Glaucoma Pharmacology A-Z

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Selecting Therapy

- Goals of primary therapy
  - Achieve lowest IOP on monotherapy
  - High response rate—few to no nonresponders
  - Maintain consistent IOP lowering
  - Obtain patient compliance and adherence by meeting their goals and expectations
- Building-block approach to medical therapy
  - Establish the strongest foundation prior to resorting to adjunctive therapy

Prostaglandin analogs

- Lower IOP by enhancing uveoscleral outflow
- They also reduce episcleral venous pressure
- PGAs work by causing up to a 26% reduction in resistance to outflow
- Breaks down collagen in the uveoscleral meshwork
- Create new channels for outflow

PGAs

- QHS dosing
- Long duration of action
- Flatten diurnal curve
- Effective on trough and peak IOP
- No systemic side effects
- Little tachyphylaxis

PGAs 2008

- Bimatoprost (Lumigan)
- Latanoprost (Xalatan)
- Travaprost, Travaprost Z (Travatan, Travatan Z)

Prostaglandin Side Effects

- Conjunctival hyperemia: Severe hyperemia
  - Lumigan 3.5%
  - Travatan 1.5%
  - Xalatan <1%
  - Rescula 1%
- Is this a transient phenomenon?
- Is it an allergic conjunctivitis?
- Is it worth stopping the drop?
Conjunctival hyperemia

- PGAs have an effect on EP receptors which are vasodilators
- The stronger the drug binds to that receptor the more pronounced the vasodilation effect will be.
- Will switching from 1 PGA to another decrease the hyperemia effect?

Prostaglandins

- Oh sure, we know they are good, but just how good are they?
  - Average IOP drop of 34%
  - Improved compliance
  - Excellent safety profiles
- In general, PGAs are the initial therapy of choice.

Prostaglandin Side Effects

- Iris pigmentation
  - Is it reversible?
  - Is it pre-cancerous?
- Xalatan – 6.7% @ 6mths
  - 16% @ 12mths
- Travatan – 3% @ 12 mths
- Lumigan – 1.9% @ 12mths
- Rescula – 1 patient
- SO?

Clinical Comparison Trials of the Once-Daily Lipids

- Evaluation of intra-class differences in efficacy and safety
- Seven published, prospective, randomized, investigator-masked, parallel-group studies
- Trials varied in duration, patient selection and characteristics, and methods of data analysis

Other Prostaglandin side effects

- CME
- Uveitis
- Reactivation of HSK
- Hypertrichosis
- Periorbital skin darkening
- One must take into consideration the benefits of low IOP with the risks of the side effects

Bimatoprost and Travoprost

<table>
<thead>
<tr>
<th></th>
<th>Parrish et al, 2003*</th>
<th>Noecker et al, 2003†</th>
<th>Cantor et al, 2005</th>
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<tbody>
<tr>
<td><strong>Sponsor</strong></td>
<td>Pfizer</td>
<td>Allergan</td>
<td>Allergan</td>
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<tr>
<td><strong>Length</strong></td>
<td>12 weeks</td>
<td>3 months</td>
<td>6 months</td>
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<tr>
<td><strong>Bimatoprost</strong></td>
<td>n = 136</td>
<td>n = 16</td>
<td>n = 76</td>
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<tr>
<td><strong>Travoprost t</strong></td>
<td>n = 138</td>
<td>n = 15</td>
<td>n = 81</td>
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<tr>
<td><strong>Latanoprost</strong></td>
<td>n = 136</td>
<td></td>
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</table>
Baseline mean IOP comparable between groups

<table>
<thead>
<tr>
<th>Time of Day</th>
<th>Mean IOP (mm Hg)</th>
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<tbody>
<tr>
<td>8 AM</td>
<td>Travoprost: 25.5, 23.8, 22.8, 22.0 (mm Hg)</td>
</tr>
<tr>
<td></td>
<td>Bimatoprost: 25.7, 23.8, 22.8, 22.3 (mm Hg)</td>
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<tr>
<td>12 PM</td>
<td>Travoprost: 25.5, 23.8, 22.8, 22.0 (mm Hg)</td>
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<tr>
<td></td>
<td>Bimatoprost: 25.7, 23.8, 22.8, 22.3 (mm Hg)</td>
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<tr>
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<td></td>
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</table>

Both medications were well tolerated

- Most common adverse event: ocular redness
  - 16 patients (20.8%) in the bimatoprost group and 12 patients (14.8%) in the travoprost group ($P = .326$)
- Ocular itching reported for 7.4% of travoprost patients and 2.3% of bimatoprost patients ($P = .278$)
- Treatment-related adverse events leading to patient discontinuations
  - 8 patients in the travoprost group exited early: 4 for lack of efficacy, 2 for ocular redness and lid erythema, 1 for ocular dryness and itching, and 1 for allergic symptoms
  - 2 patients in the bimatoprost group exited early: 1 for blurry vision

- All decrease IOP by increasing uveoscleral outflow
- All are effective at squashing the diurnal curve
- They have either no effect or a positive effect on retinal perfusion
- But does 1 work better than the others?

Bimatoprost and Latanoprost: 6-Month Safety Results

- Most common side effects:
  - Hyperemia (bimatoprost 44.4%; latanoprost 20.6%)
- Similar rates of discontinuation due to AEs
  - Bimatoprost: 4.5% overall; 2.3% for hyperemia
  - Latanoprost: 3.7% overall; 0.0% for hyperemia
- Uveitis: One patient in latanoprost group; no cystoid macular edema

- According to package inserts:
  - Latanoprost – 6.7mm
  - Unoprostone – 3-4mm
  - Bimatoprost – 8.1mm
  - Travaprost – 7.1mm
XLT Study – Parrish, Palmberg, et. al.
(AJO, May 2003, Vol. 135, No.5)
• Multicenter study to compare IOP lowering efficacy of Bimatoprost vs Latanoprost vs Travaprost
• Also compared safety profiles of the 3 drugs
• Conclusions: All 3 drugs were comparable in their ability to lower IOP at all time periods.
  – Latanoprost exhibited greater ocular tolerability

Another way to look at efficacy:
• % of IOP reduction –
  – Latanoprost – 27%
  – Unoprostone – 15%
  – Bimatoprost – 33%
  – Travaprost – 28%
• FYI: Timolol 24%

Look at their failure rate:
• Percent of pxs who didn’t reach their target IOP
  – Latanoprost – 14%
  – Bimatoprost- 6%
  – Travaprost – 8%
• SO?

What is their ability to lower IOP <17mm?
• Latanoprost – 49.5% of pxs
• Bimatoprost – 64%
• Travaprost – 56.3%

What If:
• A patient failed on Xalatan?
• If switched to Lumigan, 57% achieved target IOP
• If switched to Travatan, 45.5% achieved target IOP
• SO?- Are all prostaglandins really created equal?

• Replaced Xalatan w/ Lumigan
• Results:
  – IOP <15mm dropped from 11% to 36%
  – IOP <18mm dropped from 33% to 66%
  – Mean IOP decrease of 3.4mm
Final prostaglandin thoughts

- They are additive to other G drugs but not with each other
- Travatan and Lumigan maintain target IOP 36hrs after instillation and significant IOP drop up to 84 hrs after instillation
- Does one really work better than the others on African-Americans?
- What about BID dosing?

Beta-blocker side effects

- Respiratory-
  - Fatigue, bronchospasm, SOB!
- Cardiac –
  - Lethargy, bradycardia, lower pulse rate
- CNS depression–
  - Impotence, confusion
- But how common are they?

Beta-blockers

- 30 year history of successfully lowering IOP
- Reduces aqueous humor formation
- Adrenergic agonists
- Lowers IOP 22-28%
- Ocularly well tolerated

Beta-blocker side effects

- Cardiac problems
  - Bradycardia
  - Hypotension
  - Exercise intolerance
  - Heart block
- Respiratory problems
  - Bronchospasm
  - Status asthmaticus

Lama study (AJO 11/02)

- Conclusions:
  - ...identifies no scientific studies supporting the development of worsening claudication, depression, hypoglycemia, sexual dysfunction or impaired neuromuscular transmission
  - Recommends careful medical history and checking pulse rate and rhythm
- So?

Beta-blockers

- Timolol maleate – Timoptic, Timoptic XE (1/2, 1/4 %)
- Carteolol – Ocupress 1% (Intrinsic sympathomimetic activity)
- Levobunolol – Betagan ½%
- Timolol hemihydrate – Betimol ¼, ½%
- Istatol ¼,1/2% - QD dosing indication
- Betaxolol ¼% - cardioselective, safer?
Beta-blocker side effects

• CNS
  – Often overlooked
  – ACID
    • Anxiety
    • Confusion
    • Impotence
    • Depression
  – General decreased affect

• Diabetic problems
  – Decreased sense of caloric need due to depressed adrenergic surge

Adrenergic Agonists

• Dual mechanism of action
  1. Reduce aqueous production
  2. Enhance outflow mechanisms

• 22-28% IOP reduction
• Short duration of action
• TID dosage
• Avoid in kids

Beta-blocker side effects

• 22% of pxs have contraindication to or significant side effect from beta-blocker
• Question, query and query some more!
• Be specific
• Remember the dose relationship so:
  – ¼% rather than ½%
  – QD rather than BID
• They are real (may be anecdotal)

Beta-blocker debate

• Are they still useful?
• As initial therapy?
• QD or BID?
• 0.25% or 0.5%?
• Gel or drop?
• Monocular therapy?
• How bad are the side effects really?
• Do systemic beta-blockers affect the efficacy of the drops?
• Tell me something good about beta-blockers!

Mechanism of Action of Brimonidine-PURITE®

• Complements lipids because it decreases aqueous production
• Complements timolol because it increases uveoscleral outflow

Brimonidine Formulation Comparison

<table>
<thead>
<tr>
<th></th>
<th>ALPHAGAN P</th>
<th>ALPHAGON®</th>
</tr>
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<tbody>
<tr>
<td>Concentration of Brimonidine</td>
<td>0.1%</td>
<td>0.15%</td>
</tr>
<tr>
<td>pH</td>
<td>7.7</td>
<td>7.2</td>
</tr>
<tr>
<td>Preservative</td>
<td>PURITE®</td>
<td>BAK</td>
</tr>
<tr>
<td>Viscosity agent</td>
<td>Carboxymethylcellulose</td>
<td>Polyvinyl alcohol</td>
</tr>
<tr>
<td>Electrolytes</td>
<td>Potassium chloride, calcium chloride dihydrate, magnesium chloride hexahydrate</td>
<td>–</td>
</tr>
</tbody>
</table>
### Brimonidine-PURITE® Development Strategy

- Improved formulation
  - Enhance tolerability
  - Maintain efficacy
  - Alternative preservative to BAK
  - Vehicle based on artificial tear technology

### Effect of Brimonidine-PURITE® 0.15% Formulation on Safety

- Ocular surface exposed to 25% less drug with new formulation
  - Less allergy, redness, irritation
- Lower concentration also means fewer systemic effects as less drug enters nasolacrimal duct

### Preservative Composition of Glaucoma Agents

**Products that contain a gentle preservative, such as PURITE®, may pose less risk to the ocular surface.**

<table>
<thead>
<tr>
<th>Product</th>
<th>Company</th>
<th>Preservative Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALPHAGAN®</td>
<td>Allergan, Inc.</td>
<td>.005% PURITE</td>
</tr>
<tr>
<td>BETAGAN®</td>
<td>Allergan, Inc.</td>
<td>.005% BAK</td>
</tr>
<tr>
<td>LUMIGAN®</td>
<td>Allergan, Inc.</td>
<td>.005% BAK</td>
</tr>
<tr>
<td>Cosopt®</td>
<td>Merck &amp; Co., Inc.</td>
<td>.0075% BAK</td>
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<tr>
<td>Trusopt®</td>
<td>Merck &amp; Co., Inc.</td>
<td>.0075% BAK</td>
</tr>
<tr>
<td>Azopt®</td>
<td>Alcon</td>
<td>.01% BAK</td>
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<tr>
<td>Betoptic® S</td>
<td>Alcon</td>
<td>.01% BAK</td>
</tr>
<tr>
<td>Timoptic®</td>
<td>Merck &amp; Co., Inc.</td>
<td>.01% BAK</td>
</tr>
<tr>
<td>Timoptic® XE®</td>
<td>Merck &amp; Co., Inc.</td>
<td>.012% BDD</td>
</tr>
<tr>
<td>Roccalan®</td>
<td>Novartis</td>
<td>.015% BAK</td>
</tr>
<tr>
<td>Travatan®</td>
<td>Allcon</td>
<td>.015% BAK</td>
</tr>
<tr>
<td>Xalatan®</td>
<td>Pharmacia</td>
<td>.02% BAK</td>
</tr>
</tbody>
</table>

BAK: benzalkonium chloride; BDD: benzododecinium bromide

### Benzalkonium Chloride (BAK)

- Most commonly used preservative in glaucoma products
- BAK can accumulate and remain in ocular tissue
  - Has been shown to cause cytotoxic effects on the ocular surface in numerous studies (DeSaint, 2000; Gasset et al, 1974; Noecker, 2004)

### Brimonidine side effects

- 10-20%
  - Hyperemia
  - Allergic conjunctivitis
  - Ocular pruritis
- 5-9%
  - Burning sensation,
  - Conjunctival folliculosis,
  - Ocular allergic reaction,
  - Oral dryness,
  - Visual disturbance

- Do these worsen with time?
- How do you know if the drops are the culprit?

### Alphagan systemic side effects

- Dry mouth (~20%)
- Fatigue (1-2%)
- Drowsiness
- Decreased BP

- This drug can cross blood-brain barrier, esp in older and younger pxs

**References:**
Brimonidine questions
• What is the correct dosage?
• Which of the 3 products should be prescribed?
• Can it be used as stand alone therapy?
• Effect on diurnal curve?

CAI Side Effects
• ***Stinging***
• **Dryness**
• HA
• Bad taste
• Sulfa drug so:
  – Aplastic anemia?
  – Renal stones?
• What about Cosopt?

Carbonic anhydrase inhibitors
• Lower IOP by reducing aqueous production
• Reduce IOP by 16-22%
• Sulfa drugs!!
• Dosage question – BID or TID?
• Are they useful as stand alone drugs?

Oral CAI side effects
• Paresthesia
• Depression
• Kidney stones
• Metallic taste
• Diarrhea
• Aplastic anemia
• These are virtually non-existent with drops

CAI directory
• Trusopt – Dorzolamide 2%
• Azopt - Brinzolamide 1%
• Oral CAI
  – Acetazolamide – Diamox 250, 500mg
  – Methazolamide – 25, 50mg

CAIs make wonderful partners
• Feldman, et al 2006 –
  • 1.5-1.8 mm lower IOP as compared to brimonidine 0.15% when added to travaprost
  • This significance was present at all time points
  • BID dosing
Companion study #2
- When compared to brimonidine 2% adding them to Travaprost...
- IOP lowered by 13% w/ brimonidine
- IOP lowered by 23% w/ brinzolamide

Companion study #3
- Stewart et al, 2006
- Compared to timolol 0.5% as additive to travaprost
- No difference at all between the 2 drugs
- CAI is effective at controlling night IOP spikes (TID?)

Companion study #2
- When compared to brimonidine 2% adding them to Travaprost...
- IOP lowered by 13% w/ brimonidine
- IOP lowered by 23% w/ brinzolamide

Combination drugs
- Cosopt – timolol-dorzolamide
- Timolol ½%, Dorzolamide 2%
- This drop works better than either timolol or dorzolamide does on their own
- Cosopt is not as effective as if you were using both timolol and dorzolamide
- Same side effects as beta-blockers and CAIs
- Capice? Kapeesh?

Companion study #3
- Stewart et al, 2006
- Compared to timolol 0.5% as additive to travaprost
- No difference at all between the 2 drugs
- CAI is effective at controlling night IOP spikes (TID?)

New Combo Drugs
- Extravan – Travaprost 0.004%/Timolol 0.5%
- Combigan – Bimatoprost/Timolol 0.5%
- What do we know about these?

Oral CAI
- Is there still a place for them?
- What is the correct dosage?
- Are there precautions we need to take?

Extravan
- Dosed QD – generally in AM
- Barneby study-
  - Lowered IOP 2-3mm more than T ½ alone
  - Lowered IOP 1-2mm more than Trav alone
  - Statistically significant in 7 of 9 time points
Extravan

- Schuman Study
  - QD dosing in AM
  - Lowered IOP 7-9mm
  - Similar IOP drop if used Travatan and T ½ concommitantly
  - Consistent throughout day and for 3 months
  - Hyperemia – 14.3% w/ Extravan
  - - 23.4% w/ T ½ and Trav concommitantly

Eric’s 7 Simple Rules For Treatment

1. Choose 30% IOP decrease as initial target
2. Squash the diurnal curve (Keep IOP peak <18mm)
3. Assess risk factors for progression and rate of progression
   (CT<555, IOP >26,C/D 0.5)

Eric’s Rules cont.

4. If you are going to treat; treat aggressively
5. KISS
6. Be mindful of perfusion issues
7. Above all, do no harm

The Glaucoma Treatment Universe

2008

- Prostaglandins
- Alpha –agonist
- CAI
- Combo drugs
- Ginkgo , etc
- Beta-blockers
- Cardioselective beta-blockers
- ALT/SLT
- Trabeculectomy
- Nutrition issues

Regarding Prostaglandins:

- Generally the 1st line of treatment
- There are interindividual differences in efficacy
- Are there racial differences?
- If at first one fails; try, try , try again (with another prostaglandin)

Why wouldn’t you use a prostaglandin 1st?

Treatment paradigm – Step 2

- Prostaglandins 1st
- If not successful – try another agent by itself: Brimonidine bid or timolol
- If neither of these get IOP to desired level then add
Many Patients Require Adjunctive Therapy

- Ocular Hypertension Treatment Study (OHTS)\(^1\)
  - 817 patients with OHT; target pressure reduction = 20%
  - At month-60 visit, 39.7% of patients in the medical treatment group required 2 or more medications to reach the target IOP
- Collaborative Initial Glaucoma Treatment Study (CIGTS)\(^2\)
  - 307 newly diagnosed patients with mild to advanced glaucoma; aggressive target pressures set per formula
  - After first 2 years, >75% of patients required 2 or more medications to reach target IOP
- Even patients on the most powerful IOP-lowering medications often require adjunctive therapy\(^3\)

Consider Mechanism of Action (MOA) When Adding Medications

- Best chance of additivity by combining medications with different mechanisms
- Hypotensive lipids lower IOP by increasing aqueous outflow (uveoscleral/trabecular)
- Complement a hypotensive lipid by adding a drug that inhibits aqueous production
  - Brimonidine
  - CAI
  - Beta-blocker

Treatment Paradigm, Part III

1. Prostaglandins alone
2. Brimonidine or beta-blocker alone
3. Prostaglandin + beta-blocker or brimonidine or CAI (unless 1 of these absolutely sucked!)
4. Consider Cosopt or Combigan if (3) is not successful

Treatment paradigm, part IV

- If on 2 meds and target IOP not met...
  - 1. Consider 3\(^{rd}\) drop (Betoptic S or CAI)
  - 2. Substitute Combo drug for least successful drop
  - 3. Consider ALT or SLT
- What is maximum medical therapy nowadays?
- SLT/ALT and trabeculectomy should not be considered weapons of last choice or last chance