. At one year, 36/99 (36%) participants in the brimonidine group were lost to follow up compared with 8/79 (10%) participants in timolol group (P value < 0.001). Allergy to the study medication was the most common reason for participants dropping out of the study and was greater in the brimonidine group than the timolol group (20/99 participants in brimonidine group compared with 3/79 participants in timolol group). At four years of follow up, 54/99 (55%) participants in brimonidine group and 23/79 (29%) participants in timolol group were lost to follow up (P value < 0.001). In reference to the study design of LoGTS 2011, participants were withdrawn from the study if: their IOP increased to more than 21 mmHg; they had visual field progression; developed allergy or intolerance to a study medication; or the treating ophthalmologist decided that the participants should be discontinued from the study. In order to prevent biased study results, participants should not be excluded from clinical trials by the study investigators and should remain in the study, even if discontinuing study interventions, as part of the intent-to-treat population. The proportion of participants analyzed at the four-year endpoint for the primary visual field outcome was 45/99 (45%) in the brimonidine group and 56/79 (71%) in the timolol group. Thus, data were missing for 89/190 (47%) participants at the four-year follow up and no conclusions can be drawn from this study with regard to neuroprotective effects for the participants with missing data.

Due to the exclusion of participants after randomization, the differential rates of loss to follow up between the study groups, and inadequate handling of missing data, we assessed the study to have high risk of attrition bias.

Selective reporting—The authors of LoGTS 2011 only specified primary and secondary outcomes related to visual field progression and these outcomes differed between the design and baseline paper published in 2005 and the results paper published in 2011. In the 2005 design report, the primary outcome was defined as “significant progression of the same two or more points, on the Humphrey glaucoma change probability maps or by Progressor linear

regression analysis, in 3 consecutive (over an 8-month period) Humphrey 24-2 full threshold fields.” In the 2011 results paper, the outcome for visual field was separated into a primary outcome (“the primary outcome measure was visual field progression in either eye as determined by pointwise linear regression analysis of all study visual fields with Progressor software (Medisoft Inc., Leeds, UK)” and a secondary outcome (“a secondary outcome was visual field progression in either eye evaluated by Humphrey glaucoma change probability maps (GCPM)”).

Although not specified as outcomes for the study, other measures relevant to glaucoma were recorded at follow-up visits such as IOP, visual acuity, changes to optic nerve structure, and cup-disc ratio. Due to the variation in outcome definitions between the published reports, and the non-reporting of other outcomes that were measured and are common for glaucoma trials, we assessed the study to have a high risk of reporting bias.

Other potential sources of bias—Inclusion criteria allowed one eye or both eyes of participants to be included in this study and non-independence of eyes were taken into account when both eyes were included. Although the study was “patient-based”, visual field progression was based on the first eye with progression when both eyes were included. The authors did not report results for progression in the second eye if one eye progressed.

The study was partially funded by Allergan, Inc (Irvine, California) by an unrestricted grant and by providing study medications. Additional funding support included an unrestricted grant from Research to Prevent Blindness, Inc (New York, New York).

Due to issues related to the unit of analysis and sources of funding, we assessed the study to have other potential sources of bias.

Effects of interventions

Brimonidine 0.2% versus timolol 0.5%

Visual field progression: Visual field progression was the primary outcome of LoGTS 2011. Three methods were used to measure visual field progression:

1. Progressor pointwise linear regression analysis;
2. Humphrey glaucoma change probability maps (GCPM) using pattern deviation;
and
3. the 3-omitting method for pointwise linear regression analysis.

Agreement among the three methods for detecting visual field progression was good (overall kappa of 0.628, standard error (SE) = 0.051), with the highest agreement between the Progressor pointwise linear regression and 3-omitting method (kappa of 0.719, SE = 0.068) and the lowest agreement between GCPM and 3-omitting method (kappa of 0.554, SE = 0.079).

At the four-year follow up, 5/45 participants in the brimonidine group and 18/56 participants in the timolol group had visual field progression detected by all three methods (risk ratio (RR) 0.35; 95% confidence interval (CI) 0.14 to 0.86). These results, however, do not take

into account the higher rate of missing data in the brimonidine group compared with the timolol group (data missing for 55% of participants in brimonidine group versus 29% of participants in timolol group).

Visual acuity: Based on visual field progression detected by the Progressor pointwise linear regression analysis method, there were nine participants in the brimonidine group and 31 participants in the timolol group with visual field progression at four years. The Snellen decimal fraction acuity did not significantly change from baseline among the nine brimonidine participants with visual field progression (mean acuity $\pm$ standard deviation (SD) = 0.92 ± 0.21 at baseline and 0.89 ± 0.21 at time of progression, P value > 0.05), whereas the 31 timolol participants with visual field progression had decreased Snellen decimal acuity compared with baseline (mean acuity $\pm$ SD = 0.92 ± 0.21 at baseline and 0.82 ± 0.19 at time of progression, P value 0.008).

The study authors reported that linear regression slopes of the Snellen decimal visual acuity fraction was not statistically different between treatment groups among participants with visual field progression, participants completing the four-year follow up without visual field progression, or participants who did not complete the one-year follow up.

Intraocular pressure: At the four-year follow up, mean IOP was similar in both groups. Mean IOP was 14.2 mmHg (SD = 1.9) among the 43 participants with data available in the brimonidine group and 14.0 mmHg (SD = 2.6) among the 48 participants with data available in the timolol group (mean difference (MD) 0.20 mmHg; 95% CI -0.73 to 1.13). Among the participants who developed progressive visual field loss, IOP reduction of 20% or greater was not significantly different between groups: 4/9 participants in the brimonidine group and 12/31 participants in the timolol group with visual field loss, as determined by Progressor pointwise linear regression analysis, had IOP reduction of 20% or greater at time of progression (RR 1.15; 95% CI 0.49 to 2.70).

Vertical cup-disc ratio: Vertical cup-disc ratio outcomes were not reported by LoGTS 2011.

Adverse effects: The most common adverse effect was ocular allergy to the study medication requiring discontinuation. This adverse effect occurred more with brimonidine (20/99 participants in the brimonidine group discontinued the study for this reason) compared with timolol (3/79 participants in the timolol group discontinued the study for this reason) (RR 5.32; 95% CI 1.64 to 17.26). Six participants, five in the brimonidine group and one in the timolol group, died during the study due to causes unrelated to the study treatments (trauma, myocardial infarction, pulmonary embolism, or complications from bowel surgery).

DISCUSSION

Glaucoma is understood to be a progressive neurodegenerative disease; therefore, medical therapies that focus directly on protecting the optic nerve and preventing the death of RGCs should play a role in the future of glaucoma treatment. Furthermore, studies have shown that

interventions intended only to lower IOP, the most common risk factor for glaucoma progression, are not always effective in preventing visual field loss (Brubaker 1996; Cockburn 1983). Considered by some to be complementary or alternative therapy (NICE Guidelines), neuroprotective treatment for glaucoma endeavors to preserve vision by preventing, slowing or reversing the death of RGCs. For the purpose of examining the evidence according to this definition of neuroprotection, the scope of this review was limited by the inclusion criteria to identify studies with long-term outcomes directly related to visual field defects or to the optic nerve itself.

Summary of main results

After modifying the eligibility criteria of the review to include studies with four or more years of follow up (previously minimum follow-up period was five years), we identified and included one randomized controlled trial comparing brimonidine 0.2% with timolol 0.5% (LoGTS 2011). There were 99 participants randomized to the brimonidine monotherapy group and 79 participants randomized to the timolol monotherapy group. Although results at the four-year follow up suggested brimonidine may slow or prevent visual field progression over timolol (65% decreased risk of visual field progression in the brimonidine group compared with the timolol group; 95% CI 14% to 86%), these results do not take into account the higher rate of missing data in the brimonidine group compared with the timolol group (data missing for 55% of participants in brimonidine group versus 29% of participants in timolol group). Subgroup analyses of participants with visual field progression, participants who completed the study without visual field progression, and participants not completing the study did not show any statistical differences between treatment groups in terms of linear regression slopes of the Snellen decimal visual acuity fraction. At the four-year follow up, mean IOP was similar in both groups. The study did not report vertical cup-disc ratio outcomes. Adverse events occurred more often in the brimonidine group compared with the timolol group, with ocular allergy to the study medication requiring discontinuation being the most common adverse event (5.32 times more in the brimonidine group compared with the timolol group; 95% CI 1.64 to 17.26).

Overall completeness and applicability of evidence

The conditions covered by this review were specific to OAG. The population of interest was narrowed to patients with OAG and did not include patients with only ocular hypertension; thus, the prevention of glaucoma by neuroprotection was not studied by this review. Furthermore, although the treatment of ocular hypertension is a method commonly used to prevent glaucoma and delay vision loss, it should be considered as a separate or adjunct focus for prevention since glaucoma can occur in the absence of increased IOP (AAO Preferred Practice Pattern). Although the study authors of LoGTS 2011 reported visual field outcomes and noted that annual optic nerve photographs were taken, they did not report the correlation between visual field function and optic nerve structure changes in their results paper. It would be interesting to compare optic nerve or retinal nerve fiber layer (RNFL) changes, or both, with the visual field changes.

We defined the primary outcome for this review as the proportion of patients who developed any progression of visual field loss at follow up four years post intervention. This outcome

is consistent with current recommendations for visual function endpoints for ophthalmic studies (Csaky 2008). Although the reduction of IOP has been the outcome of interest in previous research (Danesh-Meyer 2009), it was not the primary focus of this review since lowering IOP alone is not always effective in preventing visual field loss from glaucoma. Mean change in IOP, however, was included as a secondary outcome as it is currently the most common risk factor for glaucoma disease progression and reduction may be beneficial for some patients (Seong 2009). Furthermore, the Collaborative Normal Tension Glaucoma Study (CNTGS 1998) showed that a 30% reduction in IOP had significant benefit and, since that time a 30% reduction in IOP has become the standard of glaucoma care because it is a strong predictor of glaucomatous damage. The study design of LoGTS 2011 allowed participants with any pressure below 21 mmHg to be eligible and IOP data are reported only for those with 20% reduction in IOP and visual field progression.

After one year, 36/99 (36%) participants in the brimonidine group and 8/79 (10%) participants in the timolol group were lost to follow up, and by four years, 54/99 (55%) participants in the brimonidine group and 23/79 (29%) participants in the timolol group were lost to follow up. Due to the great amount of attrition, we cannot conclude that brimonidine is more effective than timolol, since there could have been more progressors in those lost to follow up; therefore, the study results may not apply to individuals in a clinical setting.

Quality of the evidence

As noted above, there was a differential amount of missing data between treatment groups during the study, specifically 55% of participants in the brimonidine group and 29% of participants in the timolol group at four years. The high attrition rate and the difference in attrition between groups introduce a high risk of attrition bias to the study results. In the case of the brimonidine group, data are missing for the majority of participants, making results from this study inconclusive.

The study criteria allowed one eye or both eyes of participants to be included in this study. Although eyes could be interconnected, there was no accounting for non-independence between eyes. Participants were dropped from the study once visual field progression was detected in the first eye.

With regard to reporting bias, the definition of primary and secondary outcomes differed between the published baseline paper and results paper. Results for some outcomes measured were not reported (i.e., cup-disc ratio, visual acuity). The primary outcome as defined in the baseline paper was “significant progression of the same two or more points, on the Humphrey glaucoma change probability maps or by Progressor linear regression analysis, in 3 consecutive (over an 8-month period) Humphrey 24-2 full threshold fields.” The primary outcome as defined in the results paper was “visual field progression in either eye as determined by pointwise linear regression analysis of all study visual fields with Progressor software (Medisoftware Inc., Leeds, UK)”, with the secondary outcome specified as “visual field progression in either eye evaluated by Humphrey glaucoma change probability maps (GCPM).” It was not explained why the outcome definitions were changed. Also results for some outcomes measured were not reported (i.e., cup-disc ratio, visual acuity for all participants, changes to optic nerve structure).

Potential biases in the review process

We attempted to minimize biases in the review process by conducting an extensive, highly sensitive search of the literature. All steps in screening references, extracting data, and assessing studies were done in duplicate by two review authors independently. Along with including content experts and methodologists in the review team, we consulted with glaucoma specialists during the review process.

Agreements and disagreements with other studies or reviews

The endpoint for the primary outcome of this review was set at four years post intervention in order to assess the long-term effects of neuroprotection. As such we excluded 21 potentially relevant trials, ranging from two hours to three years follow-up. Five of these studies reported results for visual outcomes at follow up times two years or greater (Araie 2010; Drance 1998; Garcia-Medina 2011; Koseki 1999; Sawada 1996).

The excluded study with the longest follow up time, of three years, was conducted in Japan and included participants with normal-tension glaucoma (NTG) and mild to moderate damage (Araie 2010). The aim of the study was to determine rates of visual field loss among participants given nipradilol 0.25% versus timolol 0.5%. Of the 158 participants randomized, 146 met the study eligibility criteria and were included in the analyses (72 participants received nipradilol and 74 received timolol). During the study 13/72 (18%) participants in the nipradilol group and 11/74 (15%) participants in the timolol group were withdrawn from the study due to: adverse events; loss to follow up; use of restricted drugs; complications not related to study treatment; and change of address. At three years the study authors concluded that there was no significant difference between treatments in terms of overall visual field loss (mean deviation $\pm$ SE: -0.03 ± 0.06 dB/year in nipradilol group and -0.05 ± 0.06 dB/year in timolol group), but the superior-central subfield and the corrected pattern standard deviation measures were significantly changed within treatment groups compared with baseline (P value = 0.001). Among subgroups of participants with early visual field loss or younger participants, nipradilol showed some benefit in slowing visual field deterioration compared with timolol (mean deviation 0.29 in nipradilol group versus -0.20 in timolol group, P value 0.005 for participants with stage 1 classification; mean deviation 0.15 in nipradilol group versus -0.23 in timolol group, P value 0.039 for participants 40 years or younger).

The study with the second longest follow up time, of two and half years, also was conducted in Japan by Sawada and colleagues (Sawada 1996). It was a randomized, prospective investigation of the effect of oral brovincamine fumarate (Sabromin; 20 mg three times daily) compared to placebo (three times daily) in participants with NTG. Brovincamine fumarate is a calcium channel blocker. In Sawada's study, 28 participants were allocated to receive either brovincamine or placebo. Visual fields were tested every four months using a Humphrey Field Analyzer, with mean follow ups of 39.1 ± 8.7 months for the treatment group and 37.9 ± 10.1 months for the placebo group. In reference to visual fields analysis, 6/14 eyes had visual field improvement and 8/14 had no improvement at all. In the control group, 12/14 had no visual fields changes and 2/14 had an increased visual field loss. This study reported a beneficial effect of brovincamine on visual field in some patients with

NTG; however, the study was not able to provide a definitive conclusion due to the small number of participants included in the trial (14 in the brovincamine-treated group and 14 in the placebo-treated group). We contacted the lead author of this study and he informed us that data for longer follow up times were not collected, since brovincamine became unavailable in Japan.

Koseki 1999 investigated the effect of oral brovincamine on further deterioration of the visual field in participants with NTG. Participants with IOP less than 15 mmHg were randomly assigned to a group receiving oral brovincamine (20 mg three times daily) or to an untreated control group for two years. This study reported that oral brovincamine may retard further visual field deterioration in participants with NTG who have low to normal IOP; however, the study enrolled only a small group of participants (22 in the brovincamine group and 26 in the control group). The authors commented that the slightly better visual field performance during the study period in the brovincamine group may have been attributed to an improvement in cerebral function caused by cerebral vasodilatation rather than a reflection of protection from further glaucomatous damage.

The effects of betaxolol, timolol and pilocarpine on visual functions in patients with OAG were examined in Drance 1998. In total, 68 patients were randomized to receive one of the three treatments and visual outcomes were measured after two years. No significant difference was reported for visual field effects between the treatment groups. The author did note that although all three treatments were effective in reducing IOP, there was dissociation between reduction of IOP and protection of visual function.

The fifth excluded study with visual outcomes at follow-up times two years or greater was Garcia-Medina 2011. Participants with POAG were randomly assigned to one of three groups: oral antioxidant supplementation with omega-3 fatty acids; oral antioxidant supplementation without omega-3 fatty acids; and control. After two years, the authors reported no difference in visual field global indices between the treatment groups. This study was presented as a conference abstract, and the full report has yet to be published. Two potentially relevant phase III trials assessing the effects of memantine in patients with chronic glaucoma were identified during this review (NCT00141882; NCT00168350). Memantine has been theorized to be a promising neuroprotective agent for the treatment of glaucoma that may work by blocking N-methyl-D-aspartate (NMDA) glutamate receptors that may play a role in RGC death (Levin 2008; Lipton 2003). Positive results from preclinical data suggesting a possible clinical benefit of memantine led to clinical trials being done in humans (Hare 2009; Ju 2009; Zhong 2007). Both of the phase III memantine trials were randomized, placebo-controlled trials conducted by Allergan, Inc. To date, Allergan has not published the results of either trial, but has reported via press releases that potential beneficial effects of memantine observed in the first trial were not supported by the second trial (Cheung 2008; McKinnon 2008).

The aim of our systematic review was to summarize the evidence related to the effectiveness of different topical and oral neuroprotective agents for treating OAG in adults. Thus far, our review did not identify any clinical trials that establish evidence for neuroprotective benefits on visual field loss progression in OAG.

AUTHORS' CONCLUSIONS

Implications for practice

Recently, there has been a growing interest in using neuroprotective drugs for the treatment of glaucoma. Neuroprotective agents such as: (1) pharmacological-antagonists that inhibit excitotoxicity by activation, and N-methyl D-aspartate (NMDA) receptors like memantine; (2) alpha 2 adrenergic agonists like brimonidine; (3) calcium channel blocking agents; (4) deliverers of brain derived neurotrophic (BDNF) factor to retinal ganglion cells (RGCs); (5) antioxidants and free radical scavengers; (6) *Ginkgo biloba* extract and (7) nitric oxide synthetase inhibitors have shown promise in preventing or slowing RGC death in preclinical studies. At this time, however, it has not been shown that topical or oral neuroprotective agents are effective in preventing RGC death or in preserving the visual field in patients with open angle glaucoma (OAG).

Implications for research

Although a fair amount of cellular and animal research has been completed, the effectiveness of neuroprotective oral and topical medical therapy for treating OAG in adults remains inconclusive. Further research is needed in this area; however, there are certain barriers for research to overcome (e.g., long-term follow up of participants; selecting patient-important outcomes; variability of disease symptoms, etc.). Potential studies in this area should be designed to measure clinically meaningful outcomes, such as progression of visual field loss, in order to guide clinical practice (Osborne 2009). Further efforts should be directed towards investigating long-term visual field preservation with neuroprotective drugs, since OAG is a chronic, progressive disease.

Another complication in studying the clinical efficacy of neuroprotective agents for glaucoma is that current methodologies used to detect RGC death may not be sufficiently sensitive to show the effect of neuroprotection. Perhaps the ability to prove the efficacy of a neuroprotective drug will depend on the ability to develop and validate new endpoints related to quantitative morphological methods of assessing the retinal ganglion cell layer. The use of sophisticated optical instrumentation and new methodologies to detect cellular events early in the disease process, such as real-time in vivo imaging of an apoptotic event (termed detection of apoptosing retinal cell or DARC), may be useful quantitative measurements to assess neuroprotection in glaucoma patients.

As intraocular pressure (IOP) remains a standard measure in glaucoma research, consideration should be paid to assessing the variation of IOP. For example, one study showed that brimonidine may increase retinal blood flow while reclining, which could affect retinal blood flow autoregulation in OAG (Feke 2008). Evaluating the systemic effects of neuroprotective agents and the role they may play in clinical efficacy and basic mechanisms of action would allow us to determine whether neuroprotection is independent of IOP.

Additionally, in light of the non-significant findings reported from an expensive and time-consuming phase III trial of memantine, it is doubtful whether another long-term RCT on neuroprotection will be undertaken in the absence of promising results from other sources. Futility trials, which are designed to eliminate ineffective interventions from development

rather than determine whether interventions work, have been proposed for neuroprotection research in people with glaucoma (Quigley 2012). Compared with the costs of large-scale (sample size of thousands), long-term (three to five years) RCTs, futility trials could be done with fewer participants and shorter follow-up periods. Quigley estimated that a futility trial for a neuroprotective agent for glaucoma could be done with fewer than 100 participants followed for two years (Quigley 2012). Any neuroprotective agent found not to be futile could then be tested in a phase III RCT.

Acknowledgments

We thank Dr Roberta Scherer, Dr Jayter Silva de Paula and Dr Maria de Lourdes Veronesse Rodrigues for their comments on this review. We also acknowledge Swaroop Vedula, Xue Wang, and Anupa Shah for their assistance with the preparation of this review. We thank Iris Gordon for creating and executing the search strategies and Nancy Fitton for editing the Plain Language Summary.

We acknowledge Kanchan Ramchand for contributions to the first publication of this review (Sena 2010).

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Contract N-01-EY-2-1003, National Eye Institute, National Institutes of Health, USA. 2010 first publication of review
- Grant 1 U01 EY020522-01, National Eye Institute, National Institutes of Health, USA. 2012 update of review

References to studies included in this review

LoGTS 2011 {published data only}. Garudadri CS, Choudhari NS, Rao HL, Senthil S. A randomized trial of brimonidine versus timolol in preserving visual function: results from the Low-pressure Glaucoma Treatment Study. *American Journal of Ophthalmology*. 2011; 152(5):877–8. [PubMed: 22017843] Krupin T. A clinical trial studying neuroprotection in low-pressure glaucoma. *Eye*. 2007; 21(Suppl 1):S51–4. Krupin T. Special considerations in low-tension glaucoma. *Canadian Journal of Ophthalmology*. 2007; 42(3):414–7. [PubMed: 17508037] * Krupin T, Liebmann JM, Greenfield DS, Ritch R, Gardiner S. Low-Pressure Glaucoma Study Group. A randomized trial of brimonidine versus timolol in preserving visual function: results from the Low-Pressure Glaucoma Treatment Study. *American Journal of Ophthalmology*. 2011; 151(4):671–81. [PubMed: 21257146] Krupin T, Liebmann JM, Greenfield DS, Rosenberg LF, Ritch R, Yang JW. The Low-pressure Glaucoma Treatment Study (LoGTS) study design and baseline characteristics of enrolled patients. *Ophthalmology*. 2005; 112(3):376–85. [PubMed: 15745762] Quaranta L, Floriani I. The rate of progression and ocular perfusion pressure in the Low-pressure Glaucoma Treatment Study. *American Journal of Ophthalmology*. 2011; 152(5): 880–1. [PubMed: 22017846]

References to studies excluded from this review

Alm 2004 {published data only}. Alm A, Schoenfelder J, McDermott J. A 5-year, multicenter, open-label, safety study of adjunctive latanoprost therapy for glaucoma. *Archives of Ophthalmology*. 2004; 122(7):957–65. [PubMed: 15249358]

Anderson 2003 {published data only}. Anderson DR, Drance SM, Schulzer M. The Collaborative Normal-Tension Glaucoma Study Group. Factors that predict the benefit of lowering intraocular pressure in normal tension glaucoma. *American Journal of Ophthalmology*. 2003; 136(5):820–9. [PubMed: 14597032]

- Araie 2010{published data only}. Araie M, Shirato S, Yamazaki Y, Kitazawa Y, Ohashi Y. Nipradilol-Timolol Study Group. Visual field loss in patients with normal-tension glaucoma under topical nipradilol or timolol: subgroup and subfield analyses of the nipradilol-timolol study. *Japanese Journal of Ophthalmology*. 2010; 54(4):278–85. [PubMed: 20700793]
- Araie 2011a{published data only}. Araie M. Basic and clinical studies of pressure-independent damaging factors of open angle glaucoma. *Nippon Ganka Gakkai Zasshi*. 2011; 115(3):213–36. [PubMed: 21476309]
- Araie 2011b{published data only}. Araie M, Mayama C. Use of calcium channel blockers for glaucoma. *Progress in Retinal and Eye Research*. 2011; 30(1):54–71. [PubMed: 20933604]
- Blumenthal 2001{published data only}. Blumenthal EZ, Weinreb RN. Assessment of the retinal nerve fiber layer in clinical trials of glaucoma neuroprotection. *Survey of Ophthalmology*. 2001; 45(Suppl 3):S305–12. [PubMed: 11377454]
- Cantor 1997{published data only}. Cantor LB, Burke J. Brimonidine. *Expert Opinion on Investigational Drugs*. 1997; 6(8):1063–83. [PubMed: 15989664]
- Cellini 1999{published data only}. Cellini M, Rossi A, Moretti M. The use of polyunsaturated fatty acids in ocular hypertension. A study with blue-on-yellow perimetry. *Acta Ophthalmologica Scandinavica Supplement*. 1999; 77(229):54–5.
- Chader 2012{published data only}. Chader GJ. Advances in glaucoma treatment and management: neurotrophic agents. *Investigative Ophthalmology and Visual Science*. 2012; 53(5):2501–5. [PubMed: 22562851]
- Changhua 2003{published data only}. Changhua Y, Youqin J. A clinical study of the neuroprotection effect of *Erigeron Breviscapus* Hand-Mazz on glaucomatous patient eyes. *Chinese Ophthalmic Research*. 2003; 21(3):307–11.
- Chen 2006{published data only}. Chen CL, Tseng HY, Wu KY. Rescula as an alternative therapy for beta-blockers with long-term drift effect in glaucoma patients. *Kaohsiung Journal of Medical Sciences*. 2006; 22(6):266–70. [PubMed: 16793563]
- Cho 2010{published data only}. Cho SW, Kim JM, Park KH, Choi CY. Effects of brimonidine 0.2%-timolol 0.5% fixed-combination therapy for glaucoma. *Japanese Journal of Ophthalmology*. 2010; 54 (5):407–13. [PubMed: 21052902]
- CNTGS 1998{published data only}. Anderson DR, Drance SM, Schulzer M. Collaborative Normal-Tension Glaucoma Study Group. Natural history of normal-tension glaucoma. *Ophthalmology*. 2001; 108(2):247–53. [PubMed: 11158794] Collaborative Normal-Tension Glaucoma Study Group. Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. *American Journal of Ophthalmology*. 1998; 126(4):487–97. [PubMed: 9780093] Collaborative Normal-Tension Glaucoma Study Group. The effectiveness of intraocular pressure reduction in the treatment of normal-tension glaucoma. *American Journal of Ophthalmology*. 1998; 126(4):498–505. [PubMed: 9780094]
- Cohen 2005{published data only}. Cohen JS, Khatana AK, Greff LJ. Evolving paradigms in the medical treatment of glaucoma. *International Ophthalmology*. 2005; 25(5–6):253–65. [PubMed: 16532287]
- Cordeiro 2011{published data only}. Cordeiro MF, Levin LA. Clinical evidence for neuroprotection in glaucoma. *American Journal of Ophthalmology*. 2011; 152(5):715–6. [PubMed: 22017839]
- Danesh-Meyer 2011{published data only}. Danesh-Meyer HV. Neuroprotection in glaucoma: recent and future directions. *Current Opinion in Ophthalmology*. 2011; 22(2):78–86. [PubMed: 21252670]
- Drance 1998{published data only}. Drance SM. A comparison of the effects of betaxolol, timolol, and pilocarpine on visual function in patients with open-angle glaucoma. *Journal of Glaucoma*. 1998; 7(4):247–52. [PubMed: 9713782]
- EMGT 2002 {published data only}. Erb C. Early Manifest Glaucoma Trial update 2004. *Der Ophthalmologe*. 2005; 102(3):219–21. [PubMed: 15700191] * Heijl A, Leske MC, Bengtsson B, Hyman L, Bengtsson B, Hussein M, et al. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. *Archives of Ophthalmology*. 2002; 120(10):1268–79. [PubMed: 12365904] Leske MC, Heijl A, Hussein M, Bengtsson B, Hyman L,

- Komaroff E, et al. Factors for glaucoma progression and the effect of treatment. *Archives of Ophthalmology*. 2003; 121(1):48–56. [PubMed: 12523884]
- Evans 2003{published data only}. Bartlett JD, Evans DW. Contrast sensitivity improvements in brimonidine-treated primary open-angle glaucoma patients suggest a neuroprotective mechanism. *Investigative Ophthalmology and Visual Science*. 2002; 43 ARVO E-abstract 2201. * Evans DW, Hosking SL, Gherghel D, Bartlett JD. Contrast sensitivity improves after brimonidine therapy in primary open angle glaucoma: a case for neuroprotection. *British Journal of Ophthalmology*. 2003; 87(12):1463–5. [PubMed: 14660453]
- Frolov 2011{published data only}. Frolov MA, Gonchar PA, Barashkov VI, Kumar V, Morozova NS, Frolov AM, et al. The effect of parenteral citicoline on visual functions and life quality of patients with primary open-angle glaucoma. *Vestnik Oftalmologii*. 2011; 127(5):18–21. [PubMed: 22165093]
- Gandolfi 2004{published data only}. Gandolfi SA, Sangermani C, Cimino L, Ungaro N, Tardini M, Viswanathan A, et al. Is there a non IOP-related effect of brimonidine on visual field progression in human glaucoma? *Investigative Ophthalmology and Visual Science*. 2004; 45 ARVO E-abstract 2298.
- Garcia-Medina 2011{published data only}. Garcia-Medina, JJ.; Garcia-Medina, M.; Garrido-Fernandez, P.; Galvan-Espinosa, J. A 2-year follow-up of antioxidant supplementation in primary open-angle glaucoma. *Ophthalmic Research. Conference: SIRCOVA-ARVO Congress*; 2011; Valencia, Spain. 2011.
- Ge 2008{published data only}. Ge J. Glaucoma neuroprotection--how far is it from a dream to reality. *Chung-Hua Yen Ko Tsa Chih - Chinese Journal of Ophthalmology*. 2008; 44(5):385–7.
- Harris 1995{published data only}. Harris A, Spaeth GL, Sergott RC, Katz LJ, Cantor LB, Martin BJ. Retrobulbar arterial hemodynamic effects of betaxolol and timolol in normal-tension glaucoma. *American Journal of Ophthalmology*. 1995; 120(2):168–75. [PubMed: 7639300]
- Harris 1999{published data only}. Harris A, Arend O, Kagemann L, Garrett M, Chung HS, Martin B. Dorzolamide, visual function and ocular hemodynamics in normal-tension glaucoma. *Journal of Ocular Pharmacology and Therapeutics*. 1999; 15(3):189–97. [PubMed: 10385127]
- Hoyng 2002{published data only}. Hoyng PF, Kitazawa Y. Medical treatment of normal tension glaucoma. *Survey of Ophthalmology*. 2002; 47(Suppl 1):S116–24. [PubMed: 12204707]
- Iester 2004{published data only}. Iester M, Perdicchi A, Venturino G, Rolando M, Traverso CE, Leonardi E, et al. Short-term effects of Bimatoprost in glaucoma patients from an outpatient clinic. *Journal of Ocular Pharmacology and Therapeutics*. 2004; 20(5):393–400. [PubMed: 15650514]
- Inan 2003{published data only}. Inan UU, Ermis SS, Yucel A, Ozturk F. The effects of latanoprost and brimonidine on blood flow velocity of the retrobulbar vessels: a 3-month clinical trial. *Acta Ophthalmologica Scandinavica*. 2003; 81(2):155–60. [PubMed: 12752054]
- Kass 1989{published data only}. Kass MA. Timolol treatment prevents or delays glaucomatous visual field loss in individuals with ocular hypertension: a five-year, randomized, double-masked, clinical trial. *Transactions of the American Ophthalmological Society*. 1989; 87:598–618. [PubMed: 2562546]
- Kjellgren 1995{published data only}. Kjellgren D, Douglas G, Mikelberg FS, Drance SM, Alm A. The short-time effect of latanoprost on the intraocular pressure in normal pressure glaucoma. *Acta Ophthalmologica Scandinavica*. 1995; 73(3):233–6. [PubMed: 7493234]
- Koseki 1999{published data only}. Koseki N, Araie M, Yamagami J, Shirato S, Yamamoto S. Effects of oral brovincamine on visual field damage in patients with normal-tension glaucoma with low-normal intraocular pressure. *Journal of Glaucoma*. 1999; 8(2):117–23. [PubMed: 10209728]
- Liu 2002{published data only}. Liu CJ, Ko YC, Cheng CY, Chiu AW, Chou JC, Hsu WM, et al. Changes in intraocular pressure and ocular perfusion pressure after latanoprost 0.005% or brimonidine tartrate 0.2% in normal-tension glaucoma patients. *Ophthalmology*. 2002; 109(12):2241–7. [PubMed: 12466165]
- Mastropasqua 1998{published data only}. Mastropasqua L, Ciancaglini M, Carpineto P, Verdesca G, Ciafre M, Costagliola C. The effect of 1% apraclonidine on visual field parameters in patients with glaucoma and ocular hypertension. *Annals of Ophthalmology-Glaucoma*. 1998; 30 (1):41–5.

- McCarty 2003{published data only}. McCarty TM, Hardten DR, Anderson NJ, Rosheim K, Samuelson TW. Evaluation of neuroprotective qualities of brimonidine during LASIK. *Ophthalmology*. 2003; 110(8):1615–25. [PubMed: 12917182]
- O'Donoghue 2000{published data only}. O'Donoghue EP. A comparison of latanoprost and dorzolamide in patients with glaucoma and ocular hypertension: a 3 month, randomised study. Ireland Latanoprost Study Group. *British Journal of Ophthalmology*. 2000; 84(6):579–82. [PubMed: 10837379]
- Park 2011{published data only}. Park JW, Kwon HJ, Chung WS, Kim CY, Seong GJ. Short-term effects of Ginkgo biloba extract on peripapillary retinal blood flow in normal tension glaucoma. *Korean Journal of Ophthalmology*. 2011; 25(5):323–8. [PubMed: 21976939]
- Pfeiffer 2002{published data only}. Pfeiffer N. A comparison of the fixed combination of latanoprost and timolol with its individual components. *Graefes Archive for Clinical and Experimental Ophthalmology*. 2002; 240(11):893–9.
- Robin 1993{published data only}. Robin AL. Effect of topical apraclonidine on the frequency of intraocular pressure elevations after combined extracapsular cataract extraction and trabeculectomy. *Ophthalmology*. 1993; 100(5):628–33. [PubMed: 8098520]
- Rulo 1996{published data only}. Rulo AH, Greve EL, Geijssen HC, Hoyng PF. Reduction of intraocular pressure with treatment of latanoprost once daily in patients with normal-pressure glaucoma. *Ophthalmology*. 1996; 103(8):1276–82. [PubMed: 8764799]
- Sawada 1996{published data only}. Sawada A, Kitazawa Y, Yamamoto T, Okabe I, Ichien K. Prevention of visual field defect progression with Brovincamine in eyes with normal-tension glaucoma. *Ophthalmology*. 1996; 103(2):283–8. [PubMed: 8594515]
- Wang 2010{published data only}. Wang Y, Qiu B, Zhang CX, Ou Y, Pang L, Li Z. Neuroprotective effects of yiyanning solution on visual function of glaucoma patient. *Chinese Ophthalmic Research*. 2010; 28 (11):1087–90.

References to studies awaiting assessment

- NCT00141882 {unpublished data only}. NCT00141882. [accessed 13 November 2009 and 12 January 2012] Memantine in patients With chronic glaucoma. clinicaltrials.gov/ct2/show/NCT00141882
- NCT00168350 {unpublished data only}. NCT00168350. [accessed 13 November 2009 and 12 January 2012] Memantine in patients with chronic glaucoma. clinicaltrials.gov/ct2/show/NCT00168350

Additional references

- AAO Preferred Practice Pattern. American Academy of Ophthalmology. Primary open-angle glaucoma, preferred practice pattern. San Francisco: American Academy of Ophthalmology; 2005. Available at: www.aao.org/ppp
- AGIS 1994. Advanced Glaucoma Intervention Study. 2 Visual field test scoring and reliability. *Ophthalmology*. 1994; 101(8):1445–55. [PubMed: 7741836]
- Armaly 1980. Armaly MF, Krueger DE, Maunder L, Becker B, Hetherington J Jr, Kolker AE, et al. Biostatistical analysis of the collaborative glaucoma study. I. Summary report of the risk factors for glaucomatous visual-field defects. *Archives of Ophthalmology*. 1980; 98(12):2163–71. [PubMed: 7447768]
- Bathija 1998. Bathija R, Gupta N, Zangwill L, Weinreb RN. Changing definition of glaucoma. *Journal of Glaucoma*. 1998; 7(3):165–9. [PubMed: 9627855]
- Bonomi 2002. Bonomi L. Epidemiology of angle-closure glaucoma. *Acta Ophthalmologica Scandinavica*. 2002; 80(Suppl 236):11–3. [PubMed: 11906297]
- Brubaker 1996. Brubaker RF. Delayed functional loss in glaucoma. LII Edward Jackson Memorial Lecture. *American Journal of Ophthalmology*. 1996; 121(5):473–83. [PubMed: 8610790]
- Cheung 2008. Cheung W, Guo L, Cordeiro MF. Neuroprotection in glaucoma: drug-based approaches. *Optometry and Vision Science*. 2008; 85(6):406–16. [PubMed: 18521010]

- Cockburn 1983. Cockburn DM. Does reduction of intraocular pressure (IOP) prevent visual field loss in glaucoma? *American Journal of Optometry and Physiological Optics*. 1983; 60(8):705–11. [PubMed: 6624870]
- Csaky 2008. Csaky KG, Richman EA, Ferris FL 3rd. Report from the NEI/FDA Ophthalmic Clinical Trial Design and Endpoints Symposium. *Investigative Ophthalmology and Visual Science*. 2008; 49(2):479–89. [PubMed: 18234989]
- Danesh-Meyer 2009. Danesh-Meyer HV, Levin LA. Neuroprotection: extrapolating from neurologic diseases to the eye. *American Journal of Ophthalmology*. 2009; 148(2):186–91. [PubMed: 19464671]
- Deeks 2011. Deeks, JJ.; Higgins, JPT.; Altman, DG.; Green, S., editors. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*. The Cochrane Collaboration; 2011. Chapter 9: Analysing data and undertaking meta-analyses. Available from www.cochrane-handbook.org (updated March 2011)
- Fan 2010. Fan BJ, Figuieredo Sena DR, Pasquale LR, Grosskreutz CL, Rhee DJ, Chen TC, et al. Lack of association of polymorphisms in elastin with pseudoexfoliation syndrome and glaucoma. *Journal of Glaucoma*. 2010; 19(7):432–6. [PubMed: 20051886]
- Feke 2008. Feke GT, Pasquale LR. Retinal blood flow response to posture change in glaucoma patients compared with healthy subjects. *Ophthalmology*. 2008; 115(2):246–52. [PubMed: 17689612]
- Foster 2000. Foster PJ, Wong JS, Wong E, Chen FG, Machin D, Chew PT. Accuracy of clinical estimates of intraocular pressure in Chinese eyes. *Ophthalmology*. 2000; 107(10):1816–21. [PubMed: 11013179]
- Friedman 2004. Friedman DS, Wolfs RC, O'Colmain BJ, Klein BE, Taylor HR, West S, et al. Prevalence of open-angle glaucoma among adults in the United States. *Archives of Ophthalmology*. 2004; 122(4):532–8. [PubMed: 15078671]
- Garway-Heath 1998. Garway-Heath DF, Ruben ST, Viswanathan A, Hitchings RA. Vertical cup/disc ratio in relation to optic disc size: its value in the assessment of the glaucoma suspect. *British Journal of Ophthalmology*. 1998; 82(10):1118–24. [PubMed: 9924296]
- Glanville 2006. Glanville JM, Lefebvre C, Miles JN, Camosso-Stefinovic J. How to identify randomized controlled trials in MEDLINE: ten years on. *Journal of the Medical Library Association*. 2006; 94(2):130–6. [PubMed: 16636704]
- Gupta 1997. Gupta N, Weinreb RN. New definitions of glaucoma. *Current Opinion in Ophthalmology*. 1997; 8(2):38–41. [PubMed: 10168355]
- Hare 2009. Hare WA, Wheeler L. Experimental glutamatergic excitotoxicity in rabbit retinal ganglion cells: block by memantine. *Investigative Ophthalmology and Visual Science*. 2009; 50(6):2940–8. [PubMed: 19136701]
- Hauser 2006a. Hauser MA, Allingham RR, Linkroum K, Wang J, LaRocque-Abramson K, Figueiredo D, et al. Distribution of WDR36 DNA sequence variants in patients with primary open-angle glaucoma. *Investigative Ophthalmology and Visual Science*. 2006; 47(6):2542–6. [PubMed: 16723468]
- Hauser 2006b. Hauser MA, Sena DF, Flor J, Walter J, Auguste J, Larocque-Abramson K, et al. Distribution of optineurin sequence variations in an ethnically diverse population of low-tension glaucoma patients from the United States. *Journal of Glaucoma*. 2006; 15(5):358–63. [PubMed: 16988596]
- Heijl 2002. Heijl A, Leske MC, Bengtsson B, Hyman L, Bengtsson B, Hussein M, et al. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. *Archives of Ophthalmology*. 2002; 120(10):1268–79. [PubMed: 12365904]
- Higgins 2011. Higgins, JPT.; Altman, DG.; Sterne, JAC.; Green, S. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*. The Cochrane Collaboration; 2011. Chapter 8: Assessing risk of bias in included studies. (updated March 2011) Available from www.cochrane-handbook.org
- Hunter 2005. Hunter DJ. Gene-environment interactions in human diseases. *Nature Reviews Genetics*. 2005; 6(4):287–98.

- Ju 2009. Ju WK, Kim KY, Angert M, Duong-Polk KX, Lindsey JD, Ellisman MH, et al. Memantine blocks mitochondrial OPA1 and cytochrome c release and subsequent apoptotic cell death in glaucomatous retina. *Investigative Ophthalmology and Visual Science*. 2009; 50(2):707–16. [PubMed: 18936150]
- Kamal 1998. Kamal D, Hitchings R. Normal tension glaucoma - a practical approach. *British Journal of Ophthalmology*. 1998; 82(7):835–40. [PubMed: 9924383]
- Levin 1999. Levin LA. Direct and indirect approaches to neuroprotective therapy of glaucomatous optic neuropathy. *Survey of Ophthalmology*. 1999; 43(Suppl 1):S98–101. [PubMed: 10416753]
- Levin 2008. Levin LA, Peeples P. History of neuroprotection and rationale as a therapy for glaucoma. *American Journal of Managed Care*. 2008; 14(1 Suppl):S11–4. [PubMed: 18284310]
- Lipton 2003. Lipton SA. Possible role for memantine in protecting retinal ganglion cells from glaucomatous damage. *Survey of Ophthalmology*. 2003; 48(Suppl 1):S38–46. [PubMed: 12852433]
- McKinnon 2008. McKinnon SJ, Goldberg LD, Peeples P, Walt JG, Bramley TJ. Current management of glaucoma and the need for complete therapy. *American Journal of Managed Care*. 2008; 14(1 Suppl):S20–7. [PubMed: 18284312]
- Neacsu 2003. Neacsu A, Oprean C, Curea M, Tuchila G, Trifu M. Neuroprotection with carotenoids in glaucoma. *Oftalmologia*. 2003; 59(4):70–5. [PubMed: 15083692]
- Neufeld 1997. Neufeld AH, Hernandez MR, Gonzalez M. Nitric oxide synthase in the human glaucomatous optic nerve head. *Archives of Ophthalmology*. 1997; 115(4):497–503. [PubMed: 9109759]
- Neufeld 1998. Neufeld AH. New conceptual approaches for pharmacological neuroprotection in glaucomatous neuronal degeneration. *Journal of Glaucoma*. 1998; 7(6):434–8. [PubMed: 9871868]
- NICE Guidelines. National Collaborating Centre for Acute Care. [accessed Nov 2009] Glaucoma: Diagnosis and management of chronic open angle glaucoma and ocular hypertension. National Institute for Health and Clinical Excellence guideline. Apr. 2009 <http://www.nice.org.uk>
- Nouri-Mahdavi 2004. Nouri-Mahdavi K, Hoffman D, Coleman AL, Liu G, Li G, Gaasterland D, et al. Predictive factors for glaucomatous visual field progression in the Advanced Glaucoma Intervention Study. *Ophthalmology*. 2004; 111(9):1627–35. [PubMed: 15350314]
- Osborne 2003. Osborne NN, Chidlow G, Wood J, Casson R. Some current ideas on the pathogenesis and the role of neuroprotection in glaucomatous optic neuropathy. *European Journal of Ophthalmology*. 2003; 13(Suppl 3):S19–26. [PubMed: 12749673]
- Osborne 2009. Osborne NN. Recent clinical findings with memantine should not mean that the idea of neuroprotection in glaucoma is abandoned. *Acta Ophthalmologica*. 2009; 87(4):450–4. [PubMed: 19141144]
- Quigley 1999. Quigley HA. Neuronal death in glaucoma. *Progress in Retinal and Eye Research*. 1999; 18(1):39–57. [PubMed: 9920498]
- Quigley 2001. Quigley HA, West SK, Rodriguez J, Munoz B, Klein R, Snyder R. The prevalence of glaucoma in a population-based study of Hispanic subjects: Proyecto VER. *Archives of Ophthalmology*. 2001; 119(12):1819–26. [PubMed: 11735794]
- Quigley 2006. Quigley HA. Number of people with glaucoma worldwide in 2010 and 2020. *British Journal of Ophthalmology*. 2006; 90(3):262–7. [PubMed: 16488940]
- Quigley 2012. Quigley HA. Clinical trials for glaucoma neuroprotection are not impossible. *Current Opinion in Ophthalmology*. 2012; 23(2):144–54. [PubMed: 22249238]
- Ramakrishnan 2003. Ramakrishnan R, Nirmalan PK, Krishnadas R, Thulasiraj RD, Tielsch JM, Katz J, et al. Glaucoma in a rural population of southern India: the Aravind comprehensive eye survey. *Ophthalmology*. 2003; 110(8):1484–90. [PubMed: 12917161]
- Resnikoff 2004. Resnikoff S, Pascolini D, Etya'ale D, Kocur I, Pararajasegaram R, Pokharel GP, et al. Global data on visual impairment in the year 2002. *Bulletin of the World Health Organization*. 2004; 82(11):844–51. [PubMed: 15640920]
- RevMan 2011. The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration; 2011.

- Schwartz 1996. Schwartz M, Belkin M, Yoles E, Solomon A. Potential treatment modalities for glaucomatous neuropathy: neuroprotection and neuroregeneration. *Journal of Glaucoma*. 1996; 5(6):427–32. [PubMed: 8946301]
- Schwartz 2000. Schwartz M, Yoles E. Neuroprotection: a new treatment modality for glaucoma? *Current Opinion in Ophthalmology*. 2000; 11(2):107–11. [PubMed: 10848215]
- Seong 2009. Seong GJ, Rho SH, Kim CS, Moon JI, Kook MS, Kim YY, et al. Potential benefit of intraocular pressure reduction in normal-tension glaucoma in South Korea. *Journal of Ocular Pharmacology & Therapeutics*. 2009; 25(1):91–6. [PubMed: 19232005]
- Shields 1996. Shields, MB.; Ritch, R.; Krupin, T. Classification of the glaucomas. In: Ritch, R.; Shields, MB.; Krupin, T., editors. *The glaucomas*. 2. St. Louis: Mosby; 1996.
- Tielsch 1991. Tielsch JM, Sommer A, Katz J, Royall RM, Quigley HA, Javitt J. Racial variations in the prevalence of primary open-angle glaucoma. The Baltimore Eye Survey. *Journal of the American Medical Association*. 1991; 266(3):369–74. [PubMed: 2056646]
- Vass 2007. Vass C, Hirn C, Sycha T, Findl O, Sacu S, Bauer P, Schmetterer L. Medical interventions for primary open angle glaucoma and ocular hypertension. *Cochrane Database of Systematic Reviews*. 2007; (4)10.1002/14651858.CD003167.pub3
- Weinreb 1999. Weinreb RN, Levin LA. Is neuroprotection a viable therapy for glaucoma? *Archives of Ophthalmology*. 1998; 117(11):1540–4. [PubMed: 10565524]
- Zhong 2007. Zhong L, Bradley J, Schubert W, Ahmed E, Adamis AP, Shima DT, et al. Erythropoietin promotes survival of retinal ganglion cells in DBA/2J glaucoma mice. *Investigative Ophthalmology and Visual Science*. 2007; 48(3):1212–8. [PubMed: 17325165]

References to other published versions of this review

- Sena 2010. Sena DF, Ramchand K, Lindsley K. Neuroprotection for treatment of glaucoma in adults. *Cochrane Database of Systematic Reviews*. 2010; (2)10.1002/14651858.CD006539.pub2

APPENDICES

Appendix 1. CENTRAL search strategy

- #1 MeSH descriptor Glaucoma
- #2 glaucoma*
- #3 (#1 OR #2)
- #4 MeSH descriptor Neuroprotective Agents
- #5 neuroprotect*
- #6 MeSH descriptor Retinal Ganglion Cells
- #7 ganglion near cell*
- #8 retina* near cell*
- #9 RGC
- #10 MeSH descriptor Optic Nerve Diseases
- #11 optic near neuropath*
- #12 MeSH descriptor Memantine

*Indicates the major publication for the study

- #13 memantine
- #14 (#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13)
- #15 (#3 AND #14)

Appendix 2. MEDLINE (OvidSP) search strategy

1. randomized controlled trial.pt.
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1–7
9. exp animals/
10. exp humans/
11. 9 not (9 and 10)
12. 8 not 11
13. exp glaucoma/
14. glaucoma\$.tw.
15. or/13–14
16. exp neuroprotective agents/
17. neuroprotect\$.tw.
18. exp retinal ganglion cells/
19. (ganglion adj2 cell\$).tw.
20. (retina\$ adj2 cell\$).tw.
21. RGC.tw.
22. exp optic nerve disease/
23. (optic adj2 neuropath\$).tw.
24. Memantine/
25. memantine.tw.
26. or/16–25
27. 15 and 26

28. 12 and 27

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville et al (Glanville 2006).

Appendix 3. EMBASE (OvidSP) search strategy

1. exp randomized controlled trial/
2. exp randomization/
3. exp double blind procedure/
4. exp single blind procedure/
5. random\$.tw.
6. or/1–5
7. (animal or animal experiment).sh.
8. human.sh.
9. 7 and 8
10. 7 not 9
11. 6 not 10
12. exp clinical trial/
13. (clin\$ adj3 trial\$).tw.
14. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj3 (blind\$ or mask\$)).tw.
15. exp placebo/
16. placebo\$.tw.
17. random\$.tw.
18. exp experimental design/
19. exp crossover procedure/
20. exp control group/
21. exp latin square design/
22. or/12–21
23. 22 not 10
24. 23 not 11
25. exp comparative study/
26. exp evaluation/
27. exp prospective study/

28. (control\$ or prospectiv\$ or volunteer\$).tw.
29. or/25–28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. exp glaucoma/
34. glaucoma\$.tw.
35. or/33–34
36. exp neuroprotective agent/
37. neuroprotect\$.tw.
38. exp retinal ganglion cell/
39. (ganglion adj2 cell\$).tw.
40. (retina\$ adj2 cell\$).tw.
41. RGC.tw.
42. exp optic nerve disease/
43. (optic adj2 neuropath\$).tw.
44. Memantine/
45. memantine.tw.
46. or/36–45
47. 35 and 46
48. 32 and 47

Appendix 4. LILACS search strategy

glaucoma\$ and neuroprotect\$ or memantine

Appendix 5. metaRegister of Controlled Trials search strategy

(neuroprotection or memantine) and glaucoma

Appendix 6. ClinicalTrials.gov search strategy

glaucoma and neuroprotection

glaucoma and memantine

Appendix 7. ICTRP search strategy

glaucoma = Condition AND neuroprotection or memantine = Intervention

DATA AND ANALYSES

This review has no analyses.

Table 1

Characteristics of included studies [ordered by study ID]

LoGTS 2011		
Methods	Study design: parallel-group, randomized controlled trial. Number randomized (total and per group): 190 total participants randomized; number per group not reported Number analyzed (total and per group): Exclusions: 12 total participants randomized; number per group not reported Loss to follow up: at one year, 36/99 (36%) participants in brimonidine group and 8/79 (10%) participants in timolol group were lost to follow up; at four years, 54/99 (55%) participants in brimonidine group and 23/79 (29%) participants in timolol group were lost to follow up Study follow up: planned follow up was four years. Sample size calculation: 64 participants for 80% power to detect outcome differences between groups	
Participants	Country: USA (13 clinical centers). Age (mean $\pm$ SD): 64.9 $\pm$ 10.7 years. Gender: women (n = 113; 59.5%) and men (n = 77; 40.5%). Inclusion criteria: “Men and women, 30 years of age, with previously diagnosed LPG. Untreated LPG with Goldmann applanation IOP 21 mmHg on a diurnal (8 AM, 10 AM, 12 PM, 4 PM) curve before medication randomization.” Exclusion criteria: “History of untreated IOP > 21 mmHg, or a > 4 mmHg difference in IOP between the eyes. Advanced visual field loss (mean deviation, > 15 dB) or threat to fixation. Corrected visual acuity < 20/40 in either eye. Pigmentary or exfoliative glaucoma. History of angle-closure or an occludable angle by gonioscopy. Prior filtration surgery or laser iridotomy. Cataract surgery with posterior chamber lens implant performed less than 1 year before enrollment. Argon laser trabeculoplasty performed less than 6 months previously or for an untreated IOP > 21 mmHg. History or signs of inflammatory eye disease, ocular trauma, or potentially progressive retinal disease. History of allergy or intolerance to topical timolol, brimonidine, or to any components of these medications. Resting pulse rate < 50 beats/minute. Severe, unstable, or uncontrolled cardiovascular, renal, or pulmonary disease. Women pregnant, nursing, or contemplating pregnancy.”	
Interventions	Intervention 1: bilateral treatment with topical brimonidine 0.2% twice daily Intervention 2: bilateral treatment with topical timolol 0.5% twice daily. General procedures for all participants: topical ocular hypotensive medications were discontinued prior to study with appropriate washout periods; no other IOP-lowering agents were allowed during study period	
Outcomes	Primary outcome, as defined in baseline paper: “Significant progression of the same two or more points, on the Humphrey glaucoma change probability maps or by Progressor linear regression analysis, in 3 consecutive (over an 8-month period) Humphrey 24-2 full threshold fields.” Primary outcome, as defined in results paper: “The primary outcome measure was visual field progression in either eye as determined by pointwise linear regression analysis of all study visual fields with Progressor software (Medisoft Inc., Leeds, UK).” Secondary outcome, as defined in results paper: “A secondary outcome was visual field progression in either eye evaluated by Humphrey glaucoma change probability maps (GCPM).” Other measurements taken at baseline and follow-up visits: “patient reported ocular and systemic events; measurement of blood pressure, pulse, best-corrected visual acuity, and IOP; slit-lamp examination; and optic disc evaluation for cup-to-disc ratio and the presence or the absence of disc hemorrhage. Gonioscopy and stereoscopic optic disc photographs are performed at yearly intervals. Humphrey achromatic visual fields (full-threshold 24-2 program) are performed according to protocol guidelines at 4-month intervals after randomization.” Measurements taken “every 4 months with visual fields and yearly optic disc photographs for a minimum of 4 years.” Unit of analysis: individual (patient-based).	
Notes	Study dates: enrollment from June 1998 to August 2000. Funding source(s): Allergan, Inc (Irvine, CA); Chicago Center for Vision Research (Chicago, IL) Conflicts of interest: none reported. Publication language: English.	
Risk of bias		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	“Participants were assigned to 1 of 2 treatment groups, brimonidine tartrate 0.2% or timolol maleate 0.5% (both medications used throughout the study), according to a computer-generated randomization list stratified by center.”
Allocation concealment (selection bias)	Low risk	“The randomization assignment list is maintained and masked study medications are provided directly to the clinical centers by Fountain Valley Pharmacy (Fountain Valley, CA). Optic disc, visual field, and coordinating centers are masked from each other. Data on treatment effects and the randomization code are not provided during the course of the study.”
Masking of participants and	Low risk	“Full masking of patients, physicians, technicians, and the reading center for visual fields and optic disc photographs.”

personnel (performance bias)		
Masking of outcome assessment (detection bias)	Low risk	“Full masking of patients, physicians, technicians, and the reading center for visual fields and optic disc photographs.” “Data Center for masked computer analysis of the visual fields.”
Incomplete outcome data (attrition bias) Exclusion of participants	High risk	“12 randomized patients were subsequently excluded (10 from withdraw of a study site, 1 withdrew consent, and 1 did not meet entry criteria).” “End points requiring withdrawal from the study include the following: (1) treated IOP of more than 21mmHg that is repeatable within 1 month; (2) visual field progression; (3) development of allergy or intolerance to the study medication; (4) clinical decision by the treating ophthalmologist that it is unsafe for the patient to continue in the study.”
Incomplete outcome data (attrition bias) Rates of loss to follow-up	High risk	“Statistically more subjects assigned to brimonidine (36/99, 36.4%) dropped out prior to the year-1 examination than assigned to timolol (8/79, 10.1%) ($P < .001$). The most common reason for discontinuation before the year-1 examination was localized ocular allergy that necessitated discontinuing the study medication in 20 of the 99 (20.2%) brimonidine and 3 of the 79 (3.8%) timolol subjects ($P < .001$).”
Incomplete outcome data (attrition bias) Handling of missing data	High risk	“Collection of data from discontinued patients ceased at their final study visit. Data up to this point were included in the analysis, but discontinued patients were no longer followed as part of the study.”
Selective reporting (reporting bias)	High risk	Definition of primary and secondary outcomes differed between baseline paper and results paper. Results for some outcomes measured were not reported (i.e., cup-disc ratio, visual acuity)
Other bias	High risk	“Publication of this article was supported by an unrestricted grant to the Low-Pressure Glaucoma Study Group from Allergan, Inc, Irvine, California; the Chicago Center for Vision Research, Chicago, Illinois; and an unrestricted grant from Research to Prevent Blindness, Inc, New York, New York (Northwestern University). Study medications were provided by Allergan, Inc. Funding organizations had no role in the design and conduct of the study”

Abbreviations

>: greater than

: greater than or equal to

<: less than

: less than or equal to

IOP: intraocular pressure

LPG: low-pressure glaucoma

Table 2

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Alm 2004	Not the population of interest: 5-year, multicenter, open-label, safety study of adjunctive latanoprost therapy for glaucoma; was excluded because the people included in the study had either POAG or exfoliation glaucoma, and the results were combined for both types
Anderson 2003	Not the population of interest: RCT to study whether the benefit of lowering IOP varies according to certain traits; was excluded because the outcome measured (the benefit of lowering of IOP and how it varies according to certain traits) was not predefined as an outcome of interest of this review. Also the type of treatment used, topical or oral, was not clear
Araie 2010	Short-term trial: RCT of nipradilol versus timolol in patients with normal-tension glaucoma. Participants were followed for three years
Araie 2011a	Not a randomized trial: review of pressure-independent damaging factors of open angle glaucoma
Araie 2011b	Not a randomized trial: review of calcium channel blockers for glaucoma
Blumenthal 2001	Not a randomized trial: review of methods to assess retinal nerve fiber layers for use in trials
Cantor 1997	Not a randomized trial: review of brimonidine; however, none of the studies reported met the inclusion criteria for this review
Cellini 1999	Not a randomized trial: prospective case series of people with ocular hypertension, treated with omega-3 polyunsaturated fatty acids for three months
Chader 2012	Not a randomized trial: review of neurotrophic agents used in glaucoma
Changhua 2003	Short-term trial: evaluation of the neuroprotection effect of <i>Erigeron breviscapus</i> (vant) Hand. Mazz. (EBHM) on patients with IOP controlled-glaucoma. Participants were followed for six months
Chen 2006	Not a randomized trial: prospective case series of patients switched to Rescula after initial treatment with beta-blockers. Patients were followed for one year
Cho 2010	Short-term trial: evaluation of fixed combination of brimonidine 0.2%-timolol 0.5% nipradilol in patients with glaucoma. Participants were followed for up to six months
CNTGS 1998	Not intervention of interest: included any medical and surgical treatment to lower IOP, and was not limited to the agents listed in the protocol
Cohen 2005	Not a randomized trial: review of ocular hypotensive agents for the treatment of glaucoma and ocular hypertension
Cordeiro 2011	Not a randomized trial: editorial discussing clinical trials for neuroprotection in glaucoma
Danesh-Meyer 2011	Not a randomized trial: review of pre-clinical (animal and cellular) studies for neuroprotection in glaucoma
Drance 1998	Short-term trial: randomized, masked study of the effects of betaxolol, timolol, and pilocarpine on visual functions in OAG patients over a 24-month period
EMGT 2002	Not intervention of interest: randomized comparison of the effect of laser trabeculoplasty plus topical betaxolol hydrochloride or no initial treatment; was excluded because laser trabeculoplasty was not a predefined intervention for this review. Also exfoliation glaucoma was not included in this review
Evans 2003	Short-term trial: RCT of timolol versus brimonidine in POAG. Measurements taken at baseline and three months
Frolov 2011	Short-term trial: RCT of 1000 mg/day vs 500 mg/day intravenous citicoline for 10 days
Gandolfi 2004	Short-term trial: RCT of brimonidine 0.2% twice daily vs argon laser trabeculoplasty. Follow up was 18 months after randomization
Garcia-Medina 2011	Short-term trial: placebo-controlled RCT of oral antioxidant supplementation for POAG. follow up was 2 years
Ge 2008	Not a randomized trial: review of pre-clinical (animal and cellular) studies for neuroprotection in glaucoma
Harris 1995	Short-term trial: RCT comparing the effect of selective (betaxolol) and nonselective (timolol) beta-adrenergic blocking drugs on flow velocities in orbital vessels in 13 patients with NTG. Trial period consisted of a 1-month drug treatment double-masked cross-over design, with a 3-week washout before each drug was used
Harris 1999	Short-term trial: RCT to determine how dorzolamide alters visual function and ocular blood flow in patients with NTG. Trial period was 4 weeks
Hoyng 2002	Not a randomized trial: review of medical treatment for NTG.

Study	Reason for exclusion
Iester 2004	Short-term trial: RCT on short-term effects after switching or adding bimatoprost in POAG patients. Measurements taken at baseline, 1 h, 2 h, 1 week, 1 month and 3 months
Inan 2003	Short-term trial: randomized, open-label, parallel study on the effects of latanoprost and brimonidine on blood flow velocity of retrobulbar vessels. Measurements taken at baseline and 3 months
Kass 1989	Not the population of interest: 5-year, randomized, double-masked study on whether treatment with topical timolol maleate was effective in preventing or delaying the onset of glaucomatous visual field loss in participants with ocular hypertension
Kjellgren 1995	Short-term trial: RCT of latanoprost versus placebo given topically twice a day for 14 days in 20 patients with normal pressure glaucoma
Koseki 1999	Short-term trial: RCT to study the effect of oral brovincamine on further deterioration of visual field in patients with NTG over a 2-year period
Liu 2002	Short-term trial: RCT of latanoprost versus brimonidine in patients with NTG. Trial period was 4 weeks
Mastropasqua 1998	Short-term trial: RCT on the effect of acute administration of 1% apraclonidine on visual field parameters. Measurements taken at baseline and 2 h after administration of drops
McCarty 2003	Not the population of interest: RCT evaluating the acute neuroprotective qualities of brimonidine during LASIK, glaucoma patients were excluded
O'Donoghue 2000	Not the population of interest: RCT of latanoprost versus dorzolamide; excluded because the participants included in the study had either POAG or ocular hypertension. Trial period was 3 months
Park 2011	Short-term trial: RCT of <i>Ginkgo biloba</i> extract on ocular blood flow in patients with NTG. Follow up was 2 years
Pfeiffer 2002	Not the population of interest: RCT of latanoprost and timolol; excluded because the participants included in the study had either POAG or ocular hypertension. Trial period was 6 months
Robin 1993	Short-term trial: RCT of 1% topical apraclonidine in reducing IOP following combined cataract surgery in POAG patients. Measurements taken at baseline, 24 h, 1 week, 2 weeks and 4 weeks after surgery
Rulo 1996	Short-term trial: RCT evaluating the IOP-reducing potential and side effects of latanoprost in patients with normal pressure glaucoma. Trial period was 3 weeks for each treatment (50 µg/ml latanoprost once daily, 15 µg/ml latanoprost twice daily, and placebo)
Sawada 1996	Short-term trial: RCT of brovincamine fumarate versus placebo for NTG. Patients were followed for 2.5 years
Wang 2010	Short-term trial: RCT evaluating the protective effect of yiyanning on the optic nerve of POAG patients with controlled IOP. Participants were followed for 12 weeks

Abbreviations

IOP: intraocular pressure

LASIK: laser-assisted in-situ keratomileusis

NTG: normal tension glaucoma

OAG: open angle glaucoma

POAG: primary open angle glaucoma

RCT: randomized controlled trial

Table 3Characteristics of studies awaiting assessment *[ordered by study ID]*

NCT00141882	
Methods	Randomized, double-blind, placebo-controlled, parallel assignment study (phase III trial) Enrollment: 1100 participants.
Participants	Adults (18 to 80 years) with open angle glaucoma. Inclusion criteria: glaucoma damage on examination of the visual field and optic disc; good visual acuity (with glasses if needed)
Interventions	3 arms: high-dose memantine; low-dose memantine; and placebo
Outcomes	Primary outcome: progression of glaucoma.
Notes	Study sponsored by Allergan, Inc. Study was completed as of 18 December 2007. Study information collected from trial registration and press release by Allergan, Inc
NCT00168350	
Methods	Randomized, double-blind, placebo-controlled, parallel assignment study (phase III trial) Enrollment: 1100 participants.
Participants	Adults (18–80 years) with open angle glaucoma. Inclusion criteria: glaucoma damage on examination of the visual field and optic disc; good visual acuity (with glasses if needed)
Interventions	3 arms: high-dose memantine; low-dose memantine; and placebo
Outcomes	Primary outcome: progression of glaucoma.
Notes	Study sponsored by Allergan, Inc. Study was completed as of 18 December 2007. Study information collected from trial registration and press release by Allergan, Inc

It is not clear which trial numbers correspond to the first study completed and the second study completed. Press release only mentions that the results of the second phase III trial differed from the first phase III trial.