Disclosure:

- Michael Chaglasian, O.D. is a paid advisor, consultant and researcher for the following commercial/industry groups:
  - 1. Advisory Boards:
    - Allergan, Alcon Labs, Carl Zeiss Meditec
  - The content of this presentation is in no manner influenced by any of the aforementioned parties or companies

Objectives

1. Understand the prevalence, severity and impact of OSD and glaucoma in the population.
2. Understand the clinical signs of OSD and glaucoma.
3. Understand the histological effects of BAK on the ocular surface.
4. Be familiar with recent studies examining the effects of topical glaucoma agents on patients.
5. Be familiar with all options for treating glaucoma patient with medications that do not include BAK.

OSD is Just Like Glaucoma

- A chronic disease the increases with age
- Definitions of the disease vary
- Signs of the disease rarely match the symptoms and vice versa
- Diagnostic tests are variable, not repeatable and often inconclusive
- Treatment regimens are variable and often not effective
- Majority of patients are non-compliant

Why should we care?

A Very Current Topic
Will there be something to replace topical therapy in glaucoma in the near future?

Glaucma Care for the Future

- New Ophthalmic Drug Delivery Systems are Coming for Glaucoma.
  - The future therapy for glaucoma remains pharmacologically based (vs. laser/surgery).
  - Some new therapeutic agents will arrive.
  - But more importantly new drug delivery systems will significantly alter how we start therapy for our glaucoma patients.

New Delivery Systems

- QLT’s punctal plug drug delivery technology

Iluvien (Alimera)

- Iluvien
  - extended release intravitreal
  - delivers fluocinolone acetonide, to the retina for up to three years for treatment of DME
  - Completed Phase III Clinical Trial
  - Medidur™ Technology is a miniaturized, injectable, sustained-release drug delivery system

Subconjunctival Injection

- Anecortave acetate
  - angiostatic, initially for wet AMD
  - posterior juxtascleral injection
  - initial success of 3 month IOP reduction, then failure in large scale studies

- Latanoprost
  - Encapsulated in poly-glycolide micro particles
  - Animal studies showed up to 30 days IOP reduction post injection
Clinical Trial Completed

Injection May Replace Drops to Lower Intraocular Pressure

March 30, 2015

SOTIARY RECOMMENDATIONS
Visual Field-Index Oxidative
Neural Loss in Early Glaucoma

Glaucoma New Convention: Yields by Difference at 3 Years

Effective Non-Invasive Therapy-Cost Effective in Glaucoma


Clinical Trial Completed

DURASERT™

The Helios Insert

http://forsightvision5.com/products/helios-insert

A nanomedicine approach for ocular neuroprotection in glaucoma.

A new medical/topical option for glaucoma is coming.....

CAI? PGA? Combination? New Class??

Look and sound familiar?

- 75y/o female with primary open angle glaucoma
- Controlled IOP, moderate field loss but STABLE.
- On Xalatan, Cosopt and Brimonidine
- You pat yourself on the back, ready to conquer the next challenging patient but wait...

“that’s nice that my glaucoma is doing well, but doctor, my eyes are tearing”
We Are Treating the Whole Patient

- **Goals of Glaucoma Management**
  - Treatment
  - Lower IOP to Target
  - Preserve Vision
- **Quality of Life Considerations**
  - Long Term Impact of Medications
  - Balance of Efficacy and Side Effects
  - Do No Harm
    - Primum non nocere

Glaucoma and Ocular Surface Disease (OSD)

Overview

OSD in the Elderly

- 2,520 residents of Salisbury, MD.
- 65 years or older as of 1993.
- Standardized questionnaire (6 questions).
- Exam:
  - Schirmer
  - Rose bengal
  - Assessment of meibomian glands


OSD in the Elderly


OSD in the Elderly

14.6% reported one or more dry eye symptom “often” or “all the time.”


Age and OSD

OSD and Glaucoma

Review of Literature:
1. Moderate OSD in 20-60%
2. Severe OSD in 14-66%

Quality of Life

How do we study/measure and quantify this?
Important for documenting any claims of improvement in response to treatment options.

Ocular Surface Disease Index “OSDI”

- Developed by Outcomes Research Group at Allergan, Inc.
- 12 item questionnaire.
- Provide rapid assessment of symptoms of ocular irritation consistent with dry eye disease.
- Designed as endpoint in clinical trial testing of treatment for dry eye disease.

OSDI Severity Grading

Total OSDI Score = (Sum of Score for All Questions Answered) X (25) / (Total # of Questions Answered)
Glaucoma Management and OSD 2015

OSDI Results: 630 Glc Patients

<table>
<thead>
<tr>
<th>Severity</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>51.6%</td>
</tr>
<tr>
<td>Mild</td>
<td>21.3%</td>
</tr>
<tr>
<td>Moderate</td>
<td>13.8%</td>
</tr>
<tr>
<td>Severe</td>
<td>4.9%</td>
</tr>
</tbody>
</table>


Impact of Multiple Medications

<table>
<thead>
<tr>
<th>Number of Medications</th>
<th>OSD Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12.9</td>
</tr>
<tr>
<td>2</td>
<td>16.7</td>
</tr>
<tr>
<td>3</td>
<td>19.4</td>
</tr>
</tbody>
</table>


OSD in Glaucoma Prevalence: Summary

- Ocular Surface Disease is a Significant Problem For Many Glaucoma Patients.
- Prevalence is High, ranging from 48.4% to 60%.1,2
- Previously Reported in a Population Based Study of Elderly (~15%).3
- OSD Severity Increases With The Number of Medications Used.2,4


OSD (Glaucoma Today '08)

- Any condition that adversely affects the stability and function of the tear film.
- Common causes ➤ dry eye syndrome, blepharitis, meibomian gland dysfunction, and preservative toxicity.
- Pathology involves corneal epithelial cell changes, decreased goblet cell density, and increased inflammatory mediators.


Leung: Key Learnings

“A large proportion of patients with open-angle glaucoma or ocular hypertension had signs and/or symptoms of OSD in at least 1 eye. The co-existence of OSD and the use of BAK-containing medications may impact vision-related quality of life in this patient population.”


Additional Prevalence Data: Leung

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Observation</th>
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<tbody>
<tr>
<td>OSDI</td>
<td>59% symptoms in 1 eye</td>
</tr>
<tr>
<td>Schirmer</td>
<td>61% decreased tear production in 1 eye 35% severe deficiency</td>
</tr>
<tr>
<td>Lissamine Green</td>
<td>22% positive staining</td>
</tr>
<tr>
<td>TBUT</td>
<td>78% abnormal tear quality 65% severe decrease in tear quality</td>
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</table>

Detecting OSD

- Signs do not always match symptoms.
- Multiple approaches possible.
- Should be validated.
- Need a better system!

Signs and Symptoms

“The lack of concordance between signs and symptoms presents a problem to the diagnosis of the disease and assessment of severity.”

-M. Lemp, MD

Why Are Preservatives Needed?

- FDA requires multi-dose ophthalmic preparations to contain a preservative to reduce contamination.
- Decrease the risk of microbial contamination in the bottle.

Preservative Affect on Cornea

- Directly:
  - Modifying anatomical and physiological the epithelium which affects optical properties and epithelial barrier function.
- Indirectly:
  - Modifying tear film leading to ocular non-wetting tear disorders

The Effects of Benzylalkonium Chloride (BAK)

Preservative Systems

<table>
<thead>
<tr>
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<th>Example</th>
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<tbody>
<tr>
<td>Detergents</td>
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Preservatives in PGA’s: 2014

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<th>Drug</th>
<th>Percentage</th>
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</thead>
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<tr>
<td>XALATAN</td>
<td>0.02% BAK</td>
</tr>
<tr>
<td>LUMIGAN 0.01%</td>
<td>0.02% BAK</td>
</tr>
<tr>
<td>LUMIGAN 0.03%</td>
<td>0.005% BAK</td>
</tr>
<tr>
<td>TRAVATAN Z®</td>
<td>BAK Free soZia™</td>
</tr>
</tbody>
</table>

1. XALATAN® package insert
2. LUMIGAN® package insert
3. TRAVATAN Z® package insert

When is BAK Use Most Problematic?

- High BAK Concentration: Cell Death is Dose-Dependent.
  - High Concentration in a Single Drop or Due to The Accumulation of Dose With Multiple Drops.

<table>
<thead>
<tr>
<th>Concentration</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0001% BAK</td>
<td>Growth Arrest</td>
</tr>
<tr>
<td>0.01% BAK</td>
<td>Apoptosis</td>
</tr>
<tr>
<td>0.05-0.1% BAK</td>
<td>Necrosis</td>
</tr>
</tbody>
</table>

- Treatment of Chronic Ophthalmic Diseases, such as Glaucoma, with BAK Containing Medications.
  - Longer Duration of BAK Exposure → Increased Corneal Epithelial Cell Lysis.

BAK Impact on Ocular Surface Health

- Decreases Epithelial Cell Integrity.
  - Epithelial Barrier is Compromised.
  - Healing is Impaired.
- Increases Conjunctival Inflammatory Cells.
- Loss of Goblet Cells.
- Reduction in Tear Function.
- Decreases Tear Film Break-up Time (T/BUT).

Effects of BAK on the Ocular Surface

- Cornea:
  - Accelerates superficial desquamation.
  - Disrupts permeability barrier.
  - Triggers apoptosis by 0.01% and necrosis by 0.05%.
- Conjunctiva:
  - Increases expression of HLA-DR antigen and chemokine receptors.
  - Promotes inflammatory cell infiltration.
  - Goblet cell loss.

BAK Effect on Cornea

- BAK on Corneal Epithelial Surface
- Tear Film Instability
- Epithelial Damage
- Epithelial Cell Apoptosis
- Decrease MUC5A (gel forming mucin secreted by the goblet cells of the ocular surface)
- Increase ICAM (intracellular adhesion molecule for cell to cell adhesion: a marker for inflammation)

Dry Eye Work Shop 2007

“The single most critical advance in the treatment of dry eye came from the elimination of preservatives, such as benzalkonium chloride, from OTC lubricants.”
Chronic Effect of Preservatives

- Patients treated >1 year with preserved latanoprost (21), preserved timolol (15) or unpreserved timolol (17) were compared to normals.
- Unpreserved timolol was similar to controls.
- Preserved latanoprost and preserved timolol with 0.02% BAK showed pro-inflammatory and pro-apoptotic effects but less than 0.02% BAK alone.

Factors Contributing to Preservative Toxicity

- Concentration.
- Frequency and duration of use.
- Tear production and clearance (blink rate and corneal sensitivity).
- Contact lens use.
- Number and type of concurrent medications.
- Type of preservative.

Implications for Glaucoma Therapy

- Chronic therapy with BAK preserved medications may:
  - Promote development of dry eye and OSD
  - Increase risk of:
    - Corneal complications: haze, infiltrates, ulcers.
    - Irritation symptoms.
    - Decreased functional vision.

Summary

- Do preserved glaucoma medications have a deleterious effect on superficial eye tissues? Yes
- Are preservatives like BAK deleterious? Yes
- Are the changes dose/time dependent? Yes
- Are the changes reversible? Probably
- Is it clinically important? In many patients

Human Clinical Data

- Purpose: Examine The Safety, Tolerability and Efficacy of Travoprost BAK-free Compared to Latanoprost or Bimatoprost.

  - Methods:
    - 694 POAG or OH Patients Treated With Latanoprost or Bimatoprost Monotherapy Who Demonstrate a Need For Greater Tolerability, and Judged by The Physician to be a Good Candidate, Were Changed to Travoprost BAK Free Ophthalmic Solution and Returned for a Second Visit 3 Months Later
    - Prospective, Multi-center, Open-label, 3 Month Study With 2 Visits (Baseline And Month 3)
    - Variables Measured:
      - IOP
      - Ocular Hyperemia Grading
      - Global OSDI Score
      - Visual Acuity
      - Patient Global Preference
      - Slit-Lamp Biomicroscopy
      - Adverse Events

Conclusions

- In this evaluation of 691 POAG or OH patients treated with Latanoprost or Bimatoprost monotherapy who demonstrated a need for greater tolerability, change to BAK-free travoprost resulted in significant improvements in OSDI, hyperemia, and patient preference at 3 months.
- Patient preference may have been driven by improved functionality including driving at night, reading, sensitivity to light, grittiness, pain, blurred vision, and computer work.


Compliance Component

- “A major cause of intolerance or poor tolerance to glaucoma medication is the ocular surface changes created by treatment.”

Non BAK PGA Options

<table>
<thead>
<tr>
<th>Travatan Z</th>
<th>Unique Ionic Buffer System</th>
</tr>
</thead>
<tbody>
<tr>
<td>SofZia Preservative</td>
<td></td>
</tr>
</tbody>
</table>

When TRAVATAN® Z solution comes in contact with the positively charged ions in the tear film, the ionic buffered preservative system becomes inactive, providing a solution that is safe and gentle on the eye.

Bitmatoprost

- Lumigan
  - 0.01
  - 0.02% BAK
  - 0.03%
  - 0.005% BAK

Lumigan.com

Other Non-BAK Options for Glaucoma Patients with OSD

- Alphagan P
  – Brimonidine PURITE® 0.1%
- PURITE® (stabilized oxychloro complex) is a preservative that is effective at low concentrations.
The Only: Preservative Free PGA

Zioptan

- A Preservative Free prostaglandin analog
  - Introduced in 2003
  - Tafluprost 0.015%
  - Single use vial delivery

- Same PGA side effects:
  - Iris/Periorbital Pigmentation, Hyperemia, Deepening Orbital Sulcus, etc.

http://www.zioptan.com/zioptan/consumer/secure/index.html

Zioptan: Efficacy

- Clinical Trial:
  - IOP reduced by 6.4 – 7.5 mmHg @ 12 weeks
    - Baseline 23-26 mmHg
    - n=618
  - AJO June 2012

Zioptan Non-Clinical Data

- Tafluprost: less toxic than travoprost, latanoprost, or unoprostone.
  - Application of PF tafluprost at 5-minute intervals on 15 occasions had no toxic effects on the rabbit corneoconjunctival surface

Zioptan vs. Latanoprost

- “Both treatments had a substantial IOP-lowering effect which persisted throughout the study.”
  - 7.1 mmHg for tafluprost
  - 7.7 mmHg for latanoprost
    - at 24 months

No Difference in OSD for 3 PGAs (3 months)

- Xalatan
  - 0.02% BAK
- Lumigan 0.03%
  - 0.005% BAK
- Travatan Z
  - Sofzia
- Graded:
  - Ocular Tolerability
  - TBUT
  - Hyperemia
Cosopt PF

- dorzolamide HCL - timolol maleate 2%/0.5%
- Preservative Free
- BID dosing
- 25-30% IOP reduction when used as monotherapy
- Role:
  - COPD and other beta blocker contraindications
- Similar indications for OSD patients where BAK toxicity is a concern


Recent Cosopt PF articles

Another PF Option

- TIMOPTIC® in OCUDOSE® —
  - Preservative-free Sterile
  - Ophthalmic Solution TIMOPTIC® is supplied in OCUDOSE®, a clear, individual, unit dose container
  - Valeant Pharmaceuticals
    - Patient Care Program

BAK in Other Meds

- Simbrinza — 0.003%
- Combigan — 0.005%
- Cosopt — 0.0075%
- Rescula — 0.015%
- Azopt — 0.01%
- Trusopt — 0.0075%
- Timolol sol — 0.01%

Other Non-BAK Options for Glaucoma Patients with OSD

- Alphagan P
  - Brimonidine PURITE® 0.1%
  - Higher pH 7.8
  - Lower Concentration
- PURITE®
  - Stabilized oxychloro complex is a preservative that is effective at low concentrations.

My Typical Approach

- Glaucoma Patient
  - New or established
- History
  - Specific for dry eye symptoms
  - Questionnaire if necessary
- Thorough slit lamp
  - TBUT and Lissamine green
- With Positive Findings or Risk Factors
  - Review Medications and Treatment Options
  - Patient Education
  - Reduce the Preservative Load
Summary

• Do preserved glaucoma medications have a deleterious effect on superficial eye tissues? Yes
• Are preservatives like BAK deleterious? Yes
• Are the changes dose/time dependent? Yes
• Are the changes reversible? Probably
• Is it clinically important?
  In many patients, especially those with OSD.

Questions

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