Introduction: Principles of Glaucoma Medical Therapy
- Balance benefits with risks
- Use least amount to achieve desired response with fewest side effects
- Individualize treatment
- Focus treatment on preserving vision and the optic nerve
- Consider patient compliance

Evolution in Primary Therapy
- Over the past 15+ years, clinicians have switched from topical B-blockers to prostaglandin agents
  - Prostaglandin analogues
    - Superior efficacy - 30-35% reduction (or more!)
    - Systemic safety
    - Diurnal control of IOP
    - Convenience / enhanced compliance
    - Relatively few side effects

Prostaglandins
- Latanoprost (Xalatan) Pharmacia- Aug 1996
- Unoprostone (Rescula) Novartis- Sept 2000
- Brimatoprost (Lumigan) Allergan- March 2001
- Travoprost (Travatan) Alcon- March 2001
- Tafluprost (Zioptan)* Merck-Feb 2012
- Vyzulta (latanoprostene bunod) B&L Nov 2017

Prostaglandin: pros
- Very few systemic side effects
- Once daily administration
- Long action with flattening of diurnal curve
- Few drug/drug interactions

Prostaglandins: cons
- Mild hyperemia
  - Subsides over time, 2 weeks or less
  - While 35-50% do reports some level of hyperemia, only 3% discontinued due to hyperemia
- Eyelash growth: low incidence 0.8%
- Iris color change: benign, cosmetic change
  - 2-3%
Prostaglandins: cons

- CME
- Iritis
  - Avoid in patients with h/o iritis, as can precipitate attack
  - Consider d/c while in post-op cataract period
- Re-activation of HSV
- Non-response: 8-9%
  - Similar or better than virtually all other classes

Generic Latanoprost

- March, 2011
- Several companies
  - Apotex, Inc.
  - Mylan Pharmaceuticals, Inc.
  - B&L Pharmaceuticals
  - Greenstone, Ltd.
  - Falcon Pharmaceuticals

Generic Latanoprost

- Few studies indicate if equivalent
- Indian J of Ophth 2007 Study
  - Xalatan group had slightly lower IOP reduction than generic, 38% vs. 25%
  - If switched from generic to trade, just under 1 mm decrease (16.98 to 16.09)
  - If switched from trade to generic IOP rose just over 1 pt (14.29 to 15.36)
- Adverse effects: initial, 8/11 in trade name vs. 16/18 in generic; 11/11 switched to generic vs. only 6 of 18

Generic Latanoprost

- Bottom line:
  - Fairly similar IOP response
  - Maybe more adverse reaction in generic
  - Generics may need extra counseling etc.
  - Have back for IOP change after switch?
  - Difference among generics?
- May not have an option!!
  - Cost: Good RX 3/18
  - =$11.24 for 2.5 ml vs. $61.21 for trade, 81% less!!

Other Generic PGs

- Lumigan 0.03%
  - Generic, but not widely available
  - $56.96 vs $135.73, 58% less
  - Note: Trade name is now 0.01%
- Travatan 0.004% = $27.33 (45% less)
  - Since 2013
  - Trade name no longer available
  - Only Travatan Z = $60.66

Vyzulta (latanaprostene bunod 0.024%)

- B&L: approved Nov 2017
  - To lower IOP in patients with POAG or OC HTN
  - Once daily administration in evening
- PG analog
  - Combines PG with a nitrous oxide molecule for better efficacy
  - Dual action: increases aqueous outflow through the TM as well as uveoscleral outflow
  - In studies, IOP decreased 7.5 mm-9.1 mm
    - 1.23 mm lower than latanoprost
  - Good RX: $375 for 5 ml
Vyzulta

- Side effects: similar to all PGs
  - Increased iris pigmentation
  - Darkening of eyelid skin
  - Eye lash changes, including increased length, thickness, and or direction
  - Use in caution in pts with h/o ocular inflammation
  - Macular edema, including CME, has been reported
    - Conjunctival hyperemia 6%
    - Eye irritation 4%
    - Eye pain 3%
    - Installation site pain 2%

Beta Blockers: pros

- Good IOP response
- Few ocular side effects
  - Inexpensive
    - Multiple generics
    - ≈$4.00

Beta Blockers: cons

- Long term drift
  - After 2 years – nearly 50% change therapy
- Systemic side effects:
  - Breathing issues, pulse rate, depression, decreased libido, caution in diabetics etc, etc.
- BID administration
- Many drug/drug issues
  - Systemic b-blockers, cardiac meds (digitalis, CA channel blockers)

Rhopressa (netarsudil 0.002%)

- Rho Kinase inhibitor for the reduction of elevated IOP in pts with OAG or OC HTN
- FDA approved Dec 2017: Aerie Pharmaceuticals
  - Not yet available in pharmacies
- Once daily in evening
- Increased outflow of aqueous through TM
- IOP decrease similar in studies to timoptic bid
  - 3.9mm -4.1 mm

Rhopressa

- Conjunctival hyperemia 53%
- Common (~20%)
  - Corneal verticillata
  - Instillation site erythema
  - Conjunctival hemorrhage
- Less common (5-10%)
  - Instillation site erythema
  - Corneal staining
  - Blurred vision
  - Increased lacrimation
  - Erythema of eyelid
  - Reduced VA

Try Switching first

- Clinical trials – adding prostaglandin to timolol monotherapy – 25% further IOP reduction
- Switching from timolol to prostaglandin – similar IOP reduction
  - Approximately 23%
- Different class of medication
- Different medication with class
  - Some evidence that pt may respond better to one PG vs. another
Why Switch?

- Fewer adverse effects
- Better compliance
  - Less meds=better compliance
- Lower cost
  - Less meds=less cost

What to add next?

- "All 3 classes of meds are similarly effective in lowering mean diurnal IOP when used in combination with PGAs"

Adjunctive Therapy with Latanoprost

PURPOSE: To determine the additive IOP reduction of various topical IOP-lowering agents used adjunctively with latanoprost

METHODS:
- Retrospective evaluation of 73 eyes of 73 patients with glaucoma and inadequate IOP control on latanoprost alone
- Each patient received adjunctive treatment with an additional IOP-lowering agent (brinzolamide, brimonidine, timolol, or other beta-blockers) for 1 year

Brinzolamide vs. Timolol as Adjuncts to Latanoprost

PURPOSE: To compare the diurnal and nocturnal effects of brinzolamide and timolol on IOP in patients already receiving monotherapy with latanoprost

METHODS:
- Baseline data of 24 hr IOP were collected in a sleep laboratory while patients were receiving latanoprost monotherapy
- Measurements were taken every 2 hrs in the sitting and supine positions during the 16 hr diurnal/wake period and in a supine position during the 8 hr nocturnal/sleep period
- Patients were randomly assigned to receive an add-on treatment with either brinzolamide 1% 3 times per day or timolol 0.5% gel forming solution once every morning for 8 weeks
- Cross over to receive the other add-on treatment

Brimonidine vs. Brinzolamide as Adjuncts to Travoprost

PURPOSE: To compare efficacies of adjunctive therapy with brimonidine 0.15% or brinzolamide 1% in combination with travoprost 0.004%

METHODS:
- Patients were randomized to receive adjunctive therapy with brimonidine (N=79) or brinzolamide (N=84)
- Treatment efficacy was assessed after 1 and 3 months of concomitant therapy
- IOP was measured at 8:00 AM, noon, and 4:00 PM at baseline (on travoprost monotherapy) and after 3 months of concomitant therapy
What to add next?

- Alpha-agonist/CAI
  - Alphagan/Trusopt or Azopt
  - CAI/Alpha-agonist
  - Beta-blocker
  - Fixed combination as appropriate

FIXED COMBINATIONS

Benefits of Fixed Combinations for Glaucoma Management

- Dosing—one drop vs two drops
- Convenience may help patient compliance
- No risk of washout from second drug
- Possible cost savings (only 1 copay)


Compliance with Eyedrops

- Once daily – 49%
- More than twice daily – 39%
- More than one kind – 32%

Current Fixed Combinations

- Dorzolamide hydrochloride-timolol maleate ophthalmic solution (Cosopt®)
- Brimonidine tartrate/timolol maleate ophthalmic solution 0.2%/0.5% (Combigan™)
- Brinzolamide 1%/brimonidine 0.2% (Simbrinza™)

Cosopt

- 2% dorzolamide/0.5% timoptic
- BID
- 1st combo for glc (1998)
- Generic as well as trade name (Merck)
- Studies showed combo lowered pressure more than either timoptic or dorzolamide alone
Combigan

- Timoptic 0.5%/brimonidine 0.2% BID (Allergan)
  - October 2007
- IOP lowering effect of Combigan BID was slightly less than T 0.5% BID and brimonidine 0.2% TID concurrently
- BID administration
- Not approved as first line therapy at this time only as adjunctive

Simbrinza™

- Brinzolamide 1%/brimonidine 0.2% SUSPENSION by Alcon
  - SUSPENSION so needs to be shaken
- First combo without beta-blocker!!!
- FDA Approved: April 19, 2013
- Cost: ≈$100 for 8 ml bottle

Simbrinza™

- Efficacy proven in 2 Phase 3 randomized, multi-centered, double-masked studies
  - IOP was reduced an additional 1-3 mm vs. individual components
  - IOP reduced 21-35% at month 3 (5 to 9 mm)
- Most frequent adverse effects (3-5%)
  - Blurred vision
  - Eye irritation
  - Dygeusia (bad taste)
  - Dry mouth
  - Allergy
- Rate of discontinuation = 11%
- Beware with sulfonamide allergies

PG/Beta Blocker?

- DouTrav available in Europe (Alcon)
- Xalacom (Pfizer) also in Europe
- To date, no PG combo FDA approved in US
  - Studies have not shown that combo qd is as good as separate components
  - Increased compliance alone is not enough for FDA
- Roclatan combo: Rhopressa( netarsudil 0.002%) with latanoprost perhaps 2nd Q 2018
  - Mercury 1 and 2
    - 1-3 mm lower than each agent separately

Zioptan (tafluprost 0.0015%)

- FDA approved Feb 13th, 2012
- First preservative-free PG
- Indicated for reducing elevated IOP in patients with open-angle glaucoma or ocular hypertension

Zioptan (tafluprost 0.0015%)

- FDA approval based on 5 clinical studies of 905 pts
  - IOP lowered 6-8 mm at 3 mos, 5-8 mm at 6 mos in pts with baseline IOP of 23 to 26 mm
- Dosed once daily in the evening
- Cost: ≈ $197 for 30-day supply
  - Good RX 10/2017
Zioptan (tafluprost 0.0015%)

- Side effects:
  - Increased length, color, thickness and shape of lashes
  - Usually reversible upon d/c
  - Increased iris pigmentation
  - Redness of eyes

Cosopt PF

- Preservative-free Cosopt by Merck
  - Dorzolomide 2%/timoptic 0.5%
- FDA approved Feb 1, 2012
- Commercially available June, 2012
- 0.2 ml individual vials

Cosopt PF

- In a controlled study of 26 pts with IOP ≥ 21mm, IOP lowering effect same as traditional Cosopt
- IOP effect of Cosopt PF bid was greater (1-3 mm) than either dorzolomide 2% tid or timoptic 0.5% bid alone
- Cost: ≈$170 mos supply
  — Good RX 10/2017

TRY TO RELATE VF TO ONH APPEARANCE

When to refer

- Pt progressing despite adequate IOP
- Unable to get IOP to target despite several attempts
- Poor compliance despite several DOCUMENTED discussions
- Advanced disease
- Simply not comfortable
- BETTER TO REFER EARLY THAN LATE!!!
  - You do not want to be the last person a patient sees before he goes blind!!