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Comparative Effectiveness of Treatments for Open-Angle Glaucoma: A Systematic Review for the U.S. Preventive Services Task Force

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Background: Glaucoma is an acquired degeneration of the optic nerve and a leading cause of blindness worldwide. Medical and surgical treatments that decrease intraocular pressure may prevent visual impairment and blindness.

Purpose: To compare the effectiveness of medical, laser, and surgical treatments in adults with open-angle glaucoma with regard to decreasing intraocular pressure and preventing optic nerve damage, vision loss, and visual impairment.

Data Sources: MEDLINE, CENTRAL, and an existing database for systematic reviews (through 2 March 2011); MEDLINE, EMBASE, LILACS, and CENTRAL for primary studies (through 30 July 2012).

Study Selection: English-language systematic reviews; randomized, controlled trials; and quasi-randomized, controlled trials for most outcomes and observational studies for quality of life and harms.

Data Extraction: Two investigators abstracted or checked information about study design, participants, and outcomes and assessed risk of bias and strength of evidence.

Data Synthesis: High-level evidence suggests that medical, laser, and surgical treatments decrease intraocular pressure and that medical treatment and trabeculectomy reduce the risk for optic nerve damage and visual field loss compared with no treatment. The direct effect of treatments on visual impairment and the comparative efficacy of different treatments are not clear. Harms of medical treatment are primarily local (ocular redness, irritation); surgical treatment carries a small risk for more serious complications.

Limitation: Heterogeneous outcome definitions and measurements among the included studies; exclusion of many treatment studies that did not stratify results by glaucoma type.

Conclusion: Medical and surgical treatments for open-angle glaucoma lower intraocular pressure and reduce the risk for optic nerve damage over the short to medium term. Which treatments best prevent visual disability and improve patient-reported outcomes is unclear.

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Glaucoma is an acquired disease of the optic nerve (neuropathy) characterized by specific structural changes with associated visual field defects. More than 60 million people have glaucoma, the second most common cause of blindness worldwide (1). Glaucoma is primarily classified as open-angle or closed-angle, depending on whether the drainage area for aqueous humor in the front of the eye has an open or closed appearance.

Basic and clinical research have shown that damage to the optic nerve in glaucoma depends on intraocular pressure (IOP) (2). Decreasing IOP reduces both the incidence of glaucoma in individuals without optic nerve damage and the rate of new damage in individuals with glaucoma (3–5). Medical and surgical treatments that decrease IOP therefore may prevent visual impairment and blindness.

Commonly used medical treatments for glaucoma are topical or oral agents that decrease aqueous humor production or augment outflow. Other procedures to decrease IOP include laser trabeculoplasty, incisional surgery (such as trabeculectomy and aqueous drainage device surgery), and a host of newer procedures. The most common laser and incisional treatments are briefly described in the **Appendix** (available at www.annals.org).

In practice, the outcomes of most interest include the structure and function of the optic nerve. Nerve structure may be assessed by clinical examination, photography, or laser-based cross-sectional imaging, and function typically is assessed by automated visual field testing that maps the extent of peripheral vision. Because changes in structure and function may take several years to manifest, decreasing IOP is frequently accepted as an intermediate outcome in the evaluation of glaucoma treatments. IOP is also relevant because all currently available treatments are intended to decrease IOP as the means of slowing or stopping optic nerve damage.

We report here the comparative effectiveness of medical, laser, and incisional surgery treatments for open-angle glaucoma (OAG), with particular attention to results of interest to nonophthalmologists.

Methods

The U.S. Preventive Services Task Force (USPSTF) requested a review of evidence on the treatment of OAG to help inform their recommendations on screening for

See also:

Web-Only
CME quiz (preview on page I-30)

OAG. The protocol for this systematic review and the full report, including detailed methods (such as search strategies), are available elsewhere (6). A companion systematic review of screening for OAG is also available (7).

The systematic review addressed the following: 1) whether medical, laser, and surgical treatments for OAG decrease intraocular pressure, prevent or slow progression of optic nerve damage and visual field loss, and reduce visual impairment or improve patient-reported outcomes and 2) the harms associated with those treatments.

Data Sources and Searches

On 2 March 2011, we searched MEDLINE and CENTRAL for relevant systematic reviews published from 2009 to 2011. We screened an existing database of eye and vision systematic reviews to identify reviews published before 2009 (8). We also searched MEDLINE, EMBASE, LILACS, and CENTRAL for primary studies without imposed language, sample size, or date restrictions up to 30 July 2012.

Study Selection

Two reviewers screened systematic reviews; randomized, controlled trials (RCTs); and quasi–randomized, controlled trials that reported outcomes of treatments for OAG, as well as observational studies that reported quality of life or harm outcomes. We examined treatments currently used for OAG, including medical, laser, and incisional surgery and excluded drugs no longer in use or not approved by the U.S. Food and Drug Administration. We included studies with participants aged 40 years or older who had primary OAG or were suspected of having OAG. We excluded studies of OAG with other conditions when results were not stratified by condition. Disagreements about eligibility were resolved through discussion among reviewers.

Data Extraction and Quality Assessment

One reviewer extracted and assessed data, and a second reviewer verified; reviewers resolved disagreements through discussion. We extracted descriptions of the population, interventions, and outcomes of interest. We used the Cochrane Collaboration's tool for assessing the risk of bias of randomized and quasi-randomized trials (9) and a modified version of the Newcastle-Ottawa Scale to assess observational studies (10). We used a tool adapted from the Critical Appraisal Skills Program, Assessment of Multiple Systematic Reviews, and Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement to assess the methodological quality of systematic reviews (8). We excluded from further consideration systematic reviews that we determined to be of insufficient quality, as indicated by no risk-of-bias assessment, lack of comprehensive search, or use of inappropriate statistical methods.

Data Synthesis and Analysis

We did not abstract and synthesize data from the individual studies incorporated in the identified systematic reviews. We did abstract evidence from primary studies for interventions, comparisons, and outcomes that were not addressed by existing systematic reviews. We summarized evidence from additional primary studies that were published after the date of the last search conducted for systematic reviews. Because of appreciable variability in interventions, follow-up intervals, or assessments of outcomes, we focused on qualitative rather than quantitative synthesis. We assessed the risk of bias, consistency, directness, and precision of the body of available primary study evidence using guidance on strength of evidence in the "Methods Guide for Effectiveness and Comparative Effectiveness Reviews" (11, 12). We also assessed the strength of evidence from systematic reviews on the basis of the same domains. We derived a summary statement on strength of evidence by combining judgments for primary studies and systematic reviews. One reviewer assessed strength of evidence, and a second reviewer verified the assessments. Disagreements were resolved through team discussion.

Role of the Funding Source

The Agency for Healthcare Research and Quality (AHRQ) funded this review under a contract to support the USPSTF. The funding source had no role in study selection, quality assessment, or data synthesis. AHRQ provided project oversight and reviewed the draft evidence synthesis.

Results

Our search found 11 258 publications, of which 379 were eligible (**Appendix Figure 1**, available at www.annals.org). We also identified 169 systematic reviews, of which 23 remained eligible for inclusion after screening (**Appendix Figure 2**, available at www.annals.org). These systematic reviews also included all but 86 of the primary studies identified (**Appendix Figure 1**). Systematic review and primary study results are summarized in the **Table** and **Appendix Tables 1** to **3** (available at www.annals.org), and findings are summarized in detail in the complete report (13). We also summarized available evidence by outcome and type of comparison in an evidence map (**Figure**). The following results were judged to be most relevant to primary care physicians.

Visual Impairment and Patient-Reported Outcomes

We did not identify any systematic reviews of medical or surgical interventions for OAG that directly addressed visual impairment. We identified primary studies that met inclusion criteria; however, none were of sufficient duration or size to identify outcomes that plausibly could be related to visual impairment due to glaucoma, which is most often a slowly progressive disease. Instead, the systematic reviews and trials addressed the secondary outcome of visual acuity.

Three trials compared patient-reported outcomes between different treatment groups. The Collaborative Initial

Table. **Evidence Available for Visual Impairment and Patient-Reported Outcomes**

Studies Included, by Outcome	Comparators	Main Results	Strength of Evidence
Visual impairment			
Systematic reviews Medical: 0 Surgical: 2 Medical vs. surgical: 1	Surgical systematic reviews 1- vs. 2-site phacotrabeculectomy Endocyclophotocoagulation vs. Ahmed valve Molteno implant vs. no implant Medical–surgical systematic reviews Medical treatment vs. surgical treatment	No statistically significant differences between surgical treatments (visual acuity only) Trabeculectomy may reduce the risk for vision loss, but after adjustment for demographic and comorbid factors, the body of evidence is limited and inconclusive	Medical: Insufficient Surgical: Insufficient Medical vs. surgical: Insufficient
Primary studies Medical: 6 (747 patients) Surgical: 4 (238 patients) Medical vs. surgical: 1 (39 patients)	Medical RCTs Timolol vs. brimonidine vs. travoprost Timolol vs. carteolol Timolol vs. levobunolol Levobunolol vs. betaxolol Levobunolol vs. untreated Crossover: dorzolamide–timolol vs. travoprost vs. latanoprost Laser trabeculoplasty vs. medication Surgical RCTs Trabeculectomy vs. EX-PRESS shunt Trabeculectomy vs. deep sclerectomy with hyaluronic acid implant Deep sclerectomy with or without mitomycin C Deep sclerectomy with or without collagen implant	No study reported on visual impairment (visual acuity only) No study identified was of sufficient duration or size to identify outcomes that could be related to visual impairment due to glaucoma No study reported on visual impairment after laser or incisional surgery treatments (visual acuity) Because data were reported only in aggregate, we could not determine whether individual patients sustained a clinically important decrease in visual acuity No single treatment appeared to have a greater effect on visual acuity than any other treatment	Medical: Inconsistent, imprecise, insufficient to draw conclusions Surgical: Inconsistent, imprecise, low overall strength of evidence
Patient-reported outcomes (QOL, fear of blindness, patient preference, patient satisfaction)			
Medical vs. surgical Systematic reviews Laser vs. medical			Medical: Insufficient Surgical: Insufficient Medical vs. surgical: Insufficient
Medical RCTs Brimonidine vs. timolol Timolol–dorzolamide vs. timolol–brimonidine Timolol–dorzolamide vs. latanoprost Timolol gel vs. timolol solution		There is no evidence that treatment of glaucoma improves patient-reported outcomes There is little evidence that treatments themselves influence patient QOL Type of treatment does not influence QOL Among medical treatments, patients prefer the treatment that is less frequently applied	Medical: Studies do not directly address the questions Surgical: Insufficient
Medical vs. surgical RCTs Trabeculectomy with or without 5-fluorouracil vs. β-blockers Betaxolol + laser trabeculoplasty vs. no treatment		One high-quality RCT showed that fear of blindness was decreased compared with immediately after diagnosis, regardless of type of treatment	Medical–surgical: Consistent, imprecise, overall insufficient strength of evidence

QOL = quality of life; RCT = randomized, controlled trial.

Glaucoma Treatment Study (CIGTS) randomly assigned 607 patients with glaucoma to topical medications or trabeculectomy. No differences in the Visual Activities Questionnaire Total or Peripheral Vision subscale scores were reported; however, for the Acuity subscale, the surgically treated group reported more dysfunction at 2-, 6-, and 30-month follow-up (14). Surgical patients reported approximately 22% more bothersome symptoms on the Symptom Impact Glaucoma Total score than those in topical treatment group. The CIGTS also reported a decrease in the fear of blindness in both the pharmacologic and surgical groups (15).

The Early Manifest Glaucoma Trial (16) randomly assigned 255 patients with early glaucoma to no treatment or to a combination of topical betaxolol 0.5% and laser trabeculoplasty. No difference in quality of life measured with a visual function questionnaire was noted between groups. Javitt and colleagues (17) treated 219 patients with brimonidine 0.2% or timolol 0.5% for 4 months and assessed quality of life with the Short-Form 36 instrument. The change in Short-Form 36 scores varied from only 1 to 3 units (on a scale of 0 to 100), and no group differences were identified.

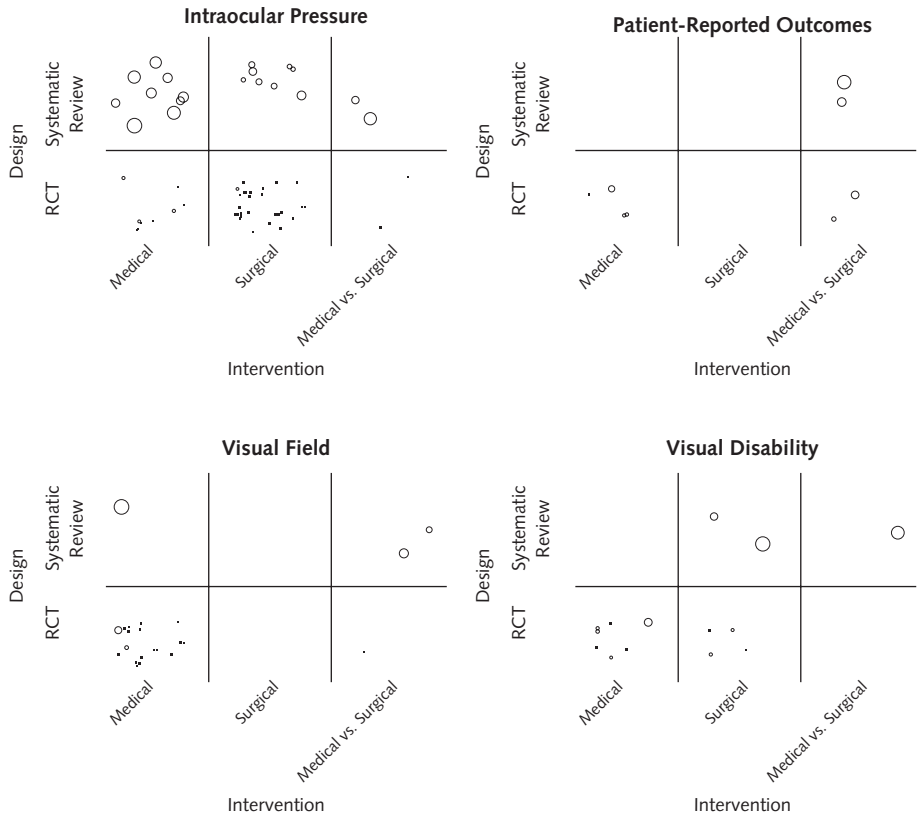
On the basis of these findings, we judged the overall strength of evidence for glaucoma treatments preventing visual impairment, and the evidence linking glaucoma treatments to patient-reported outcomes as insufficient to permit conclusions to be drawn.

Effect on Intraocular Pressure

Medical Therapy

Systematic reviews comparing timolol with travoprost (18) and latanoprost (19) showed prostaglandin analogues to be more effective at decreasing IOP. Two systematic reviews concluded that bimatoprost 0.03% decreased IOP more effectively than did latanoprost at 3 months (risk difference [RD], 12 [95% CI, 4 to 21]), although this difference was not present at 1 and 6 months (20, 21). Both Li and Eyawo and their respective colleagues (18, 21) concluded that mean IOP reduction was similar with travoprost and latanoprost. For the comparison of bimatoprost with travoprost, Eyawo and colleagues reported a sig-

Figure. **Evidence addressing the key outcomes of patient-reported outcomes, visual disability, visual field or optic nerve damage, and intraocular pressure.**



The studies are also categorized according to the interventions being compared: medical, surgical, or medical vs. surgical. Primary studies and systematic reviews are indicated with dots, with the size of the circle proportional to the number of participants. RCT = randomized, controlled trial.

nificant difference in favor of bimatoprost at 3 or more months of follow-up (weighted mean difference, 0.88 [CI, 0.13 to 1.63]), whereas Li and colleagues concluded that bimatoprost and travoprost were similarly effective (weighted mean difference, 0.08 [CI, −0.62 to 0.79]) (18).

All but 3 of the studies assessing medical treatments for decreasing IOP were included in systematic reviews. Two studies examined brand and generic latanoprost and found that both decreased IOP equivalently, by 6 to 7 mm Hg (22, 23). A single study also showed that latanoprost (7.5 mm Hg) and the combination of brimonidine–timolol (7.0 mm Hg) both decreased IOP by the same amount (24).

We judged the strength of evidence from these 3 most recent trials to be low. However, with the addition of the consistent high-quality systematic reviews, the conclusion that topical glaucoma medications decrease IOP is well-supported, as is the conclusion that prostaglandin agents are superior to other monotherapies with regard to decreasing IOP.

Surgical Therapy

Wilkins and Wormald and their respective colleagues (25, 26) reported that the addition of antimetabolites to trabeculectomy reduced IOP among participants enrolled in the included studies. Wilkins and associates determined that participants receiving intraoperative mitomycin C had an average IOP 5.4 mm Hg lower than that among participants receiving placebo or no treatment at 12 months. A similar finding was reported for postoperative 5-fluorouracil (weighted mean difference, −4.7 [CI, −6.6 to −2.7]) (25).

Rolim de Moura and colleagues (27) found no difference in the risk for treatment failure when diode and argon laser trabeculoplasty were compared at 1-year (relative risk [RR], 3.0 [CI, 0.4 to 24]) and 2-year (RR, 0.50 [CI, 0.1 to 2.4]) follow-up and when selective laser trabeculoplasty was compared with argon laser trabeculoplasty at 1 year (RR, 1.3 [CI, 0.8 to 1.9]). In participants randomly assigned to argon laser trabeculoplasty, treatment failed twice as often as in participants receiving trabeculectomy (CI, 1.4 to 3). Rolim de Moura and colleagues further reported

that the risk for an IOP of 22 mm Hg or greater (failure) at 1 year was 92% lower among participants receiving argon laser trabeculoplasty than among those receiving continued medical treatment in one trial (RR, 0.08 [CI, 0.02 to 0.3]) and 60% lower in a second trial (RR, 0.4 [CI, 0.2 to 0.8]) (27). At 24 months, the risk for failure was lower with argon laser trabeculoplasty than with medical treatment alone (RR, 0.8 [CI, 0.7 to 0.9]).

Burr and colleagues (28) compared trabeculectomy with medical therapy. At 1 year, the IOP in participants randomly assigned to trabeculectomy was 6.1 mm Hg lower than that in participants receiving medical treatment (CI, 4.3 to 8.0; 2 RCTs). Single included RCTs also reported outcomes at longer follow-up. At 2 to 4 years of follow-up, IOP was 1.6 mm Hg lower among those receiving trabeculectomy (CI, −0.7 to 3.9 mm Hg), with a 3.4–mm Hg difference in favor of trabeculectomy at 5 years (CI, 1.0 to 5.8 mm Hg) in one trial. A second trial reported lower IOP in the group receiving trabeculectomy at 5 years (1.9 mm Hg lower [CI, 0.9 to 3.0 mm Hg lower]).

We identified 28 RCTs of the following interventions: trabeculectomy ($n = 6$ RCTs), adjuvants with trabeculectomy ($n = 13$), surgical techniques in combined cataract and glaucoma surgery ($n = 2$), deep sclerectomy ($n = 2$), and variations on laser trabeculoplasty ($n = 5$). **Appendix Table 1** and the **Figure** show results of these studies. Collectively, the systematic reviews and primary studies provide high-level evidence that trabeculectomy decreases IOP more than do so-called nonpenetrating surgeries and that trabeculectomy with antimetabolites decreases IOP more than does trabeculectomy alone. Trabeculectomy also decreased IOP more than medications did, at least after 1 year. The primary studies alone provide a moderate strength of evidence that laser trabeculoplasty effectively decreases IOP. Studies failed to show any benefit with regard to the ability of many trabeculectomy techniques and adjuvants other than antimetabolites to decrease IOP.

Effect on Optic Nerve Damage and Visual Field Loss

Vass and colleagues (29) reported that any topical medical treatment (including β-blockers and unspecified topical medications) had a protective effect on incident worsening of visual field defect when compared with placebo or no treatment (odds ratio [OR], 0.6 [CI, 0.5 to 0.8]). β-Blockers were also protective when compared with placebo (OR, 0.7 [CI, 0.5 to 1.00]), as was timolol when compared with carteolol (29). Participants receiving timolol, however, experienced 2-fold higher odds of visual field defects than participants receiving levobunolol (CI, 1.2- to 4.1-fold).

Maier and colleagues (30) summarized the evidence from 5 RCTs that randomly assigned ocular hypertensive participants to medical or surgical treatment, or to no treatment. Participants receiving topical medications were 44% less likely to experience progression of visual field loss and optic disc damage than participants receiving no treatment (hazard ratio, 0.6 [CI, 0.4 to 0.8]). Medically or surgically treated patients with primary OAG were 35% less likely to experience progression of field loss and optic disc damage than those receiving no treatment.

Burr and associates (28) reviewed the evidence from 3 RCTs of initial medical treatment versus initial trabeculectomy for preventing the progression of visual field loss and optic nerve damage. One trial found that trabeculectomy resulted in less visual field progression than medical treatment (OR, 2.56 [CI, 1.12 to 5.83]), whereas the other 2 trials found no clear difference in the risk for progression (trial 1: OR, 0.69 [CI, 0.29 to 1.67]; trial 2: change in visual field mean deviation, −0.28 [CI, −0.59 to 0.03]).

Two trials included in Rolim de Moura and colleagues' review (27) compared argon laser trabeculoplasty with medications in patients with newly diagnosed glaucoma. The risk for visual field loss after argon laser trabeculoplasty was similar to that after medical treatment at 2 years (RR, 0.70 [CI, 0.42 to 1.16]).

We identified 21 RCTs addressing this outcome, and 2 recent RCTs addressed the comparative effectiveness of topical medications. The Low-pressure Glaucoma Treatment Study by Krupin and colleagues (31) randomly assigned 178 patients with glaucoma and "normal" IOP to brimonidine or timolol. The brimonidine group had field worsening less often than did the timolol group (9% vs. 39%; $P = 0.001$) during median follow-up of 30 months. The European Glaucoma Prevention Study (32) randomly assigned 1081 participants to placebo or topical dorzolamide and found no difference in risk for disease progression (by optic disc criteria) (hazard ratio, 0.86 [CI, 0.58 to 1.26]).

The 3 systematic reviews provide high strength of evidence that decreasing IOP by medical therapies or laser or incisional surgery reduces optic nerve damage as assessed by functional (visual field) or structural measures. The strength of evidence assigned to the 20 primary studies that reported visual field outcomes was low, and the evidence for the one study that reported optic nerve outcomes was insufficient. We did not identify any systematic review or primary study comparing surgical interventions for OAG that included these outcomes. Finally, the strength of evidence available from primary studies comparing medical with surgical treatments was also insufficient to allow conclusions to be drawn (**Appendix Table 2** and **Figure**).

Harms of Medical Therapy

Aptel and colleagues (33) noted that the risk for conjunctival hyperemia (redness) was 1.7 times higher with use of bimatoprost than with latanoprost (CI, 1.4 to 2.0). Cheng and Wei (20), Eyawo and colleagues (21), and Honrubia and associates (34) reported similar results for the same comparison. Cheng and Wei (20) further noted no differences in eye irritation (RD, 1 [CI, −3 to 4]), ocular inflammation (RD, −1 [CI, −2 to 1]), cystoid

macular edema (RD, 0 [CI, −2 to 2]), and iris pigmentation (RD, 0 [CI, −1 to 2]) with use of bimatoprost versus latanoprost.

Participants randomly assigned to latanoprost experienced less redness than did those receiving travoprost (18, 21, 33, 34). Eyawo and colleagues reported 49% lower odds of redness with latanoprost compared with travoprost. Li and associates further noted that travoprost 0.004% increased the odds of redness compared with travoprost 0.0015% (OR, 1.6 [95% CI, 1.3 to 2.0]). Redness, dry eye, and increased pigmentation did not differ between latanoprost, brimonidine, or dorzolamide (35, 36). Participants using brimonidine had an increased risk for fatigue.

Li (18), Vass (29), Zhang (19), and Loon (37) and their respective colleagues compared timolol with brimonidine, prostaglandin analogues (travoprost, latanoprost), other β-blockers, and placebo. Although the odds of participant dropout due to drug-related adverse events was increased 2-fold with timolol versus betaxolol (OR, 2.4 [CI, 1.0 to 5.5]), the odds of dropping out were lower among participants receiving timolol than those receiving brimonidine (OR, 0.21 [CI, 0.14 to 0.31]) (29). Participants receiving travoprost (18) or latanoprost (19) had 6 times the odds and twice the odds, respectively, of dropping out of the study because of redness than patients receiving timolol. Both drugs increased iris pigmentation.

Redness and iris pigmentation also were related to use of latanoprost when compared with fixed and concomitant administration of timolol and dorzolamide. Cox and colleagues (38) concluded that adverse event reporting in studies of fixed versus concomitant medication formulations was inconsistent and that causality of adverse effects could not be determined.

Appendix Table 3 summarizes the systematic reviews that address the harms of medical therapy for glaucoma. Collectively, they identified primarily localized adverse effects, such as eye irritation, redness, and iris color change. As the most commonly used medical therapy, the prostaglandin agents do not have systemic adverse effects or known interactions with other systemic medications.

Harms of Surgical Therapy

Chai and Loon (39) and Cheng and associates (40) concluded that adverse effects were more frequent with trabeculectomy than with nonpenetrating surgeries. Hypotony (RR, 0.29 [CI, 0.15 to 0.58]), hyphema (RR, 0.50 [CI, 0.3 to 0.84]), shallow/flat anterior chamber (RR, 0.19 [CI, 0.08 to 0.45]), and cataract (RR, 0.31 [CI, 0.15 to 0.64]) were all more frequent among participants treated with trabeculectomy than among those who had viscocanalostomy and deep sclerectomy. Cheng and colleagues (40) noted a higher risk for choroidal detachment with trabeculectomy than with both viscocanalostomy (RD, −0.15 [CI, −0.24 to −0.05]) and deep sclerectomy (RD, −0.16 [CI, −0.25 to −0.07]).

Wilkins and coworkers (25) noted that wound leak (OR, 1.84 [CI, 0.72 to 4.66]), hypotony (OR, 1.80 [CI, 0.79 to 4.12]), and cataract (OR, 1.80 [CI, 1.00 to 3.22]) were reported more often among those receiving intraoperative mitomycin C. Diode laser trabeculoplasty treatment resulted in a lower, but not statistically significant, risk for peripheral anterior synechiae (RR, 0.5 [CI, 0.2 to 1.8]) and early IOP spikes (RR, 0.7 [CI, 0.2 to 2.1]) than argon laser trabeculoplasty (27).

Burr and colleagues (28) reported greater odds of cataract (OR, 2.7 [CI, 1.6 to 4.4]) and cataract surgery up to 3 years after intervention (hazard ratio, 2.7 [CI, 1.5 to 4.9]) with trabeculectomy than with medication. Surgical complications of trabeculectomy included serous choroidal detachment (11%), hyphema (11%), encapsulated blebs (12%), and shallow or flat anterior chamber (14%).

Rolim de Moura and colleagues (27) reported an elevated risk for systemic (RR, 4.9 [CI, 0.6 to 41.2]) and ocular (RR, 1.5 [CI, 0.9 to 2.6]) adverse effects with concurrent treatment with laser trabeculoplasty and β-blockers versus no treatment. The authors also reported an 11-fold increased risk (CI, 5.6- to 22.1-fold) for peripheral anterior synechiae with argon laser trabeculoplasty versus medical treatment.

Discussion

High-level evidence from systematic reviews and multiple randomized trials suggests that medical treatment for glaucoma decreases IOP and protects against worsening visual field loss. Of the large studies evaluating medical therapy for glaucoma, both the Ocular Hypertension Treatment Study and the Early Manifest Glaucoma Trial showed a decreased rate of visual field loss and progressive optic nerve damage among participants treated with medications. No systematic review or individual study has included head-to-head comparisons of different glaucoma medications to assess their ability to prevent optic nerve damage or visual field loss. On the basis of systematic reviews and additional primary studies, both medical therapy and trabeculectomy decrease the risk for incident or worsening of visual field loss, but initial trabeculectomy may be more effective in this regard.

Prostaglandins are currently the most effective topical medications for decreasing IOP, an important and easily measured intermediate outcome on the path to vision loss. On the other hand, the prostaglandin agents are more likely to cause conjunctival hyperemia than is timolol. Within the class of prostaglandins, latanoprost is less likely to cause hyperemia than travoprost or bimatoprost is; all 3 agents are similar with regard to ocular irritation, inflammation, cystoid macular edema, and changes in iris pigmentation. Rarely, there may be systemic harms from medical therapy that do not occur with trabeculoplasty or incisional glaucoma surgery. That being said, important systemic adverse effects of some classes of glaucoma medi-

cations warrant the attention of both eye care specialists and primary care physicians (41).

As the most common incisional surgery for glaucoma, trabeculectomy decreases IOP to a mean level in the low to mid teens. Its IOP-decreasing effect is potentiated by the use of intraoperative mitomycin C but does not appear to be increased by alterations in surgical technique or the addition of implants designed to modulate wound healing. Trabeculectomy also decreases IOP more than does laser trabeculoplasty or medical therapy but is associated with greater risk for adverse outcomes.

Studies examining laser trabeculoplasty consistently show a decrease in IOP with treatment but are not adequate to permit conclusions about the type of laser used or the number of applications. Treating with lasers decreases IOP and, when compared with medical treatment alone, reduces the number of medications needed to keep IOP at the same level.

Our review found insufficient evidence to permit conclusions about the comparative effectiveness of any glaucoma treatments on visual impairment or patient-reported outcomes. We searched for but found no studies linking treatment directly to either of these important outcomes. If visual impairment and patient-reported outcomes are indeed considered important end points in glaucoma management, future studies should address them; doing so will require longer follow-up than has been common in studies conducted to date.

Trabeculectomy, when compared with the nonpenetrating procedures of deep sclerectomy or viscocanalostomy, produces more hypotony, hyphema, shallow anterior chambers, cataract, and choroidal detachment. Conclusive evidence also shows that intraocular glaucoma surgery increases the risk for cataract when compared with laser trabeculoplasty and medical treatment. Intraocular glaucoma surgery also carries the rare but serious risk for intraocular infection, which does not occur with laser or medical treatment.

Our ability to synthesize the available evidence was limited by several factors. First, many studies were excluded because they enrolled participants with different glaucoma diagnoses but did not stratify analyses by glaucoma type. For example, we excluded the Advanced Glaucoma Intervention Study because it enrolled participants with both angle-closure glaucoma and OAG and did not analyze the outcomes separately for OAG.

Second, the reporting of outcomes of glaucoma treatments is inadequately standardized, preventing synthesis of results across studies. These deficiencies can be overcome by more rigorous study methods and reporting, as outlined in the World Glaucoma Association publication, "Guidelines on Design and Reporting of Glaucoma Surgical Trials" (42).

Third, as with any systematic review, both selective reporting and publication bias by the original authors may limit the validity of the results we report. This review relied heavily on existing systematic reviews to subsume much of the available literature. We used this approach to leverage the work of others and thus ensure a manageable scope for this review (43). We limited inclusion to systematic reviews considered of high quality, including completion of a comprehensive search, thus limiting possible publication bias. However, we cannot be sure how information bias in the systematic review (accuracy of data abstraction and assessment, for instance) might have influenced the results of the reviews. In addition, no methods for the integration of quality assessment and strength of evidence for both primary studies and systematic reviews are available. We thus developed post hoc methods to assign a single overall strength of evidence to the conclusions supported by the systematic review and trial evidence.

This review supports the role of medical, surgical, and laser treatments in decreasing IOP in patients with glaucoma, and we were able to draw some conclusions about the relative effectiveness of particular treatment options. Although evidence suggests that these treatments prevent progressive visual field loss and optic nerve damage, we did not identify high-level evidence comparing those treatments with one another. We also failed to find evidence linking treatment of any kind to patient-reported outcomes or visual impairment, which should be considered the outcomes of most interest.

Resources for clinical research in glaucoma should be directed to studies that address the links between treatment and outcomes that lack RCT evidence—the empty or nearly empty boxes in the **Figure**. These include head-to-head comparisons of the current major categories of glaucoma medications with regard to prevention of optic nerve structural damage and visual field loss. RCTs comparing new so-called minimally invasive glaucoma procedures to an appropriate alternative, such as trabeculectomy or cataract surgery alone, also are sorely needed to help guide clinicians in making treatment decisions.

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Appendix: Search Strategy

PUBMED

("Ocular Hypertension"[mh] OR "ocular hypertension"[tiab] OR "Intraocular Pressure"[mh] OR "intraocular pressure"[tiab] OR "glaucoma, open-angle" [mh] OR "Open angle glaucoma" [tiab] OR "low tension glaucoma" [tiab] OR "normal tension glaucoma" [tiab] OR "pseudoexfoliative glaucoma" [tiab] OR "pseudoexfoliative syndrome" [tiab]) AND ("Trabeculectomy"[mh] OR trabeculectomy[tiab] OR "Laser Coagulation"[mh] OR "laser coagulation"[tiab] OR photocoagulation[tiab] OR "sclerostomy"[mh] OR sclerostomy[tiab] OR canaloplasty [tiab] OR viscocanalostomy[tiab] OR "glaucoma drainage implants"[mh] OR "glaucoma drainage implants"[tiab] OR shunt[tiab] OR "laser therapy"[tiab] OR "laser surgery"[tiab] OR apraclonidine[tiab] OR "brimonidine"[Substance Name] OR brimonidine[tiab] OR "Timolol"[mh] OR Timolol[tiab] OR "Betaxolol"[Mesh] OR Betaxolol [tiab] OR "Levobunolol"[mh] OR "Metipranolol"[mh] OR "Carbonic Anhydrase Inhibitors"[mh] OR "Carbonic Anhydrase Inhibitors"[tiab] OR "dorzolamide"[Substance Name] OR dorzolamide[tiab] OR "Acetazolamide"[mh] OR Acetazolamide[tiab] OR "Cholinergic Agents"[mh] OR "Pilocarpine"[mh] OR Pilocarpine[tiab] OR "Carbachol"[mh] OR "Prostaglandins, Synthetic"[mh] OR Prostaglandins[tiab] OR travoprost[tiab] OR bimatoprost[tiab] OR latanoprost[tiab] OR "isopropyl unoprostone"[Substance Name] OR "Antihypertensive Agents"[mh] OR "Epinephrine"[mh] OR Epinephrine[tiab]) AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh]) 6747 titles.

EMBASE

('intraocular hypertension'/exp OR 'ocular hypertension':ab,ti OR 'intraocular pressure'/exp OR 'intraocular pressure':ab,ti OR 'open angle glaucoma'/exp OR 'open angle glaucoma':ti,ab OR 'low tension glaucoma':ti,ab OR 'normal tension glaucoma':ti,ab OR 'pseudoexfoliative glaucoma':ti,ab OR 'pseudoexfoliative syndrome':ab,ti) AND ('trabeculectomy'/exp OR trabeculectomy:ab,ti OR 'laser coagulation'/exp OR 'laser coagulation':ab,ti OR photocoagulation:ab,ti OR 'glaucoma surgery'/exp OR sclerostomy:ab,ti OR canaloplasty:ab,ti OR viscocanalostomy:ab,ti OR 'glaucoma drainage implant'/exp OR 'glaucoma drainage implants':ab,ti OR shunt:ab,ti OR 'laser therapy':ab,ti OR 'laser surgery':ab,ti OR apraclonidine:ab,ti OR 'brimonidine'/exp OR brimonidine:ab,ti OR 'timolol'/exp OR timolol:ab,ti OR 'betaxolol'/exp OR betaxolol:ab,ti OR 'levobunolol'/exp OR 'metipranolol'/exp OR 'carbonate dehydratase inhibitor'/exp OR 'carbonic anhydrase inhibitors':ab,ti OR 'dorzolamide'/exp OR dorzolamide:ab,ti OR 'acetazolamide'/exp OR acetazolamide:ab,ti OR 'cholinergic receptor stimulating agent'/exp OR 'pilocarpine'/exp OR pilocarpine:ab,ti OR 'carbachol'/exp OR 'prostaglandin derivative'/exp OR prostaglandins:ab,ti OR travoprost:ab,ti OR bimatoprost:ab,ti OR latanoprost:ab,ti OR 'isopropyl unoprostone'/exp OR 'antihypertensive agent'/exp OR 'adrenalin'/exp OR epinephrine:ab,ti) AND ('randomized controlled trial':pt OR 'controlled clinical trial':pt OR randomized:ab OR placebo:ab OR 'clinical trial'/exp OR randomly:ab OR trial:ti) NOT (animals/exp NOT humans/exp) 3728 titles.

LILACS

glaucoma$ AND (Trabeculectom$ OR 'Laser Coagulation'$ OR photocoagulation$ OR sclerostomy$ canaloplast$ OR viscocanalostom$ OR 'glaucoma drainage implants' OR 'glaucoma drainage implant'$ OR shunt OR 'laser therapy' OR laser surgery OR apraclonidine OR brimonidine] OR Timolol$ OR Betaxolol$ OR Levobunolol$ OR Metipranolol$ OR 'Carbonic Anhydrase Inhibitors'$ OR dorzolamide$ OR Acetazolamide$ OR 'Cholinergic Agents'$ OR Pilocarpine$ OR Carbachol$ OR Prostaglandins$ OR travoprost$ OR bimatoprost$ OR 'isopropyl unoprostone' OR 'Antihypertensive Agents' OR Epinephrine$) 282 titles.

Cochrane

glaucoma AND (Trabeculectomy OR 'Laser Coagulation' OR photocoagulation OR sclerostomy canaloplasty OR viscocanalostomy OR 'glaucoma drainage implants' OR 'glaucoma

drainage implant' OR shunt OR 'laser therapy' OR laser surgery OR apraclonidine OR brimonidine] OR Timolol OR Betaxolol$ OR Levobunolol OR Metipranolol OR 'Carbonic Anhydrase Inhibitors' OR dorzolamide OR Acetazolamide OR 'Cholinergic Agents' OR Pilocarpine OR Carbachol OR Prostaglandins OR travoprost OR bimatoprost OR 'isopropyl unoprostone' OR 'Antihypertensive Agents' OR Epinephrine) 501.

Definitions

Aqueous drainage devices: Any of several plastic implants that consist of a tube inserted into the eye and a plate connected to the tube that is sewn to the sclera and covered by conjunctiva. Aqueous humor moves through the tube and out of the eye to drain on top of the plate into the space between the plate and the conjunctiva.

Cyclophotocoagulation: A procedure in which laser energy is used to damage the processes of the ciliary body, reducing the amount of aqueous humor produced and thereby decreasing IOP.

Laser trabeculoplasty: A procedure in which laser energy (argon, YAG, diode) is applied to the trabecular meshwork in an effort to reduce resistance to the outflow of aqueous humor. The procedure is performed as part of an office visit and requires topical anesthesia.

Trabeculectomy: The most commonly performed incisional surgery for decreasing intraocular pressure in patients with glaucoma. With local anesthesia, a passageway is created at the junction between the cornea and sclera that allows the aqueous humor to flow from the anterior chamber to the space between the sclera and the conjunctiva, thereby decreasing IOP.

Inclusion and Exclusion Criteria

Population

Age and Follow-up. We included studies in which more than 95% of the population was older than 40 years of age or had a mean age greater than 50 years. The included studies also must have had follow-up of 1 month (medical treatment studies) or a mean of 1 year (surgical studies).

Glaucoma Definitions. To be eligible for inclusion, studies must have enrolled patients with the following: primary open-angle glaucoma (OAG), ocular hypertension, normal-tension glaucoma, low-tension glaucoma, pigmentary glaucoma, or pseudoexfoliative glaucoma. We excluded studies whose participants had the following: angle-closure glaucoma, juvenile or congenital glaucoma, traumatic glaucoma, neovascular glaucoma, secondary OAG, refractory glaucoma, or inflammatory glaucoma (uveitis).

Interventions

Medical Treatment. We included studies that involved the following agents: nonselective β-adrenergic receptor blockers, such as timolol, levobunolol, and metipranolol; β_1-selective β-blockers, such as betaxolol; α_2 agonists, such as apraclonidine and brimonidine; carbonic anhydrase inhibitors, such as brinzolamide, acetazolamide, and dorzolamide; cholinergic agents, such as carbachol; prostaglandin analogues, such as travoprost, bimatoprost, and latanoprost; and combined therapies, such as dorzolamide–timolol and brimonidine and timolol. Studies that used the following drugs were excluded: epinephrine, dipivefrin, apraclonidine, pilocarpine, systemic β-blockers, and any agents that are not approved by the U.S. Food and Drug Administration.

Surgical Interventions. Eligible studies used the following laser or surgical therapies: argon and selective laser trabeculoplasty, trabeculotomy, aqueous drainage (with Baerveldt, Ahmed, Krupin, or Molteno implants), cyclophotocoagulation (transscleral and endoscopic), deep sclerectomy, and viscocanalostomy. Eligible studies could also have used any of the following specialized surgical devices: iScience microcatheter (iScience, Menlo Park, California) (canaloplasty), Trabectome (NeoMedix, Tustin, California) (modified trabeculotomy), EX-PRESS shunt (Alcon, Fort Worth, Texas) (modified trabeculectomy), iStent (Glaukos, Laguna Hill, California) (trabecular bypass), or gold shunt (SOLX, Waltham, Massachusetts) (trabecular bypass). We excluded studies that combined surgery for cataract and glaucoma published before April 2000 because these were included in the "Treatment of Coexisting Cataract and Glaucoma" review, published by the Agency for Healthcare Research and Quality in 2003 (44–47).

Study Design

For questions about visual acuity, IOP, and visual field/optic nerve, we included only randomized, controlled trials and quasi–randomized, controlled trials. For the question addressing adverse events and harms, we included observational studies (cohort studies, case–control studies, cross-sectional and crossover studies, case reports or case series with more than 100 patients/eyes, and medication-switch studies). We did not restrict sample sizes for the included studies except for case series; for that study type, we included only case series with more than 100 patients or eyes.

Other Inclusion and Exclusion Criteria

Other topics considered eligible included assessment of adherence to glaucoma medical therapy or study medications as primary or secondary treatment or as add-ons to other therapy. Surgical studies could use glaucoma surgery combined with other procedures. Studies of adjuvant therapy and other modifications were also included. We excluded the following: economic studies, studies with physiology as the primary outcome, studies of cataract surgery alone, studies of treatment for surgical complications, studies of IOP variations after surgery and treatment of IOP after surgery, studies of anesthesia variations, and studies of filtering blebs and their revision.

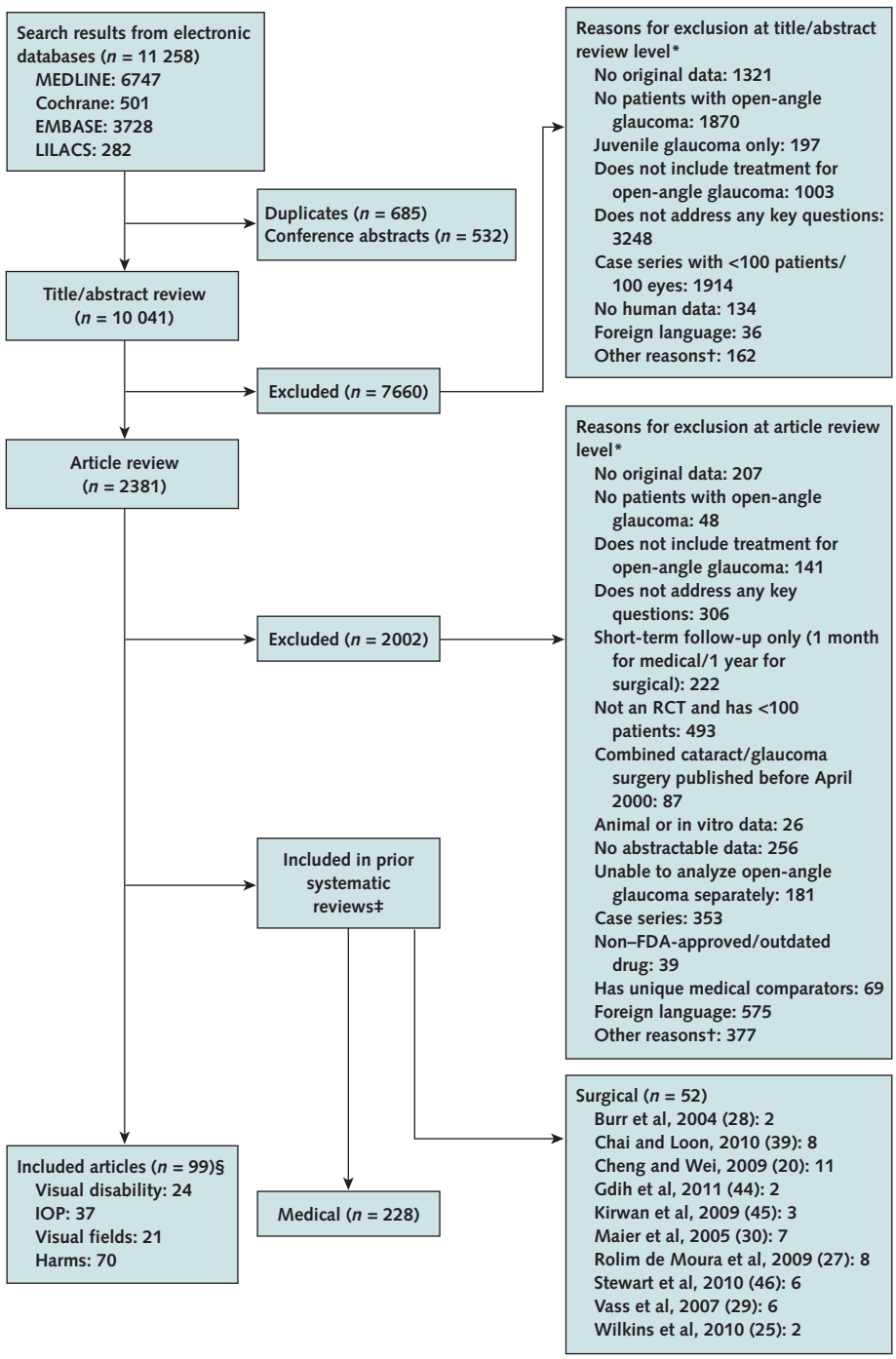
44. **Gdih GA, Yuen D, Yan P, Sheng L, Jin YP, Buys YM.** Meta-analysis of 1-versus 2-Site Phacotrabeculectomy. Ophthalmology. 2011;118:71-6. [PMID: 20691480]

45. **Kirwan JF, Rennie C, Evans JR.** Beta radiation for glaucoma surgery. Cochrane Database Syst Rev. 2009:CD003433. [PMID: 19370589]

46. **Stewart WC, Kristoffersen CJ, Demos CM, Fsadni MG, Stewart JA.** Incidence of conjunctival exposure following drainage device implantation in patients with glaucoma. Eur J Ophthalmol. 2010;20:124-30. [PMID: 19927268]

47. **Jampel HD, Lubomski LH, Friedman DS, Robinson KA, Congdon N, Quigley HA, et al.** Treatment of coexisting cataract and glaucoma. Evidence-Based Practice Center. Rockville, MD: Agency for Healthcare Research and Quality; 2003:1-3.

Appendix Figure 1. **Summary of evidence search and selection: primary literature.**



The sum of the numbers under "Reasons for exclusion" is larger than the total number excluded because multiple reviewers assessed each article. The search identified 11 258 titles; 10 041 were eligible after abstract review. After applying our exclusion criteria, we included 2381 articles for full-text review; we excluded 2002 on the basis of our exclusion criteria and 280 because they were included in previous systematic reviews. For the final analysis, we included 75 RCTs and 24 observational studies addressing adverse effects (16 medical treatment and 8 surgical treatment). FDA = U.S. Food and Drug Administration; IOP = intraocular pressure; RCT = randomized, controlled trial.

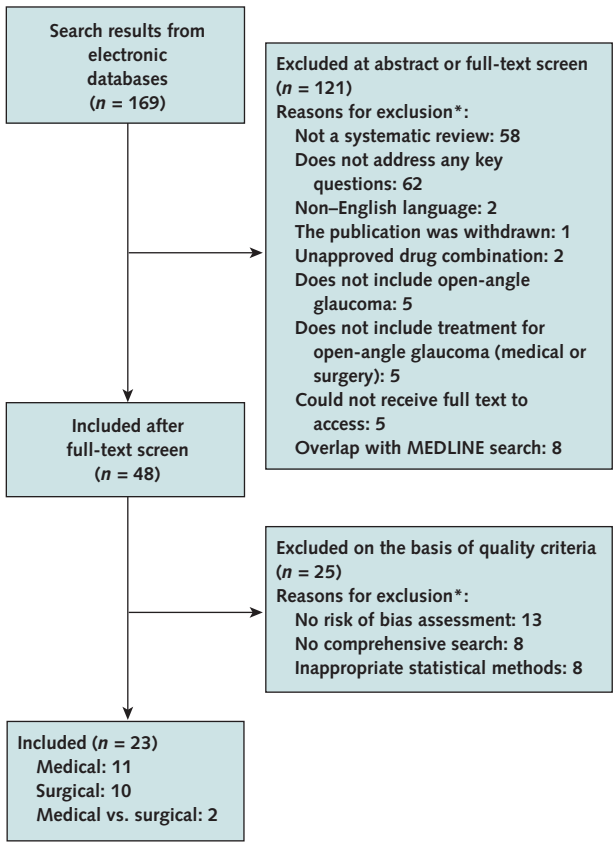
* Total may exceed number in corresponding box because articles were excluded by 2 reviewers at this level.

† Total may exceed number in corresponding box because some articles were covered by more than 1 systematic review.

‡ Total may exceed number in corresponding box because articles may apply to more than 1 key question.

§ Other reasons: Comparisons of case series, patient education reports, laboratory or autopsy data, letter or commentaries, drugs out of the list, library could not retrieve.

Appendix Figure 2. **Summary of evidence search and selection: systematic reviews.**



The sum of the numbers under "Reasons for exclusion" is larger than the total number excluded because multiple reviewers assessed each article. We identified 169 systematic reviews from the search in the databases. After exclusion at abstract level, we included 48 for full-text review. From those we excluded 25 on the basis of quality criteria. We included for our review a total of 23 systematic reviews. Eleven reviews addressed the comparative effectiveness of medical treatment of open-angle glaucoma, 10 addressed questions of surgical treatment, and 2 compared medical versus surgical treatments for open-angle glaucoma. One additional review addressed the comparative effectiveness of glaucoma surgeries versus one another as well as surgeries versus medical treatments for open-angle glaucoma.

* Total may exceed number in corresponding box because articles were excluded by 2 reviewers at this level.

Appendix Table 1. Evidence Available for the Outcome of Reduced Intraocular Pressure

Studies Included, *n*	Comparators	Main Results	Strength of Evidence
Systematic reviews			
Medical: 8	Latanoprost vs. bimatoprost Timolol vs. travoprost Latanoprost vs. dorzolamide–timolol Latanoprost vs. brimonidine Latanoprost vs. dorzolamide Latanoprost vs. bimatoprost vs. travoprost Timolol vs. brimonidine Timolol vs. latanoprost	Prostaglandins decrease IOP better than do dorzolamide, brimonidine, and timolol The prostaglandins appear similar in extent at which they decrease IOP, but some studies have reported a greater reduction in IOP with bimatoprost The combination dorzolamide–timolol has effect similar to that of prostaglandins	High
Circadian IOP: 8	Prostaglandin analogues Latanoprost vs. dorzolamide–timolol Latanoprost vs. bimatoprost	Results from systematic reviews comparing one prostaglandin to another were inconsistent	Insufficient
Surgical: 8	Trabeculectomy vs. deep sclerectomy Trabeculectomy + antimetabolites β-radiation Laser trabeculoplasty Aqueous shunts Trabeculectomy vs. medical treatment Efficacy and safety of viscocanalostomy	Trabeculectomy decreases IOP more effectively than do nonpenetrating surgeries Deep sclerectomy and argon laser trabeculoplasty are less likely to achieve complete success than trabeculectomy Addition of antimetabolites to trabeculectomy significantly reduces IOP among participants, as does use of postoperative 5-fluorouracil Addition of β-radiation to trabeculectomy does not reduce IOP more than trabeculectomy alone	High
Medical vs. surgical: 2	Medical vs. surgical treatment	IOP of participants randomly assigned to trabeculectomy is lower than that of participants receiving medical treatment at 1 y Risk for failure was lower with argon laser trabeculoplasty than with medical treatment	Moderate
Primary studies			
Medical: 3 (597 patients)	Latanoprost brand vs. latanoprost generic Brimonidine–timolol vs. latanoprost	Latanoprost and brimonidine–timolol decrease IOP by a similar amount Brand and generic latanoprost are equivalent with regard to IOP reduction	Consistent, imprecise, low overall strength of evidence
Circadian IOP: 6 (214 patients)	Latanoprost vs. bimatoprost Latanoprost vs. timolol vs. brimonidine Latanoprost vs. dorzolamide vs. timolol Latanoprost vs. bimatoprost vs. travoprost Timolol solution vs. timolol gel	Conclusions were limited because 1 study contained most of the data All topical medications reviewed decreased IOP throughout 24-h cycle Prostaglandins appear to reduce IOP more during the 24-h cycle than do β-blockers, topical carbonic anhydrase inhibitors, and α-agonists, but the evidence is weak Although the IOP-decreasing effects of prostaglandins appear to vary appreciably during the 24-h period, results were inconsistent and the reported difference was small	Imprecise, inconsistent, low overall strength of evidence
Surgical: 28 (1834 patients)	Trabeculectomy with adjuvants (mitomycin C, 5-fluorouracil, Ologen implant [Aeon Astron Corp., Taipei, Taiwan], amniotic graft, polytetrafluoroethylene membrane) Trabeculectomy techniques and variations (deep sclerectomy, EX-PRESS shunt) Trabeculectomy with combined techniques (viscocanalostomy–iridectomy fornix vs. limbus) Combined cataract–glaucoma surgery Laser trabeculoplasty	Trabeculectomy decreases IOP Use of mitomycin C 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 mitomycin C have not been shown to further decrease IOP Trabeculectomy decreases IOP more than do nonpenetrating surgeries Location of conjunctival incision or presence or absence of peripheral iridectomy has no effect on how much combined cataract surgery and trabeculectomy decreases IOP 2-site surgery might further decrease IOP over 1-site surgery Laser trabeculoplasty effectively decreases IOP in patients with glaucoma; effectiveness does not seem to vary with type of laser used Data available for the role of aqueous drainage devices in OAG are inadequate to permit conclusions	Consistent, precise, moderate overall strength of evidence
Medical–surgical: 2 (220 patients)	Medical treatment vs. trabeculectomy	Incisional surgery decreases IOP more than do lasers or medications Initial treatment with lasers reduces need for medications to achieve same IOP	Consistent, imprecise, low overall strength of evidence

IOP = intraocular pressure; RCT = randomized, controlled trial.

Appendix Table 2. **Evidence for the Outcomes of Visual Field Loss and Optic Nerve Damage**

Studies Included, *n*	Comparators	Main Results	Strength of Evidence
Systematic reviews			
Medical: 1	Medical vs. surgical treatment	Medical treatment for glaucoma protects against visual field progression	High
Surgical: 0		No surgical studies presented conclusive data	
Medical–surgical: 2	Trabeculectomy vs. medical treatment Medical or surgical vs. no treatment	Medically and/or surgically treated patients are less likely to experience progression of field loss and optic disc damage compared with participants receiving no treatment Some trials showed that worsening was more likely for medically treated participants than for participants randomly assigned to laser trabeculoplasty or trabeculectomy	High
Primary studies			
Medical: 20 (4155 patients)	Timolol vs. brimonidine vs. travoprost Timolol vs. carteolol Timolol vs. latanoprost Timolol vs. betaxolol Latanoprost vs. bimatoprost Latanoprost vs. travoprost vs. dorzolamide–timolol	Most medical studies are too small or too short to be conclusive Treatment of ocular hypertension with medicines preserves visual fields better than does no treatment	Inconsistent, imprecise, low overall
Surgical: 0		No surgical studies presented conclusive data	
Medical–surgical: 1 (191 patients)	Laser trabeculoplasty vs. medication	No changes in visual field	Single study, representing insufficient evidence to permit conclusions

RCT = randomized, controlled trial.

Appendix Table 3. **Evidence for Harms Associated With Treatments for Open-Angle Glaucoma**

Studies Included, *n*	Comparators	Main Results	Strength of Evidence
Systematic reviews			
Medical: 11	Latanoprost vs. bimatoprost Latanoprost vs. bimatoprost vs. travoprost Latanoprost vs. dorzolamide–timolol Latanoprost vs. brimonidine Latanoprost vs. travoprost vs. bimatoprost Travoprost vs. latanoprost vs. bimatoprost vs. timolol Timolol vs. brimonidine Timolol vs. latanoprost	Participants receiving timolol were less likely to drop out of studies because of adverse effects than those receiving brimonidine, latanoprost, travoprost, or betaxolol	
Surgical: 10	Efficacy and safety of viscocanalostomy Nonpenetrating filtering surgery β-radiation during trabeculectomy 1-site phacotrabulectomy vs. 2-site phacotrabulectomy Intraoperative mitomycin C vs. placebo during trabeculectomy Posttrabeculectomy injections of 5-fluorouracil	Adverse effects occurred more often in participants randomly assigned to trabeculectomy than to those assigned to other nonpenetrating surgeries Harms were reported for the addition of antimetabolites to primary trabeculectomy Addition of β-radiation to trabeculectomy resulted in significantly higher risk for cataract when compared with trabeculectomy alone Harms associated with glaucoma drainage devices have not been adequately compared with harms of other procedures in OAG treatment	
Medical–surgical: 2	Medical vs. surgical treatment	Trabeculectomy is associated with cataract worsening and increased need for cataract surgery over time compared with 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	
Primary studies			
Medical: 21 RCTs, 16 observational	Timolol vs. brimonidine vs. travoprost Timolol vs. carteolol Timolol vs. latanoprost Timolol vs. betaxolol Latanoprost vs. bimatoprost Latanoprost vs. travoprost vs. dorzolamide–timolol Topical medication vs. observation Latanoprost vs. bimatoprost latanoprost vs. timolol vs. brimonidine Latanoprost vs. dorzolamide–timolol	Prostaglandins produce more ocular redness than does timolol Among the prostaglandins, latanoprost is less likely to cause redness than is bimatoprost or travoprost	Unable to assess because of heterogeneity in outcomes and comparisons across studies
Surgical: 26 RCTs, 8 observational	Trabeculectomy with adjuvants (mitomycin C, 5-fluorouracil, Ologen implant [Aeon Astron Corp., Taipei, Taiwan], polytetrafluoroethylene membrane, amniotic graft) Trabeculectomy techniques and variations Combined cataract–glaucoma surgery Laser trabeculoplasty Deep sclerectomy with or without mitomycin C Deep sclerectomy with or without collagen implant	Profile of harms does not differ between 1- and 2-site combined cataract and glaucoma surgery Reports of adverse effects across studies that addressed questions related to combined surgery for coexisting cataract and glaucoma varied by intervention under consideration	Unable to assess because of heterogeneity in outcomes and comparisons across studies
Medical–surgical: 2 RCTs, 0 observational	Trabeculectomy vs. medical treatment Medical or surgical vs. no treatment	Primary studies did not systematically address harms	Unable to assess because of heterogeneity in outcomes and comparisons across studies

OAG = open-angle glaucoma; RCT = randomized, controlled trial.