New Ways to Manage the Patient with Glaucoma

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New Ways to Manage the Patient with Glaucoma

- 24 hour IOP monitoring in glaucoma management – Malik Kahook
- Glaucomatous Adherence, the Iceberg Below the Surface – Steven Mansberger
- New Medications to Treat Glaucoma – Robert Prouty

New Medications to Treat Glaucoma
Robert Prouty
Old Drugs – New Places

- Akorn is now the provider of the Merck line of glaucoma agents
  - Timolol PF
  - CoSopt PF
  - Zioptan

New Drugs

- NiCox – Latanoprost
  - Latanoprost Bunod
- Rho Kinase Inhibitors
  - With and Without Latanoprost
Latanoprostene bunod (Vesneo)

- Novel nitric oxide-donating prostaglandin F2-alpha analog
- Valeant Pharmaceuticals subsidiary, Bausch + Lomb, and Nicox S.A.
- Expect to file in the U.S. in First Half of Q2 2015
- Expect to launch in the U.S. in First Half of 2016
- Goal is for U.S. sales ~$500 million+, Global Sales ~$1 billion+
Latanoprostene bunod (Vesneo)

- The pivotal Phase 3 program includes two separate randomized, multicenter, double-masked, parallel-group clinical studies, APOLLO and LUNAR.
- Designed to compare the efficacy and safety of VESNEO administered once daily (QD) against timolol maleate 0.5% administered twice daily (BID) in lowering IOP in patients with open-angle glaucoma or ocular hypertension.
- The primary endpoint of both studies, which include a combined total of 840 patients, was the reduction in mean IOP measured at specified time points during three months of treatment.
- The Phase 3 studies are pivotal for U.S. registration and are being conducted in North America and Europe.

Latanoprostene bunod (Vesneo)

- The primary endpoint of non-inferiority to timolol maleate 0.5% was achieved in both Phase 3 studies.
- Additionally, VESNEO showed a reduction in mean IOP of 7.5 to 9.1 mmHg from baseline between 2 and 12 weeks of treatment in the two Phase 3 studies.
- This IOP effect was statistically superior (p < 0.05) to timolol in both studies.
- VESNEO also showed positive results on a number of secondary endpoints.
- There were no significant safety findings in either study.
  - The collection of patient safety data for a total of up to 12 months is still ongoing.

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A randomised, controlled comparison of latanoprostene bunod and latanoprost 0.005% in the treatment of ocular hypertension and open angle glaucoma: the VOYAGER study

Randall J. Neiweib, Thomas J. Chau, Rathi Ravindralah Strand, James L. Findsley

BJO. J Clin Ophthalmol. published online December 8, 2014

ABSTRACT

AIM: To assess the efficacy and safety of latanoprostene bunod (VESNEO; 0.005%) and latanoprost (LYSTAR; 0.005%) in lowering intraocular pressure (IOP) in patients with either open-angle or angle-closure glaucoma.

METHODS: All patients were randomised to receive either VESNEO 0.005% (n=206) or LYSTAR 0.005% (n=205) in the treatment of open-angle or angle-closure glaucoma or ocular hypertension. All subjects underwent an examination at baseline and at weeks 2, 4, 8, 12, and 24.

RESULTS: Significantly greater IOP reduction was observed at week 4 for VESNEO compared to LYSTAR (9.5 mmHg vs. 7.4 mmHg; p<0.001). At week 24, the mean IOP reduction was 11.2 mmHg for VESNEO and 8.7 mmHg for LYSTAR (p=0.001).

CONCLUSIONS: VESNEO was more efficacious than LYSTAR in reducing IOP in patients with open-angle or angle-closure glaucoma or ocular hypertension.

In conclusion, VESNEO 0.005% had greater IOP reduction compared to LYSTAR 0.005% in reducing IOP in patients with open-angle or angle-closure glaucoma or ocular hypertension. The collection of patient safety data for a total of up to 12 months is ongoing.
New Medication  
Rho Kinase Inhibitors

- Rho kinase inhibitors
  - Reduce cellular stiffness in trabecular meshwork
  - Target trabecular meshwork cells to enhance outflow
  - May offer neuroprotective as well as anti-inflammatory effects
  - Aerie and Altheos
New Glaucoma Medications

- Aerie Pharmaceuticals
  - Two compounds
    - Dual action Rho kinase (ROCK) + norepinephrine transport (NET) inhibitor
      - AR-13324 lowers IOP by enhance outflow through TM (ROCK) and inhibit aqueous production (NET)
    - Triple action ROCK + NET + latanoprost
      - PG324 fixed combination of AR-13324 and latanoprost
        » Additional IOP reduction through uveoscleral outflow
  - Both agents are once per day dosage
  - Excellent efficacy and safety profile to date
    - Hyperemia an issue

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**Triple-Action Rhopressa™**

Mechanisms of Action:
1. ROCK inhibition relaxes TM, increases outflow
2. NET inhibition reduces fluid production
3. ROCK inhibition lowers EVP

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**Quadruple-Action Roclatan™**

FIXED COMBINATION OF RHOPRESSA™ WITH LATANOPROST

MOAs:
1. ROCK inhibition relaxes TM, increases outflow
2. NET inhibition reduces fluid production
3. ROCK inhibition lowers EVP
4. PGA receptor activation increases uveoscleral outflow
Rhopressa

- Rocket 1 - 400 person phase 3 study Rhopressa efficacy study done over 3 months
  - Non-inferiority to Timolol
  - Results 2nd quarter 2015
- Rocket 2 – 3 month efficacy along with 12 month safety study
  - Results mid-late 2015
- Rocket 3 – 12 month safety study only
- Phase 3 of Roclatan expected to start in mid 2015

Double-masked, Randomized, Dose—Response Study of AR-13324 versus Latanoprost in Patients with Elevated Intraocular Pressure

Jason Bakaranah, MD, Hane B. Daher, MD, Brian Lyons, OD, MD, Casey C. Kapczynski, MD, Gan D. Namiki, MD, FRCOphth for the AR-13324 CS02 Study Group

**Objectives:** AR-13324 is a small-molecule inhibitor of Rho kinase and a xanthineogenic transporter. The objectives of this 28-day study were to evaluate the ocular hypotensive efficacy and safety of AR-13324 ophthalmic solution compared with a positive control, latanoprost ophthalmic solution, in patients with open-angle glaucoma or ocular hypertension.

**Design:** Double-masked, randomized study in 22 private-practice ophthalmology clinics.

**Participants:** Participants were required to be adults with at least 1 eye with a measured intraocular pressure (IOP) in the range of 21 to 30 mmHg.

**Methods:** Patients were randomized to receive AR-13324 ophthalmic solution 0.01%, 0.02%, or latanoprost 0.005% every day. Baseline IOPs were 21.7 ± 2.5 mmHg for AR-13324 and 21.8 ± 2.4 mmHg for latanoprost.

**Main Outcome Measures:** The primary efficacy endpoint was the mean diurnal IOP across subjects within the treatment group at day 28.

**Results:** Randomized and treated were 204 patients (107 in the AR-13324 0.01% treatment group, 107 in the AR-13324 0.02% treatment group, and 107 in the latanoprost treatment group). The mean IOP readings were 22.4 ± 2.8 mmHg at baseline, 18.9 ± 2.6 mmHg (4.9 mmHg reduction) during day 14, and 18.7 ± 2.5 mmHg during day 28. The mean diurnal IOP (24-hour) was significantly lower in the AR-13324 0.01% (p < 0.001) and AR-13324 0.02% (p < 0.001) treatment groups compared with the latanoprost treatment group. The 5.7 mmHg IOP reduction in AR-13324 0.01% did not meet the criteria for noninferiority to latanoprost. The most frequently reported adverse event was conjunctivitis, with a combined incidence of 15%, 16%, and 18%, respectively. On day 28, 16% of patients reported being satisfied with the treatment, and 14% reported being satisfied with the treatment. At the end of the study, 14% of patients reported being satisfied with the treatment, and 14% reported being satisfied with the treatment. The most common adverse events were conjunctival hyperemia, which were more common in patients with AR-13324 than in patients with latanoprost.

**Figure 2:** Mean ± standard error of the mean (SEM) diurnal intraocular pressure (IOP) in the modified intent-to-treat population.
Figure 3. Mean ± standard error of the mean (SEM) change in intraocular pressure (mmHg, modified intent-to-treat population). mITT = modified intent-to-treat.

Ocular Hypotension Effect of the Rho Kinase Inhibitor AR-12286 in Patients With Glaucoma and Ocular Hypertension:

**METHODS:** Subjects (N = 400) with chronic open-angle glaucoma were randomized to receive either AR-12286 or placebo once daily. After a 7-day baseline period, dosing occurred from the evening for 7 days, then twice daily for 7 days. Primary and secondary efficacy end points were mean IOP at each dosing time point (8 am, 12 pm, 4 pm, and 8 pm) and mean change in IOP from baseline, respectively.

**RESULTS:** AR-12286 produced statistically and clinically significant reductions in mean IOP that were dose dependent. For all subjects, the mean IOP reduction ranged from 1.5 mmHg to 18.2 mmHg (p < 0.05, vs. placebo) for the 3 concentrations. The largest IOP reduction was produced by 0.02% AR-12286, after twice daily dosing (up to ~4.4 mmHg, 20%). The 0.01% concentration, dosed once daily, was the lowest producing a significant IOP reduction. The 0.001% concentration was once (1.5 mmHg) and was not significant. IOP was measured, especially before and after. After once-daily evening dosing, IOP was seen in less than 100% of patients.

**CONCLUSIONS:** AR-12286 was well tolerated and produced statistically and significantly greater IOP reductions compared with placebo in patients with chronic open-angle glaucoma.
New Glaucoma Medications

- **Altheos**
  - Has rights to Asahi Kasei Pharma Corp.'s preclinical AK138 series of selective Rho kinase inhibitors that is now called ATS907

New Glaucoma Medications

- **Amakem Therapeutics**
  - ROCK inhibitor AMA0076
  - Aim is for reduced hyperemia due to its quick penetration into TM
  - Mean IOP reduction 20% in phase I trials
  - 3-5 years away
Upcoming Medications

- Adenosine receptor agonists
  - Works on tm
  - Trabodenoson
  - Phase 2 trials

New Glaucoma Medications

- Ono Pharmaceuticals – ONO-9054 10mg and 30 mg/mL dose groups
  - Developing novel FP/EP-3 prostaglandin
    - Dual receptor agonist to lower IOP
  - Phase I safety and tolerability studies complete
  - Phase I showed 35% IOP reduction with up to 33 hour IOP drop
  - 3-5 years away

Neuroprotection

- Refers to mechanisms that protect neurons from apoptosis arising from insult or progressive neurodegenerative diseases
  - Parkinson, Alzheimers
- Only a few medications are FDA approved for neuroprotection
- Some glaucoma patients progress despite reduced IOP
  - Pressure independent factors
  - Neuroprotection offers hope of protecting vision via a different means than reducing IOP
- Currently according to clinical trials.gov, there are 9 clinical trials for neuroprotection in glaucoma
  - Allergan’s Memantine study which was completed several years ago
Neuroprotection

- N-methyl-D-aspartate receptor antagonists
  - Memantine
  - Was not effective in clinical trial
- Nitric Oxide Synthase Antagonists
  - Inhibit NOS that is released by astrocytes
- Antioxidants
- Calcium Channel and Angiotensin Blockers
- Stem Cell Therapies

Neuroprotection

- Neurotrophic growth factor-releasing cells to rescue dying retinal ganglion cells
- Pluripotent stem cells induced from patient’s own skin fibroblasts may led to optic nerve regeneration

New Glaucoma Medications

- AJiSee Pharma
  - Germany company developing neuroprotective agent
  - Indicated for Glaucoma and Age related macula degeneration
  - Company’s name derived from amyloid beta, a peptide believed to play a role in development of Alzheimer’s and other diseases
  - Age related accumulation of Aβ in retinal ganglion cells is associated with glaucoma or retinal epithelial cells (AMD)
    - Toxic to retinal tissues
  - Compound MRZ-99030 impedes formation of Aβ oligomers and promotes formation of nontoxic forms
  - Agent administered as eyedrop
  - Phase I results completed in rodent model were promising
  - 3-5 years in future
Drug Delivery Systems for Glaucoma

- Amorphex Therapeutics
  - A polymer, similar to a contact lens, that contains the drug and sits under the upper eyelid
  - Releases the drug over several months
- Envisa Therapeutics
  - Implantable extended-release device
- pSivida and SKS Ocular
  - Delivery devices
- Kala Pharmaceuticals
  - Drops that can get into the eye more easily
- Ocular Therapeutix
  - Tear duct plugs containing medication
- Mati Therapeutics Inc.
  - Punctal plug device
- Graybug
  - Sustained release

Objectives for Drug Delivery

- Ensure drug delivered to the site of action in the eye
- Reduce side effects of topical medications
- Improve compliance
- Improve clinical outcomes

Glaucomatous Adherence, the Iceberg Below the Surface
Steven Mansberger
Glaucoma Adherence

- Taking medications as prescribed
- Ocular hypertensive medications used 94% of time to treat OHTN and Glaucoma patients
- Treatment reduces development or worsening of glaucoma by approximately 60%
- However, adherence to prescribed treatments is poor
- Studies show compliance varies
  - One study 56% of patients used 75% of drops
  - Study using pharmacy records show only 50% of patients have refill of medication at 6 months

Glaucoma Adherence

- Three factors related to adherence
  - Acceptance
    - If the patient does not believe he/she has a problem requiring therapy, will NOT take the medication
  - Persistence
    - Patient has to take the medication for the duration of the disease without losing interest or letting the medicine run out
    - Can the patient get the correct dose into the eye?

Glaucoma Adherence

- What is the cost of adherence?
  - Cost of poor adherence in medicine is staggering
    - Estimated $100 Billion annually
    - 125,000 deaths
    - 20% of all hospitalizations
  - Cost of poor adherence in glaucoma not clear
  - Assumption is that it leads to increased progression and visual impairment
  - Also waste unused medications, require additional medications, and if disease worsens, greater amount of care
Glaucoma Adherence

- Alternative view is that poor adherence leads to fewer costs because less medications used
- This is unlikely since medication cost accounts for a small fraction of costs of glaucoma
  - Productivity losses
  - Visual impairment costs

How Do We Determine Adherence?

- Difficult to measure
- Patients routinely overstate their level of adherence as compared to objective measures
- IOP is a poor surrogate for adherence since patients commonly increase their adherence in the day prior to office visit
- Pharmacy reports accurate for large groups but questionable for individual patient
- Objective dose monitor are best method but available for only one medication

How Do We Determine Adherence?

- Clinicians can purchase MEMS cap (Medication Event Monitoring System)
  - Bottle within bottle design to objectively measure compliance
  - Requires extra steps such as unscrewing MEMS cap, removing eyedrop bottle, replacing the cap.
  - Obtrusive which hinders its usefulness
Why Do Glaucoma Patients Not Use Their Medications?

• Multiple reasons
  – Higher costs
  – Patient education
  – Longer travel distance
  – Younger (<50yo) and Older Age (>80yo)
  – Complexity of treatment regimen

How Do You Address Adherence with Your Glaucoma Patients?

• Poor adherence may be a condition in itself
  – Requiring constant vigilance, reinforcement and cooperation between clinician and patient
• One must address the problem and establish good rapport
• Ask about adherence using “open ended” questions in a “safe” environment
  – “It can be hard to use your eyedrops. How often do you think you miss them?”
• Patient will overstate how often they use their drops and not state when they are having difficulty with insertion
• Watch how people put drops in using artificial tear bottle
Can the Patient Get the Correct Dose into the Eye?

- 20% of compliant patients did not get a single drop into their eyes
- Most did not realize they did not get eyedrop into the eye
- Others instilled too many drops
- Most patients wasted drops and almost all touched bottle tip to eye
- Universally every one thought they were doing a great job

Getting Drops into the Eyes

- Not getting eyedrops into the eyes becomes even more of a concern (and a problem) when patient has reduced vision
- In scenario of glaucoma patient with reduced vision and borderline control, doctor questions patient compliance
  - Possible patient not able to instill eyedrop
- Another issue is that a 90 day supply of eyedrops not analogous to 90 supply of pills
  - May patients run out before the intended time

Getting Drops into the Eyes

- Experienced glaucoma patients average 1.8 drops hitting their eye per successful instillation
  - Twice the correct amount
  - Took 7 drops in each attempt to get 1.8 drops in
  - Most bottles only have 20% extra for waste
- In this situation, some patients may be out of medications for a period of time
  - Some may start to skip doses to get bottle to last longer
- Insurers tend to be strict about when they will refill medications
### Getting Drops into the Eyes

**Instillation: What Goes Wrong**
- Criteria for good instillation
  - Gets drop into eye
  - Only uses one drop
  - Does not touch bottle to eye
- Only about 1/3rd of patients meet all 3 criteria on single installation

### Getting Drops into the Eyes

**Instillation: What Goes Wrong**
- Not being able to open bottle
  - Tamper proof seal can be troublesome
- Not keeping the eye open
- Not using gravity to their advantage
  - Patients standing up, hold bottle perpendicular to eye and the drop goes straight down to the floor or the cheek
  - Have patient lay down in bed with head on pillow and look into bottle tip

### Getting Drops into the Eyes

**Instillation: What Goes Wrong**
- Not bracing the bottle
  - Use other hand or against the nose
- Not looking at the bottle
  - Some patients look away
- Let the bottle touch the eye
  - Studies have shown 19% of bottles contaminated after 4 weeks of use
  - 40% after 8 weeks of use
  - 91% of bacteria were gram positive
Getting Drops into the Eyes

• Putting Too Many Drops into the Eye
  – May be function of lack of corneal sensitivity or fine motor skill limitations
  • Cool drops in refrigerator

Help the Patient Improve

• Let the patient know that drop instillation is difficult for most individuals
  – Focus attention on their technique
• Ask patient to demonstrate
• Teach the patient ways to address specific delivery problems
  – If problem due to fine motor skills, enlist family member to instill drops
  – Switch to another form of therapy such as laser

Help the Patient Improve

• Technique
  – Wash hands
  – Use fingers to hold both lids open
  – Look at the bottle tip
  – Brace hand holding the bottle against nose or hand holding lids open
  – Minimize distance from bottle tip
  – Make sure bottle is positioned above eye
  – Keep bottle chilled
24 hour IOP monitoring in glaucoma management
Malik Kahook

Systolic Elevation of Intraocular Pressure in Young Adults

- The increase pattern of intraocular pressure (IOP) is contrasted in two groups of normal young adults, with and without the normal postural change from supine to the sitting position.
- Measurements were taken at different times of the day and night to determine the effect on IOP.
- Graph showing IOP changes over the 24-hour period with and without postural change.
Chronopathology and IOP

Summary

• IOP exhibits a circadian pattern
  – Peak level occurs during the night
• Presuming there is a chronopathology for glaucomatous damage with the greatest risk at night
  – Therapy should be based upon use of agent that offers 24 hour control
• IOP lowering agents differ in their ability to lower IOP throughout a 24 hour period
Table 2. Diurnal and Nocturnal IOP in Both Body Positions

<table>
<thead>
<tr>
<th></th>
<th>Older Group ($n = 15$)</th>
<th>Younger Group ($n = 16$)</th>
<th>$P$ (t-test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diurnal sitting</td>
<td>15.3 ± 2.4</td>
<td>15.8 ± 1.9</td>
<td>0.594</td>
</tr>
<tr>
<td>Diurnal supine</td>
<td>20.1 ± 2.2</td>
<td>20.0 ± 1.2</td>
<td>0.950</td>
</tr>
<tr>
<td>Nocturnal sitting</td>
<td>14.8 ± 2.9</td>
<td>17.4 ± 2.3</td>
<td>0.008</td>
</tr>
<tr>
<td>Nocturnal supine</td>
<td>19.6 ± 2.8</td>
<td>21.3 ± 1.6</td>
<td>0.036</td>
</tr>
</tbody>
</table>

IOPs (mm Hg) are mean ± standard deviation and represent the average of both eyes. The diurnal period was 7 AM to 11 PM, and the nocturnal period was 11 PM to 7 AM.
Diurnal Intraocular Pressure in Untreated Exfoliation and Primary Open-angle Glaucoma

Objective: To describe and compare the diurnal intraocular pressure (IOP) variation in patients with exfoliation glaucoma (EFG) and primary open-angle glaucoma (POAG).

Patients and Design: We prospectively investigated 24-hour IOP variation in patients with newly diagnosed exfoliation glaucoma and POAG. All patients were admitted to our ophthalmology department for 24-hour IOP monitoring. For our study, we compared 40 patients with EFG and 20 patients with POAG.

Results: Patients with EFG showed a significantly higher mean range of IOP (14.1±1.4 mm Hg for EFG, compared to 11.5±1.4 mm Hg for POAG, p=0.004). Higher maximum IOP (mm Hg) for EFG was 58.5±12.1 compared to 29.1±10.4 for POAG, p=0.001. Similarly, higher minimum IOP (mm Hg) for EFG was 27.8±6.8 compared to 21.0±5.7 for POAG, p=0.001. The range of IOP (mm Hg) for EFG was 58.5±12.1 compared to 29.1±10.4 for POAG, p=0.001.

Conclusions: Significant fluctuations in the diurnal curve of the IOP distinguishes EFG from POAG and may be an important factor in predicting and subsequent proper response to medical therapy.

Arch Ophthalmol. 1993;111:88–95

<table>
<thead>
<tr>
<th>Measure</th>
<th>Exfoliation Glaucoma</th>
<th>Primary Open-angle Glaucoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 AM</td>
<td>27.8±6.8</td>
<td>21.0±5.7</td>
</tr>
<tr>
<td>6 AM</td>
<td>30.5±10.1</td>
<td>22.6±6.5</td>
</tr>
<tr>
<td>10 AM</td>
<td>34.8±11.8</td>
<td>24.5±5.5</td>
</tr>
<tr>
<td>2 PM</td>
<td>30.5±6.4</td>
<td>21.6±4.8</td>
</tr>
<tr>
<td>6 PM</td>
<td>28.5±12.1</td>
<td>22.7±6.8</td>
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<tr>
<td>10 PM</td>
<td>29.1±10.4</td>
<td>21.0±7.1</td>
</tr>
<tr>
<td>Maximum IOP</td>
<td>38.2±11.1</td>
<td>38.0±6.5</td>
</tr>
<tr>
<td>Minimum IOP</td>
<td>24.7±8.1</td>
<td>18.4±4.2</td>
</tr>
<tr>
<td>Range</td>
<td>58.5±12.1</td>
<td>29.1±10.4</td>
</tr>
</tbody>
</table>

*−IOP indicates intraocular pressure. P < .001 for all comparisons.

Is IOP Variation Over a 24 Hour Period Important?
Long-Term Reproducibility of Diurnal Intraocular Pressure Patterns in Patients with Glaucoma

Pierre Axal, MD, PhD,1,2 Ayanee Lewis, MD,1 Christophe Chiquet, MD, PhD,1 Nihad Aryan-Chak, MD,1 Christian Nadal, MD, Jean-Paul Remont, MD

Purpose: To evaluate the long term reproducibility of diurnal intraocular pressure (IOP) patterns in patients with glaucoma.

Methods: We reviewed the records of patients with POAG who underwent 6 diurnal IOP curve measurements from 6:00 AM to 10:00 PM. Three IOP measurements were performed at each hour and the IOP was recorded at 30-minute intervals. The data were analyzed using statistical software. The IOP was measured using a Goldmann applanation tonometer and the IOP was recorded at 6:00 AM, 10:00 AM, 11:00 AM, noon, 1:00 PM, 2:00 PM, and 3:00 PM. All studies were performed in a single session.

Results: The intraclass correlation coefficient (ICC) of IOP values at each time point was similar to that of POAG, with ICCs ranging from 0.29 to 0.72 at all points. The diurnal IOP curve for patients with POAG without anti-hypertensive medications (5 time points with ICC = 0.72) and patients with anti-hypertensive medications (5 time points with ICC = 0.70) were analyzed. The diurnal IOP curve for POAG patients following surgery was analyzed from 6:00 AM to 10:00 PM (6 time points with ICC = 0.75). The diurnal IOP curve for POAG patients following surgery was analyzed from 6:00 AM to 10:00 PM (6 time points with ICC = 0.75). The diurnal IOP curve was repeated 9 times in the same patient, with an ICC of 0.75.

Conclusions: Patients with POAG do not manifest a reproducible diurnal IOP pattern from month to month. A single diurnal IOP curve in patients with POAG points to characteristic IOP fluctuations and has limited value in clinical practice.
Usefulness of Diurnal IOP

- In eyes suggestive of primary open-angle glaucoma but whose sporadic IOP measurements are always within normal range, diurnal testing may demonstrate an abnormal elevation in IOP
  - Help confirm the diagnosis
  - Document peak IOP on which to base my therapy
- In glaucomatous eyes with normal IOP on sporadic office measurement but whose nerves or visual fields are deteriorating, diurnal IOP measurement often demonstrate IOPs peaking above the sporadic measurements
  - Prove to both doctor and patient the necessity for increasing therapy
- Additionally, in eyes with advanced glaucoma precluding monitoring by fields or disc photography, the use of diurnal IOP is an important measure to monitor for progression

Usefulness of Diurnal IOP

- If the diurnal IOP measurements are normal on 1 day, it does not prove it is normal on a subsequent day
- However, if the IOP does spike out of the habitual or normal range, then such a diurnal IOP measurement is valuable
- Like many tests in medicine, diurnal monitoring may only be useful if an abnormality is found
  - that does not reduce its value, especially in a test where the cost is minor, and there are no possible major complications
Usefulness of Diurnal IOP

- This test is not repeatable over the short term
  - Does not negate its value
  - Many tests are complicated by repeatability issues, but it does not mean they are not valuable in clinical practice
  - An example is visual field testing which are plagued by both reliability and reproducibility problems, but that does not mean the data is not useful
  - The data obtained in both IOP monitoring and visual field examination would have greater value if they were always reliable and reproducible, but we have to do the best with what we have
  - Until technology provides the clinician with noninvasive, 24-hour IOP monitoring, we will have to use office IOP measurements
  - Obtaining IOP measurements, even if not repeatable over the short term, is still better in selected cases than sporadic measurements

- One routine is to measure the IOP at 0730, 1230, and 1630 hours
  - Patients can leave the office and return for the brief IOP check

Usefulness of Diurnal IOP

- Diurnal IOP curve on any given day may not tell the whole story
- As diurnal IOP variation often is different from day to day, the absence of an IOP spike on a particular day does not preclude the possibility of a daytime spike on a different day
- Unfortunately, the optimal number and timing of IOP measurements necessary to adequately characterize IOP variation has not yet been established
- A single-day diurnal IOP curve may not tell us as much as we might hope about IOP variation on other days

Continuous IOP Monitoring

- Combination of decrease in blood pressure with increase IOP during sleep could compromise optic nerve circulation in susceptible individuals
  - 24 hr continuous monitoring important
- Three approaches to accurately measure IOP without measurement noise
  - Self tonometry
  - Permanent continuous IOP monitoring
  - Temporary continuous IOP monitoring
Self Tonometry

- Patients would monitor their IOP over time with easy-to-use devices
- Easiest approach in regards to continuous monitoring
- Adapt current device such as Noncontact tonometer or Rebound tonometer
- Does not allow for nocturnal measurements

Permanent Continuous Monitoring

- Provide daytime and nighttime IOP measurements through self-contained implant
- Accessed remotely with wireless technology
- Ideal for advanced glaucoma
- Would not be measuring the surface but rather taking IOP measurements directly inside the eye
  - Subject to less noise

Permanent Continuous Monitoring

- Recent idea is incorporating telemetric IOP device with IOL
- Digital signal would be sent form IOL to eyeglasses worn by patient
- Alarm raised at certain point
- Long-term stability is unknown
Temporary Continuous Monitoring

- Non-invasive contact lens based systems that measure IOP over 24-48 hour period
- Recognize IOP fluctuations which may be significant
- Silicone contact lens which has strain gauge
  - must fit tight to reduce noise
- Corneal health issues with tight lens
- Sensimed system in use in Europe that has contact lens, antennae system and recorder
  - not yet validated or available in US
Triggerfish Contact Lens IOP Device

- The lens is designed to provide a much more accurate, longer-term assessment of the IOP.
- Consists of a clear, silicone contact lens ringed by a strain gauge and a microprocessor and antenna that transmits data to an external receiver.
- The gauge continuously monitors the shape of the cornea, indicating greater or lesser intraocular pressure.
- Information about IOP fluctuations is immediately transmitted via radio frequencies from the lens’ microprocessor to a recording receiver.
- The microprocessor is powered by an induction loop which uses a magnetic field around the eye to generate the tiny amounts of required electricity.
  - Induction loops are also used to power hearing-aid implants.

• The Triggerfish is intended to be worn for just 24 hours, then discarded.
• Glaucoma patients would wear the device once every six or so months.
• Obtain a detailed description of the patient’s IOP and eye health.
• “It’s the difference between seeing a single movie frame and watching a full-length motion picture.”
• Better understand what is happening to the eye, providing earlier and more accurate diagnoses.
• Detect changing conditions and adjust or alter treatments more effectively.
• Personalized medicine for the eye.
Figure 1. Placement of the semiretrobulbar "triggerfish" and antenna.

Figure 1. The wireless sensor is in place. A soft patch containing the antenna is applied around the eye and transmits the information via wire to the recorder that the patient wears in a pocket fixed around the neck and waist. The patient can continue to wear her spectacles during monitoring (patient consent was obtained for publication of this photograph).