PHARMACOLOGICAL MANAGEMENT OF GLAUCOMA

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INTRODUCTION

Medication is usually the first choice in the management strategy for patients with glaucoma. The medications used typically aim to reduce the intraocular pressure (IOP) by increasing the rate of aqueous outflow and/or reducing the production of aqueous humor. The various families of glaucoma medications have specific modes of action as well as side effects and contraindications.

When prescribing medications, important factors should be considered including the following:

- Potency
- Additive effects
- Interactions with other medications
- Comorbidities
- Side effects
- Method and ease of administration
- Cost (this may not be relevant in some parts of the world)

Patients who present in an emergency with acute angle closure are given medications to reduce the IOP and corneal edema and to reduce the level of pain. The medications used help to prepare the patient for laser therapy or surgery.

MEDICAL MANAGEMENT

There are many options currently available to lower the IOP in patients with glaucoma. The future offers further potential for medications providing neuro-protection as well as the use of stem cells in glaucoma management.

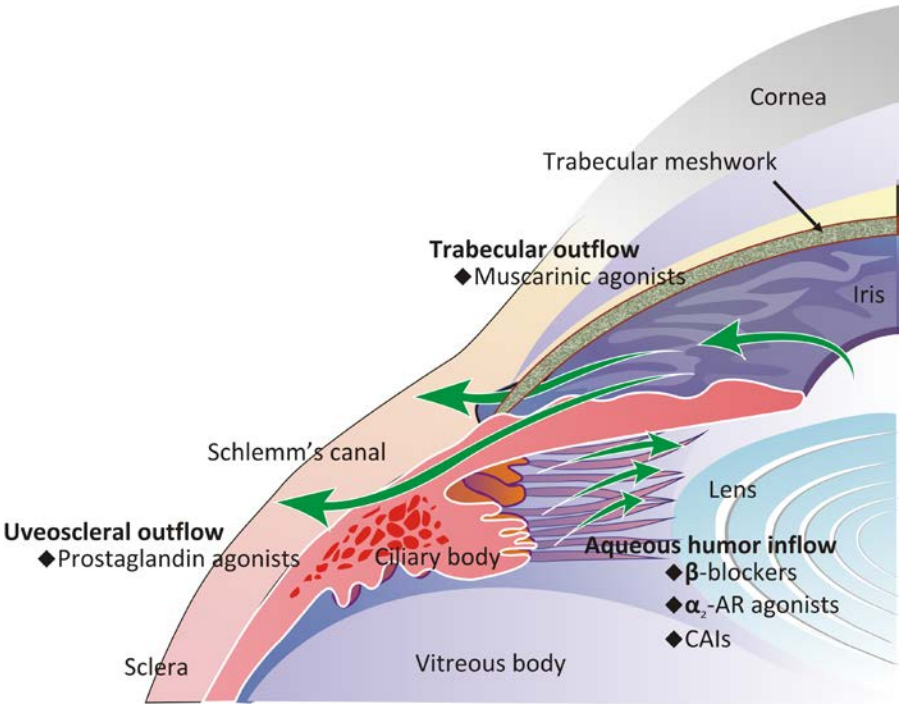

Figure 17.1: *Glaucoma medications and their mode of action*

ESTABLISHING AN IOP BASELINE

Effective management of glaucoma requires accurate and repeatable measurements of the IOP. Prior to commencing any treatment it is necessary to establish a baseline IOP value that takes into account any diurnal variation in pressure.

Diurnal variation in IOP is determined by making multiple measurements of the pressure at various times throughout the day. It is recommended that at least three IOP measurements are taken at various times of the day (morning, afternoon and evening) to set a baseline.

TARGET PRESSURE

When initiating treatment for glaucoma it is important to set a target pressure to help slow further progression of the disease.

The target pressure is not a static value - it must be reset if the patient continues to progress at an unacceptable rate. Generally, the more damaged the optic nerve, the greater is the required IOP reduction.

A classification of mild, moderate and severe damage is shown in Table 17. 1.

Damage	Target Pressure Reduction	Visual Field Changes	Optic Nerve Damage
Early/Mild	20-30%	• MD <-5 dB AND • < 18 points below 5% • < 10 pts below 1% on PSD • No central points < 20 dB	• Thinning of superior or inferior rim • No notches or wedge defects
Moderate	30-40%	• MD -5 to -10 dB OR • 18-36 points below 5% level OR • 10-20 below 1% on PSD OR • Central points between 10-20 dB in one hemifield	• Early notch in superior OR inferior • OR relative thinning in both superior or inferior rim • Early wedge
Advanced	40-50%	• MD > -10 dB OR • >36 points below 5% OR • >20 points below 1% on PSD OR • <20 dB in both hemifields centrally OR • Any point in central 5 degrees < 10 dB	• Early notch of superior and inferior or complete notch • Complete wedge

Table 17.1: *Indicators of mild, moderate and severe damage*

LOWERING THE IOP

Medications used for the long-term management of glaucoma fall into five categories as follows:

- Prostaglandins
- Beta-Adrenergic Blockers
- Alpha Adrenergics
- Carbonic Anhydrase Inhibitors
- Miotics

It is usual to commence therapy with a single topical medication (monotherapy). The addition of further medications to the regimen produces a combination therapeutic approach to lowering the IOP.

Lack of success to control IOP with medications often results in use of laser trabeculoplasty. The main considerations for the laser procedure are:

- Age – Success rate declines with time and may need adjunctive therapy in as little as two years
- Certain secondary glaucomas (PDS, Pseudo-exfoliation)

Filtering surgery is a procedure that is employed if other techniques for treating glaucoma are less than successful. However, there are a number of risks associated with filtration surgery e.g. often cataract surgery is required within five years.

Figure 17.2: *Topical medications for lowering IOP*

WHERE TO START?

Generally a monotherapy technique is employed unless the IOP is very high or the nerve damage is severe. The monotherapy selected is based on efficacy, safety, and tolerability of the drug and the patient's status and needs. A proven sequence of therapy is as follows:

- Prostaglandins
  - Best systemic safety profile
  - Change within group before adding another medication if not reaching the target pressure. Studies suggest that switching within the class of prostaglandins can give you up to 3 mmHg further reduction in IOP.
- Beta Blockers
  - Sometimes used as a second line therapy or utilized in cases of cost issues.

Additives (if not reaching target pressure) are as follows:

- Alpha Agonists
  - In normal tension glaucoma, some are using this as a first line therapy for neuro-protection
- Topical Carbonic Anhydrase Inhibitors (CAI)
- Then:
  - Combination drops: Combigan, Cosopt or Simbrinza

Disclaimer

This text serves simply as a general guide to medications. Not all the medications, side effects and contraindications related to the treatment of glaucoma are discussed, only the most common and relevant. New medications are constantly being developed. Before a clinician commences a patient on a course of medication, it is advised that the product information is carefully read and an further expert opinion sought if required.

Note: Further pharmacological information on the below drugs can be found the Ocular Pharmacology chapter *Glaucoma Treatment.*

PROSTAGLANDINS

Prostaglandin medications are usually the first-line agent for glaucoma management.

They belong to the group of eicosanoids and are derived from arachidonic acid which is a polyunsaturated fatty acid. Some of their features are as follows:

- Prostaglandins used are prodrug of prostaglandin F2α
  - Selective for F2α prostaglandin (FP) prostanoid receptor
- Produced as mediators along the inflammation pathway (Figure 17.3)

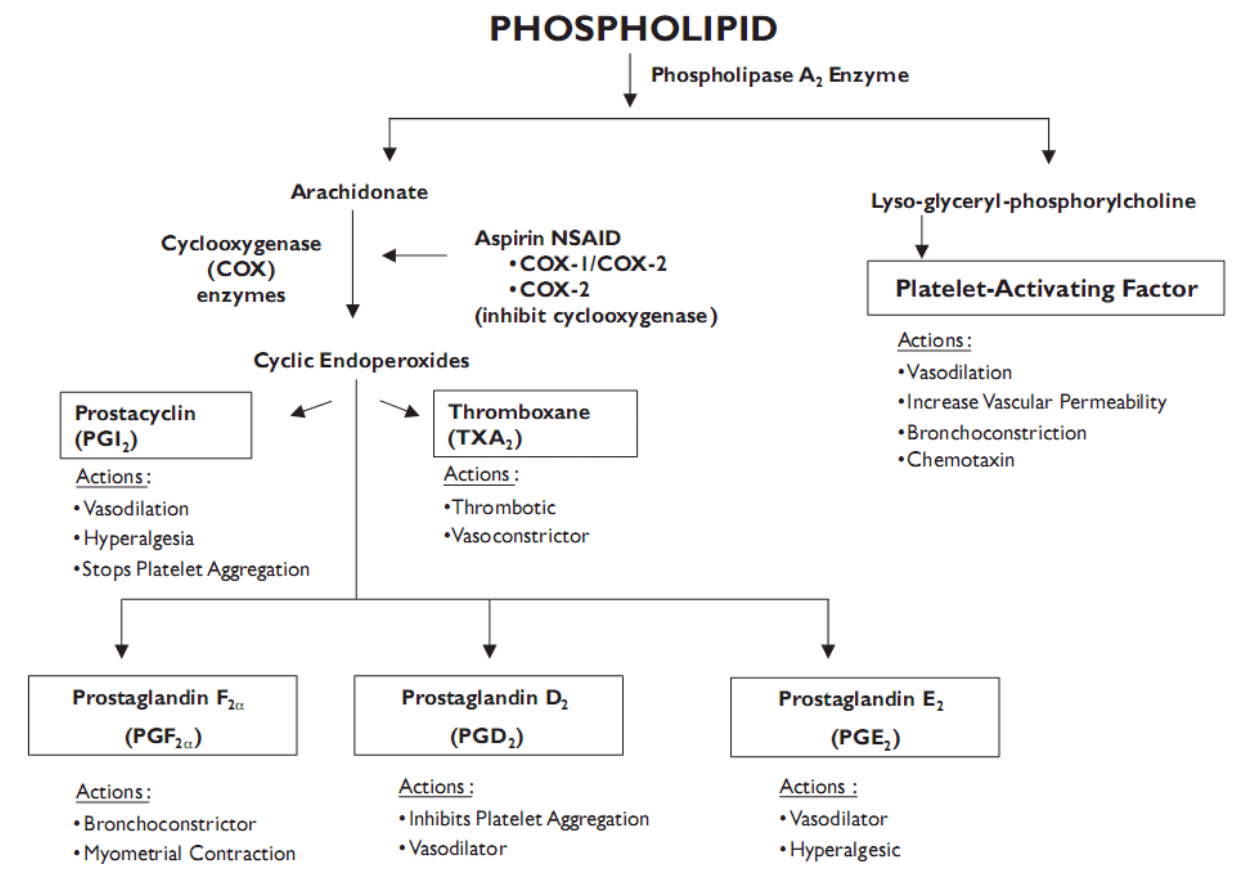

Figure 17.3: *The inflammatory pathway*

http://www.anesthesiaprogress.com/identifying-and-treating-patients-at-risk-the-inflammatory-response.html

MECHANISM OF PROSTAGLANDIN (PG) ACTION

Prostaglandins (Table 17. 2) generally work by relaxing muscles in the eye's interior structure to allow better outflow of fluids, thus reducing buildup of IOP. They increase trabecular outflow even though there is a non-clinically significant increase in the production of aqueous.

There are many PG receptors found in the cells within the trabecular meshwork, ciliary muscle and sclera.

The proposed mechanism of action of PG is as follows:

- Regulation of matrix metalloproteinases and remodeling of extracellular meshwork i.e. loosening of intracellular spaces within ciliary body.

Company	Brand Name	Generic Name
Pfizer Inc.	Xalatan ™	Latanoprost 0.005%
Alcon, Inc	Travatan™, Travatan™ Z	Travoprost 0.004%
Allergan Inc.	Lumigan™	Bimatoprost 0.03%
Novartis	Rescula ™	Unoprostone Isopropyl 0.15%
Merck	Zioptan ™	Trafluprost 0.0015%

Table 17.2: *List of Prostaglandin Analogs*

XALATAN (0.005%)

The main features of Xalatan are as follows:

- Also known as latanoprost (Figure 17.4)
- One drop used in the evening
- Preserved with BAK
- Average IOP lowering ranges from 27%-35%
  - Scandinavian Study (Rowe, 2007): night-time administration of latanoprost provided lower average IOPs than when administered in the morning
    - evening reduced by 35%, morning reduced by 31%
- 5-year data shows minimum diurnal and longitudinal drift in IOP control
- Was the first prostaglandin to achieve FDA approval as a first line therapy
- Additive with other anti-glaucoma medications (except pilocarpine)
- At least as equipotent to Timolol (was the gold standard)
  - Studies suggest that latanoprost is more effective and better tolerated

Figure 17.4: *Xalatan bottle and packaging*

SIDE EFFECTS OF LATANOPROST

The side effects of latanoprost include the following:

- Punctate keratopathy
- Foreign body sensation
- Blurred vision

- Eye pain
- Conjunctival hyperemia
- Iris colour change (Figure 17.5)
- Increased lash length
- Periorbital pigmentation and fat atrophy

Figure 17.5: *Which eye is on latanoprost 0.005%?*

GENERIC LATANOPROST

- Latanoprost 0.005% became generic recently
  - Only prostaglandin that is generic
- Much more cost effective
- Is branded latanoprost 0.005% equivalent to generic latanoprost?
- Bio-equivalence for ophthalmic drops is different from other medications
  - To be bio-equivalent:
    - Same active ingredient (within 85% - 125 % range in concentration)
    - Based on bioavailability principles of rate and extent of absorption
      - Easier for systemic drugs than ophthalmic drugs because we cannot measure the concentration in the blood to compare
- There are major differences in the manufacture of generic products
  - Bottles differ in size, composition, dropper tip, drop size
  - Inactive ingredients can vary
  - Differences in viscosity enhancing agents, preservatives, pH, osmolarity and buffers
  - Variations in pharmacokinetics e.g. solubility, ocular penetration and metabolism

TRAVATAN

The main features of Travatan are as follows:

- Also known as travoprost 0.004%
- One drop in the evening
- Same efficacy as latanoprost (27-35%)
- Preserved with benzalkonium chloride (BAK)
- May have greater affinity for the prostanoid prostaglandin F (FP) receptor than latanoprost
- Comparison between latanoprost 0.005% qd and Timolol 0.5% bid (Figure 17.6)

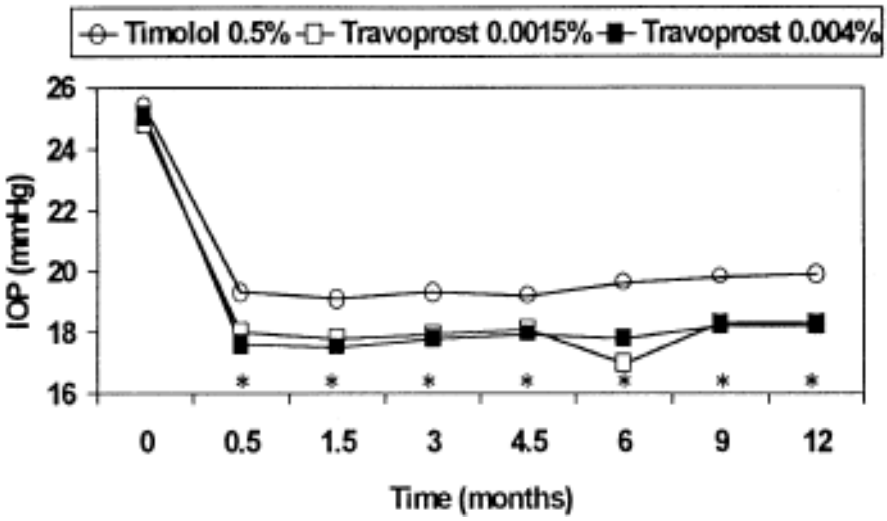

Figure 17.6: *Comparison of three glaucoma medications*
Netland PA, Landry T, Sullivan EK, et al: Travoprost compared with latanoprost and timolol in patients with open-angle glaucoma or ocular hypertension. Am J Ophthalmol 2001; 132:472.

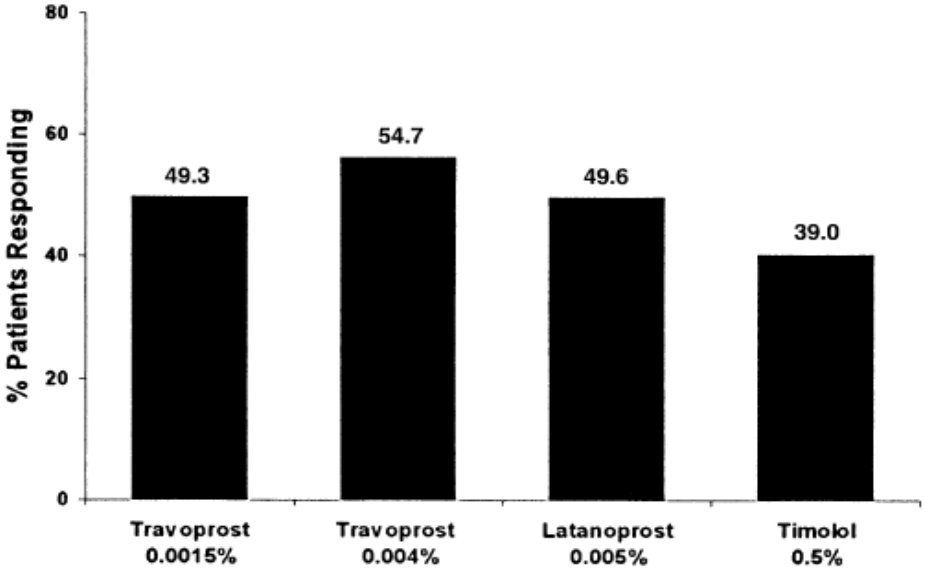

Figure 17.7: *Statistically significant difference in patient response (i.e. ability to lower IOP by 30%)*
Netland PA, Landry T, Sullivan EK, et al: Travoprost compared with latanoprost and timolol in patients with open-angle glaucoma or ocular hypertension. Am J Ophthalmol 2001; 132:472.

Side effect	Travoprost 0.004%	Timolol 0.5%	latanoprost 0.005%
Hyperemia	49.5	14.0	27.6
Pain	8.0	1.5	3.6
Discomfort	7.5	7.5	2.6
Pruritis	7.5	2.0	6.1
Foreign Body Sensation	7.0	1.0	3.1
Cataract	7.0	3.5	3.1
Dry Eye	4.5	1.5	1.0
Blepharitis	3.5	0.5	3.6
Iris Discoloration	3.0	0	5.1

Table 17.3: *Comparison of Ocular Adverse Events Travoprost 0.004% vs. Timolol 0.5% vs. latanoprost 0.005%*

TRAVATAN-Z

This medication has the same formulation as Travatan but is BAK-free to reduce ocular surface symptoms.

Some of the features of Travatan-Z (Figure 17.8) are as follows:

- *SofZia*
  - Preservative containing selective concentrations of borate, zinc and sorbital
  - Upon contact with tear film – the buffered preservative system becomes inactive
- Studies show equivalency of action to Travatan with BAK (Figure 17.9) and an improvement in ocular surface disease symptoms (Figure 17.10)
  - No statistically significant difference between ocular toxicity with Travatan-Z and preservative free artificial tears

Figure 17.8: *Travatan-Z bottle and packaging*

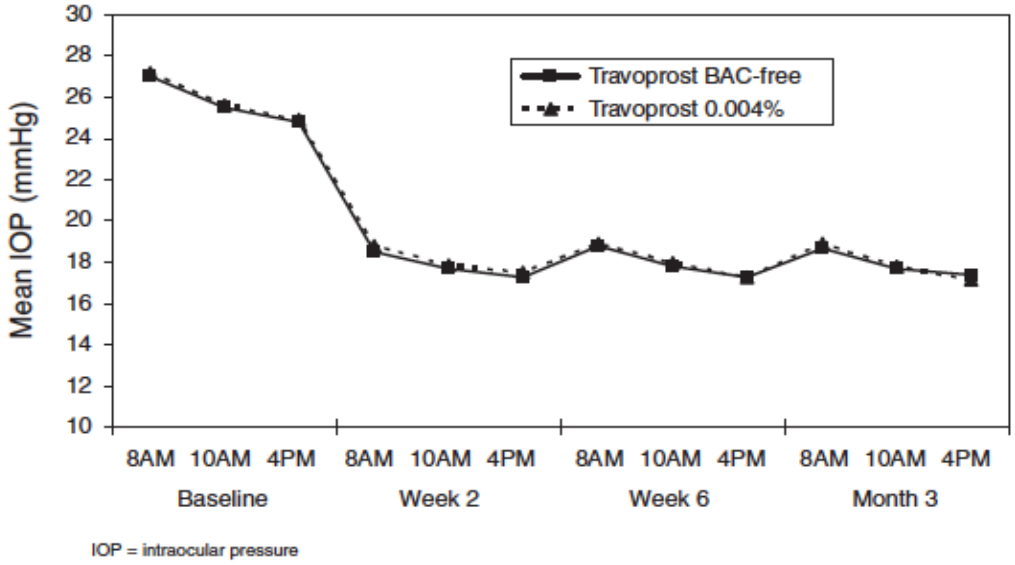

Figure 17.9: *Equivalence in performance*

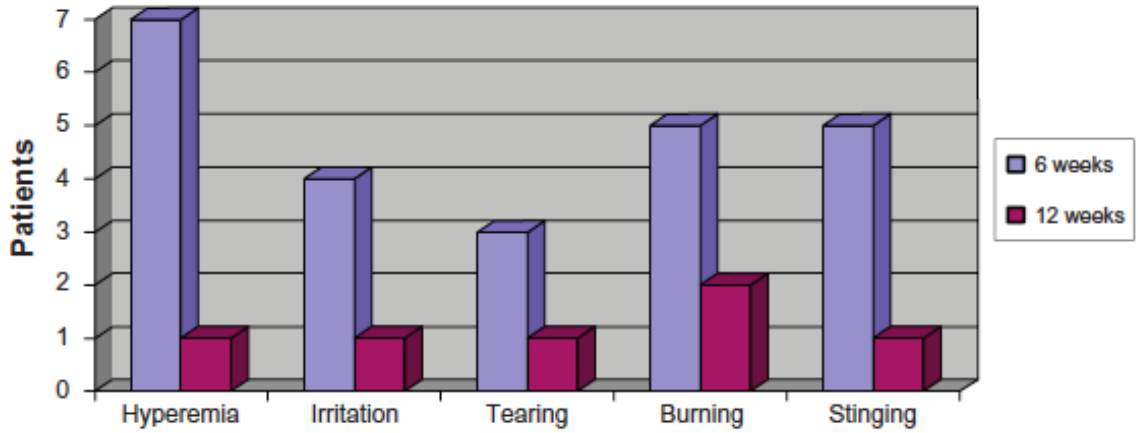

Figure 17.10: *Reduction in symptoms*

LUMIGAN

The main features of Lumigan (Figure 17.11) are as follows:

- Also known as Bimatoprost 0.01% or 0.03%)
- Available since 2001
- One drop in the evening
- Technically a prostamide
  - Has an ethyl amide
  - Mechanism of action to FP receptor is slightly different although the mechanism is unclear
  - May work through an uncharacterized specific prostamide receptor
  - Works to decrease IOP by conventional trabecular and uveoscleral pathway (more conventional pathway than other prostaglandins)
- IOP lowering effect is greater than Timolol but similar to latanoprost 0.005% (Figure 17.12)

- Non-responders to latanoprost may respond to Bimatoprost
- Side effect profile tends to be worse than latanoprost 0.005%
  - More hyperemia
- The 0.03% strength was discontinued in the USA in 2012

Figure 17.11: *Lumigan bottle and packaging*

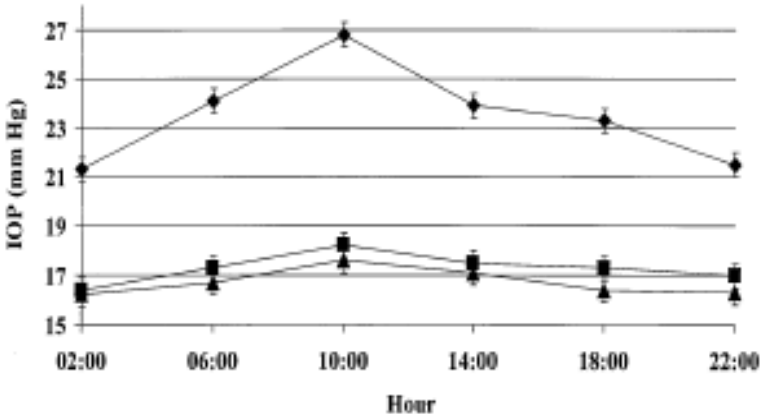

Figure 1. Comparison of intraocular pressure (IOP) (standard error) at baseline (◆) versus latanoprost (■) and bimatoprost (▲) for the diurnal curve.

Figure 17.12: *Comparison of IOP lowering with latanoprost and Bimatoprost*

Table 2. Adverse Events

Event	Latanoprost	Bimatoprost	P Value
Conjunctival hyperemia	6	15	0.004
Stinging/burning on instillation	8	5	0.45
Itching	4	3	1.00
Dry eye	3	3	0.68
Punctate epitheliopathy	3	2	0.48
Foreign body sensation	2	2	0.62
Watering	2	1	1.00
Lid erythema/dermatitis	0	3	0.25
Headache	2	0	0.50
Change in eyelid color	0	2	0.50
Dry mouth	0	1	1.00

n = 42 patients.

Konstas AG, Katsimbris JM, Lallos N, et al: latanoprost 0.005% versus bimatoprost 0.03% in primary open-angle glaucoma patients. Ophthalmology 2005; 112:262–266.

Table 17.4: *Comparison of adverse events with latanoprost and Bimatoprost*

SIDE EFFECTS WITH BIMATOPROST 0.03%

The main side effects with Lumigan are as follows:

- Ocular irritation
- Iritis
- Cystoid macular edema
- Skin and conjunctival hyperemia
- Eyelash growth
- Hyperpigmentation of the skin (reversible)

Lumigan RC

Also known as Bimatoprost 0.01%

- Developed for improved tolerability
- Found similar IOP lowering in comparison studies to bimatoprost 0.03% (Figure 17.13)
- *BAK* at 0.2 mg/mL (0.02%) is higher than Lumigan (0.05mg/mL) or 0.005%

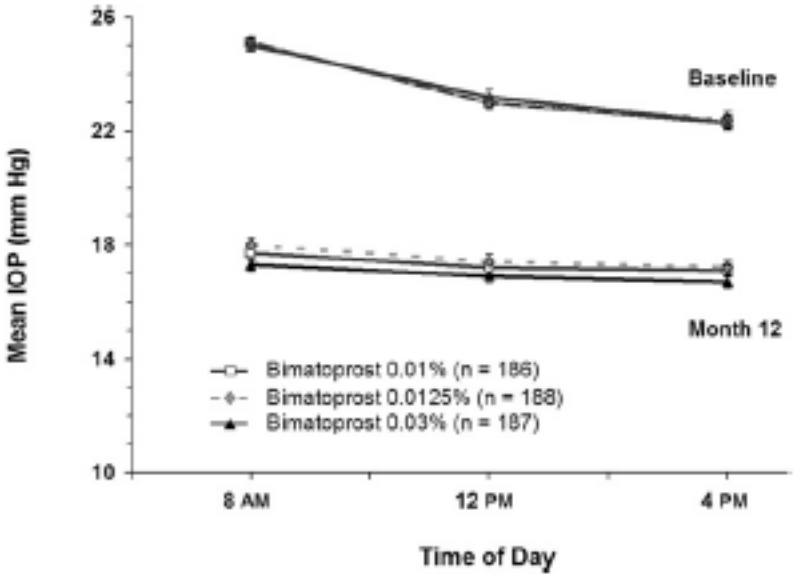

Figure 17.13: *Similar IOP lowering with different concentrations*

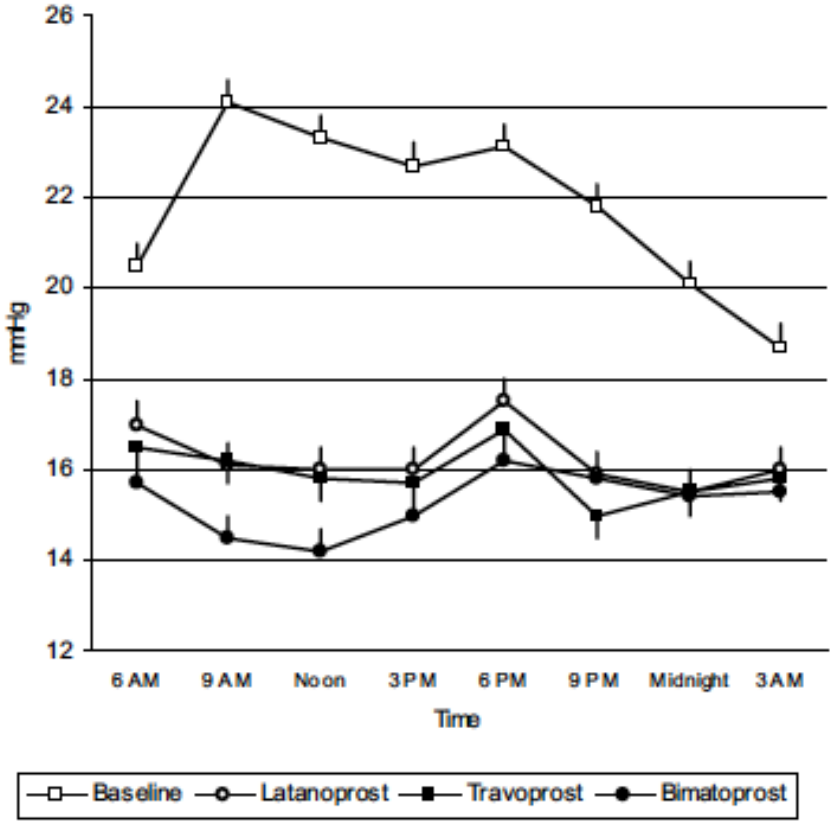

Figure 17.14: *Comparison of IOP lowering with latanoprost, Travoprost, and Bimatoprost*
Orzalesi N, Rossetti L, Bottoli A, Fogagnolo P: Comparison of the effects of latanoprost, travoprost, and bimatoprost on circadian intraocular pressure in patients with glaucoma or ocular hypertension. Ophthalmology 2006; 113:239–246.

UNOPROSTONE 0.15%

The main features of Unoprostone are as follows:

- Also known as Rescula
- Twice daily dosing (bid)
- Prostaglandin prodrug – acts by a different mechanism
- Affinity for FP receptor has been shown to be 100-fold less than latanoprost

Figure 17.17: *Packaging for Rescula*

TAFLUPROST 0.0015%

The main features of Tafluprost are as follows:

- Also known as Zioptan
- One drop in the evening
- First preservative-free prostaglandin
- Similar efficacy
- Superior safety profile and improved quality of life
- Strong consideration for severe ocular surface disease patients

Available in Japan, North America and several European countries

Figure 17.15: *Packaging for Zioptan*

SUMMARY OF PROSTAGLANDINS

- Superior once per day dosing
- Shown to blunt the IOP morning spike
- If not getting desired IOP response, switch within class of prostaglandins first before adding on another medication
- Additive to most other ocular hypotensive medications (except pilocarpine)
- Because they have a different mechanism of action, they have a good safety profile with little/no systemic adverse reactions

CONTRAINDICATIONS TO PROSTAGLANDINS

- Is an inflammatory mediator so caution in patients with ocular inflammation
- Topical PGs have been associated with cystoid macular edema (CME) so caution should be taken in patients at higher risk of developing CME

BETA-ADRENERGIC BLOCKERS

Historically, beta-blockers were the first line therapy for ocular hypotensive anti-glaucoma medication. They are prescribed now as an adjunct to, or in combination with, prostaglandins.

The main features of beta-blockers are as follows:

- Once or twice a day dosing (except Timoptic-XE which is once daily dosing in the morning)
- Mechanism of action
  - Specific mechanism of action is the blockade of beta receptors in the ciliary body thereby reducing intraocular pressure by decreasing aqueous humor production (Figure 17.19)
    - Shown to decrease aqueous production by around 20-30%
  - No change in aqueous outflow
  - Inhibition of cyclic adenosine monophosphate (cAMP) production in the ciliary body
- 'Cons' of B-Blockers: dosing schedule and side effects
  - Physiological functions attributed to sympathetic nervous system activity

Company	Brand Name	Generic Name
Akorn Ophthalmics	Timolol Maleate USP	Timolol Maleate 0.5%
Johnson & Johnson	Betimol ™	Timolol hemihydrate 0.25%, 0.5%
Merck & Co. Inc.	Timoptic-XE ™	Timolol maleate ophthalmic gel forming solution 0.25%, 0.5%
Allergan Inc.	Betagan ™	Levobunolol HCl ophthalmic solution, USP 0.25%, 0.5%
Bausch & Lomb Inc.	OptiPranolol ™	Metipranolol 0.3%
CIBA Vision	Ocupress™	Carteolol 1.0%
Alcon, Inc.	Betoptic ™ S	Betaxolol HCl 0.25%, 0.5% *cardioselective – only one
ISTA Pharmaceuticals	Isatol ™	Timolol Maleate Ophthalmic Solution 0.5%

Table 17.5: *List of Beta blockers*

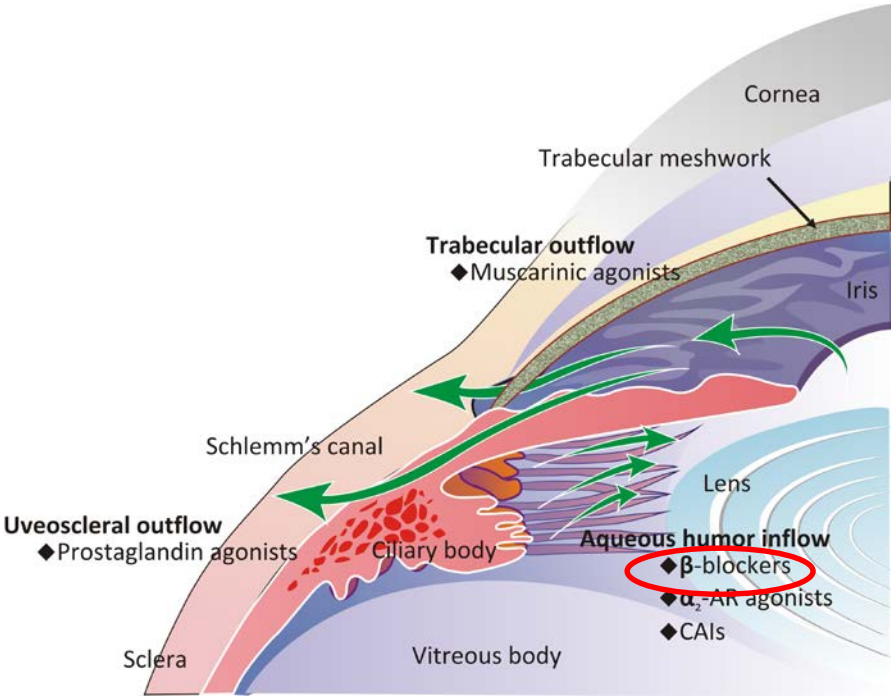

Figure 17.16: *Action of beta-blockers*

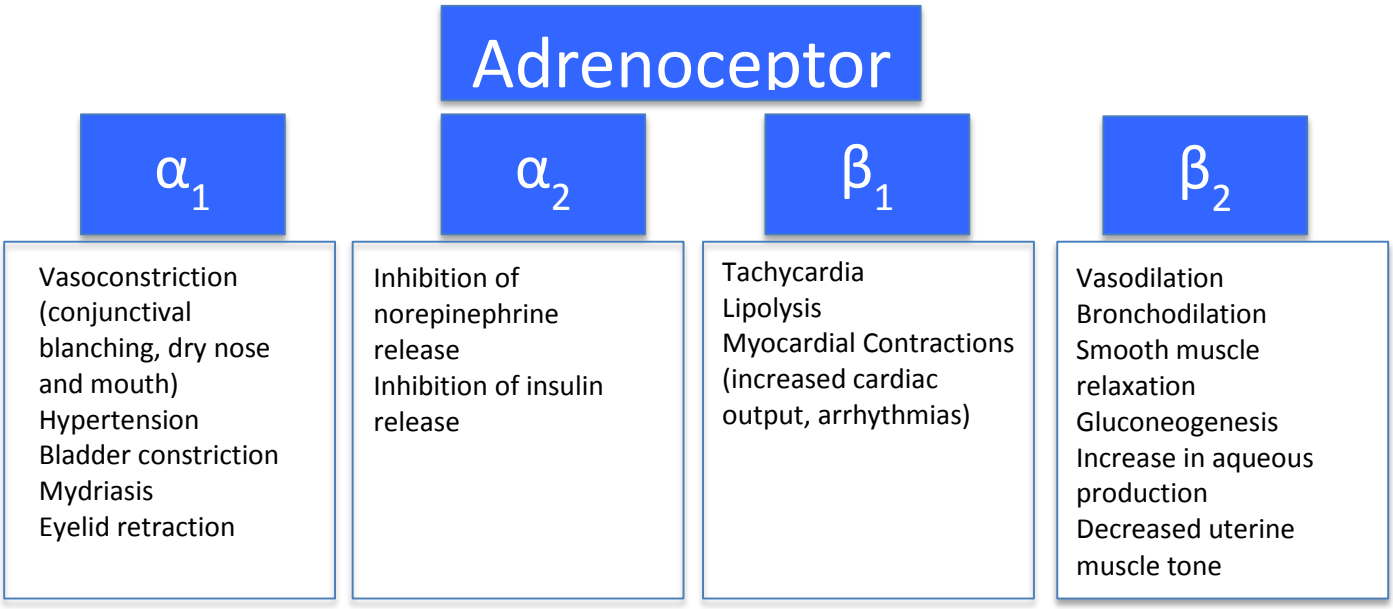

Figure 17.20: *Adrenoceptors (NE = norepinephrine)*

BETA ADRENERGIC BLOCKERS: NON-SELECTIVE

Timolol 0.25%/0.5%, Levobunolol 0.25%/0.5%, Metipranolol 0.3%

The main features of these beta-blockers are as follows:

- Gold standard that all other medications are measured against for FDA approval
- IOP lowering range 21-32% (average 25%)
  - IOP lowering effect is similar for all non-selective beta blockers
- Once or twice daily dosing
  - Usually start with once a day dosing in the morning
- Can cause a rapid decline in IOP after 1 hour of topical application
  - Shown to maintain 30-35% reduction during first 24 hour period with weak decrease at 3-4 hours
- Does not work well overnight
  - Systemic system already decreased
  - Aqueous production is minimal overnight
- Caution on patients who are already on a systemic beta-blocker
- Tachyphylaxis has been shown to start after only 3 months of treatment
  - Recommend close monitoring of patients on this as monotherapy within the first year
- Main concerns is the effect on systemic conditions
  - Commonly develop systemic side effects even though found in low levels in the serum

CONTRAINDICATIONS

- **Pulmonary Conditions:** bronchospasm, bronchorrhea, apnea, asthma, severe chronic obstructive pulmonary disease (COPD)
- **Cardiovascular disease:** reduces the heart rate and can worsen congestive heart failure

Other important systemic side effects include:

- Affects lipid profile: decreases HDL and increases triglycerides
- Central nervous system: disorientation, memory impairment, anxiety, depression, fatigue, emotional instability, hallucinations, decreased libido

Non-preserved

Expensive – longer half life

Gel formulation: increase contact time, decrease systemic side effects

Figure 17.17: *Many faces of Timolol*

LEVOBUNOLOL AND METIPRANOLOL

Similar efficacy to Timolol
Greater effect on heart rate

Similar efficacy to timolol
Available in Europe

Figure 17.18: *Betagan and OptiPranolol bottles and packaging*

Common ocular adverse effects of beta-blockers include the following:

- Burning
- Itching
- Blurred vision
- Foreign body sensation
- Eyelid swelling
- Eyelid erythema
- Conjunctiva erythema
- Uveitis (one study using Metipranolol)

Dosing considerations for beta-blockers include the following:

- Start every morning with 0.25%
  - Evidence suggests this is enough
- To increase effect:
  - Change to 0.5%
  - Switch to bid dosing
    - Do not dose at night: use in the morning and afternoon

BETA ADRENERGIC BLOCKERS: PARTIALLY-SELECTIVE

Carteolol 1.0%

The main features of Carteolol are as follows:

- Also known as Ocupress (Figure 17.23)
- Similar efficacy to Timolol
- Non-selective with partial beta-agonist activity
  - Intrinsic sympathomimetic activity
  - Better for cholesterol and triglycerides
- Still contraindicated for patients with severe cardiovascular disease and pulmonary disease

Figure 17.19: *Ocupress packaging*

BETA ADRENERGIC BLOCKERS: SELECTIVE BETA-1 BLOCKER

Betaxolol 0.25%/0.5%

- Also known as Betoptic or Betoptic S
- More affinity for cardiac beta-1 receptors than pulmonary beta-2 receptors
- Strictly bid dosing
- Similar efficacy to Timolol
  - However, studies suggest lowering is 1-2 mmHg less than with Timolol
  - Because of its selectivity it is not as potent
- Contraindicated in patients with severe pulmonary dysfunction and cardiovascular disease
  - Still decreases heart rate

ALPHA ADRENERGICS

The mechanism of action of alpha adrenergic compounds is to stimulate alpha receptors in the ciliary body, iris, and trabecular meshwork.

- Primarily inhibit aqueous production
- Small role in stimulating uveoscleral outflow
- Possible neuro-protective properties – studies done in rats, not humans

The main features of these compounds are as follows:

- IOP lowering of 20-25%
- TID dosing if monotherapy; BID dosing if adjunctive

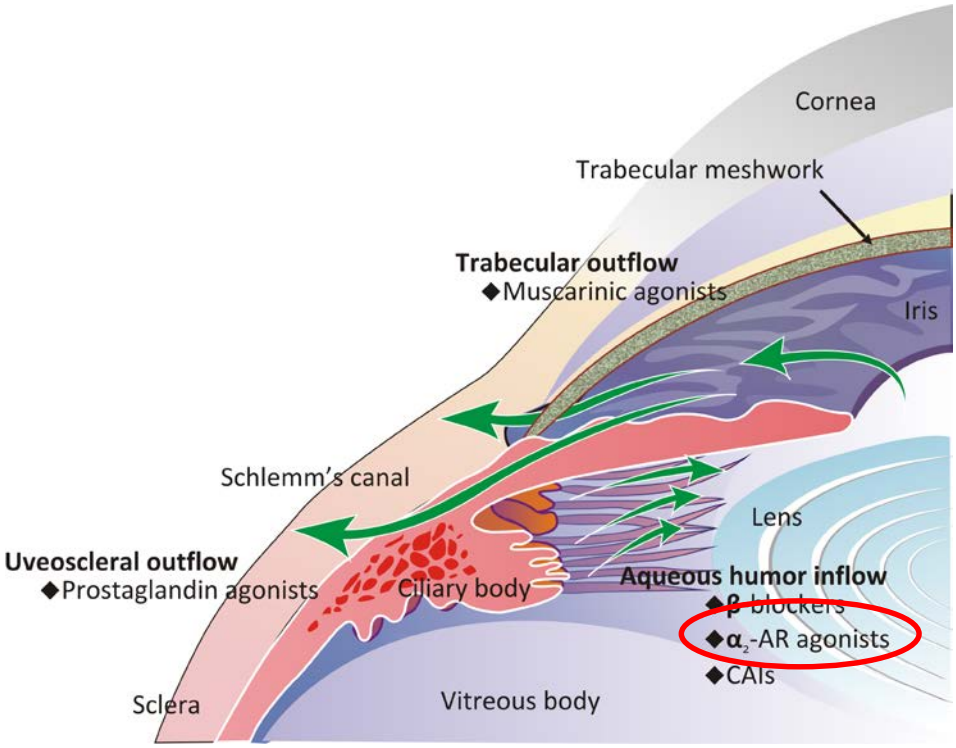

Figure 17.20: *Mode of action of alpha agonists*

ALPHA AGONISTS

- Epinephrine hydrochloride introduced in late 1950s – naturally occurring sympathomimetic agonist with activity at both alpha and beta receptors – unstable
- Dipivefrin – prodrug of epinephrine
- Caused improved outflow (and also possible increase in production because of stimulation of beta receptors)
- Many side effects including:
  - Pallor
  - Perspiration
  - Syncope
  - Elevation of pulse and blood pressure

Clinically relevant ocular drugs are as follows:

Company	Brand Name	Generic Name
Alcon, Inc.	Iopidine ™	Apraclonidine HCl 0.5%, 1.0%
Allergan Inc.	Alphagan ™ P	Brimonidine tartrate 0.1%, 0.15%, 0.2%

Table 17.6: *Alpha agonist compounds*

Apraclonidine (0.5% and 1.0%)

- Also known as Iopidine
- Relatively selective for alpha-2 receptors but still stimulates alpha-1
- Approximately a 20% reduction in IOP
  - Although a 30% reduction is initially often achieved and therefore used pre/post operatively prior to intraocular surgery
- Was associated with tolerance problems in 25% of patients and allergy in greater than 25%, therefore no longer used in chronic treatment cases
- Used in laser pre and post ops such as LPI and SLT
- Tachyphylaxis after 4-12 weeks may occur

ALPHA ADRENERGIC: ALPHA-2 SELECTIVE AGENTS

Brimonidine 0.2%/0.15%/0.1%

The main features of Brimonidine are as follows:

- Also known as Alphagan-P (0.1%)
- Purite preservative to decrease incidence of allergy (which was commonly seen in the 0.2% concentration with BAK preservative before this medication came out) and to improve comfort level
- More selective for alpha-2 adrenoceptor compared to Apraclonidine
  - 25-32 fold more sensitive
- Less prone to hypersensitivity than Apraclonidine – but still has a 10% incidence
- Equipotent to timolol, but improved safety profile
- Caution:
  - Patients with cardiovascular disease, liver or renal failure
    - Little effect seen in the literature
  - Patients taking CNS and monoamine oxidase (MAO) inhibitors (anti-depressants)
    - May cause drowsiness

- Ocular Side Effects:
  - Dry nose and mouth (Apraclonidine)
  - Allergic conjunctivitis
  - Hyperemia (32% at higher concentrations)
  - Itching
  - Less commonly:
    - Burning sensation
    - Blepharitis
    - Conjunctival hemorrhage, edema, redness
    - Epiphora
    - Irritation
    - Foreign body sensation
    - Visual disturbance

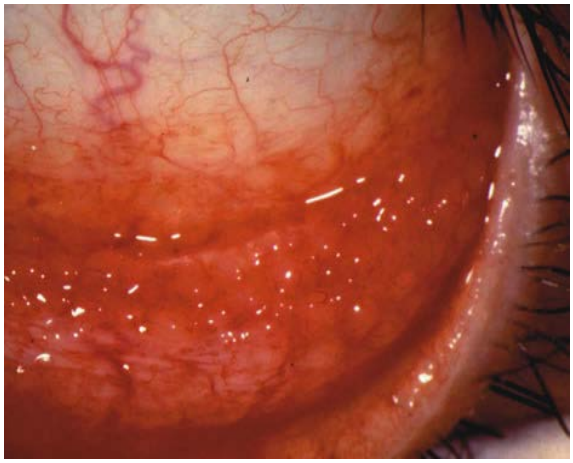

Figure 17.21: *Alpha adrenergic hypersensitivity reaction*

CARBONIC ANHYDRASE INHIBITORS

Carbonic anhydrase inhibitor (CAI) drugs work by decreasing the rate of aqueous humor production. Their specific mechanism of action is inhibition of the enzyme carbonic anhydrase. This decreases aqueous production in the ciliary body.

Discovery of excess of bicarbonate in the aqueous humor plus carbonic anhydrase activity in the ciliary body led to the introduction of acetazolamide (oral) for treatment of glaucoma.

Some of the features of CAI drugs are as follows:

- Immediate and significant IOP response with oral acetazolamide
  - Systemic side effects were significant
- Carbonic Anhydrase Inhibitors are usually used in combination with other anti-glaucoma eye drops and not used alone
- This classification of drug is also used in oral form (pills)
  - Dosage for topical drops: 2-3 times a day
  - Dosage for oral: 250 mg to 1 gram per day

Company	Brand Name	Generic Name
Alcon, Inc.	Azopt ™	Brinzolamide ophthalmic suspension 1.0% *drop form
Merck & Co. Inc.	Trusopt ™	Dorzolamide HCl 2% *drop form
Duramed Inc.	Diamox sequels ™	Acetazolamide 500mg *oral form
	Diamox	Acetazolamide 125 or 250 mg tablets *oral form
Akorn Ophthalmics	GlaucTabs (Neptazane)	Methazolamide 25 or 50mg *oral form

Table 17.7: *List of Carbonic Anhydrase Inhibitors*

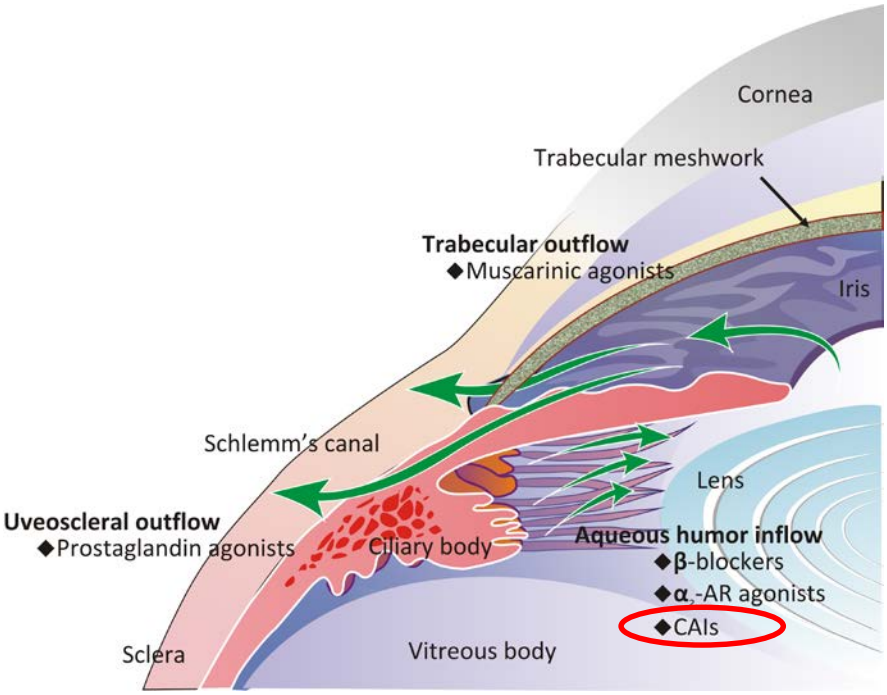

Figure 17.22: *Action of Carbonic Anhydrase Inhibitors*

ORAL CAI

The main features of oral CAI drugs are as follows:

- Primarily used for short term control of IOP
- This classification of drug is also used in oral form
  - Acetazolamide (Diamox) 250 mg q4-6 hours
- Short acting 35% reduction in IOP
- Contraindicated in sulfa allergies and renal or advanced pulmonary problems (due to acidosis)
- CAI drugs have many side effects including:
  - Tingling
  - Malaise Symptom Complex (fatigue, depression, weight loss, decreased libido)
  - Gastric irritation (take with food)

- Altered kidney function and renal stones (need to check for this before starting treatment)
- Hypokalemia
- Psychosis/depression/confusion
- Rare but important is aplastic anemia

TOPICAL CAI

The main features of topical CAI drugs are as follows:

- IOP lowering effect of approximately 20%
- Much more commonly used as an adjunctive therapy
- TID dosing if monotherapy, BID dosing if adjunctive
- Mechanism of action:
  - Decrease in aqueous production by inhibiting passage of carbonic anhydrase into aqueous chamber

Dorzolamide HCl 2%

- Also known as Trusopt
- 1-2 mm Hg less IOP lowering than timolol
- Very effective in combination with timolol
- Contraindicated in patients with sulfa allergy
- Ocular side effects include:
  - 33% incidence of stinging
  - Punctate keratitis
  - Bitter taste
  - Allergic reactions

Brinzolamide 1%

- Also known as Azopt
- Suspension that allows for more buffering to a neutral pH than dorzolamide
- Also very effective in combination with timolol but with less stinging
- Contraindicated in patients with sulfa-allergies
- Mild topical and systemic side effects include:
  - Keratitis
  - Corneal edema

MIOTICS

The first agents used to lower IOP were miotic drugs (Table 17.8). Now they are used only in small amounts, generally reserved for acute angle closure glaucoma.

The main features of miotics are as follows:

- IOP reduction of approximately 25%
- Dosing requirements up to qid
- Mechanism of Action:
  - Parasympathomimetic, direct-acting and indirect-acting cholinergics
  - Cause the pupil to constrict, which assists in opening the narrowed or blocked angle where drainage occurs
  - Reduce resistance to aqueous humor trabecular meshwork outflow thereby increasing outflow
  - Specific mechanism of action for direct-acting cholinergics is to stimulate muscarinic receptors and indirect-acting cholinergics is to block acetyl-cholinesterase

There are many adverse reactions to miotics including the following:

- Blurred vision
- Difficulty with night vision
- Brow ache
- Accommodative spasm
- Burning

Company	Brand Name	Generic Name
Alcon, Inc.	Isopto ™ Carpine	Pilocarpine HCl 1.0%, 2.0%, 4.0%, 6.0%, 8.0% *direct-acting
Alcon, Inc.	Isopto ™ Carbochol	Carbachol 0.75%, 1.5%, 3% *direct/indirect-acting
Alcon, Inc.	Pilopine HS ™ Gel	Pilocarpine HCl gel 4% *direct acting
Bausch & Lomb Inc.	Pilocarpine HCl Ophthalmic Solution USP	Pilocarpine HCl ophthalmic solution USP 0.5%, 1.0%, 2.0%, 3.0%, 4.0%, 6.0% *direct-acting

Table 17.8: *Available topical miotic formulations*

COMBINATION PRODUCTS

Study results show that half of individuals with glaucoma require more than one type of medication to control IOP. For this reason, ophthalmic pharmaceutical companies have produced combination eye drops that can include two different anti-glaucoma medicines in the same bottle (Table 17. 9).

Typically these combined medications have the additive effect of reducing IOP.

Company	Brand Name	Generic Name
Merck & Co. Inc.	Cosopt ™	Dorzolamide HCl & Timolol Maleate
Pfizer Inc.	Xalacom ™	latanoprost & Timolol Maleate
Allergan Inc.	Combigan ™	Brimonidine Tartrate & Timolol Maleate
Alcon, Inc.	Duo Trav ™	Travoprost & Timolol Maleate
Alcon, Inc.	Simbrinza ™	Brinzolamide/brimonidine tartrate

Table 17.9: *Combination glaucoma medications*

Cosopt
(timolol 0.5% + dorzolamide 2%)

Xalacom
(timolol 0.5% + latanoprost 0.005%)

Combigan
(timolol 0.5% + brimonidine 0.2%)

DUOTRAV
(timolol 0.5% + travaprost 0.004%)

Azarga
(timolol 0.5% + brinzolamide 1%)

Figure 17.23: *Combination glaucoma medication bottles and packaging*

NEW COMBINATION DRUG

- SIMBRINZA™ (brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2% is a fixed combination of a carbonic anhydrase inhibitor and an alpha 2 adrenergic receptor agonist
- First combo drop without a beta-blocker

Figure 17.24: *Simbrinza bottle and packaging*

COMBINATION PRODUCT INDICATIONS

Rarely initiate therapy with a combination medication. Try one of the single ingredient drugs first.

Add a second drug via a combination product if initial single drug failed to meet target pressure but there was a documented positive response that the second drop brought the patient closer to the target goal. Try the other ingredient drug as a therapeutic trial (if the initial drug selected proves inadequate in achieving target pressure range).

ADHERENCE AND COMPLIANCE CONSIDERATIONS

Medical management of glaucoma usually commences with topical eye drops. Adherence to the prescribed medication regimen is important in the successful management of glaucoma.

The patient must be able to effectively administer the drops required. However, in cases where the person is unable to administer the eye drops effectively, or when the target IOP cannot be achieved, oral acetazolamide (CAI) may be used. Oral delivery is associated with increased risk of side effects and up to 50% of patients do not tolerate the medication.

Systemic use of beta-blockers is not as effective in lowering IOP as topical medications. The concurrent use of topical and systemic beta-blockers is not recommended.

The main features of adherence to a treatment regimen are as follows:

- Studies suggest noncompliance rates range from 28% to 59%
- Factors that may decrease adherence include:
  - Patient Factors
    - Poor understanding of disease and why they are on medication (perception)
      - Asymptomatic disease
    - Mental status
    - Motivation
    - Other co-morbidities
    - Inability to afford medications
  - Treatment Factors
    - Complexity
      - i.e. the number of other medications they are using
    - Side effects and tolerability
  - Patient-physician relationship
    - Compliance has been shown to improve when patient is satisfied with the doctor
    - Continuity of care
- Ways to improve adherence include:
  - Education
  - Simplify the regimen
  - Instruction sheet on drop application and schedule of when to administer drops
  - Ask questions at follow up appointments

WHEN TO REFER

- Suspicion of any secondary glaucoma (depending on scope of practice)
- Patient is progressing despite maximum medical management
  - No further medical treatment is available, appropriate, or likely to provide a clinically significant lowering of IOP
- You feel uncomfortable managing the patient
  - Keep in mind: goal of glaucoma therapy is to sustain vision-related quality of life and to maintain visual field and structural integrity of the optic nerve
- Suspicion of neurological etiology
- Patient may benefit from laser (SLT/ALT) treatment
  - Poor compliance on medication
- Patient is seeking another opinion or is interested in laser therapy

WHEN TO RE-CHECK AFTER DIAGNOSIS AND INITIATION OF MEDICATION

- **IOP**
  - 1 month for mild
  - 1 week for moderate to severe damage
    - If IOP > target pressure, patient is likely spiking
    - If IOP > target pressure, may need to modify treatment or re-set target pressure

- **Visual Fields**
  - 6 months
  - Then 3-6 months for first 18 months
  - Then yearly – unless suspecting progression of the disease

- **RNFL Assessment (with instrumentation)**
  - Same as visual fields

- **Stereoscopic Optic Nerve Photos**
  - Yearly