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

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Disclosures

- Financial disclosures:
  - Speakers Bureaus/Consultant:
    - Alcon
    - Allergan
    - Optovue
    - Zeiss-Meditec
    - VSP
    - B&L
    - Ivantis
  - 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

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

Glucoma

- The most common types:
  - Primary Open Angle Glaucoma
  - Angle Closure Glaucoma
  - Acute or Chronic
  - Secondary Glaucomas
  - Pseudoxfoliation
  - Pigment Dispersion
  - Uveitic
  - Angle Recession
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>22.3</td>
<td>7.4</td>
</tr>
<tr>
<td>India</td>
<td>5.6</td>
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</tr>
<tr>
<td>South Asia</td>
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<tr>
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<td>Latin America</td>
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</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>

POAG = primary open-angle glaucoma, CACG = chronic angle-closure glaucoma.

Adapted from: Slagnell MK. Dr. Optometry. OCT 10: 2015.

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
- 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

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

None, Nada, Zero, Zilch. The big Goose Egg!

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%

Peak IOP Outside Office Hours for 2/3 of Eyes

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 = inborn 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

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 = inborn 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!

- Refined 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.

- A Video Atlas ~

http://gonioscopy.org/

Wallace L.M. Alward
Frederick C. Bliedt Chair in Ophthalmology
Director, Glaucoma Service
University of Iowa Carver College of Medicine
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

Measurement of optic disc size with direct ophthalmoscope

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

Size of light spot – size of average optic disc

Optic Disc Size

Size of cup varies with size of disc
Large discs have large cups in healthy eyes

Small: avg vertical diameter <1.5 mm (1.1 X 1.3 = 1.43)
Average: avg vertical diameter >2.2 mm (1.7 X 1.3 = 2.21)

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

- More recent “ISNT” research:
  - “The ISNT rule has limited utility in the diagnosis of open-angle glaucoma.”
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
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
- By the time there is a 5 dB loss, there is a corresponding 25% loss of RGCs

1Quigley HA, Addicks EM. Green WR. Arch Ophthalmol. 1982; 100:135
Visual Fields: Highly Variable OHTS

- 86% of visual field abnormalities not replicated on retesting

1st VF abnormal (GHT Outside Normal Limits)
2nd VF normal (GHT Within Normal Limits)
3rd VF abnormal (GHT Outside Normal Limits)

Visual Field Progression

Event Analysis

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."
Visual Field Index

- 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 Bar
- Shows vision loss in terms of %
- Enhanced visual presentation

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

Summary of Functional Tests

<table>
<thead>
<tr>
<th>Advantage</th>
<th>SITA SAP</th>
<th>SITA SWAP</th>
<th>FDT Matrix</th>
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</thead>
<tbody>
<tr>
<td>“Gold Standard”</td>
<td>As fast as SITA SAP</td>
<td>Possibly more sensitive</td>
<td>More portable</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tolerates blue</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Possibly more sensitive</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Variability does not increase with severity</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Disadvantages</th>
<th>Not sensitive enough to detect early glaucoma</th>
<th>Limited clinical evaluation</th>
<th>Limited clinical evaluation</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Variability</td>
<td>Cataract effects</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Best use</th>
<th>Baseline VF and following progression in advanced disease</th>
<th>Early diagnosis</th>
<th>Early diagnosis</th>
</tr>
</thead>
</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?

Independent Risk Factors for Progression

<table>
<thead>
<tr>
<th>Factor</th>
<th>Level of Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated IOP</td>
<td>Low</td>
</tr>
<tr>
<td>&gt; 32 mm Hg (2 points)</td>
<td>Medium</td>
</tr>
<tr>
<td>CCT below 500 µm</td>
<td>High</td>
</tr>
<tr>
<td>Disc hemorrhage (2 points)</td>
<td></td>
</tr>
<tr>
<td>Pseudoexfoliation/Pigment</td>
<td></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.

<table>
<thead>
<tr>
<th>dB Loss per Year</th>
<th>Rate of Progression</th>
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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>

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
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)
- Confocal Scanning Laser Ophthalmoscopy (CSLO)
- Optical Coherence Tomography (OCT)

Glaucoma Clinical Workup
Digital Tomography Deficiencies
- 2D measurement are stacked to achieve a 3D assessment
  - An inferred estimate of the RNFL height is based on a depth of 50 microns
  - All estimates of glaucoma status are based on a multivariate analysis
    - This regression analysis (Moorfields regression analysis) also compensates for age and identifies glaucomatous eyes with a relatively high level of sensitivity and specificity

GDx Basic Principles
- The amount of retardation from the RNFL is directly proportional to the RNFL thickness

GDx Basic Shortcomings
- The crystalline lens and cornea have significant birefringence which is highly variable. As such, the macula was used as a reference to variably compensate in the interpretation of the reflected RNFL birefringence (GDx VCC).
- It measures NFL thickness but only inferentially measures loss based on normative database.
  - 540 healthy eyes with 271 glaucomatos eyes
    - 18-82 yo in healthy with 25-89 yo glaucomas

GDx Basic Shortcomings

- Ocular movement such as nystagmus can render GDx measurements meaningless.
- Older patients, high myopia, or lightly pigmented fundus eyes, are subject to increased birefringence with an abnormal s/n ratio which can provide erroneous readings.
- PPA can be a confounding factor if it falls within the measurement circle.
  - The circle can be enlarged to avoid scanning the PPA region and increase the reliability of measurements yet that adds variability.

Correlation of the Deviation Map with Visual Fields

- But GDx does NOT assist in differentiating in congenital NFL decreases or myopic ONH decreases
  - Basically it measures but does NOT interpret

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:
  - Cornea
  - Angular structures
  - Macular Ganglion cell layers

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 macular 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 Deviation Map

% loss =

actual scan value – normal value

normal value

color coded map

- Percent loss value at each pixel location relative to normals (based on age-adjusted normative database) of over 300 healthy eyes
  - Blue = thinning 20%-30% relative to normal
  - Black = 50% loss or greater

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%)

David Huang, MD, PhD. www.AI2Tech.net
GCC Change Analysis

- Thickness Maps
- Deviation Maps
- Significance Maps
- Trend Analysis
- GCC parameter 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.

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

The “Prosta-somethings”

Travoprost (Travatan™)
Latanoprost (Xalatan™)
Tafluprost (Zioptan™)
Bimatoprost (Lumigan™)

The “Prosta-somethings”
- The most common 1st line Tx in nearly all glaucoma types
- Increased uveoscleral outflow
  - ~30%-40% mean IOP decr
  - qhs use

Topical CAI’s
- IOP decr about 9%-20%
  - Depending on the iris color
  - tid use
    - Often used bid
  - Brinzolamide is equivalent to Dorzolamide (Trusopt™)
    - More physiologic pH
    - less burning on use
Adrenergics
- Alpha₂ agonist (Brimonidine 0.15% & 0.2%)
  - 16% allergy rate (10% for Alphagan P!)
- Decreased aqueous production & increased uveoscleral outflow
- Minimal tachyphylaxis reported
  - 21% IOP decr
  - tid use
- bid as effective & best compliance

Beta-Blockers
- Non-selectives
  - 20%-30% IOP reduction
  - Available as a generic
  - Qday use (best in am!)
    - Timolol maleate
    - Timolol Gel (Timolol-XE®)
      - Gel formulation increase contact time-penetrance
    - Timolol Hemihydrate (Betimol®)
      - A levosomer of Timolol

Beta-Blockers
- B₁ Selective
  - Selectivity = less efficacy
  - 15%-25% IOP reduction
  - Available as a generic
  - bid use
    - Betaxolol (Betoptic®, S)
      - “S” = styrene molecule that increases contact time and penetrance

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 PP® (was Merck but now is Akorn)
  - Preservative Free!!

Combinations
- Simbrinza™ (Alcon)
  - Brinzolamide 1% & Brimonidine 0.2%
  - As effective as separate dosing
  - Better convenience & compliance
    - Less stings!!
  - 21%-35% IOP decr
  - tid use
    - Used bid in Europe
Cholinergics Anticholinesterases
- Pilocarpines
  - 1/2%, 1%, 2%, 4%, 6% concentrations
  - NOT to be used with uveitis!
  - Significant side-effects
    - start lower % and increase to max effect
  - qid use

Oral CAI’s
- Acetazolamide (Diamox)
  - Generic available
  - Decreases secretion of aqueous
  - Sulfonamide derivative
  - Significant side-effects
    - Dosages:
      - Diamox: 250mg bid –qid
      - Sequels: 500mg bid

Oral CAI’s
- Methazolamide (Neptazane)
  - Decreases secretion of aqueous
  - Sulfonamide derivative
  - Dosages:
    - 50mg-100mg bid to tid

Back to the Future!
- Nutritional Treatments:
  - Blood flow enhancers
    - Mirtogenol® (120 mg b.i.d.)
      - commercial composition of Bilberry extract (Mirtoselect®) and French maritime pine bark (Pycnogenol®)
    - Gingko biloba (80 mg b.i.d.)
      - also works as an antioxidant
  - Calcium channel blockage (i.e. Nifedipine)
    - Increase blood flow therefore poss neuroprotection
      - Significant SE’s noted in studies (1/3 dropout from SE’s)
    - Headaches, flushing, dizziness, swelling, low BP, nausea
  - Lomerizine HCl (Santen’s DE-090)
    - Only CA++ antagonist being developed as oral glaucoma treatment
    - Excellent safety and minimal SE’s to date
In combination with E and Omega 3 (DHA), shown to stabilize VF
- Vitamin D
- Early '14 study supported association of Vit. D deficiency with presence of glaucoma
- No supplementation needed but may want to test for deficiency in NTG

**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 (N₂O) “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

**Prostaglandins**

- Current commercial PGAs all bind to the PGF₂α receptor
  - Bimatoprost may also bind to PGEP₁
- Newest research is in PGEP₂,₄
  - Early studies suggest a decrease in IOP that was long-lasting and greater than PGF₂α
  - PGEP₂ was less stable in aqueous solution
  - Allergan’s Butaprost binds to PGEP₂
  - ONO Pharmaceuticals’ ONO-0476
    - Prodrug of prostanoid EP₂

**NO-Prostaglandins**

- Nitric Oxide-Donating Prostaglandin F₂-Alpha PGA s:
  - Pfizer/Nicox Research are investigating NO-Donating Bimatoprost 0.004% (NCX 470)
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.

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

Rho Kinase Inhibitors

- Current 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 + Latanoprost

Rho Kinase Inhibitors

- Current status:
  - Roclatan:
    - Essentially, Rhopressa + Latanoprost
  - 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

Adenosine Receptor Agonists

- Like ROCK inhibitors, these molecules can work on the TM but much less is known of them

  - A1 adenosine receptor (A1-AR) agonists:
    - A1 agonists have been found to protect normal cells from undergoing apoptosis via the down regulation of death signals
    - Therefore, potentially neuroprotective
Adenosine Receptor Agonists

- A<sub>1</sub> receptors:
  - Stimulation of A<sub>1</sub> adenosine receptor in the TM causes a improvement in metabolic activity which helps to clear the pathway for the aqueous to flow out of the eye (lowering IOP)
  - This metabolic activity takes the form of an increase or upregulation of proteases - such as Protease A or MMP-2 - that digest and remove accumulated proteins which can block the flow of aqueous humor out of an eye with glaucoma

RNAi (RNA Interference)

- Interference RNA (RNAi) is a promising technology with therapeutic applications
  - Sylentis is developing a treatment based on silencing the action of genes involved in aqueous humor production and/or genes which regulate its drainage, so as to reduce IOP
  - Discovered in plants in the 1990s, RNAi consists of highly efficient selective & specific inhibition of gene expression

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Product (Company)</th>
</tr>
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<tbody>
<tr>
<td>Prostaglandins</td>
<td>PF-217329 (PF2 agonist/Phae) d/c’d</td>
</tr>
<tr>
<td></td>
<td>EP2 agonist, (Allergan) Astressis</td>
</tr>
<tr>
<td></td>
<td>NCK 470 (Hilex &amp; Phae)</td>
</tr>
<tr>
<td></td>
<td>Latanoprost &amp; AR-13264 combo (Aerie’s Ruckten)</td>
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<tr>
<td>ROCK Inhibitors</td>
<td>AR-13264 (Aerie’s Ruckten)  AR-13165 (Aerie) d/c’d</td>
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<td>ARPA9075 (Aerie)</td>
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<td>K-115 (Keneka’s Rapastil) (Gilead) in Europe</td>
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<td></td>
<td>H-1317 (Hemopure Ltd ROCK by D.Western Therapeutics)</td>
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<td></td>
<td>1999853607 (Edunoxol) RB3 (Sanofi-Novartis) d/c’d</td>
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<td></td>
<td>DE-104 (Genentech) d/c’d</td>
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<tr>
<td></td>
<td>AT7907 (Athera) d/c’d</td>
</tr>
<tr>
<td>Sustained Delivery</td>
<td>DDS subcutan implant (Allergan)</td>
</tr>
<tr>
<td></td>
<td>Pencilis subcutan (Pharm Italia)</td>
</tr>
<tr>
<td></td>
<td>Pencilis subcutan (Boehringer Ingelheim)</td>
</tr>
<tr>
<td>Other</td>
<td>AG-262271; Masurcic selective compounds (Acadia-Allergen)</td>
</tr>
<tr>
<td></td>
<td>SAD 448 (sensabloc; CY 1.2 agonist;Novartis) d/c’d</td>
</tr>
<tr>
<td></td>
<td>ENO-8875 (adenosine-1 agonist;Inotek’s Trabodenosin)</td>
</tr>
</tbody>
</table>

Adenosine Receptor Agonists

- A<sub>1</sub> Adenosine receptor agonists:
  - Trabodenoson (Inotek INO-8875)
    - Appears to work primarily by increasing the outflow of aqueous via the TM pathway

RNAi (RNA Interference)

- RNAi is mediated by small fragments of double-stranded RNA, consisting of 19-23 nucleotides, which promote degradation of mRNA, thus inhibiting synthesis of the proteins for which they code
- As this mechanism is used naturally by cells to regulate gene expression in a way that is both non-toxic and highly effective, RNAi has great therapeutic potential
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?

Marijuana Laws in 50 States
- Marijuana is now legal in some form or decriminalized in 27 states and the District of Columbia
- Legal
- Decriminalized
- Medical use only
- Illegal

Note: Federal law prohibits the possession, selling or importing of marijuana. Recreational laws reduce the penalties associated with the use or possession of small amounts of marijuana. Sources: National Conference of State Legislatures; National Organization for the Reform of Marijuana Laws

PDW Research Center

What it refers to: MLS L7
History of MJ use

- The director of the White House Office of National Drug Control Policy (ONDCP) asked the Institute of Medicine (IOM) to review the evidence for the potential benefits and risks associated with the use of marijuana
  - The IOM is a non-governmental, apolitical, non-profit organization of scientists

History of MJ use

- The report of the 18-month IOM study was first released to both the ONDCP and the public in March 1999
  - There is remarkable consensus about the potential of cannabinoid drugs for medical use
  - There are far less convincing data about proven medical benefits

MJ & Glaucoma

- Glaucoma ranks among the most frequently cited reasons for using medical marijuana and is one of the indications for which the federal government once granted permission for compassionate marijuana use
- Research findings from as early as the 1970s show that both marijuana and THC reduce IOP

MJ & Glaucoma

- Despite its illegality, millions of Americans use marijuana regularly

![Reported medical uses of marijuana](chart.png)

MJ & Glaucoma

- The first such reports generated considerable interest because at the time conventional medications for glaucoma caused a variety of adverse side effects
  - Pilocarpine and Diamox were among the few drugs available to treat glaucoma in the late 1970s
- Currently other treatments for the disorder have since eclipsed marijuana-based medicines

MJ & Glaucoma

- Several clinical studies have found that synthetic cannabinoids or marijuana reduce IOP as well as do most conventional glaucoma medications
  - This is true whether administered orally (eaten), intravenously or by inhalation
  - NOT when they are applied directly to the eye
  - In most trials a single dose of marijuana or cannabinoid maintained this effect for three to four hours
MJ & Glaucoma

- Researchers have yet to explain how marijuana and cannabinoids reduce IOP
- Marijuana reduces blood pressure and reduced blood pressure could decrease blood flow to the optic nerve, counteracting the benefits of reducing IOP

MJ & Glaucoma

- The short duration of effect means that marijuana-based medicines must be taken up to 8 X per day, which most patients are unlikely to do!
  - Other medicines reduce IOP equally well and need only be taken once or twice a day
  - This is an important difference because patients need to control IOP continuously due to the progressive nature of glaucoma

MJ & Glaucoma

- There is no question that marijuana-based medicines can be used to lower IOP but, like several other glaucoma medications that have fallen into disuse, their drawbacks outweigh their benefits
  - This was not the case when the first reports of marijuana's effects on IOP were published in the 1970s when there were relatively few drugs (all of which caused troubling side effects) were available to treat the condition

MJ & Glaucoma

- Those drugs have since been superseded by more effective and less problematic medications which seems the likely fate of marijuana-based treatments for glaucoma as well

Societal Concerns

- So for glaucoma….
  - There are far better management regimens now available
  - 3-4 hr efficacy ≠ good control
  - Constant intoxication ≠ good citizens
  - Health concerns ≠ future safety profile
  - Colorado ODs can be certified for DEA Schedules 3 narcotic – 5
  - Marijuana is still Schedule 1

Deadline for Public Comment: Jan. 16, 2012
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 …”

- 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

Societal Trends

- Wide Variability In Potency Plagues Medical Marijuana Edibles, JAMA Study (Forbes 6/23/2015 @ 5:06PM)
  - 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 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!