Current management of glaucoma

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Purpose of review

This study reviews current concepts in the goals of glaucoma therapy, interventional sequence, and options for the management of glaucoma in light of recent clinical trials.

Recent findings

Recent randomized prospective trials of ocular hypertension and glaucoma have provided evidence for more specific treatment goals in glaucoma therapy. In addition, the advent of the prostaglandin analogs, advances in laser technology, and innovative techniques for filtering surgery have expanded the armamentarium that ophthalmologists use in the treatment of glaucoma.

Summary

Despite continued advances in laser and incisional surgery, medical therapy still appears to be the primary means by which intraocular pressure is controlled. Initial medical therapy has changed with the introduction of prostaglandin analogs, which are replacing β-antagonists as the drug of first choice. Laser trabeculoplasty, using either photocoagulative (argon and diode) or photodisruptive (frequency doubled Nd:YAG) lasers, is still reserved for patients who do not improve with medical therapy, although there is good evidence that initial laser trabeculoplasty is just as effective as initial medical therapy. Trabeculectomy with antifibrotic agents (5-fluorouracil or mitomycin C) is still the next step in intraocular pressure control, and glaucoma drainage implants are reserved for refractory cases. Cyclophotocoagulation is a last resort procedure because of poor visual outcomes and is reserved for patients with intractable pain and vision thought not to be useful.

Keywords

glaucoma, prostaglandin, SLT, filtering surgery

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Introduction

The management of glaucoma typically proceeds from interventions that are the safest and the least invasive, to those that expose the patient to greater risk and are the most invasive. Glaucoma therapy involves medicines, lasers, and incisional surgery.

Treatment modality follows diagnosis, and the type and severity of disease must be determined before an appropriate intervention can be selected. Recent, large, prospective studies have examined more closely the role of intraocular pressure (IOP) lowering in the prevention of progression of glaucomatous disease. The Collaborative Normal Tension Glaucoma Study, Advanced Glaucoma Intervention Study, Collaborative Initial Glaucoma Study, Ocular Hypertensive Treatment Study, and the Early Manifest Glaucoma Treatment Study all provide evidence that reduction of IOP reduces the rate of disease progression.

Goals of glaucoma therapy

The goal of glaucoma therapy in ocular hypertension is to lower IOP by at least 20% in patients at moderate to high risk. In patients with perimetry-proven glaucoma, IOP should be lowered by at least 30% in early to moderate glaucoma, and perhaps 40% to 50% in severe glaucoma. A number of prospective, randomized clinical trials, including the Collaborative Normal Tension Glaucoma Study [1,2], Advanced Glaucoma Intervention Study [3], Collaborative Initial Glaucoma Study [4], Ocular Hypertension Treatment Study [5••], and Early Manifest Glaucoma Study [6••] provide evidence that the above treatment parameters may be useful in setting the initial IOP goal in patients with glaucoma. However, because of individual variability in susceptibility to damage of the optic nerve, continued vigilance for progression, using automated static perimetry and optic nerve stereo photography, is necessary to determine whether individual patients will progress at the initial target IOP [7]. Visual fields and optic nerve photos should be monitored for signs of change, and IOP should be lowered an additional 15% if progression is detected [7].

Glaucoma management options

Medical therapy

There are three general categories of management options available for IOP lowering. Each has been shown to be effective in lowering IOP and preventing glaucoma progression. Most clinicians begin with medical therapy, then go on to laser surgery, and finally perform surgery if

the IOP is not adequately controlled [Fig. 1]. This stepwise approach reflects the safety and efficacy of these treatments, although several clinical trials have studied using laser first [8] or incisional surgery first [4,9], and have gotten comparable results to medicine first.

Table 1 shows the available classes of medication used for chronic management of glaucoma. All work by lowering IOP, either by improving aqueous humor outflow or reducing its production [10]. The exact mechanisms by which this is accomplished may differ between classes. For instance, prostaglandin derivatives improve aqueous outflow primarily through the uveoscleral pathway, whereas cholinergic agonists exert their effect on the trabecular meshwork outflow system exclusively.

The osmotic agents (mannitol, glycerin, urea) are included in the interest of completeness. These potent agents are used in two situations: (1) in the acute management of elevated IOP (such as acute angle closure glaucoma), or (2) before incisional surgery where the IOP is elevated or the eye may be open for a long time, to prevent expulsive suprachoroidal hemorrhage. The mechanism of action of these drugs, as traditionally taught, is to shrink the vitreous by increasing the osmotic gradient between the plasma and the eye, thereby lowering the IOP by reducing the volume in the eye. The exact mechanism whereby these drugs work is still unclear, however [11].

When prescribing initial medical therapy for glaucoma or ocular hypertension, there are a number of factors to consider. Efficacy, side effects, cost, convenience of dosing, and a new possible consideration, differences in diurnal fluctuation, all must be considered. Entire monographs have been written to address these issues [11,12].

Table 2 shows the approximate range of IOP lowering that one may expect based on well-performed controlled clinical trials of these medications. More complete summaries are available in the references [11–13,14•]. Classes of medications have been split into individual medications when appropriate. For instance, betaxolol, a β-1 selective β-blocker, is not as effective as nonselective β-blockers such as timolol or levobunolol. And unoprostone, a prostaglandin derivative, is less effective than latanoprost [15,16•] and, most likely, the other medications in that class group. There are conflicting data in the literature regarding differences in efficacy between latanoprost and bimatoprost. Several studies have shown a minor (0.5 to 2 mm Hg) difference in IOP-lowering effect in favor of bimatoprost [17–19•], although all but one of these [19•] failed to show a statistically significant difference with properly performed statistical analyses. An initial report on travoprost purported a better response to travoprost than latanoprost in black subjects [20]. However, this was true at only a few time points, and proper statistical analysis of these data, taking into account differences in baseline IOPs, fails to show a difference in favor of one drug over the other in black patients [21]. Subsequent studies comparing travoprost and latanoprost or bimatoprost have failed to detect any statistically significant differences in response in black subjects [22•,23•]. In the only randomized prospective trial comparing latanoprost, bimatoprost, and travoprost, no statistically significant differences in IOP lowering were found, even in a subanalysis of black subjects [23•]. So, regarding efficacy within the prostaglandin derivative class, the only conclusive studies show that unoprostone is significantly less effective at lowering IOP than the other three in this class. Latanoprost, bimatoprost, and travoprost appear to have similar efficacy.

Table 1. Mechanism of action of glaucoma medications

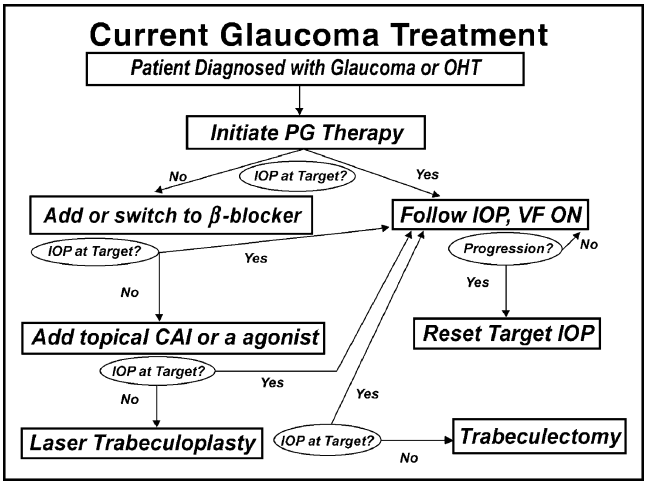
	Decrease aqueous production	Increase aqueous outflow
Prostaglandin derivatives		X
β-Antagonists	X	
α-Agonists	X	X
Carbonic anhydrase inhibitors	X	
Cholinergic agonists		X

Table 2. Relative monotherapy efficacy and approximate percentage intraocular pressure lowering of currently available topical glaucoma medications

Weaker (10–20%)	Medium (20–25%)	Stronger (25–35%)
Betaxolol	Nonselective β-antagonists	Latanoprost
Unoprostone	α-Agonists	Bimatoprost
Topical carbonic anhydrase inhibitors	Cholinergic agonists	Travoprost

Adapted with permission [13].

Figure 1. Glaucoma treatment decision tree



Treatment options for glaucoma, based on responses. CAI, carbonic anhydrase inhibitors; IOP, intraocular pressure; OHT, ocular hypertension; ON, optic nerve; PG, prostaglandin; VF, visual field.

One important point is that the above efficacies are from clinical trial data from patients with open angle glaucomas who started with IOPs in the mid to upper 20s. If one starts with a higher IOP, then percentage lowering may be more than if one starts at a lower IOP. Also, these approximations only apply if the medicine is used at the frequency recommended by the package insert. In particular, the topical carbonic anhydrase inhibitors and brimonidine are labeled as three times daily medications because twice-daily dosing results in significant trough effects when used as monotherapy [24–26]. However, in combination therapy with a nonselective β-blocker, these two medications seem to be equivalent whether used twice daily or three times daily.

Our decision about which medication to choose for our patient is never really based on efficacy alone. Otherwise, all of our patients with glaucoma would be on systemic carbonic anhydrase inhibitors! Ocular and systemic tolerability, dosing regimen, and cost must be considered as well.

Table 3 rates classes of topical glaucoma medications, and medications within classes where they differ, on the basis of the frequency and severity of ocular side effects [13]. Cholinergic medicines, such as pilocarpine, have excellent efficacy and cost, but have been largely abandoned because of the severity of their ocular side effects compared with newer agents available. Brimonidine has a relatively high rate of allergic response, and the discontinuation rate for this medication because of ocular adverse events is relatively high compared with the other medications. In a well-performed 12-month study comparing brimonidine to timolol, the discontinuation rate was 45% for brimonidine, primarily because of ocular adverse events, compared with only 17% for timolol [26].

Within the prostaglandin derivative class, latanoprost and unoprostone appear to have better ocular tolerability than travoprost and bimatoprost, specifically because of the higher rate and severity of ocular hyperemia associated with the latter two medications [23]. An excellent table comparing the frequency of ocular adverse events reported in the Phase 3 clinical trials on the prostaglandins may be found in [12], pages 132 to 133.

Table 3. Relative frequency/severity of ocular side effects of current topical glaucoma medications

Low	Medium	High
Latanoprost	α-Agonists	Cholinergic agonists
Unoprostone	Topical carbonic anhydrase inhibitors	
β-Antagonists	Bimatoprost	
	Travoprost	

Adapted with permission [12,13].

Table 4. Relative frequency/severity of systemic side effects of current topical glaucoma medications

Low	Medium	High
PG derivatives	Brimonidine (infants)	Nonselective β-antagonists
Cholinergic agonists	Topical carbonic anhydrase inhibitors	
	Betaxolol	

PG, prostaglandin. Adapted with permission [13].

In general, topical medications for glaucoma are very well tolerated systemically [10]. There are minor differences, however, in individual medications and in particular patient groups. For example, nonselective β-blockers are usually well tolerated, but may cause an exacerbation of respiratory symptoms in patients with reactive airway disease (such as asthma) and bradycardia in susceptible patients. Impotence and decreased exercise tolerance have also been reported with β-blockers. Betaxolol, a β-1 receptor selective antagonist, has fewer respiratory side effects, although the other side effects mentioned for the β-blockers are no less in betaxolol-treated patients. Brimonidine has been associated with respiratory and cardiac depression in infants and is contraindicated under age 2, and caution is indicated in all pediatric patients and nursing mothers. Both brimonidine and topical carbonic anhydrase inhibitors can cause fatigue and drowsiness in adults (elderly patients are particularly susceptible), and thus are not as well tolerated systemically as the prostaglandin derivatives and cholinergic agonists. In addition, many patients complain of a metallic taste perversion while using topical carbonic anhydrase inhibitors. Table 4 rates the available topical glaucoma agents according to systemic side effects.

Dosing regimen is an important factor in patient compliance. Although there is good evidence in the ophthalmic literature to suggest that compliance is worse with four times daily compared with twice daily dosing regimens [27,28], evidence for differences in compliance between twice daily and every day dosing is lacking. In fact, a large review of the literature on compliance with oral medications found 70% compliance with twice daily or every day dosing [29], compared with 52% for three times daily dosing and 42% with four times daily dosing.

Differences in the cost of glaucoma medications are mostly related to the availability of these medicines in generic form. The nonselective β-blockers and cholinergic agonists have been around for more than 25 years; thus, generics are available and relatively inexpensive ($0.38 to $0.50 per day for bilateral therapy with generics *vs* $0.90 to $1.33 per day for newer agents) [30•]. A generic form of brimonidine recently became available, and the cost to pharmacies is approximately half the cost of the branded formulation [31]. However, it is unclear

whether pharmacies will pass this cost-savings on to patients to the same degree.

A recent study suggests that high diurnal fluctuation of IOP, even in treated patients, can result in more progression compared with patients who do not show high diurnal fluctuations [32]. A subsequent study showed that latanoprost-treated patients show less diurnal variation in IOP than patients treated with timolol or dorzolamide [33]. There is an excellent review on the importance of diurnal fluctuation in glaucoma management by Jacob Wilensky, MD, in this edition of Current Opinion in Ophthalmology.

Although IOP-lowering therapy medically has been shown to be beneficial in delaying or preventing the onset of glaucoma in ocular hypertensives and delaying or preventing visual field loss in those with glaucoma, there must be a consideration of the potential downside of therapy in general and of specific therapies. For example, in a 90-year-old ocular hypertensive patient with no visual field loss, observation to see if the patient develops glaucoma might be better than lowering the IOP by 20%, especially if your therapy introduces the risk of ocular or systemic side effects or high medication costs. At the other end of the spectrum, let's consider a 60-year-old patient with severe, progressive glaucoma who has IOPs in the mid-20s on maximal medical therapy and has already received laser trabeculoplasty. The risk of permanent disability is high without IOP lowering, and the benefits of successful trabeculectomy are high. One would probably be willing to accept the small risk of complications from trabeculectomy surgery in this case.

There is some debate as to whether treating IOP early provides more benefit than waiting until one establishes that glaucoma is present and, if it is, what the rate of progression is. Advocates of early treatment believe that prolonged elevation of IOP triggers a series of events that results in progressive loss of ganglion cells even after IOP is adequately controlled. This hypothesis may explain why some patients continue to progress despite adequate control of IOP [34]. If this is true, it suggests early intervention for elevated IOP is necessary. If early treatment turns out not to be very important, then waiting for signs of manifest glaucoma (optic nerve changes or visual field abnormalities) is a reasonable strategy in ocular hypertension management. Observing patients with glaucoma for evidence of progression to determine the rate of progression and then tailoring treatment to reduce this rate is a reasonable option. This debate is an important one in public health circles, because treating everyone with ocular hypertension is a costly endeavor. The Framingham Eye Study [35] and The Baltimore Eye Survey [36] found that 4% to 7% of people older than age 40 have elevated IOP; thus, treating all of them would place a tremendous burden on health care resources. Phase II of the Ocular Hypertension Treatment Study has just received funding to try to answer this important issue.

Laser surgery

Laser surgery for open angle glaucoma generally refers to laser trabeculoplasty, although endolaser laser photocoagulation of the ciliary processes has become more widely used in the management of glaucoma. Photocoagulation of the ciliary processes, using either an endolaser or transscleral technique, has generally been reserved for eyes refractory to all other medical or surgical treatments. Some have advocated endolaser cyclophotocoagulation as a viable earlier treatment modality [37,38] in developed countries, and others have advocated transscleral cyclophotocoagulation in developing countries [39], where healthcare resources do not permit the usual stepwise approach to glaucoma management that are available here in the United States and the remainder of the developed world.

Laser trabeculoplasty has been used in the management of open angle glaucomas for more than 20 years. Initially performed with the argon blue-green wavelength [40,41], the same effect may be achieved using argon green, diode green, and a frequency-doubled Nd:YAG laser, known as selective laser trabeculoplasty. There are some advantages to laser trabeculoplasty when compared with medical treatment or incisional surgery. It does reduce IOP in most patients, there is no risk of bleeding or infection because it is relatively noninvasive, there is less dependence on patient compliance to provide IOP control, and the IOP becomes less susceptible to diurnal variation [42].

Laser trabeculoplasty results in an IOP reduction of 20% to 30% in most patients. However, the effect wears off in 5% to 10% of patients per year, and the 5-year and 10-year success rate is approximately 50% and 32%, respectively [43]. The poor long-term success may be because of progression of the disease with worsening IOP or structural changes in the trabecular meshwork over time, such as scarring and fusion of trabecular beams [44,45].

The Glaucoma Laser Trial was a prospective, randomized study comparing the efficacy and safety of medical therapy first versus argon laser trabeculoplasty (ALT) first in the management of glaucoma [8]. In each previously untreated patient, one eye was randomized to ALT first and the other to medical therapy with timolol 0.5% first. Two-year success rates for the Glaucoma Laser Trial showed a success rate of 44% if eyes were treated with laser alone, or controlled with a combination of laser first and any medication at 2 years. This gave support to laser therapy when compared with the 30% figure for eyes treated with timolol 0.5% alone. Seventy percent of eyes treated with laser followed by timolol alone had

controlled IOP at 2 years, whereas 66% of eyes treated with a stepwise medical regimen alone were successful at 2 years. Eighty-nine percent of patients thought that the idea of laser trabeculoplasty is a reasonable initial treatment for glaucoma.

Despite the successful results of laser trabeculoplasty as an initial treatment modality in the Glaucoma Laser Trial, members of the American Glaucoma Society (who were polled 1 to 2 years after the results of the Glaucoma Laser Trial were published) were only rarely or never performing this procedure as an initial management option [46].

Selective laser trabeculoplasty (SLT) is a frequency-doubled Nd:YAG laser that delivers a brief duration (3 nS), large spot (400 μm), relatively low-energy (approximately 0.75 mJ) spot to the trabecular beams [47]. It reportedly targets pigmented trabecular meshwork cells, possibly stimulating them to divide and provide improved outflow through the trabecular meshwork [48]. Histologic studies in human cadaver eyes have demonstrated much less damage to surrounding trabecular beams with SLT compared with ALT [49]. This may result in improved long-term success and the ability to retreat the meshwork in the future with more success using SLT compared with ALT. There is a single prospective randomized trial comparing ALT and SLT in the literature by Damji *et al.* [50]. In this 6-month trial, they found the same degree of IOP lowering using both lasers, approximately 21%. Just under half of patients in each group had already undergone ALT, therefor this group of patients would not be expected to be particularly responsive to further laser treatment.

In the only published report on SLT used as initial therapy for glaucoma, Melamed *et al.* [51••] found an average 30% drop in IOP in the overall group, a number similar to that obtained with initial medical therapy with prostaglandin derivatives shown in other studies with similar baseline IOPs. A randomized prospective trial comparing initial SLT to initial medical therapy is ongoing [52].

Incisional surgery

Incisional surgery has traditionally been reserved for patients who do not improve with medical and laser therapy for glaucoma, except in congenital and infantile glaucomas. Trabeculectomy remains the most commonly performed incisional surgery for glaucoma. This may be performed with antifibrotic agents, such as 5-fluorouracil or mitomycin C in high-risk patients [53–56]. There is reasonable evidence that these agents enhance success in primary filtering surgery (those with no prior incisional surgery) [57]. Although deep sclerectomy and viscocanalostomy (nonpenetrating filtration surgery) have gained popularity overseas, their use in the United States is fairly limited, even among glaucoma subspecialists. This is because studies have not shown IOP lowering in most patients to be as good as trabeculectomy, although the complication rate is less [58•,59••]. Glaucoma drainage implants have traditionally been reserved for patients who have refractory glaucoma (neovascular, inflammatory) or those who have not improved with trabeculectomy or have conjunctival scarring from previous ocular surgery. Success rates with these devices are comparable to that of trabeculectomy, although there are limited data from randomized prospective trials [60].

Trabeculectomy has been used for more than 20 years for the surgical management of glaucoma and is currently the most widely used incisional procedure worldwide. When initial trabeculectomy was compared with medical therapy in the Collaborative Initial Glaucoma Study, it was found to provide lower IOPs than medical therapy, although the rate of visual field progression was negligible in both groups [4]. There was no difference in quality of life noted between the initial trabeculectomy versus medical group, either [61]. Other advantages of trabeculectomy over medical therapy include stabilization of IOP (minimizing diurnal fluctuation), less reliance on patient compliance to take medications, and less dependence on patient financial resources to stay compliant with treatment.

Despite these advantages, in developed countries trabeculectomy is still performed after medications and laser surgery have failed. This is probably because of the risk of immediate visual loss from complications of surgery, such as choroidal effusion, hypotony maculopathy, suprachoroidal hemorrhage, or optic nerve snuffing. There are also long-term risks to vision, such as hypotony maculopathy, bleb infections, and cylindrical changes in the cornea.

Glaucoma drainage implants are most commonly used in patients with glaucoma refractory to trabeculectomy or with neovascular [62,63] or inflammatory glaucomas [64•]. Recently, however, there has been interest in performing glaucoma drainage tube implants as an alternative to trabeculectomy in primary procedures [60]. More studies are needed to determine the safety and efficacy of glaucoma drainage implants compared directly to trabeculectomy.

Treatment algorithm

The figure represents our thought process in treating glaucoma. This algorithm is not meant to be a cookbook approach to treatment. Rather, it forms the architecture of a decision-making tree that must be tempered with the individual situation of the patient and an overall gestalt of the nature of that patient's disease.

First, the decision to initiate treatment in an ocular hypertensive patient is variable. This decision is based upon an individual patient's risk factors for the development of glaucoma, such as level of IOP elevation, optic nerve appearance, family history of glaucoma, race, age, central corneal thickness, and the patient's own preference for preventative medicine therapy. Generally, therapy is initiated with medications, although laser trabeculoplasty is a reasonable first-line agent. Of the classes of medicines available for lowering IOP, the prostaglandins have the best balance between efficacy (25% to 30% lowering), safety, and ease of dosing regimen. If the patient cannot afford prostaglandin therapy, then a topical β-blocker can be started if there are no systemic contraindications. If only a minimal decrement in IOP is seen, the patient is switched to a different class of medicine, usually the β-blockers, because of their efficacy, tolerability, and ease of dosing. If the IOP does go down a bit with a prostaglandin, but is not at target IOP, a β-blocker is added. Then, if these maneuvers are unsuccessful, one can add a topical carbonic anhydrase inhibitor, usually in the form of the fixed combination of timolol 0.5% and dorzolamide, again attempting to keep the dosing regimen simple. If this does not work, the dorzolamide is stopped and substituted with brimonidine. Once three or four medicines have been tried and the IOP remains refractory, laser trabeculoplasty is performed. If it seems unlikely that laser will make enough of an impact on IOP, trabeculectomy is recommended. Usually primary trabeculectomy is completed with intraoperative and possibly postoperative 5-fluorouracil, unless the patient has risk factors for scarring, such as young age or prior incisional eye surgery, in which case intraoperative mitomycin C is used.

Conclusion

Although there are a number of options that have been studied as initial management of IOP in glaucoma and ocular hypertension, medical management still appears to be the most widely used treatment initially. Within medical management, prostaglandins make the most sense for initial therapy, although only one of them (latanoprost) has actually been approved for first line therapy [10]. Laser trabeculoplasty is still mostly used in patients for whom medical therapy does not provide adequate IOP lowering, although results from the glaucoma laser trial indicate that initial treatment with laser trabeculoplasty is a reasonable option. If SLT turns out to be repeatable, it may quickly surpass standard ALT as the laser treatment of choice for open angle glaucoma. Despite results from the Collaborative Initial Glaucoma Trial, showing equivalent outcomes in patients treated with trabeculectomy initially as an alternative to medical therapy, the complications of surgery and short-term visual results have prevented trabeculectomy from being adopted as an initial treatment for glaucoma in most patients. Whether or not to use antifibrotic therapy at the time of trabeculectomy, and which one to choose, is variable among glaucoma specialists. Most glaucoma specialists are using adjunctive antifibrotic agents at the time of trabeculectomy [65].

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • Of special interest
- •• Of outstanding interest

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