Continuing Education

Glaucoma: Overview & Treatment Options

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Learning Objectives:

After this article, the readers should be able to:

- Describe the prevalence of glaucoma and list risk factors.
- Discuss characteristics of open-angle glaucoma.
- Discuss characteristics of closed-angle glaucoma.
- Outline treatment options for glaucoma.

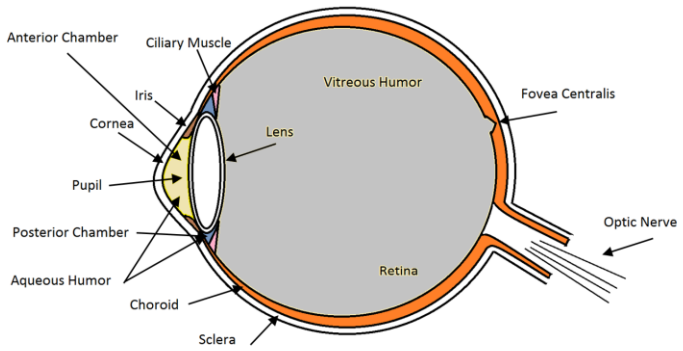
Introduction

A group of ocular disorders, known as the glaucomas, cause damage to the optic nerve and leads to visual impairment.[1] These disorders are the second leading cause of blindness in the United States following cataracts, and more than half of those with glaucoma are "blind" to the fact that they have it.[1,2,3] Glaucoma has been termed the "sneak thief of sight" because of its ability to cause damage without exhibiting signs and symptoms until there is significant progression.[1,2] For this reason, the true impact of glaucoma on the population is uncertain, but researchers offer insight into the prevalent of this group of ocular disorders by estimating glaucoma to affect 60 million people worldwide.[1,2,4] About three million of those reside in the U.S. with African Americans composing a much larger portion of this population than Caucasians.[1,2,5] While glaucoma can affect anyone at any age, those who are over 60 years old, have diabetes, have other family members with glaucoma, and those with extreme nearsightedness are at a greater risk.[2] Currently, there is no cure for glaucoma, but a growing understanding of the pathophysiology behind it hopefully means a cure is only a blink away.

Epidemiology

Glaucoma affects more than 60 million people worldwide, and is the leading cause of irreversible blindness in the world.[6] Patients with glaucoma often remain asymptomatic, so many of them are unaware that they are even affected by it. It is estimated that less than 50% of people with glaucoma are aware of it.[7] Glaucoma is differentiated between two different forms: open-angle and closed-angle.

Anatomy of the Eye[6,8,19]



The outer coat of the eye consists of the cornea, sclera and conjunctiva. The sclera is a protective coating for the eye, and the conjunctiva helps cover the anterior portion of the eye and the eyelids.[8] The cornea is a transparent structure that allows light rays to pass through to the retina, and also functions as the best place for ophthalmic medications to enter the eye. The iris, choroid and ciliary body compose the uveal tract, which helps control the amount of light that enters the eye. The ciliary body helps hold the lens in place, and also plays a role in the secretion of aqueous humor. Aqueous humor is a watery fluid that plays an important role in providing nourishment to the cornea and lens. It is stored in the anterior chamber of the eye, which composes the area between the cornea and the iris, as well as the posterior chamber, which is between the iris and the lens. The sympathetic and parasympathetic nervous system both play a role in regulating function of the eye. The

ciliary muscles that support the pupil contract (miosis) and are innervated by parasympathetic nerve fibers. Sympathetic fibers innervate the dilator pupillae muscle, blood vessels of the ciliary body and the extraocular muscles, which cause pupil dilation (mydriasis). Due to this relationship, cholinergic medications cause miosis, and anticholinergic medications cause mydriasis as well as cycloplegia, which is a decreased ability to accommodate light and may lead to blurry vision. Likewise, sympathomimetics cause mydriasis, but do not affect light accommodation.[8]

Diagnosis

Glaucoma in general is characterized by damage to the optic nerve, which may result in vision loss. There is an increase in intraocular pressure (IOP), caused from a buildup of aqueous humor due to lack of proper drainage. Over time, this increased pressure puts pressure on the optic nerve, and can cause serious damage.[2]

Glaucoma may progress without causing any symptoms, which makes early detection important. Neural damage and vision loss may occur as the disease advances, which may result in inability to perform daily tasks. Patients will typically begin to lose their peripheral vision first, followed by central vision as the disease progresses over time. There is no gold standard test for diagnosing glaucoma, which makes diagnosis difficult. The appearance of the optic nerve head and nerve fiber layer changes as the disease progresses and more damage is done, which can be seen through ophthalmoscopic examination. However, by the time it is detectable, up to 30-50% of retinal ganglion cells may be lost. Recently developed laser scanning imaging techniques including confocal scanning laser ophthalmoscopy, scanning laser polarimetry and optical coherence tomography may provide more objective data for the diagnosis of glaucoma.

Open-Angle Glaucoma

Primary open-angle glaucoma (POAG) affects up to 3 million people in the US and about 60.5 million people worldwide. It is responsible for over 80% of the cases of glaucoma in the United States. The occurrence of POAG increases with age, and has a higher incidence in African-Americans and those of Mexican ancestry than Caucasians. The defining characteristics are an open iridocorneal angle and cupping of the optic-nerve head, as well as a corresponding loss in vision.

For patients with POAG, aqueous humor outflow from the anterior chamber is impaired due to degeneration of the trabecular meshwork. These factors cause damage to the retinal ganglion cells, which may result in axonal degeneration and permanent loss of vision. Some patients may experience vision loss caused by high intraocular pressure.[6]

Intraocular pressure is affected by the regulation of aqueous humor. Aqueous humor is created in the ciliary body, and its drainage is controlled through two different pathways: the trabecular meshwork and uveoscleral outflow, which help determine the IOP. Filtration depends on pressure gradients, including blood pressure and IOP, which can play a role in aqueous humor formation. For patients with open-angle glaucoma, there is an increased resistance to aqueous outflow through the trabecular meshwork to the Schlemm's canal. Increased IOP may cause damage to posterior portions of the eye, including the lamina cribrosa, which is a small hole that allows passage of the optic nerve fibers.[9] The lamina cribosa is a weak point in the wall of the eye, and increased IOP may cause deformation of it, which causes nerve damage. Ocular hypertension can cause

blockade of axonal transport, as well as cause vision problems. During periods of increased IOP and stress on the eye, there may also be mitochondrial dysfunction in the retinal ganglion cells and astrocytes.[10] Progressive deterioration of vision typically occurs, which begins in the midperiphery and may progress until there is severe loss in field of vision.

A typical IOP for an average patient is between 10-21 mmHg, but it is constantly changing due to blood pressure, posture, aqueous humor formation and pulse changes. IOP is typically measured by different types of tonometry, which include indentation tonometry, applanation tonometry or non-contact using an air pulse. The Pascal tonometer is a new method, as well as contact lens based devices that can remotely monitor IOP changes over 24 hours.[11] Only about 5-8% of the population experience IOP greater than 21 mmHg,[1] which typically occurs in older people (greater than age 70). For patients with closed-angle glaucoma, they may experience IOPs of greater than 40.[1]

While there is a strong correlation between IOP and glaucoma, many patients with elevated IOP never develop glaucoma, and conversely, many people with normal IOP can develop glaucoma. In any event, reducing intraocular pressure has been shown to slow the onset and progression of glaucoma, and since it is the only modifiable risk factor, it is the primary focus of glaucoma treatments.[6]

Closed-Angle Glaucoma

Closed-angle glaucoma (CAG) is much less common than POAG, but results in severe vision loss at a much higher rate.[12] It is a medical emergency, and usually occurs as a sudden blurring or loss of vision corresponding to a rapid increase in IOP. CAG is often associated with painful red eye, blurred vision, headache, and nausea and vomiting. The pupil is typically dilated and poorly reactive to light, and the cornea is hazy due to the elevated IOP. CAG can be differentiated from open-angle through examination of the angle at the site of aqueous outflow in the eye. In CAG the site is obstructed by the position of the iris, and which results in a closed angle of at least 270 degrees. This site can be examined through the use of gonioscopy, in which a lens is placed on the eye and the examiner is able to check the angle configuration and assess for angle closure.[6]

People that are at higher risk for CAG includes those of Asian ethnicity, female sex, and older age. These patients are typically characterized by having a crowded anterior segment, as well as a shallow central anterior chamber depth, and short axial length of the eye. First-degree relatives of patients are at greater risk than the general population.[1,6,8]

Therapeutic Goals

Treatment of POAG focuses on lowering IOP and preventing or minimizing visual impairment due to optic nerve damage. For CAG, the primary goal is to prevent or reverse angle closure.[13,14] Lowering IOP is important for both types of glaucoma, and in general, lowering a patient's IOP 20-30% is considered an appropriate reduction.[1,8] By decreasing IOP, risk of new or progressive damage to the optic nerve is minimized. Along with lowering IOP, another goal is finding a drug regimen that balances maximum therapeutic effect while minimizing side effects. Enhancing a patient's involvement in the treatment and management of their disease can often improve outcomes too and should be an important focus in their care.[1,13,14]

Instillation Technique

Placing anything in the eye is difficult for many patients and proper technique can help

improve efficacy and decrease frustration and side effects. All patients should wash their hands before administering any eye drops. Once the patient is comfortable and is ready to instill the medication, they should tilt their head back slightly and gently pull down on their lower lid to form a pocket. Patients should look up before placing any drops in the eye because this keeps the drops from hitting the sensitive part of the eye. This should all be done without touching the tip of the bottle to the eye or with the fingers. Some eye drops for glaucoma can cause discomfort, but it is important for patients to refrain from excessive blinking after administration to ensure the medication stays in the eye. When multiple eye drop medications need to be administered for glaucoma, separating their placement by at least 5-10 minutes ensures the drug has had adequate time to reach its site of action.[1,8]

Many of the medications used to treat glaucoma can have systemic side effects especially after prolonged use. Nasolacrimal occlusion (NLO) is a method that can help reduce the possibility of and degree of systemic side effects. Closing the eyes and placing the pads of the fingers on the tear ducts with a slight, firm pressure after the drops are instilled accomplish this. This keeps the medication from draining into the nasolacrimal duct, which keeps the medicine in the eye, maximizing benefit and minimizing side effects.[1,8]

Treatment

There are several drug classes that are used to lower IOP in glaucoma patients: prostaglandin analogs, nonselective beta blockers, alpha agonists, topical carbonic anhydrase inhibitors (CAI), and a number of combination products. There is not a designated first line agent, but nonselective beta blockers or prostaglandin analogs are the classes most often tried first due to established efficacy and general tolerability. Alpha agonists and topical CAIs are appropriate options when nonselective beta blockers or prostaglandin analogs are contraindicated, ineffective, or intolerable. In addition to other drug therapies, there are more invasive surgical options for patients, which can stop or prevent progression of their disease.[1,8]

Prostaglandin Analogs

The prostaglandin analogs are commonly prescribed for initial treatment of glaucoma and are potent topical agents for lowering IOP. These agents help patients reach and maintain a stable IOP throughout the day.[8] They work by increasing aqueous uveoscleral outflow as well as trabecular outflow.[1] This mechanism allows them to lower a patient's baseline IOP by 25-33% and makes them a good choice for monotherapy or adjunct therapy.[13] These agents are able to achieve adequate IOP lowering with less frequent dosing than with agents in other classes, which improves adherence.[1,8]

Adverse Effects

Prostaglandin analogs are widely well tolerated. Local irritation is the most common side effect; however, the preservative free product has a decreased likelihood of causing discomfort with use. Periocular hyperpigmentation and increased eyelash growth can also occur which are benign but irreversible. Less common and more serious side effects of prostaglandin analogs include uveitis, macular edema and herpetic keratitis, and these warrant discontinuation of the drug.[1,13,16]

Table 1: Topical Prostaglandin Agents for Glaucoma

Generic (Brand)	Properties	Dose Form	Strength	Usual Dosage	Comments
Latanaprost (Xalatan)	Prostanoid agonist	solution	0.005%	one drop QHS	BID dosing may be less effective and cause iris and eyelid pigmentation; store unopened bottle in refrigerator; opened at room temperature up to 6 weeks
Travaprost (Travatan Z)	Prostanoid agonist	solution	0.004%	one drop QHS	BID dosing may be less effective and cause iris and eyelid pigmentation; may be more effective than latanoprost and timolol in African Americans
Bimatoprost (Lumigan)	Prostamide agonist	solution	0.01%, 0.03%	one drop QHS	BID dosing may be less effective and cause iris and eyelid pigmentation
Tafluprost (Zioptan)	Prostanoid agonist	preservative free solution	0.0015%	one drop QHS	Less irritation due to lack of preservatives

QHS: every evening at bedtime. BID: Twice daily.

Topical Beta-adrenergic Blockers

Beta blocking agents reduce aqueous humor production from the ciliary body by blocking beta adrenergic receptors in the ciliary epithelium in order to lower IOP. These agents are used as monotherapy initially and most are administered twice a day. These medications have been shown to decrease IOP up to 25%, depending on strength and dosing frequency.[8,13] While beta blocking agents are very effective at lowering IOP, it is important to note that decreasing IOP may not correlate with vision preservation. Tachyphylaxis occurs with these agents in 20-25% of patients who have been on long-term therapy, and switching to another agent may be necessary.[1,8,15]

Adverse Effects

The most common side effect of all of these products is eye irritation, such as burning and stinging. Eye irritation can be caused by the preservatives found in these products and can sometimes be minimized by switching to another agent. Other local effects beta blockers can cause are corneal anesthesia, blurred vision, dry eyes, and blepharitis (eyelid inflammation). Some patients may experience conjunctivitis, uveitis, or keratitis, but these are rare. The most important concern with these agents is the systemic side effects they can potentially cause. Although these are topical products, they are still able to cause systemic side effects including decreased pulse and blood pressure, bronchospasm, negative inotropic effects, and central nervous system (CNS) effects. The local and CNS effects are seen most often, but precautions should be taken with all patients, especially those with preexisting cardiovascular or pulmonary diseases. Due to these side effects, this class of drugs may not be appropriate in patients with cardiovascular or pulmonary disorders.[1,8,13]

Table 2: Topical Beta-adrenergic Blockers for Glaucoma

Generic (Brand)	Properties	Dose Form	Strength	Usual Dosage	Comments
Betaxolol (Betopic-S)	Relative beta$_1$-selective	solution suspension	0.5% 0.25%	One drop BID One drop BID	Beta blocker of choice in patients with HF or pulmonary disease; eye irritation occurs less often with suspension
Carteolol (Ocupress)	nonselective, intrinsic sympathomimetic	solution	1%	One drop BID	Use with caution in patients with HF or pulmonary disease
Levobunolol (Betagan)	non-selective	solution	0.25%, 0.5%	One drop BID	Use with caution in patients with HF or pulmonary disease
Metipranolol (OptiPranolol)	nonselective	solution	0.3%	One drop BID	Use with caution in patients with HF or pulmonary disease; higher instance of stinging and burning; corneal anesthesia
Timolol (Timoptic) Timolol gel forming solution (Timoptic XE)	nonselective	solution gelling solution	0.25%, 0.5% 0.25%, 0.5%	One drop daily or BID One drop daily (gel increases ocular bioavailability)	Use with caution in patients with HF or pulmonary disease; exceeding BID dosing does not further reduce IOP; tachyphylaxis can occur; corneal anesthesia

BID: twice a day, HF: heart failure

Alpha Agonists

Brimonidine and apraclonidine are the two alpha$_2$ agonists used for glaucoma, and they reduce aqueous humor production. Brimonidine specifically, is also able to increase uveoscleral outflow to lower IOP, and it is recommended over apraclonidine.[1] Apraclonidine is used most often postsurgically or as adjunct therapy for lowering IOP.[8] These agents typically lower IOP by 20-25%.[13]

Adverse Effects

In general, these agents are well tolerated and similar in efficacy to beta blockers. Eye discomfort occurs more often with apraclonidine use than with brimonidine. When this irritation occurs, it is similar to an allergic reaction, and it warrants discontinuation of the medication. Systemic side effects with alpha agonists include dry mouth, dizziness, fatigue, and lowering of blood pressure and pulse.[1,13] Directing patients to practice NLO when using these drugs diminishes the likelihood they will experience systemic side effects.

Table 3: Topical Alpha Agonist Agents for Glaucoma

Generic (Brand)	Properties	Dose Form	Strength	Usual Dosage	Comments
Apraclonidine (Iopidine)	specific alpha$_2$ agonist	solution	0.5%, 1%	one drop BID to TID	Local irritation is common; tachyphylaxis can occur
Brimonidine (Alphagan P)	specific alpha$_2$ agonist	solution	0.15%, 0.1%	one drop BID to TID	Systemic side effects more common

TID: three times a day

Table 4: Topical Cholinergic Agents for Glaucoma

Generic (Brand)	Properties	Dose Form	Strength	Usual Dosage	Comments
Carbachol (Carboptic, Isopto Carbachol)	Irreversible	solution	1.5%, 3%	one drop BID to TID	
Pilocarpine (Pilocar, Isopto Carpine)	Irreversible	solution	0.25%, 0.5%, 1%, 2%, 4%, 6%, 8%, 10%	one drop BID, TID, or QID	Common side effects are decreased vision and brow ache
(Pilopine HS)		gel	4%	Once daily QHS	
Echothiophate (Phospholine Iodide)	Irreversible	solution	0.125%	one drop daily or BID	Increased cataract formation; has to be reconstituted

QHS: every evening at bedtime

Cholinergic Agonists

Direct acting cholinergic agonists work to increase outflow of aqueous humor through the trabecular meshwork.[1] Echothiophate is unique from the other agents in its class in that it inactivates pseudocholinesterase, which secondarily blocks true cholinesterase.[8] These agents need to be administered frequently to see maximum benefit from use; side effects are common, which limits their use in initial treatment of POAG. Pilocarpine is an option that is available in a wide range of strengths, and patients with darker eyes often require higher strengths to lower IOP. Carbachol has a longer duration of action than pilocarpine solution, but carbachol has a higher incidence of side effects. Carbachol is sometimes used when patients fail therapy with or cannot tolerate, pilocarpine.[8]

Adverse Effects

These agents have a high incidence of causing local discomfort and systemic side effects; this limits their use since other agents lower IOP just as effectively with a lower incidence of side effects. Echothiophate has the highest rate of adverse effects compared to pilocarpine and carbachol. Iris cysts, conjunctival thickening, and nasolacrimal duct occlusion are potential side effects from echothiophate, therefore this agent is not commonly prescribed. Echothiophate is used

mainly in patients with aphakia (patients without lenses) or pseudoaphakia (artificial lenses) because it can lead to cataracts. Systemic side effects of pilocarpine such as sweating, nausea, vomiting, diarrhea, and heart block increase in patients using strengths >4%. Carbachol has a similar side effect profile to that of pilocarpine, but they are more exaggerated and last longer with carbachol than with pilocarpine.[1,13] NLO technique improves efficacy while reducing side effects for this class of drugs.[8]

Carbonic Anhydrase Inhibitors

The topical carbonic anhydrase inhibitors (CAIs) reduce aqueous humor production of the ciliary body similar to the beta blocking agents, but they do this by blocking the secretion of sodium and bicarbonate ions of the ciliary body to the aqueous humor. Similar to other medications used for glaucoma, CAIs can be used as monotherapy or adjunct therapy. They do not lower IOP as much as beta blockers or prostaglandin inhibitors, but they are able to reduce IOP by up to 30%. Topical CAIs lower IOP less than oral CAIs. Systemic CAIs, decreases aqueous humor inflow, but they are used less frequently because they are more likely to cause systemic side effects. Using topical CAIs in conjunction with systemic CAIs has not been shown to decrease IOP further, and is therefore not recommended.[1,13,16]

Adverse Effects

Patients with a sulfur allergy cannot use CAIs due to potential cross reactivity. The topical agents can cause burning, stinging, tearing, lid reactions, corneal edema, and photophobia.[13] The risk of systemic side effects is low with topical CAIs, but practicing NLO further reduces the likelihood patients will experience systemic side effects.[8] With systemic CAIs, patients may notice a metallic taste in their mouth, fatigue, depression, kidney stones, and decreased libido. All of these side effects make systemic CAIs less desirable for treating elevated IOP.[1,8]

Table 5: Carbonic Anhydrase Inhibitors – Topical and Oral

Generic (Brand)	Properties	Dose Form	Strength	Usual Dosage	Comments
Brinzolomide (Azopt)	Carbonic anhydrase type II inhibition	suspension	1%	one drop BID or TID	less burning and stinging compared to dorzolamide
Dorzolamide (Trusopt)	Carbonic anhydrase type II inhibition	solution	2%	one drop BID or TID	
Acetazolamide (Diamox)	Carbonic anhydrase type II inhibition	tablet	250 mg, 500 mg	250 mg QID or 500 mg BID	Oral dose form
Methazolamide (Neptazane)	Carbonic anhydrase type II inhibition	tablet	25 mg, 50 mg	25 to50 mg BID to TID	Oral dose form.

BID: Twice daily. TID: Three times daily.

Table 6: Topical Combination Products for Glaucoma

Generic (Brand)	Dose Form	Strength	Usual Dosage
Timolol-dorzolamide (Cosopt)	solution	0.5%/2%	one drop BID
Timolol-brimonidine (Combigan)	solution	0.5%/0.2%	one drop BID
Brinzolomide-brimonidine (Simrinza)	solution	1%/0.2%	one drop TID

BID: Twice daily. TID: Three times daily.

Combination Products for Glaucoma

There are three combination products that may help reduce IOP further while improving patient adherence. Having these combination drugs also eliminates the 5-10 minute wait between instillation of two different eye drops; however, they are generally more expensive, since the products by themselves are generic, while the combination is sometimes only available as brand.[1]

Acute CAG

Acute CAG treatment is aimed at rapidly lowering very high IOP through hyperosmotic agents, pilocarpine therapy, and other IOP lowering agents that decrease aqueous humor. Often when IOP is severely elevated (>60 mmHg), it can take some time for a patient's eye(s) to respond to treatment. If CAG is only in one eye, the other eye should be treated as well to prevent the development of CAG in that eye.[1,14]

Surgical options

Most patients with CAG are candidates for a surgical procedure called an iridotomy. With an iridotomy, a hole is put in the iris to help aqueous humor flow easily to the anterior chamber. With acute CAG, before an iridotomy can be performed, IOP must be lowered.[14,17] Trabeculoplasty is used in patients with POAG to alter the drainage angle of the eye and improve aqueous humor flow.[1] Surgery in POAG is often considered in patients who are unable to adhere to therapy with IOP lowering agents.[1,18] Each of these surgical procedures have risks, and it is up to the physician to determine if the benefit for having one of these procedures outweighs the risks. Surgery is preventative and unable to reverse vision damage that has already occurred.[1] Iridotomies may cause temporary blurry vision or corneal swelling and rarely bleeding.[14,17] Patients who receive a trabeculoplasty may experience inflammation of the iris and cornea, a temporary decrease in vision, and potentially the formation of scar tissue.[13,18]

Conclusion

The glaucomas are a group of diseases that can lead to deterioration of vision and blindness with little warning. Because these diseases involve the eye, treatment is highly specific to the patient in order to avoid unnecessary complications while achieving maximum benefit. There are many different available drug options to treat elevated IOP in glaucoma to aid in tailoring therapy to individual patients. Prostaglandin analogs and beta blockers are often the most successful glaucoma agents due to their ability to lower IOP while having minimal side effects as well as being inexpensive. Understanding how each class of drugs works and their side effects can improve patient response and adherence, allowing them to preserve a very important quality of life--sight.

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