Draft Comparative Effectiveness Review

Number XX

Comparative Effectiveness of Treatment for Glaucoma

Prepared for:
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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the State Children's Health Insurance Program (SCHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting Comparative Effectiveness Reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

We welcome comments on this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to epc@ahrq.hhs.gov.

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Structured Abstract

Objectives

Glaucoma is a leading cause of visual impairment and blindness both in the United States and worldwide. Treatment of glaucoma focuses on the reduction of intraocular pressure (IOP), which secondarily prevents the worsening of visual field loss and may therefore prevent visual impairment and blindness. Given developments in the treatment of glaucoma, and the introduction of new surgical modalities, it is appropriate to update the evidence on the safety and effectiveness of glaucoma treatments. The objective of this comparative effectiveness review is to summarize the evidence regarding the safety and effectiveness of medical, laser, and other surgical treatments for open-angle glaucoma in adults.

Data Sources

We searched MEDLINE, EMBASE, LILACS, and CENTRAL through 29 October 2010. No restrictions were used based on date or language of publication. We also conducted a search in MEDLINE and CENTRAL for systematic reviews that address the key questions of interest (from 2009 to 2 March 2011) and screened an existing database of eye and vision systematic reviews to identify relevant open-angle glaucoma systematic reviews published prior to 2009.

Review Methods

Two reviewers independently assessed citations resulting from the searches for primary studies according to the inclusion criteria. Disagreements about eligibility were resolved through discussion among reviewers. Using custom designed and pilot tested data abstraction forms one reviewer assessed the risk of bias and extracted descriptions of the study, including details about the population, intervention(s) and outcomes of interest. A second reviewer verified the data. The results of the searches for systematic reviews were also screened independently by two reviewers. Details about the eligible systematic reviews were abstracted included elements related to the methodological rigor of the systematic reviews.

Results

We identified a total of 23 systematic reviews. Twelve reviews address the comparative effectiveness of medical treatment of open-angle glaucoma, 9 address questions of surgical treatment, and one compares medical versus surgical treatments for open-angle glaucoma. One additional review addressed the comparative effectiveness of surgical versus surgical and medical versus surgical treatments for open-angle glaucoma. In addition, we identified a total of 66 RCTs and 11 observational studies addressing adverse effects (8 medical treatment and 3 surgical treatment). We identified no studies that evaluated either medical or surgical glaucoma treatments with regard to their impact on visual impairment. We also found no good evidence linking treatment with relative improvements in patient-reported outcomes. No studies addressed the possible link between intermediate treatment outcomes (iIOP, changes in optic nerve structure or visual field) and the final outcomes of visual impairment or patient reported outcomes. There is clear evidence, however, that both medical and surgical treatments can lower IOP and reduce the risk of progression by both visual field and optic nerve criteria. Among medical treatments, the prostaglandin agents are superior to other classes of medication. While

laser trabeculoplasty decreases intraocular pressure, the laser technology used does not appear to make a difference in pressure lowering. With regard to incisional surgeries, trabeculectomy provides more pressure lowering than the class of non-penetrating procedures. As expected, incisional surgeries produce more significant side effects than do medical treatments.

Conclusions

We did not find evidence addressing direct or indirect links between glaucoma treatment and visual impairment or patient-reported outcomes. This should be an area of focus in future glaucoma trials, but trials would need to be of adequate size and duration to detect differences between groups. However, we did find that a number of medical and surgical treatments clearly lower IOP and can prevent visual field loss and optic nerve damage. While we found direct comparisons between some treatments, there are significant gaps in our knowledge of comparative effectiveness that represent areas in which future research could be directed.

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Executive Summary

Background

Glaucoma is a leading cause of visual impairment and blindness both in the United States and worldwide. It is estimated to affect 60.5 million people worldwide.[1] Glaucoma is defined as an acquired disease of the optic nerve (neuropathy), characterized by a typical appearance of the optic nerve and by visual field defects that correspond to the areas of optic nerve structural damage. Depending upon whether the optic nerve damage is associated with an open or closed appearance to the drainage channels for aqueous humor in the front of the eye, the glaucoma is referred to as open-angle (the subject of this report) or closed-angle.

Mild glaucoma damage to the optic nerve may be asymptomatic, but as the damage worsens, the patient begins to have difficulty with peripheral vision, contrast sensitivity, glare, and moving from light to dark and dark to light, symptoms that affect day to day function and quality of life. In its most severe form, glaucoma results in total, irreversible blindness.

Although deficient blood supply to the optic nerve, inadequate structural support for the neurons that make up the optic nerve, and insufficient supplies of neurotrophins needed to maintain the health of the optic nerve have been hypothesized as risk factors for glaucoma, experimental models and other evidence from human participants have shown that elevated intraocular pressure (IOP) results in damage to the optic nerve in a pattern characteristic of glaucoma.[2] Furthermore, studies have demonstrated correlations between the level of IOP and the risk of having glaucoma as well as the worsening of glaucoma once present. Other studies have demonstrated that lowering IOP, even from "normal levels" reduces both the incidence of glaucoma in individuals who do not have glaucoma damage but are at high risk for its development, and the rate of progression of glaucoma in individuals with established glaucoma.[3-5] Therefore, the treatments for glaucoma today all center around the reduction of IOP, which secondarily prevents the worsening of visual field loss and may therefore prevent visual impairment and blindness.

Treatments for Open-Angle glaucoma

Decisions regarding when to initiate treatment to lower IOP, and what treatment modality to use for lowering IOP in a given individual, are fraught with uncertainty. Medical, laser, and incisional surgical treatments are used to treat glaucoma. The most common currently used medical treatment includes several classes of eye drops including prostaglandin analogs, beta-adrenergic antagonists, oral and topical carbonic anhydrase inhibitors, and alpha-adrenergic agonists. Laser trabeculoplasty is an office-based procedure that lowers the IOP by increasing the outflow of aqueous humor from the eye. Incisional surgery to lower the IOP comprises procedures that have been performed for decades, such as trabeculectomy and aqueous drainage device surgery, as well as a host of newer procedures, such as non-penetrating deep sclerectomy, canaloplasty, endoscopic cyclophotocoagulation, and alternative methods of trabecular bypass.

Methods

Topic Development

The Agency for Healthcare Quality and Research (AHRQ) requested the formulation and refinement of the Comparative Effectiveness Review (CER) topic "Effectiveness of screening and treatment for glaucoma."

In consultation with AHRQ, we identified a small group of stakeholders to serve as members of a Key Informant Group. The Key Informant Group helped shape the key questions relevant to the topic by providing input regarding the populations and clinical subgroups, interventions, and outcomes of interest to clinicians, policy makers, payers, and consumers.

We incorporated the feedback of the Key Informants into a draft of the key questions, analytic framework, and inclusion criteria which was posted to the AHRQ website for public comment from 22 April to 20 May 2010. Key questions and Inclusion criteria were finalized after consideration of the public comments received.

A Technical Expert Panel (TEP) was selected to provide broad expertise and perspectives specific to the topic under development. The TEP reviewed a protocol outlining a proposed methodological approach for the completion of the comparative effectiveness review, provided information to the investigators to aid in the refinement of the inclusion criteria and literature search strategies and recommended approaches to specific issues as requested. The final protocol entitled Comparative Effectiveness of Treatment for Open-Angle Glaucoma was posted to the AHRQ website on 16 November 2010.

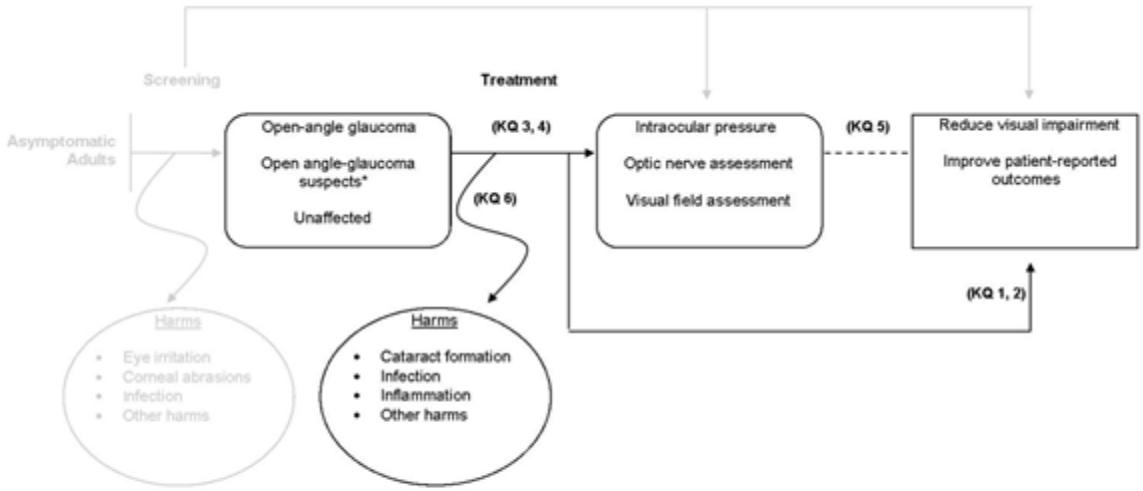
Analytic Framework

The analytic framework derived from the topic development phase (Figure 1) is a modified version of a larger framework depicting the impact of both screening and treatment for open-angle glaucoma. The following key questions (KQs) are represented in the framework.

- Key Question 1:Do medical, laser, and other surgical treatments for open-angle glaucoma reduce visual impairment?
- Key Question 2: Does treatment of open-angle glaucoma improve patient-reported outcomes?
- Key Question 3: Do medical, laser, and other surgical treatments for open-angle glaucoma lower intraocular pressure?
- Key Question 4: Do medical, laser, and other surgical treatments for open-angle glaucoma prevent or slow the progression of optic nerve damage and visual field loss?
- Key Question 5: Does lowering intraocular pressure or preventing or slowing the progression of optic nerve damage and visual field loss reduce visual impairment and change vision-related quality of life?
- Key Question 6: What are the harms associated with medical, laser, and other surgical treatments for open-angle glaucoma?

Figure 1 focuses on the treatment portion of the framework and depicts the key questions within the context of the inclusion criteria. In general, the figure illustrates how treatment of open-angle glaucoma may reduce visual impairment (KQ1) and/or improve patient-reported outcomes (KQ2). It shows how treatment of open-angle glaucoma may reduce intraocular pressure (KQ3) and/or prevent or slow the progression of optic nerve damage and visual field loss (KQ4). The framework also illustrates that there may be a relationship between the intermediate outcomes of visual field loss and optic nerve damage and the final health outcomes of visual disability and quality of life (KQ5). Finally, the potential harms of treatment (KQ6) are illustrated in the framework.

Figure 1. Analytic Framework for Treatment of Open-Angle Glaucoma



Search Strategy

To identify evidence relevant to the key questions in the analytic framework, we searched the following databases for primary studies: MEDLINE, EMBASE, LILACS (Latin American and Caribbean Literature on Health Sciences) and CENTRAL (the Cochrane Central Register of Controlled Trials). We developed a search strategy for MEDLINE, accessed via PubMed, based on an analysis of the medical subject headings (MeSH) terms and text words of key articles identified a priori and adapted this search strategy for searches of EMBASE (using EMTREE terms) and CENTRAL. We searched the literature without imposed language, sample size or date restrictions, but excluded non-English language studies at the time of full text review. We searched relevant systematic reviews to identify any additional eligible articles. The initial search included all articles in the databases as of 29 October 2010.

We also conducted a search in MEDLINE and CENTRAL for systematic reviews that addressed the key questions of interest. For MEDLINE, the search included the topic strategy as noted above combined with the term "AND systematic[sb]" and was limited to systematic reviews published from 2009 to 2011. The search for systematic reviews was conducted on 2 March 2011. We screened an existing database of eye and vision systematic reviews prepared to identify relevant open-angle glaucoma systematic reviews published prior to 2009.[10]

Study Inclusion Criteria

We included randomized controlled trials (RCTs) and quasi-randomized controlled trials of medical, laser, and incisional surgical treatments for open-angle glaucoma for inclusion as primary studies for Key Questions 1, 2, 3, and 4. For Key Questions 5 and 6, we included

observational study designs, cohort and case control studies, in addition to randomized and quasi-randomized controlled trials.

We included studies of participants with primary open-angle glaucoma or open-angle glaucoma suspects. The definition of "glaucoma suspect" is not standardized so any group in a study with this label was included. Other specific conditions that were considered to be open-angle glaucoma were: low/normal tension glaucoma, pseudoexfoliation, pigmentary glaucoma, and steroid-responsive glaucoma. In keeping with the usual clinical distinction between adult and juvenile glaucomas, only studies with participants aged 40 years and older were considered.

We specifically excluded the following conditions: juvenile/congenital glaucoma, traumatic glaucoma, neovascular glaucoma, refractory glaucoma, and inflammatory glaucoma.

There were no limitations based on stage or severity of disease, disease etiology, comorbid ocular or other medical conditions, geographic location, or demographic characteristics, e.g., gender, race/ethnicity.

Interventions

We first identified currently utilized treatments for open angle glaucoma and then included studies of medical (eye drops and systemic treatment), laser, and incisional surgery. The most commonly used topical medical interventions include prostaglandin analogs, beta-adrenergic blockers, alpha-adrenergic agonists, and carbonic anhydrase inhibitors. We also included the currently available combination drops (timolol-brimonidine and timolol-dorzolamide). Drugs no longer in use or not approved by the U.S. Food and Drug Administration were specifically excluded.

Studies of the impact of medical intervention on diurnal intraocular pressure were included if outcomes were assessed over a 24 hour period and participants were admitted to a hospital, sleep laboratory, or other facility overnight.

In terms of office-based laser treatments for open angle glaucoma, we included studies of laser trabeculoplasty without regard for the technology used (argon, diode, YAG).

We also searched for articles evaluating the currently utilized incisional surgeries: trabeculectomy, aqueous drainage devices, deep sclerectomy, and viscocanalostomy. Because of a desire by surgeons to find a more predictable procedure for lowering intraocular pressure, there has been a proliferation of new specialized devices intended to treat open angle glaucoma. To assess the evidence for or against their use, studies of the iScience microcatheter, the Trabectome, the ExPRESS shunt, the Glaukos iStent, and the Solx gold shunt were all included.

Because glaucoma is frequently managed simultaneous with cataract, we included studies of combined cataract and glaucoma surgical procedures published after April 2000. Studies published prior to this period are summarized in the AHRQ report entitled Surgical treatment of coexisting cataract and glaucoma.[8]

Article Screening and Abstraction

We screened potentially relevant citations (primary studies and systematic reviews) using the web-based systematic review software, DistillerSR (http://systematic-review.net/). Citations identified by the search strategies were first uploaded to DistillerSR before two reviewers independently assessed titles and abstracts according to the inclusion criteria. We classified the titles and abstracts as 'include', 'exclude' or 'unsure'. Disagreements about eligibility were resolved through discussion among reviewers.

Citations tagged as 'unsure' by both reviewers, 'unsure' by one reviewer and 'include' by the other, or 'include' by both reviewers, were carried forward to full-text screening. Two reviewers independently applied the same inclusion criteria as used during abstract screening.

Non-English language articles were also removed from further consideration at this stage. We resolved any disagreements regarding inclusion through discussion or, as needed, adjudicated unresolved conflicts during a team meeting.

Data abstraction forms were designed and pilot tested. For those studies that were included at the full text stage, one reviewer extracted descriptions of the study, including details about the population, intervention(s) and outcomes of interest, using the systematic review software, DistillerSR. A second reviewer verified the data. We again resolved disagreements through discussion.

Comparators

Key Questions 1, 2, 3, 4, and 6 explored comparisons of medical, laser, and incisional surgical treatments for open-angle glaucoma to each other (e.g., medical versus laser, medical versus medical) or to no treatment (placebo). For Key Questions 1, 2, 3, 4, and 6 we also included studies in which the intervention was a laser or incisional surgical treatment for glaucoma but the comparator was a combined or staged procedure for cataract and glaucoma (glaucoma surgical treatments combined or staged with phacoemulsification or extra capsular cataract extraction).

Outcomes

For key question 1, the proportion of participants with moderate, severe, and profound visual impairment as defined in the International Classification of Diseases, Clinical Modification, 9th Revision (ICD-9-CM).[9] The ICD-9 criteria define moderate visual impairment as best corrected visual acuity of between 20/70 and 20/160, severe visual impairment as acuity between 20/200 and 20/400 or a visual field of 20 degrees or less, and profound visual impairment as an acuity of 20/500 to 20/1000 or no more than 10 degrees of visual field. If presented, we also planned to consider other, non-standard measurements of visual impairment as defined by included studies. We included visual acuity outcomes among the treatment groups of interest (Early Treatment of Diabetic Retinopathy Study or Snellen) as reported in included studies (e.g., mean visual acuity or proportion of participants in pre-specified visual acuity categories).

Key question 2 deals with patient reported outcomes so we considered participants' mean total or relevant item/subscale scores as measured by any validated questionnaire, e.g., National Eye Institute Visual Functioning Questionnaire (NEI-VFQ). To be considered, an instrument needed to address the primary outcome of vision-related quality of life (primary outcome) or the secondary outcomes of treatment convenience, patient satisfaction, patient preference or utility, or adherence with medication.

Key question 3 addresses the ability of treatment to lower intraocular pressure. As standard outcomes, we included the proportion of participants with intraocular pressure measurements at the pre-specified levels of $\leq$ 18 mmHg or $\geq$ 20% decrease in intraocular pressure from baseline levels. Since the analysis of intraocular pressure may vary appreciably by trial, we planned to consider other intraocular pressure outcomes as reported in included studies.

To assess the ability of treatments to reduce either visual field loss or optic nerve structural damage (KQ4), we utilized two standard outcomes: the proportion of participants with progressive optic nerve damage as defined by included studies and as observed via fundus photography or other imaging of the posterior pole, and the proportion of participants with progression of visual field loss as defined by the Early Manifest Glaucoma Trial and as measured via automated threshold perimetry.[5] We also planned to consider other assessments of visual field loss as defined by included studies.

Key Question 5 explores the association of 1) lowering intraocular pressure or 2) preventing or slowing the progression of a) optic nerve damage and b) visual field loss (intermediate outcomes of treatment) and final health outcomes (reduced visual impairment and improved vision-related quality of life) among the populations of interest. The outcomes for KQ4 were therefore the same as those described above in Outcomes for Key Questions 1, 2, 3, and 4.

Finally, we compared the proportion of participants experiencing the following adverse events among the treatment groups of interest:

Potentially Serious:

- Cataract formation (visually significant cataract requiring surgery or report of cataract surgery)
- Low intraocular pressure (hypotony)
- Decreased visual acuity
- Infection (e.g., blebitis, endophthalmitis)
- Inflammation
- Strabismus
- Peripheral anterior synechiae
- Retinal tear and detachment
- Systemic allergic reaction
- Loss of an eye
- Need for additional surgery
- Hyphema
- Transient decrease in central vision
- Systemic side effects
- Choroidal (detachment, effusion, hemorrhage)
- Cardiac arrhythmia
- Death

Less likely to be serious

- Eye irritation
- Eye watering
- Eye redness
- Patient discomfort
- Ocular surface disease
- Other patient complaint
- Skin discoloration
- Conjunctival injection
- Iris color change
- Punctal stenosis
- Conjunctival foreshortening

We assessed medical treatment outcomes at a minimum of one month post intervention. We included outcomes reported at 6 months (2-9 months) and one year (10–18 months) as reported in included studies. The exception was diurnal medical treatment studies in which the investigators report outcomes assessed over a twenty-four hour period. For studies of surgical interventions, we assessed outcomes at a minimum of one year (10–18 months) and at annual intervals thereafter as reported in included studies.

Risk of Bias Assessment

We used the Cochrane Collaboration's tool for assessing the risk of bias of randomized and quasi-randomized trials.[11] Two reviewers assessed the included studies for sources of systematic bias according to the guidelines in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions and evaluated the studies for the following criteria: sequence generation and allocation concealment (selection bias), masking of participants, study investigators, and outcome assessors (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other sources of bias. Masking of investigators and participants might not be possible with some of the interventions being examined, but was noted when mentioned. We reported judgments for each criterion as 'Low risk of bias', 'High risk of bias' or 'Unclear risk of bias (information is insufficient to assess)'. The two reviewers resolved disagreements through discussion.

Two reviewers assessed the methodological rigour of observational studies using a modified version of the Newcastle Ottawa Scale (NOS).[12] The NOS includes domains to assess the quality of study group selection (representativeness, selection, case definitions), comparability of cohorts/cases and controls on the basis of the design or analysis, and ascertainment of exposure(s) or outcome(s) adequacy of follow-up, non response rate and financial or other conflicts of interest. Each item query required a yes, no, or unable to determine/not reported response. In addition, reviewers provided an overall assessment of the quality of each study as "good" "fair" or "poor" using the reporting bias, selection bias, and confounding domains as a basis for the assessment.

We used a tool adapted by Li (2010) from the Critical Appraisal Skills Program, Assessment of Multiple Systematic Reviews (AMSTAR), and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement to assess the methodological quality of systematic reviews.[10] We used the following criteria, adapted from Li, to determine which systematic reviews were of sufficient quality to be considered for inclusion in this review: comprehensive search for primary studies (searches of more than one bibliographic database); risk of bias assessment; appropriate analysis methods (no pooled arm analysis).

Rating the Evidence

We assessed the quantity, quality and consistency of the body of available primary study evidence addressing Key Questions 1 through 6. We used an evidence grading scheme recommended by the GRADE Working Group, adapted by AHRQ in the Methods Guide for Effectiveness and Comparative Effectiveness Reviews (http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=328) and recently published in the Journal of Clinical Epidemiology.[13 14]

Although we included systematic reviews that addressed our key questions and consider systematic reviews as the highest level of evidence for addressing questions of therapy, we were unable to adapt the evidence grading scheme to incorporate evidence from systematic reviews. We assessed the quality and consistency of the best available primary study evidence, including assessment of the risk of bias in relevant studies, as well as aspects of consistency, directness, and precision as described in the Methods Guide for Effectiveness and Comparative Effectiveness Reviews and by Owens (2010).[13 14] For each outcome of interest, two reviewers graded the major outcomes for each Key Question and then the entire team discussed their recommendations and reached consensus.

Data Synthesis

When we identified existing systematic reviews of sufficient quality (based on the criteria outlined in Quality Assessment) that addressed the key questions, we cited these reviews as evidence and did not abstract and synthesize data from the studies incorporated in those reviews. We abstracted evidence from additional primary studies for interventions, comparisons, and outcomes that were not addressed by existing systematic reviews and searched for and summarized evidence from additional primary studies that have been published or identified after the date of last search conducted for the systematic review. We adapted the recommendations of Whitlock (2008) for incorporating systematic reviews in complex reviews to include providing a narrative summary of the review methods (i.e., inclusion/exclusion criteria, search strategy, statistical methodology) and findings (i.e., number of studies included, quantitative and qualitative results) and in the instance of multiple reviews, evaluate the consistency across reviews addressing the same key question.[15]

Due to appreciable variability in interventions, follow-up intervals, or assessments of outcomes, we did not combine the results of primary studies in a meta-analysis and instead present a narrative summary. The plan for the analysis of primary studies, including the assessments of heterogeneity, reporting bias, measures of treatment effect, data synthesis, and subgroup analysis was included in the protocol for this review.

Results

We identified a total of 23 systematic reviews. Twelve reviews address the comparative effectiveness of medical treatment of open-angle glaucoma, 9 address questions of surgical treatment, and one compares medical versus surgical treatments for open-angle glaucoma. One additional review addressed the comparative effectiveness of surgical versus surgical and medical versus surgical treatments for open-angle glaucoma.

We identified a total of 66 RCTs. We also identified 11 observational studies addressing adverse effects (8 medical treatment and 3 surgical treatment). Our major findings are summarized by key question. Table A provides a summary of the key points.

Medical treatment of Open-Angle Glaucoma

Key Question 1: What is the comparative effectiveness of medical treatments for reducing visual impairment?

- No studies of medical therapy were identified that directly addressed outcomes related to visual impairment.
- The available studies addressing secondary outcomes of change in visual acuity and visual field loss are of too short a duration to answer this question given than glaucoma is typically a slowly progressive disease that may take many years to cause clinically or statistically significant changes.

Key Question 3: What is the comparative effectiveness of medical treatments for lowering intraocular pressure?

- Prostaglandins lower IOP more than dorzolamide, brimonodine, and timolol.
- The prostaglandins appear similar in their IOP lowering effect, but some studies have reported more IOP lowering with bimataprost.

- The combination dorzolamide/timolol appears to lower IOP a similar amount as prostaglandins.

Key Question 4: What is the comparative effectiveness of medical treatments for preventing or slowing the progression of optic nerve damage and visual field loss?

- A systematic review of medical treatment for glaucoma determined treatment to be protective against visual field progression. This review included the results of both the Early Manifest Glaucoma Trial and the Ocular Hypertension Treatment Study.
- Other included primary studies are insufficiently large or not of long enough duration to detect differences in the rates of optic nerve damage or visual field loss. Given the slowly progressive nature of glaucoma, the large trials of glaucoma therapy have demonstrated the need to follow hundreds of subjects for 5 or more years to detect change.
- No studies addressed the comparative effectiveness of glaucoma medications with respect to their relative ability to prevent optic nerve damage or visual field loss.

Key Question 6: What are the harms associated with medical treatments for open-angle glaucoma?

- The prostaglandin agents produce more ocular redness than does timolol.
- Within the prostaglandins, latanoprost is less likely to cause redness.
- A systematic review found that subjects on timolol were less likely to drop out of studies due to side effects than those on brimonidine, latanoprost, travoprost, or betaxolol.

Surgical Treatment of Open-Angle Glaucoma

Key Question 1: What is the comparative effectiveness of laser and other surgical treatments for reducing visual impairment?

- No studies reported on visual impairment after laser or other surgical treatments.
- Visual acuity was not assessed as a primary outcome in any identified study comparing laser and other surgical treatments for glaucoma.
- No single treatment appeared to have a greater effect on visual acuity than any other treatment.

Key Question 3: What is the comparative effectiveness of laser and other surgical treatments for lowering intraocular pressure?

- Trabeculectomy lowers intraocular pressure.
- The use of mitomycin C intraoperatively with trabeculectomy results in lower intraocular pressures than when it is not used.
- Other alterations in surgical technique, location of surgery, and adjuvants other than mitomycin C have not been shown to provide additional pressure lowering.
- Trabeculectomy lowers intraocular pressure more than non-penetrating surgeries.
- The intraocular pressure lowering effect of combined cataract surgery and trabeculectomy is not affected by the location of the conjunctival incision or the presence or absence of a peripheral iridectomy but may be more in 2-site (cataract and trabeculectomy performed using different incisions) than 1-site (cataract and trabeculectomy performed using the same incision) surgery.
- Laser trabeculoplasty effectively lowers IOP in glaucoma subjects and effectiveness does not seem to vary with the type of laser used.
- The data available for the role of aqueous drainage devices in open-angle glaucoma are inadequate to draw conclusions.

Key Question 4: What is the comparative effectiveness of laser and other surgical treatments for preventing or slowing the progression of optic nerve damage and visual field loss?

- No comparative studies looking at laser and surgical treatments presented data on whether or not these procedures slow the progression of optic nerve damage and visual field loss.

Key Question 6: What are the harms associated with laser and other surgical treatments for open-angle glaucoma?

- Trabeculectomy results in more complications than non-penetrating surgeries.
- The profile of harms does not differ between one and two site combined cataract and glaucoma surgery.

Medical versus Surgical Treatment of Open-Angle Glaucoma

Key Question 1: What is the comparative effectiveness of medical versus surgical treatment for reducing of visual impairment?

- Although it appears that trabeculectomy may reduce the risk of vision loss after adjusting for demographic and comorbid factors, the body of evidence is limited and inconclusive.

Key Question 3: What is the comparative effectiveness of medical versus surgical treatment for lowering intraocular pressure?

- Incisional surgery lowers IOP more than lasers or medications.
- Initial treatment with lasers tends to reduce the need for medications to achieve the same IOP.

Key Question 4: What is the comparative effectiveness of medical versus surgical treatment for preventing or slowing the progression of optic nerve damage and visual field loss?

- Trabeculectomy first may lead to better preservation of visual field than medicines first in more advanced glaucoma.
- The Collaborative Initial Glaucoma Treatment Study (CIGTS) included surgical techniques and medications that are current and found no difference in change in visual field (and did not report on change in the optic nerve).
- Treatment of ocular hypertension with medicines preserves visual fields better than no treatment.

Key Question 6: What harms are reported in studies of medical versus surgical treatments for open-angle glaucoma?

- Trabeculectomy is associated with cataract worsening and an increased need for cataract surgery over time when compared to medical treatments for glaucoma.
- Intraocular surgery rarely results in severe vision loss due to infection and or bleeding. These risks are not associated with medical or laser treatments.
- Laser trabeculoplasty can produce peripheral anterior synechiae, whereas medical treatment does not.

Additional Key Questions

Key Question 2: Does treatment of open-angle glaucoma improve patient-reported outcomes?

- There is no evidence that treatment of glaucoma improves patient-reported outcomes.
- There is little evidence that the treatments themselves used for OAG influence patient QOL.

- Several studies suggest that the type of glaucoma treatment does not have an influence on QOL.
- There is some evidence that among medical treatments, patients prefer the treatment that is less frequently applied.
- There is evidence from one high quality RCT that glaucoma treatment reduces fear of blindness regardless of the type treatment.

Key Question 5: Does lowering intraocular pressure or preventing or slowing the progression of optic nerve damage and visual field loss reduce visual impairment and change vision-related quality of life?

- There are no studies addressing the relationship between the intermediate outcomes of intraocular pressure reduction, prevention of optic nerve damage, or prevention of visual field loss and the outcomes of visual impairment and vision-related quality of life.

Future Research

The available evidence demonstrates definitively that intraocular pressure can be lowered by medications, laser treatments, and surgery. High quality randomized controlled trials have also shown that reduction of intraocular pressure slows the development and progression of damage to the optic nerve and slows visual field loss. Although logical to presume that slowing glaucoma damage would lead to preservation of vision-related quality of life and reduction in visual impairment, this link has not been demonstrated in the research literature.

One specific area that would benefit from research is the association between treatment and visual impairment and/or patient reported outcomes. One important reason such work has not yet been done is that the time from diagnosis to visual impairment in a treated glaucoma patient may be many years to decades. Nevertheless, such a link is important to establish.

Another general area that requires additional quality evidence is the relative risks and benefits of medical and surgical treatments for glaucoma. The number of studies that adequately compare two or more treatments over time is too small to draw any significant conclusions about the comparative effectiveness of most currently used therapies.

As a general comment on the available literature on glaucoma treatments, the field would benefit from more rigorous study design and more standardized reporting of outcomes. The World Glaucoma Association publication "Guidelines on Design and Reporting of Glaucoma Surgical Trials" should serve as a basis for all trials of new and existing treatments.[129]

Table A. Summary of the Outcomes, Comparators and Main results per Key Question.

	Outcomes	Studies Included	Comparators	Main results	Strength of evidence
KQ1	Visual impairment • Visual acuity	• Medical o SRs: 0 o RCTs: 11 • Surgical o SRs: 2 o RCTs: 4 • Medical-Surgical o SRs: 1 o RCTs: 0	Medical RCTs Timolol - Brimonidine-Travoprost Timolol - Carteolol Timolol - Levobunolol Levobunolol - Betaxolol Levobunolol - Untreated Cross over; Dorzolamide-Timolol, Travoprost - Latanoprost Laser-Medical Surgical SRs One vs two-site phacotrabeculectomy Endocyclophotocoagulation vs Ahmed valve Molteno implant vs no implant RCTs Trabeculectomy vs. Ex-press shunt Trabeculectomy vs. NPDS with hyaluronic acid implant NPDS +/- MMC NPDS +/- collagen implant	• No studies reported on visual impairment as main outcome. • Studies addressing secondary outcomes, too short to answer this question • No single treatment appeared to have a greater effect on visual acuity than any other treatment • Trabeculectomy may reduce the risk of vision loss, but, the body of evidence is limited and inconclusive	• Medical Studies: Insufficient • Surgical Studies: Low
KQ2	Patient reported outcomes • QOL • Fear of blindness • Patient preference • Patient satisfaction	• Medical o SRs: 0 o RCTs: 4 • Surgical o SRs: 0 o RCTs: 0 • Medical-Surgical o SRs: 1 o RCTs: 2	RCTs Brimonidine - Timolol Timolol/ Dorzolamide - Timolol + Brimonidine Timolol/ Dorzolamide - Latanoprost Timolol gel - Timolol solution Trabeculectomy +/- 5FU - beta-blockers Betaxolol + ALT - No treatment	• There is no evidence that treatment of glaucoma improves patient-reported outcomes. • There is little evidence that the treatments themselves influence patient QOL. • The type of treatment does not have an influence on QOL. • Among medical treatments, patients prefer the treatment that is less frequently applied. • One high quality RCT shows that glaucoma treatment reduces fear of blindness regardless of the type treatment.	• For all outcomes: Insufficient
KQ3	• Reduction of Intraocular pressure (IOP)	• Medical o SRs: 9 o RCTs: 0 24 hours o SRs: 2	24 hours RCTs: Latanoprost – Bimatoprost Latanoprost-Timolol-Brimonidine Latanoprost- Dorzolamide -Timolol Latanoprost -Bimatoprost -Travoprost	• Prostaglandins better than dorzolamide, brimonodine, and timolol. Within prostaglandins, Bimatoprost showed better results. • The combination dorzolamide/timolol	• 24 hours: Low • Surgical Studies: Moderate

		o RCTs: 5 • Surgical o SRs: 9 o RCTs: 16 • Medical-Surgical o SRs: 2 o RCTs: 2	Surgical Surgical SRs Trabeculectomy vs NPDS Trabeculectomy + Antimetabolites Beta radiation Laser trabeculoplasty Aqueous shunts Trabeculectomy vs medical treatment Surgical RCTs Trabeculectomy techniques and variations Trabeculectomy + adjuvants NPDS Combined cataract-glaucoma surgery	has similar effect than prostaglandins. • Trabeculectomy lowers IOP. • Intraoperative mitomycin C results in lower IOP • Other alterations in surgical technique, location of surgery, and adjuvants do not provide improvement in IOP reduction. • Incisional surgery lowers IOP more than lasers or medications. • Initial treatment with lasers tends to reduce the need for medications to achieve the same IOP	
KQ4	• Visual fields loss • Optic Nerve damage	• Medical o SRs: 1 o RCTs: 17 • Surgical o SRs: 0 o RCTs: 0 • Medical-Surgical o SRs: 3 o RCTs: 1	Medical RCTs Timolol- Brimonidine- Travoprost Timolol –Metipranolol –Carteolol Timolol -Carteolol Timolol – Latanoprost Timolol – Betaxolol Latanoprost - Bimatoprost Latanoprost Travoprost - Dorzolamide/Timolol Topical hypotensives –Observation Medical vs Surgical SRs Trabeculectomy vs medical treatment Medical or surgical vs No treatment	• A SR determined medical treatment for glaucoma to be protective against visual field progression. (It included the results of both the Early Manifest Glaucoma Trial and the Ocular Hypertension Treatment Study. • Most other included medical studies are too small or too short to be conclusive. • No surgical studies presented conclusive data. • Treatment of ocular hypertension with medicines preserves visual fields better than no treatment	• Medical: Low • Surgical: Insufficient • Medical-surgical: Insufficient
KQ5	• Quality of life	• Medical o SRs: 0 o RCTs: 1 o Observational: 1 • Surgical o SRs: 0 o RCTs: 0 o Observational: 0	Medical treatment in general	• There is no evidence to show the relationship between intraocular pressure reduction, prevention of optic nerve damage, or prevention of visual field loss and the outcomes of visual impairment and vision-related quality of life.	• Insufficient
KQ6	• Harms	• Medical o SRs: 11 o RCTs: 18 o Observational: 8 • Surgical o SRs: 8 o RCTs: 22	All comparators above	• The prostaglandin agents produce more ocular redness than timolol. Within the prostaglandins, latanoprost is less likely to cause redness. • A SR found that subjects on timolol were less likely to drop out of studies due to side effects than those on	• Grading was not completed as harms were not the main outcome of the studies included.

		o Observational: 3 • Medical-Surgical o SRs: 2 o RCTs: 2 o Observational: 0		brimonidine, latanoprost, travoprost, or Betaxolol • Trabeculectomy results in more complications than non-penetrating surgeries. • The profile of harms does not differ between one and two site combined cataract and glaucoma surgery. • Trabeculectomy is associated with cataract worsening and an increased need for cataract surgery over time when compared to medical treatments for glaucoma. • Intraocular surgery rarely results in severe vision loss due to infection and or bleeding. These risks are not associated with medical or laser treatments. • Laser trabeculoplasty can produce peripheral anterior synechiae, whereas medical treatment does not	

Introduction

The Agency for Healthcare Research and Quality (AHRQ) Effective Health Care Program requested a comparative effectiveness review of various treatment options for glaucoma. The topic was selected through the Effective Health Care Program nomination process and from a review of the scientific medical literature.

Background

Glaucoma is a leading cause of visual impairment and blindness both in the United States and worldwide. It is estimated to affect 60.5 million people worldwide.[1] Glaucoma is defined as an acquired disease of the optic nerve (neuropathy), characterized by a typical appearance of the optic nerve and by visual field defects that are usually midperipheral and in the nasal visual field. Depending upon whether the optic nerve damage is associated with an open or closed appearance to the drainage channels for aqueous humor in the front of the eye, the glaucoma is referred to as open-angle (the subject of this report) or closed-angle.

Mild glaucoma damage to the optic nerve may be asymptomatic, but as the damage worsens, the patient begins to have difficulty with peripheral vision, contrast sensitivity, glare, and adjusting from light to dark and dark to light--symptoms that affect day to day function and quality of life. In its most severe form, glaucoma results in total, irreversible blindness.

Although deficient blood supply to the optic nerve, inadequate structural support for the neurons that make up the optic nerve, and insufficient supplies of neurotrophins needed to maintain the health of the optic nerve have been hypothesized as risk factors for glaucoma, experimental models and other evidence from human participants have shown that elevated intraocular pressure (IOP) results in damage to the optic nerve in a pattern characteristic of glaucoma.[2] Furthermore, studies have demonstrated correlations between the level of IOP and the risk of having glaucoma as well as the worsening of glaucoma once present. Other studies have demonstrated that lowering IOP reduces both the incidence of glaucoma in individuals who do not have glaucoma damage but are at high risk for its development, and the rate of progression of glaucoma in individuals with established glaucoma.[3-5] Therefore, the treatments for glaucoma today all focus on the reduction of IOP, which secondarily prevents the worsening of visual field loss and may therefore prevent visual impairment and blindness.

Treatments for Open-Angle Glaucoma

Decisions regarding when to initiate treatment to lower IOP, and what treatment modality to use for lowering IOP in a given individual, are fraught with uncertainty. Medical, laser, and incisional surgical treatments are all used to treat glaucoma. The most commonly used medical treatment includes several classes of eye drops, such as prostaglandin analogs, beta-adrenergic antagonists, carbonic anhydrase inhibitors, and alpha-adrenergic agonists, as well as systemic carbonic anhydrase inhibitors. Laser trabeculoplasty is an office procedure that lowers IOP by increasing the outflow of aqueous humor from the eye. Incisional surgery to lower IOP includes procedures that have been performed for decades, such as trabeculectomy and aqueous drainage device surgery, as well as a host of newer procedures, such as non-penetrating deep sclerectomy, canaloplasty, endoscopic cyclophotocoagulation, and alternative methods of trabecular bypass.

Rationale For A Comparative Effectiveness Review

Although there is high level evidence from randomized controlled trials (RCTs) of medical and laser therapy versus observation in patients with early glaucoma, initial medical therapy compared to initial surgical therapy in patients with established glaucoma, and laser therapy versus surgical therapy in participants not controlled with medical therapy, are addressed only by single RCTs that also do not, in most cases, include novel medical and surgical treatments.[5-7]

Given developments in the treatment of glaucoma, including the realization of the importance of adherence to medical therapy, and the introduction of new surgical modalities, it is appropriate to update the evidence on the safety and effectiveness of glaucoma treatments.

Purpose for Evidence Report

The objective of this comparative effectiveness review is to summarize the evidence regarding the safety and effectiveness of medical, laser, and other surgical treatments for open-angle glaucoma (OAG) in adults.

Key Questions

Key Question 1. Do medical, laser, and other surgical treatments for OAG reduce visual impairment?

KQ1a: What is the comparative effectiveness of medical treatments for reducing visual impairment?
KQ1b: What is the comparative effectiveness of laser and other surgical treatments for reducing visual impairment?
KQ1c: What is the comparative effectiveness of medical versus surgical treatment for reducing of visual impairment?

Key Question 2. Does treatment of OAG improve patient-reported outcomes?

Key Question 3. Do medical, laser, and other surgical treatments for OAG lower intraocular pressure?

KQ3a: What is the comparative effectiveness of medical treatments for lowering intraocular pressure?
KQ3b: What is the comparative effectiveness of laser and other surgical treatments for lowering intraocular pressure?
KQ3c: What is the comparative effectiveness of medical versus surgical treatment for lowering intraocular pressure?

Key Question 4. Do medical, laser, and other surgical treatments for OAG prevent or slow the progression of optic nerve damage and visual field loss?

KQ4a: What is the comparative effectiveness of medical treatments for preventing or slowing the progression of optic nerve damage and visual field loss?

KQ4b: What is the comparative effectiveness of laser and other surgical treatments for preventing or slowing the progression of optic nerve damage and visual field loss?
KQ4c: What is the comparative effectiveness of medical versus surgical treatment for preventing or slowing the progression of optic nerve damage and visual field loss?

Key Question 5. Does lowering intraocular pressure or preventing or slowing the progression of optic nerve damage and visual field loss reduce visual impairment and change vision-related quality of life?

Key Question 6. What are the harms associated with medical, laser, and other surgical treatments for OAG?

KQ6a: What are the harms associated with medical treatments for OAG?
KQ6b: What are the harms associated with laser and other surgical treatments for OAG?
KQ6c: What harms are reported in studies of medical versus surgical treatments for OAG?

Methods

Topic Development

The Agency for Healthcare Quality and Research (AHRQ) requested that the XXXX Evidence-based Practice Center (XXXX EPC) assist with the formulation and refinement of the Comparative Effectiveness Review topic "Effectiveness of screening and treatment for glaucoma."

In consultation with AHRQ, the XXXX EPC identified a small group of stakeholders to serve as members of a Key Informant Group. The Key Informant Group helped shape the Key Questions (KQs) relevant to the topic by providing input regarding the populations and clinical subgroups, interventions, and outcomes of interest to clinicians, policy makers, payers, and consumers.

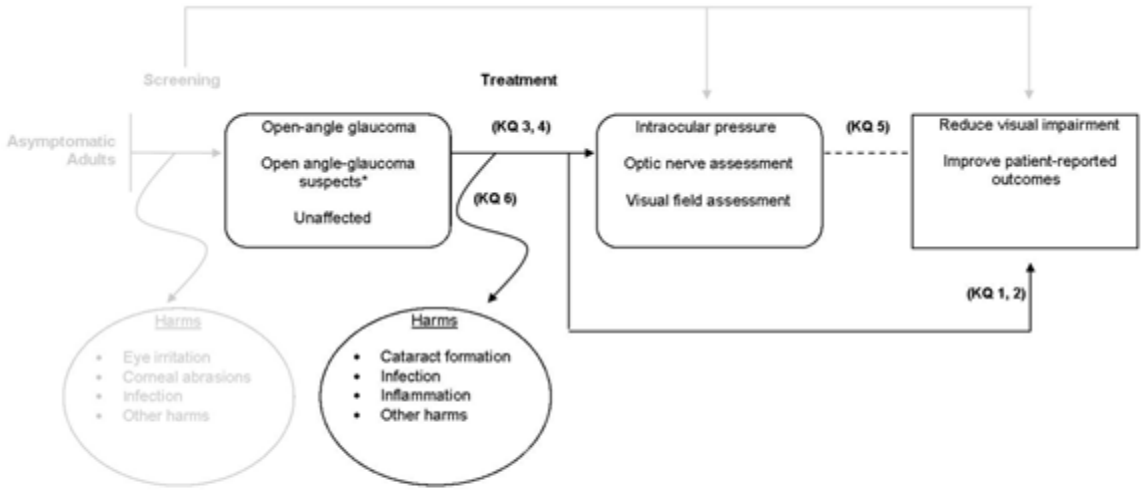
The XXXX EPC investigators incorporated the feedback of the Key Informants into a draft of the KQs, analytic framework, and inclusion criteria which was posted to the AHRQ Web site for public comment from April 22 to May 20, 2010. KQs and Inclusion criteria were finalized after consideration of the public comments received.

A Technical Expert Panel was selected to provide broad expertise and perspectives specific to the topic under development. The Technical Expert Panel reviewed a protocol outlining a proposed methodological approach for the completion of the comparative effectiveness review, provided information to the XXXX EPC to aid in the refinement of the inclusion criteria and literature search strategies and recommended approaches to specific issues as requested by the XXXX EPC. The final protocol entitled Comparative Effectiveness of Treatment For Open-Angle Glaucoma was posted to the AHRQ Web site on November 16, 2010.

Analytic Framework

The analytic framework (Figure 1) is a modified version of a larger framework depicting the impact of both screening and treatment for open-angle glaucoma (OAG). The figure focuses on the treatment portion of the framework and depicts the KQs within the context of the inclusion criteria. In general, the figure illustrates how treatment of open-angle glaucoma may reduce visual impairment (KQ1) and/or improve patient-reported outcomes (KQ2). It shows how treatment of open-angle glaucoma may reduce intraocular pressure (KQ3) and/or prevent or slow the progression of optic nerve damage and visual field loss (KQ4). The framework also illustrates that there may be a relationship between the intermediate outcomes of visual field loss and optic nerve damage and the final health outcomes of visual disability and quality of life (KQ5). Finally, the potential harms of treatment (KQ6) are illustrated in the framework.

Figure 1. Analytic Framework for Treatment of Open-Angle Glaucoma



Study Selection

Types of Studies

We included randomized controlled trials (RCTs) and quasi randomized controlled trials of medical, laser, and incisional surgical treatments for OAG for inclusion as primary studies for KQs 1, 2, 3, and 4. We included observational study designs, cohort and case control studies, in addition to randomized and quasi RCTs for KQs 5 and 6.

We also included systematic reviews that address the KQs as described in Data Synthesis.

Types of Participants

We included studies of participants with primary or secondary chronic OAG or OAG suspects aged 40 years and older (specific exclusions are listed below). These types of glaucoma may also be described in the literature as the following conditions:

- Ocular hypertension
- Low tension glaucoma
- Pseudoexfoliative glaucoma/pseudoexfoliation syndrome
- Pigmentary glaucoma
- Steroid-responsive glaucoma
- Normal tension glaucoma

We excluded the following conditions: juvenile/congenital glaucoma, traumatic glaucoma, neovascular glaucoma, refractory glaucoma, and inflammatory glaucoma.

We considered studies that enrolled participants diagnosed with included and excluded glaucoma types (as described above) if the investigators conducted analyses of included subgroups and if we were able to abstract data for the included glaucoma types only.

We included studies in which at least 95 percent of the participants are aged 40 and older or those in which the mean age is greater than 50 years. If the age was not specified, the study was excluded.

There were no limitations based on stage or severity of disease, disease etiology, comorbid ocular or other medical conditions, geographic location, or demographic characteristics, (e.g., gender, race/ethnicity).

Types of Interventions and Comparisons

We included studies of medical (eye drops and systemic treatment), laser, and incisional surgery treatments for OAG.

Medical Treatments

We considered studies of the following agents for this review:

- Prostaglandin analogs
  - Bimatoprost
  - Latanoprost
  - Travoprost
- Beta adrenergic antagonists
  - Timolol
  - Levobunolol
  - Betaxolol
  - Carteolol
- Topical and oral carbonic anhydrase inhibitors
  - Acetazolamide
  - Brinzolamide
  - Dorzolamide
- Alpha2 adrenergic agonists
  - Brimonidine
- Combination medical treatments
  - Dorzolamide plus timolol
  - Brimonidone plus timolol

We included preparations of the above-mentioned agents by trade, generic/chemical name in Appendix F.

We included studies of the impact of medical intervention on diurnal intraocular pressure if outcomes were assessed over a 24-hour period and participants were admitted to a hospital, sleep laboratory, or other facility overnight.

We excluded from this review studies of the following medical interventions that are no longer commonly used to treat glaucoma:

- Pilocarpine
- Apraclonidine
- Epinephrine

- Unoprostone
- Dipivaphrin
- Ocusert
- Iopidine
- Metipranolol
- Systemic β-blockers

We also excluded treatments that were not approved by the Food and Drug Administration (i.e., experimental treatments).

Laser and Incisional Surgical Treatments

We considered for this review studies of the following laser and incisional surgical treatments as well as use of devices that are designed to increase aqueous outflow.

Office-Based Laser Treatments

- Argon and selective laser trabeculoplasty (SLT)

Surgical Procedures

- Trabeculectomy
- Aqueous drainage devices
    - Baerveldt implant
    - Ahmed implant
    - Krupin implant
    - Molteno implant
- Cyclophotocoagulation - trans-scleral and endoscopic
- Deep sclerectomy
- Viscocanalostomy

Specialized Surgical Devices

- iScience microcatheter (canaloplasty)
- Trabectome® (modified trabeculotomy)
- ExPRESS shunt (modified trabeculectomy)
- Glaukos iStent™ (trabecular bypass)
- Solx gold shunt® (trabecular bypass)

Surgical Treatment of Coexisting Cataract and Glaucoma

We included studies of combined cataract and glaucoma surgical procedures published after April 2000. Studies published prior to this period are summarized in the AHRQ report entitled *Surgical treatment of coexisting cataract and glaucoma*.[8]

We excluded from this review studies of the following surgical interventions or surgery-related conditions or complications:

- Cataract surgery alone among participants with glaucoma
- Treatment of surgical complications
- Intraocular pressure variations after surgery and treatment of IOP after surgery
- Intraocular pressure fluctuation after surgery

- Variations in anesthesia
- Assessment or treatment of filtering blebs alone (bleb survival, revision of blebs, comparisons of blebs, bleb failure)

Comparators

KQs 1, 2, 3, 4, and 6 explored comparisons of medical, laser, and incisional surgical treatments for OAG to each other (e.g., medical versus laser, medical versus medical) or to no treatment. For KQs 1, 2, 3, 4, and 6, we also included studies in which the intervention is a laser or incisional surgical treatment for glaucoma but the comparator is a combined or staged procedure for cataract and glaucoma (glaucoma surgical treatments combined or staged with phacoemulsification or extra capsular cataract extraction).

Outcomes

Key Question 1

Primary Outcome

The proportion of participants with moderate, severe, and profound visual impairment (as defined in the International Classification of Diseases, Clinical Modification, 9th Revision[9]). We also considered other measurements of visual impairment as defined by included studies.

Secondary Outcome

We included visual acuity outcomes among the treatment groups of interest (Early Treatment of Diabetic Retinopathy Study or Snellen) as reported in included studies (e.g., mean visual acuity or proportion of participants in pre-specified visual acuity categories).

Key Question 2

We considered participants' mean total or relevant item/subscale scores as measured by any validated questionnaire, e.g., National Eye Institute Visual Functioning Questionnaire (NEI-VFQ), for the following patient-reported outcomes among the treatment groups of interest:

Primary Outcome

Vision-related quality of life (vision-related functional loss as well as the impact of functional loss on activities of daily living)

Secondary Outcomes

- Treatment convenience
- Patient satisfaction
- Patient preference values or utility values
- Adherence to medical treatment

Key Question 3

Primary Outcome

We included the proportion of participants with intraocular pressure measurements at pre-specified levels as outlined below among the treatment groups of interest. Since the analysis of intraocular pressure may vary appreciably by trial, we considered other intraocular pressure outcomes as reported in included studies.

- Intraocular pressure ≤ 18 mmHg

- ≥ 20 percent decrease in intraocular pressure from baseline levels

Key Question 4

Primary Outcomes

- The proportion of participants with progressive optic nerve damage as defined by included studies and as observed via fundus photography or other imaging of the posterior pole.
- The proportion of participants with progression of visual field loss as defined by the Early Manifest Glaucoma Trial and as measured via automated threshold perimetry.[5] We also considered other assessments of visual field loss as defined by included studies.

Key Question 5

Key Question 5 explores the association of 1) lowering intraocular pressure or 2) preventing or slowing the progression of a) optic nerve damage and b) visual field loss (intermediate outcomes of treatment) and final health outcomes (reduced visual impairment and improved vision-related quality of life) among the populations of interest. The outcomes were as described above in Outcomes for Key Questions 1, 2, 3, and 4.

Key Question 6

We compared the proportion of participants experiencing the following adverse events among the treatment groups of interest:

- Eye irritation
- Eye watering
- Eye redness
- Patient discomfort
- Cataract formation (visually significant cataract requiring surgery or report of cataract surgery)
- Low intraocular pressure (hypotony)
- Decreased visual acuity
- Infection (e.g., blebitis, endophthalmitis)
- Inflammation
- Strabismus
- Ocular surface disease
- Retinal tear and detachment
- Other patient complaint
- Skin discoloration
- Conjunctival injection
- Iris color change
- Punctal stenosis
- Conjunctival foreshortening
- Peripheral anterior synechiae
- Systemic allergic reaction
- Loss of an eye

- Need for additional surgery
- Hyphema
- Transient decrease in central vision
- Systemic side effects
- Choroidal (detachment, effusion, hemorrhage)
- Cardiac arrhythmia
- Death

We also included other harms as reported in included studies.

Timing of Outcomes

Medical treatments

We assessed medical treatment outcomes at a minimum of one month post intervention. We included outcomes reported at 6 months (2-9 months) and one year (10–18 months) as reported in included studies. The exception was diurnal medical treatment studies in which the investigators report outcomes assessed over a twenty-four hour period.

Surgical treatments

We assessed outcomes at a minimum of one year (10–18 months) and at annual intervals thereafter as reported in included studies.

Setting

Eye care provider clinical settings only (ophthalmologists and optometrists)

Search Strategy

We searched the following databases for primary studies: MEDLINE, EMBASE, LILACS (Latin American and Caribbean Literature on Health Sciences) and CENTRAL (the Cochrane Central Register of Controlled Trials). We developed a search strategy for MEDLINE, accessed via PubMed, based on an analysis of the medical subject headings (MeSH) terms and text words of key articles identified a priori and adapted this search strategy for searches of EMBASE (using EMTREE terms) and CENTRAL (Appendix A). We searched the literature without imposed language, sample size or date restrictions, but excluded non-English language studies at the time of full text review. We searched relevant systematic reviews to identify any additional eligible articles. The databases were last searched on October 29, 2010.

We also conducted a sensitive search in MEDLINE and CENTRAL for systematic reviews that address the KQs of interest. For MEDLINE, the search included the topic strategy, as noted above, combined with the term “AND systematic[sb]” and was limited to systematic reviews published from 2009 to 2011. The search for systematic reviews was conducted on March 2, 2011. We screened an existing database of eye and vision systematic reviews prepared to identify relevant OAG systematic reviews published prior to 2009.[10].

Abstract Screening

We screened potentially relevant citations (primary studies and systematic reviews) using the Web-based systematic review software, DistillerSR (http://systematic-review.net/). Citations identified by the search strategies were uploaded to DistillerSR and managed in the following manner: Two reviewers independently assessed titles and abstracts resulting from the literature searches according to the inclusion criteria. We classified the titles and abstracts as 'include', 'exclude' or 'unsure'. Disagreements about eligibility were resolved through discussion among reviewers. A copy of the abstract review form is included in Appendix B.

Full-Text Screening

Citations tagged as 'unsure' by both reviewers, 'unsure' by one reviewer and 'include' by the other, or 'include' by both reviewers, were promoted to full-text screening. Two reviewers independently applied the same inclusion criteria as used during abstract screening. Non-English language articles were also removed from further consideration at this stage. We resolved any disagreements regarding inclusion through discussion or, as needed, during a team meeting.

Data Abstraction

Data abstraction forms were designed and pilot tested. One reviewer extracted descriptions of the study, including details about the population, intervention(s) and outcomes of interest, using the systematic review software, DistillerSR. A second reviewer verified the data. We resolved disagreements through discussion.

Risk of Bias Assessment

We used the Cochrane Collaboration's tool for assessing the risk of bias of randomized and quasi RCTs.[11] Two reviewers assessed the included studies for sources of systematic bias according to the guidelines in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions using the following criteria: sequence generation and allocation concealment (selection bias), masking of participants, study investigators, and outcome assessors (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other sources of bias. Masking of investigators and participants might not have be possible with some of the interventions being examined, but was noted when mentioned. We reported judgments for each criterion as 'Low risk of bias', 'High risk of bias' or 'Unclear risk of bias (information is insufficient to assess)'. The two reviewers resolved disagreements through discussion.

Two reviewers assessed the methodological rigor of observational studies using a modified version of the Newcastle Ottawa Scale.[12] The Newcastle Ottawa Scale includes domains to assess the quality of study group selection (representativeness, selection, case definitions), comparability of cohorts/cases, and controls. On the basis of the design or analysis, and ascertainment of exposure(s) or outcome(s) adequacy of follow-up, non-response rate and financial or other conflicts of interest. Each item query required a yes, no, or unable to determine/not reported response. In addition, reviewers provided an overall assessment of the quality of each study as "good" "fair" or "poor" using the reporting bias, selection bias, and confounding domains as a basis for the assessment.

We used a tool adapted by Li (2010) from the Critical Appraisal Skills Program, Assessment of Multiple Systematic Reviews; and the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement, to assess the methodological quality of systematic reviews.[10] We used the following criteria, adapted from Li, to determine which systematic reviews were of sufficient quality to be considered for inclusion in this review: comprehensive search for primary studies (searches of more than one bibliographic database); risk of bias assessment; and appropriate analysis methods (no pooled arm analysis).

Rating Body of Evidence

We assessed the quantity, quality and consistency of the body of available primary study evidence addressing KQs 1 through 6. We used an evidence grading scheme recommended by the GRADE Working Group, adapted by AHRQ in the Methods Guide for Effectiveness and Comparative Effectiveness Reviews (http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=328) and recently published in the Journal of Clinical Epidemiology.[13 14]

Although we included systematic reviews that addressed our KQs and consider systematic reviews as the highest level of evidence for addressing questions of therapy, we were unable to adapt the evidence grading scheme to incorporate evidence from systematic reviews. We assessed the quality and consistency of the best available primary study evidence, including assessment of the risk of bias in relevant studies, as well as aspects of consistency, directness, and precision as described in the Methods Guide for Effectiveness and Comparative Effectiveness Reviews and by Owens (2010).[13 14] For each outcome of interest, two reviewers graded the major outcomes for each of the KQs and then the entire team discussed their recommendations and reached consensus.

Data Synthesis

When we identified existing high-quality systematic reviews that addressed the KQs, we cited these reviews as evidence and did not abstract and synthesize data from primary studies. We abstracted and synthesized data from primary studies that addressed interventions, comparisons, and outcomes that were not identified in systematic reviews, and those studies that had been published or identified after the date of last search conducted for the systematic review. We adapted the recommendations of Whitlock (2008) for incorporating systematic reviews in complex reviews and provided a narrative summary of the review methods (i.e., inclusion/exclusion criteria, search strategy, statistical methodology) and findings (i.e., number of studies included, quantitative and qualitative results). Similarly, in the instance of multiple reviews, we evaluated the consistency across reviews addressing the same key question.[15]

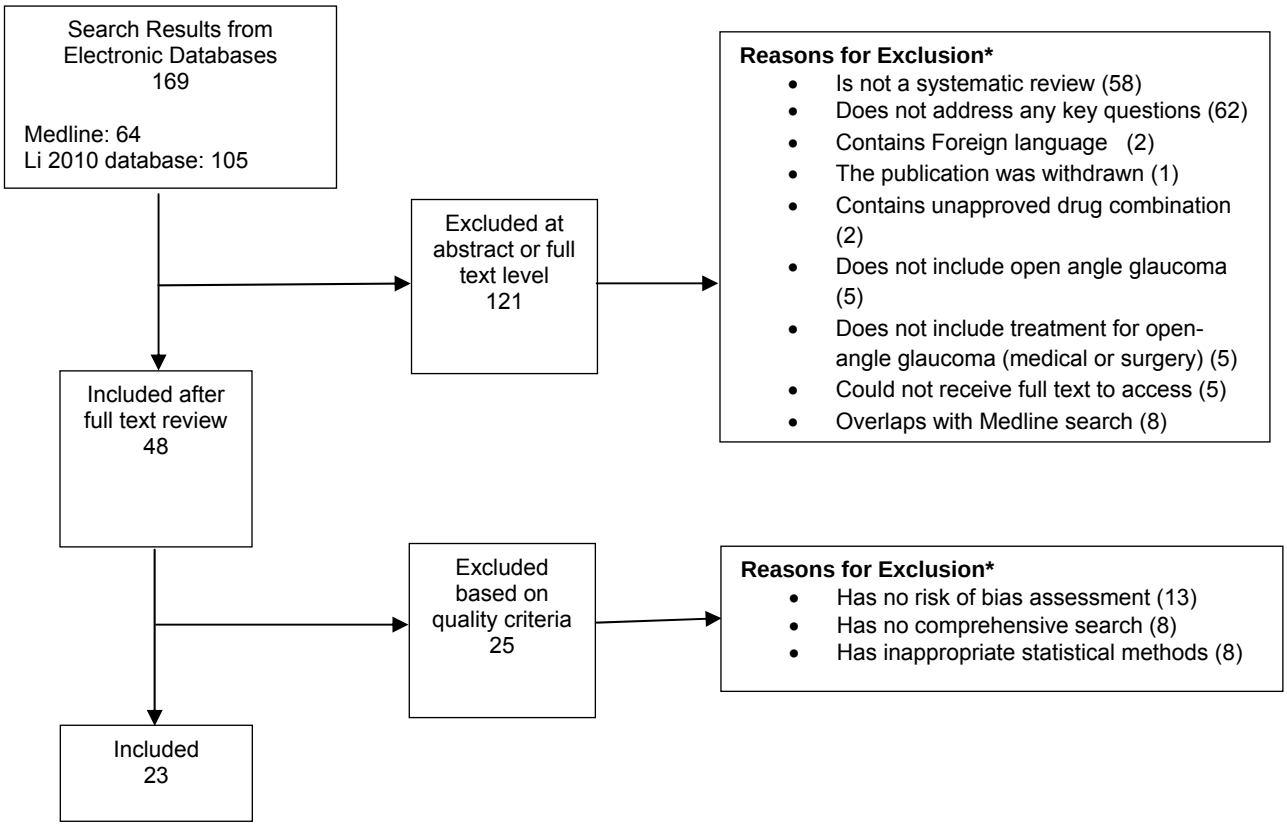
Because there was appreciable variability in devices, parameters, thresholds, and measurement of outcomes, we did not combine the results using meta-analysis and instead presented a narrative summary.

The plan for the analysis of primary studies, including the assessments of heterogeneity, reporting bias, measures of treatment effect, data synthesis, and subgroup analysis was included in the protocol for this review.

Results

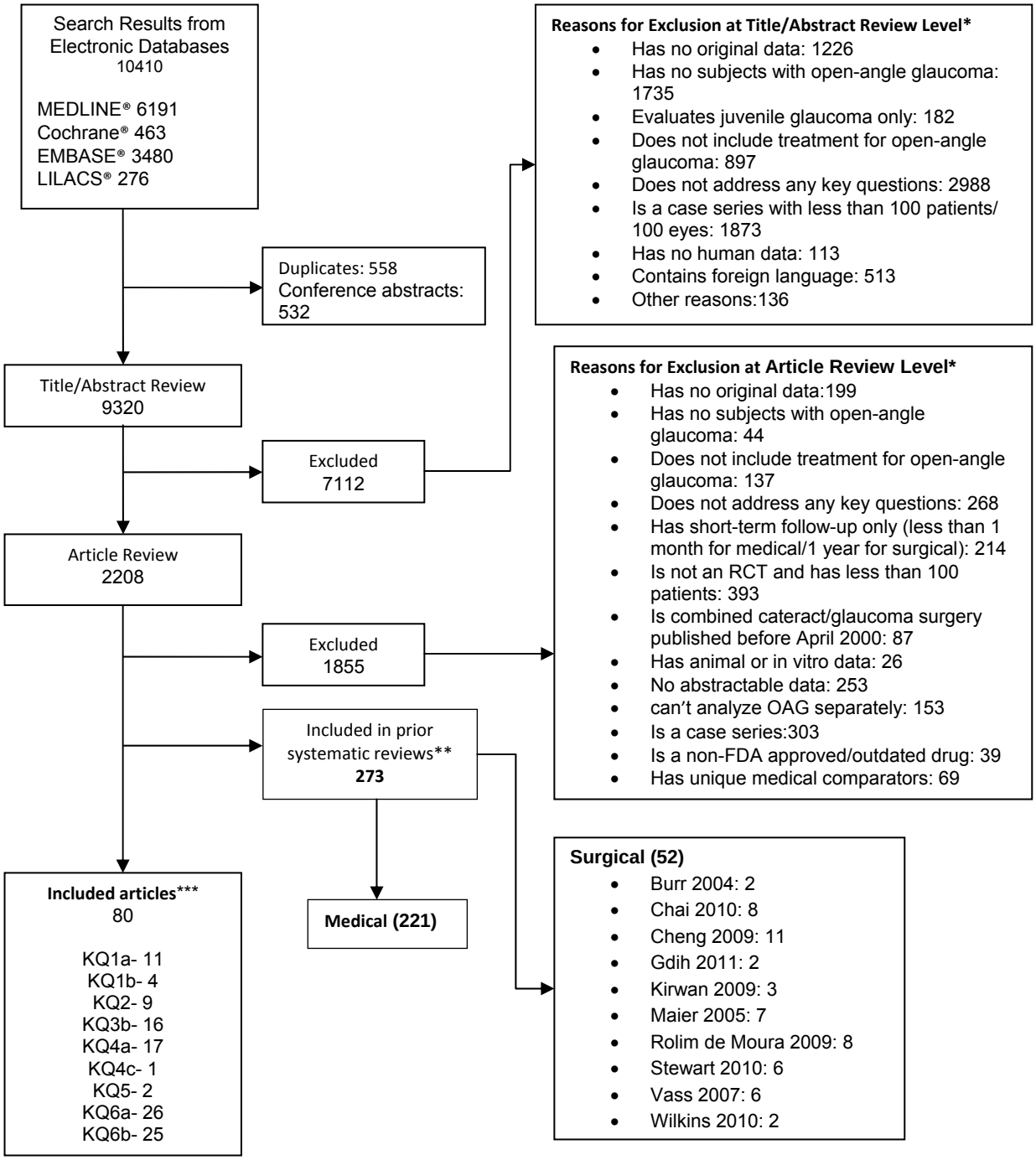
We identified 66 RCTs (KQs 1a, 1b, 2, 3—diurnal, 3b, 3c, 4a, 4c, 5, 6a, 6b and 6c), 14 observational studies (KQs 6a and 6b) and 23 systematic reviews (KQs 1b, 1c, 2, 3a, 3—diurnal, 3b, 3c, 4a, 4c, 6a, 6b, and 6c). Details of all studies and systematic reviews are included in Evidence Tables in Appendix C. A listing of included articles, with reason(s) for exclusion is provided in Appendix D.

Figure 2. Systematic Review Literature Search Treatment of Open-Angle Glaucoma



* Total may exceed number in corresponding box, as articles excluded by two reviewers at this level.

Figure 3. Primary Study Literature Search for Treatment of Open-Angle Glaucoma



* Total may exceed number in corresponding box, as articles were excluded by two reviewers at this level.
**Total may exceed number in corresponding box, as some articles were covered by more than one systematic review.
*** Total may exceed number in corresponding box, as articles may apply to more than one key question

Table 1. Summary of Literature for Treatment of Open-Angle Glaucoma

Question and Comparison	Systematic Reviews	Randomized Controlled Trials	Observational Studies
Medical Treatments			
KQ1a	0	11	NA
KQ3a	9	0	NA
KQ3 – diurnal	2	5	NA
KQ4a	1	17	NA
KQ6a	11	18	8
Surgical			
KQ1b	2	4	NA
KQ3b	9	16	NA
KQ4b	0	0	NA
KQ6b	8	22	3
Medical-Surgical			
KQ1c	1	0	NA
KQ3c	2	2	NA
KQ4c	3	1	NA
KQ6c	2	2	0
Additional Questions			
KQ2	2	9	NA
KQ5	0	1	1

Narrative summaries of the evidence identified for KQs 1, 3, 4, and 6 are presented within each of the following treatment comparison groups: Medical treatment, Surgical treatment, and Medical versus Surgical treatment. KQs 2 and 5 are discussed under subheadings identified by key question. For each question and comparison, evidence from systematic reviews is discussed first, followed by evidence from primary studies.

Medical Treatment of Open-Angle Glaucoma

Systematic Reviews of Medical Interventions for Open-Angle Glaucoma

We included 12 systematic reviews that address the comparative effectiveness of medical interventions for open-angle glaucoma (OAG) (Appendix C). The most common comparisons included head-to-head comparisons of prostaglandin analogs,[16-21] prostaglandin analogs compared to timolol,[22 23] latanoprost compared to brimonidine,{50102}[20] timolol compared to brimonidine,[24] and concomitant compared to fixed combination medications.[25 26] Vass (2007) provided an overview of various topical medical treatments compared to placebo, no treatment, or another medical treatment.[27] While all systematic reviews included participants with OAG, some reviews also included studies that enrolled participants with mixed or "other" glaucoma (approximately 2 percent of participants), and chronic-angle closure glaucoma (included in population in a minimum of one trial in a single systematic review).

Key Question 1a: What is the comparative effectiveness of medical treatments for reducing visual impairment?

Key Points

- No studies of medical therapy were identified that directly addressed outcomes related to visual impairment.
- The available studies addressing secondary outcomes are of too short a duration to answer this question.

Evidence from Systematic Reviews

We did not identify any systematic reviews of medical interventions for OAG that included outcomes related to visual impairment.

Detailed Analysis of Primary Studies

We identified eleven studies comparing medical therapies for glaucoma that also reported something about vision-related outcomes. Unfortunately, none of these reported any outcomes related to actual impairment but rather were limited to the secondary outcomes of visual acuity and visual field mean defect. Of the 11 studies, eight reported on the visual field and six on visual acuity.

Two studies demonstrated some improvement in visual field performance. The study by Prata (2009) comparing timolol, brimonidine, and travoprost, showed an overall decrease in mean deviation (-6.56 to -5.72, p=0.045) in treated subjects.[28] A study of betaxolol to levobunolol by Marcon (1990) demonstrated some improvement in visual field performance in 1 of 20 subjects.[29]

Two additional studies reported no change in visual field over the course of the studies. A cross-over study of dorzolamide-timolol, travoprost, and latanoprost showed no significant change in visual field mean deviation or pattern standard deviation over 9 months of treatment,[30] and a study of timolol and carteolol showed no change in the visual field over 16 weeks.[31] The 9-month study used non-standard definitions of progression (2dB loss in mean deviation or one point with a decrease in threshold of 10dB) that would not be expected to be seen over the short duration of the study.

Four studies produced results suggestive of a decline in visual field but none were able to demonstrate any statistical significance. A study of carteolol vs. timolol presented the distribution of changes in visual field mean defect, which suggests that there was a net decline in both groups. But again, no statistics were provided.[32] Tuulonen (1989) compared laser trabeculoplasty to topical medications and demonstrated visual field decline in both groups (-7.4 to -8.6 with laser, -9.1 to -9.4 with medications), though neither decline was statistically significant.[33]

Reports of visual acuity outcomes were similarly variable. The study comparing betaxolol to levobunolol by Marcon (1990) included two subjects (10 percent) with improved visual acuity.[29] The comparison of dorzolamide-timolol, travoprost, and latanoprost by Chiselita (2005) showed no change in visual acuity over 9 months of treatment.[30] Yamamoto (1996) found no subjects lost two or more lines of vision over 16 weeks in their trial of timolol and carteolol.[31] Ravalico (1994) compared levobunolol to no treatment in ocular hypertensives and reported “no variation” in visual acuity, though no criteria were provided.[34]

Two studies reported worsening of visual acuity at some point during the study but neither outcome was believed to be due to treatment. Berson (1985) compared levobunolol to timolol and found that 57 subjects had a decline of two or more lines of visual acuity at some point, but that these were transient.[35] Similarly, Schuman (1997) found a decrease of two or more lines of acuity in 5.9 percent of their brimonidine treated group and 9.5 percent of their timolol treated group, at 12 months.[36]

Table 2 Grading of Evidence

Number of studies; participants	Risk of bias	Consistency	Directness	Precision	Strength of evidence
Visual impairment/ Visual acuity					
9;813	RCT/Medium	Inconsistent	Direct	Imprecise	Insufficient

Conclusions

None of the studies identified were of sufficient duration or size to identify outcomes that could plausibly be related to visual impairment due to glaucoma, which is most often a slowly progressive disease.

Key Question 3a: What is the comparative effectiveness of medical treatments for lowering intraocular pressure?

Evidence from systematic reviews and primary studies addressing diurnal intraocular pressure (IOP) measurements are discussed separately.

Key Points

- Prostaglandins lower IOP more than dorzolamide, brimonodine, and timolol.
- The prostaglandins appear similar in the extent at which they lower IOP , but some studies have reported a greater drop in IOP with bimataprost.
- The combination dorzolamide/timolol appears to lower IOP the same amount as prostaglandins.

Summary of Evidence from Systematic Reviews

Prostaglandin Analogs (head to head comparisons)

Two systematic reviews included comparisons of bimatoprost and latanoprost. In both reviews the investigators concluded that bimatoprost lowered IOP more effectively than latanoprost.[17 18] The difference in the proportion of participants achieving an IOP less-than or equal-to 17 mm Hg was greater with bimatoprost at 3 months, (Risk difference (RD), 12; 95 percent confidence interval (CI), 4 to 21, two trials), but no difference was found at 1 and 6 months.[17] Cheng (2008) also noted a significant mean percent reduction in morning IOP (2.6 percent at 1 month, 2.4 percent at 3 months, and 5.6 percent at 6 months)[17] and Eyawo (2009) reported significant mean IOP reduction at 3 or more months of follow-up (weighted mean difference (WMD), 0.73; 95 percent CI, 0.10 to 1.37, eight trials).[18]

Both Eyawo (2009) and Li (2006) compared travoprost to latanoprost and to bimatoprost.[18 22] Both reviews concluded that mean IOP reduction was similar when comparing travoprost to latanoprost. Li (2006) and Eyawo (2009) differed in their conclusions regarding bimatoprost versus travoprost, as Eyawo reported a significant difference in favor of bimatoprost at 3 or more months of follow-up (WMD, 0.88; 95 percent CI, 0.13 to 1.63, eight trials),[18] while Li concluded that bimatoprost and travoprost were similarly effective (WMD 0.08; 95 percent CI, -0.62 to 0.79, five trials).[22]

Prostagladin Analogs Versus Timolol

Studies comparing Timolol with travoprost [22] and latanoprost, [23] showed prostaglandin analogs more effective at lowering IOP. The percent IOP reduction from baseline to 1 month was 4 percent greater for participants randomized to latanoprost compared to travoprost at 1 month (95 percent CI, 1.2 to 6.3, three trials) and 5 percent greater at 6 months (WMD 5.0; 95 percent CI, 2.8 to 7.3, four trials). The mean reduction in IOP after 3 or more months was 0.81 mmHg lower for participants receiving travoprost (95 percent CI, -1.16 to -0.45, four trials).

Concomitant Versus Fixed Combination Medical Treatments

Cheng (2009) reported no difference in the mean percent reduction in IOP at 10 a.m., when they compared latanoprost to dorzolamide/timolol combination treatment.[25] Cox (2009) undertook a more general analysis of concomitant versus fixed combinations including travoprost, brimonidine, dorzolamide, bimatoprost, or latanaprost combined with a beta blocker.[26] Overall concomitant administration resulted in a larger mean difference in IOP from baseline to 3 months, although the difference was significant only when IOP was measured at 2 hours (WMD, 0.39; 95 percent CI 0.04 to 0.75, six trials) and 8 hours (WMD, 0.50; 95 percent CI, 0.16 to 0.85, four trials) after a dose of medication.

Other Comparisons

- Loon (2008) concluded that timolol and brimonidine were similarly effective after comparisons of the two medications in eight trials of varying follow-up periods, and after conducting subgroup analyses of trials of less than and more than 6 months of follow-up (three and five trials respectively).[24]
- Fung (2007) and Hodge (2008) compared latanoprost and brimonidine. Fung (2007) concluded that use of latanoprost resulted in a lower mean reduction of IOP in a group of heterogeneous trials of varying duration (WMD 1.10; 95 percent CI, 0.57 to 1.63, 14 trials).[19] Subgroup analyses of trials of less than 6 months duration and those with 8 or more months of follow-up supported the trend of lower mean IOP among those using latanoprost, with a mean difference in IOP lowering of 1.64 mm Hg in trials of greater than or equal to 8 months (95 percent CI, 0.92 to 2.36, four trials). Hodge (2008) reported no difference in mean IOP at 3 months (WMD, -1.04l 95 percent CI, -3.01 to 0.93, three trials). [20]
- Hodge (2008) compared latanoprost and dorzolamide. Participants receiving latanoprost had lower IOP on average at 3 months (WMD, -2.64; 95 percent CI, -3.25 to -2.04, three trials).[20]

Detailed Analysis of Primary Studies

We did not include a detailed analysis of primary studies as we deemed the systematic review evidence to be sufficient to address this question.

Grading of Evidence

We relied on the evidence from systematic reviews and were unable to adapt the evidence grading scheme to incorporate evidence from systematic reviews.

Conclusions

As single agents, prostaglandins are currently the most effective at lowering IOP. Some studies have found greater IOP lowering with bimataprost, but this has not been a consistent finding. The combination of dorzolamide and timolol appears to lower IOP about the same amount as prostaglandins.

Studies of Diurnal Intraocular Pressure

Key Points

- Our conclusions regarding the effect of topical therapies in lowering IOP over the 24-hour time period were limited due to the fact that one study contained almost all the data.
- All the topical medications reviewed appear to lower IOP throughout the 24-hour cycle.
- Prostaglandins appear to lower IOP more over the 24-hour cycle than beta blockers, topical carbonic anhydrase inhibitors and alpha agonists, but the evidence for this is weak.
- While the IOP lowering effects of prostaglandins appear to vary appreciably over the 24-hour time period, the results were inconsistent and the reported difference in the amount of IOP lowering was on the order of 1 mmHg.
- Results from systematic reviews comparing one prostaglandin to another are were inconsistent.

Summary of Evidence from Systematic Reviews

Aptel (2008) performed a meta-analysis of mean IOP reduction for head-to-head comparisons of prostaglandin analogs based on IOP measurements taken at 8 a.m., 12 p.m., 4 p.m., and 8 p.m.[16] IOP reduction was significantly greater with use of bimatoprost, when compared to latanoprost, at all time periods. Mean IOP reduction of bimatoprost was greater than travoprost at 8 a.m. and 12 p.m., but not different at the 4 p.m. and 8 p.m. time periods.[16] In addition, travoprost had roughly the same effectiveness as latanoprost at lowering IOP across all time periods under investigation.

Cheng (2008) looked at the percent reduction in diurnal IOP from baseline in three trials comparing bimatoprost and latanoprost and found that mean reduction was not different at follow-up (.25 percent at 1 month and 2.1 percent at 3 months).[17]

Cheng (2009) compared latanoprost to dorzolaminde/timolol combination treatment (including studies of both fixed and concomitant administration of dorzolamide/timolol) and found no difference in diurnal mean percent reduction in IOP at any time point (1, 2, 3, and 6 months).[25]

Detailed Analysis of Primary Studies

The medications used to lower IOP may not have equal effectiveness at different time points during the day. It's possible that some medications work better at night than others while others may work better during the daytime hours. The main way to assess this difference is to measure the IOP over the entire 24-hour period. Five RCTs met the inclusion criteria. IOP outcomes for the five RCTs were largely reported graphically and so we provide a narrative summary of the findings.

Quaranta (2008) studied latanoprost versus bimatoprost in 40 newly diagnosed participants with glaucoma with IOP less than or equal to 21 mmHg when measured once every two hours from 8 a.m. until 8 p.m.[37] The trial randomized participants to either bimatoprost or latanoprost for 8 weeks, followed by a 24-hour IOP assessment. Participants then crossed over to the other drug for another 8 weeks, followed by a 24-hour IOP assessment. There was no difference over the 24-hour period between the two treatments. IOP dropped between 1.5 and 3.5 mmHg at different time points with an average drop of 2 mmHg from a mean of 15.5 mmHg. Blood pressure (monitored over 24 hours) did not change when using either medication.

A separate study, by the same authors involved a cohort of 27 newly diagnosed glaucoma patients with IOP greater than or equal to 23 mmHg and less than or equal to 32 mmHg (computed by taking the average of the two highest IOP measurements between 8 a.m. and 6 p.m.) The study randomized the patients to timolol 0.5 percent, brimonidine 0.2 percent, dorzolamide 0.2 percent (all given twice a day) and latanoprost (given once a day) in a crossover design in which all four medications were used by each of the patients for six weeks followed by four-week washout periods.[38] Latanoprost lowered IOP about 1 mmHg more than the other medications over the 24-hour time period, and no differences were seen when comparing the other medications to themselves. All drugs decreased IOP at all time points over the 24 hours. Both brimonidine and timolol lowered IOP less during sleeping hours than latanoprost. Brimonidine and timolol lowered systolic blood pressure and diastolic blood pressure compared to baseline over the 24 hours, and brimonidine lowered it the most, especially at night.

Larsson (2001) randomized 27 participants with IOP greater than 21 mmHg (who did not have glaucoma) to four weeks of either timolol 0.5 percent gel (once a day in the morning) or latanaprost (once a day in the evening) with a washout of four weeks before crossover.[39] Latanoprost lowered IOP more than timolol gel at every time point by an average of about 1.5 mmHg with a slightly greater reduction observed during sleeping hours. The study saw no differences in systolic blood pressure, diastolic blood pressure or heart rate were noted over the 24 hours.

In a randomized 8-week trial, Yildrin (2008) compared latanoprost, bimatoprost and travaprost in 48 participants with IOP greater than 22 mmHg who had not previously received IOP lowering therapy.[40] All three medications lowered IOP at all time points. The only observed difference between the medications was travaprost lowered IOP more than the other two at 8 a.m. and 10 a.m.

Orsalezi (2006) compared latanoprost, bimatoprost and travaprost in 44 patients with either primary OAG or ocular hypertension (OHT) and IOP greater than 21 mmHg, who had not

previously received prostaglandin. The trial was a randomized cross-over study in which patients used the drugs for 1 month prior to each 24-hour measurement.[41] All three medications lowered IOP by about 7 mmHg, however bimatoprost lowered IOP more at most time points by about one mmHg. None of the medications had any effect on blood pressure.

Table 3 Grading of Evidence

Number of studies; participants	Risk of bias	Consistency	Directness	Precision	Strength of evidence
Diurnal intraocular pressure					
5; 186	RCT/Medium	Inconsistent	Direct	Imprecise	Low

Conclusions

Of the available monotherapies, prostaglandins appear to lower IOP most throughout the diurnal period. Combination timolol/dorzolamide appears to be equally effective. Most findings are from single studies comparing specific agents, so the evidence is relatively weak.

Key Question 4a: What is the comparative effectiveness of medical treatments for preventing or slowing the progression of optic nerve damage and visual field loss?

Key Points

- A systematic review of medical treatment for glaucoma determined treatment to be protective against visual field progression. This review included the results of both the Early Manifest Glaucoma Trial and the Ocular Hypertension Treatment Study.
- Most other included studies are not large enough or don't have a long enough duration to detect differences in the rates of optic nerve damage or visual field loss.
- No studies addressed the comparative effectiveness of glaucoma medications with respect to their ability to prevent optic nerve damage or visual field loss.

Summary of Evidence from Systematic Reviews

Vass (2007) reported that any topical medical treatment (including beta blockers and studies with unspecified topical medications) had a significant protective effect on incident visual field defect progression when compared to placebo or no treatment (odds rations [OR]. 0.62; 95 percent CI, 0.47 to 0.81, 10 trials). Beta blockers were also protective when compared to placebo (OR, 0.67; 95 percent CI, 0.45 to 1.00, eight trials), as was timolol when compared to carteolol.[27] Participants randomized to timolol, however, experienced a two-fold higher odds of visual field defects when compared to participants receiving levobunolol (95 percent CI, 1.17 to 4.14, two trials).

Detailed Analysis of Primary Studies

Two studies reported an improvement in visual field with topical medical treatment. Prata (2009) showed an improvement in mean deviation across their entire population of subjects taking timolol, brimonidine, or travoprost.[28] This was only a 4-week study and included no control group. The study of betaxolol versus levobunolol by Marcon (1990) found one subject of 20 whose visual field improved over 12 weeks of treatment, though criteria were not specified.[29]

An additional seven studies found no change in visual field parameters. The subanalysis of the Ocular Hypertension Treatment Study by Herman (2006) regarding cataract formation, reported no statistically significant change in either foveal sensitivity or visual field mean deviation.[42] An evaluation of dorzolamide-timolol versus travoprost versus latanoprost showed no change in mean deviation or pattern standard deviation after 9 months.[30] The comparison of timolol to betaxolol by Rainer (2003) revealed an improvement in the mean deviation for the betaxolol group alone but no significant difference in final mean deviation between the two groups.[43] The study of timolol, metipranolol, and carteolol by Mirza (2000) did not find any change in visual field parameters over 3 months.[44] Using a custom analysis of visual field point clusters of the Octopus G1 pattern, Vainio-Jylha and Vuori (1999) found no changes in visual fields over their 24-month study of betaxolol and timolol.[45] Finally, the study of timolol versus carteolol by Yamamoto (1996) found no change in visual field over 16 weeks.[31]

An additional nine studies were identified in which visual field measures worsened. The crossover study of latanoprost and timolol by Evans (2008) did not report on all visual field outcomes but did find that the latanoprost-then-timolol group had a statistically significant worsening of mean deviation (-1.49 to -2.41, p=0.04).[46] Dirks (2006), comparing latanoprost to bimatoprost, found one subject in the latanoprost group worsened by unspecified visual field criteria.[47] The European Glaucoma Prevention Study compared dorzolamide to placebo and found that in both groups, visual field worsened at a similar rate over 5 years.[48] Similarly, a study of ocular hypertensives randomized to placebo or timolol found less disease progression in the treated group but the difference was not statistically significant.[49] A study of brimonidine and timolol treatment found that two subjects of 48 and 46 (enrolled respectively in each group) worsened but, again, the criteria were not specified.[50] Messmer (1991) randomized subjects to betaxolol or timolol and found that both groups improved during the initial 6 months and then worsened.[51] Without clear statistical analysis, they report that the slope of the mean sensitivity in the betaxolol group was more positive. Another study of carteolol and timolol using the Octopus G1 pattern reports the distribution of the slope of the mean defect. This analysis seems to show disease progression in both groups but there are no analyses.[32] The comparison of laser trabeculoplasty by Tuulonen (1989) found that both groups worsened and there was no statistically significant difference between the two.[33] Finally, Berry (1984) compared timolol and betaxolol and found that three of 35 eyes treated with betaxolol and two of 43 eyes treated with timolol worsened, although their conclusion was that this was due to "normal variation".[52]

Only one additional primary study was identified that addressed optic nerve changes. The European Glaucoma Progression Study found statistically similar risk of disease progression (by optic disc criteria) in the dorzolamide and placebo groups.[48]

Table 4 Grading of Evidence

Number of studies : participants	Risk of bias	Consistency	Directness	Precision	Strength of evidence
OUTCOME					
Visual field					
17;2745	RCT/ Low	Inconsistent	Direct	Imprecise	Low
Optic nerve changes					
1;1076	RCT/Low	N/A	Direct	Imprecise	Insufficient

Conclusions

A systematic review of medical treatment for glaucoma found treatment to be protective against visual field progression. Most other studies were not large enough or not of a long enough duration to detect differences in the rates of optic nerve damage or visual field loss. No other systematic reviews or individual studies addressed the comparative effectiveness of glaucoma medications with respect to their ability to prevent optic nerve damage or visual field loss.

Most of the primary studies found in our search were of inadequate duration to detect any changes in the optic nerve or visual field. Of the large studies evaluating medical therapy for glaucoma, both the Ocular Hypertension Treatment Study and the Early Manifest Glaucoma Study showed a decreased rate of visual field loss and progressive optic nerve damage in those subjects treated with medications. Among such studies, only the European Glaucoma Prevention Study (EGPS) failed to find such a difference between treatment and placebo. Two important limitations of the EGPS were the relatively high loss to follow up and the fact that the response to placebo treatment was significantly higher than in prior studies. Based on the results of the Ocular Hypertension Treatment Study and the Early Manifest Glaucoma Trial, medical treatments decrease the risk of progression by 50 percent or less.

None of the primary studies were appropriately designed to compare rates of progression by visual field or optic nerve criteria between any two or more medications.

Key Question 6a: What are the harms associated with medical treatments for open-angle glaucoma?

Key Points

- The prostaglandin agents produce more ocular redness than does timolol.
- Within the prostaglandins, latanoprost is less likely to cause redness.

- A systematic review found that subjects on timolol were less likely to drop out of studies due to side effects than those on brimonidine, latanoprost, travoprost, or betaxolol.

Summary of Evidence from Systematic Reviews

Bimatoprost was associated with a higher risk of conjunctival hyperemia when compared to other prostaglandin analogs. Aptel (2008) noted that the risk of conjunctival hyperemia was 1.7 times higher among participants receiving bimatoprost when compared to participants receiving latanoprost (95 percent CI, 1.44 to 2.02, five trials).[16] Cheng (2008), Eyawo (2009), and Honrubia (2009) reported similar results for the same comparison.[17 18 21] Aptel (2008) and Li (2006) reported similar results after comparing bimatoprost to travoprost. [16 22] However, in one trial Eyawo (2009) found the opposite result (higher risk among those using travoprost).[18] Cheng (2008) further noted that there were no significant differences in other adverse effects such as eye irritation, ocular inflammation, cystoid macular edema, and iris pigmentation with use of bimatoprost versus latanoprost.[17]

Aptel (2008), Eyawo (2009), Honrubia (2009), and Li (2006), reported the harms related to use of latanoprost versus travoprost.[16 18 21 22] In these systematic reviews, participants randomized to latanoprost were less likely to experience conjunctival hyperemia when compared to travoprost. From a meta-analysis of six randomized trials, Eyawo (2009) reported a 49-percent lower odds of conjunctival hyperemia among participants exposed to latanoprost compared to those given travoprost. Li (2006) further noted that comparisons of travoprost 0.004 percent to travoprost 0.0015 percent in four trials showed that participants receiving travoprost 0.004 percent were at increased odds of conjunctival hyperemia compared to those receiving 0.0015 percent (OR, 1.64; 95 percent CI, 1.32 to 2.04).[22]

There were no significant differences in reports of harms such as conjunctival hyperemia, dry eye, and increased pigmentation between latanoprost, brimonidine (α2 adrenergic agonist) or dorzolamide (carbonic anhydrase inhibitor) as reported by Fung (2007) and Hodge (2008).[19 20] However, there was an increased risk of fatigue reported by participants using brimonidine.

Li (2006), Loon (2008), Vass (2007), Zhang (2001) conducted separate comparison of timolol with brimonidine (α2 adrenergic agonist), prostaglandin analogs (travoprost, latanoprost), other β adrenergic antagonists, and placebo.[22-24 27] While there was a two-fold increase the odds of participant drop out due to drug-related adverse events among participants randomized to timolol versus betaxolol (OR. 2.40; 95 percent CI, 1.04 to 5.53, five trials), the odds of dropping out were lower among participants randomized to timolol when compared to those receiving brimonidine (OR, 0.21; 95 percent CI, 0.14 to 0.31, three trials).[27] As to the comparison of timolol with prostaglandin analogs, participants receiving either travoprost [22] or latanoprost [23] had six times the odds and twice the odds, respectively, of dropping out of the study due to conjuctival hyperemia, compared to patients receiving timolol. Both drugs also significantly increased iris pigmentation.

Conjunctival hyperemia and iris pigmentation were also significantly related to use of lantanoprost when compared to fixed and concomitant administration of timolol and dorzolamide. Cox (2008) concluded that adverse event reporting in studies of fixed versus concomitant medication formulations was inconsistent and the authors were thus unable to determine whether reports were associated with use of medications under investigation.[26]

Detailed Analysis of Primary Studies

We included 17 randomized controlled trials [37 47 30 48 53 54 55 44 50 56 57 58 31 59 35 52 36] and eight observational studies [60 61 62 63 64 65 66 67] that reported harms of medical treatment (See evidence tables 12 and 13 in Appendix C).

One of the primary studies, (an RCT that measured change in diurnal IOP), addressed harms of treatment and found no difference between bimatoprost and latanoprost with regard to ocular discomfort, conjunctival hyperemia, and ocular surface disease.[37]

Conjunctival Hyperemia

Conjunctival hyperemia is the most commonly reported adverse effect among the observational studies of medical treatment for OAG. Denis (2010) [60] conducted an open label uncontrolled 3-month study of once-daily use of 0.005 percent latanoprost in 258 ophthalmology practices that included 600 participants with OHT or OAG. Conjunctival hyperemia occurred in 10.7 percent of participants with an IOP between 20 and 23 mmHg and in 8.5 percent of participants with an IOP of 24 mmHg or greater. Eye pain was also reported among 3 percent of participants in each group. Chiselita (2007) [64] conducted an open label study of travoprost among 1,133 participants (1,109 analyzed). The most frequently reported adverse event was conjunctival hyperemia (6 percent) with severe cases requiring the withdrawal of travoprost in 10 participants. Thelen (2006) [65] reviewed medical data for 353 OHT participants treated with lananoprost for approximately two years. During this period the most frequently reported adverse event was ocular hyperemia, occurring in 20.7 percent of participants (73). Zimmerman (2003) [66] conducted a historically controlled study of 3.534 participants (3.245 analyzed) who were switched from prior monotherapy to latanoprost. Over the six months of follow-up the most frequently reported adverse effect was conjuntival hyperemia occurring in 2 percent of participants, and burning eyes, occurring in 1.4 percent of participants.

Other Harms

Barnett (2010) {#256} conducted a retrospective analysis of 1,636 Ocular Hypertension Treatment Study participants to determine the risk of retinal vein occlusion (RVO) among those randomized to medication versus those randomized to no treatment. Although there were 26 cases of RVO, the proportion of participants who developed RVO over 9 years of follow-up was 1.4 percent in the medication group and 2.1 percent in the control group ($p = 0.14$).

Farris 2008 {#878} conducted a retrospective study of 97 participants with 128 eyes receiving various concomitant medications with latanoprost and 60 eyes receiving travoprost. Within 3 months, two eyes in the concomitant treatment group experienced irritation (1.6 percent).

Sharpe (2007) [63] reviewed the charts of 236 participants using latanoprost and 137 using bimatoprost. Within 12 months of treatment, 6 percent of participants receiving bimatoprost and 1 percent receiving latanoprost experienced periocular pigmentation ($p = 0.004$).

Arıcı (2000) [67] compared the occurrence of ocular surface adverse effects among 24 OAG participants receiving betaxolol, 27 OAG participants receiving timolol, 26 OAG participants using betaxolol and dipivefrin hydrocholoride, and 30 control participants. OAG participants using topical medications were more likely to have fewer normal results from Schirmer's tests and tear break up time tests and also have higher conjunctival impression cytology scores ($p < 0.01$) than those in the control group.

Grading of Evidence

Because studies assessed a variety of different harms we did not complete a grading of evidence table for this question. There are a number of issues with assessing harms. For example, harms were not the primary outcome for the studies, meaning that the studies were not powered to detect differences. We judged the overall strength of evidence to be insufficient to make firm determination of differential harms for one therapy compared to another.

Conclusions

The harms of medical therapy for glaucoma are not consistently reported in a way that allows them to be easily analyzed across studies. Of the currently used medications, the prostaglandin agents are more likely to cause conjunctival hyperemia (redness) than timolol. Within the class of prostaglandins, latanoprost is less likely to cause redness than travoprost or bimatoprost and all three agents are similar with regard to ocular irritation, inflammation, cystoid macular edema, and iris pigmentation.

In a systematic review of timolol compared to other medications, subjects taking brimonidine, latanoprost, travoprost, or betaxolol were more likely to drop out of a study due to side effects than subjects taking timolol.

Surgical Treatment of Open-Angle Glaucoma

Systematic Reviews Of Surgical Interventions For Open-Angle Glaucoma

We included 10 systematic reviews that address the comparative effectiveness of surgical interventions for the treatment of OAG (Appendix C).

Chai (2010) and Cheng (2010) discuss comparisons of viscocanalostomy versus trabeculectomy,[68 69] with Cheng (2010) also compared viscocanalostomy to trabeculectomy with antimetabolites and deep sclerectomy to trabeculectomy (with or without antimetabolites).[69]

Wilkins (2005) and Wormald (2001) reviewed RCTs that compared primary trabeculectomy with antimetabolites versus trabeculectomy with placebo versus no treatment.[70 71] Wilkins (2005) included trials of the antimetabolite mytomycin C (MMC) and Wormald (2001) included trials of 5-Fluorouacil.

Kirwan (2009) compared trabeculectomy with beta radiation versus trabeculectomy with or without placebo.{#20054}

Rolim de Moura (2007) assessed the effectiveness of diode versus argon laser trabeculoplasty as well as SLT or trabeculectomy versus argon laser trabeculoplasty.{#50026}

Minckler (2006) compared the individual effectiveness of various aqueous shunts. The study also compared the effectiveness of these shunts with trabeculectomy and endocyclophotocoagulation.[72]

Finally, we identified four reviews addressing the comparative effectiveness of treatments for coexisting cataract and glaucoma.[8 70 73 74] Comparisons include one-site versus two-site phacotrabeculectomy; [73] extracapsular cataract extraction or phacoemulsification and trabeculectomy with intraoperative (MMC) versus extracapsular cataract extraction or phacoemulsification and trabeculectomy with placebo or no treatment[70] or with a postoperative injection of 5-Fluorouacil versus placebo or no treatment.[74].

Key Question 1b: What is the comparative effectiveness of laser and other surgical treatments for reducing visual impairment?

Key Points

- No studies reported on visual impairment after laser or other surgical treatments.
- We could not determine whether individual patients sustained a clinically important decrease in visual acuity, because in all our identified studies comparing laser and other surgical treatments for glaucoma, visual acuity outcomes were reported as a mean value and not assessed as a primary outcome.
- No single treatment appeared to have a greater effect on visual acuity than any other treatment.

Summary of Evidence from Systematic Reviews

Liu (2010) and Minckler (2006) addressed visual acuity outcomes after surgical treatment of glaucoma.[72 73] Liu (2010) found no difference in the percent of patients with a post operative best corrected visual acuity of 20/40 or better (two trials) when one-site phacotrabeculectomy was compared to two-site phacotrabeculectomy. Minckler (2006) reported that participants receiving endocyclophotocoagulation had a 0.24 higher mean difference in logMAR visual acuity at 24 months when compared to those receiving the Ahmed implant. A comparison in one trial of single plate Molteno implant with corticosteroids versus single plate Molteno implant alone revealed that participants receiving the implant with corticosteroids were 22 percent more likely to have stable vision at follow-up (unchanged or within one line difference from baseline) than those receiving the implant only. None of these differences were statistically significant.

Detailed Analysis of Primary Studies

We did not identify any studies that reported on the primary outcome of visual impairment. We identified four studies that reported on the secondary outcome of visual acuity.

De Jong (2009) reported a change from baseline visual acuity at 12 months in an RCT comparing trabeculectomy with Ex-press minishunt, both using intraoperative mitomycin C (MCC) at a concentration of 0.2 mg/ml (the duration of exposure was not specified).[75] Visual acuity was measured on an Early Treatment of Diabetic Retinopathy Study chart, but the manuscript does not specify whether patients were refracted either preoperatively or at 12 months. Two-thirds of patients had visual acuity that was unchanged, and about one-sixth had improved visual acuity and about one-sixth had decreased visual acuity. No definition of what constituted a change in acuity was provided.

Russo (2008) reported logMAR visual acuity results at 4 years in a trial in which patients received either a trabeculectomy or a non-penetrating deep sclerectomy with hyaluronic acid implant, both with MCC 0.2 mg/ml for two minutes.[76] They report that the mean logMar visual acuity in the trabeculectomy eyes changed from 0.8 (+/- 0.1) preoperatively to 0.4 (+/- 0.1) at 4 years, and that in the non-penetrating deep sclerectomy eyes the visual acuity changed from 0.7 (+/- 0.1) preoperatively to 0.6 (+/- 0.1) at 4 years. Although this would suggest an improvement in visual acuity after both procedures, especially in the trabeculectomy group, the authors conclusion that there was more vision loss in the trabeculectomy group makes their findings uninterpretable.

Mielke (2006) performed an RCT in West Africa comparing non-penetrating deep sclerectomy with and without intraoperative application of 0.25 mg/ml of MCC for 2 minutes.[77] In the group without MCC, three of 21 eyes (14 percent) lost more than two lines of Snellen acuity with a mean follow-up of 18.3 months, and in the group receiving MCC, three of 18 eyes (17 percent) lost more than two lines of Snellen acuity with a mean follow-up of 14.3 months.

Shaarawy (2005) randomly performed a nonpenetrating deep sclerectomy in one eye of 13 patients and a nonpenetrating deep sclerectomy with a collagen implant in the fellow eye.[78] They report aggregate visual acuity, expressed in Snellen fractions. In the eyes not receiving the collagen implant the preoperative, two-year, and four-year acuities were 0.67 (+/- 0.18), 0.56 (+/- 0.20), and 0.58 (+/- 0.20), respectively, and in the eyes receiving the collagen implant 0.66 (+/- 0.30), 0.58 (+/- 0.30), and 0.57 (+/- 0.3), respectively. The authors comment that the postoperative acuity was no different from the preoperative acuity, but offer no statistical support for their conclusion.

Table 5 Grading of Evidence

Number of studies : participants	Study Design/Risk of Bias	Consistency	Directness	Precision	Strength of evidence
OUTCOME					
Visual impairment/ Visual acuity					
4; 223	RCT/ Low	Inconsistent	Direct	Imprecise	Low

Conclusions

The literature is uninformative in addressing the question of the comparative effectiveness of laser and other surgical procedures in reducing visual impairment from glaucoma because no studies provide data on visual impairment.

Key Question 3b: What is the comparative effectiveness of laser and other surgical treatments for lowering intraocular pressure?

Key Points

- Trabeculectomy lowers IOP.
- The use of MCC intraoperatively with trabeculectomy results in lower IOP than when it is not used.
- Other alterations in surgical technique, location of surgery, and adjuvants other than MCC have not been shown to result in an added pressure decrease.
- Trabeculectom lowers IOP more than non-penetrating surgeries.
- The location of the conjunctival incision or the presence or absence of a peripheral iridectomy has no effect on how much combined cataract surgery and trabeculectomy lowers IOP. However, two-site surgery might produce an added pressure drop over one-site surgery.

- Laser trabeculoplasty effectively lowers IOP in glaucoma subjects; effectiveness does not seem to vary with the type of laser used.
- The data available for the role of aqueous drainage devices in OAG are inadequate to draw conclusions.

Summary of Evidence from Systematic Reviews

The authors of the included systematic reviews of trabeculectomy compared to non-penetrating filtering surgeries concluded that trabeculectomy is a more effective surgical intervention for lowering IOP. Chai (2010) noted that the mean IOP of participants receiving trabeculectomy was 3.64 mmHg lower at 12 months (six trials) and 3.42 mmHg lower at 24 months (three trials) than the IOP of participants treated with viscocanalostomy.[68] The outcomes were statistically significant, but the included studies enrolled participants with primary chronic angle closure glaucoma (1.7 percent of total included participants). Cheng (2010) confirmed this finding among participants with OAG.[69] In Cheng's study, there were fewer participants achieving normal endpoint IOP without medications or surgery (complete success) after one year in the viscocanalostomy group when compared to the trabeculectomy group (RD, -0.16; 95 percent CI, -0.30 to -0.02; three trials) and to the trabeculectomy with antimetabolite group (RD, -0.39; 95 percent CI, -0.53 to -0.24; three trials).

In a meta-analysis of five trials comparing deep sclerectomy to trabeculectomy, fewer deep sclerectomy participants achieved complete success (RD, -0.10; 95 percent CI, -0.19 to 0.00).[69] This finding was mirrored in an analysis of deep sclerectomy with MMC versus trabeculectomy with MMC (RD, -0.16, 95 percent CI, -0.32 to -0.01; two trials).

Wilkins (2005) and Wormald (2001) reported that the addition of antimetabolites to trabeculectomy significantly reduced IOP among participants enrolled in the included studies.[70][74] Wilkins (2005) determined after pooling the results of two trials that participants receiving intraoperative MMC had an average IOP that was 5.41 mm Hg lower than participants receiving placebo or no treatment at 12 months. A similar finding was reported among participants receiving postoperative 5-FU (WMD, -4.67; 95 percent CI, -6.60 to -2.74; two trials).

The addition of beta radiation to trabeculectomy does not appear to reduce IOP more than trabeculectomy alone as Kirwan (2009) reported no difference in the mean IOP of participants treated with trabeculectomy and beta radiation compared to participants receiving trabeculectomy only, at one year after surgery (WMD, -0.97; 95 percent CI, -2.56 to 0.62; two trials).[79]

Rolim de Moura (2007) reported (in two studies) no difference in the risk of failure (defined as an IOP greater than or equal to 22) when diode and argon laser trabeculoplasty were compared at one year (relative risk [RR], 3.0; 95 percent CI, 0.37 to 24.17) and two years follow-up (RR, 0.50; 95 percent CI, 0.10 to 2.43) and when SLT was compared to argon laser trabeculoplasty at one year (RR, 1.27; 95 percent CI, 0.84 to 1.90).[80] When argon laser trabeculoplasty was compared to trabeculectomy across two trials at 24 months, participants randomized to argon laser trabeculoplasty were 2.03 times more likely to be at risk for failure than participants randomized to trabeculectomy (95 percent CI, 1.38 to 2.98).

Three of the four systematic reviews addressing surgical treatments for coexisting cataract and glaucoma include pooled results for IOP, but these analyses also include results of studies with angle closure glaucoma participants in addition to OAG participants. Liu (2010) pooled the results of five trials that compared one-site to two-site phacotrabeculectomy and concluded that two-site phacotrabeculectomy significantly lowered IOP by an average of 6

percent more than one-site phacotrabeculectomy, from baseline to 12 or more months after surgery.[73] Wilkins (2005) reported significant improvements in mean IOP at 12 months with the addition of MMC to extracapsular cataract extraction with trabeculectomy when compared to placebo or no treatment (WMD, -3.34; 95 percent CI, -4.16 to -2.51; three trials).[70] Wormald (2001) noted no significant difference in mean IOP at 12 months when postoperative 5-FU is used as an antimetabolite versus placebo or no treatment (WMD, -1.02; 95 percent CI, -2.40 to 0.37).[74] Jampel (2003) provided a qualitative synthesis of the evidence on surgical treatment of coexisting cataract and glaucoma from literature searches conducted between 1980 and April 2000.[8] The investigators found that use of the antimetabolite MMC improves outcomes and is more beneficial than 5-FU, that there are no differences in outcomes with limbal- and fornix-based conjunctival incisions, and that the risk of postoperative cataract increases with glaucoma surgery. Jampel (2003) concluded that the evidence did not support use of one strategy for IOP control over any other and that more research is needed particularly addressing the long-term progression of visual field loss and optic nerve damage.

Minckler (2006) reported the results of trials of aqueous shunts for all types of glaucoma.[72] Overall, trabeculectomy performed better than the Ahmed implant. The mean IOP in the trabeculectomy group was 3.81 mm Hg lower than the IOP in the Ahmed implant group (two trials). Outcomes from single trials comparing endocyclophotocoagulation and Ahmed implant failed to show a difference in mean IOP at 12 months (MD 1.14; 95 percent CI, -1.93 to 4.21) and 24 months (MD, 0.66; 95 percent CI, -2.98 to 4.30). The comparisons of various shunts to each other or a single shunt compared with or without the use of antimetabolites were from single studies addressing these questions. Minckler (2006) reported no difference in mean IOP at 12 months when the Ahmed or Molteno implants were compared with or without the addition of MMC. Additionally there were no differences in high-pressure versus standard Ahmed implant, double-plate Molteno and Schocket shunts and single-plate Molteno implants with or without use of oral corticosteroids. As of the January 2006 search date for this review, there were few studies of aqueous shunts and thus the authors concluded that the evidence was insufficient for reaching any conclusions regarding the comparisons included in the review.

Detailed analysis of Primary Studies

Trabeculectomy has long been considered the mainstay of incisional surgery for lowering IOP. It's often performed at the same time as cataract surgery, because many patients have concurrent cataract and glaucoma. We included 19 randomized controlled trials: Three involving trabeculectomy technique, six evaluating adjuvants at the time of trabeculectomy, four comparing trabeculectomy with variations of trabeculectomy or other glaucoma surgery, two addressing surgical techniques in combined cataract and glaucoma surgery, two addressing combining cataract surgery with glaucoma surgery other than trabeculectomy, and one studying deep sclerectomy.

Trabeculectomy Techniques

Location of Surgery

Sanders (1993) in Scotland randomized 60 presumably Caucasian patients undergoing fornix-based trabeculectomy without antifibrosis agent to three different ocular sites for the surgery--nasal, superior, or temporal.[81] No patient had undergone previous laser or intraocular surgery. At 18 months after surgery, the mean IOP was 14.5, 17.5 and 18.2 mm Hg for the three sites respectively. The IOPs for the nasal versus the temporal sites were statistically significantly

different (p = 0.01). Although the numbers were too small for statistical analysis, eyes with a nasal trabeculectomy seemed to have more discomfort, more wound leaks, and were associated with more corneal dellen.

Fornix vs Limbus Conjunctival Incision

El Sayyad (1999) randomly assigned one eye to fornix-based trabeculectomy and one eye to limbus-based trabeculectomy in 28 patients undergoing bilateral first-time trabeculectomies.[82] Postoperative injections of 5-FU were used. Starting from a similar preoperative IOP of 33 mm Hg in each eye, IOPs were similar in both eyes, with a mean of 12 mm Hg at one year after surgery and 13 mm Hg at two years after surgery. Two late bleb leaks were noted in the limbus-based eyes and none in the fornix-based eyes.

Laser Suture Lysis vs. Adjustable Sutures

Kobayashi (2010) randomized 50 Japanese patients with OAG undergoing a fornix-based trabeculectomy with MMC to either scleral flap sutures requiring laser suture lysis after surgery or adjustable sutures that could be manipulated with a forceps.[83] Both groups had a preoperative IOP of approximately 27 mm Hg. One year after surgery the IOP was 12.9 mm Hg in the adjustable suture group and 12.3 in the laser suture lysis group.

Trabeculectomy with Adjuvants

Mitomycin C. Reibaldi (2008) recalled patients who participated in a clinical trial in which patients with primary OAG received a limbus-based trabeculectomy with either balanced salt solution or 0.2 mg/ml of MMC applied on a sponge for 2 minutes.[84] The preoperative IOP was 25 mm Hg in both groups with an average of three medications in each group. Of the 133 patients who entered the study, 114 were re-examined at a mean of 10 years in both groups, with mean IOP of 13.3 mm Hg in the MMC treated group and 14.7 in the balanced salt solution group (p=0.014). Using Kaplan-Meier curves, the authors determined that the success rate, defined as an IOP of 18 mm Hg or less was 75 percent for MMC and 55 percent for balanced salt solution (p=0.02).

Length of Mitomycin C Application. Kim (1998) randomized phakic patients undergoing their first trabeculectomy to receive either a 0.50-1 minute or a 3-5 minute application of 0.5 mg/ml of MMC.[85] A limbus-based conjunctival flap was used. These eyes were compared to a group of similar historical controls that did not received MMC. The preoperative intraocular pressures, which ranged from 29.7 to 32.7 mm Hg were not statistically significant. The mean intraocular pressure and mean number of postoperative medications at one year, estimated from the figures, were 15 mm Hg with one postoperative medication, 12 mm Hg with 0.5 postoperative medication, and 11 mm Hg with 0.3 medications (for the **no MMC, 0.5-1 minute exposure to MMC, and the 3-5 minute exposure to MMC groups respectively).**

5-Fluorouracil vs. Fibrinolytic Drug. Quaranta (2000) randomized eyes undergoing their first trabeculectomy, done with a fornix-based flap, to either postoperative injections of (5-FU)or sulodexide, a fibrinolytic drug, on 10, 17, 24, 31, and 38 days after surgery.[86] Preoperative IOP was comparable in both groups at about 27 mm Hg, and at one year after surgery was 15.5 mm Hg in the sulodexide eyes and 14.8 mm Hg in the 5-FU eyes. There were two bleb leaks requiring surgical repair in the 5-FU group and none in the sulodexide group**.**

Olegen Implant

Rosentreter (2010) randomized 20 eyes of 20 Caucasian patients undergoing fornix-based trabeculectomy to either MMC 0.2 mg/ml for three minutes or an Olegen (porous collagen-glycosaminoglycan matrix) implant placed on top of the scleral flap.[87] Despite the small number of patients limiting the power of the study, the authors were able to conclude that the IOP at one year after surgery (11.3 mm Hg for the MMC treated group and 15.6 mm Hg for the Olegen treated group) as well as the requirement for IOP lowering medications (0.0 for the mitomycin treated group versus 0.8 for the Olegen treated group), were both statistically significant (p=0.01 for IOP and p=0.05 for medications).

Amniotic Graft

Eliezer (2006) randomized 32 patients, undergoing trabeculectomy using a limbus-based incision without an antifibrosis agent, to either receive or not receive an amniotic membrane graft intraoperatively.[88] The amniotic membrane graft was sewn to the sclera, over the trabeculectomy flap because of its potential to decrease scarring and improve the success of the surgery. At one year, the IOP was 15.2 mm Hg in the eyes not receiving amniotic membrane and 12.8 in eyes receiving amniotic membrane, however this difference was not statistically significant (p=0.3).

Polytetrafluoroethylene Membrane

Cillino (2008) performed an RCT to evaluate the effect of placing a pericardial expanded polytetrafluoroethylene membrane underneath the scleral flap during trabeculectomy in eyes without previous ocular surgery.[89] Sixty Caucasian patients with either OAG or pseudoexfoliation glaucoma, were randomized to one of four groups: trabeculectomy alone, trabeculectomy with MCC, trabeculectomy with membrane, or trabeculectomy with both MCC and membrane. Preoperative IOPs ranged from 28 to 35 mm Hg. At one year after surgery, mean IOP ranged from 16.4 to 17.4 mm Hg, with no difference between the four groups. Avascular blebs were noted in eyes receiving MCC but not in the other two groups.

Trabeculectomy Compared To Trabeculectomy Variants And Other Glaucoma Procedures

Minitrab**.** Thimmarayan (2006) randomly assigned 60 eyes of 54 subjects to either a conventional trabeculectomy (although they do not describe the surgical technique) or a "mini-trabeculectomy" in which a smaller than usual fornix-based conjunctival flap is made, and in which a scleral tunnel is created instead of a scleral flap.[90] Ten percent of the eyes received postoperative 5-FU on an "as needed" basis. IOP was lowered in both groups from 28 mm Hg preoperatively to 16 mm Hg 15 months after surgery. The mini-trabeculectomy group appeared to have more hypotony, and shallower anterior chamber depths in the immediate postoperative period, but evidently the differences did not reach statistical significance.

Das (2002) randomly assigned 80 eyes of 80 subjects with OAG to either a limbus-based trabeculectomy without antifibrosis agent or a fornix-based trabeculectomy using a small incision and avoiding Tenon's capsule.[91] The preoperative IOP was 30 mm Hg in each group. At one year after surgery the mean IOP was 18.9 in the trabeculectomy group and 16.6 mm Hg in the small incision group (p=0.6), with 0.38 IOP-lowering medications in the trabeculectomy group as opposed to 0.25 IOP-lowering medications in the small incision group (p=0.025). There were no differences noted in either early or later postoperative complications between the two groups.

Ex-Press Shunt. De Jong (2009) performed an RCT comparing two limbus-based trabeculectomies using MCC. One with the implantation of an Ex-press minishunt underneath a trabeculectomy flap and one without in 80 eyes of 78 patients.[75] The preoperative IOP was 22.8 mm Hg in the Ex-press group and 21.5 mm Hg in the trabeculectomy group, and one year after surgery the respective IOPs were 12.0 mm Hg and 13.9 mm Hg, respectively (p=0.02). Complications were not common and similar between the two groups.

Deep sclerectomy with SK-Gel. Russo (2008) enrolled 93 Italian patients with primary OAG, who had baseline IOP of about 25.5 mmHg and had not had previous surgery, in a randomized comparison of non-penetrating deep sclerectomy with SK-Gel versus traditional trabeculectomy with MCC, and followed subjects at three and four years.[76] Mean IOP was similar between the two groups at 36 and 48 months, but on average fewer medications were required in the trabeculectomy group. At 4 years, the two groups appeared to have differential outcomes with 72 percent of the trabeculectomy group having IOP greater than 21 mmHg without medicines versus 51 percent in the deep sclerectomy group ($p<0.05$). However, there were no statistically significant differences in achieving this IOP criterion when allowing for medication use by patients. Cataracts and flat anterior chambers were more common with trabeculectomy. In summary, IOP outcomes were similar, but more medications were required in the deep sclerectomy group.

Combined Cataract and Trabeculectomy Surgery Techniques

Peripheral **I**ridectomy. Kaplan-Messas (2009) performed a small clinical trial in which patients undergoing either trabeculectomy with MCC (n=11) or combined phacoemulsification and trabeculectomy with MCC (n=36), were randomized to either receive, or not receive, a peripheral iridectomy at the time of surgery.[92] Given that their power to detect differences between the two groups must have been low, they found no difference in reduction of IOP with or with peripheral iridectomy. One eye in the group without an iridectomy had iris incarceration in the wound as opposed to none in the group with an iridectomy**.**

Fornix vs limbus conjunctival incision. Kozobolis (2002) performed bilateral phacoemulsification and trabeculectomy with MCC using a two-site (separate incisions for the phacoemulsification and trabeculectomy) approach in 22 patients.[93] One eye was randomly assigned to a fornix-based trabeculectomy and the other to a limbus-based trabeculectomy. At one year after surgery there was no difference in the mean IOP (15 mm Hg) or the mean number of IOP lowering medications (0.3). Although the numbers were small, the authors observed faster visual recovery after surgery in the fornix-based trabeculectomies. but more bleb leaks.

Combined cataract and other (non-trabeculectomy) glaucoma surgery

Micro-bypass stent. Fea (2010) randomized patients with OAG under medical treatment needing cataract surgery to either phacoemulsification cataract surgery alone or phacoemulsification cataract surgery plus implantation of a single micro-bypass stent (iStent, Glaukos).[94] The preoperative IOP was 17.9 mm Hg on an average of 2.0 medications in the iStent group and 17.3 mm Hg on an average of 1.9 medications in the control group. Sixteen months after surgery (after a one month washout of all IOP lowering medications) the IOP was lower in the group receiving the iStent (16.6 mm Hg) than in the group not receiving the iStent (19.2 mm Hg, p=0.04).

Comparing Trabeculectomy with Viscocanalostomy

Kobayashi (2007) randomized one eye of each of 40 Japanese patients with primary OAG and visually significant cataract to either phacoemulsification cataract surgery with limbus-based trabeculectomy or to phacoemulsification cataract surgery and viscocanalostomy.[95] MMC was applied at a concentration of 0.4 mg/ml for 3 minutes. The preoperative IOP of the eyes randomized to viscocanalostomy was 24.0 mm Hg on an average of 2.8 medications, In the trabeculectomy group, IOP was 23.7 mm Hg on an average of 2.6 medications. There were no significant differences in IOP between the two groups at 1, 3, 6, and 12 months after surgery. At 12 months, the mean IOP was 14.9 mm Hg on an average of 0.2 medications in the viscocanalostomy group and 14.1 mm Hg on an average of 0.1 medications in the trabeculectomy group.

Other Glaucoma Operations

Deep sclerectomy with and without mitomycin C. Mielke (2006) performed a small RCT of 39 Nigerian patients with POAG without prior surgery to assess the benefit of using MMC in deep sclerectomy.[77] Deep sclerectomy (with or without MMC) resulted in an IOP of less than 18 mmHg at 18 months in less than 25 percent of both groups. The study was underpowered to determine if IOP differed between the two groups.

Laser Trabeculoplasty.

One study compared argon laser trabeculoplasty to SLT.[96] As initial laser treatment in subjects already on medical therapy, the two procedures showed similar efficacy with IOP decreasing 6.01 mmHg in the SLT group and 6.12 mmHg in the argon laser trabeculoplasty group (p = NS). When used in eyes that had failed prior angle treatment, SLT resulted in a greater reduction in IOP than argon laser trabeculoplasty (6.24 mmHg versus 4.65 mmHg, $p<0.01$)

Another study of titanium-sapphire laser trabeculoplasty compared to argon laser trabeculoplasty found no significant difference in the reduction of IOP between the two (8.3 versus 6.5 mmHg, p = non-significant).[97]

Finally, the study by Frenkel (1997) found that 35 applications over 120 degrees resulted in similar reduction of IOP when compared to 50 applications over 180 degrees (3.9 mmHg versus 4.4 mmHg, p = 0.63).[98]

Table 6 Grading of Evidence

Number of studies : participants	Risk of bias	Consistency	Directness	Precision	Strength of evidence
OUTCOME					
Intraocular pressure					
119;1120	RCT/Medium	Consistent	Direct	Precise	Moderate

Conclusions

Trabeculectomy has been repeatedly demonstrated to lower IOP to a mean level in the low to mid teens. Its IOP lowering effect is potentiated by the use of MCC intraoperatively, but does not appear to be increased by alterations in surgical technique, or the addition of implants designed to improve wound healing. One small study reported slightly lower IOPs with the Express mini-shunt compared to trabeculectomy. Combined cataract surgery with glaucoma surgery lowers IOP more than cataract surgery alone, but less then trabeculectomy alone.

The studies identified regarding laser trabeculoplasty consistently show a decrease in IOP with treatment but are not adequate to draw strong conclusions with regard to the type of laser used or the number of applications.

Key Question 4b: What is the comparative effectiveness of laser and other surgical treatments for preventing or slowing the progression of optic nerve damage and visual field loss?

Key Points

- No comparative studies looking at laser and surgical treatments presented data on whether or not these procedures slow the progression of optic nerve damage and visual field loss.

Summary of Evidence from Systematic Reviews

We did not identify any systematic reviews of surgical interventions for OAG that included outcomes related to optic nerve damage or visual field loss.

Detailed Analysis of Primary Studies

We did not identify any primary studies of surgical interventions for OAG that included outcomes related to optic nerve damage or visual field loss. However, outcomes related to optic nerve damage and visual field loss are discussed in reference to Key Question 4c, comparing the effectiveness of medical and surgical interventions.

Key Question 6b: What are the harms associated with laser and other surgical treatments for open-angle glaucoma?

Key Points

- Trabeculectomy results in more complications than non-penetrating surgeries
- The profile of harms does not differ between one- and two- site combined cataract and glaucoma surgery

Summary of Evidence from Systematic Reviews

Chai (2010) and Cheng (2010) concluded that adverse effects were experienced more often by participants randomized to trabeculectomy when compared to participants randomized to other nonpenetrating filtering surgeries.[68 69] Hypotony, hyphema, shallow/flat anterior chamber, and cataract were all more frequent among participants treated with trabeculectomy

compared to viscocanalostomy and deep sclerectomy. Cheng (2010) additionally noted a significantly higher risk of choroidal detachment among participants receiving trabeculectomy versus both viscocanalostomy and deep sclerectomy.[69]

Wilkins (2005) and Wormald (2001) reported harms for the addition of antimetabolites to primary trabeculectomy. The risk of epithelial toxicity was 5.85 times greater with the addition of postoperative 5-FU in participants receiving primary trabeculectomy (95 percent CI, 2.04 to 16.83).[74] Wilkins (2005) noted that wound leak, hypotony, and cataract were more often reported among those receiving preoperative MMC, but these differences were not statistically significant.[70]

The addition of beta radiation to trabeculectomy resulted in significantly higher risk of cataract when compared to trabeculectomy alone (RR, 2.89; 95 percent CI, 1.39 to 6.00).[79] The risk of hypotony was higher while the risk of bleb leaks was lower, but the confidence intervals overlapped the line of no difference.

Diode laser trabeculoplasty treatment resulted in a lower, but not significant, risk of peripheral anterior synechiae (RR, 0.54; 95 percent CI, 0.17 to 1.76, one trial) and early IOP spikes (RR, 0.66; 95 percent CI, 0.21 to 2.14, three trials) when compared to argon laser trabeculoplasty.[80]

Reports of adverse effects across studies that addressed questions related to combined surgery for co-existing cataract and glaucoma varied by intervention under consideration. There were no differences in the risk of hyphema, choroidal detachment, and hypotony when one-site phacotrabeculectomy was compared to two-site phacotrabeculectomy.[73] The odds of wound leak (1.88), hypotony (1.65), and endophthalmitis (3.44 and 1.14) were greater among participants randomized to receive MMC with trabeculectomy in addition to cataract extraction (Wilkins (2005)).[70] Additionally the risk of wound leak was 17 percent lower among participants receiving postoperative 5-FU with cataract extraction and trabeculectomy while the risk of epithelial toxicity was three times greater among those receiving 5-FU (95 percent CI, 1.56 to 5.92). As it was with primary trabeculectomy, epithelial toxicity was significantly different among participants exposed and not exposed to 5-FU.

Reports of the complications of aqueous shunts across the five trials included in the Minckler (2006) review were not amenable to meta-analysis due to the unavailability of key data from the original manuscripts.[72] Minckler (2006) noted that there were limited reports of choroidal hemorrhage with the single-plate, double-plate, and pressure-ridge double-plate Molteno implants. One study reported several cases of choroidal complications, corneal complications, and strabismus with the 350-mm and 500-mm Baerveldt implants (13/55 and 19/52 respectively for choroidal hemorrhage; 17/55 and 19/52 for corneal failure; and 10/55 and 8/52 for strabismus). Other harms noted include no light perception, phthisis, tube exposure, retinal detachment, and infection.

Detailed Analysis of Primary Studies

We included 22 randomized controlled trials [87 83 97 96 75 92 76 84 90 88 77 93 99 91 86 82 100 101 81 102 103 89] and three observational studies [104 105 106] that addressed questions of harms related to surgical treatment of OAG.

Nassiri (2008) reviewed the medical records of 61 participants receiving one-site phacotrabeculectomy and 52 participants receiving two-site phacotrabeculectomy.[104] Over a 1-year follow-up period, the percent difference in the mean of corneal endothelial cell area was

greater with two-site phacotrabeculecomy (38.04 percent) than one-site (32.46 percent) ($p<0.001$).

Jeganathan (2008) conducted a case control study of 29 cases of delayed suprachoroidal haemorrhage (DSCH) identified over a 10-year period from a total of 2,752 glaucoma surgeries.[105] Prior intraocular surgery (pars plana vitrectomy and penetrating keratoplasty) was associated with a 4.4 higher odds of DSCH. Other risk factors included postoperative hypotony defined as an IOP less than or equal to 3 mm Hg within the first week (OR 2.7; 95 percent CI 1.8 to 4.3). There was no association of DSCH with combined surgeries or preoperative or immediate postoperative IOP.

Shingleton (2002) conducted a retrospective study of 117 participants (126 eyes) randomized to phacotrabeculectomy with MCC with peripheral iridotomy (PI) (66 eyes) or without PI (60 eyes).[107] The most frequently reported harms/complications included posterior capsule opacification among participants receiving PI (34.8 percent) and those not receiving PI (40 percent) and capsulotomy (22.7 percent and 11.7 percent among the PI and no- PI group respectively).

Grading of Evidence

Because studies assessed a variety of different harms, we did not complete a grading of evidence table for this question. There are a number of issues with assessing harms. For example, harms were not the primary outcome for the studies, meaning that the studies were not powered to detect differences. We judged the overall strength of evidence to be insufficient to make firm determination of differential harms for one therapy compared to another.

Conclusions

Trabeculectomy, when compared to the non-penetrating procedures of deep sclerectomy or viscocanalostomy, produces more hypotony, hyphema, shallow anterior chambers, cataract, and choroidal detachment.

There is no clear difference in harms produced by one-site versus two-site combined cataract extraction and trabeculectomy.

The harms associated with glaucoma drainage devices have not been adequately compared to the harms of other procedures in the treatment of OAG.

Medical versus Surgical Treatment of Open-Angle Glaucoma

This section summarizes systematic reviews, and any additional primary studies not included in those systematic reviews, of medical versus surgical treatment of OAG. It also includes various combinations of medical and surgical treatment versus other treatment (medical, surgical, or no treatment).

Systematic reviews of medical versus surgical interventions for open-angle glaucoma

We included two systematic reviews that summarize comparisons of surgical and medical treatments of OAG. One additional systematic review includes comparisons of medical and/or surgical treatments with a concurrent no treatment group among participants with ocular hypertension, OAG, or normal-tension glaucoma.

Burr (2004) summarized the evidence from three RCTs addressing the effect of initial medical treatment versus initial trabeculectomy for preventing the progression of visual field loss and optic nerve damage.[108] Two of the studies assessed patients with "severe" glaucoma, one assessed "mild" glaucoma and the final one did not state the baseline glaucoma status. Medicines and surgical techniques have evolved since this review -- two of the studies were initiated before 1990 when prostaglandins were not available. Furthermore, visual field testing has also evolved substantially.

Maier (2005) reviewed five clinical trials of participants with ocular hypertension randomized to either medical and/or surgical treatment to lower IOP or to no treatment.[109]

Rolim de Moura (2007) summarized the evidence from 19 randomized controlled trials comparing laser trabeculoplasty alone to medical treatment, another surgical treatment (trabeculectomy), and a different type of laser trabeculoplasty.[80] Rolim de Moura (2007) also included comparisons of laser trabeculoplasty plus medical treatment to no treatment and comparisons of alternative trabeculoplasty techniques (six studies - not discussed in this report).

Key Question 1c: What is the comparative effectiveness of medical versus surgical treatment for reducing of visual impairment?

Key Points

- Although it appears that trabeculectomy may reduce the risk of vision loss, after adjusting for demographic and comorbid factors, the body of evidence is limited and inconclusive.

Summary of Evidence from Systematic Reviews

Burr (2004) reported that in two trials with reports of visual acuity outcomes, there were no significant differences in visual acuity (mean or loss of two or more Snellen lines) when trabeculectomy was compared to medical treatment.[108] The investigators of a third trial reported that participants receiving trabeculectomy experienced a 53 percent lower risk of losing two or more Snellen lines of visual acuity (0.3 LogMAR) after adjustments for demographic factors and comorbidities including cataract requiring surgery (95 percent CI, 0.31 to 0.74).

Detailed Analysis of Primary Studies

We did not identify any primary studies of medical versus surgical interventions for OAG that included outcomes related to visual impairment or visual acuity.

Grading of Evidence

Not applicable as we did not identify evidence from primary studies addressing this question.

Conclusions

There is limited evidence in the literature regarding visual acuity outcomes when comparing medical to surgical treatments for glaucoma.

Key Question 3c: What is the comparative effectiveness of medical versus surgical treatment for lowering intraocular pressure?

Key Points

- Incisional surgery lowers IOP more than lasers or medications.
- Initial treatment with lasers tends to reduce the need for medications to achieve the same IOP.

Summary of Evidence from Systematic Reviews

Burr (2004) reported that the IOP of participants randomized in two trials to trabeculectomy was 6.14 mmHg lower than participants receiving medical treatment at one year (95 percent CI, 4.25 to 8.02).[108] In the third included trial, the mean difference at one year was on average 3.6 mmHg lower with trabeculectomy (95 percent CI, 2.78 to 4.42).

In one trial, there was a 1.6 mmHg difference in IOP between 2 to 4 years of follow-up (95 percent CI, -0.69 to 3.89), and a 3.4 mm Hg difference in favor of trabeculectomy at 5 years (95 percent CI, 1.04 to 5.76, one trial). In another trial that followed participants for 5 years, the mean difference in IOP in the group receiving trabeculectomy was 1.9 mm Hg (95 percent CI, 0.85 to 2.95). This finding was not statistically significant.

Rolim de Moura (2007) reported that the risk of experiencing an IOP greater than or equal to 22 mmHg (failure) at one year among participants receiving argon laser trabeculoplasty versus medical treatment was 92 percent lower in one trial (95 percent CI, 0.02 to 0.31) and 59 percent lower in a second trial (95 percent CI, 0.22 to 0.77).[80] At 24 months, the risk of failure was 20 percent lower with argon laser trabeculoplasty compared to medical treatment (95 percent CI, 0.71 to 0.91, two trials).

Detailed Analysis of Primary Studies

Only a small number of articles compared IOP outcomes between medical and surgical therapy and the treatments compared were dissimilar. We therefore did not perform meta-analysis.

Tuuolonin (1989) enrolled 191 consecutive Finnish treatment-naive phakic patients with primary OAG or pseudoexfoliation glaucoma (PXG) in an RCT comparing laser trabeculoplasty to medical therapy.[33] Outcomes from 39 participants were available at one year. Nearly half of the patients receiving laser were subsequently treated with medications. The reduction of IOP was slightly greater in the laser trabeculoplasty group.

Lai (2004) randomized one eye of each patient (n=29) to either SLT or medical therapy (baseline IOP was about 26 mmHg, medications used were not stated).[110] While more medications were required in the eyes that did not have SLT, the IOP was lowered about 8.5 mmHg in both groups (however, nearly one-fifth required surgery within 5 years). Eyes treated with SLT required fewer medications over 5 years of follow-up (total 24 subjects).

Migdal (1986) was included in existing systematic reviews but we include a brief description here.[111] In this study, Migdal (1986) randomized 168 primary OAG patients with IOP greater than or equal to 24 mmHg (mean around 35 mmHg) to medicines (pilocarpine, sympathomimetic, and/or timolol), laser (360 degrees in two sessions) or trabeculectomy without antimetabolite. Mean IOP was similar in the medicine and laser groups (around 21 mmHg with

some having failed and advanced to other therapy) and around 14 mmHg in the surgery group at one year. Failures of each therapy were excluded from mean IOP reported values in all follow-up reports,[112] but almost none of those assigned to surgery developed IOP greater than 22 mmHg whereas about 20 percent in the medicine group and 30 percent in the laser group had elevated IOP within 5 years (which meant that IOP could not be kept below 23 mmHg with pilocarpine alone).

Table 7 Grading of Evidence

Number of studies : participants	Risk of bias	Consistency	Directness	Precision	Strength of evidence
OUTCOME					
Intraocular pressure					
2; 220	RCT/Medium	Consistent	Direct	Imprecise	Low

Conclusions

IOP is lowered more by trabeculectomy than by laser or medical treatment. Treating with lasers lowers IOP and when compared to treating with medications reduces the number of medications needed to keep IOP at the same level.

Key Question 4c: What is the comparative effectiveness of medical versus surgical treatment for preventing or slowing the progression of optic nerve damage and visual field loss?

Key Points

- Trabeculectomy first may lead to better preservation of visual field than medicines first in more advanced glaucoma.
- The Collaborative Initial Glaucoma Treatment Study included surgical techniques and medications that are current and found no difference in change in visual field (and did not report on change in the optic nerve).
- Treatment of ocular hypertension with medicines preserves visual fields better than no treatment.

Summary of Evidence from Systematic Reviews

Maier (2005) summarized the evidence from five RCTs, which randomized participants with ocular hypertension to either medical and/or surgical treatment to lower IOP, or to no treatment.[109] Participants receiving topical medications were 44 percent less likely to experience progression of visual field loss and optic disc damage when compared to participants receiving no treatment (HR 0.56; 95 percent CI, 0.39 to 0.81). Among participants with primary OAG (two trials), medically and/or surgically treated participants were 35 percent less likely to experience

progression of field loss and optic disc damage when compared to participants receiving no treatment. This finding was mirrored in a subgroup analysis (two trials) of participants with normal tension glaucoma (HR 0.70; 95 percent CI, 0.48 to 1.02).

Burr (2004) reviewed the evidence from three RCTs addressing the effect of initial medical treatment versus initial trabeculectomy for preventing the progression of visual field loss and optic nerve damage.[108] In one trial, at a mean of 4.6 years of follow-up, 26 percent of participants undergoing trabeculectomy compared with 47 percent medically treated participants experienced progression of visual field severity of one stage or more (OR, 2.56; 95 percent CI, 1.12 to 5.83).

In the second trial that examined participants with IOP less than 22 mm Hg at 5 or more years of follow-up, visual field progression was more likely in medically treated participants than those receiving trabeculectomy. Using the mean of the first three visual field scores compared to the mean of the last three scores, medically treated participants scored on average four points higher than those in the trabeculectomy group (MD, 3.92; 95 percent CI, 2.02 to 5.82). In this same trial, the investigators found no difference in progression of visual field loss measured by Humphrey automated perimetry in the trabeculectomy group (71 percent) versus the medical treatment group (63 percent) (OR, 0.69; 95 percent CI, 0.29 to 1.67).

In the third trial, there was no difference in the mean change in visual field score at one year in the unadjusted analysis (MD, -0.5; 95 percent CI, -1.10 to 0.10) and five years (MD, 0.30; 95 percent CI, -0.45 to 1.05), but the investigators reported a significant difference after adjusting for demographic factors (age, gender, race) and baseline visual field score. The medical treatment group's change in visual field score was lower than the trabeculectomy group (MD, -0.36; 95 percent CI, -0.67 to -0.05) suggesting less progression among those receiving medical treatment. Further adjustments for the incidence of cataract requiring surgery resulted in mean scores that were not different among the groups of interest (MD, -0.28; 95 percent CI, -0.59 to 0.03).

Two trials included in the Rolim de Moura (2007) review compared ALT to medications in newly diagnosed glaucoma patients and reported on visual field outcomes.[80] The risk of visual field loss among participants randomized to laser trabeculoplasty was 23 percent lower when compared to participants receiving medical treatment at one year (RR, 0.77; 95 percent CI, 0.46 to 1.28) and 30 percent lower at two years (RR, 0.70; 95 percent CI, 0.42 to 1.16).

Detailed Analysis of Primary Studies

A limited number of trials with optic nerve and visual field outcomes met our inclusion criteria. Given the methodological heterogeneity of these studies, we present a narrative summary of the results.

Two studies, included in existing systematic reviews, warrant mention. Jay (1989) enrolled 116 newly diagnosed patients with primary OAG who had untreated IOP greater than 25 mmHg on two occasions in an RCT comparing medical therapy (up to three medications followed by trabeculectomy) to trabeculectomy from 1980 - 1985.[102] Additional therapy was provided at the discretion of the treating clinician. Visual fields were followed using a Tubingen perimeter and categorized by severity with a one grade worsening of the visual field considered "progression." Those undergoing surgery had more stable fields than those started with medical therapy. Based on results from survival analysis, surgery appeared to preserve visual field more in those with mild field loss than those with more severe field loss at baseline. This study showed

a benefit of surgery first on the visual field, but the baseline IOP was very high (in the upper 30s) for the group as a whole and the results may not apply to those with lower baseline IOP.

In a study included in the existing systematic reviews, Migdal (1986) assessed visual field outcomes using Friedman automated visual field tests in 168 POAG patients randomized to surgery, medicines (pilocarpine, sympathomimetics, and/or timolol) or laser SLT and found that visual field score did not change significantly over 5 years in the surgery group, but did worsen in both the other arms.[112]

Our systematic review identified on eligible RCT. Tuuolonin (1989) enrolled 191 consecutive Finnish treatment-naive phakic patients with primary OAG or PXG in an RCT comparing laser trabeculoplastySLT to medical therapy and reported on 39 of these at one year.[33] No significant changes in visual field or optic nerve were noted in the two groups, but duration of follow-up was short and the number of patients completing one year was small.

Table 8 Grading of Evidence

Number of studies : participants	Domains pertaining to strength of evidence	Consistency	Directness	Precision	Strength of evidence
OUTCOME	Risk of bias	Consistency	Directness	Precision	
Visual field					
1;191	RCT/High	Not Applicable	Indirect	Imprecise	Insufficient
Optic nerve changes					
1;191	RCT/High	Not applicable	Direct	Precise	Insufficient

Conclusions

Based on systematic reviews and additional primary studies, both medical and surgical treatments decrease the risk of incident or worsening of visual field loss, but initial surgery may be more effective in this regard.

Key Question 6c: What harms are reported in studies of medical versus surgical treatments for open-angle glaucoma?

Key Points

- Trabeculectomy is associated with cataract worsening and an increased need for cataract surgery over time when compared to medical treatments for glaucoma.
- Intraocular surgery rarely results in severe vision loss due to infection and or bleeding. These risks are not associated with medical or laser treatments.
- Laser trabeculoplasty can produce peripheral anterior synechiae, whereas medical treatment does not.

Summary of Evidence from Systematic Reviews

Burr (2004) reported a significantly higher risk of cataract (OR, 2.69; 95 percent CI, 1.64 to 4.42) and cataract surgery at up to three years post intervention (HR, 2.72; 95 percent CI, 1.51 to 4.89) in the trabeculectomy group compared to the medication group.[108] Surgical complications included serous choroidal detachment (11 percent), hyphema (11 percent), encapsulated blebs (12 percent), and shallow or flat anterior chamber (14 percent) (one trial, 517 eyes, but reports also encompass fellow eyes not enrolled in the trial).

Rolim de Moura (2007) reported an elevated risk of systemic (RR 4.88) and ocular (RR 1.5) adverse effects among participants receiving laser trabeculoplasty with beta blockers versus no treatment, but each of these outcomes were reports from single trials and were not statistically significant.[80] There was, however, an 11-fold increase in the risk of peripheral anterior synechiae among participants randomized to argon laser trabeculoplasty when compared to participants receiving medical treatment (95 percent CI, 5.63 to 22.09, two trials).

Detailed Analysis of Primary Studies

We included two randomized controlled trials that reported harms related to medical versus surgical treatment of OAG.[33] [102] We did not identify any observational studies.

Harms were not covered in a systematic fashion in the primary studies.

Grading of Evidence

Grading was not completed as harms were addressed in a variety of ways (i.e., different outcomes) in the two RCTs identified addressing this question.

Conclusions

The evidence is conclusive that intraocular glaucoma surgery increases the risk of cataract and cataract surgery when compared to laser trabeculoplasty and medical treatment. Laser trabeculoplasty does not carry the risk of ocular discomfort associated with intraocular glaucoma surgery or medications. Medical therapy can produce systemic harms that are not produced by trabeculoplasty or intraocular glaucoma surgery. Ocular side effects are greater in the first 2 years after trabeculectomy than with medical therapy, but are similar after 2 years. Intraocular glaucoma surgery carries the rare but serious risk of intraocular infection, which does not occur with laser or medical treatment.

Key Question 2: Do medical treatments, lasers and other surgical treatments improve patient-reported outcomes?

Key Points

- There is no evidence that treatment of glaucoma improves patient-reported outcomes.
- There is little evidence that the treatments themselves used for OAG influence patient quality of life (QOL).
- Several studies suggest that the type of glaucoma treatment does not have an influence on QOL.

- There is some evidence that among medical treatments, patients prefer the treatment that is less frequently applied.
- There is evidence from one high-quality RCT that glaucoma treatment reduces fear of blindness regardless of the type of treatment.

Summary of Evidence from Systematic Reviews

Two systematic reviews addressed the relationship between medical versus surgical treatment of OAG and patient-reported outcomes, and the included studies are summarized in the analysis of primary studies section that follows.[80 108]

Detailed Analysis of Primary Studies

We identified nine trials that met our eligibility criteria and assessed patient-reported outcomes. Three trials reported QOL outcomes and one of these also reported fear of blindness as an outcome.[113-115] Two trials reported patient preference.[116 117] One trial reported patient satisfaction and convenience.[118] Three additional trials used a QOL instrument that was not publicly available and were not analyzed for that reason.[119-121] We thus include six trials in our narrative summary.

Four trials compared medical treatments, including one that compared a solution to a gel. One trial compared trabeculectomy to medical treatment and another trial compared laser plus medical treatment to no treatment. The six trials varied in diagnosis, age, race and severity of glaucoma and risk of bias. We did not perform a meta-analysis due to appreciable variability in interventions, outcomes, and follow-up intervals. The studies are described in detail in Evidence Table 25 (Appendix C) and those included in the analysis are summarized in Summary Table below.

Table 9 Summary of Evidence for Key Question 2

Study	Design and size	Interventions	Outcomes	Overall Risk of Bias	Results
CIGTS 2001 [114]	RCT 607 patients,	Primarily trabeculectomy (with or without 5-fluorouracil) vs. Primarily medications, starting with topical beta-blocker	-QOL -Fear of blindness - Symptom (frequency and bothersomeness)	Low	- QOL: No differences. - Symptoms: Overall decrease in both groups. Surgical patients reporting 22% more symptom bothersomeness related to visual function -Fear of blindness decreased in both groups
EMGT 2005 [115]	RCT 255 patients	No treatment vs. Betaxolol and ALT,	-QOL	Low	No difference
Javitt 2000 [113]	RCT 219 patients	Brimonidine vs. Timolol	-QOL	Medium	No difference

Solish 2004 [118]	RCT 492 patients	Timolol/ Dorzolamide fixed combination vs. Timolol and Brimonidine	-Convenience -Satisfaction	Medium	Both treatments were convenient for >80% of patients and satisfied > 82% of the patients.
Konstas 2003 [117]	Randomized cross-over trial 54 patients	Latanoprost vs. Timolol/Dorzolamide fixed combination	-Preference	Medium	80 % preferred lanatanoprost vs. 20% timolol/dorzolamide
Schenker 1999 [116]	Randomized cross-over trial 202 patients	Timolol Gel vs. Timolol Solution	-Preference	Medium	-71% preferred timolol gel vs. 29% timolol solution -compliance was higher with timolol gel

Outcomes

Quality of Life

The Early Manifest Glaucoma Trial (EMGT) was the only study to compare QOL before treatment and after treatment, and found no difference.[115] Comparison between different treatment groups was made in three trials (Collaborative Initial Glaucoma Treatment Study (CIGTS) 2001, EMGT 2005, Javitt 2000). The CIGTS Study, comparing medical treatment to surgical trabeculectomy, reported no significant time-specific differences between treatment groups in either the Visual Activities Questionnaire Total or Peripheral Vision subscale scores; however, with the Acuity subscale, time-specific treatment group differences were observed at 2-, 6-, and 30-month follow-up periods, with more dysfunction reported by the surgically treated group.[114] In addition, surgical patients reported approximately 22 percent more symptom bothersomeness on the Symptom Impact Glaucoma Total score. There were no treatment group differences noted in model-based results for the disease-specific measure of patient perceptions.[122] In the EMGT, a Swedish version of the National Eye Institute Visual Function Questionnaire-25 was administered to subjects in the two arms of the study, those treated with laser trabeculoplasty and betaxolol 0.5 percent, and those who were not treated. Treatment was not associated with a change in the QOL as assessed by the National Eye Institute Visual Function Questionnaire-25. Lastly, Javitt (2000) compared brimonidine 0.2 percent and timolol 0.5 percent treated individuals over 4 months and QOL was assessed with the SF-36.[113] The changes of the SF-36 scores only varied during the study from 1 to 3 units on a scale of 0-100, which was not statistically significant.

Satisfaction and Convenience

Solish (2004) assessed patient satisfaction and convenience after 1 and 3 months of treatment with either the fixed combination (both drugs in one bottle) of timolol 0.5 percent and dorzolamide 2 percent, or the unfixed combination (separate bottles) of timolol 0.5 percent and brimonidine 0.2 percent.[118] They found no statistically significant differences between the two drugs alone and in fixed combination. Eight-seven percent of patients treated with the fixed combination of dorzolamide/timolol reported the treatment to be convenient versus 80 percent treated with the concomitant administration of the two drugs (p=0.056). Eighty-seven percent of

patients treated with the fixed combination of dorzolamide/timolol were satisfied with the treatment versus 85 percent treated with the concomitant administration of the two drugs (p=0.643). The study was funded by the manufacturer of the fixed combination product.

Preference

In one trial (Konstas, 2003), the subjects preferred latanoprost over the fixed combination of timolol maleate/dorzolamide (80 percent vs 20 percent, p<0.0001), mostly because of convenience (latanoprost was administered only once a day).[117] In the other trial (Schenker (1999)) the patients preferred timolol gel given once a day over timolol solution (71 percent vs 29 percent) given twice a day after 6 weeks on each treatment (p<0.001), because of the reduced frequency of administration.[116]

Fear of Blindness

The only study that assessed fear of blindness found a decrease in both groups (pharmacological and surgical) (CIGTS, 2001) throughout the course of the study.[114] At baseline, 34 percent of all patients reported moderate amount or a lot of worry about blindness. After 5 years this number decreased to 11 percent. The authors could not detect any association between the initial treatment assignment and fear of blindness.

Table 10 Grading of Evidence

Number of Studies; Subjects	Risk of Bias: Design/ Quality	Consistency	Directness	Precision	Strength of Evidence
QOL					
3 ; 1081	RCT/ low	Consistent	Direct	Imprecise	Insufficient
Satisfaction and Convenience					
1; 492	RCT/ medium	Not applicable	Direct	Imprecise	Insufficient
Preference					
2; 256	Randomized cross-over/ medium	Consistent	Direct	Imprecise	Insufficient
Fear of Blindness					
1; 607	RCT/ low	Not applicable	Direct	Imprecise	Insufficient

Conclusions

OAG generally is asymptomatic until late in its clinical course, and treatment is generally considered to slow or stop the course of disease rather than improve symptoms. For this reason, it's understood that the initiation of treatment is not expected to improve patient-reported outcomes. Hence, the goal is to select an effective treatment with the least treatment-related

adverse outcomes. Therefore, it is not surprising that few studies compare patient-reported outcomes before and after the initiation of treatment. In the EMGT, subjects treated with eye drops and laser treatment reported the same QOL as those subjects who were observed without treatment. In the CIGTS, patients undergoing trabeculectomy surgery reported more eye-related symptoms in the first 2 years after surgery when compared to the group randomized to medical treatment.

The reduction in fear of blindness with initiation of treatment in the CIGTS must be kept in context. These were newly diagnosed patients who had no fear of blindness before diagnosis, and so naturally would have had concerns about blindness after learning of their diagnosis. This fear of blindness diminished over time, as they realized that there were not rapidly losing vision, and may not have been a treatment effect.

Key Question 5: Does lowering intraocular pressure or preventing or slowing the progression of optic nerve damage and visual field loss reduce visual impairment and change vision-related quality of life?

Key Points

- There are no well-executed studies addressing the relationship between the intermediate outcomes of IOP reduction, prevention of optic nerve damage, or prevention of visual field loss and the outcomes of visual impairment and vision-related QOL.

Summary of Evidence from Systematic Reviews

We did not identify any systematic reviews that address the relationship between the intermediate outcomes of IOP reduction, prevention of optic nerve damage, or prevention of visual field loss and the outcomes of visual impairment and vision-related QOL.

Detailed Analysis from Primary Studies

Two studies were identified in which some link was made between the intermediate outcomes of IOP reduction, prevention of optic nerve damage, and prevention of visual field loss and the final outcomes of decreased visual impairment and vision-related QOL.[28 123] The study by Prata (2009) was motivated by the hypothesis that decreasing IOP alone can result in an improvement in visual function.[28] All 54 subjects received pressure-lowering medication such that there was an overall reduction in IOP from 24.8 mmHg to 16.9 mmHg ($p<0.001$). After four weeks of treatment, the authors reported an increase in both visual field mean deviation from -6.56 to -5.72 ($p=0.02$) and a visual analog scale[124] from 6.96 to 7.52 ($p=0.045$). These results, while suggestive that lowering IOP alone may be beneficial for visual function and patient-reported quality of vision, are severely limited by the fact that there was no control group that did not receive pressure-lowering medications.

The second study, by Montemayor (2001), is a cross-sectional evaluation of the relationship between quality of life, visual function, and numbers of glaucoma medications.[123] While there were no significant correlations between objective measures of visual function (visual acuity, visual field mean deviation) and quality of life, they did find correlation between the Visual Function Assessment[125] and quality of life as measured by the EQ-5D health status tool.[126] These results only indirectly address Key Question 5 by measuring the correlation

between visual field damage and QOL, which does not infer a relationship, and the study also does not consider reduction in visual field loss.

Table 11 Grading of Evidence

Number of studies : participants	Risk of bias	Consistency	Directness	Precision	Strength of evidence
Visual Impairment					
2; 278	RCT and Observational (cross-sectional) studies/Medium	Inconsistent	Indirect	Imprecise	Insufficient

Conclusions

In addition to finding no studies showing a direct link between treatment and visual impairment or patient-reported outcomes, we also found no link between those final outcomes and the intermediate outcomes addressed by Key Questions 3 and 4. Future studies might advance the field by evaluating this indirect link.

Discussion

In the analytic framework we developed to structure this work, the ultimate outcome of treating open-angle glaucoma (OAG) is the prevention of visual impairment and the maintenance or improvement of patient-reported outcomes like quality of life. These outcomes are evaluated in Key Questions 1 and 2. Recognizing that studying these final outcomes of glaucoma treatment directly requires large studies of long duration, we also included in the analytic framework the intermediate outcomes of intraocular pressure (IOP), rate of visual field loss, and rate of optic nerve damage as each of these outcomes is almost certainly linked to the final outcomes of interest. Key questions 3 and 4 address the link between treatment and these intermediate outcomes. In an effort to gather all evidence linking treatment to changes in visual impairment and quality of life, Key Question 5 was included to assess the link between the intermediate outcomes reported by most glaucoma trials (IOP, visual field, optic nerve) and the ultimate outcomes of visual impairment and self-reported declines in quality of life.

Because glaucoma can be treated both medically and surgically, our evaluation was further structured to compare medications to other medications, medications to surgeries, and surgeries to other surgeries. This was done because it made the most sense from a clinical perspective. The key questions were therefore evaluated within each of these three categories.

We identified no studies that evaluated either medical or surgical glaucoma treatments with regard to their impact on visual impairment (Key Question 1). Our methods were designed to use standard definitions of visual disability based on visual acuity and visual field loss, but it is likely that even alternative definitions would not have resulted in the identification of any appropriate studies. Glaucoma is a slowly progressive disease and recent publications indicate that the average untreated glaucoma patient would require more than 20 years to lose most of

his/her visual field.[127] Most clinical trials cannot enroll a large enough number of subjects and follow them long enough to detect a difference in the proportion progressing to severe vision loss. A small number of studies provided data on visual acuity or visual field outcomes that might have been used to evaluate this question, but either the data reported were not adequate to determine rates of visual disability or the studies were of too short a duration to ascertain relative differences in glaucoma progression.

We also found no good evidence linking treatment with relative improvements in patient-reported outcomes (Key Question 2). There is some evidence that patients prefer less frequent dosing of medications and there is evidence that treatment of any kind reduces the fear of blindness, but we found nothing linking treatment to more important outcomes like vision-related quality of life.

As mentioned above, we attempted to find an indirect link from treatment to the final outcomes via Key Question 5. Unfortunately, no studies were found that adequately evaluated the link between any of the intermediate outcomes and the final outcomes in the analytic framework.

Taking Key Questions 1, 2, and 5 together, we therefore did not find evidence for direct nor indirect links between treatment of glaucoma and the prevention of visual impairment or worse patient-reported outcomes. As noted above, since glaucoma is a slowly progressive disease (even if untreated), it's not surprising that no studies of these links were identified. The required duration of such studies would present significant challenges, primarily in terms of the follow up of the subjects for a long enough period of time to ascertain relative differences in the outcomes.

In contrast to the lack of evidence for Key Questions 1,2, and 5, the past decade has seen significant progress in terms of information related to the intermediate outcomes of IOP (Key Question 3) and changes in visual field and optic nerve (Key Question 4). With regard to IOP, there is good evidence that a number of treatments can significantly lower IOP relative to no treatment.

Medical therapy for glaucoma has been available for over a century and there is good evidence that all of the currently used medications lower IOP. Among medications, the prostaglandin agents are consistently superior to the other classes in terms of their pressure lowering ability. Specifically, latanoprost has been shown to be superior to timolol, brimonidine, and dorzolamide. This result is consistent with the NICE guidelines from 2009 regarding glaucoma medications.[128] It is also now clear from large clinical trials (Collaborative Normal-Tension Glaucoma Study, Early Manifest Glaucoma Trial, and Ocular Hypertension Treatment Study) that treatment with medications decreases the risk of visual field loss or optic nerve damage. The reduction in the risk of visual field loss or optic nerve damage was close to 50 percent in these major trials. The topical medications included in this review have been shown to be superior to placebo with regard to visual field loss and/or optic nerve damage, but there is not adequate evidence to suggest the superiority of one medication over another.

Laser trabeculoplasty has also been shown to decrease IOP in OAG. Although multiple types of laser are currently in use, there is no evidence to support the use of one technology over another. Specifically, our results, similar to the conclusions provided in the National Institute for Health and Clinical Excellence glaucoma guidelines,[128] support the equivalence of argon laser trabeculoplasty and SLT. Furthermore, laser trabeculoplasty and topical medications have similar ability to prevent visual field loss due to glaucoma.

As with medications and laser, incisional surgeries lower IOP. In terms of relative effect, trabeculectomy lowers pressure more than non-penetrating procedures like viscocanalostomy and deep sclerectomy. There is also good evidence that trabeculectomy with the antimetabolite mitomycin-C lowers pressure more than the same procedure without mitomycin-C. Interestingly, there is no evidence to support a reduction in IOP when mitomycin-C is used with the non-penetrating procedures. Although many variations on the basic trabeculectomy have been evaluated, including differences in technique and in adjuvants, there's no good evidence that any of them provides additional reduction in IOP.

Based on the evidence we analyzed, it is likely that trabeculectomy is superior to medications in terms of preventing visual field loss. Taken together, the current best evidence supports the contention that medication and laser trabeculoplasty have similar efficacy but that trabeculectomy is superior to both with respect to the intermediate outcomes addressed by Key Questions 3 and 4.

There is, of course, a downside to any treatment in the form of side effects and complications. In general, the harms produced by medications are not vision threatening and most commonly include signs and symptoms like conjunctival hyperemia and ocular irritation. There is evidence that the prostaglandin agents are more likely to cause conjunctival hyperemia than are the other classes of medication, and that latanaprost is the least likely to cause this of the three prostaglandins that have been most widely used and studied (latanaprost, bimataprost and travoprost). On the other hand, timolol is more likely to result in systemic side effects like shortness of breath or bradycardia, though these are rarely severe.

As expected, the complications of surgery are more significant compared to those of medications, and they include cataract formation, choroidal effusions, hyphema, and flattening of the anterior chamber. If these complications are severe, they can result in vision loss. Among surgical treatments, these complications are more common in trabeculectomy than in non-penetrating surgeries and are likely more common in trabeculectomies done with mitomycin-C than in those performed without it.

The fact that the treatment that is most likely to lower IOP and prevent visual field and optic nerve progression (trabeculectomy) is also the one with the most significant side effects is a challenge to clinical decision making. When deciding from among medications, laser, and incisional surgery, a clinician would ideally perform some sort of patient-specific risk-benefit analysis to determine which intervention is most appropriate, given the risk of progression. Even if this were something clinicians were good at, the fact is that there are no good studies that clearly quantify the relative risks and benefits of various treatments to inform such an analysis.

In conclusion, we did not find direct or indirect links between glaucoma treatment and visual impairment or patient-reported outcomes. This should be an area of focus in future glaucoma trials, but trials would need to be of adequate size and duration to detect differences between groups. We did find, however, that a number of treatments clearly lower IOP and can prevent visual field loss and optic nerve damage. While we found direct comparisons between some treatments, the remaining gaps noted above also represent an area in which future research could be directed.

Future Research Needs

The available evidence demonstrates definitively that intraocular pressure can be lowered by many types of medications, laser treatments, and surgery. High-quality randomized controlled trials have also shown that reduction of intraocular pressure slows the development and progression of damage to the optic nerve and slows visual field loss. Although logical to presume that slowing glaucoma damage would lead to preservation of vision-related quality of life and reduction in visual impairment, this link has not been demonstrated in the research literature. Below we utilize the Patient problem, Intervention, Comparison, and Outcome framework to outline areas of research that might help resolve this gap.

As a general comment on the available literature on glaucoma treatments, the field would benefit from more rigorous study design and more standardized reporting of outcomes. The World Glaucoma Association publication "Guidelines on Design and Reporting of Glaucoma Surgical Trials" should serve as a basis for all trials of new and existing treatments.[129]

Lack Of Association Between Treatment And Visual Impairment

Population

- Patients with moderate visual loss from glaucoma, i.e., those at risk for visual impairment

Interventions

- Studies evaluating all interventions are needed: medical therapy, laser trabeculoplasty, incisional surgery

Outcomes

- Visual impairment as measured by standard definitions (e.g., International Classification of Diseases)
- Functional measures of impairment: reading, driving, other activities of daily living
- Long-term trials or patient registries (i.e., greater than 10 years) are needed to determine the relative impact of treatments on visual impairment
- All studies of glaucoma treatments should routinely include measures of visual impairment

Lack Of Association Between Treatment And Patient-Reported Outcomes

Population

- Open-angle glaucoma patients in need of treatment

Interventions

- Studies evaluating all interventions are needed: medical therapy, laser trabeculoplasty, incisional surgery

Outcomes

- Assessment of patient-reported outcomes prior to the start of therapy to provide appropriate basis for assessing these outcomes after therapy

Assessment of the Relative Risks and Benefits of Treatment

Population

- Glaucoma patients in need of treatment
- Provide sub-analysis or complete stratification by risk

Interventions

- Studies evaluating all interventions are needed: medical therapy, laser trabeculoplasty, incisional surgery

Outcomes

- All studies of glaucoma treatments should be designed to provide information on the comparative effectiveness of one treatment versus the most appropriate "standard".

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Abbreviations

AHRQ	Agency for Healthcare Research and Quality
CI	Confidence interval
EPC	Evidence-based Practice Center
5-FU	5-Fluorouracil
HR	Hazard ratio
IOP	Intraocular pressure
logMAR	Logarithm of the minimum angle of resolution
MD	Mean deviation
MMC	Mitomycin-C
OR	Odds ratio
QOL	Quality of life
RCT	Randomized controlled trial
RD	Risk difference
RR	Relative risk
SD	Standard deviation
SLT	Selective laser trabeculoplasty
WMD	weighted mean difference