Pharmacological Treatment and Management Protocols for Glaucoma: An Optometric Approach
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Background

Glaucoma is considered the leading cause of irreversible blindness in the world, and second leading cause of blindness worldwide next to cataracts (1). Currently almost half a million people in Canada, nearly 3 million people in the United States, and over 60 million people worldwide have glaucoma (2). The condition is especially common in those of African black heritage, being 4 times more prevalent than in those of Caucasians (3), as well as being up to 10 times greater risk of progression in blacks compared to whites (4). Asians have been shown to have greater risk of narrow angle glaucoma than other ethnicities (5). Due to the often slow and painless damage to the retinal nerve fiber layer, at least half of those with glaucoma are unaware that they have the condition. Some studies have shown no symptomatology or visual field loss when half or more of the approximately 1.2 million retinal nerve fibers are lost (6-9).

There are several types of glaucoma, divided broadly into primary (originating on its own) and secondary (originating from another pathological source) forms, and open and closed angle forms (Table 1). The most common type is primary open angle glaucoma (POAG).

Table 1. Glaucoma types, categorized within primary or secondary, and open or closed angle forms.
Regardless of the type of glaucoma, the commonality is gradual retinal nerve fiber layer (RNFL) loss and accompanying neuroretinal rim thinning of the optic nerve. This results in the characteristic thinning of the optic disc rim (typically starting inferiorly, then superiorly, temporally, and finally nasally) with exposure of the lamina cribrosa. Other signs, such as rim notching, bayoneting of retinal vessels over the neural rim, laminate striae, alpha and beta peripapillary atrophy, and (in the case of normotensive glaucoma) splinter or Drance hemorrhages off the optic disc may present to the optometrist. Pallor of the disc is not as common in glaucoma as in other neuropathies such as chronic optic neuritis, toxic neuropathy, and ischemic neuropathies (10).

Various instruments are currently useful for identifying and monitoring glaucoma and glaucoma progression (Table 2). The optometrist should have these instruments available for managing patients with glaucoma.

Table 2. Recommended instruments for managing patients with glaucoma

<table>
<thead>
<tr>
<th>Tonometer</th>
<th>Visual field analyzer</th>
<th>Retinal camera</th>
<th>Retinal nerve fiber analyzer</th>
<th>Pachymeter</th>
<th>High plus biomicroscopy lens</th>
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There are more esoteric tests available in helping diagnose and manage glaucoma, including genetic testing. Other less-common tests are the Ocular Response Analyzer (Reichert, Corp.; New York, USA) which measures corneal hysteresis, corneal deformation analyzers such as the Corvis ST (Oculus; Wetzlar, Germany), ocular pulse analyzers (Dicon/Paradigm Medical; Salt Lake, USA: PASCAL; Zeimer Group, Port, Switzerland) which look at the vascular flow rhythm and amplitude, electrophysiological testing such as the electroretinogram (ERG) and visual-evoked potential (VEP), various unique stimulus visual field tests such as frequency-doubling technology (FDT) perimetry, and other advanced retinal imaging technology (i.e. multispectral imaging, retinal Doppler flowmetry, etc.) under current investigation.

Glucoma was traditionally defined as a disease of elevated eye pressure, leading to specific optic nerve damage and visual field loss. Currently, eye pressure has been removed from the definition, as patients with normal untreated eye pressure (typically between 10-21mmHg) can have glaucoma. However, the primary treatment for glaucoma at the time of this article is still to lower the intraocular pressure, by medicinal, laser, and/or incisional surgical means. Neuroprotection and gene therapy for glaucoma are being actively researched and may likely serve as future treatment modalities (11).

Pathophysiology

There is still debate as to the specific process by which glaucoma occurs. Many types of glaucoma appear to have polygenic (involving both genes and environment) and multifactorial elements (including complex inheritance and genetic patterns) in development and progression. Three classic theories are 1) direct mechanical damage to the retinal nerve fibers, affecting internal organelles and axoplasmic flow, 2) ischemia of the optic nerve due to reduced blood flow to the optic nerve, and 3) apoptosis, or ‘programmed cell death’, which may have a genetic propensity (12).

The ciliary body produces aqueous via the non-pigmented ciliary epithelium, a single cell layer that borders the ciliary body and posterior iris with the anterior vitreal face (Figure 1). This cell layer has within the cell membrane the enzyme carbonic anhydrase (CA), which produces the aqueous (13). Roughly 80 percent of the aqueous flows from the ciliary body into the posterior chamber (behind the iris but in front of the anterior vitreal face), through the pupil, and out through the trabecular meshwork and Schlemm’s canal to the venous system. The other 20 percent leave the eye through the uveo-scleral tissue (Figure 2)(14). If one considers the eye a ‘closed sink’, the ‘tap’ would be the ciliary body, the ‘drain’ would be the trabecular meshwork, and the ‘overflow hole’ would be the uveo-scleral tissue. Several types of open-angle glaucoma show a disruption in this sink – usually a dysfunction at the ‘drain’ (trabecular meshwork). Closed-angle glaucomas show a definite problem in outflow due to direct or indirect blockage of the trabecular meshwork.
Figure 1. Non-pigmented ciliary body histological section showing the ciliary processes and ciliary muscle. The darkly-stained layer of cells along the edge of the ciliary processes is the non-pigmented ciliary epithelium where the action of enzyme carbonic anhydrase produces aqueous. (From http://www.xalatan.com/hcp/image_library/glaucoma/G_068_49_glaucoma_carbonic_anhydrase_inhibitors_cais_.asp)
Recent efforts in genetic testing have shown a strong link to mutations in cells of the trabecular meshwork, leading researchers to link glaucoma to reduced aqueous outflow (15). Direct ocular tissue, blood, or saliva samples can be analyzed and mutations confirmed using established gene sequencing methods. Currently there are at least 15 genetic tests to help confirm various types of glaucoma. More notable ones are the MYOC gene for POAG, the OPTN, TBK1, and OPA1 genes for NTG (OPTA1 causes primary optic atrophy, which shares features with NTG), and the CYP1B1 and LTBP2 genes for congenital glaucoma. As sensitivity
and specificity of these and other genetic tests increase over the years, application towards targeted gene therapy may become more viable in the future (16).

Several risk factors for glaucoma should be identified. A key risk factor is the patient being of black race, as there is a much higher chance of glaucoma as well as progression of glaucoma. Aside from rare congenital glaucoma (where large and sometimes hazy corneas are noted in the infant) and juvenile forms of glaucoma, typically patients over 40 years of age are at higher risk for glaucoma than younger patients. Family history of glaucoma is variable, but a greater risk is usually present if the patient’s siblings have been diagnosed with glaucoma. Vascular disease may also be a relative risk factor; patients with diabetes, hypertension, hyperlipidemia, Reynaud’s Syndrome, or other systemic vascular disease should be looked at more closely. Retinal vascular disease (i.e. vascular occlusion) may increase the risk. Smokers and those who drink in excess may also be factors to consider. Steroid medications (topical or systemic) are known to increase IOP in ‘steroid responders’ (patients who have in increase in ocular pressure and/or posterior subcapsular cataracts with corticosteroid use), another risk(17).

Once a comprehensive case history and battery of pertinent tests is run, a patient may be considered to have low to no risk of glaucoma, risk factors for glaucoma, ocular hypertension (traditionally considered above 21mmHg uncorrected by pachymetry), glaucoma suspicion (based on IOP, visual field, and/or other objective tests), or glaucoma (the specific type of glaucoma determined by the case history and tests performed). Often repeat testing is needed to help confirm or rule-out the diagnosis. Table 3 lists the indications to initiate treatment.

Table 3. Indications for glaucoma treatment

<table>
<thead>
<tr>
<th>Indications</th>
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<tr>
<td>Established glaucoma</td>
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<tr>
<td>Glaucoma one eye, ocular hypertension other eye</td>
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<tr>
<td>Ocular hypertension one or both eyes</td>
</tr>
<tr>
<td>Intraocular Pressure (IOP) level</td>
</tr>
<tr>
<td>Rising IOP</td>
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<tr>
<td>Risk factors &amp; suspect ocular hypertension</td>
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<tr>
<td>One eye, suspect ocular hypertension</td>
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<tr>
<td>IOP &gt; 21 with history of retinal vascular occlusion</td>
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Main Treatments

Current treatment for glaucoma includes pharmaceutical, laser, and incisional surgical. These treatment options aim to lower intraocular pressure (IOP). The following are categories of pharmaceutical treatments. Almost all of these agents are in topical ophthalmic formulations.

Adrenergic Agonists

dipiverfrine
Carrying the original trade name of Propine (Alcon) as well as a generic version, dipivefrine (Dipivalyl epinephrine aka DPE) was one of the earliest topical ophthalmic eyedrops for lowering intraocular pressure. It is a pro-drug that converts to epinephrine on entry into the eye. Dipivefrine is sympathomimetic, directly stimulating the alpha-receptors on the non-pigmented ciliary body, indirectly reducing aqueous production, as well as facilitate uveoscleral outflow. IOP lowering is between 15-20% from baseline. Available as a 0.1% solution, typical dosage is 1 drop in the affected eye(s) every 12 hours.

Figure 4. Propine (dipivefrin HCL 0.1%) ophthalmic solution. (From http://dxline.info/drugs/propine)

As the smooth iris dilator muscle also carries alpha receptors, dipivefrine also dilates the pupil, which may paradoxically raise intraocular pressure (and, in narrow-angle cases, potentially cause an angle closure; as such, this medication is contraindicated with those patients). Some cross-stimulation of beta receptors also occur, which can indirectly increase aqueous production. Usually the IOP rises within 2 hours of instillation, followed by a slow reduction in IOP below baseline occurs over the next 8-10 hours. Other potential side-effects of dipivefrin are adenochrome deposits (silver-like in appearance) in the conjunctiva, cystoid macular edema (CME) – particularly in patients with aphakia or pseudophakia – and ocular irritation and lacrimation. Systemic side effects may include headaches, tachycardia, arrhythmia, and headaches. Dipivefrine is not used typically in current treatment of most glaucomas, but is noted in this article for historical reference.
**Cholinergic Agonists**

Pilocarpine

Pilocarpine (trade name Diocarpine, Isopto Carpine, Miocarpine, Pilopine, Pilopine HS, Akarpine, AK-Pilo, Pilo Stat, Pilagan, Ocucarpine, others, generic) is a parasympathomimetic, directly stimulating the acetylcholine receptors on the iris sphincter and ciliary body striated muscles. The net force muscular contractions result in expansion of the trabecular meshwork, increasing aqueous outflow and reducing IOP. Several ophthalmic formulations are available (0.25-10% solutions, 4% gel, 1%-3% membrane solution), with 1% or 2% solution being the most commonly used. Typical IOP reduction is 20% from baseline, when taking the eyedrop form four times per day. The Pilopine HS gel can be used as a 2-3cm strip applied in the lower cul-de-sac at bedtime. The slow-release membrane insert (trade name Pilosert; available as 1% solution Pilo-20 and 2-3% solution Pilo-40) is placed in the lower eyelid cul-de-sac for 1 week, then replaced, resulting in similar IOP reduction to the eyedrop. Combination eyedrops with a beta-blocker (trade name Betoptic Pilo) or epinephrine (trade names P1E1, E-Pilo-1, P2E1, P3E1) are also available, but used rarely.


Pilocarpine is also used in the diagnosis of Adies tonic pupil (notable pupillary constriction after 15 minutes from instilling 0.125% drop in the eye diagnoses) and a mechanically-fixed pupil (0.5-1% is typically used to diagnose). In rare cases, pilocarpine may be used in treatment of accommodative esotropia.

Pupillary constriction also occurs with pilocarpine, leading to miosis. Difficulty seeing at night may occur as a result; particularly in patients with cataracts. Rarely, pupillary block may appear as a dangerous side-effect. Because the iris is pulled taught during pupillary constriction, an
increased iris/aqueous surface area results. This may increase the iris-aqueous breakdown during inflammatory conditions such as iritis, resulting in greater inflammation. Similarly, iris neovascularization (aka rubeosis iridis) may be a contraindication when using pilocarpine. As the ciliary body muscles are stimulated, accommodation resulting in pseudomyopia may occur with pilocarpine, and patients may experience visual fluctuation when using this medication. Pilocarpine also may cause browache/headaches, excess lacrimation, and an increased risk of retinal detachment at-risk patients (high myopes and/or patients with retinal tears, breaks, holes, or lattice degeneration). Systemically, pilocarpine can cause salivation, perspiration, systemic hypotension, bradycardia, bronchospasm, abdominal pain, diarrhea, and nausea/vomiting.

Because of numerous unwanted side-effects, pilocarpine should be avoided or used with caution in patients under age 40, patients with a history of uveitis, cataracts (especially posterior subcapsular), retinal holes/breaks/tears/detachments, high myopes, and iris neovascularization. The drug should also be avoided in patients with notable gastro-intestinal, breathing, and/or heart problems.

While pilocarpine has lost favor over other glaucoma medications, it is beneficial to have a bottle (usually of 1% or 2% solution) in an emergency kit for cases of acute angle closure attacks. Pilocarpine will assist in maintaining an open trabecular meshwork, temporarily eliminating or reducing the severity of attack. One to two drops in the affected eye in-office is usually enough, in combination with other glaucoma treatment. Care should be taken not to overdose, as secondary pupillary block may rarely occur.

Carbachol

Carbachol (trade names Carbastat, Carboptic, Isopto Carbachol, Miostat, others, generic), also known as carbamylcholine, is a ‘sister-drug’ to pilocarpine. It is available in several concentrations (0.75%, 1.5%, 2.25%, 3%) as an ophthalmic solution. Dosage is two drops in the eye up to three times daily. Mechanism of action, IOP reduction and side-effects are similar to pilocarpine.

Figure 6. Isopto Carbachol (carbachol 1.5% ophthalmic solution). (From https://healthy.kaiserpermanente.org/static/drugency/images/ALC02230.JPG )
Adrenergic Antagonists

Beta-blockers

When timolol arrived in 1978, a new era in glaucoma treatment had arrived. With an average 25% IOP reduction on only a twice-daily dose, timolol maleate soon became a first-line treatment for glaucoma. Available in 0.25% or 0.5% solutions, several trade names are available: Timoptic, Timoptic-XE (gel form), Timoptic Ocudose (preservative-free form), Betimol (hemihydrate form), Ista1ol, Blocadren, among others, as well as generic. Other beta-blockers soon became available – levobunolol 0.25%, 0.5% solutions (trade name Betagan, generic), metipranolol 0.3% solution (trade name Optipranolol, generic), carteolol 1% solution (trade name Ocupress, generic), and betaxolol (trade names Betoptic 0.5% solution, Betoptic S 0.25% suspension, Betaxon 0.5% L-isomer).

Figure 7. Various topical ophthalmic beta-blockers. From left to right: timolol 0.25% solution, timolol 0.5% gel-forming solution, Betagan (levobunolol) 0.5% solution, OptiPranolol (metipranolol) 0.3% solution, carteolol 1% solution, Betoptic S (betaxolol) 0.25% suspension. (From http://www.hexal-elements.de/sandoz_ca/2/images/products/8570_btl_timolol_0.25pc-240x240.png, http://www.rxzone.us/images/products/big/533083.jpg, http://pimg.tradeindia.com/01967109/b/1/Levobunolol-HCL-0-5-.jpg, https://healthy.kaiserpermanente.org/static/drugency/images/BSL02750.JPG, http://www.ocusoft.com/Images/Product_Images/744-3-21.jpg, https://d4fuqqd5l3dbz.cloudfront.net/products/tms/Package_3434.JPG)
Figure 8. Timoptic (timolol) Ocudose preservative-free ophthalmic solutions. (From http://www.fda.gov/ohrms/dockets/ac/04/slides/2004-4040S1_03_FDA-Lee_files/slide0060_image013.jpg)

As aqueous production on the non-pigmented ciliary epithelium of the ciliary body indirectly requires beta-receptor stimulation, beta-blockers serve to prevent this process, ultimately reducing aqueous production and IOP. All topical ophthalmic beta-blockers are non-selective - meaning they inhibit both beta-1 and beta-2 receptors – except for betaxolol (which is primarily beta-1 selective only). As the heart carries more beta-1 receptors, and the lung carries more beta-2 receptors, it is thought that betaxolol may be safer than other beta-blockers to use in patients who have a history of lung or breathing problems, if a beta-blocker was needed. Betaxolol is noted for stinging and burning on instillation (noted with the other beta-blockers), and the suspension Betoptic S helps reduced this effect. Corneal superficial punctuate keratopathy and blurred vision can also occur from all the beta blockers, partly thought to be due to the preservative (usually benzalkonium chloride) in the solution. Preservative-free vials of timolol (Ocudose 0.25% and 0.5%) are available for patients sensitive to the preservative.

Although a ‘gold standard’ in glaucoma treatment for decades, beta-blockers have several potential systemic side-effects. Because beta-1 receptors are plentiful on the heart, beta-blockers can slow the heart rate (bradycardia), resulting in lowered blood pressure. A patient taking systemic beta-blockers for hypertension may not obtain any further IOP benefit if a topical beta-blocker is concurrently used. Beta-2 receptors in the bronchiole tubules and lungs may also be affected, resulting in constricted airways and difficulty breathing. Beta-blockers have also been known to cause central nervous system depression, fatigue, and reduced libido. Lipid levels and glucose levels can be aggravated by the use of beta-blockers. Rarely, hallucinations and dizziness may occur from using beta-blockers. Carteolol is somewhat unique in that it may have ‘intrinsic sympathomimetic activity’ – meaning it does not cross the blood-brain barrier as readily as other beta-blockers, as well as not altering the lipid levels as much. Regardless, all the aforementioned side-effects, while uncommon when using topical ophthalmic formulations, should always be considered when prescribing beta-blockers.
Potential contraindications for prescribing beta-blockers would be in patients who have asthma or other breathing problems, chronic obstructive pulmonary disease (COPD), heart conditions (i.e. congestive heart failure), nocturnal hypotension, depression, reduced libido, lipid disorders, and diabetes. Care should also be taken in patients who do physically demanding activities (i.e. walking/running/sports) as well as in patients already taking a systemic beta-blocker. Blood pressure and pulse should be taken as a baseline before prescribing beta-blockers, and afterward. There is evidence of reduced ocular perfusion pressure (OPP) in patients with glaucoma; question as to whether beta-blockers can lower the OPP further is currently under research(18). As well, the patient should be questioned as to any difficulty breathing, performing physical activities, depression, reduced drive, and fatigue.

Studies have shown that IOP reduction may be just as effective with once-daily dosing, as well as with 0.25% rather than 0.5% (19-21). Since once-daily on a lower percentage may increase compliance as well as reduce potential side-effects and cost, this dosing (usually in the morning) may be a good first-time treatment approach. Due to the depressive-nature of the medication and risk of significant nocturnal hypotension and bradycardia, evening dosing is not recommended(22).

Along with being inexpensive in generic form, timolol is available (as 0.5% concentration) in combination drops with other glaucoma medications, which will be discussed later in this article.

**Carbonic anhydrase inhibitors (CAIs)**

The enzyme carbonic anhydrase primarily produces aqueous in the non-pigmented ciliary epithelium. Inhibition of this enzyme reduces aqueous production, lowering IOP. Two topical ophthalmic CAIs are currently available: dorzolamide 2% solution (trade name Trusopt, generic) and brinzolamide 1% suspension (trade name Azopt). Indicated dosage for either CAI is one drop three times daily, although some practitioners have found twice daily dosing to also be effective in lowering IOP. Typical IOP reduction is between 15-20% from baseline; as this IOP reduction is not as robust as other medications, topical CAIs are often used as an adjunct medication with another drug, rather than as monotherapy.
Topical CAI side-effects are usually less serious than those of beta-blockers, but should be considered. Potential ocular adverse reactions include superficial punctuate keratopathy, ocular allergy, sting/burn/discomfort, and decreased endothelial cell function (carbonic anhydrase is present on corneal endothelial cells, and helps to reduce corneal edema via actively transporting water from the cornea stroma to the anterior chamber). Systemically, the patient may report a bitter taste, appetite loss, and infrequently headaches, nausea, and/or fatigue. Due to the presence of carbonic anhydrase throughout the body, rare blood dyscrasias, urolithiasis, tinnitus, parasthesias, and electrolyte disturbances have been reported. These side-effects are more often with the systemic CAIs. Being a sulfa-based drug, CAIs should be used with relative caution in patients with sulfa allergies; however, the chemical structure of the CAI does not typically correspond with the sulfa-based drugs that patients may react to, and so may be safe to use in these patients(23).

Both dorzolamide and brinzolamide are also available in combination glaucoma medications, which will be discussed later in this article.

Oral CAIs include acetazolamide (trade name 125mg or 250mg Diamox, 500mg Diamox sequels, generic), methazolamide (trade names 50mg or 50mg; Glauctabs, MZM, Neptazane, generic), and dichlorphenamide (50mg; trade name Daranide). These medications serve as diuretics, and reduce swelling from conditions such as idiopathic intracranial hypertension and mountain sickness. In addition to highly-elevated IOP as an ocular disease emergency acute indication, they may also be used for chronic treatment of pseudotumor cerebri and advanced glaucoma that is not responding to other medicinal, laser, or incisional surgical treatment.
Systemic side-effects with oral CAIs are similar to the topical CAIs, and more likely to occur, especially with long-term use. Oral CAIs are primarily indicated for in-office emergency use for highly-elevated IOP (i.e. above 40mmHg). IOP reduction can be marked, reducing IOP up to 50% or more from baseline within a few hours. Methazolamide, while more expensive than acetazolamide, is a smaller tablet for equal efficacy, and has slightly less side-effect risk. At the time of this article, dichlorphenamide is currently not available (although it was not removed for safety or efficacy reasons). The enteric-coated Diamox sequels 500mg tablet is not recommended in lowering acute IOP, due to its slow-release formulation. The practitioner should have a container of 250mg acetazolamide tablets available in an emergency kit. Typical in-office dosage for highly-elevated IOP is two 250mg tablets by mouth with water.

Topical CAIs should be used with caution or contraindicated in patients with compromised corneas (i.e. penetrating keratoplasty, Fuchs’ dystrophy, etc.) or sulfa sensitivity. CAIs should be avoided in patients with blood dyscrasias (i.e. sickle cell, thallasemia). Long-term use of oral CAIs for glaucoma is not advisable unless all other options have been explored and the patient is at significant risk for losing sight. Communication and monitoring with the patient’s primary caregiver, specialists, and/or glaucoma surgeons is recommended in these situations.

**Prostaglandin Analogues**

While 1978 was a banner year for introducing beta-blockers as a treatment modality for glaucoma, 1996 was the next significant milestone in topical ophthalmic drugs for glaucoma. It was this year that the first prostaglandin analogue topical solution indicated for glaucoma was approved, by the name of latanoprost (0.005%; trade name Xalatan). This was followed in 2000 and 2001 by bimatoprost (0.01%, 0.03% solutions; trade name Lumigan) and travoprost (0.004% solutions; trade name Travatan), respectively. Travatan Z, having the same
concentration but using a milder proprietary preservative (SofZia) than benzalkonium chloride, was introduced in 2006. In 2010 tafluprost (0.0015% solution; trade names Taflotan, Zioptan) became the first preservative-free prostaglandin analogue for glaucoma, available in single-use vials. Each of these medications showed comparable IOP reduction of between 30-35% from baseline, with just one drop once daily dose (usually before bedtime). Generic latanoprost arrived in 2011, allowing greater affordability for patients. At the time of this article, generic versions of bimatoprost and travoprost are expected, and other prostaglandin analogues for glaucoma are currently in production. While the mechanism of action of prostaglandin analogues in reducing IOP is not fully understood, an increase in the permeability of uveoscleral tissue to aqueous outflow appears to be implicated(24).

Figure 11. Prostaglandin analogue ophthalmic solutions. From left to right: Xalatan (latanoprost) 0.005%, Travatan Z (travoprost) 0.004%, Lumigan (bimatoprost) 0.01%, Zioptan (tafluprost) 0.0015% preservative free solution. (From http://blog.ictforhealth.com/wp-content/uploads/2011/09/Xalatan.jpg, https://www.sightnation.com/files/imagecache/full/5-mL-Bottle-and-Carton.jpg, http://www.allergan.com/assets/images/US/products/lumigan.jpg, http://www.revoptom.com/CMSImagesContent/2012/7/093_ro0712_tr-1.gif)

Because of the significant IOP reduction with only one drop per day dose, along with virtually no systemic side effects, many practitioners prescribe prostaglandin analogues as a first-line treatment for glaucoma. Some unique ocular peculiarities do exist with these medications, however, and the patient should be informed of them. These include eyelash lengthening and thickening (which may be a preferable side-effect to some patients) as well as iris darkening (this effect is usually seen more often with hazel eyes). Conjunctival irritation and injection can be common, and patients may note morning redness to their eyes. Other ocular side-effects include darkening of the periorcular skin and thinning of the eyelid subcutaneous fat (termed prostaglandin-associated periorbitopathy, or PAP), which can be reversible upon discontinuation of the prostaglandin. Since prostaglandins are inflammatory mediators, a higher risk of uveitis and/or cystoid macula edema (this last condition particularly in patients with aphakia or pseudophakia) is possible, but rare. Patients with history of herpes simplex keratitis should be informed of the rare but potential risk of reactivation of herpetic keratitis with these drugs.

Rescula
A unique sub-category of prostaglandins is the docosanoid/prostamide drug named unoprostone isopropyl (DHA aka docosahexanoic acid 0.15%; trade name Rescula). A slightly different chemical structure, it is indicated for one drop twice daily, reducing IOP by about 15% from baseline. There is some evidence of a neuroprotective property in that the drug has been found to inhibit endothelin(25). Rescula is used more as an adjunct medication, and mechanism of action and side-effects should be considered similar to the other prostaglandin analogues.

![Figure 12. Rescula (uniprostone isopropyl) 0.15% ophthalmic solution. (From https://healthy.kaiserpermanente.org/static/drugency/images/SUC00150.JPG )](https://healthy.kaiserpermanente.org/static/drugency/images/SUC00150.JPG)

**Alpha-2 Agonists**

Derivatives of clonidine, the alpha-2 receptor agonist apraclonidine (trade name Iopidine) and its relatively newer sister drug brimonidine (trade name Alphagan) have been part of the glaucoma treatment regimen for several years. Both stimulate the alpha-2 adrenergic receptors, considered to be a ‘negative feedback’ receptor when alpha-1 receptors are maximally stimulated, resulting in lowered aqueous secretion. They also increase uveoscleral outflow by an as-yet determined mechanism(26). The term ‘dual-mechanism’ has been coined for these drugs as a result. Typical dosage is one drop three times per day in the affected eye(s), reducing IOP usually at least by 20 percent from baseline. Many clinicians prescribe twice daily dosing. Apraclonidine is available as a 0.5% solution, while brimonidine is available as a 0.1% (trade name only currently), 0.15%, and 0.2% (these latter two percentages available generically) solution. There are currently three combination eye drops that have brimonidine as one of the active ingredients; these combination drops will be discussed later in this article.
Fig. 13. Alpha-2 agonist ophthalmic solutions. Iopidine (apraclonidine) 0.5% (LEFT), Alphagan P 0.1% (MIDDLE), brimonidine 0.2% (RIGHT).

Apraclonidine was shown to exhibit tachyphylaxis – limited effect over time. The effectiveness of the drug begins to wane after 1 month of use, with minimal effectiveness after 3 months. As such, this drug is usually indicated for short-term adjuncive use and/or for IOP reduction after intraocular surgery (usually laser procedures such as laser trabeculoplasty or peripheral iridotomies). Brimonidine has a longer-acting IOP reduction duration, and is often used as an adjunct treatment when initial treatment with a different category glaucoma drug is not achieving the target pressure.

Side-effects from alpha-2 agonists are minimal but notable. Because of initial reports citing allergic response to the brimonidine, lower percentages of the drug were manufactured, as well as a proprietary non-BAK (benzalkonium chloride) preservative called Purite (trade name Alphagan P) for patients who are allergic to BAK. Stinging/burning/tearing/hyperemia/blanced conjunctiva/lid retraction was also reported as uncommon side-effects, and usually short-term only. One beneficial side-effect is the mild inhibition of pupillary dilation with these drugs; since the dilator muscle acts via alpha-1 receptors, the alpha-2 receptor stimulation by these drugs inhibits dilator action, allowing the opposite-acting iris sphincter muscle to gain more effect. This may help reduce night glare and/or post-refractive surgery or cataract surgery glare. There is also anecdotal evidence in animal and human studies that brimonidine may have potential ‘neuroprotective’ characteristics that help preserve the optic nerve and visual field (27).

Systemic side-effects of alpha-2 agonists are rare, but include headache, fatigue, dry mouth, and rhinitis. A significant risk is severe central nervous system depressive state in children.
when taking these drugs, resulting in bradycardia, apnea, somnolescence, and respiratory depression, among other side-effects. Because of these potentially serious adverse reactions, they are not recommended for infantile or pediatric glaucoma treatment (28).

**Combination Drugs**

There are an increasing number of combination glaucoma eye drops on the market over the last decade. All combination drops except one (trade name Simbrinza) have timolol 0.5% as one of the combined drugs.

The first combination glaucoma drop on the market was the CAI dorzolamide 2% + timolol 0.5% ophthalmic solution (trade name CoSopt) Indicated for one drop twice daily for an average 30 percent reduction in IOP from baseline, many practitioners prescribe this drop in the morning only, to similar effect. Side-effects of the drop are comparable with those of each active ingredient drug, and should be approached with similar caution. As of this article, this is the only combination glaucoma eyedrop that is also available in generic formulation, as well as single-use vial preservative-free formulation.


In Canada and Europe, a correlate drop to CoSopt is the CAI brinzolamide 10mg/mL+ timolol 5mg/mL ophthalmic suspension (trade name Azarga). Because this drug is in suspension form, there is slightly less sting propensity than CoSopt. However, side-effects similar to CoSopt should be considered when prescribing Azarga.
The alpha-2 agonist brimonidine 0.2% + timolol 0.5% ophthalmic solution (trade name Combigan) followed as the second combination glaucoma drop, also indicated as one drop twice daily. Initial 1-year trials of Combigan showed a reduction in IOP of 7.6mmHg average from baseline(29). Side-effects for each drug within Combigan should be considered when prescribing.

The prostaglandin analogue travoprost 0.004% + timolol 0.5% ophthalmic solution (trade name DuoTrav) and latanaprost 0.005% + timolol 0.5% (trade name Xalacom) have been
available outside of the United States for several years. Studies are ongoing to determine the effectiveness of these combination medications in treating glaucoma.

Figure 17. Combination prostaglandin+beta-blocker ophthalmic solutions. Left to right: DuoTrav (travaprost+timolol), Xalacom (latanoprost+timolol).

The prostaglandin bimatoprost 0.3mg/mL + timolol 5mg/mL ophthalmic solution (trade name Ganfort) and a unique triple-combination drug of dorzolamide 2% + brimonidine 0.2% + timolol 0.5% ophthalmic solution (trade name Krytantek) are available in Latin America. There are currently independent and comparative studies to evaluate the effectiveness of these medications.
Figure 18. Other combination glaucoma solutions. Left to right: Ganfort (bimatoprost+timolol), Krytantek (dorzolamide+brimonidine+ timolol).


At the time of this article, the only combination glaucoma medication that does not have timolol as an active ingredient is brinzolamide 1% + brimonidine 0.2% ophthalmic suspension (trade name Simbrinza). On an indicated one drop three times daily basis, IOP reduction was between 5 to 9mmHg from baseline in initial evaluative study(30). Side-effects were similar to the independent drop. Like Azarga, Simbrinza is a suspension, and must be shaken before each instillation.

Figure 19. Simbrinza (brinzolamide+brimonidine) ophthalmic suspension.  
(From http://www.globalpharmasectornews.com/wp-content/uploads/2013/04/Simbrinza.jpg)
Monitoring progression

Once diagnosis of glaucoma has been established, baseline tests will help set the bar that is needed to hopefully slow and/or prevent optic nerve damage and accompanying vision loss. Often more than one baseline functional visual field test is required, especially if visual field loss is seen and reliability is questionable. Repeat visual fields later on may also be necessary. Objective tests such as GDx (Carl Zeiss Meditec; Jena, Germany) and OCT RNFL analysis (several manufacturers) are very helpful in evaluating and following subtle structural changes, yet are just one ‘piece of the puzzle’ in monitoring glaucoma. Detailed stereoscopic optic nerve evaluation, particularly of the inferior and superior rim tissue, is still a mainstay test in managing glaucoma, and should be performed on each visit. Stereo optic nerve images are helpful in documenting these rim changes, as well as noting any Drance hemorrhages (splitter/flame hemorrhages, typically on the disc margin, most often inferior-temporal margin).

Pachymetry and determination of the CCT (central corneal thickness) has also been found to be important in establishing a baseline and helping determine a target pressure, as seen in the OHTS (Ocular Hypertensive Treatment Study) and other studies(31-33). Gonioscopy is particularly important in following narrow angle or angle closure risk patients, but also key in identifying and following pigment deposition, pseudoexfoliative deposits, synechiae, neovascularization, angle recession, dysgeneses, and other abnormalities.

Figure 20. Some examples of secondary glaucoma biomicroscopy findings. (From http://cdm15925.contentdm.oclc.org/cdm/landingpage/collection/p15925coll4 )
Fuchs heterochromic cyclitis, iris atrophy/transillumination, trabecular meshwork pigment deposition, posterior synechiae, iridodyalysis, pseudoexfoliation, ACIOL with pupillary block.

Although IOP is no longer considered part of the definition of glaucoma, the measurement of IOP, at the time of this article, remains the most direct way of determining if the medication is working. The hope is that lowered IOP is helping to reduce nerve fiber layer loss and subsequent visual field loss. As such, tonometry is critical at each visit. This can be performed using any of several types of tonometry (non-contact, tonopen, rebound, dynamic contour, Schiotz, digital, phosphene, other) although the Goldmann applanation tonometer has traditionally been considered the ‘classic’ measurement over the last several decades. Diurnal (and nocturnal) IOP curves may also complicate the measurements, as IOP is usually higher in the early morning, lowering during the course of the day and early evening until bedtime, where the IOP rises up again during sleep. Patients with glaucoma tend to have a greater diurnal curve than patients without glaucoma, making IOP monitoring challenging(34). Serial tonometry (taking multiple IOP measurements across an entire day) may be necessary to determine highest IOP readings. Follow-up visits may need to be scheduled at that peak baseline IOP time in order to determine treatment effectiveness. Showing the patient their IOP trend over time is often helpful in encouraging their compliance with medications.

Almost all of the major landmark glaucoma studies have shown that, even with treatment, glaucoma can still progress. Of those studies, currently only one (the Advanced Glaucoma intervention Study) showed halting of visual field progression if IOP was kept under 18mmHg, with an average of 12mmHg(35). While this may be challenging, and particularly confounding in patients with normotensive glaucoma where the IOP is already low, other studies have shown that each millimeter lowering of IOP may slow the progression of glaucoma over 5 years by at least 10 percent (Early Manifest Glaucoma Trial, Canadian Glaucoma Study, New York Glaucoma Progression Study)(36-38). This emphasizes the importance of continuing to lower eye pressure in patients with glaucoma.

Based on the above information, and comprehensive history and testing, target pressures should be established. Ideally this should be a range (i.e. ‘mid-teens’) rather than a single number (i.e. 17mmHg), as diurnal curves, treatment compliance, and other measurement elements usually factor into variations in IOP readings. Generally, the more severe the nerve damage and/or visual field loss, the lower the target pressure should be. A typical target pressure for early glaucoma may be a 20% reduction from baseline if mild nerve fiber loss is seen with no threshold visual field loss. In another patient, a 30% reduction may be indicated due to more nerve damage and/or field loss. Corneal thickness and other findings (i.e. biomicroscopy observations, risk factors) may also influence the reduction in IOP desired. A monocular trial with follow-up (usually no sooner than 2 weeks, to allow the drug to work) is helpful in determining treatment effectiveness, and then bilateral treatment can be started at the follow-up if treatment in both eyes is indicted. In highly-elevated (i.e. upper 20s to 30s) IOP in both eyes, starting the patient with treatment in both eyes is clinically-appropriate to reduce further damage. It is important to note that treatment initiation, follow-up, and target pressure
is highly individualized for each patient and practitioner, based on all findings. It is also important to know that the target IOP is a ‘moving target’, and may be raised or lowered at any time depending on the past and current exam findings.

With primary open angle glaucoma, once treatment has shown to reduce IOP to at or below the target pressure(s), IOP checks are ideally done quarterly to determine stability. Evaluation of the optic nerves with stereoscopic biomicroscopy should also be performed at each visit. If Drance hemorrhages are noted, more aggressive treatment (i.e. increasing or adding another drop) may be needed. Visual fields, if reliable and either clear of defects or mild in defects, should be monitored at least bi-annually. Nerve fiber analysis should have annual readings. If the glaucoma is a secondary form (i.e. pigmentary, pseudoexfoliation, etc.) more frequent testing may be indicated, and other tests performed more regularly (i.e. gonioscopy) to evaluate for any changes. Any treatment modifications (i.e. increasing or reducing drop dosage, adding or removing a drop, changing the dose timing) should be followed more closely than 3 months (i.e. between 2 weeks to a month) to ensure effectiveness.

Table 3 shows a typical management protocol for a patient with diagnosed open-angle glaucoma or a patient who is a glaucoma suspect. Note that this protocol can be altered, both in terms of follow-up times and types of tests performed, based on examination findings and clinical judgment.

Table 3. Management protocol for a patient with open-angle glaucoma or a glaucoma suspect. Modified from American Optometric Association Clinical Practice Guidelines: Care of the Patient with Open-Angle Glaucoma[39].

<table>
<thead>
<tr>
<th>Pre-treatment Visit</th>
<th>Post-treatment Visit (2 weeks to 1 month after Pre-Treatment Visit)</th>
<th>Follow-up Visit (3 months or more frequently if indicated)</th>
<th>Follow-up Visit (6 months or more frequently if indicated)</th>
<th>Referral/Consult</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Pertinent history</td>
<td>• History of drop compliance and note any reported side-effects</td>
<td>• History of drop compliance, any side-effects or symptoms</td>
<td>• As 3-month visit, but include threshold visual fields</td>
<td>• If adequate IOP reduction not met and/or advanced progression noted</td>
</tr>
<tr>
<td>• Rule-out systemic/ocular contraindications to treatment</td>
<td>• Visual acuities, pupils, slit lamp, tonometry, gonioscopy, threshold visual fields (repeated at later date for reliability if needed), dilated stereo optic disc evaluation</td>
<td>• Visual acuities, pupils, slit lamp examination, tonometry, stereo optic disc evaluation</td>
<td></td>
<td>• Referral/consult letter to glaucoma specialist with copy to patient’s primary care provider</td>
</tr>
<tr>
<td>• Visual acuities, pupils, slit lamp, tonometry, gonioscopy, threshold visual fields</td>
<td>• Blood pressure and pulse (especially if beta-blocker used in treatment)</td>
<td>• Measure blood pressure and pulse (if Beta-blocker used in treatment)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Ancillary testing (e.g. pachymetry, nerve fiber analysis) if needed</td>
<td>• Repeat threshold visual field if needed</td>
<td>• Perform ancillary tests if needed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Baseline blood pressure and pulse</td>
<td>• Ancillary testing if needed</td>
<td>• Continue treatment regimen or modify if needed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Establish target IOP (or IOP range)</td>
<td>• Begin treatment binocularly if target IOP/IOP range met and other findings stable or improved</td>
<td>• Consult to patient’s primary care provider if treatment modifications made</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Initiate monocular therapeutic drop trial (unless significant IOP elevation in both eyes and/or advanced cupping/field loss – then initiate binocular trial immediately)</td>
<td>• Increase dosage, change meds, or add meds if target not met RTC x 2wks</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Current accepted first-line medicinal treatment of glaucoma is prostaglandin analogues, usually instilled in the affected eye(s) at bedtime. Should target IOP not be reached and/or structural damage and/or visual field loss is noted, a beta-blocker is often added, usually in the morning. While 0.25% beta-blocker concentration has been shown to be effective, patients of black race may benefit more from 0.5% concentration, due to binding of some of the medication by iris melanin. Should target IOP still not be reached, the beta-blocker dose may be increased to twice daily in addition to the evening prostaglandin. Evening beta-blocker use is not recommended due to risk of hypotensive events and nocturnal breathing problems. Patients should have their blood pressure and pulse evaluated regularly when taking glaucoma medications – in particular, beta-blockers. Patients who are taking beta-blockers should also be questioned if they are experiencing any breathing problems, fatigue, depression, or other symptoms, and discontinuance should be done if there is a strong correlation of these symptoms with the timing of the medication.

If the patient does not respond to the above glaucoma drugs, or they have reactions/contraindications, carbonic anhydrase inhibitors or alpha-2 agonists can be used. These may be used in place of the beta-blocker, as adjunct treatment with the prostaglandin. The practitioner may consider prescribing them twice daily (even though three times daily is the dosage on the label) to increase compliance and reduce cost. Like the beta-blocker, alpha-2 agonists should be avoided in the evening; primarily this is due to an effectiveness rather than safety reason. Carbonic anhydrase inhibitors can be used in the evening if desired; however it should be instilled at a time well ahead (i.e. at least an hour) of prostaglandin instillation. A few patients prefer or do better with morning prostaglandin instillation, so these medications may on rare occasion be reversed in terms of dosage timing.

Should single-drug treatments not be achieving the set target goals, combination glaucoma drops may be the next step. As CoSopt is currently the only one also available in generic form, this may be an economical approach, and may be used once in the morning, in place of the single beta-blocker. Azarga, Ganfort, and Krytantek are other options for practitioners outside the United States. It may then be increased to twice daily (again, avoiding evening use) if necessary. Combigan (if no beta-blocker contraindication) and Simbrinza (if there is contraindication to beta-blocker) may be used similarly to CoSopt. DuoTrav and Xalacom may be preferred for morning use for safety, due to the beta-blocker within those drugs.

Pilocarpine would be a much later choice as an additive drop, if all other combinations fail. Pilocarpine’s key primary indication, however, would be in the case of acute angle closure glaucoma or intermittent angle closure/narrow angle glaucoma cases. It may also be helpful to prescribe for patients whose angles still may close even after laser and/or surgical treatment, in order to prevent further attacks. Certain secondary glaucomas that have obstruction of the trabecular meshwork (i.e. pigmentary, pseudoexfoliative) may benefit from pilocarpine’s effect of opening the drainage angle. This drop usually remains a later treatment option, however. Propine and Rescula are far less-prescribed compared to other glaucoma medications, and may be considered as niche drugs for very select few patients who require rare additional or alternative treatments once prior options have been explored.
Figure 21 shows a basic protocol flowchart for pharmacological treatment of glaucoma.

Figure 21. Basic protocol flowchart for current pharmacological treatment of glaucoma. PGA = prostaglandin analogue, HS = nighttime, B-blocker = beta-blocker, Combo = combination medication CAI = carbonic anhydrase inhibitor, AFT = afternoon, EVE = evening.

**Unconventional Treatments**

**Marijuana**

The active ingredient of the marijuana plant, also known as the cannabis plant, is tetrahydrocannabinol (THC). The mechanism by which THC reduces IOP is poorly understood; it may involve stimulation of CB1 (cannabinoid 1) receptors in the uveal tissues, reducing aqueous production and increasing uveo-scleral outflow. Reduction in calcium influx in the ciliary body (reducing aqueous production) as well as prostaglandin-mediated pathways have also been postulated. IOP reduction is between 25-30% from baseline when smoking marijuana; however, the reduction is only for 3-4 hours. To maintain round-the-clock IOP reduction, marijuana would have to be smoked 6 to 8 times per day. Along with numerous systemic side-effects including psychotropic effects, fatigue/sleepiness, hunger, and reduced blood pressure with tachycardia, THC can cause variable pupil size changes, conjunctival hyperemia, and reduced tear production. Oral (sublingual gel caps) and topical ophthalmic (i.e. Canasol, MediGrace Industries, Jamaica) formulations have been used used over the last several years, and are still being investigated. Synthetic variants of THC are also currently under research. Although several states in the United States allow, or are in the process of allowing, medical use of marijuana for several conditions, currently marijuana is considered a Class I (highest addiction/dependency potential) DEA category controlled substance (40).

**Alcohol**
Studies have shown inconsistent and minimal effect of IOP change when drinking alcoholic beverages. IOP may increase temporarily with initial alcohol consumption due to volume load, then reduce slightly over several hours through osmotic and diuretic effects. While anecdotal evidence of neuroprotective effects with red wine has been noted, the effect on the optic nerve is not determined. Potential cardiovascular benefits with a moderate (i.e. one glass per evening) red wine may be offset by higher risk of liver disease and other systemic side-effects such as sedation, depression, poor coordination/judgment, and other psychotropic effects including addiction. Certain strong alcohol content drinks such as poorly-distilled vodka and homemade ‘moonshine’ may have dangerous toxic effects on the optic nerve, leading to toxic optic neuropathy. Active use of alcohol consumption for treating glaucoma should be discouraged (41-43).

Other Alternative Treatments

Some patients may ask or self-treat with supplements, often obtained over-the-counter. Examples of these supplements include the Ginko biloba plant and bilberry. These substances have been found to potentially increase vascular perfusion and help improve night vision, respectively (44, 45). Other substances such as omega-3 supplements (fish oil, flaxseed oil), have some evidence of potential benefits with open-angle glaucoma (46). Several formulations claiming ‘glaucoma treatment’ are available online and in stores; patients should be cautioned as to the lack of scientific studies with many of these formulations at this time. Concurrent use of supplements with traditional medicinal treatment may be permissible if there are no serious side-effects from the supplement treatment. The various supplements, indications/contraindications, and mechanisms of action are outside of the scope of this article.

Lifestyle changes may be adopted by patients; examples include exercise/walking (which may provide temporary IOP reduction, unless vasalva/straining is involved, which may briefly increase IOP during times of strain), meditation/biofeedback/acupuncture (questionable benefit of these seen in current literature), reduction of toxins (i.e. smoke, heavy metals such as lead) and diet. Currently the complexity of organic versus processed foods, genetically-modified organic (GMO) food, food types and amounts, make it difficult to provide specific recommendations as to what is best for treating glaucoma. A well-balanced diet in moderation of intake is recommended for overall general health (47, 48).

Surgical referral criteria

Several indications for surgical (including laser, incisional, cryotherapy and/or implant) treatment of glaucoma are indicated in Table 3. In general, the younger the patient with glaucoma, the more likely they are to have surgical treatment in order to maintain vision throughout their life. Other factors may be the severity of glaucoma findings, as well as poor IOP control with maximal medicinal therapy, or difficulty instilling medications.

Table 3. Indications for surgical referral for glaucoma

<p>| Young patients |</p>
<table>
<thead>
<tr>
<th>Advanced glaucoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute angle closure glaucoma</td>
</tr>
<tr>
<td>Congenital/infantile glaucoma</td>
</tr>
<tr>
<td>Complex/post-surgical glaucoma</td>
</tr>
<tr>
<td>Progression even with maximal medicinal therapy</td>
</tr>
<tr>
<td>Minimal to no IOP reduction with maximal medicinal therapy</td>
</tr>
<tr>
<td>Difficult compliance/instillation/cost factors with medicinal therapy</td>
</tr>
</tbody>
</table>

Certain forms of glaucoma, such as acute angle closure, malignant glaucoma, or infantile/congenital glaucoma, require urgent surgical treatment in order to preserve vision. Surgical treatment in these cases may involve peripheral iridotomies/iridectomies, gonioplasty, and/or cataract extraction (to deepen the anterior chamber), among other procedures.

Often medicinal treatment continues after surgical treatment is performed. While surgery can reduce IOP, the amount may not be significant enough to halt progression. The practitioner should monitor surgical sequelae such as filtration blebs and implants for patency and lack of inflammation/infection, as well as patency of peripheral iridotomies/iridectomies over time. Any complications or progression of glaucoma should be communicated to the surgeon for potential re-treatment or modification of treatment, both surgically and medicinally.

**Treating highly elevated IOP**

When a patient presents with confirmed highly-elevated IOP (for example, 40mmHg or higher) prompt treatment in-office is recommended. Regardless of the type of glaucoma that is causing the elevated IOP, medicinal treatment is relatively consistent. The patient first should be asked if they have any allergies or side-effects to any medicines, including anesthetics. Examination of the anterior segment of the eye, including gonioscopy and/or anterior segment imaging (by OCT or ultrasound biomicroscopy) should be performed. Once no pertinent contraindications are determined, the patient can be given two 250mg tablets of acetazolamide to take by mouth with water in the chair. Being sulfa-drugs, carbonic anhydrase inhibitors (CAIs) such as acetazolamide (and its sister drug methazolamide) have a relative contraindication in patients with sulfa allergies; however, the chemical structure of carbonic anhydrase inhibitors is different than the sulfa-based substances (i.e. sulfa-based antibiotics) that are more closely linked with allergic reactions. Interestingly, sulfa-based drugs such as CAIs have a small risk of causing angle closure glaucoma due to ciliary body edema and anterior rotation of the iris-lens diaphragm. In practice, however, the benefit of reducing IOP significantly with an oral CAI outweighs the risk, particularly if the patient with highly elevated IOP has a wide open drainage angle, or already presents with acute angle closure.

If an oral CAI is contraindicated, alternative oral medication includes hyperosmotic solutions such as isosorbide 1.5g/kg body weight (trade name: Ismotic) or glycerin 50% (trade name: Osmoglyn). These solutions are usually poured into a cup with cracked ice to reduce nausea.
and given in-office. Glycerin is contraindicated in patients with diabetes due to its high sugar content. Oral isosorbide is currently not available at the time of this article.

![Figure 22. Oral hyperosmotic solutions. Ismotic (isosorbide 45%) (LEFT), Osmogly (glycerin 50%).](http://www.clinicalpharmacology.com/apps/images/photo_us_h/034/osmo050t.jpg)

Rarely prochlorperazine suppository (Compazine) may be indicated if nauseousness during an angle closure attack prevents digestion of oral medications.

Once oral treatment is initiated in the chair, sequential in-office treatment with topical glaucoma medications is initiated. Medications used should have aqueous suppressant mechanisms – the beta-blockers, carbonic anhydrase inhibitors, and alpha-2 agonists are examples – as they are faster acting. One drop of each of the aforementioned categories of medications, spaced 5 minutes apart, can be placed in the affected eye. Punctal occlusion for 1 minute after each drop instillation is recommended to 1) retain the medication on the eye facilitating greater ocular absorption, and 2) to reduce systemic absorption, lowering the risk of side-effects. This is especially important with the beta-blocker, as there are more potential systemic side-effects with this medication. The safest beta-blocker is Betoptic S (betaxolol 0.25% suspension) due to its beta-1 receptor specificity. If there are significant contraindications to beta-blocker use, this medication category can be excluded from the treatment regimen.
Following initial sequential instillation of topical aqueous suppressants, gonioscopy can be repeated. This time, however, the gonioscopy lens may be used therapeutically by applying further compression on the cornea (inducing corneal wrinkling). Also termed dynamic gonioscopy, the purpose for this greater compression is two-fold: firstly, it allows repeated view of the angle to establish appearance of the most posterior structures, and determines anatomical variations such as pigment/ pseudoexfoliative deposition, peripheral anterior synechiae/neovascularization, angle dysgenesis, and/or a plateau iris. Secondly, the applied pressure physically facilitates aqueous outflow through the trabecular meshwork(49). Ideally a small surface diameter gonioscopy lens (such as a Sussman or Posner lens) is preferred for corneal compressions. Pressure should be applied for 30 seconds on, then release for 30 seconds, then repeat the pressure on-off again a few more times. Once repeat gonioscopy is performed, IOP can be re-measured, and the sequential aqueous suppressant drop instillation described above can be repeated.


The entire process of drop instillation-gonioscopy-IOP measurement can be repeated up to 3 more times in-office, until IOP is at a lower level (usually mid-20s or lower) satisfactory for discharging the patient. The patient should be provided with glaucoma drops to take at home (typically a beta-blocker, carbonic anhydrase, and/or alpha-2 agonist) and is seen the next day for follow-up. Ideally a threshold visual field, optic nerve imaging, and/or retinal nerve fiber analysis should be performed at this follow-up visit as ‘baseline’ tests to determine any future progression. Depending on exam findings, the patient should be referred to a glaucoma surgeon for further evaluation and potential treatment. If the patient has had an acute angle closure attack, they should have peripheral iridotomies or iridectomies (usually of both the
affected eye and the fellow eye as prophylaxis) ideally within 24 hours from initial attack presentation. On rare occasion a patient who as had maximal surgical treatment for angle closure, and yet still experiences angle closure attacks, may have a bottle of pilocarpine 1% or 2% prescribed as a ‘carry-with’ drop in case an attack occurs. These patients may need to know the symptoms of an imminent angle attack; this author has the patient who presents with highly elevated IOP perform self-digital tonometry with their fingers in the chair, to feel the difference in the rigidity of the globe between their affected eye and normal eye.

If the patient presents with angle closure attack, one drop of pilocarpine (either 1% or 2%) may be added to the in-office treatment regimen. Unlike the other sequential drops, pilocarpine should be instilled only once to facilitate opening of the drainage angle. Further drops of pilocarpine may increase risk of pupillary block, and so one-time use is recommended. There is debate among clinicians as to whether IOP should be dropped below 40mmHg before instilling pilocarpine, as the higher IOP can cause temporary ischemia and brief inactivation of the iris sphincter muscle, restricting pilocarpine’s effect. Pilocarpine should also be avoided in cases of uveitic/inflammatory glaucoma, as it may increase the iris-aqueous interface, potentiating the inflammation.

Prostaglandin analogues should also be avoided for in-office use of highly elevated IOP, as its effect is more slow-acting than aqueous suppressants. Like pilocarpine, prostaglandins should be avoided in cases of uveitic/inflammatory glaucoma due to the inherent ‘inflammatory mediator’ nature of this medication. There is also some potential that prostaglandin analogues may be counter-productive when used concurrently with pilocarpine.

On occasion other adjunct topical treatments may be indicated. Should corneal edema (particularly epithelial edema) occur from acute highly-elevated IOP, topical hyperosmotics such as glycerin 50% (Ophthalgan), sodium chloride 2% to 5% (AK-NaCl, Adsorbonac, Muro-128) or glucose 40% (Glucose 40) may be applied to help clear edema and facilitate view. In cases of inflammatory glaucoma, topical steroids may actually help facilitate lowering IOP by reducing trabecular meshwork and ciliary body inflammation. Steroids should be used concurrently with topical glaucoma medications in these situations.

Figure 24 shows a flow-chart protocol for treating highly-elevated IOP.

*Consider betaxolol 0.25% (Betoptic S) or topical carbonic anhydrase inhibitor - i.e. dorzolamide (Trusopt) or brinzolamide (Azopt) as alternative if contraindications to non-selective beta-blocker

**Consider methazolamide 50mg po x 2 (q 12h) if patient has kidney condition.

^Consider glycerin po 1.5g/kg body wt. alternative if isosorbide not available and patient does not have diabetes or renal problems.
Conclusion

If there are three axioms for the clinical management of glaucoma, they are:

1) Glaucoma is often challenging to both diagnose and explain to patients
2) Glaucoma findings can vary and show inconsistencies over time
3) Glaucoma medicinal treatment may be difficult due to poor compliance

While future treatments such as neuroprotection, stem cell implantation, and gene therapy hold promise for novel ways to treat glaucoma, reduction of IOP remains the mainstay clinical treatment as of the time of this article. In the future, routine clinical application of 24-hour IOP monitoring may also aid in both diagnosis and management of glaucoma. Once determination of glaucoma (or high risk of glaucoma) is made, the challenge of maintaining satisfactory IOP reduction becomes paramount. This is complicated by many factors, including drug cost, convenience of instillation, side-effects, and lifestyle changes. Several studies have shown that compliance with taking glaucoma drops reduces significantly with increased dosage and/or types of medication. The goal is to slow or halt progression of the disease over the course of a patient’s lifetime with the minimum amount of treatment and the least side-effects. With diligent evaluation, thorough patient education, and appropriate treatment and management, practitioners will continue to strive towards this goal.

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