Before we delve into today’s topic…

“Half of what you learn during your training will be shown to be either dead wrong or out of date within five years of your graduation…

NOBODY can tell which half!

And… the most important thing to learn is how to learn on your own.”

—David Sackett, MD, 1934-2015

IOP

- Elevated IOP is the greatest risk factor for developing glaucomatous damage
- Lowering IOP is the only means currently of managing glaucoma
- Topical drops to lower IOP are the preferred initial means to “treat” glaucoma
- Issues in measuring IOP
  - How is baseline IOP established?
  - What are the influences on an IOP measurement?
  - What is the “sampling rate” of IOP?
  - The future of IOP monitoring

A pinhole view of IOP

Our working definition of POAG

POAG is a progressive, chronic optic neuropathy in adults in which intraocular pressure (IOP) and other currently unknown factors contribute to damage and in which there is a characteristic acquired atrophy of the optic nerve and loss of retinal ganglion cells and their axons in the presence of an gonioscopically open anterior chamber angle.

—ala AAO PPP, AOA CPG
There are some other good reasons...

SIMBRINZA™ (brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2%
Initial U.S. Approval: 2013

--- INDICATIONS AND USAGE ---

SIMBRINZA™ is a fixed combination of a carbonic anhydrase inhibitor and an alpha2-adrenergic receptor agonist indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. (1)

There are some other good reasons...

There are some other good reasons...

Issues in “treating” glaucoma

How much to lower IOP when Glaucoma or OHT is diagnosed
- Risk of progression indices

Medical Therapy
- Cost and side effects issues
- Adherence issues
- Optimize and maximize protection to match risk

Initial therapy
- Topical PGA
- SLT

Advancing topical therapy
- ICU
- beta-blocker
- alpha-agonist
- fixed-combination (FC) drop

Recent publications regarding IOP-lowering influences

And just last year...

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use VYZULTA safely and effectively. See full prescribing information for VYZULTA.

VYZULTA (latanoprost bunion ophthalmic solution) 0.024%, for topical ophthalmic use
Initial U.S. Approval: 2017

--- INDICATIONS AND USAGE ---

VYZULTA is a prostaglandin analog indicated for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension. (1)
Case example

Mid -50s WM

- First seen at UAB Eye Care 4/24/2014
- 54 WM Engineer is referred to UAB Eye Care as a “glaucoma suspect.”

Past Medical History

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hernia Sx, Tinnitus</td>
<td>Hernia Sx - couple years ago, all okay now. Past Hx of bad rxn to Penicillin</td>
</tr>
<tr>
<td></td>
<td>Past Hx of Tinnitus</td>
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<tr>
<td></td>
<td>Pt. thinks he has Sleep apnea? *</td>
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</tbody>
</table>

*SA5 ruled out – new Dx = heart murmur (cardiac ultrasound)
No medications

Past / Present Ocular History

<table>
<thead>
<tr>
<th>Disease</th>
<th>Date Diagnosed</th>
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<tbody>
<tr>
<td>Glaucoma</td>
<td>Negative</td>
</tr>
<tr>
<td>Cataracts</td>
<td>Negative</td>
</tr>
<tr>
<td>Age-Related Macular Degeneration</td>
<td>Negative</td>
</tr>
<tr>
<td>Eye Injury</td>
<td>Negative</td>
</tr>
<tr>
<td>Retinal Disease</td>
<td>Negative</td>
</tr>
<tr>
<td>Other Diseases</td>
<td>Negative</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Negative</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>Negative</td>
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<tr>
<td>Amblyopia</td>
<td>Negative</td>
</tr>
<tr>
<td>Dry Eye</td>
<td>Negative</td>
</tr>
<tr>
<td>Refractive</td>
<td>Glasses Full-time</td>
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<tr>
<td>Other</td>
<td>H/o transient dipl/intermittent dipl, resolved spectacle adjustment</td>
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Social History

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<tr>
<th>Drugs</th>
<th>None</th>
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<tr>
<td>Alcohol</td>
<td>None</td>
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<tr>
<td>Tobacco</td>
<td>None</td>
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Medications

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<tr>
<th>Date</th>
<th>Name</th>
<th>Strength</th>
<th>Form</th>
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<tbody>
<tr>
<td>4/21/2014</td>
<td>Advil</td>
<td></td>
<td></td>
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<tr>
<td>6/9/2010</td>
<td>Ibuprofen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4/24/2014</td>
<td>Zyrtec</td>
<td>10 mg</td>
<td>Add'l Sig</td>
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</table>
### Ophthalmic findings

- **BSCVA**: 20/20
- **-2.25 – 0.50 X 090**
- **-2.50 – 0.75 X 090**
- **Pupils** – normally reactive w/o RAPD
- **IOP history** (Goldmann)
  - 13/14 (4/24/2014)
  - 16/15 (7/22/2014)
- **Pachymetry**: 587µ, 586µ
- **Anterior segment** – unremarkable
- **ACA** – open; **AC - D&Q**

---

### Ophthalmic findings

- **Lens (LOCSIII)**: NO 1 / NC2 CS 0 PSC 0 (OD = OS)
- **Optic disc**
- **VF**
- **OCT**
- **What do you expect?**

---

### Reliable data?

- *(Where’s the blind spot?)*
- **GHT,**
- **PSD,**
- **PD significance**

---

### OCT scan quality

- Good scan quality
- Note segmentation markers
- Symmetry
- Ave RNFL thickness
- C/D size
- Disc margin
- Note RNFL defects.
- RNFL profile
- And, **RNFL average sectors** are within reference range.
- But clock hour IT OS, OS show thinning.
Excellent scan quality

Note the island of GCC thinning IT OD that corresponds to RNFL defect AND the raphe respect. And, RNFL average sectors are within reference range.

What are our next steps?

- Reviewing the data
  - Good VA
  - (-) family history of glaucoma
  - ? SAS / (+) heart murmur // no beta-blocker meds.
  - Normal IOP
- Apparently clean VF
- Evidence of ONH / RNFL damage

Diagnostic labeling

- Glaucoma suspect
- Glaucoma
- Pre-perimetric glaucoma
- ?

Repeated visual field !!!

Reliable data?

GHT,
PSD,
PD significance
Management

- Critical questions
  - Degree of damage
  - Burden of treatment
  - Life span

Alternatives

- No treatment at this time
- Follow, repeating all tests X 6 mo
- ? Other ?

Most recent visit

- IOP = 19/20

- Updated disrupted sleep status — diagnosed with SAS and using CPAP device. Reportedly, “…feeling much better.”
- Does this change our thinking?
Corneal Hysteresis in Glaucoma
Predictive of Progression in Prospective, Longitudinal Study (DIGS)

- IOP of 30 is not so bad with a CH of 11.
- IOP of 20 is very bad with a CH of 6.


Percentage per year change in VFI

What about complementary technologies?
- How would OCT-A influence your management?
- What about electrodiagnostic testing?

Considerations in management
- Does the patient understand the risks and benefits of treatment?
- What is the risk of vision/sight loss over his lifetime? (25 years?)
- What is his likelihood of adherence to treatment if offered/accepted?
- What would be his “target IOP”?
- With what would be the initial treatment option?
Another example

“To treat or not to treat and if so, how?”

VF Series – 1: 2004 (baseline)

VF Series – 2: 2005

RB 9/24/1938 (AA/F)

ONH
(5/2006)

PACHYMETRY: 642/591

RB 9/24/1938 (AA/F) - IOP Range

- 17-24 (OD)
- 15-21 (OS)
- PACHYMETRY: 642/591

Frequency Doubling Technology (FDT) Perimetry Results (4/6/05)

“Threshold”
No flags (OD, OS)
(4/6/05)

Retest!
(OS)

Dilemma?
or Direction?

(4/08 As OHT (IOP range 17-24, 15-21):
Risk calculation (1-5% - low)

VF Series – 3: 2/19 2010 (Bad day or
calculation?)

Fundus photos 4/5/2006

5/10/2011

Repeat the VFI (5/10/2011)

RB 9/24/1938 (AA/F)

- VA 20/20 to 20/20- with mild NS changes
- BP good
- PR: 60

- 4/08 As OHT (IOP range 17-24, 15-21):
- Risk calculation (1-5% - low)
Change analysis

5/10/2011 – look closely

5/10/2011 – look closely

Treat or not?

Need more evidence?
- OCT
  - RNFL
  - MRNFL (GCC)
  - ONH
Update

- 11/11 – IOP: 18/13 Switch to Lumigan 0.01%
- 12/11 – IOP: 20/14 Continue L. 0.01%
- 1/12 – IOP: 21/15 Switch to T-Z
- 2/12 – IOP unchanged: Switch to Combigan qAM
- 3/12 – IOP unchanged: Switch to Alop tid
- 5/12 – no IOP response = SLT recommendation
- 6/13 – IOP = 17 mm Hg OD, OS
- 6/14 – IOP 17/15 mm Hg OD, OS
- 6/15 – IOP 14/15 mm Hg OD, OS

Choosing an initial “treatment” strategy

56,000 Ways To Treat Glaucoma*
From ignorance our comfort flows. The only wretched are the wise.
Matthew Prior (1664–1721)

The trouble with the world is that the stupid are cocksure
and the intelligent are full of doubt. –Bertrand Russell


Guidance on initiating therapy - Delphi Panel

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<th>MEDIC T AIRY</th>
<th>MEDIC A R AGRE EM T</th>
<th>E SULT</th>
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<tbody>
<tr>
<td>1. Medical therapy is the preferred initial therapy for established primary open-angle glaucoma (POAG)</td>
<td>SL</td>
<td>84</td>
</tr>
<tr>
<td>2. Minocycline therapy is the only effective current treatment for POAG</td>
<td>SL</td>
<td>84</td>
</tr>
</tbody>
</table>

Adherence . . . for the long term

Patterns of Glaucoma Medication Adherence over Four Years of Follow-Up

Considerations in the medical management of glaucoma / OHT

- “Baseline” IOP?
- Target IOP
- Severity of damage at initial presentation
- Burden of treatment
  - Ocular surface
  - Side-effects / Systemic issues
  - Cost of medications
  - Likelihood of adherence to regimen*
- Potential lifespan

Which PA is best?

- It depends!
  - Meta Analyses suggest slight superiority of bimatoprost.
  (e.g., Apfel F, Cucherat M, Denis P. Efficacy and tolerability of prostaglandin-timolol fixed combinations: a meta-analysis of randomized clinical trials. Eur J Ophthalmol. 2011 May 19:0.)


Adherence ... for the long term

Patterns of Glaucoma Medication Adherence over Four Years of Follow-Up

For most patients who were newly prescribed glaucoma medications, adherence patterns observed in the first year of treatment reflect adherence patterns over the subsequent 3 years. Importantly, in those with suboptimal adherence patterns over the first year may have a large impact on long-term adherence. Ophthalmology 2016 123;115 (5): 998-1004 © 2016 by the American Academy of Ophthalmology.

Factors influencing IOP

### Physiological factors
- CCT
- Shared variation
- Arterial (pulse) pressure
- Posture
- Blood flow
- Exercise
- Accommodation
- Axial length / refractive error
- Corneal dystrophies

### Situational influences on IOP
- Eye rubbing
- Necktie
- Head position
- Fluid intake
- Medications
- Weight lifting
- Scleral indentation
- Wind instrument playing

### Extraneous influences on IOP
- And...
- Jumps in intraocular pressure.

CONCLUSIONS: Acute performance of jump squat and ballistic bench press lead to a significant increase of IOP, and 5 min of rest are enough to return baseline IOP values. There is a strong linear association between the increase in load and the IOP rise for both exercises, and bench press execution produces a significantly higher IOP increase when compared with the jump squat for the same relative loads.
An additional confounder surrounding IOP and our “sampling”

**QUESTION:** How many seconds elapse in the quarterly interval from one visit to the subsequent one for a patient whom you are monitoring for glaucoma progression?

**ANSWER:** about 8,000,000. [8 million]

---

**Example**

53 yo treated glaucoma patient (PGA qhs + timolol/IVCA comb); excellent reproducibility for two overnights; blue & yellow.


---

**Example**

52 YO Asian female glaucoma suspect (PGA qhs Rx’d but may have been noncompliant); good reproducibility pattern for two overnights; blue & yellow.

Example

Poor reproducibility in a 20 GS for two overnights with spikes (n.b., pt has poor sleep habits). [App on your iPhone]

Home tonometry - more frequent data gathering but not continuous.

News / 03.22.2017
FDA Cleared icare® HOME, An Innovative Device Poised To Revolutionize IOP Self-Monitoring.

Baseline IOP

- Establishing a baseline IOP with several measurements guards against making the wrong call.

For example, a single IOP of 34 mmHg might suggest the need for a treatment recommendation and encourage a reduction to 20 mmHg (>30%) when that initial measurement may be an aberration.

So, baseline IOP is critical to establish.
Practical Considerations

- Establish the diagnosis
  - Use multiple IOP measurements to determine a baseline IOP
- Consider charting a diurnal IOP pattern
- Use all data available (history, medications, vocational and avocational activities, physical findings including stereo photos and digital imaging as well as VF testing.)

Recent thoughts on baseline IOP

- Asymmetry is damped with multiple IOP measurements.
- Predictions of efficacy are impossible but may be more accurate when more data are gathered.


Baseline IOP suggestions – “measure twice, cut once”

<table>
<thead>
<tr>
<th>Study visits</th>
<th>V1</th>
<th>V2</th>
<th>V3</th>
<th>V4</th>
<th>V5</th>
<th>V6</th>
<th>V7</th>
</tr>
</thead>
<tbody>
<tr>
<td>First eye</td>
<td></td>
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<tr>
<td>Second eye</td>
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</tbody>
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Note: V1-2 were the recruitment visits; V3-4 (V5, V6) were untreated baseline visits and weeks 5-10 (11) were posttreatment visits. The first eye refers to the eye that measured the highest monocular pressure at recruitment. An alloblinded treatment with timolol 0.5%


Target IOP Defined

≡ the pressure at which the patient shows stabilization (i.e., no progression)

Canadian Perspective

“Target IOP is a dynamic concept, needing constant reevaluation.”

“What is lacking are established guidelines for determining the target IOP range that can be used in general ...practice.”

An alternative suggestion (‘market IOP’)  
What it means:

With a high risk of vision loss, the emphasis on lowering IOP increases.

If there is a relatively lower risk of vision loss, then there is greater emphasis on guarding against the risks of therapy.


Alternative target IOP guidance

- Target IOP needs to be individualized as progression is highly variable and IOP is only partly responsible.
- Once rate of progression has been determined (by a sufficient # of VFs) and treatment advanced accordingly, e.g., slower progression for NTG but faster for PXG.

What about advancing therapy?

- Options include
  - Switching to an alternative topical therapy or adding additional topical drops
  - SLT
  - Trabeculectomy

What about advancing therapy by adding another medication?

- Single agent?
  - Consensus guideline suggests tCAI
- A constellation of drops?
  - Using additional dosages is likely to decrease adherence
- Fixed combination drop? Beta-blocker containing or BB-free?

Consider this scenario

The pharmacist calls you and asks, “Can I give your patient a generic equivalent of this PGA?” Your response would be:

A. Sure, they are bioequivalent
B. No, they only have the same active ingredient as the original product
C. Go ahead, we’ll see how it performs
D. No, my child is on a NAMEYOURFAVORITEPHARMA scholarship at Vanderbilt
“Generic ophthalmic medications contain the same active ingredients as their brand-name predecessors.”

□ But, is the bioavailability the same? (i.e., what is the other 99.995%)?

What influences bioavailability?

□ Excipients
  □ Buffers
  □ Antioxidants
  □ Thickening agents
□ pH
□ Preservatives
□ Tonicity
□ Drop size
□ Bottle composition

Issues with generics

□ $/Pharmacy substitution
□ Insurance coverage
□ Medicare part D vs. Private Pay

Approaching the generic substitution issue with patients

□ Some patients prefer a branded product
□ When $ is a consideration, discuss the situation
□ Generics may not have equivalent bioavailability, so monitor more closely/frequently
  Ask patients to bring their bottles to visits
□ Have the dispensing pharmacist understand why what you have prescribed for the patient
Approaching the generic substitution issue with patients

- Consider options
  - Pharmaceutical manufacturers' plans/coupons
  - Other classes of drugs
  - Fewer doses / day, and other off-label options, etc.

Impact of generic latanoprost


Conclusions

Given that cost can significantly deter adherence, switching patients to generic medications may help improve patients' drug-regimen adherence. A considerable number of patients discontinued glaucoma drug use altogether when generic latanoprost became available. [We] should work with insurers and pharmacists to prevent such discontinuation of use as generic forms of other PGA agents become available.

Lipid Family Receptors

Lipid Family Receptors

- Cannabinoids
- Prostaglandins
- Prostamides

What about weed?

Information is current as of Sept. 14, 2017.

AGS position statement

- Treatment modalities (to lower IOP)
  - Medication
  - Laser
  - Surgery

  - Marijuana as an alternative
    - Frequent dosing
    - SEs
    - Inadequate topical formulations
    - May be neuroprotective


AGS position statement

- Bottom line: NO scientific evidence for its use to treat glaucoma.
Nocturnal hypoperfusion as a glaucoma risk factor

### Perfusion to the ONH

Example comparing DOPP and mean OPP

120/80 IOP = 20; DOPP = 60 [80-20]

What IOP do we measure? diastolic

Significant difference between DOPP and MOPP

Which to use???

Comparing DOPP to MOPP calculation

MOPP = \( \frac{2}{3} \text{DBP} + \frac{1}{3} (\text{SBP}-\text{DBP}) - \text{IOP} \)

\( \frac{2}{3} [80 + \frac{1}{3} (40)] - 20 \) results in 42

---

*Recent association between nocturnal BP dips and ODH in NTG

A reduction of nocturnal blood pressure (BP) in the range of 10%–20% relative to daytime BP levels is usually observed in normotensive subjects and in the majority of hypertensive patients. This dip is termed "physiologic," while BPs that exhibit excessive (>20%) or minimal (<10%) dips at night are termed "nonphysiologic" dippers.

over-dippers = progressors
Recent association between nocturnal BP dips and ODH in NTG

Over-dippers = progressors

How should glaucoma be managed comprehensively?

- First, lower IOP

New directions in glaucoma treatment

- Yes, treatment
- Beyond IOP reduction, regulation of blood flow...
  - Systemically (regulating blood pressure and monitoring perfusion pressure)
  - Locally - endothelial-cell activity by modulating Nitric Oxide (NO) This is the NEXT BIG THING!
  - Regulation of aqueous dynamics at the trabecular meshwork by vascular modulation
  - In addition, the application of NO-donating compounds for the lowering of IOP directly

Future options for medical management - targeting the site of glaucoma, the TM

- Rho-kinase inhibitors (Rhopressa and Roclatan, netarsudil/latanoprost ophthalmic solution, 0.02%/0.005%, Aerie)
- Completed 12-month safety evaluation, Rocket (Canada)
- Completed 3-month efficacy study (USA), Mercury
- FDA-Approved December 2017

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- Completed 12-month safety evaluation, Rocket (Canada)
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- FDA-approved December 2017

- *MOAs
  - increase fluid outflow through the trabecular meshwork, (1° drainage)
  - increase fluid outflow through the uveoscleral pathway, (2° drainage)
  - reduce fluid production in the eye, and
  - reduce episcleral venous pressure (EVP).
Other future directions for medical management of glaucoma

- Drug delivery (continuous, episodic)
- "Neuroprotection" & Neuroregeneration

How should glaucoma be managed comprehensively?

- Second, consider increasing perfusion (may be a consequence of lowered IOP)
  - Topical treatments? (betaxolol, brimonidine, brinzolamide, Gingko Biloba)
  - Exercise, weight loss
  - Lower cholesterol, blood sugar levels
  - Treat underlying vascular disorders (HT, SAS, CVD)
  - Etc.

The effects of antioxidants on ocular blood flow in patients with glaucoma

Alex Harris, Jozi Gross, Nicholae Movie, Thuy Do, Anh-Huong, Willy Garcia and Boost Sainly


Study design

- 45 patients with confirmed glaucoma on IOP-lowering treatment (placebo controlled, X-over)
- Baseline and post-administration (@ 1 month) measurements
  - IOP
  - OPP
  - Retrobulbar (ultrasound) and retinal capillary (Doppler) blood flow

Results

- Increased peak systolic and/or end diastolic velocities among the active group (but not placebo)
- Reduced vascular resistance in central retinal and short posterior ciliary arteries
- Increased superior and inferior temporal retinal artery mean blood flow
- Enhanced retinal capillary density

SO, what were they given?

- Anti-oxidant/Supplement formulation

Reference

SO, what were they given?

How should glaucoma be managed comprehensively?

- Third, reduce oxidative stress (Ca++ blockade [BUT, not systemic β-blockers], supplements)

How should glaucoma be managed comprehensively?

- Third, reduce oxidative stress (Ca++ blockade [BUT, not systemic β-blockers], supplements)

Consider this:

- Is glaucoma AION that happens over a lifetime?

- OR

- Is AION glaucoma that happens overnight?

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- Is glaucoma AION that happens over a lifetime?

- OR

- Is AION glaucoma that happens overnight?

Consider this:

- Is glaucoma AION that happens over a lifetime?

- OR

- Is AION glaucoma that happens overnight?

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Thank you!