### Glaucoma Pharmacology A-Z

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#### Aerie – Advisory Board
- Allergan – Consultant, Advisory Board
- Sun Pharmaceuticals – Advisory Board
- AMO – Consultant, Advisory Board
- Bausch & Lomb – Consultant, Speaker bureau
- Glaukos – Consultant
- Sensimed – Advisory Board

#### 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**
- **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**

#### Prostaglandin Analogs Are Most Prescribed Category

- **Beta-blockers are 2nd Most Prescribed**

<table>
<thead>
<tr>
<th>Prostaglandin Analogs</th>
<th>% of IOP-Lowering Medication Prescriptions by Category, Feb 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostaglandin analogs</td>
<td>Beta Blockers</td>
</tr>
<tr>
<td>(1)</td>
<td>20%</td>
</tr>
</tbody>
</table>

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

8 PROSTAGLANDINS 2017
- Bimatoprost (Lumigan) 0.01%
- Latanoprost (Xalatan)
- Travoprost, Travaprost Z, (Travatan, Travatan Z)
- Zioprost(afiluprost)
- Vyzulta??
- Xelpros??

9 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?

10 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 – Oh Really!!
- Will switching from 1 PGA to another decrease the hyperemia effect?

11 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
- SO?

12 OTHER PROSTAGLANDIN SIDE EFFECTS
- CME
- Uveitis
- Reactivation of HSK
- Hypertrichosis
- Periorbital skin darkening
- Periorbital fat atrophy
- One must take into consideration the benefits of low IOP with the risks of the side effects
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.

BIMATOPROST AND TIMOLOL 12-MONTH STUDY

Mean IOP at Month 12

<table>
<thead>
<tr>
<th>Time of Day</th>
<th>Timolol (n = 241)</th>
<th>Bimatoprost QD (n = 474)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 AM</td>
<td>26.8</td>
<td>23.6</td>
</tr>
<tr>
<td>10 AM</td>
<td>24.7</td>
<td>21.3</td>
</tr>
<tr>
<td>12 PM</td>
<td>22.2</td>
<td>19.1</td>
</tr>
<tr>
<td>2 PM</td>
<td>20.1</td>
<td>17.8</td>
</tr>
<tr>
<td>4 PM</td>
<td>17.8</td>
<td>15.5</td>
</tr>
<tr>
<td>6 PM</td>
<td>15.4</td>
<td>13.1</td>
</tr>
<tr>
<td>8 PM</td>
<td>12.8</td>
<td>10.5</td>
</tr>
</tbody>
</table>

*P < .001 vs timolol

BIMATOPROST AND TIMOLOL EFFICACY OVER 4 YEARS

Mean IOP Across 48 Months

<table>
<thead>
<tr>
<th>Month</th>
<th>Timolol (n = 35)</th>
<th>Bimatoprost QD (n = 78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>16.0</td>
<td>12.6</td>
</tr>
<tr>
<td>12</td>
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<td>9.4</td>
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<tr>
<td>18</td>
<td>9.4</td>
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<tr>
<td>24</td>
<td>6.0</td>
<td>3.6</td>
</tr>
<tr>
<td>36</td>
<td>3.6</td>
<td>1.2</td>
</tr>
<tr>
<td>48</td>
<td>1.2</td>
<td>0.8</td>
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</tbody>
</table>

*P ≤ .043

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
BIMATOPROST AND TRAVOPROST

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Pfizer</th>
<th>Allergan</th>
<th>Allergan</th>
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</thead>
<tbody>
<tr>
<td>Length</td>
<td>12 weeks</td>
<td>3 months</td>
<td>6 months</td>
</tr>
<tr>
<td>Bimatoprost</td>
<td>n = 136</td>
<td>n = 16</td>
<td>n = 76</td>
</tr>
<tr>
<td>Travoprost</td>
<td>n = 138</td>
<td>n = 15</td>
<td>n = 81</td>
</tr>
</tbody>
</table>

Travoprost (0.004%)

Baseline mean IOP comparable between groups

Parrish et al. 2003
Noecker et al. 2003
Cantor et al. 2005

Mean IOP at Week 12

Baseline mean IOP comparable between groups

Mean IOP (mm Hg)

8 AM 12 PM 4 PM 8 PM

Mean IOP at Month 6

Percentage of Patients Achieving ≥20% IOP Reduction at 9 AM

P = .058

Bimatoprost
Travoprost

P = .038
P = .095
P = .099

Percentage of Patients Achieving ≥20% IOP Reduction at 9 AM

Bimatoprost (n = 136)
Travoprost (n = 138)

BIMATOPROST AND TRAVOPROST: 6-MONTH STUDY

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 and 1 for ocular redness and lid erythema

BIMATOPROST AND LATANOPROST: 3 MONTH STUDY

Study population: previously treated patients
Approximately 50% on latanoprost at screening
Among-group differences not statistically significant;
Latanoprost: 25.7, 23.7, 22.3, 22.3 (8 AM, 12 PM, 4 PM, 8 PM; mm Hg)
Bimatoprost: 24.8, 23.2, 22.2 (8 AM, 1 PM, 4 PM, 8 PM; mm Hg)

Mean IOP at Week 12

Baseline mean IOP comparable between groups

Mean IOP (mm Hg)

8 AM 12 PM 4 PM 8 PM

Time of Day
BIMATOPROST AND LATANOPROST: 6-MONTH STUDY

Mean IOP at Month 6

<table>
<thead>
<tr>
<th>Time of Day</th>
<th>Latanoprost</th>
<th>Bimatoprost</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 AM</td>
<td>24.9</td>
<td>25.0</td>
</tr>
<tr>
<td>12 PM</td>
<td>23.3</td>
<td>24.0</td>
</tr>
<tr>
<td>4 PM</td>
<td>22.5</td>
<td>22.6</td>
</tr>
</tbody>
</table>

Baseline mean IOP:
- Latanoprost: 24.9, 23.3, 22.5 (8 AM, 12 PM, 4 PM, mm Hg)
- Bimatoprost: 25.0, 24.0, 22.6 (8 AM, 12 PM, 4 PM, mm Hg)

Mean (SEM) IOP (mm Hg)
- P < .001
- P < .001
- P = .008

Baseline mean IOP consistently lower throughout the day with bimatoprost.

Response Rate at Month 6

<table>
<thead>
<tr>
<th>Time of Day</th>
<th>Latanoprost</th>
<th>Bimatoprost</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 AM</td>
<td>79</td>
<td>77</td>
</tr>
<tr>
<td>12 PM</td>
<td>62</td>
<td>51</td>
</tr>
<tr>
<td>4 PM</td>
<td>55</td>
<td>45</td>
</tr>
</tbody>
</table>

P = .003
P < .001
P = .002

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

Most common side effects:
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PROSTAGLANDINS

- 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?
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%

WHAT IS THEIR ABILITY TO LOWER IOP <17MM?

- Latanoprost – 49.5% of pts
- Bimatoprost – 64%
- Travaprost – 56.3%

LOOK AT THEIR FAILURE RATE:

- Percent of pts who didn’t reach their target IOP
  - Latanoprost – 14%
  - Bimatoprost – 6%
  - Travaprost – 8%

SO?
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

ARE GENERICS REALLY AS GOOD AS BRANDED PRODUCTS?

WHAT ELSE IS NEW?

- Ziopan (Tatufrostruct) – Merck
  - Unit dose vial
  - QHS dosing
  - Unpreserved
  - Studies show 6-8 mm Hg drop in IOP from baseline of 24-26
  - Excellent safety profile
CLINICAL THOUGHTS ON ZILOPTAN

- Definite a kinder, gentler PGA
- Unit dose vials a perceived benefit
- Compliance enhanced!
- IOP decrease not as robust as other PGAs

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?

A new PGA coming… SOON!!!

- Latanoprostene bunod 0.024%
  - Nitric oxide donating prostaglandin
  - P2-alpha analog
  - 1 drop QHS
  - Nicox (marketed by B&L)
  - Vyzulta – available 2018!!

VYZULTA – LATANOPROST BUNOD 0.024%

- Nitric-oxide donating PGA
- B & L
- QD dosing
- Reduces IOP 7.5 – 9.1mm superior to timolol
- How does it compare to the other PGAs?!
- How is it different?!
- How is it better?!

VYZULTA

- Adding NO donor increases outflow through Schlemm’s Canal and t.m.
- Increases relaxation of these tissues
- Non-inferior to timolol (LUNAR Study)
- However…nearly twice as many eyes had IOP lowered >25% as compared to timolol

VYZULTA – MEDEIROS ET AL AJO, 2016

- Additional 1.2mm lowering of nocturnal IOP
- Hyperemia rate-9%
- Eye irritation – 7.2%
LBN AND OPP

- LBN exhibited better ocular perfusion pressure than timolol, especially at night!!!
- Better IOP reduction at night as well
- Liu et al, AJO 2016

LATANOPROSTENE BUNOD (LBN)

- Phase 2 study
- Head to head study vs Xalatan
- 413 patients
- LBN consistently lowered IOP in a dose-dependent manner
- Significantly lower IOP than Xalatan at day 28 (also at day 7 and 14)
  - 98mm Hg lower at all time points
- Slightly higher hyperemia rate

ONE MORE NEW PGA!!

- Xelpros (Sun Pharmaceuticals)
  - Latanoprost BAK-free drops
  - New delivery option
  - Multi dose bottle
  - Similar in efficacy to latanoprost
  - Has not been compared to Xalatan
  - What about side effect profile?
  - What about cost?

BETA-BLOCKERS

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

- Timolol maleate – Timoptic, Timoptic XE (1/2, 1/4 %)
- Carteolol – Ocupress 1% (intrinsic sympathomimetic activity)
- Levobunolol – Betagan ½%
- Timolol hemihydrate – Betimol ½, ½%
- Istranol ½/2% - QD dosing indication
- Betaxolol 1/4% - cardioselective, safer?
**BETA-BLOCKER SIDE EFFECTS**

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

**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-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

**BETA-BLOCKER SIDE EFFECTS**

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

**THE BIGGEST PROBLEM WITH TOPICAL BETA-BLOCKERS?**

- Decreased Perfusion To The Optic Nerve Head!!
- Especially At Night!!
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!

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

Mechanism of Action of Brimonidine-PÜRITE®

- Complements PGAs 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>ALPHAGAN®</th>
</tr>
</thead>
<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: DUAL MECHANISM OF IOP LOWERING

- Enhances uveoscleral outflow
- Suppresses aqueous humor production (inflow)

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 (De Santis, 2000; Gassner et al., 1974; Noecker, 2004)

**PURITE® IS A GENTLE PRESERVATIVE**

SEM of rabbit corneal epithelium (800X)

Unreated  | PURITE® QID 7 days  | BAK QID 7 days

**SEM of rabbit corneal epithelium (800X)**

**Ocular Bioavailability of Brimonidine in Different Formulations**

- Brimonidine-PURITE® 0.15% formulation shows bioavailability in the aqueous humor comparable to brimonidine 0.2% BAK

*P = .04 vs brimonidine 0.15% BAK

**Means IOP at Trough (8 AM)**

**MEAN CHANGE FROM Baseline at Month 12**

ALPHAGAN® P 0.1% demonstrates IOP-lowering efficacy equivalent to ALPHAGAN® 0.2% over 12 months

**Adverse Events Typically Associated with Brimonidine 0.2% Are Lower with Brimonidine-PURITE® 0.15%**

**MEANS IOP at PEAK (10 AM)**

**Eric E. Schmidt, O.D., F.A.A.O.**

Omni Eye Specialists
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**BRIMONIDINE-PURITE® 0.15% HAS SIGNIFICANTLY LOWER INCIDENCE OF OCULAR ALLERGY**

- BRIMONIDINE-PURITE® 0.15%
- BRIMONIDINE 0.2%

<table>
<thead>
<tr>
<th>Percentage of patients</th>
<th>BRIMONIDINE-PURITE® 0.15% (n = 381)</th>
<th>BRIMONIDINE 0.2%* (n = 383)</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
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<tr>
<td>14</td>
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*Original ALPHAGAN®

**EFFECT OF BRIMONIDINE-PURITE® 0.1% FORMULATION ON SAFETY**

- Ocular surface exposed to 50% less drug with new formulation
  - Less allergy, redness, irritation
- Lower concentration also means fewer systemic effects as less drug enters nasolacrimal duct

**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 pts

**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?
- What happens if hypersensitivity to 0.2% Brimonidine occurs?

**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?

**NEUROPROTECTION??**

- Does it really exist?
- Does Alphagan promote neuroprotection?
FEKE ET AL, AJO 2014
- Effect of brimonidine on retinal vascular autoregulation and short-term visual function in NTG

FEKE STUDY
- Identified NTG pts who had retinal blood flow changes upon postural change
- Those pts were placed on Alphagan P 0.15% x 8 weeks then retested
- 14/17 demonstrated an improvement in postural induced retinal blood flow
- This did not show improvement in visual function

BRIMONIDINE MAY NOT WORK AT NIGHT
- Fan et al, J Glaucoma 2014; 23(5)
- Increased uveoscleral meshwork outflow during day with corresponding IOP reduction
- Drug has no effect on aqueous outflow, episcleral venous pressure or outflow facility
- There is a dramatic reduction in uveoscleral outflow at night

ALPHAGAN ALSO HAS A SHORT DURATION OF ACTION
- So what does this mean clinically?!!

CARBONIC ANHYDRASE INHIBITORS
- Lower IOP by reducing aqueous production
- Reduce IOP by 16-22%
- Sufa drugs!!
- Dosage question – BID or TID?
- Are they useful as stand alone drugs?

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

- **Stinging**
- **Dryness**
- HA
- Bad taste
- Sulfa drug so:
  - Aplastic anemia?
  - Renal stones?
- What about Cosopt?

ORAL CAI SIDE EFFECTS

- Paresthesia
- Depression
- Kidney stones
- Metallic taste
- Diarrhea
- Aplastic anemia

- These are virtually non-existent with drops

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?)

ORAL CAI

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

CAI 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
**COMINATION DRUGS**

- Cosopt – timolol-dorzolamide
- Timolol 1/3%, 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!

**Mean IOP-10 AM**

- Brimonidine/timolol fixed combination

**COMBIGAN™**

(Brimonidine Tartrate/Timolol Maleate Ophthalmic Solution) 0.2%/0.5%

- Fixed combination of brimonidine and timolol
  - Alpha-agonist brimonidine
  - Beta-blocker timolol
- Preserved with 0.005% benzalkonium chloride (BAK)
  - Generic timolol is preserved with 0.01%
  - Complementary mechanisms of action

**DIURNAL MEAN IOP AT MONTH 12**

- Dose all treatments
- Dose brimonidine

**TREATMENT-RELATED ADVERSE EVENTS**

- Brimonidine and timolol monotherapies are approved for first line therapy
  - Statistical significance does not necessarily correlate to clinical significance
**FIXED COMBINATION VS CONCOMITANT THERAPY: EQUIVALENT MEAN IOP**

- Fixed Brimonidine/Timolol BID (n = 188)
- Concomitant Brimonidine BID + Timolol BID (n = 183)

**NEXT STEP FROM A BETA-BLOCKER**

- Additional IOP lowering achieved with fixed combination after beta-blocker run-in

**COMBIGAN™ AND COSOPT® AS MONOTHERAPY: MEAN IOP**

- Mean IOP reductions from baseline at month 3 were 7.7 mm Hg with COMBIGAN™ and 6.7 mm Hg with Cosopt® (P = .040)

**COMBIGAN™ IN ADJUNCTIVE THERAPY WITH A PGA: MEAN IOP**

- Mean IOP (mm Hg)

<table>
<thead>
<tr>
<th>Month</th>
<th>Fixed-combination brimonidine/timolol BID (n = 121)</th>
<th>COMBIGAN™ (brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5%  + PGA (n = 37)</th>
<th>Cosopt® (dorzolamide hydrochloride-timolol maleate ophthalmic solution) (n = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 2</td>
<td>16.3</td>
<td>12.2</td>
<td>15.2</td>
</tr>
<tr>
<td>Week 6</td>
<td>15.8</td>
<td>12.9</td>
<td>15.3</td>
</tr>
<tr>
<td>Week 12</td>
<td>15.6</td>
<td>13.1</td>
<td>15.4</td>
</tr>
</tbody>
</table>

**COMBIGAN™ and Cosopt® Tolerability and Comfort**

- Patients with OAG/OHT requiring additional IOP lowering
- Two subgroups
  - Monotherapy: COMBIGAN™ (brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5% (n = 54) and Cosopt® (dorzolamide hydrochloride-timolol maleate ophthalmic solution) (n = 47)
  - Adjunctive: COMBIGAN™ added to PGA (n = 37) and Cosopt® added to PGA (n = 42)
- IOP 2 hours after morning dose
- Pooled data from 2 studies at 10 sites with identical protocols (Canada)
OCULAR COMFORT: COMBIGAN™ (BRIMONIDINE TARTRATE/TIMOLOL MALEATE OPHTHALMIC SOLUTION) 0.2%/0.5% AND COSOPT® (DORZOLAMIDE HYDROCHLORIDE-TIMOLOL MALEATE OPHTHALMIC SOLUTION) 0.2%/0.5% AND COSOPT® (DORZOLAMIDE HYDROCHLORIDE-TIMOLOL MALEATE OPHTHALMIC SOLUTION) 0.2%/0.5%

30–40 Seconds After Drop Instillation

Percentage of subjects rating treatment as most comfortable

- COMBIGAN™
- Cosopt®
- Treatments equally

n = 30

*P < .0001 vs Cosopt®

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TREATMENT-RELATED ADVERSE EVENTS

- Conjunctival hyperemia
- Eye pain
- Adverse reactions associated with therapy
- Conjunctival or ocular dryness

* Oral dryness and adverse events related to conjunctival allergy/inflammation significantly less

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COMBINATION DRUG #3

- Cosopt PF
  - Preservative free
  - Unit dosage vial
  - Able to lower IOP as good as preserved, branded Cosopt
  - BD
  - So??!

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COMBINATION DRUG #4

- Simbrinza (Alcon)
  - Brinzolamide 1.0%/Brimonidine 0.2%
  - TID Dosing
  - Approved for adjunctive therapy
  - Adjunctive to what??

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SIMBRINZA

- 5-9 mm Hg IOP reduction
  - Baseline IOP = 22 -36mm Hg
  - 21- 35% IOP reduction
  - TID dosing
SIMBRINZA

• Compared to Azopt head-to-head
• Compared to Brimonidine 0.2% head-to-head
• Statistically superior to either of the components in lowering IOP 2-3 mths
• At all time points

SIMBRINZA – SAFETY DATA

• Side effects are similar to each of the component drugs
• D/C rate – 11%
  - 3-5% incidence rate of:
    - Blurred vision
    - Ocular irritation
    - Bad taste
    - Dry mouth
    - Ocular allergy

NEW GLAUCOMA DRUGS – TAPPING THAT PIPELINE!!!

• Nothing New For The Past 5 Years
• All Of A Sudden – BOOM!
• Rhopressa
• Roclatan
• Vyzolta
• Trabodenoson
• Xelpros
• Bimatoprost SR

WHAT’S TO LIKE ABOUT RHOPRESSA?

• New MOA so… it is absolutely different
• It should be additive
• Definitely works better at lower IOP
• What about side effects?
  - High rate of hyperemia: 50% (80% mild and transient)
  - Conj hemorrhages – 10%
  - Reduced level of BAK

ROCK-INHIBITORS

• 2 drugs in the works – Aerie
• Rhopressa – Novel molecule
  - Works on different receptor sites
  - Effective IOP reduction with fewer side effects
  - No lash growth or skin darkening
  - Targed trabecular meshwork
• Roclatan – combo drug
  - Rhopressa and latanoprost
  - Availability 2017-2018

RHOPRESSA (NETARSUDIL) – AERIE PHARMACEUTICALS

• New class of drugs – Rho-kinase inhibitor
• MOA = “Triple Action”
  - relaxes trabecular meshwork similar to pilocarpine (enhances outflow)
  - lowers episcleral venous pressure
  - blocks fibrotic response at t.m. (increases perfusion)
• QD dosing
• Looks especially effective at IOP 25 mmHg or less
• 4th Quarter 2017!!!
ROCLATAN – AERIE

- Fixed Combination drug – Rhopressa + latanoprost
- QD dosing
- “Quadruple acting” MOA – (adds increased uveoscleral outflow)
- IOP lowering better than either of its components
- Potential to be very effective – lowered IOP an additional 2-3 mm compared to Rhopressa (and other PGAs)

- Currently in Phase 3
- Anticipating Late 2018 release

ROCLATAN

- What do we think?
- Side effects- same as Rhopressa
- Place in therapy?
- Clinical impressions
- Cost concerns

BIMATOPROST SR

- Biodegradable sustained-release implant
- Injected intracamerally using single use applicator
- Implant is visible in irido corneal angle
- Could make a big impact on non-compliance issues
- Lowers IOP over a 4-6 month period

BIMATOPROST SR

- Phase 1 data
  - Proved safety and good tolerance
- Phase 2 data
  - 2 weeks
    - IOP 23.8 in Bimatoprost group
    - 24.1 in timolol group
  - At 6 months
    - 20.1 in implant group
    - 19.0 in timolol group

- Second study showed IOP decrease of 7.2 -9.5 mm Hg
- At month 6, 70% of subjects did not require topical IOP gtt
- Biggest side effect is transient hyperemia and FB sensation
- Implications for ODs

ONE FINAL WORD ABOUT GLAUCOMA DRUGS

- A lot of money is being spent on delivery systems
- These may be cheaper alternatives
- Optometry cannot sleep on this
NOVEL DRUG DELIVERY SYSTEMS - THE NEXT FRONTIER

- Drug Eluting Punctal Plugs
  - QLT – latanoprost
  - 75-80% retention rate
  - Results: 3-4 mm drop in IOP

- Ocular Therapeutix – Intracameral latanoprost
  - Good sustained release of drug but doesn’t lower IOP as good as topical Xalatan

- SOOOOO!!!!

BRIMONIDINE DRUG-ELUTING PLUGS

- Similar technique to inserting collagen lacrimal plugs
- Early studies show better and more sustained IOP release than latanoprost plugs
- Good safety profile
- SOOOO>>>>>>>>

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<55, 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

IOP LOWERING WITH MONOTHERAPY IS IDEAL

- Initial therapy with PGA can provide > 30% IOP lowering
- Monotherapy may reduce the risk of adverse events, drug interactions, and exposure to preservatives
- Monotherapy is convenient, may help patient compliance, and may have lower acquisition cost
PATIENTS ON MORE THAN ONE IOP-LOWERING MEDICATION

- 2 Medications: 69.8%
- 3 Medications: 5.2%
- 4 Medications: 24.4%

Source: Verispan’s PDDA, MAT Nov 2006.

HOWEVER, PATIENTS ON MONOTHERAPY MAY NOT ACHIEVE TARGET IOP

- In a study of ocular hypertension patients (OHTS)1
  - At month 60, 60.40% required 2 or more medications to reach 20% IOP reduction
- In patients treated with PGAs2
  - Adjunctive medication use was 30.2% with latanoprost, 22.2% with bimatoprost, and 22.5% with travoprost

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

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?

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 therapy3

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

• The Paradigm is Changing
• Be Creative
• Understand your options
• Understand what you are trying to Achieve
• VF Preservation and Neuroretinal Rim Preservation
• Be aware of side effects

TREATMENT PARADIGM, PART IV

• If on 2 meds and target IOP not met…
  • What is maximum medical therapy nowadays?
  • SLT and trabeculectomy should not be considered weapons of last choice or last chance