“Decision Making in Glaucoma: When to pull the trigger”
COPE #41665-GL

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Disclosures
* Financial disclosures:
  - Speakers Bureau/Consultant:
    - Alcon/Novartis
    - Allergan
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    - Zeiss-Meditec
    - VSP
    - B&L
  - I have no personal financial interests in any of these companies

Glaucoma is an Optometric Problem
- ~ 2.5 million Americans are diagnosed with Glaucoma
  - 1% – 2% of those > 40 years
  - 1.6% > 40 (Framingham Eye Study)
- As many as 95,000 Americans lose some degree of sight to Glaucoma each year
  - 12,000 become blind

It is estimated that 1 million Americans with glaucoma are undiagnosed.

Risk Factors for Glaucoma
- In general, patients are at risk for glaucoma if they have the following:
  - High IOP
  - Family history of glaucoma
  - African ancestry
  - High myopia
  - Cardiovascular risk
  - Age
  - Other: Chronic steroid use/previous eye surgery

European Glaucoma Society: Terminology and Guidelines for Glaucoma, I998:63

Glaucoma
- The most common types:
  - Primary Open Angle Glaucoma
  - Angle Closure Glaucoma
    - Acute or Chronic
  - Secondary Glaucomas
    - Pseudoxfoliation
    - Pigment Dispersion
    - Uveitic
    - Traumatic/Angle Recession

Primary Open Angle Glaucoma
- ~2.5 million Americans have POAG
  - About 1/3 of the POAG is undiagnosed
  - ~ 25% of all cases of POAG are African Americans
Prevalence of POAG and CACG

<table>
<thead>
<tr>
<th>Group</th>
<th>Angle-Closure (million)</th>
<th>Open-Angle (million)</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>22.5</td>
<td>7.4</td>
</tr>
<tr>
<td>India</td>
<td>5.6</td>
<td>5.6</td>
</tr>
<tr>
<td>South Asia</td>
<td>4.2</td>
<td>4.2</td>
</tr>
<tr>
<td>Europe</td>
<td>6.6</td>
<td>6.9</td>
</tr>
<tr>
<td>Africa</td>
<td>0.05</td>
<td>7.0</td>
</tr>
<tr>
<td>Latin America</td>
<td>0.5</td>
<td>1.3</td>
</tr>
<tr>
<td>Near East</td>
<td>0.3</td>
<td>0.7</td>
</tr>
<tr>
<td>Total</td>
<td>33.5</td>
<td>33.1</td>
</tr>
</tbody>
</table>


Risk Factors
- Race: African Americans -5X > whites
- Comparison of prevalence of Glaucoma in LALES Latinos and African-Americans and Whites in the Baltimore Eye Study

Secondary Glaucomas
- Pseudoexfoliation Syndrome (PEX):
  - 1.6%-2.3% of population > 50 yo in US
  - Pseudoexfoliative Glaucoma (PEG) most commonly occurs between 60-80 yo
  - PEX is 2-3X more common in women
  - PEX is reported unilateral in 50%-70% of cases on initial diagnosis
- Pigment Dispersion Syndrome (PDS):
  - ~2.5% of whites in the US
  - 20%-60% of PDS ➔ OHTN
  - 25%-50% of PDS ➔ PDG

Secondary Glaucomas
- Uveitic
  - Estimated to be 7.6% to 23% among patients with uveitis
  - Surgery is required in children > adults
  - 59% of children and in 35% of adults
- Traumatic/Angle Recession
  - Of those eyes with angle recession, very few (~ 0-20%) develop glaucoma
  - In those that do develop glaucoma, the onset is extremely variable

How do ODs become more accurate in diagnosis?
- Refined MHx assessment
  - Remember that IOP alone does not determine glaucoma!
    - Poor sensitivity & specificity
    - Sensitivity 79%
    - Specificity 64%

When to pull the trigger
- It is my observation that many ODs question themselves as to “when to pull the trigger”
  - To soon = mistake and meds cost $$$
  - To late = increases professional liability (malpractice) exposure
  - How many ODs have been sued for starting a patient on meds too soon?

None, Nada, Zero, Zipch, The big Goose Egg!

References:
Peak IOP Outside Office Hours for 2/3 of Eyes (10:00p-7:00a)

IOP is Higher at Night

Med Effects on Diurnal/Nocturnal IOP

How do ODs become more accurate in diagnosis?

How do ODs become more accurate in diagnosis?

Refined MHx assessment
- Remember that IOP alone does not determine glaucoma!
- Compromised ocular hemodynamics
  - Vascular dysregulation
    - Primary (PVD) & Secondary (SVD)
    - PVD = abnorm tendency to inefficiently OBF respond
    - Primarily Endothelin modulated (ET-1 dysregulation)
    - Variable up & down regulation/perfusion
    - SVD = systemic disease related tendency to respond
    - More consistent down regulation/perfusion

Refined MHx assessment
- Remember that IOP alone does not determine glaucoma!
- Compromised ocular hemodynamics
  - Vascular dysregulation
    - Primary (PVD) & Secondary (SVD)
    - PVD = abnorm tendency to inefficiently OBF respond
    - Women > men
    - Academics > blue collar
    - Low BP – Cold hands – low thirst – longer sleep onset
      (need feet to warm before they can sleep)
How do ODs become more accurate in diagnosis?

- Refined MHx assessment
  - Remember that IOP alone does not determine glaucoma!
  - Compromised ocular hemodynamics
    - Vascular dysregulation
      - Primary (PVD) & Secondary (SVD)
      - SVD = systemic disease related tendency to respond
      - MS = Giant cell arteritis – Lupus – RA – Anorexia – Liver cirrhosis - etc
    - Basically all chronic inflammatory autoimmune
    - Essentially no interference with autoregulation yet down regulated

- Refined Ocular assessment
  - Gonioscopy
    - Is Gonioscopy required on all glaucoma patients?
    - Does it need to be done more than once?
    - I only get paid once in their lifetime!

Revised MHx assessment

- Remember that IOP alone does not determine glaucoma!
- Compromised ocular hemodynamics
  - Vascular dysregulation
    - Primary (PVD): & Secondary (SVD)
    - PVD is a major risk but SVD is a minor risk in POAG!

Glaucoma Clinical Workup

- AAO Preferred Practice Pattern Guidelines:
  - Perform gonioscopy periodically (e.g., 1-5 years).
- AOA Clinical Practice Guidelines:
  - To rule out the development of an angle closure component in the glaucoma, gonioscopy should be repeated periodically.

How do ODs become more accurate in diagnosis?

- Refined MHx assessment
- Refined Ocular assessment
- Refined ONH assessment
Five Rules for Assessment of the Optic Disc in Glaucoma

1. Observe the scleral ring to identify the limits of the optic disc and its size

Optic Disc Size

Size of light spot ~ size of average optic disc

Small aperture (5 degree) of Welch-Allyn direct ophthalmoscope

Size of light spot = size of average optic disc

Large discs have large cups in healthy eyes

Optic Disc Size

Small discs: avg vertical diameter <1.5 mm
(1.1 x 1.3 = 1.43)
Large discs: avg vertical diameter >2.2 mm
(1.7 x 1.3 = 2.21)

Small, Average, Large

Five Rules for Assessment of the Optic Disc in Glaucoma

1. Observe the scleral ring
2. Identify the size of the rim

“ISNT” Rule

Rim width
Distance between border of disc and position of blood vessel bending

ISNT rule
 Inferior > Superior > Nasal > Temporal

“ISNT” Rule

- Original “ISNT” research:
  - “It was broadest in the inferior optic disc region ($P < 0.001$), followed by the superior, nasal and temporal ($P < 0.001$) regions.”
  - “The ISNT rule is useful in differentiating normal from glaucomatous optic nerves and is unaffected by race.”
“ISNT” Rule
- Original “ISNT” research:
  - “The ISNT rule was applicable in 71% of normal eyes and 68% of early glaucoma eyes.”

“ISNT” Rule
- More recent “ISNT” research:
  - “Violation of the ISNT rule occurs with greater frequency in the pediatric population with large optic disc cups of nonglaucomatous origin, compared with the pediatric population with normal optic discs”

“ISNT” Rule
- More recent “ISNT” research:
  - “The ISNT rule has limited utility in the diagnosis of open-angle glaucoma.”

“ISNT” Rule
- More recent “ISNT” research:
  - Law SK, Kornmann HL, et al, Evaluation of the “IS” Rule to Differentiate Glaucomatous Eyes From Normal, J Glaucoma. May ’14
  - “…we agree with the conclusion of Morgan et al, that the ISNT rule has only limited utility in the diagnosis of glaucomatous optic neuropathy…”
  - “We demonstrated that a diagnostic test that combines the different features of the optic disc (increase of CDR and ISNT or IS rule) may improve the diagnostic accuracy of glaucoma based on optic disc evaluation.”

Five Rules for Assessment of the Optic Disc in Glaucoma
1. Observe the scleral Ring
2. Identify the size of the Rim
3. Examine the Retinal nerve fiber layer
4. Examine the Region of parapapillary atrophy

Five Rules for Assessment of the Optic Disc in Glaucoma
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3. Examine the Retinal nerve fiber layer
4. Examine the Region of parapapillary atrophy
Five Rules for Assessment of the Optic Disc in Glaucoma

1. Observe the scleral Ring
2. Identify the size of the RNFL
3. Examine the Retinal nerve fiber layer
4. Examine the Region of parapapillary atrophy
5. Look for Retinal and optic disc hemorrhages

How do ODs become more accurate in diagnosis?
- Refined MHx assessment
- Refined Ocular assessment
- Refined ONH assessment
- Refined VF interpretation

Visual Fields: Poor Sensitivity
- A large number of RGCs often are lost prior to detectable visual field abnormalities
- As many as 50% optic nerve fibers can be lost prior to a standard perimetric defect \(^1,2\)
- By the time there is a 5 dB loss, there is a corresponding 25% loss of RGCs\(^2\)

\(^1\) Quigley HA, Addicks EM, Green WR, Arch Ophthalmol. 1982; 100:135
\(^2\) Quigley HA, Duker JS, Green WR. Arch Ophthalmol. 1989; 107:433

Visual Fields: Highly Variable OHTS
- 86% of visual field abnormalities not replicated on retesting\(^3\)

Visual Field Progression

\(^3\) VF defect defined as GHT outside normal limits, CFPQ < 50%, or both
Glaucma Progression Analysis (GPA)

- GPA has been found to have high specificity in determining glaucoma progression
- A recent study suggests:
  - “GPA criterion of ‘likely progression’ has high specificity on average, but some patients are more prone to false-positive alerts than others
  - This report may help to avoid false-positive decisions on progression in patients with uncharacteristically large variability and frequent response errors.”


Change Analysis

- The VFI is less sensitive to a worsening cataract or removal of a cataract than is mean deviation index (MDI).
- The predictive value of VFI depends on the validity of the assumption that “past performance predicts future performance”.


Visual Field Index

- Central points weighted more heavily than on periphery
- Reduces cataract effect to the measurement of VF loss

Visual Field Index Bar

- Shows vision loss in terms of %
- Enhanced visual presentation
Visual Field Index

VF Index plotted against age:
- Characterizes trend significance over next 5 years
- Aids in interpretation & patient education
- Helps formulate individualized treatment decisions

Summary of Functional Tests

<table>
<thead>
<tr>
<th>Advantages</th>
<th>SITA SAP</th>
<th>SITA SWAP</th>
<th>FDT Matrix</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Gold Standard”</td>
<td></td>
<td></td>
<td>More portable</td>
</tr>
<tr>
<td>As fast as SITA SAP</td>
<td></td>
<td></td>
<td>Tolerates blur</td>
</tr>
<tr>
<td>Possibly more sensitive</td>
<td></td>
<td></td>
<td>Possibly more sensitive</td>
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</table>

<table>
<thead>
<tr>
<th>Disadvantages</th>
<th>SITA SAP</th>
<th>SITA SWAP</th>
<th>FDT Matrix</th>
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<tbody>
<tr>
<td>Not sensitive enough to detect early glaucoma</td>
<td></td>
<td></td>
<td>Limited clinical evaluation</td>
</tr>
<tr>
<td>Limited clinical evaluation</td>
<td></td>
<td></td>
<td>Variability</td>
</tr>
<tr>
<td>Variability</td>
<td></td>
<td></td>
<td>Cataract effects</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Best use</th>
<th></th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Baseline VF and following progression in advanced disease</td>
<td></td>
<td></td>
<td>Younger patients</td>
</tr>
<tr>
<td>Early diagnosis</td>
<td></td>
<td></td>
<td>Early diagnosis</td>
</tr>
</tbody>
</table>

The “5Rs” of Progression

1. **Record** baseline structure and function.
2. **Risk** evaluation.

Developing a Risk Profile

- Each patient must be assessed individually
- Establish baseline risk and reassess from exam to exam
- **Criteria**
  - Stage of disease
  - Life expectancy
  - How old is the patient?
  - How long did the patient’s parents live?
  - How is the patient’s overall health?

Developing a Risk Profile

- Each patient must be assessed individually
- Establish baseline risk and reassess from exam to exam
- **Criteria**
  - Stage of disease
  - Life expectancy
  - Other risk factors

Independent Risk Factors for Progression

<table>
<thead>
<tr>
<th></th>
<th>Elevated IOP</th>
<th>CIGTS</th>
<th>CRNRT</th>
<th>EMGT</th>
<th>ESPS</th>
<th>OHTS</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td>24 to 32 mm Hg</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Elevated IOP</td>
<td>&gt; 32 mm Hg (2 points)</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Central corneal thickness</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Disc hemorrhage</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Visual field (higher PSD)</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Cup-to-disc ratio</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Visual field (greater MD)</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Retinal neovascularization</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Low ocular perfusion pressure</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Abnormal baseline HRT/OCT/OCTa</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Race (nonwhite)</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
</tbody>
</table>
Independent Risk Factors for Progression
- **Elevated IOP**
  - 24 to 32 mm Hg
  - > 32 mm Hg (2 points)
- **CCT below 500 µm**
- **Disc hemorrhage (2 points)**
- **Pseudoexfoliation/Pigment**

<table>
<thead>
<tr>
<th>Number of Points</th>
<th>Level of Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>Low</td>
</tr>
<tr>
<td>2</td>
<td>Medium</td>
</tr>
<tr>
<td>&gt; 2</td>
<td>High</td>
</tr>
</tbody>
</table>

The “5Rs” of Progression
1. **Record** baseline structure and function
2. **Risk** evaluation
3. **Repeat** fields and imaging/photos
4. **Rate** of progression
5. **Reassess** and revise management plan and re-establish baseline

The “5Rs” of Progression

<table>
<thead>
<tr>
<th>dB Loss per Year</th>
<th>Rate of Progression</th>
</tr>
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<tbody>
<tr>
<td>&lt; 0.5</td>
<td>Low</td>
</tr>
<tr>
<td>0.5-1.5</td>
<td>Moderate</td>
</tr>
<tr>
<td>&gt; 1.5</td>
<td>High</td>
</tr>
</tbody>
</table>

How do ODs become more accurate in diagnosis?
- Refined MHx assessment
- Refined Ocular assessment
- Refined ONH assessment
- Refined VF interpretation
- Refined NFL assessment

3 Imaging technologies have been shown to be effective in detecting and managing ocular pathologies
- **Scanning Laser Polarimetry (SLP)**
  - Measures birefringence
- **Confocal Scanning Laser Ophthalmoscopy (CSLO)**
- **Optical Coherence Tomography (OCT)**

Scans & Analysis
- Fast RNFL (delineated): Three circular scans with a 3-mm diameter are used to image the peripapillary region of the ONH to create a TWAN image.
- Fast Optic Disc (Monocular): Utilizes a 6-line raster scan (6mm) through the ONH at each 12 clock hours. Each individual scan can be reviewed.
- Fast Macula (Bilaterally): The Stratus uses a 6-line radial pattern to image the macula (6 mm).
TD Stratus OCT Deficiencies

- Acquisition times are slow so movement artifact affects accuracy
- Database is VERY limited in patients >80 yo
- Database is VERY limited in patients outside -12.00 or +8.00
  - Highly myopic eyes have a wide range of “normal” RNFL thickness
  - Moderately myopic individuals may have thinner peri-papillary RNFL at the superior and inferior poles when measured by OCT.
  - Interpreting a myopic glaucoma suspect’s RNFL status needs to take into account these limitations.


Fourier Domain OCT Advantage

- Faster speed also allows for greater density of sampling points and reduces artifacts from eye-movements
  - RTVue FD OCT has 26,000 A scans/sec vs Stratus TD OCT with 400 A scans/sec

Fourier Domain OCT Advantage

- FD OCT has twice the depth resolution as TD OCT
  - 5 microns vs 10 microns
- Allows imaging and segmentation of:
  - Anterior segment
  - Macula
OCT Advantages

- Anterior segment OCT scanning has always been possible but improved resolution has made the new generation OCTs far superior.
  - Cornea:
  - Angle structures:
  - Macular Ganglion Cell layers (GCC)

Ganglion Cell Loss in the Macula

- Histologic studies have shown ganglion cell loss in the macula
- Desatnik et al, found macular ganglion cells are lost in early glaucoma
- Yucel et al, showed loss of cells in the parvocellular layers of the LGN implicating central ganglion cell loss

Macular Ganglion cell density

- 50% of ganglion cells located in central 4.5mm (16°)
- Peak ganglion cell density is 15,000 cells/mm² in macula (white region left)
- Area represents only 7.3% of total retinal area
- RTVue Ganglion cell complex map covers central 6mm area

Diagnostic Accuracy with TD OCT: Macula vs RNFL

- Medeiros et al, found the diagnostic accuracy of peripapillary RNFL thickness was significantly more accurate than macula thickness
- Wollstein et al, found similar results where RNFL thickness was significantly more accurate for detecting glaucoma than macula thickness

Progression: Macula vs RNFL

- Using TD OCT, Medeiros et al, compared the accuracy for detecting progression using RNFL versus macula thickness and found the RNFL was significantly more sensitive and specific than macula thickness

TD OCT Study Limitations

- Major disadvantage in these studies is that TD OCT typically measures full retinal thickness only (does not isolate ganglion cells)
- TD OCT does not have enough depth resolution to image and segment the ganglion cells accurately and reliably
GCC Thinning in Glaucoma

Overlay of the RNFL and GCC

GCC Report: Normal

GCC Deviation Map

color coded map shows regions where the change from normal reaches statistical significance
- Green = values within normal range (p-value 5% to 95%)
- Yellow = borderline results (p-value < 5%)
- Red = outside normal limits (p-value <1%)

 GCC Change Analysis

David Hong, MD, PhD www.A2O_ERRORS

GCC Change Analysis
Revisiting the Macula

- Can imaging the ganglion cells in macula with FD OCT improve glaucoma detection?

Diagnostic Accuracy: GCC vs FD OCT RNFL

- Rao et al, found GCC had similar accuracy levels as FD RNFL
- Seong et al, found similar results
- Kim et al, found values were higher for RNFL vs GCC in a group of advanced glaucoma patients, but GCC values were higher than RNFL in a group of early glaucoma patients

VF& OCT results show poor correlation in advanced RNFL loss

- A retrospective study of patients with early to advanced glaucoma showed a wide variation in mean deviation in patients with advanced RNFL loss when comparing visual field sensitivity with retinal nerve fiber layer thickness.
- Jessica Neuville, OD, presented at AAOpt 2010, a study that suggests the OCT
  - is moderately correlated to visual function in early loss,
  - is a poor predictor of visual function at advanced levels of RNFL loss

GCC Summary

- GCC thickness correlates well with VF
- More reproducible and more accurate for detecting glaucoma than macula thickness with TD OCT
- Similar accuracy for detecting glaucoma as FD OCT RNFL thickness
- Best in early glaucoma

What value is digital technology?

They offer an expert opinion but the new generation OCTs are far superior

How do ODs become more accurate in diagnosis?

- Refined MHx assessment
- Refined Ocular assessment
- Refined ONH assessment
- Refined VF interpretation
- Refined NFL assessment
- Refined Management selection
**Medicinal Management**
- Prostaglandin Derivatives
- Topical CAI’s
- Adrenergics
- Beta-Blockers
- Combos
- Cholinergics/Anticholinesterases
- Oral CAI’s

**Prostaglandin analogues**
- Zioptan™ (was Merck but now is Akorn)
  - Tafluprost 0.0015%
  - The only preservative free PGA!!
- ~30% - 35% IOP decr
- QHs use
  - Vials often hold > 4 drops

**Combinations**
- Cosopt® (was Merck but now is Akorn)
  - Timolol 1/2% & dorzolamide
  - As effective as separate dosing (?)
  - Better convenience & compliance
    - Still stings!!
  - 32%-38% IOP decr
  - BID use
- Cosopt PF® (was Merck but now is)
  - Preservative Free!!
  - BID use

**Combinations**
- Simbrinza™ (Alcon/Novartis)
  - Brinzolamide 1% & Brimonidine 0.2%
  - As effective as separate dosing
  - Better convenience & compliance
    - Less sting!!
  - 21%-35% IOP decr
  - TID use
    - Used BID in Europe

**CAI’s**

**Current Medication Paradigm**
Glaucoma Medications in the Pipeline

<table>
<thead>
<tr>
<th>New MOAs</th>
<th>ROCK/NET Inhibitor (qd)</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>AR-13324 (Aerie)</td>
<td>ROCK/NET Inhibitor (qd)</td>
<td>Phase 3</td>
</tr>
<tr>
<td>K-115 (Kowa)</td>
<td>ROCK Inhibitor (bid)</td>
<td>Phase 3 (Japan)</td>
</tr>
<tr>
<td>AMA0076 (Amakern)</td>
<td>ROCK Inhibitor (bid)</td>
<td>Phase 2a</td>
</tr>
<tr>
<td>INO-8875 (Inotek)</td>
<td>Adenosine-A1 agonist (bid)</td>
<td>Phase 2</td>
</tr>
<tr>
<td>OPA-6666 (Arcus)</td>
<td>Adenosine-A2a agonist (bid)</td>
<td>Phase 1/2</td>
</tr>
<tr>
<td>SYL040012 (Sylentis)</td>
<td>RhoAI beta blocker (bid)</td>
<td>Phase 2</td>
</tr>
</tbody>
</table>

All new MOA’s work at the TM

<table>
<thead>
<tr>
<th>New PGAs</th>
<th>NO donating latanoprost (qd)</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOL-30259 (B&amp;L)</td>
<td>NO donating latanoprost (qd)</td>
<td>Phase 3</td>
</tr>
<tr>
<td>NCX-470 (Pfizer)</td>
<td>NO donating bimatoprost (qd)</td>
<td>Phase 1</td>
</tr>
<tr>
<td>DE-117 (Sandoz)</td>
<td>EP2 agonist (qd)</td>
<td>Phase 2a</td>
</tr>
<tr>
<td>ONO-9054 (Otsu)</td>
<td>EP2/EP3 agonist (qd)</td>
<td>Phase 1</td>
</tr>
</tbody>
</table>

Prostaglandins
- Current commercial PGA’s all bind to the PGFP_{2a} receptor
  - Bimatoprost may also bind to PGEP_{1}
- Newest research is in PGEP_{2a}
  - Early studies suggest a decrease in IOP that was long-lasting and greater than PGFP_{2a}
  - PGFP_{2} was less stable in aqueous solution
  - Allergan’s Butaprost binds to PGEP_{2}
  - ONO Pharmaceuticals’ ONO-0476
  - Prodrug of prostanoic EP_{2}

Nitric Oxide Donation
- In the past, nitric oxide (NO) was considered “toxic” as one of several environmental pollutants (i.e. cigarette smoke & smog)
  - ≠ nitrous oxide (N_{2}O) “Laughing Gas”
- By late ’90s, it was determined that NO is a fundamental player in general body physiology as a messenger molecule
  - Essential to daily functions ranging from BP regulation & digestion to antimicrobial defense

NO-Prostaglandins
- Nitric Oxide-Donating PGF_{2α} PGA’s:
  - Pfizer/Nicox Research are investigating NO-Donating Bimatoprost 0.004% (NCX 470)

Rho Kinase Inhibitors
- Mechanism:
  - Rhokinase is a serine/threonine kinase that serves as an important downstream effector of Rho GTPase
  - It plays a critical role in regulating the contractile tone of smooth muscle tissues in a calcium-independent manner
  - ROCK inhibitors reduce IOP by enhancing aqueous humor drainage through the trabecular meshwork
  - ROCK inhibitors also appear to lower the episcleral venous pressure, which contributes approximately half of IOP in healthy subjects
Rho Kinase Inhibitors

- Several companies with phase I to III trials
- Likely not to be packaged with BAK
- Amenable to alternative delivery modes:
  - Punctal plugs, gel vehicle etc.

Projected Medication Paradigm

- AAs, Blk, CAIs
- Fluid Inflow/Production
- Ciliary Processes

- 3′-CAs & AAs
- Fluid Outflow
- Secondary Drain (Draining)
- EVP

Rho Kinase Inhibitors

- Status:
  - April 2014: Rhopressa Phase 3 Trial (Rocket 1) Misses Primary Endpoint
  - All end points of subjects <26 were met but not about above
  - FDA allowed modification of study endpoints
  - Phase 2 as met and Phase 3 is underway
  - AMA0076 (Amakem) goes forward

Rho Kinase Inhibitors

- Current status:
  - Roclatan:
    - Essentially, Rhopressa + Xalatan
    - Netarsudil 0.02% + Latanoprost 0.005%

Triple-Action Rhopressa™

Mechanism of Action:
1. ROCK inhibition relaxes TM, increases outflow
2. NET inhibition reduces fluid production
3. ROCK Inhibition lowers EVP
Fluid**  
- Fluid Outflow: Primary Drain (TM)  
- Lower EVP (Episcleral Venous Pressure)  
- NET = reduced fluid production  
- Enhanced uveoscleral outflow

**Rho Kinase Inhibitors**
- **Status:**
  - **Roclatan™:**
    - June 2014: Phase 2b results:
      - All clinical endpoints met
      - Efficacy >Latanoprost by 1.6-3.2 mm Hg at all time points
      - Hyperemia remains the #1 adverse reaction reported
    - Sept 2016: Phase 3 “Mercury 1”
      - Achieved primary endpoints at IO’s > 20 but < 36
      - Demonstrated statistical superiority over both latanoprost and Rhopressa™
    - “If Mercury 1 and 2 are successful, we expect to file the NDA for Roclatan™ near year-end 2017…”

**Surgical Management**
- Is ALT/SLT a better option than primary Tx than medication?
- Early decisions were based on the Glaucoma Laser Trial (GLT) of 1995
Interpreting the GLT Results
- Initial treatment with ALT is at least as effective as initial treatment topical medication in patients with POAG in terms of control of IOP, optic disc and visual field
- Ultimately, ALT will need to be supplemented with other modes of intervention
- What about SLT????

SLT as an alternative to PGAs
- SLT vs. latanoprost for IOP control in OHT and POAG
- 12-month study
- 90°, 180°, 360° SLT
- Success criterion
  - 20% - 30% IOP reduction from baseline

SLT as an alternative to PGAs
- Results
  - More 360° SLTs (60%) achieved success criterion (> 30% IOP reduction) than did 90° or 180°
  - Latanoprost-treated eyes achieved success criterion in more cases than 90° or 180° and did as well as 360° in maintaining diurnal IOP reduction

Controversies in Treatment
- Dude….Can you prescribe medical marijuana for my glaucoma?

MJ Use in the USA
- There has been a significant change in the attitude of acceptance of use of marijuana in the U.S.
  - Over 50% of the states now approve the use of MJ for either medical or recreational (or both) use.
Cannabinoid Consequences

- To date, only one large-scale study has sought to determine the frequency with which MJ smokers develop cancer
  - No association was found between MJ use and any other type of cancer, including cancers normally linked to tobacco smoking
  - The study was limited by how many of its participants were younger than the average ages when many cancers appear as well as by the short duration of their MJ use

Cannabinoid Consequences

- Exposure to cannabinoids can also affect the cardiovascular system
  - Both smoked MJ and synthetic THC have been shown to raise heart rate
  - from 20%-100% above normal in some cases
  - THC can also exaggerate the drop in BP that occurs when a person rises to standing after lying down causing syncope
  - People at risk for cardiovascular disease would be wise to avoid MJ and THC

Cannabinoid Consequences

- Fertility research on MJ users has yielded conflicting results
  - The few studies that have been conducted to assess THC's effects on human reproduction have produced results that are consistent with those of the animal studies
  - In a study of Jamaican women (they prepared it as a tea to relieve morning sickness), no neurobiological or behavioral differences were detected between newborn babies of those who used MJ and those who did not

Cannabinoid Consequences

- Memory
  - One study involving over 1,000 individuals found that chronic cannabis use is associated with cognitive decline
    - greater deterioration being observed in those individuals presenting a more persistent use
  - Among the various cognitive domains studied, memory is one of the most frequently identified as being negatively affected by cannabis
Chronic use & RGC’s
- **Association Between Regular Cannabis Use and Ganglion Cell Dysfunction**
  - 52 participants (18-35 yo)
  - 28 regular cannabis users (24 male/4 female)
    - At least 7 consumptions per week over the last 30 days with (+) THC on urine analysis
    - Also + tobacco users
  - 24 controls (20 male/4 female)
    - No history of THC. (-) THC on urine analysis and (-) tobacco user

Chronic use & RGC’s
- **Association Between Regular Cannabis Use and Ganglion Cell Dysfunction**
  - **Findings:**
    - There was a significant increase in the N95 implicit time (latency) of the pattern ERG (pERG) in cannabis users with a median of 8.4 milliseconds difference between controls and users
    - It is unclear if this increase in latency (delay in processing) is permanent or disappears after withdrawal from use

Chronic use & RGC’s
- **Association Between Regular Cannabis Use and Ganglion Cell Dysfunction**
  - **Conclusion:** Our results demonstrate a delay in transmission of action potentials by the ganglion cells in regular cannabis users, which could support alterations in vision. Our findings may be important from a public health perspective since they could highlight the neurotoxic effects of cannabis use on the CNS as a result of how it affects retinal processing.

Chronic use & RGC’s
- **Association Between Regular Cannabis Use and Ganglion Cell Dysfunction**
  - **Commentary:** However, the conclusion that cannabis causes retinal ganglion cell dysfunction cannot be made with any degree of certainty based on the evidence provided in the current study. This question should be reexamined with some urgency, using a degree of scientific rigor, which may be challenging in jurisdictions where cannabis consumption is illegal.

Cannabinoid Consequences
- In summary, there are many reasons to worry that for people who might choose to use MJ as medicine (and especially those who smoke it) the drug could actually add to their health problems

Societal Trends
- May 7, 2015: “Texas could be on board with legalized cannabidiol before the end of this session, as the Texas Senate voted 26-5 to approve SB 339…. Epilepsy patients in Texas would have access to medicinal oils containing a therapeutic component found in marijuana …”
Societal Trends

- **April 16, 2015:** “Georgia Governor Signs "Haleigh's Hope Act" on CBD Oil for Kids.”
  - The bill takes effect immediately, and allows the possession of up to 20 ounces of cannabis oil if a doctor signs off on the treatment.

- **Wide Variability In Potency Plagues Medical Marijuana Edibles, JAMA Study (Forbes 6/23/2015)**
  - According to a paper published this morning in *JAMA*...shows that the active chemicals in edible cannabis products can vary from 1% to 155% the amount listed on the product label.

Societal Trends

- **Doug McIlwraith of 24/7 Wall Street:** “The next 11 states to legalize marijuana (in Nov ‘16)…”
  - Massachusetts
  - Nevada
  - California
  - New York
  - Vermont
  - Minnesota
  - Connecticut
  - Maryland
  - Rhode Island
  - Maine
  - Delaware

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Societal Trends

- **Healthy Kids Colorado Survey**
  - Approximately 17,000 randomly selected youth from 157 middle and high schools throughout the state participated in the 2015 survey.

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Marijuana laws in the US

Legislation ranges from permitting the medical use of marijuana, up to a certain threshold (usually a few ounces) and may allow sales (most in Washington, DC). Decriminalization removes criminal penalties, including jail time, for possession of a small amount, but typically leaves a civil fine in place.

<table>
<thead>
<tr>
<th>Legal</th>
<th>Medical and recreational</th>
<th>Decriminalization</th>
<th>Fully Legal</th>
</tr>
</thead>
</table>

Source: Marijuana Policy Project
Credit: German Lopez

June 8, 2016: Ohio became the 25th state to legalize medical marijuana.
Societal Trends

- **Healthy Kids Colorado Survey**

  ![Graph showing youth marijuana use](image)

<table>
<thead>
<tr>
<th>Year</th>
<th>1999</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
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<th>2004</th>
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</thead>
<tbody>
<tr>
<td>Users</td>
<td>43%</td>
<td>39%</td>
<td>30%</td>
<td>28%</td>
<td>25%</td>
<td>22%</td>
<td>21%</td>
</tr>
</tbody>
</table>

  - Have used marijuana at least once in their lifetime
  - Have used marijuana at least once in the last 30 days

Societal Concerns

- Full legalization of marijuana….
  
  - I will leave THAT to your personal politics!

Things we already know…

- Third party insurers have greatly changed the medical care environment
- Nationwide, nearly 65% of the average ODs gross income is coming from a third party insurer
- Older adults make up >1:6 patients and >1:7 practice revenue dollars
- Glaucoma can be “owned” by Optometry!

Thank You!