Glaucoma Management and Ocular Surface Disease

Michael Chaglasian, O.D.
Illinois Eye Institute
Illinois College of Optometry
mchaglas@ico.edu
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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

A Very Current Topic

Glaucoma and Dry Eye: A Tough Combo

Why should we care?
Will there be something to replace topical therapy in glaucoma in the near future?

Glaucoma 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

Mini Drug Pump

- MEMS – pump that is refillable, enables long-term use, and possesses broad drug compatibility
- The pumping mechanism is based on electrolysis and the pump includes a drug refill port as well as a check valve to control drug delivery

Replenish MicroPump

- Replenish, Inc. is developing a small, refillable, implantable ocular drug pump.
- The pump can be programmed to dispense precise nanoliter-sized doses (a drug flow sensor gives closed-feedback) of drugs every hour, day or month as needed over six to nine months before the next refill.

Iontophoresis

- Iontophoresis uses an electrical current to drive drugs in the form of ions through a tissue or membrane.

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

Age and Glaucoma


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

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


OSD and Glaucoma

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

Cornea 2006

Incidence and Prevalence of Glaucoma in Severe Ocular Surface Disease

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 Results: 630 Glc Patients

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Normal</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
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<tr>
<td>60%</td>
<td>51.6%</td>
<td>48.4%</td>
<td>21.3%</td>
<td>13.3%</td>
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<tr>
<td>n=325</td>
<td>n=134</td>
<td>n=84</td>
<td>n=87</td>
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</table>

OSDI Severity Grading

<table>
<thead>
<tr>
<th>Score</th>
<th>Normal</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-12</td>
<td>0-22</td>
<td>23-32</td>
<td>33-100</td>
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</tbody>
</table>

Total OSDI Score =
(Sum of Score for All Questions Answered) X (25)
(Total # of Questions Answered)


Impact of Multiple Medications

<table>
<thead>
<tr>
<th>Number of Medications</th>
<th>OSDI Score</th>
<th>N=253</th>
<th>N=227</th>
<th>N=114</th>
</tr>
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<tr>
<td>1</td>
<td>12.9</td>
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<td>2</td>
<td>16.7</td>
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<tr>
<td>3</td>
<td>19.4</td>
<td></td>
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</tr>
</tbody>
</table>

Impact of Multiple Medications

N= 253                         N=227                        N=114

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.”


Leung: Key Learnings

Each additional BAK-containing eye drop = ~2x higher odds of an abnormal lissamine green result.

(OR=2.03; 95% CI: 1.06 to 3.89; P=0.034)
OSD in Glaucoma Prevalence: Summary

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


OSD (Glaucoma Today ’08)

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

Dry Eye Cascade

1. ABNORMAL TEAR FILM CAUSES & CONTRIBUTORS
   - Aqueous Deficient Dry Eye
   - Evaporative Dry Eye
   - Meibomian gland dysfunction
   - Contact Lens
   - LASIK
   - Anti-Venom Disease
   - Alcohol Use
   - Pollution
   - Computer Use
   - Anti-Depressants
   - Quaternary Ammonium (i.e. BAK)

OBSERVABLE PATHOPHYSIOLOGIES

OBSERVABLE CYTOKINES

INFLAMMATION

Evaporative Dry Eye

1. Meibomian gland dysfunction results in a decrease in lipid volume and is a leading cause of evaporative dry eye disease.

OSD Affects Quality of Life

1. Impact on patients’ day-to-day lives comparable to that of moderate-to-severe angina.1
2. % of Patients reporting interference with daily life functions:2
   - Night time driving: 32.3%
   - Reading: 27.5%
   - Computer work: 25.7%
   - Watching TV: 17.9%

OSD Affects Quality of Vision
Unfortunately, Just Can’t Feel Vision

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

Diagnostic Tools

Tear Film Break-Up Time
Injection
Rose Bengal Staining
Lissamine Green Staining

Fluorescein Staining
Blink Rate
Schirmer Testing
Osmolarity

DTS Study Group Most Commonly Used Diagnostic Tests

Clinician Ratings for Diagnostic Tests

Highest
Lowest
History
TBUT
Schirmer test
Cotton thread test

M. Chaglasian, O.D.

8
Lissamine Green Staining

Lissamine green is a dye, used for staining cells which are devitalized or have lost their normal mucin surface. Wratten 25 filter. The lissamine green staining appears black.

Photos Courtesy of Terrence P. O'Brien, MD  
Milton Hom, OD

The Effects of Benzylalkonium Chloride (BAK)

Why Are Preservatives Needed?

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

Preservative Systems

BAK is a Common Preservative

- Quaternary ammonium compound.
- Cationic surfactant properties (a detergent).
- In majority of ophthalmic medications (72%), ranging in concentrations from 0.004-0.02%.
- Preserves multi-dose containers from microbial contamination.
- Enhances corneal penetration of some drugs by causing epithelial separation.
- Efficacy impact on some drugs.
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

Preservatives in IOP-Lowering Medications

<table>
<thead>
<tr>
<th>Generic (Trade Name)</th>
<th>Concentration</th>
<th>Preservative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brimonidine (Alphagan®)</td>
<td>0.05% BAK</td>
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</tr>
<tr>
<td>Brimonidine with Propa (Alphagan-P®)</td>
<td>0.005% SOC</td>
<td></td>
</tr>
<tr>
<td>Brinzolamide (Azopt®)</td>
<td>0.1% BAK</td>
<td></td>
</tr>
<tr>
<td>Levobunolol (Betagan®)</td>
<td>0.05% BAK</td>
<td></td>
</tr>
<tr>
<td>Bimatoprost (Lumigan®)</td>
<td>0.005% BAK</td>
<td></td>
</tr>
<tr>
<td>Latanoprost (Xalatan®)</td>
<td>0.02% BAK</td>
<td></td>
</tr>
<tr>
<td>Timolol (Timoptic®)</td>
<td>0.01% BAK</td>
<td></td>
</tr>
<tr>
<td>Travoprost (Travatan®)</td>
<td>0.015% BAK</td>
<td></td>
</tr>
<tr>
<td>Dorzolamide/Timolol (Cosopt®)</td>
<td>0.02% BAK</td>
<td></td>
</tr>
<tr>
<td>Dorzolamide (Trusopt®)</td>
<td>0.0075% BAK</td>
<td></td>
</tr>
</tbody>
</table>

Preservatives in PGA’s: 2014

<table>
<thead>
<tr>
<th>Generic</th>
<th>Concentration</th>
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<tbody>
<tr>
<td>XALATAN</td>
<td>0.02% BAK</td>
</tr>
<tr>
<td>LUMIGAN</td>
<td>0.01%, 0.02% BAK</td>
</tr>
<tr>
<td>LUMIGAN</td>
<td>0.03%, 0.005% BAK</td>
</tr>
<tr>
<td>TRAVATAN Z®</td>
<td>BAK Free sofZia™</td>
</tr>
</tbody>
</table>

When is BAK Use Most Problematic?

- **High BAK Concentration:**
  - Cell Death is Dose-Dependent
    1. High Concentration in a Single Drop or
    2. Due to The Accumulation of Dose With Multiple Drops
  - Treatment of Chronic Ophthalmic Diseases, such as Glaucoma, with BAK Containing Medications
    1. Longer Duration of BAK Exposure → Increased Corneal Epithelial Cell Lysis

BAK Impact on Ocular Surface Health

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

- TEAR FILM INSTABILITY
- EPITHELIAL DAMAGE
- EPITHELIAL CELL APOPTOSIS

Decrease MUC5A

(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.”


**BAK Adversely Affects TBUT in 30 Healthy Volunteers**

*Decrease in TBUT at 3 hours from baseline was significantly lower in the BAK-free group than in the preserved carteolol (P=0.04).† Significantly lowered compared with baseline (P=0.001).


**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.


**Is Chronic Exposure to BAK a Big Deal?**

“The Single Most Critical Advance in the Treatment of Dry Eye Came with The Elimination of Preservatives, such as BAK from OTC Lubricants.”

Stephen Pflugfelder, MD

“BAK is Largely Responsible for the Ocular Toxicities and Inflammation Associated with the Chronic Use of Many Ophthalmic Solutions.”

Christoph Baudouin, MD, PhD

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.

Other Clinical Effects on Chronic Glaucoma Medications

- Decreased mucus layer of the tear film.\(^1\)
- Reduced tear secretion, basal Schirmer's and TBUT.\(^2,3\)
- Increased Rose-Bengal staining of cornea.\(^4\)
- Foreshortening of the inferior conjunctival fornix.\(^5\)
- Inflammatory cell infiltration in trabecular meshwork.\(^6\)

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 Tolerance, 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:
  - Patient Global Preference
  - Slit-Lamp Biomicroscopy
  - Adverse Events
  - Global OSDI Score
  - Visual Acuity

Experience with BAK-Free Glaucoma Medications

Human Clinical Data

1 Herreras JM et al Ophthalmol 1992
2 Nuzzi R. et al Int. Ophthalmol, 1998,
3 Ariei MK et al Clin Experimental Ophthalmol 2000
5 Schwab IR et al, Ophthalmol 1992
6 Baudouin C et al, Ophthalmol 1999

References:

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Study Results
Patient Preference

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<th>N (%)</th>
<th>P-Value</th>
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<tr>
<td>XALATAN*/LUMIGAN*</td>
<td>191 (28%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>TRAVATAN Z Solution</td>
<td>500 (72%)</td>
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</tr>
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Symptoms Improved:
- Photophobia, pain, grittiness, blurred vision

Functional Improvements:
- Driving at night, reading, and computer use.

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

- **Travatan Z**
  - SofZia Preservative

  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.

Bitimatoprost

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

Lumigan.com
Latanoprost Generic

• Latanoprost ophthalmic solution is supplied as a sterile, isotonic, buffered aqueous solution of latanoprost with a pH of approximately 6.7 and an osmolality of approximately 267 mOsm/kg.

• Each mL of latanoprost contains 50 micrograms of latanoprost. Benzalkonium chloride, 0.02% is added as a preservative.

• The inactive ingredients are: sodium chloride, sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate anhydrous, and water for injection.

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.

PURITE® Is a Gentle Preservative

SEM of rabbit corneal epithelium (800X)

Untreated PURITE® QID 7 days BAK QID 7 days

The clinical significance of these data is unknown.


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.

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 corneconjunctival 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

http://cosoptpf.com/consumer/index.html
Recent Cosopt PF articles

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

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.

PURITE® Is a Gentle Preservative

SEM of rabbit corneal epithelium (800X)

Un-treated

PURITE® QID 7 days

BAK QID 7 days

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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