

PSS NEWS

A Distance Learning Format for COPE Continuing Education in Optometry

The Medical Management of Glaucoma

2.0 Hours -- COPE 68144 - GL

This program is supported by an educational grant from Alcon

Deepak Gupta, OD

Learning Objectives

1. To learn about the various management options for glaucoma
2. To review the major medical therapeutic agents used in managing glaucoma patients
3. To highlight differences between the prostaglandin analogs

The primary goal in glaucoma management is to slow or halt the progressive optic-nerve damage and associated visual-field loss to the point where your patient will maintain their visual function for the duration of their life. Medical therapy works for roughly 80-90% of patients and is classically maximized before progressing to laser, then conventional surgical treatment. If needed, laser therapy consists of either argon laser trabeculoplasty (ALT) or selective laser trabeculoplasty (SLT). Both procedures are relatively safe, but both have the disadvantage of uncertain effectivity and lack of longevity. Conventional surgery is usually reserved for cases where medical and laser therapy fail.

Theoretically, there are seven different drug classes used in the medical management of glaucoma. However, in practice, there are really only 4 classes routinely used and that is what we will focus on.

Beta-Adrenergic Receptor Antagonist (Beta-Blockers)

There was a time when Beta-blockers were considered the gold standard of glaucoma therapy. Timolol (Timoptic, Timoptic XE- gel forming solution), levobunolol (Betagan) metipranolol (Optipranolol), carteolol 1 percent (Ocupress) are all nonspecific beta-blockers that reduce aqueous fluid production, resulting in a 22-26% IOP reduction. Beta-blockers were introduced in the 1970's and revolutionized the glaucoma management protocol. Prior to the emergence of beta-blockers, the most common agents used were pilocarpine and echothiopate. Both agents demonstrated significant side effects and were quickly replaced by the beta blockers, which rapidly became the drug of choice for many glaucoma patients.

Ocular side effects of beta-blockers are mild including stinging, blurred vision (particularly with the gel formulations) and, on rare occasions, allergic conjunctivitis and corneal anesthesia.

Systemic side effects of beta-blockers include cardiovascular (bradycardia, heart block and

aggravation of congestive heart failure, hypercholesteremia), pulmonary (bronchospasm in asthma patients) and CNS (hallucinations, insomnia, depression, impotence). This is particularly a problem because many glaucoma patients are older and suffer from cardiovascular and respiratory conditions. Betaxolol 0.25 percent (Betoptic S) is a beta 1 selective blocker (cardioselective and pulmonary sparing) that is theoretically better for patients with asthma or COPD. However, there are still some “cross-reactions” so this drug should still be used with caution in these patients. Carteolol has intrinsic sympathomimetic activity so it doesn’t decrease heart rate or increase cholesterol as much as other beta-blockers, but it also doesn’t lower IOP as much as the non-specific beta-blockers. There have been roughly 40 deaths in the literature attributed to the use of topical beta blockers. Although statistically this number is very small, it is much higher than any other topical glaucoma agent.

Unlike some of the other glaucoma medications in which side effects show up right away, some side effects in beta-blockers do not manifest until months or years after treatment is initiated. Therefore, careful monitoring is needed even in patients who experienced no initial side effects. In addition, beta-blockers experience a phenomenon known as “drift”, which refers to a slow, steady rise in IOP after months or even years of treatment. Up to one half of patients who initially respond favorably may eventually need to be switched to another medication 1.

Topical beta-blockers solutions were typically prescribed BID, but we now know that QD works for many patients. We now also know that the 0.25% formulation is as effective as the 0.5% solution. The most notable exception to this rule is African-American patients who may still require the 0.5% solution and BID dosing.

Although many patients demonstrate a 22 to 27% IOP reduction with beta-blocker therapy, the one

aspect of IOP which this agent does not help is flattening the diurnal curve. In recent years we have found significant fluctuations in IOP over the course of the day can contribute to the progression of glaucomatous optic nerve damage. Therefore, therapeutic goals in glaucoma should be geared at both lowering IOP and flattening this diurnal curve.

With the emergence of new glaucoma medications in recent years, many doctors (including myself) no longer use beta-blockers as their drug of choice in glaucoma management. This is due to factors such as relatively poor safety profile, long-term drift, and failure to adequately flatten the diurnal curve. Some patients even demonstrate visual field deterioration even though their IOP is controlled with beta-blockers. Instead, beta-blockers are reserved for patients on whom other drugs prove inadequate or as adjunctive therapy when a different drug class fails to adequately lower IOP.

Alpha-Adrenergic Receptor Agonists

The initial agent in this drug class was apraclonidine 1% (Iopidine). Unfortunately, this drug demonstrates significant adverse reactions with allergic blepharoconjunctivitis and tachyphylaxis, so it is rarely used in long-term glaucoma therapy.

Brimonidine 0.15 percent is a selective alpha-2 agonist and is the only drug in this class used in glaucoma therapy. This agent works by decreasing aqueous humor production and increasing uveoscleral outflow. Brimonidine-P incorporates a new preservative, Purite (oxychloro complex), that breaks down to sodium chloride and water. This is a vast improvement from the more commonly used preservative BAK, which is frequently associated with ocular allergies. For patients who did not have a sensitivity to the preservative, brimonidine is also available in a generic formulation.

Ocular side effects of brimonidine include ocular irritation in nearly one quarter of patients. This is a vast improvement from the previous formulation of brimonidine which demonstrated ocular irritation in 40 to 50 percent of patients. Systemic side effects include dry mouth in nearly one-third of patients, fatigue and drowsiness in 5 percent and a few cases of headaches. Brimonidine should not be used in young children with juvenile glaucoma because of possible CNS involvement and reports of apneic spells and cyanosis.

Brimonidine is effective in lowering IOP and is often dosed BID, although the recommended dosing is TID. The main problem with doing this is that some patients may experience a mid-afternoon, transient elevation in IOP after the morning dose has worn off and before the patient has instilled the evening drop. Since significant fluctuations in IOP have been shown to be an independent risk factor in glaucoma, this can be a serious problem. Even so, studies have shown that it still has an IOP-lowering effect similar to timolol 1. When used as adjunctive therapy, brimonidine has a significant additive effect when used with other glaucoma drugs. One of the more useful aspects of this drug may turn out to be its feature of neuroprotection. Although studies have not yet definitively confirmed its role in this area, research is ongoing.

Carbonic Anhydrase Inhibitors (CAIs)
The CAIs lower IOP by decreasing aqueous production through the reversible and noncompetitive binding of the enzyme carbonic anhydrase. Acetazolamide (Diamox) and Methazolamide (Neptazane) are the two most common systemic CAIs. Although indicated for COAG, they are rarely used for chronic therapy anymore due to the release of topical CAIs. Acetazolamide is the only CAI available in an injectable formulation for acute forms of glaucoma. Systemic side effects of this drug

class are mild and include paresthesias, metallic taste, nausea and GI upset. There are also reports of CNS side effects such as confusion, depression, malaise, fatigue and decreased libido also are common. Whether topic or systemic, these compounds contain sulfonamides, and should be avoided in patients with sulfa allergies.

Topical CAIs – dorzolamide (Trusopt) and brinzolamide (Azopt) - have similar IOP-lowering efficacy and a better safety profile than the oral agents. They are both dosed TID as primary therapy and BID in adjunctive therapy. Neither drug is as effective as timolol 0.5 percent or systemic CAIs in reducing IOP 2. The main difference between the two is that there is less ocular irritation with brinzolamide.

Systemic side effects of the topical drugs are rare, but include bitter taste, nausea, diarrhea, and gastroenteritis. Ocular side effects are relatively common and include eye stinging, dry eyes, blepharitis, and superficial punctate keratitis. Both drugs inhibit bicarbonate function, so there is some concern that corneal endothelial function may be compromised with long-term use. Until more research is done, it is wise to use these drugs with caution in patients with guttata, endothelial compromise, and those with significant ocular surface disease.

Although approved for primary therapy, topical CAIs are primarily used as second- or third-line adjunctive agents and are additive to beta-blockers, adrenergics, and prostaglandin analogs. Many doctors use them as a last resort before sending a patient for surgery or for chronic therapy for patients refusing surgery.

Combination Products

There are three basic combination products for use in patients with glaucoma:
Cosopt is a combination product of dorzolamide and timolol.

Combigan is a combination of brimonidine and timolol

Lastly, Simbrinza is a combination of brinzolamide and brimonidine..

Combination products are nice to add as second line agents because you are really adding two medications at once and the patient's regimen is only minimally more complicated.

Prostaglandin Analogs

There are three prostaglandin analogs (Brimaprost, Travaprost Z, and Latanoprost), all of which are potent ocular hypotensive agents with similar side effect profiles. These medications are extremely popular as primary glaucoma therapy due to their excellent efficacy, safety index and tolerability. They flatten the diurnal curve and achieve anywhere from 25 to 35% IOP reduction. In fact, many patients reach target pressure with a single agent with QHS dosing. If used in adjunctive therapy, they are additive to most other glaucoma medications.

Latanoprost

Latanoprost 0.005 percent (Xalatan) is a prostaglandin analog that biochemically loosens the intercellular spaces within the face of the ciliary body, enhancing uveoscleral outflow.

Ocular side effects include conjunctival hyperemia, eyelash thickening and elongation of eyelashes and irreversible iris discoloration. This is usually seen in patients with mixed colored irises—most often green-brown or blue/gray-brown. As of yet, there have been no reported cases in patients with solid-colored (pure blue or pure brown) irises. This drug can cause iritis and cystoid macular edema (CME) in predisposed patients, such as those with a history of uveitis or CME, aphakia, a YAG posterior capsulotomy, or an anterior chamber IOL.

Systemic side effects are rare and mild; the most common complaints are upper respiratory signs, mild myalgia, and non ocular allergy or eczema.

There also have been a few reports of migraine headache, hypertension, and exacerbation of Herpes simplex corneal infections.

Studies have shown that latanoprost 0.005% QHS reduces IOP more than timolol 0.5% bid, with a much better safety profile⁵. If used as second-line therapy, latanoprost is additive to all other glaucoma drugs with the exception of pilocarpine. The cholinergic agonist pilocarpine(now rarely used) causes the contraction of the longitudinal muscle of the ciliary body, reducing uveoscleral outflow and dampening the effectiveness of latanoprost. Of the three prostaglandin analogs, this one has been around the longest.

Travoprost

Travoprost 0.004% (Travatan and Travatan Z) is an FP prostanoid receptor agonist that enhances uveoscleral outflow, with an IOP-lowering efficacy of 26-36%. The drug has the same basic side effect profile of latanoprost, but with less incidents. This drug comes in a foil pouch which, once opened, leaves the drug with a six week expiration at room temperature.

Travatan Z features a new preservative which is theoretically better for patients with ocular surface disease. The concept behind this drug is that over the course of many years, patients taking topical glaucoma medications exhibit some level of ocular surface disease due to preservative toxicity.

Bimatoprost

Bimatoprost is a prostamide, which works either by stimulating the PGF2-alpha receptor or some other unidentified receptor. Mechanistically, bimatoprost works by producing both a 35-percent increase in trabecular outflow facility and a 50-percent increase in uveoscleral outflow.

Bimatoprost's greatest strength is the ability to significantly lower IOP and flatten the diurnal curve. In clinical trials, bimatoprost caused an

average IOP drop of approximately 33 percent with no significant diurnal variation. When compared to timolol 0.5% b.i.d., once-daily bimatoprost was superior in all measures of IOP-lowering efficacy 4.

The most common adverse effects with bimatoprost are hyperemia, eyelash growth and ocular pruritus. Roughly 5 to 8 percent of patients discontinue bimatoprost for tolerability issues due to hyperemia (the most of any prostaglandin). Instilling artificial tears 15-30 minutes prior to dosing can reduce the hyperemia. Since the hyperemia resolves within two weeks in most patients, I usually warn patients of this when initiating treatment. If it does not resolve after several weeks and I think it will cause compliance issues in a patient, I switch to another drug.

The Latest and Greatest

This past year we saw two new options in the management of glaucoma: Rhopressa and Vyzulta. Rhopressa (netarsudil ophthalmic solution) is a Rho kinase inhibitor, which is believed to reduce IOP by increasing the outflow of aqueous humor through the trabecular meshwork route. The exact mechanism is unknown.

Vyzulta has a dual mechanism of action. The latanoprost acid, a prostaglandin analog, works primarily within the uveoscleral pathway. The second component, butanediol mononitrate releases nitric oxide, which helps relax the trabecular meshwork. This is what is so exciting about this drug -- it works directly on decreasing the resistance in the trabecular meshwork. Until now, enhancing outflow through the trabecular pathway was limited to the use of laser trabeculoplasty and poorly tolerated miotics.

In my practice, nearly all of my patients have achieved a greater IOP lowering with Vyzulta than with a prostaglandin alone.

Here is the way I utilize it in my practice:

All newly diagnosed patients are started on Vyzulta. It is well-tolerated, convenient once-a-day dosing, and lowers IOP more than just a prostaglandin alone.

Any patients needing additional therapy or IOP lowering. In previous years, I would not have hesitated to add a second medication or to possibly send this patient out for an SLT. However, now I switch that patient to Vyzulta instead and have achieved excellent clinical success.

Lastly, most patients currently on PG therapy will be switched over even if they are doing well. Why? Because we know that the lower the IOP the better the long term outcome. The truth is that most patients with glaucoma will eventually progress so why not treat them more aggressively now to delay the onset of that progression.

What's the downside? The cost, of course. As with any new name brand medication, the cost is high when it is first launched. However, over time, that cost comes down and we are starting to see that with Vyzulta now. One way to deal with this, particularly for your non-Medicare patients, is to take advantage of the "Pay No More than \$35 or \$45" discount cards. These can be easily found at www.vyzulta.com or www.Rhopressa.com.

Keep in Mind

With the quality of glaucoma medications on the market, we can usually find one that the patient responds to. In many cases, failure to respond is more an issue of compliance than efficacy. With regard to compliance, it has been reported that one quarter to one half of patients default from glaucoma therapy. The following are things you can do to increase compliance:

1. Simplify the medication regimen. Use the minimum necessary medication in the

minimum dosing to reach the target IOP. According to most studies, taking more than two drops per day dramatically increases non-compliance.

2. Talk to your patient. The single most important component in increasing patient compliance is comprehensive patient education. Because of the lack of symptoms and slow progression of glaucoma, patients underestimate its seriousness. You should remind them that glaucoma is a blinding disease and that treatment increases the chances that they can lead a life free from functional visual disability. While this task is time consuming, it is better than sending a patient for surgery due to poor IOP control.

Therapeutic Pearls

- ◆ It is important to realize that each treatment in glaucoma is specifically tailored to a patient. Many eye care practitioners initiate glaucoma therapy with prostaglandin products or even an alpha-2 agonist. The prostaglandin analogs are potent IOP lowering agents, are easily administered by the patient once daily, have minimal systemic and ocular side effects, have no tendency for long-term drift, and they flatten diurnal curves.
- ◆ Carefully consider risk factors. For example, age. An older patient is more likely to have glaucoma, but a younger patient has many years of potential useful vision. You may initiate treatment earlier and more aggressively on a younger patient than an older one because you have a longer theoretical time period over which you are trying to preserve their vision.
- ◆ Involve your patient. This is a disease your patient will have to deal with for the rest of their life. The more they know about it, the more compliant they will be.
- ◆ If a patient is on a beta-blocker and not achieving adequate IOP control, consider replacing the medication with one of the prostaglandin analogs instead of adding it.
- ◆ After initiating treatment, or changing treatment, always see a patient back for follow-up to ensure that the medication worked. Although the medications work for roughly 80 to 90% of patients, this means that one in five may not respond to therapy. Always try to have your patients back for their follow-up appointments at various times of the day to check for diurnal changes.
- ◆ Don't be afraid to get a second opinion. If you are unsure if your patient's disease is progressing, send the patient to another optometrist who can provide assistance. Although we can not legally call ourselves glaucoma specialists, there are many optometrists who are fully capable of managing even the most complicated cases.

1 Boger WP, III. Short-term escape and long-term drift. The dissipation effects of the beta-adrenergic blocking agents. *Surv Ophthalmol* 1983; 28: 235-240.

2 Cantor LB. The evolving pharmacotherapeutic profile of brimonidine, an alpha2-adrenergic agonist, after four years of continuous use. *Exp Opin Pharmacother*. 2000; 1:815-834.

3 Strahlman E, Tipping R, Vogel R, for the International Dorzolamide Study Group. A double-masked, randomized 1-year study comparing dorzolamide (Trusopt), timolol, and betaxolol. *Arch Ophthalmol* 1995; 113(8): 1009-1016.

4 Camras CB, et al. Latanoprost treatment for glaucoma: effects of treating for 1 year and switching from timolol. *Am J Ophthalmol* 1998; 126: 390-399.

5 Targeting IOP Therapy, A first look at bimatoprost. *Survey of Ophthalmology* May 2001; 45, supplement 4: S335-S368.

CONTINUING EDUCATION QUIZ

This article is worth two (2.0) continuing education credits. This COPE-approved program is accredited by the University of Alabama at Birmingham College of Optometry.

Once you have registered for the course, you will be given an access code and go to www.flexiquiz.com where you will take the quiz. To earn credit, you must receive a grade of 70% or greater.

Please note that all 50 states have different rules and regulations concerning the acceptance of correspondence/internet continuing education. Please verify with your state board of optometry as to the amount of allowable hours and acceptable categories/topics in your particular state.

-
1. Medical therapy works for roughly what percentage of glaucoma patients?
 - A. 90-100%
 - B. 80-90%
 - C. 70-80%
 - D. 60-70%
 2. Which of the following are surgical procedures for patients with glaucoma?
 - A. Argon laser trabeculoplasty (ALT)
 - B. Selective laser trabeculoplasty (SLT)
 - C. Trabeculectomy
 - D. All of the above
 3. How many different drug classes are approved for long term care of the patient with open angle glaucoma?
 - A. 4
 - B. 5
 - C. 6
 - D. 7
 4. For most optometrists, which of the following is the correct order for the overall management scheme in glaucoma?
 - A. Medical therapy, then laser, then conventional surgery
 - B. Laser, then conventional, then medical
 - C. Conventional surgery, then laser, then medical
 - D. Conventional surgery, then medical, then laser
 5. All of the following are topical Beta-Blockers EXCEPT:
 - A. Timolol
 - B. Levobunolol
 - C. Pilocarpine
 - D. Carteolol
 6. Beta-blockers are generally contraindicated in patients with:
 - A. Myopia
 - B. Blepharitis
 - C. Asthma or COPD
 - D. Cataracts
 7. What is the name of the new preservative in Brimonidine?
 - A. Pyrex
 - B. Purite
 - C. Benzalkonium Chloride
 - D. Methylcellulose
 8. Carbonic Anhydrase Inhibitors should be avoided in patients with allergies to what drug class?
 - A. Sulfa
 - B. Iodine
 - C. Fluorescein
 - D. Mydriacyl
 9. Which of the following CAIs is the only one available in injectable formulation for acute forms of glaucoma?
 - A. Acetazolamide
 - B. Methazolamide

- C. Dorzolamide
D. Brinzolamide
10. The brand name drug Cosopt is a combination product of which two drugs?
A. Timolol and latanoprost
B. Timolol and unoprostone
C. Brinzolamide and latanoprost
D. Timolol and dorzolamide
11. Which of the following is TRUE about Cosopt?
A. It shows good efficacy
B. The side effects are similar to those of each individual agent
C. The BID dosing helps improve a patient's compliance
D. All of the above
12. Which of the following is not a reason why the prostaglandin analogs have become so popular in glaucoma management?
A. They significantly flatten the diurnal curve
B. They cause no ocular side effects at all
C. They achieve excellent IOP reduction
D. They can be used with daily dosing
13. All of the following are in the prostaglandin analog class of drugs EXCEPT:
A. Latanoprost
B. Timolol
C. Travatoprost
D. Bimatoprost
14. The prostaglandin drugs can cause iritis and cystoid macular edema in patients with:
A. history of uveitis
B. aphakia
C. anterior chamber IOL
D. all of the above
15. Which of the prostaglandin analogs has the highest incidence of hyperemia?
A. Bimatoprost
B. Latanoprost
C. Travatoprost
D. Unoprostone
16. Which of the prostaglandin analogs has the highest incidence of iris discoloration?
A. Latanoprost
B. Bimatoprost
C. Travatoprost
D. Dorzolamide
17. According to the author, which of the prostaglandin analogs has the greatest IOP lowering effect?
A. Latanoprost
B. Travatoprost
C. Bimatoprost
D. None – they are all basically the same
18. As mentioned in the article, what is the maximum number of drops per day a patient may take before noncompliance dramatically increases?
A. One
B. Two
C. Three
D. Four
19. What is the name of the drug in research for its neuroprotective properties which is currently used for patients with Parkinson's syndrome?
A. Memantine
B. Timolol
C. Latanoprost
D. Unoprostone
20. What target IOP should you aim for when initiating treatment for glaucoma?
A. 10 – 20 % reduction
B. 20 – 30 % reduction
C. 30 – 40 % reduction
D. There is no "pre-set" value. Target IOP should be based on a individual patient's overall assessment.