Glaucoma Update: New Tools and Treatment Options

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Disclosure

- Michael Chaglasian, O.D. is a paid advisor, consultant or researcher for the following commercial/industry groups:
  - Allergan, Alcon Labs, Bauch+Lomb, Carl Zeiss Meditec, Topcon Medical, Heidelberg Engineering, Reichert

Ocular Hypertension

- What is this condition?
- Who has OHTN?
- What are the risk factors?
- Who should be treated for OHTN?
- Is treatment beneficial?
- How should these patients be followed?

Ocular hypertension is a condition in which the following criteria are met:

- An intraocular pressure greater than 21 mm Hg in one or both eyes, as measured by applanation tonometry on 2 or more occasions
- Absence of glaucomatous defects on visual-field testing
- Normal appearance of the optic disc and nerve fiber layer
- Anatomically normal, open angles on gonioscopy
- Absence of ocular conditions contributing to the elevation of pressure, such as narrow angles, neovascular conditions, and uveitis

CASE AC

- 53 year old
- Myopia, no sig. medical history
- No family history glaucoma
- GAT= 27 OD, 25 OS
- Gonioscopy= Open to CB 360° OU

Ocular Hypertension

- 119 million people in US over age 40
- 4.8 – 9.5 million people have OHT
- The number of affected people will increase with the aging of the population
- Managing this large group of people is associated with substantial costs for examinations, tests and treatment

CASE AC: IOP 27 OD; 25 OS

Visual Fields

Treat or Observe?
Glaucoma Risk Factors

Evidence Based

- **Age:**
  - Most commonly occurs after age 60 (risk increases with age)
  - Earlier in those with a Family History

- **Race:**
  - African, Hispanic, Asian

- **Family history**
  - First degree relatives (OR 2.9; Tielsch et al)

- **Elevated Intraocular pressure**

- **Other ocular factors:**
  - Thin central corneal thickness, narrow angles, increased cup:disc ratio, exfoliation

- **Systemic factors:**
  - Low Perfusion Pressure, hypotension

- **Genetic factors:**

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**Does Treatment of Ocular Hypertension Prevent POAG?**

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Protective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graham</td>
<td>yes</td>
</tr>
<tr>
<td>Shin</td>
<td>yes</td>
</tr>
<tr>
<td>Kitizawa</td>
<td>yes</td>
</tr>
<tr>
<td>Epstein</td>
<td>yes</td>
</tr>
<tr>
<td>Kass</td>
<td>yes</td>
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<tr>
<td>Miglior</td>
<td>no</td>
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<tr>
<td>Schulzer</td>
<td>no</td>
</tr>
<tr>
<td>Heijl</td>
<td>no</td>
</tr>
<tr>
<td>Kamal</td>
<td>no</td>
</tr>
<tr>
<td>David et al.</td>
<td>no</td>
</tr>
</tbody>
</table>

Limitations of previous studies:
- Varying endpoints
- Varying treatment regimens
- Small sample sizes

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**Ocular Hypertension Treatment Study (OHTS) Primary Goals**

- Evaluate the safety and efficacy of topical ocular hypotensive medication in delaying or preventing the development of POAG in individuals with elevated IOP
- Identify baseline demographic and clinical factors that predict which participants will develop POAG

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**The OHTS Entry Criteria**

- Age 40 - 80
- Normal visual fields
  - Humphrey 30-2
- Normal optic discs
- Untreated IOP:
  - 24 to 32 mm Hg in one eye
  - 21 to 32 mm Hg in fellow eye

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**Primary POAG Endpoints**

Log Rank P-value <0.001, Hazard Ratio 0.40, 95% CI (0.27, 0.59)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Observation</th>
</tr>
</thead>
</table>

- Medication reduced incidence of POAG in OHT participants by more than 50% at 5 years from 9.5% in the Observation Group to 4.4% in the Medication Group.

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**Baseline Predictive Factors for the Development of POAG**

- Age
- IOP
- Vertical C/D Ratio
- PSD
- CCT

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**Pachymetry**

OHTS/GPS 2007
POAG Endpoints by Central Corneal Thickness and Baseline IOP (mmHg) in Observation Group* OHTS Data

<table>
<thead>
<tr>
<th>Baseline IOP (mmHg)</th>
<th>Central Corneal Thickness (microns)</th>
<th>OHTS Data through 8 Nov 2001</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;23.75 to ≤ 25.75</td>
<td>&gt;23.75 to &lt; 25.75</td>
<td>17%</td>
</tr>
<tr>
<td>≥ 25.75</td>
<td>&gt;25.75 to &lt; 555</td>
<td>9%</td>
</tr>
<tr>
<td>&lt; 555</td>
<td>&gt;555 to &lt; 588</td>
<td>2%</td>
</tr>
<tr>
<td>&gt;588</td>
<td>12%</td>
<td>12%</td>
</tr>
<tr>
<td>&gt;588</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>&gt;588</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>&gt;588</td>
<td>36%</td>
<td>36%</td>
</tr>
</tbody>
</table>

Risk Factors

- Self-identified race not significant predictor of POAG in a multivariate model.
- Race not significant when central corneal thickness and baseline cup-disc ratio included.

OHTS/EGPS Risk Calculator

http://ohts.wustl.edu/risk/calculator.html

Pachymetry: 3 Outcomes

- Thin: <555 µ High Risk
- Average: 555-588 µ No change in Risk
- Thick: >588 µ Low Risk

The predictions derived using these methods are designed to aid, but not to replace clinical judgment.

Risk Calculator Limitations

- A number of factors described as predictive in previous studies either did not add to the explanatory power of the OHTS–EGPS pooled model or were not assessed in this study. These include:
  1. Disc Hemorrhages
  2. Ocular Perfusion Pressure
  3. Family History of glaucoma
  4. Ocular Perfusion Pressure
  5. Life Expectancy: much higher lifetime risk for younger pts

Why Not Treat Everyone?

- Costs of Therapy:
  - Monetary costs
    - Number Needed to Treat from OHTS = 20
    - Overall impact to healthcare system and to the patient personally
  - Side Effects
    - Minor for most but should not be ignored
  - Quality of Life Costs

How to Manage OHTN?

- Available on web free of charge
- http://ohts.wustl.edu/risk

Using the OHTS/EGPS Prediction Model for the Development of POAG

- http://ohts.wustl.edu/risk
How to Incorporate Information From OHTS Into Clinical Practice?

Managing OHTN

- Most OHT patients are at low risk. Many low risk OHT patients can be followed without medication.
- Delaying treatment for 7.5 years resulted in only a small absolute increase in POAG in low risk participants.
- Starting treatment of POAG at diagnosis has no major negative effect on prognosis over 5 years.

High risk OHT patients may benefit from more frequent examinations and early treatment taking into consideration:

- Patient age
- Health status
- Life expectancy
- Personal preference

Follow these Patients More Closely

- Frequent VF x 10-2
- OCTs
- ONH examination

Taking Glaucoma risk assessment to the next level:
THE ROLE OF CORNEAL HYSTERESIS

Ocular Response Analyzer

Michael Chlagasian, OD
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Section 1: Introduction to Corneal Hysteresis

What is Corneal Hysteresis (CH)?

- The only in vivo measurement of corneal biomechanical stresses.
- CH specifically reflects the ability of the cornea to dissipate energy.
- CH not a measure of corneal thickness.
- Not a characterization of stiffness.

CH: Not a surrogate for other parameters (slide a)

CH: Average Values in Normal Subjects

CCT in mm

<table>
<thead>
<tr>
<th>Value</th>
<th>n</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>535</td>
<td>96</td>
<td>533, 535</td>
</tr>
<tr>
<td>550</td>
<td>129</td>
<td>550, 553</td>
</tr>
<tr>
<td>555</td>
<td>108</td>
<td>553, 557</td>
</tr>
</tbody>
</table>

* CI units are mmHg

CCT is the corneal thickness (in mm). CH is the corneal hysteresis (in mmHg).

3. Lam A. Et Al. Optom Vis Sci. 2007 Sep;84(9):909-14
Section 2: Clinical Evidence

Why is CH relevant in Glaucoma?

(Low) CH has been consistently shown to be independently and strongly associated with or predictive of glaucoma progression.

Corneal Hysteresis

Association Between Corneal Biomechanical Properties and Glaucoma Severity

Lower Corneal Hysteresis is Associated With More Rapid Glaucoma Progression: A Prospective Longitudinal Study

Conclusions: Corneal Hysteresis was the parameter most associated with progressive field worsening.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>CH (mmHg) 8.2</th>
<th>GAT index CH</th>
<th>IOP 0.99</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>100</td>
<td>0.66</td>
<td>0.98</td>
<td>0.79</td>
</tr>
<tr>
<td>Clinical Hysteresis</td>
<td>531.8 ± 0.81</td>
<td>0.61</td>
<td>1.03</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Section 2: Clinical Evidence – Study 1

Corneal Hysteresis found to be associated with progression

- The first observational study to investigate the relationship of Corneal Hysteresis to a variety of other parameters in a glaucoma population.
- 280 POAG or suspected POAG patients were included in the study.
- Patients were randomized to receive single-blind treatment or control according to ONH criteria, with an IOP measurement, glaucoma history, and intraocular pressure greater than 21 mmHg.
- AIT, OHTS, and visual field loss measurements (HIS) were recorded.
- Among patients with three or more reliable fields over three or more years, the correlation reliability index is less than three years, progress was defined as having advanced (CMT defined as “measurable” if previously normal, and/or visually impaired as evidenced by an abnormal HMT or PTA having worsened by 1 or greater per year in either HMT or PTA).
- A logistic model was not used to assess any interactions between.

Section 2: Clinical Evidence – Study 2

CH associated with progression in NTG eyes

- Among patients with progression by visual field’s progression, CH was significantly lower than normal.
- CH was defined by repeatable HMT test, correlation reliability index, and VF loss.
- Patients were allocated to two groups based on the mean value of CH.
- Mean CH was 15.06 mmHg.
- CH and an unfavorable outcome were correlated and accepted with increased odds of progression, including CH, age, normal visual fields, and SOA.

Section 2: Clinical Evidence – Study 3

CH Associated with Asymmetric Glaucoma Progression

- CH was the best discriminative index for the worse eye in asymmetric OAG.
- CH lower in 80% of worse eyes.

Section 3: Corneal Hysteresis and The Structural Continuum

WHY CORNEAL HYSTERESIS IS A BIOMARKER FOR GLAUCOMA: EVIDENCE

- The Evidence suggests that CH is reflective of pressure-independent mechanisms involved in glaucoma pathogenesis and associated changes to the optic nerve.

Section 3: CH and the structural continuum

Evidence that CH is a biomarker for glaucoma risk

- Of the 39 eyes with low CH, 26 (66.7%) showed progression of VF damage over 21 years.
- Of the 41 eyes with high CH, 36 (87.8%) showed progression of VF damage over 21 years.
- Of the 52 eyes with low CH, 40 (76.9%) showed progression of VF damage over 21 years.
- Of the 45 eyes with high CH, 40 (88.9%) showed progression of VF damage over 21 years.
Section 3: CH and the structural continuum

Conclusion based on evidence in the literature

The eye is a mechanical structural continuum

The evidence suggests that CH is reflective of overall ocular tissue properties

CH appears related to pressure-independent mechanisms involved in glaucoma pathogenesis and associated changes to the optic nerve

Section 4: Ocular Response Analyzer Technology

The instrument

- 2002: Clinical research with ORA commences
- 2005: The 1st generation ORA was made commercially available
- 2012: Generation II ORA was launched
- 3rd Generation "ORA G3" introduced September 2015

Measures:
• Corneal Hysteresis (CH)
• Goldmann-correlated IOP (IOPG)
• Corneal compensated IOP (IOPCC)

Section 4: Ocular Response Analyzer Technology

Interpretation of measurement values

Spectral Domain: Many Options

Still Valuable: But Perhaps Limited Future

[Spectral Domain: Many Options]

Cirrus SD OCT

- Glaucoma Applications:
  - RNFL
  - Optic Disc
  - Ganglion Cell Analysis
- Retinal Application:
  - Not Covered here

Stratus

Stratus

GDx

Optos OCT SLO
How to “Read” a Printout

- FIRST!: Signal Strength
  - A KEY indicator of image quality
  - Should be 7/10 or higher on Cirrus
  - DO NOT interpret poor quality scan as “red” disease
- Well centered image
- No evidence of movement artifact
- Review Plots and Displays
  - Thickness Map and Deviation Map
  - Quadrant and Sector Plots
  - TSNIT and Optic Nerve B-Scan Tomograms

Glaucoma – RNFL Thickness Analysis

- The RNFL thickness map shows the patterns and thickness of the nerve fiber layer within the 6mm x 6mm cube
- The RNFL deviation map is overlaid on the OCT fundus image to illustrate precisely where RNFL thickness deviates from a normal range

Glaucoma – RNFL Thickness Analysis

- A TSNIT (temporal-superior-nasal-inferior-temporal) circle, with a radius of 1.73mm, is established around the disc
- The LSO fundus image is shown with an OCT fundus overlay. The red circle indicates the location of the RNFL TSNIT circle

Normative Data: Glaucoma

- Average RNFL Thickness
- RNFL Symmetry
- Rim Area
- Disc Area
- Average C/D Ratio
- Vertical C/D Ratio
- Cup Volume

Distribution of Normals:
- Color coded indication of normative data comparison for RNFL and ONH.
- The thickest 5% fall in the white area.
- 90% of measurements fall in the green area.
- The thinnest 5% fall in the yellow area or below.
- The thinnest 1% fall in the red area.
- Measurements in red are considered outside normal limits.
- Values within the frame vary when the disc area does not match with normative data.

Zeiss: Cirrus OCT Printouts

- Measures thickness for the sum of the ganglion cell layer and inner plexiform layer (GCL + IPL layers) using data from the Macular 200 x 200 or 512 x 128 cube scan patterns.

Cirrus: Ganglion Cell Analysis

- Ganglion Cell Layer
- Inner Plexiform Layer
- Theory that the RNFL is too variable and not important in macular assessment

Ganglion Cell Analysis - Zeiss
Glaucoma Update

Anatomy: Ganglion Cell Layer and IPL

Cirrus: Ganglion Cell Analysis

The analysis contains:
- Data for both eyes (OU)
- Thickness Map – shows thickness measurements of the GCL + IPL in the 6mm by 6mm cube and contains an elliptical annulus centered about the fovea.
- Deviation Maps – shows a comparison of GCL + IPL to normative data.
- Thickness table – shows average and minimum thickness within the elliptical annulus.

Macular/Ganglion Cell Analysis for Glaucoma: Key Points

- Is a "complement" to traditional RNFL scans
- Has a large number of false positives.
- Should NOT be used as the sole basis of a diagnosis for glaucoma.
- Not proven to make an earlier diagnosis.

What are practitioners' most common misunderstandings of imaging technology?

"The thought that these devices can diagnose glaucoma in the absence of corroborating clinical evidence is, in my opinion, the most common (and potentially dangerous) misunderstanding. The limited normative databases against which scans are compared can never cover the remarkably varied appearance and structure of the optic nerve we encounter in normal individuals."

James Brandt, MD

Red Disease!

Glaucoma versus red disease: imaging and glaucoma diagnosis

Read a Printout Summary

- Image Quality
- Step by step to review most plots.
- RNFL and Optic Nerve
- Localized vs. Diffuse
- Normative Data
- Red Disease

Glaucoma Case EXAMPLES

CASE MZ
IOP in high teens
CCT= 560

CASE CM
38 yo
GAT= 22 OD 25 OS
Visual Field Testing
Remains an essential exam component.
In fact, indications for more frequent testing on patients.

Central Field Loss is Important
- Understanding if there is central visual field loss (within 10° of fixation) is important for the patient
  • Decreased reading speed and errors
  • Altered driving ability – reading signs
  • Increased risk of falls
- Peripheral visual field loss
  • Asymptomatic (unless bilateral and severe)
  • Does not impact function as significantly

Central Visual Fields and Glaucoma
- Recent papers have suggested that the 24-2 test pattern has limited ability to detect central field defects
  • 50% of retinal ganglion cells are found within 4.5mm of fovea
  • Macula region comprises only 10% of overall visual field area though it is responsible for 60% of area of visual cortex
  • Damage to central 10° associated with diminished contrast sensitivity, reduced reading ability

The Central Field in Glaucoma
- Does the 24-2 detect functional vision loss in the central 10° in all cases?
  • Points in test grid are 6° apart in a grid pattern
- Is there a role for a complementary test such as the 10-2 in which 55 points are placed in a 10° area that are 2° apart?
  • Will this detect small scotomas that fall between the cracks?
- Is glaucoma a disease that involves the macula region early in the condition?

Use 24-2 mostly
- 24-2 tests 54 points
- 30-2 = 76 points
- For severe loss: 10-2 or size V
- Spacing: 24-2 and 30-2 every 6 degrees
- Spacing: 10-2 every 2 degrees

Key Information on the Single Field Analysis Printout:
1. Demographics
   • Testing Conditions
2. Reliability Indices
   • FL, FP, FN
   • Gaze Tracking
3. Total Deviation
4. Glaucoma Hemifield Test (GHT)
5. Global Indices
   • VFI, MD, PSD
Reliability Indices:
- Fixation Losses
  - Checks the blind spot
  - Over 20-25% suggests compromised test
  - However, many artifactually high results
  - BS not located
  - Head Tilt
  - High FP
- Gaze Tracking

Gaze Tracking

Reliability Indices:
- False Positives
  - Most important index
  - Rates of 10-15% or higher indicate significantly compromised results

Total Deviation Probability Plots
- Symbols used to show % of normal pts with a sensitivity that low or lower
- For example, 0.5% symbol indicates that less than 0.5% of normal subjects will have sensitivity that low

Pattern Deviation Plots
- Shows sensitivity losses after an adjustment has been made to remove any generalized depression.
- Highlights only significant localized visual field loss
- Uses decibels and probability symbols like total deviation plots

Comparing Total and Pattern Deviation
- TD
  - Uniformity abnormal
- PD
  - Clear
  - Some scattered points may still show
- Assessment:
  - Cataract

Global Indices
- VFI
  - Visual Field Index
- MD
  - Mean Deviation
- PSD
  - Pattern Standard Deviation

Visual Field Index (VFI)
- Recently developed staging index, designed to be less affected by cataract (vs. MD)
- VFI is approximately 100% in normal fields and approaches 0% in peripherally blind fields.
- More useful for progression analysis

Mean Deviation (MD)
- Shows how much on average the whole field departs from age-normal values.
- Is sensitive for generalized depression and very large localized defects
- Range: 0 to -30-35 dB
**Glaucoma Hemifield Test: GHT**

- Outside Normal Limits
- Early Localized Defect
- Borderline (localized defect)
- Generalized Depression of Sensitivity
- Abnormally High Sensitivity (high FP)
- Within Normal Limits

**Early Glaucoma Defects**
- Arcuate Defects
- Paracentral Defects
- Nasal Steps

**Factors Affecting the Measurement of Progression**
1. Difficulty in detecting change in a chronic, slowly progressive disease
2. Patients are usually treated so it is difficult to establish the natural history of progression
3. Normal test-retest variability vs. progression

**Functional Assessments for Glaucoma:**
- Standard Visual Field Tests
  - Is disease present?
  - How bad is it?
  - Is it getting worse?

**Glaucoma Progression Analysis**
- Establish visual field status.
- Establish visual field rate of progression.
- Today's visual field.
- Complete repair of current visual field exams including HVF, VFI, GPA analysis and GPA alert.

**Case WS**
- 65 yo Patient
- POAG:
  - OD worse than OS
  - Pre-Tx IOP: 32 OD; 24 OS
  - Currently: 22 OD; 21 OS
  - ONHs and VFs =>

**Factors Affecting the Measurement of Progression**
1. Difficulty in detecting change in a chronic, slowly progressive disease
2. Patients are usually treated so it is difficult to establish the natural history of progression
3. Normal test-retest variability vs. progression

**Visual Field Index (VFI)**
- Central points weighted more heavily than those on periphery
- Reduces cataract contribution to the measurement ofVF loss

**Glaucoma Hemifield Test:**

**Plain language classification of test results:**
1. Outside Normal limits
   - Early Localized Defect
2. Borderline (localized defect)
3. Generalized Depression of Sensitivity
4. Abnormally High Sensitivity (high FP)
5. Within Normal Limits

Looking for a cluster of 2-3+ adjacent defects (P< 1%, P< 0.5%) on the Patten Deviation Plot (must also be on the Total Deviation Plot)

**Glaucoma Progression Analysis**
- Establish initial visual field state.
- Visual Field Index (VFI) Rate of Progression Analysis.
- Today's Visual Field.
- Complete repair of current visual field exams including HVF, VFI, GPA analysis and GPA alert.

**HFA GPA VFI Summary**

<table>
<thead>
<tr>
<th>A</th>
<th>VFI = 89%</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>VFI = 81%</td>
</tr>
</tbody>
</table>

*B has more damaged central points and lower VFI than A*
1.1

• Event analysis (GPA alert) indicates “Likely Progression”.
• Slope is nearly flat and the confidence interval is narrow.
• Patient is 75 years old.

EXAMPLE

Rate of Progression

Most OAG patients will not be impaired.
Even worst AGIS group had modest change
Worst group lost 3 decibels in 8 years = 0.4 dB/year

OAG patients should be subdivided into (at least) 2 groups
stable cases = 0.1 dB/year
progressive cases
0.9 dB/year “catastrophic”

How Often to Repeat VFs?

At 1 field per year, >10 years to detect average progression
At 3 fields per year, find average in 4 years, catastrophic in 2 years.

How many fields per year? And when?

For the new glaucoma patient with real field loss

- Consider doing 3 fields in first year and one every 6 months the next year
- At a total of 5 in 2 years, good identification of the catastrophically worsening patient
- Then scale back to 1 per year
- Many already known to be generally stable don’t need this intensity

VF Testing Guidelines = 3/yr!

Prostaglandin Analogs

- Lumigan
- Xalatan

VF Testing Guidelines

TRAVATAN Z

Michael Chaglasian, OD
Travatan Z: Non BAK option

When TRAVATAN® Z solution comes in contact with the positively charged ions in the tear film, the ionic buffered preservative system becomes inactive, providing a solution that is safe and gentle on the eye.

Lumigan 0.01%

The Only: Preservative Free PGA

Zioptan

- A Preservative Free prostaglandin analog
  - Introduced in 2003
  - Tafluprost 0.015%
  - Single use vial delivery

- Same PGA side effects:
  - Iris/Periorbital Pigmentation, Hyperemia, Deepening Orbital Sulcus, etc.

Small Switch Study (2010)

Conclusion:
- Preservative-free tafluprost was better tolerated than the commercially available formulation of latanoprost
- Patients (n=158) who were recruited to the study because exhibiting symptoms/syptoms of ocular surface side-effects.
- The drugs appeared to have equal IOP reducing effect.

Generic Ophthalmics

- Prostaglandins
  - Latanoprost
  - Travoprost
  - Brimonoprost 0.03%
- Alpha Agonist
  - Brimonidine 0.2%
- CAI
  - Dorzolamide 2%
- Beta Blockers
  - Timolol
  - Levobunolol
- Fixed Combination
  - Dorzolamide/timolol

80% of all Rxs

“March 2011

Multiple Suppliers
- Including Pfizer/Greenstone and Falcon

Latanoprost Generic

- March 2011

- Multiple Suppliers
  - Including Pfizer/Greenstone and Falcon

In 2010 alone, the use of FDA-approved generics saved $158 billion, an average of $3 billion every week.”
Generic Latanoprost

What's the Next Generic?

What is best to add to a patient who is on a PGA?

ADJUNCTIVE MEDICATIONS:

Topical CAIs
Currently available:
- Brinzolamide 1% (Azopt)
- Dorzolamide 2%
  - Generic availability
- Consistent, moderate, mono-therapy IOP reductions
  - 15-20%, ~4 to 6 mm Hg
- FDA Labeled as TID agents

Agents Used in Combination with Prostaglandins: Effect on IOP

Alpha Agonists
- Alphagan-P 0.1% (Allergan)
  - 3 BAK→ Punte (-toxicity)
  - Less ocular allergy
- Aqueous suppressant and:
  - ↑ uveoscleral outflow
  - ↑ Neuroprotection?
- Bid vs. Tid dosing
- ??? Neuroprotection!

No Nocturnal IOP Lowering with Brimonidine 0.1% TID

Brimonidine Neuroprotective?

Overview:
- To compare brimonidine to timolol maleate in preserving visual function in low-pressure glaucoma
  - randomized, double-masked, multicenter clinical trial
- Outcome:
  - Low-pressure glaucoma patients treated with brimonidine who do not develop allergy
  - BRAHMS, Dr. Berson, MD
  - Publication date:
  - AJO Mar 2011

Azopt shows Nocturnal IOP Lowering:

Overview:
- To compare brimonidine to timolol maleate in preserving visual function in low-pressure glaucoma
  - randomized, double-masked, multicenter clinical trial
- Outcome:
  - Low-pressure glaucoma patients treated with brimonidine who do not develop allergy
  - BRAHMS, Dr. Berson, MD
  - Publication date:
  - AJO Mar 2011
Issues with Data/Conclusions
- Failure rate of beta blockers:
  - much higher than our collective clinical experience: EMGT, OHTS
  - Extrapolating the Kaplan-Meier survival graph to 5 years would predict a 100% progression rate for the patients taking timolol
- Side effect rate of brimonidine:
  - ~30% drop out due to side effects (0.2%)
- Degree of IOP lowering in treatment groups:
  - Approximately the same between the 2 drugs

Generic Brimonidine
- 0.2%
  - Risk of increased allergy
- 0.15% (expensive and hard to find)

Generic Timolol

Advantages of Fixed Combinations
- Dosing—1 drop vs 2 drops
- Convenience
- Potential to improve compliance
- No risk of washout from second drug:
  - Washout impedes absorption, thereby reducing efficacy
- Possible cost savings:
  - Only 1 copay

Timolol Fixed Combinations
- Cosopt®
  - Dorzolamide hydrochloride/timolol maleate solution
- Generic dorzolamide/timolol maleate ophthalmic solution

Fixed Combination: Combigan
- Combigan (Allergan)
  - Brimonidine 0.2% and timolol 0.5%
  - BID dosing
- Less allergy than brimonidine alone:
  - timolol is a buffer

Cosopt PF (Akorn)
- dorzolamide HCL – timolol maleate 2%/0.5%
- Preservative Free
- BID dosing
- 25-30% IOP reduction when used as monotherapy
- Role:
  - COPD and other beta blocker contraindications
  - Similar indications for OISD patients where BAK toxicity is a concern


Cosopt PF

SIMBRINZA™ Suspension (Brinzolamide/Brimonidine)
- Additional 1-3 mm Hg IOP lowering compared to the individual components
- Delivers 21-35% IOP lowering efficacy
- Only fixed combination without a beta blocker
- Adverse events profile consistent with those of the individual components
- Creates new treatment possibilities for lowering IOP

No Night-time IOP lowering effect. Many glaucoma specialists have shifted away from using timolol by itself.
SIMBRINZA™ Suspension Has Two Active Compounds with Complementary MOAs

SIMBRINZA™ Suspension is a fixed combination that is beta blocker-free 2, 3

Brimonidine
Brinzolamide

SIMBRINZA™ Suspension Has Two Active Compounds with Complementary MOAs 1

+ = SIMBRINZA™ Suspension

New and Upcoming Meds

Vesneo

- Latanoprostene bunod 0.024%
  - Nitric oxide donating PGA
  - Thus a "dual" action PGA
- Adds improved outflow through the trabecular meshwork by inhibiting actomyosin contractility in TM cells and relaxing/ opening the meshwork.
  - Trials (vs timolol) show IOP reduction of 7.6 – 9.1 mmHg
- Approved! Bausch+Lomb Summer 2016

Rho Kinase Inhibitors

- "ROCK" Inhibitors: family of protein kinases
  - The enzyme and the pathway play a critical role in regulating the contractile tone of smooth muscle
  - Research in the last decade has identified ROCK as an important mediator of aqueous outflow through the trabecular meshwork
  - Lowers resistance to aqueous outflow in the trabecular meshwork
  - Potential of restoring normal TM function
  - No other medication works in this fashion

Rho Kinase Inhibitors (Arie)

- Rhopressa: "triple action"
  - Reduces aqueous production
  - Increases TM outflow
  - Decreases episcleral venous pressure (increased outflow)
- Phase 3 Trial 2015
  - Did not meet primary endpoints
  - But did meet in patients with lower IOP
  - FDA allowing to re-submit
  - Hyperemia is an issue:
    - Noted in 35%, though 85% reported as mild

Rho Kinase Inhibitors (Arie)

- Roclatan
  - Rhopressa and latanoprost (quadruple action)
- Phase 2 Trials Completed w/ 35% IOP lowering
  - Exceeded latanoprost by up to 3 mmHg
  - Hyperemia 40%

Trabodenoson (Inotek)
Trabodenoson
- A selective adenosine mimetic (novel)
- Adenosine A1 receptors in the TM
- Upregulates proteases (MM-2) which digest and remove hydrolized proteins that clog the TM
- Thus improving/reversing normal TM outflow
- Phase 2 Trials Completed: (dosing, concentration)
  - QD dosing: alone or in combo w/PGA
  - No ocular side effects
  - Significantly Lowered IOP
- Phase 3 trials are enrolling

The Helios Insert
- Sustained release travoprost
- Intra-canalicualr depot
- Punctal plug delivery system
- 3 Month Release time period
- Ocular Therapeutix
  - Phase 2 Clinical Trials underway

OTX-TP
- Sustained release travoprost
- Intra-canalicualr depot
- Punctal plug delivery system
- 3 Month Release time period
- Ocular Therapeutix
  - Phase 2 Clinical Trials underway

My glaucoma patient is continuing to progress. What’s new and best?

An Update on SLT
Michael Chaglasian, OD, FAAO
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Illinois College of Optometry
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- 57 yr, W, F
- -7.50 Myopia
- Good Medical Health
- CCT: 562, 571
- GAT: 19-23 / 18-23mmHg
- Pre-treatment: 26/31; 12 months ago
- Current Meds:
  - PGA qhs OU
  - Fixed Combination OU
- Target IOP OD: ≤ 12 mmHg

Questions
- Is this patient a candidate for laser procedure?
- Is this patient a candidate for surgical procedure?
- What are the Pros and Cons?
- What are facts about the pros and cons?
Is SLT better than ALT?

- **Conclusions:**
  - Laser trabeculoplasty is successful in lowering intraocular pressure for patients with open angle glaucoma.
  - At this time, there is no literature establishing the superiority of any particular form of laser trabeculoplasty.

Is it better than medical therapy?

- **Conclusions:**
  - IOP reduction was similar in both arms after 9 to 12-month follow-up.
  - These results support the option of SLT as a safe and effective initial therapy in open-angle glaucoma or ocular hypertension.
  - SLT may be the best or most preferred treatment option for some patients.

Is SLT repeatable?

- **Conclusions:**
  - “We found that a repeat 360-degree SLT provided additional IOP reduction, which was not as marked as that with the first treatment session.”
  - Generally no, to a very modest extent (~2 mmHg).

Repeat SLT

- **Conclusions:**
  - Overall, poorly studied.
  - **45 eyes/25 subjects**
  - **Avg 28 m post 1st Tx @ 24 m**
  - **29% > 20% IOP lowering**
  - **39% > 15% lowering**
  - Repeat Tx was less effective than initial

Do topical medications affect SLT?

- **Conclusions:**
  - Topical medications do not adversely, nor favorably, affect SLT success.
  - Success rate of 67% at 6 months.
  - Factors:
    - Pigmentation of the anterior chamber angle, class of antiglaucoma medications, diabetes, sex, central thickness, pseudophakia, washout of eye drops, and previous argon laser trabeculoplasty treatment are not associated with SLT treatment efficacy.

How good is SLT with topical maximal therapy?

- **SLT with ≥3 mmHg Reduction**
  - **30% Non-Responders**
  - **70% Responders**

Somewhat

Does SLT work on nocturnal IOP?

- **Conclusions:**
  - SLT response was delayed in pseudophakic patients.
  - While the long-term effectiveness of SLT is the same in both groups.

Yes!
Does SLT work after cataract surgery?

- Results:
  - There were no significant differences in the IOP lowering effects between the two methods at any time point during the follow-up period (12m).
  - Mean IOP reduction:
    - 75% subjects ≥ 15% decrease from baseline.
    - Approx. 3-4 mmHg.

- Conclusions:
  - Prostaglandin analogs and LTP are both cost-effective options for the management of newly diagnosed mild open-angle glaucoma.
  - Assuming optimal medication adherence, PGAs confer greater value compared with LTP.
  - However, when assuming more realistic levels of medication adherence (making them 25% less effective),
    - Then at current prices for PGAs ($330/yr), LTP may be a more cost-effective alternative.

Incisional Glaucoma Surgery

Traditional filtering or glaucoma drainage devices remain the surgery of choice for patients with advanced glaucoma.

Is SLT more cost effective?

- Conclusions:
  - Prostaglandin analogs and LTP are both cost-effective options for the management of newly diagnosed mild open-angle glaucoma.
  - Assuming optimal medications adherence, PGAs are more effective compared with LTP.
  - However, when assuming more realistic levels of medication adherence (making them 25% less effective),
    - Then at current prices for PGAs ($330/yr), LTP may be a more cost-effective alternative.

Traditional Options

- Trabeculectomy with Mitomycin C (MMC):
  - Bleb forming procedure
  - Risk of bleb leak and complications
  - Long-established procedure with vast experience

- Glaucoma Drainage Device:
  - External or internal implants
  - Risk of bleb leak and complications
  - Typical role is following failed procedures

Why not just do a CE/Phaco?

- Cataract Extraction
  - Generally only appropriate for early stage OHTN glaucoma that is not progressing (or ACG)
  - Much less effect for moderate glaucoma
  - Can reduce use of topical medications
  - Is not long lasting.

Data from OHTS:

- ~ 3-4 mmHg lower
- ~ 16% lower
- ~ 36 months (at least)

Traditional Filtering or Glaucoma Drainage Devices remain the surgery of choice for patients with advanced glaucoma.

What’s New Surgically?

MIGS

- Micro Invasive Glaucoma Surgery
- An unmet need for surgical intervention for mild to moderate glaucoma patients with coexisting cataract.
- MIGS combined with cataract surgery will have an increasing role in managing these patients

Newest Surgical Procedures

- MIGS
  - Micro Invasive Glaucoma Surgery
- Emerging category of devices and procedures
  - Alternative to multiple medications
  - Often combined with cataract extraction
  - Differing definitions and can be grouped into two categories

Methods of lowering IOP with MIGS

1. Schlemm’s canal
   - Trabectome (NeoMedix), iStent (Glaukos)
2. Suprachoroidal space
   - None FDA-approved, Cypass — Transcend
3. Supranasal space
   - None FDA-approved, Aquesys XEN
4. Intra-Canalicular
   - Hydrus MicroShunt