BOOST YOUR GLAUCOMA DRUG KNOWLEDGE

It's helpful to know the treatment options available.

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Because there is no one-size-fits-all plan for treating patients with glaucoma, it is the clinician's responsibility to know the ins and outs of the medications on the market to ensure informed decision-making. Glaucoma rarely progresses quickly, which means practitioners generally have time to measure the efficacy of prescribed medications, adjust regimens as needed, and evaluate the need for more aggressive treatment.

There is only one proven way to halt progression of glaucoma, which is by lowering IOP; fortunately, there are many pharmacologic options available to accomplish this. Treating each patient as an individual and finding the best recipe for IOP reduction makes glaucoma management an ever-changing and rewarding journey. This article takes a look at the most commonly prescribed glaucoma medications and noteworthy attributes that should be considered in their use. A more comprehensive list of available glaucoma drugs can be found in the Table.

FIRST-LINE TREATMENT

Prostaglandin analogues are the tried-and-true first-line medication class prescribed to lower IOP in the treatment of patients with glaucoma. These drugs work by increasing uveoscleral outflow. A 5 mm Hg to 8 mm Hg reduction in baseline IOP can be expected, with considerable flattening of the diurnal curve.[1] Care must be taken when these drugs are used in patients who have a history of inflammatory conditions or of recurrent herpes simplex. Common side effects include increased eyelid pigmentation, conjunctival hyperemia, elongation and darkening of eyelashes, and iris darkening.[2] This class of drugs, which includes latanoprost (Xalatan, Pfizer), bimatoprost (Lumigan Allergan), and others discussed below, has the benefit of allowing once daily dosing (at night, to minimize side effects) and being available in some generic formulations.

Another advantage is the availability of alternatives for patients sensitive to the preservative benzalkonium chloride (BAK). Travoprost ophthalmic solution 0.004% (Travatan Z, Novartis) and tafluprost ophthalmic solution 0.0015% (Zioptan, Akorn) are formulated without BAK. Additionally, the FDA recently approved latanoprost ophthalmic emulsion 0.005% (Xelpros, Sun Ophthalmics), which uses the company's proprietary swollen micelle microemulsion technology to allow latanoprost to be soluble without BAK while lowering IOP an average of 6 mm Hg to 8 mm Hg.[3]

Latanoprostene bunod ophthalmic solution 0.024% (Vyzulta, Bausch + Lomb) is a modified prostaglandin analogue with a dual mechanism of action.[4] It breaks down into latanoprost acid and nitric oxide inside the eye. The latanoprost acid works like other prostaglandins to increase uveoscleral outflow, and the nitric oxide's mechanism of action is thought to relax the trabecular meshwork to increase aqueous humor outflow. The drug has the same side effects as other prostaglandin analogues (eg, redness, pain, lash growth, increased pigmentation of the iris and periorbital area).[5]

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TABLE. Drugs Commonly Used in the Treatment of Glaucoma*

CLASS	GENERIC NAME	TRADE NAME (MANUFACTURER)	MECHANISM OF ACTION	COMMON KNOWN SIDE EFFECTS	NOTES
Prostalgandin Analogue			Increases uveo-scleral outflow of fluid from the eye	Eye color change, darkening of eyelid skin, eyelash growth, droopy eyelids, sunken eyes, stinging, eye redness, and itching	
	latanoprost ophthalmic emulsion 0.005%	Xelpros (Sun Ophthalmics)			BAK-free
	latanoprost ophthalmic solution 0.005%	Xalatan (Pfizer)			Available in generic form
	bimatoprost ophthalmic solution 0.01%	Lumigan (Allergan)			Some formulations available in generic form
	travoprost ophthalmic solution 0.004%	Travatan Z (Novartis)			BAK-free
	tafluprost ophthalmic solution 0.0015%	Zioptan (Akorn)			BAK-free
	latanoprostene bunod ophthalmic solution 0.024%	Vyzulta (Bausch + Lomb)	Increases uveo-scleral and aqueous humor outflow		
Beta Blocker			Decreases production of fluid	Low blood pressure, reduced pulse rate, fatigue, shortness of breath	Second most often used class of medication
	timolol maleate ophthalmic solution	Timoptic 0.25% and 0.5% (Bausch + Lomb)			Available in generic and preservative-free formulations
Alpha-Adrenergic Agonist			Decreases production of fluid and increases drainage	Burning or stinging, fatigue, headache, drowsiness, dry mouth and nose, higher likelihood of allergic reaction	
	brimonidine tartrate ophthalmic solution 0.2%	Alphagan (Allergan)			Preserved in BAK; available in generic form
	brimonidine tartrate ophthalmic solution 0.1% or 0.15%	Alphagan P (Allergan)			Preserved in stabilized oxychloro complex (Purite, Allergan)
Miotic			Increases outflow		Blurred or dim vision, headache, redness of eyelids, tearing or swelling of the eye, itching or redness of the eye, stinging, burning, or discomfort in the eye
	pilocarpine HCl ophthalmic solution 1%, 2% and 4%	Isopto Carpine (Alcon)			Preserved with BAK; available in generic form
	pilocarpine HCl ophthalmic gel 4%	Pilopine HS (Alcon)			Gel formulation

CLASS	GENERIC NAME	TRADE NAME (MANUFACTURER)	MECHANISM OF ACTION	COMMON KNOWN SIDE EFFECTS	NOTES
Combination Agents					
	dorzolamide HCl 1%/ timolol maleate 0.5% sterile ophthalmic solution	Cosopt (Akorn)			Available in generic form and as a preservative-free formulation
	brimonidine tartrate 0.2%/timolol maleate ophthalmic solution 0.5%	Combigan (Allergan)			
	brinzolamide 1%/ brimonidine tartrate ophthalmic suspension -0.2%	Simbrinza (Alcon)			Includes no beta blocker
Carbonic Anhydrase Inhibitor, Topical			Decreases aqueous production	Stinging, burning, eye discomfort	
	dorzolamide ophthalmic solution 2%	Trusopt (Santen)			Available in generic form
	brinzolamide ophthalmic suspension 1%	Azopt (Alcon)			
Carbonic Anhydrase Inhibitor, Oral			Decreases aqueous production	Tingling hands and feet, fatigue, upset stomach, memory problems, frequent urination	
	acetazolamide 125 mg and 250 mg				Available in generic form
	acetazolamide 500 mg				Available in generic form
	methazolamide 25 mg and 50 mg				Available in generic form
	dichlorphenamide 50 mg	Keveyis (Strongbridge Biopharma)			
Rho Kinase Inhibitor			Increases drainage of aqueous	Eye redness, corneal deposits, stinging, and small scleral bleeds	
	netarsudil ophthalmic solution 0.02%	Rhopressa (Aerie Pharmaceuticals)			
	netarsudil ophthalmic solution 0.02%/ latanoprost 0.005%	Rocklatan (Aerie Pharmaceuticals)			

* Not an exhaustive catalogue of available therapeutics.
Abbreviation: BAK, benzalkonium chloride
Source: Glaucoma medications and their side effects. Glaucoma Research Foundation. www.glaucoma.org/gleams/glaucoma-medications-and-their-side-effects.php. Accessed March 1, 2019.

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The APOLLO, LUNAR, and VOYAGER studies compared latanoprostene, dosed every night at bedtime, versus timolol 0.5% twice daily and latanoprost 0.005%. Latanoprostene was shown to be noninferior to the comparators, with a greater reduction in mean IOP from baseline.[4,6,7] The JUPITER study reported an average 26.5% reduction in baseline IOP in normotensive glaucoma patients using latanoprostene.[8] In the VOYAGER study, latanoprostene was found to lower the IOP by an average of 1.23 mm Hg more than latanoprost 0.005% alone.[8]

Prostaglandin analogues are not an option for all patients, however, which is why it is fortunate that we have a solid lineup of adjunctive and secondary options available.

OTHER OPTIONS

Beta Blockers

Beta blockers for glaucoma have been around since 1978. Contraindications to their use include asthma or chronic bronchitis, diabetes, dysrhythmia, and heart failure.[9] Beta blockers can be expected to reduce baseline IOP by between 20% and 30%, and they work by decreasing aqueous humor production.[10] Because this class of drugs is known to suppress the adrenergic system, there is an argument to support dosing them once daily in the morning rather than twice daily, to avoid nocturnal hypotension that can lead to reduced perfusion pressure.[11]

Alpha Adrenergic Agonists

This class of drugs plays an important role in the management of glaucoma. Brimonidine tartrate ophthalmic solution 0.2% (Alphagan, Allergan), preserved with BAK, and brimonidine tartrate ophthalmic solution 0.1% or 0.15% (Alphagan P, Allergan), preserved with stabilized oxychloro complex (Purite, Allergan), have the same efficacy across concentrations. It has been shown that, when dosed twice a day, the expected IOP reduction with brimonidine from baseline is between 4 mm Hg and 6 mm Hg.[12]

Because of its short half-life, brimonidine is recommended to be dosed three times a day as monotherapy and twice a day when in combination with another medication. Brimonidine has a dual method of action, suppressing aqueous humor production and increasing uveoscleral outflow.[12] Side effects seen with alpha agonists include burning or stinging, fatigue, headache, drowsiness, and dry mouth and nose.[5] Follicular conjunctivitis is a concern with increased risk in formulations that contain a higher percentage of the active drug. The Low-Pressure Glaucoma Treatment Study compared timolol maleate 0.5% to brimonidine 0.2% by assessing visual field progression in patients with low-pressure glaucoma.[13] A statistical difference in endpoints was found, raising the question of whether brimonidine possesses neuroprotective properties.[14] Despite these findings, controversies remain on this study.[15]

Carbonic Anhydrase Inhibitors

Topical Therapy

There are two topical ophthalmic formulations in this drug class. Brinzolamide ophthalmic suspension 1% (Azopt, Alcon) can be dosed twice or three times daily in monotherapy, and dorzolamide ophthalmic solution 2% (Trusopt, Santen, and others) is dosed twice daily in monotherapy. Both are dosed twice daily when in combination with another medication. The expected reduction in IOP is 4 mm Hg to 6 mm Hg.[16]

Brinzolamide has the benefit of less stinging and burning on instillation, as its pH is 7.6, compared with dorzolamide's pH of 5.6. Brinzolamide is available only as a branded drug, while dorzolamide 2% is available in a generic formulation.

The mechanism of action of this class of drugs is blockage of carbonic anhydrase in the ciliary epithelium, which is involved in the production of aqueous humor.[17] It is important to remember to use this class of drugs with caution in patients with reduced endothelial cell counts, cornea guttata, or Fuchs dystrophy because the decrease in metabolism of carbonic anhydrase can lead to corneal edema.[18] The most common reported side effects are blurred vision and dysgeusia.

Oral Therapy

The most commonly used drug in this group, acetazolamide 125 mg or 250 mg, is available generically. This oral drug is typically dosed up to four times a day. The maximum effect occurs at approximately 3 hours and can last as long as 12 hours.

A better tolerated formula, often referred to by eye care professionals as Diamox Sequels, but now available from generic manufacturers, is a 500 mg pill. Given once or twice daily, its effect can last a full 24 hours. Although the drug is effective, it is known for its significant side effects, which include paresthesias of the skin; tingling and numbness of the teeth, lips, and extremities; abnormal taste, especially with carbonation; headaches; drowsiness; malaise; fatigue; gastrointestinal upset; diuresis; renal stones; depression; anorexia; weight loss; mental confusion; transient myopia; and more.[18] It is important to remember that oral carbonic anhydrase inhibitors are contraindicated in children, those who are pregnant, and those with sulfa allergies, kidney stones, liver dysfunction, hypokalemia, severe chronic obstructive pulmonary disease, and blood dyscrasias, specifically sickle cell anemia.[18]

Other oral carbonic anhydrase inhibitors include methazolamide (generic; available in 50 mg and 100 mg), which is typically dosed twice or thrice daily and has been found to be less effective at lowering IOP than acetazolamide,[18] and dichlorphenamide 50 mg tablets (Keveyis, Strongbridge Biopharma).

Miotic

Pilocarpine is a cholinergic agonist that allows excess fluid to drain from the eye. In the past, the drug was used

Photo courtesy of Jacob Lang, OD, FAAO

topically to treat open-angle glaucoma and angle-closure glaucoma until surgery could be performed, but it is now typically used only as a last resort because of its side effects. Typically dosed four times daily, pilocarpine is now more commonly used in the treatment of narrow-angle glaucoma and pigmentary glaucoma. It is important to note that spikes in IOP have been observed in individuals using this drug during exercise.[19] Pilocarpine is available in strengths of 1%, 2%, 4%, and 6%. It is good practice to titrate up the percentage to avoid as much as possible the drug's side effects of brow ache and induced myopia.[20]

Combination Drugs

Three combination drugs are approved in the United States for the treatment of glaucoma, and all are dosed twice daily. The combination dorzolamide HCl 2%/timolol maleate 0.5% sterile ophthalmic solution (Cosopt, Akorn) is available in preserved and preservative-free formulations. Brinzolamide 1%/brimonidine tartrate ophthalmic suspension 0.2% (Simbrinza, Alcon) is the only combination drug on the market that doesn't contain a beta blocker. Brimonidine tartrate 0.2%/timolol maleate ophthalmic solution 0.5% (Combigan, Allergan) is a third drop combining two mainstay glaucoma drugs.

All three formulations are great options for improving compliance and reducing the eye's exposure to preservatives.

RECENT ADDITIONS TO THE TOOLBOX

Rho Kinase Inhibitors

Rho kinase inhibitors are a new class of drugs in the world of glaucoma management. Netarsudil ophthalmic solution 0.02% (Rhopressa, Aerie Pharmaceuticals) is thought to lower IOP by increasing outflow through the trabecular meshwork, although its exact mechanism is unknown. Netarsudil is dosed once daily in the evening, and an average lowering of IOP by 3.9 mm Hg to 4.1 mm Hg can be expected, similar to timolol 0.5% twice a day, as was shown in the ROCKET 1, 2, and 4 studies.[21] Netarsudil's common sides effects include conjunctival hyperemia, conjunctival hemorrhages (petechial and diffuse), and reversible corneal verticillate.[22,23]

The combination netarsudil 0.02%/latanoprost 0.005% (Rocklatan, Aerie Pharmaceuticals) was approved by the FDA in March for once-daily use at night. In the Mercury 1 trial, an additional reduction of 1 mm Hg to 3 mm Hg was found with this combination drug compared with latanoprost 0.05% or netarsudil 0.02% alone, with 50% of patients experiencing conjunctival hyperemia.[24]

WITH NEW OPTIONS COME BETTER OUTCOMES

Treatment and management of glaucoma is complex, but with advances in pharmaceutical and surgical options eye care practitioners can tailor treatment to each patient's needs. As new options continue to emerge, effective management for patients with even more advanced disease may become attainable. ■

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