Disclosure

- Michael Chaglasian has the following disclosures:
  - 1. Advisory Board: Allergan, Inc., Alcon Labs, Merck
  - 2. Research Support: Optovue
  - 3. Speakers Bureau: Alcon, Pfizer, Carl Zeiss Meditec

- The content of this presentation is in no manner influenced by any of the aforementioned parties or companies

Objectives

1. Understand the role of pachymetry and the OHTS risk calculator for patients with ocular hypertension.
2. Review the key elements of visual field interpretation for the glaucoma patient.
3. Be familiar with the identification of visual field progression using available software analysis.
5. Current research on new glaucoma medications. What’s on the horizon
Case 1

Ocular Hypertension

Pachymetry

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

Baseline IOP (mmHg)

- >25.75
- >23.75 to ≤ 25.75
- ≤ 23.75

Central Corneal Thickness (microns)

- ≤ 555
- >555 to ≤ 588
- >588

* through 8 Nov 2001
Pachymetry: 3 Outcomes

- **Thin:** <555 µ High Risk, <525
- **Average:** 555-588 µ No change in Risk
- **Thick:** >588 µ Low Risk, >600

Applied to patients with ocular hypertension

Online Risk Calculator

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

Also iPhone/Droid Apps

Risk Calculator
**iPhone App**

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**Risk Calculator Outcomes:**

**Guide to Patient Management**

**5-Year Risk for Progression of OHTN → Glaucoma**

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Range</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>&lt;5%</td>
<td>Monitor</td>
</tr>
<tr>
<td>Moderate</td>
<td>5%-15%</td>
<td>Consider treatment</td>
</tr>
<tr>
<td>High</td>
<td>&gt;15%</td>
<td>Treatment</td>
</tr>
</tbody>
</table>

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

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**OHTS – EGPS 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. Myopia, Disc Hemorrhage
  2. Diabetes
  3. Race (?)
  4. Family history of glaucoma
  5. Exfoliation syndrome and pigment dispersion
Correction Values

<table>
<thead>
<tr>
<th>Corneal Thickness (µm)</th>
<th>Correction Value</th>
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</thead>
<tbody>
<tr>
<td>485</td>
<td>7</td>
</tr>
<tr>
<td>465</td>
<td>6</td>
</tr>
<tr>
<td>445</td>
<td>5</td>
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<tr>
<td>205</td>
<td>-7</td>
</tr>
<tr>
<td>185</td>
<td>-8</td>
</tr>
</tbody>
</table>

Correction values according to corneal thickness of 545 µm

Conversion Charts: don’t really work

Do Not Adjust IOP Based on CCT

Adjusting Intraocular Pressure for Central Corneal Thickness Does Not Improve Prediction Models for Primary Open-Angle Glaucoma

Risk Calculator

In conclusion, the 5-year risk of developing POAG for an individual with ocular hypertension can be simply calculated from age, IOP, CCT, VCDR, and PSD using the risk calculator available at http://fohs.wustl.edu/risk (accessed March 1, 2011), which can be downloaded free of charge. The results of our analyses suggest that the influence of corneal thickness as a prognostic factor for the development of POAG is not entirely through its effect on IOP measurement, but that CCT is a biomarker for structural or physical factors involved in the pathogenesis of POAG.
Clinical Pearls for Challenging Cases

Pachymetry: 3 Outcomes

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

Applied to patients with ocular hypertension

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IOP and CCT

- “Assuming that CCT can be used as a correction factor for GAT is a misinterpretation of the results of OHTS... that couldn’t be further from the truth. Adjusting IOP based on CCT is attempting to instill a degree of precision into a flawed measurement. You may actually correct in the wrong direction. The issues related to the most accurate tonometry need to include the material properties of the cornea”

> James Brandt, MD, Director, Glaucoma Services, UC Davis

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Should Pachymetry be Repeated Over Time? No

Changes in Central Corneal Thickness over Time

*The Ocular Hypertension Treatment Study*

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M. Chaglasian, OD
However, obtain multiple (3) readings on one day.

Central Corneal Thickness: Will One Measurement Suffice?

**Objective:** To evaluate the measurement of central corneal thickness (CCT) in a cohort of glaucoma patients over a month. All measurements were then applied to the criteria described in the Dutch Hypermature Study (DHS).

**Design:** Cohort study.

**Method:** Fifteen patients were recruited from a glaucoma clinic at Western Eye Hospital. Central corneal thickness was measured using an ultrasonic hand-held pachymeter by a trained observer. Patients’ CCTs were measured at 3 consecutive time points.

**Inclusion criteria:** All patients had a Schirmer’s test of 5 mm in one eye or less.

**Results:** Posterior subcapsular lens opacities were found in 8/15 eyes. Corneal thickness readings were stable over 1 month. Mean ± SD corneal thickness measurements were 521 ± 27.8 μm, 522 ± 28.4 μm, and 522 ± 26.8 μm for the first, second, and third measurements respectively. Two patients had increased corneal thickness readings on the second reading. 20% of eyes required re-measurement in both the first and second eyes.

**Conclusions:** Reproducibility of CCT measurements is high and consistent with standard deviation between 22-27 μm. Practical implications of OCT, based on this study, may show OCT measures of CCT are not interchangeable with Ultrasound pachymetry.

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Is Optical/OCT pachymetry the same as Ultrasound? No

- OCT typically **under measures** CCT
  - range 15-55 microns
  - Corneal Edema from topical anesthetic?
  - Corneal “compression” from probe?

- As Ultrasound units were used in OHTS, it’s not appropriate to substitute an OCT based CCT measurement.

- **CPT 76514:**
  - Ophthalmic ultrasound, echography, diagnostic; corneal pachymetry, unilateral or bilateral.
CCT is a RF for Visual Field Loss

Central Corneal Thickness as a Risk Factor for Advanced Glaucoma Damage

- Do not measure CCT on every patient.
  - Risk is for ocular hypertensives

- Thin CCT following LASIK does not increase the risk for glaucoma
  - Note: IOP likely significantly underestimated

- Presence of corneal disease/surgery precludes the use of CCT as a risk factor
Case 2

Early Glaucoma?

Should we treat pre-perimetric glaucoma?

Why wouldn’t you Treat?

- Visual Function of patients with PPG can remain normal for many years.

- Most patients progress slowly, especially when IOP is not too high.
  - Regular follow up can detect progression which is then an indication for intervention

- Elderly patients with reduced life expectancy (be careful here)
Why wouldn't you Treat?

- No clear evidence that treatment improves quality of life.

- Negative Impact of Treatment:
  - Side effects, Personal Costs,

- Public Health View Point
  - Resources should be directed to those who really need it: 1.5 million undiagnosed.

Why should you treat?

- Optic nerve / RNFL damage is permanent
  - Places patient at higher risk

- Risk of disease progression
  - Evidence from clinical trials
    - Ocular Hypertension Study (OHTS)
    - Diagnostic Innovations Study (DIGS)

Rate of Progression

[Graph showing rate of progression with visual function on the y-axis and time on the x-axis.]

Caprioli AJO 2008
Primary POAG Endpoints*
Log Rank P-value <0.001, Hazard Ratio 0.40, 95% CI (0.27, 0.59)

☐ Medication  ☐ Observation

Proportion POAG

Months

*through 8 Nov 2001

Appearance of Mild VF Defect

Appearance of Dense VF Defect
The Humphrey Visual Field Analyzer Printout

Single Field Analysis (SFA) Interpretation

- Demographics/Patient info
- Test name
- Reliability Indices
- Gray Scale
- Deviation Plots
  - Total/Pattern probability plots
- Statistical analysis
- Global indices
- Glaucoma Hemifield Test (GHT)
Patient Demographics

- Correct DOB is essential as pt’s test results are compared to age appropriate normative data.

<table>
<thead>
<tr>
<th>Clinical Pearls for Challenging Cases 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. Chaglasian, OD</td>
</tr>
</tbody>
</table>

Three Indices of Reliability

- False Positive errors
- False negative errors
- Fixation loss rate
  - Gaze tracker

Fixation Losses

- Fixation loss rates more than 20% may indicate a compromised test result
  - Patient moving their eye away from the fixation target
Methods to Monitor Fixation

- Blindspot check
  » adds time to test
- Gaze Tracker with HVF
  » faster test
  » in some pts gaze tracker won't initialize
  » This is due to pupil dilation
- Eye monitoring
  » you watch the patient
  » no proof

False Positive Errors

- Very Important
  - Most Important Reliability
  - The patient pressed the button when no stimulus was presented.
  - Above 15% is strongly suggestive of a compromised test

False Negative Errors

- The pt failed to respond to a stimulus 9 dB brighter than a stimulus that the pt saw at the same location previously.
- Limited Value in glaucoma management
  - b/c they naturally increase as part of the disease process
- Can accept up to 25 – 30% error rate
**Total Deviation Plots**
- Indicates all test locations that are outside of normal limits.
- Threshold sensitivity is compared to age-compared norms at each test point to produce the total deviation decible plots.

**Total Deviation Decibel Plot**
- Negative values indicate sensitivities that are below the median age-corrected sensitivity.
- Positive values indicate higher than normal sensitivities.

**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 symbols like total deviation plots.

Comparing Total and Pattern Deviation

- If TD = PD, essentially no generalized loss.
- TD with a normal PD: something blurring the stimulus (cataract, uncorrected Rx, etc).

Glaucoma Hemifield Test: Very Good Indice to Use
CASE 3
Progression

Ocular Perfusion Pressure
risk factor for glaucoma
New Evidence

Ocular Perfusion Pressure (OPP) = BP - IOP
(BP is mean arterial pressure, diastolic BP, or systolic BP)

Ocular Perfusion Pressure

■ The differential between arterial BP and IOP

- Ocular perfusion is regulated to maintain constant blood flow to the optic nerve despite fluctuating blood pressure and IOP
- The major cause of reduced blood flow is thought to be secondary to vascular dysregulation in susceptible patients, resulting from abnormal/insufficient auto-regulation.
Lower Diastolic, Systolic, or Mean Pressure Reduces Perfusion Pressure

Perfusion Pressure Is a Result of A Delicate Balance Between IOP and Blood Pressure

Lower Perfusion Pressure Is Associated with Increased Risk for Open Angle Glaucoma

Hayreh SS. Trans Am Acad Ophthalmol 1974; 78: 240-54

OPP and Glaucoma Progression:
Population Studies

- Baltimore Eye Survey (AA and Caucasian)\(^1\)
  - 6x excess of POAG in subjects with lowest category of Ocular Perfusion Pressure (OPP)
- Egna-Numarkt Study (Caucasian)\(^2\)
  - Lower Diastolic Ocular Perfusion Pressure (DOPP) associated with marked, progressive increase in frequency of POAG
- Barbados 4 yr Eye Study (African-Caribbean)\(^3\)
  - 4-year risk of developing glaucoma increased dramatically at lower perfusion pressure
- Proyecto Ver (Hispanic)\(^4\)
  - Found lower Diastolic Perfusion Pressure (DPP) associated with increased risk of POAG


\(^2\) Leske et al. Ophthalmology 114 (11), November 2007

Ocular Perfusion Pressure (OPP) = BP – IOP
(BP is mean arterial pressure, diastolic BP, or systolic BP)

Low ocular perfusion pressure has been shown to be strongly associated with the prevalence of glaucoma progression in multiple population-based surveys

- Baltimore Eye Survey (AA and Caucasian)\(^1\)
  - 6x excess of POAG in subjects with lowest category of Ocular Perfusion Pressure (OPP)
- Egna-Numarkt Study (Caucasian)\(^2\)
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  - Found lower Diastolic Perfusion Pressure (DPP) associated with increased risk of POAG

\(^1\) Tielsch JM, Katz J, Sommer A, Quigley HA, Javitt J. Arch Ophthalmol 1995;113:216-21
Los Angeles Latino Eye Study

- Cross-sectional study of 6,357 Latinos, >40 years in Los Angeles, CA.
- Persons with low diastolic and systolic perfusion pressures had a higher risk of POAG.
- DOPP <50 mmHg, the prevalence of glaucoma rapidly increases linearly.

POAG Risk Factors at year 9
Barbados Eye Study

Studies Summary

- These large studies provide strong evidence among different populations for the relationship between vascular deficits and the prevalence, incidence and progression of glaucoma

- Some Limitations,
  - no direct measure of ocular blood flow
  - Varied definitions of hypertension
Clinical Control of OPP

- Lower IOP improves OPP
  - Remains number 1 goal!!
  - Measure blood pressure on your patients

- Higher systemic BP improves OPP, but you do not necessarily want to raise BP:
  - Stroke #3 cause of death in US behind CVD & CA!
  - Avoid drugs that lower systemic BP beyond patient’s desired systemic control.
  - Communicate with PCP
  - Look for nocturnal hypotension.

Nocturnal Hypotension and OPP

- Low blood pressure (BP) at night, coupled with high IOP in supine position, compromise OPP.
  - ? Up to 50% of patients with HTN
  - Using systemic BP meds in the AM to minimize nocturnal hypotension makes sense.

- Using IOP lowering drugs that lower IOP while sleeping makes sense.
  - Avoiding IOP meds that LOWER systemic BP at night (beta blockers, alpha agonists) makes sense.

Case WS

- DOPP=
  - DBP of 68 mmHg @ 2PM and IOP of 12 mmHg
  - Gives 56 mmHg
- Nocturnal BP with Holter Monitor
  - DBP @ 2AM = 58
- Nocturnal IOP (estimate)
  - IOP of 12 mmHg @ 2PM = ?? @ 2AM ~ 18 mmHg
- Nocturnal DOPP
  - 58 - 18 = 40 mmHg, potentially a high risk
Medications

Prostaglandin Analogs

TRAVATAN Z
Lumigan
Xalatan

Latanoprost Generic

- March 2011
  - Expected Availability April
- Fast changeover during reminder of year
  - Branded Xalatan to Latanoprost generic
  - Managed Care Formulary contracts go through December 2011
- Multiple Suppliers
  - Including Pfizer/Greenstone and Falcon
  - Unknown questions about efficacy and side effects
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%

SECOND LINE AGENTS:
alternatives to PGAs, or for adjunctive therapy
Criteria for the Choice of Adjunctive Therapy

- Incremental efficacy
  - The main reason for changing initial monotherapy is the need for additional IOP lowering\(^1\)
  - The purpose of adjunctive therapy is to obtain target IOP\(^2\)
- Other considerations
  - Compliance
  - Tolerability
  - Safety

Options for Adjunctive Therapy

<table>
<thead>
<tr>
<th>Products:</th>
<th>Additional Mean IOP Reduction when Added to a PGA (at 3 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fixed Combinations</strong></td>
<td></td>
</tr>
<tr>
<td>Combigan(^{26})</td>
<td>6.9 mm Hg(^{1})</td>
</tr>
<tr>
<td>Cosopt(^{2})</td>
<td>5.2 mm Hg(^{1})</td>
</tr>
<tr>
<td>Simbrinza</td>
<td>5.6 mm Hg</td>
</tr>
<tr>
<td><strong>Alpha-agonists</strong></td>
<td></td>
</tr>
<tr>
<td>Alphagan(^{2}) P</td>
<td>3.3 mm Hg(^{2})</td>
</tr>
<tr>
<td><strong>Carbonic anhydrase inhibitors (CAIs)</strong></td>
<td></td>
</tr>
<tr>
<td>Azopt(^{2})</td>
<td>3.1 mm Hg(^{2})</td>
</tr>
<tr>
<td>Trusopt(^{2})</td>
<td>3.1 mm Hg(^{2})</td>
</tr>
<tr>
<td><strong>Beta-blockers</strong></td>
<td></td>
</tr>
<tr>
<td>Timotol</td>
<td>2.5 mm Hg(^{2})</td>
</tr>
</tbody>
</table>

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


Azopt TID shows Nocturnal IOP Lowering On Top of PGA:

Alpha Agonists

- **Alphagan-P 0.1% (Allergan)**
  - $\Rightarrow$ BAK $\Rightarrow$ Purite ($\downarrow$ toxicity)
  - Less ocular allergy
- **Aqueous suppressant and:**
  - $\Uparrow$ uveoscleral outflow
- **TID dosing**
- **Generic Brimonidine**
  - 0.2%, 0.15%

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No Nocturnal IOP Lowering with Brimonidine


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Generic Timolol

- **Limitations**
  - Systemic SEs
  - Limited additional IOP with PGA
  - No nocturnal effect
- **Advantages**
  - Low cost ($4/bottle)
  - QD dosing
Beta Blockers as Adjunctive Therapy to a Prostaglandin Analogue

24 Hour Diurnal Control: Timolol vs. Latanoprost

Best Adjunctive Therapy?

J Glaucoma 1999;8:24-30.


Overall = CAI
Advantages of Fixed Combinations

- Dosing—1 drop vs 2 drops
- Convenience
- Potential to improve compliance\(^1\)
- No risk of washout from second drug\(^2\)
  - Washout impedes absorption, thereby reducing efficacy\(^3\)
- Possible cost savings
  - Only 1 copay


Timolol Fixed Combinations

- Dorzolamide hydrochloride/timolol maleate ophthalmic solution (Cosopt\(^\text{®}\))
  - Generic dorzolamide/timolol maleate ophthalmic solution

Timolol Fixed Combination

- Combigan (Allergan)
  - Brimonidine 0.2% and timolol 0.5%
  - BID dosing
- Less allergy than brimonidine alone
**Non-Timolol Fixed Combination**

**SIMBRINZA™ Suspension**
For the Treatment of Elevated Intraocular Pressure (IOP)

- A fixed-dose combination of brinzolamide 1% and brimonidine 0.2%

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**Simbrinza Mono-Therapy**

- IOP Reduction at All Time Points at Month 3 (Study 1)^1,2

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**Simbrinza Adjunctive to PGA**

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Is there anything else that can be done?

Possibly:
- Offer Nocturnal IOP control
- Offer Improved DOPP

Add a CAI or Fixed Combination

Letter to PCP, explain OPP and Low BP related Risk
? Adjust BP Meds
New Medications?
Aerie Pharmaceuticals Inc.

Product Candidate and Mechanism

<table>
<thead>
<tr>
<th>Product</th>
<th>Mechanism</th>
<th>Phase of Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhopressa™</td>
<td>Triple-action 1, 2, 3 - ROCK/NET inhibition</td>
<td>Phase 3 registration trials commenced in July 2014</td>
</tr>
<tr>
<td>Roclatan™</td>
<td>Quadruple-action 1, 2, 3 - Combination of triple-action Rhopressa™ and latanoprost, a PGA</td>
<td>Phase 2b clinical trial completed June 2014 Phase 3 registration trials expected to begin mid-2015</td>
</tr>
</tbody>
</table>

http://www.aeriepharma.com/aerietech.html

Roclatan™

- **A quadruple action** fixed-dose combination product expected to enter Phase 3 registration trials in mid-2015
- A combination of Rhopressa™ with latanoprost.
  - (i) Through ROCK (Rho Kinase) inhibition, it increases fluid outflow (TM)
  - (ii) It reduces episcleral venous pressure
  - (iii) Through NET (norepinephrine transporter) inhibition, it reduces the production of eye fluid.
- Phase 3 efficacy data expected by mid-2016
- If approved by FDA, expect U.S. commercial availability by mid-2018
- Based on Phase 2b clinical data - lowering IOP on average over 21% greater than market leading latanoprost and generating IOP reductions of over 35% in half of the patients in the study - nearly twice that of latanoprost in the same study.¹

Questions / Discussion

mchaglas@ico.edu

Thanks!