disclosures

Consultant: Shire/Takeda
Advisory Board and/or speakers bureau:
Alcon/Novartis, Allergan, Bausch + Lomb, Innova Medical, Santen, Purdue, Takeda
Board of Directors:
VP, Sjogren’s Society of Canada
Prevalence of Glaucoma

- Global prevalence 40-80 years is 3.54%
  (95% CrI, 2.09-5.82)
  - 64.3M in 2013;
  - 76.0M in 2020
  - 111.8M in 2014
- Varies with racial group and age
Topical Anti-glaucoma Medications

• To date, topical medications are the mainstay of treatment for POAG and other forms
  – Also Laser, MIGS, surgery
• Most are simple dosing regimens, and effective IOP lowering
  – E.g. PGA/BB q.d.
• More than one medication is often needed, however, to achieve target pressure
OSD + glaucoma?
Why OSD + glaucoma?

- Glaucoma expected to be 80M worldwide in 2020
- OSD is present in at least 15% of older populations
- OSD is much more common in persons with glaucoma
- Multiple/daily exposures to drugs/preservatives can worsen OSD
  - Multiple medications are required
- Both conditions can impact QoL
- And more....
Both are chronic diseases that both increase in frequency with age and progress with age. Both are often confounded by a mismatch in symptoms and signs. Methods of assessment for both conditions vary amongst clinicians and are constantly changing.

Neither disease will be cured — treatment is palliative, lifelong and the disease and/or its management causes some degree of reduced QoL. Both require diligent care on part of the patient — patients with chronic diseases face certain amount of non-adherence due to cost, education, many other patient factors.

Treatment can be complex and variably effective or ineffective. Structural loss (especially end stages) can result in vision loss. Diagnostic tests used are often variable and not conclusive for disease or progression.
Ocular Surface Disease Exacerbated Glaucoma: Optimizing the Ocular Surface Improves Intraocular Pressure Control

Ruchika Batra, MRCPth, Rajen Tailor, MRCPth, and Shabbir Mohamed, FRCSEd

Purpose: To describe a series of 4 patients with inadequately controlled primary open angle glaucoma (POAG) and ocular surface disease (OSD) in whom a combination approach was used to manage the OSD resulting in improved intraocular pressure (IOP) control.

Patients and Methods: A retrospective review of 4 patients referred to a tertiary ophthalmology clinic by their local general practitioners (GPs) or ophthalmologists for worsening visual symptoms, discomfort, and blurred vision.

Results: All 4 patients had evidence of OSD with signs of dry eye disease, cicatricial conjunctivitis, and ocular surface staining. After a comprehensive assessment, a combination approach was used to manage the OSD. This included the use of preservative-free lubricants, artificial tears, and topical medications to control the glaucoma. The measures included changing the anti-glaucoma medications to preservative-free alternatives and adding lubricants and tear supplements to the treatment regimen.

Efficacy, safety, and improved tolerability of travoprost BAK-free ophthalmic solution compared with prior prostaglandin therapy

Preservative-free treatment in glaucoma: who, when, and why?

M. Sahn1, R. Ghanem1, J. Oster2, and M. Mazzetti

Preservative use in topical glaucoma medications

BENZONATONIUM CHLORIDE IN GLAUCOMA MEDICATIONS

ROBERT NOUGERI, MD, MBA1, AND KIMBERLY V. MILLER

Effects of benzalkonium chloride- or polyquad-preserved fixed combination glaucoma medications on human trabecular meshwork cells

David A. Ammar, Malik Y. Khashaw
The impact of topical intraocular pressure lowering medications on the ocular surface of glaucoma patients: A review

Kofi Asiedu a,b, Sampson Listowell Abu b

a Eye Clinic, Tumaini Medical Centre ARS, Junction East Legon, Accra
b Department of Ophthalmology and Visual Science, University of Alabama, Birmingham

Received 2 May 2018; revised 25 June 2018; accepted 11 July
Available online 1 September 2018

Assessment of Corneal Changes Associated with Topical Antiglaucoma Therapy Using in vivo Confocal Microscopy

Elmira Baghdasaryana, Tudor C. Tepelusa, Laura A. Vickersb, SriniVas R. Sadda b, Olivia L. Leea,b, Ping Huanga

a Doheny Image Reading Center, Doheny Eye Institute, and b Department of Ophthalmology, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA

Application of In Vivo Confocal Microscopy in Dry Eye Disease

Yukihiro Matsumoto and Osama M. A. Ibrahim

Department of Ophthalmology, Keio University School of Medicine, Tokyo, Japan
Ocular Surface Disease in patients with Glaucoma

- How much OSD in patients with glaucoma?
- Is there something in the eyedrop bottles contributing to OSD?
- Are some topical meds better than others?
- What is the relationship between the number of medications used and the OSD?
- Does the OSD affect the adherence to treatment?
- Do we treat the OSD in those patients with glaucoma differently to those patients without?
  - How aggressive do we get in treating the OSD?
- Is IOP affected by OSD?
  - “OSD Exacerbated Glaucoma”
- Other treatment options without drops?
Prevalence of DED symptoms in glaucoma

- Probably at least half (48.4%) of patients with glaucoma have OSD
  - Lows of 39% (Malaysia, Thailand)
  - ~60% (US, Brazil, international study)
  - Highs of 75% (Croatia)

<table>
<thead>
<tr>
<th>Authors</th>
<th>Number of subjects</th>
<th>Prevalence</th>
<th>Diagnostic cut off (OSDI)</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barisic et al. (2014)</td>
<td>Glaucoma group: 110 Control group: 50</td>
<td>Glaucoma group: 75% Control group: 35%</td>
<td>≥13</td>
<td>Croatia</td>
</tr>
<tr>
<td>Skalicky et al. (2012)</td>
<td>Glaucoma group: 101 Control group: 23</td>
<td>Glaucoma group: 47.6% Control group: 21.7%</td>
<td>≥13</td>
<td>Australia</td>
</tr>
<tr>
<td>Leung et al. (2008)</td>
<td>Glaucoma group: 101 Control group: none</td>
<td>Glaucoma group: 59% Control group: none</td>
<td>≥13</td>
<td>the United States</td>
</tr>
<tr>
<td>Ramli et al. (2015)</td>
<td>Glaucoma group: 105 Control group: 102</td>
<td>Glaucoma group: 39% Control group: 26%</td>
<td>≥13</td>
<td>Malaysia</td>
</tr>
<tr>
<td>Ruangvaravate et al. (2018)</td>
<td>Glaucoma group: 109 Control group: none</td>
<td>Glaucoma group: 38.5% Control group: none</td>
<td>≥13</td>
<td>Thailand</td>
</tr>
<tr>
<td>Costa et al. (2013)</td>
<td>Glaucoma group: 158 Control group: none</td>
<td>Glaucoma group: 62.7 Control group: none</td>
<td>≥13</td>
<td>Brazil</td>
</tr>
<tr>
<td>Garcia-Feijoo et al. (2010)</td>
<td>Glaucoma group:448 Control group: none</td>
<td>Glaucoma group: 59.2% Control group: none</td>
<td>≥13</td>
<td>International multicenter study</td>
</tr>
<tr>
<td>Fechtner et al. (2010)</td>
<td>Glaucoma group:630 Control group: none</td>
<td>Glaucoma group: 48.4% Control group: none</td>
<td>≥13</td>
<td>United States</td>
</tr>
</tbody>
</table>

DEQ 5

1. Questions about EYE DISCOMFORT:
   a) During a typical day in the past month, how often did your eyes feel discomfort?
      Rarely  Sometimes  Frequently  Constantly
      1       2       3       4
   b) When your eyes felt discomfort, how intense was this feeling of discomfort at the end of the day, within two hours of going to bed?
      Never  Not at all  Intense  Very intense
      0 1 2 3 4

2. Questions about EYE DRYNESS:
   a) During a typical day in the past month, how often did your eyes feel dry?
      Rarely  Sometimes  Frequently  Constantly
      1       2       3       4
   b) When your eyes felt dry, how intense was this feeling of discomfort at the end of the day, within two hours of going to bed?
      Never have it  Not at all  Intense  Very intense
      0 1 2 3 4

3. Questions about WATERY EYES:
   a) During a typical day in the past month, how often did your eyes look or feel excessively watery?
      Never  Rarely  Sometimes  Frequently  Constantly
      0 1 2 3 4

Score: 2 + 1 + 2 + 2 + 0 = 7
There’s an app for that....

Dry Eye OSDI Questionnaire

Medical

RM 64 yo man (DOB 12/07/1944)
RM 64 yo man (DOB 12/07/1944)

Systemic:

• (+) family history (2 x paternal aunts dx in 80s/90s, blindness – father passed at 83)
• (-) cardiac, (-) BP (hyper or hypo tension), (-) thyroid, (-) diabetes, (-) smoking
• (-) vascular dysregulation (migraine, fainting, cold hands/feet, Raynauds)
• Low heart rate (~55 bpm); tendency to snore/poor sleep
• No medications or supplements

IOP: 17mmHg in 1996

OPTIC NERVE: 0.3 OU in 1996

VF: no history

Gonioscopy: CB360; min pigment
<table>
<thead>
<tr>
<th>06/08/2010</th>
<th>OD</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA</td>
<td>6/6</td>
<td>6/6</td>
</tr>
<tr>
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<tr>
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<td></td>
</tr>
<tr>
<td>BP</td>
<td>120/65 RAS; 55bpm</td>
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Staining

**Oxford system**
(Bron et al 2003).

- Developed to quantify epithelial damage in dry eye
- Uses a chart with a series of panels labeled A–E in order of severity (absent, minimal, mild, moderate, severe)
- The whole exposed ocular surface is considered, without separating the cornea and the conjunctiva, and the number of dots representing the staining increases logarithmically.

**NEI/Industry Workshop system**
(Lemp 1995)

- CONJUNCTIVA: Both nasally and temporally, the conjunctiva is divided into a superior paralimbal area, an inferior paralimbal area and a peripheral area with a grading scale of 0–3 and with a maximal score of 9 for the nasal and temporal conjunctiva.

**van Bijsterveld**
(van Bijsterveld 1969)

- Maximum possible score with this system is 9

---


Staining - OSS

Ocular Staining Score (OSS)

<table>
<thead>
<tr>
<th>Conjunctiva: Lissamine Green</th>
<th>Cornea: Fluorescein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade</td>
<td>Dots</td>
</tr>
<tr>
<td>0</td>
<td>0 - 9</td>
</tr>
<tr>
<td>1</td>
<td>10 - 32</td>
</tr>
<tr>
<td>2</td>
<td>33 - 100</td>
</tr>
<tr>
<td>3</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>

Patches of confluent staining = +1
Staining in papillary area = +1
One or more filaments = +1

Positive ≥ 3

Maximum Score = 12


https://www.researchgate.net/publication/256083715/figure/fig1/AS:297925642080267@1448042416681/Figure-1-Comparison-of-the-scoring-of-keratoconjunctivitis-sicca-by-the-van-Bijsterfeld.png
## IOP

- IOP history

### PROGRESS TABLE: RM

<table>
<thead>
<tr>
<th>MONTH</th>
<th>IOP: OD 552um</th>
<th>IOP: OS 548um</th>
<th>C/D: OD</th>
<th>C/D: OS</th>
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</thead>
<tbody>
<tr>
<td>1996</td>
<td>17</td>
<td>17</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>06-04-2009</td>
<td>15</td>
<td>16</td>
<td>.4/.45</td>
<td>0.6</td>
</tr>
<tr>
<td>11-05-2009</td>
<td>13</td>
<td>13</td>
<td>0.5</td>
<td>0.6</td>
</tr>
<tr>
<td>26-11-2009</td>
<td>11</td>
<td>10</td>
<td>0.5</td>
<td>0.6/.55</td>
</tr>
<tr>
<td>20-05-2010</td>
<td>11</td>
<td>10</td>
<td>0.5</td>
<td>0.6</td>
</tr>
<tr>
<td>26-05-2010</td>
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<tr>
<td>18-06-2010</td>
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<td>0.6</td>
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<tr>
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<td></td>
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<tr>
<td>11-11-2010</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>15-11-2010</td>
<td>12</td>
<td>12</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Treatment

…? Treat the glaucoma or treat the ocular surface disease….?

• GLAUCOMA
  – Set a target pressure and start a treatment (usually PGA)

• OCULAR SURFACE
  – History (including questionnaires),
  – Physical examination
  – Develop a plan
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<tr>
<td>Date: 06/08/2010</td>
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### SIDE EFFECT REPORTING FORM

Reporting suspected side effects (also known as adverse reactions) to marketed health products in Canada may contribute to the identification of previously unrecognized rare or serious side effects, which may lead to changes in the product’s safety information.

Instructions on how to complete and submit this form and information about confidentiality can be found on Page 2. Complete all mandatory fields, marked by an asterisk (*), and provide as much detail as possible for the remaining fields.

#### A) About the person who had the side effect

<table>
<thead>
<tr>
<th>Reference # (if applicable)</th>
<th>1. Age</th>
<th>2. Sex</th>
<th>3. Height</th>
<th>4. Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Years</td>
<td>Months</td>
<td>cm</td>
<td>kg</td>
</tr>
</tbody>
</table>

5. Medical history and other related information (allergies, pregnancy, smoking/alcohol use, liver disease, etc.)

#### B) Reporter information

1. Name  
2. Telephone  
3. Province/Territory

4. Address  
5. E-mail

6. Preferred language  
7. Organization (if applicable)

8. Select one that best describes you:  
   - Consumer or other non-health professional  
   - Physician  
   - Pharmacist  
   - Other health professional (specify) __________

9. Has this also been reported to the manufacturer?  
   - Yes  
   - No

#### C) Side Effect

1. Seriousness of the side effect:  
   - Death (yyyy-mm-dd) __________  
   - Life-threatening  
   - Admitted to hospital  
   - Lengthened hospital stay  
   - Disability  
   - Birth defect  
   - Needed medical attention

2. Recovered after the side effect?  
   - Yes  
   - No  
   - Recovering (explain) __________

3. Side effect start date (yyyy-mm-dd)  
4. Side effect end date (yyyy-mm-dd)

5. Describe the side effect (timeliness, treatment, etc.) __________

#### D) Suspected health product

1. Product name  
2. Strength  
3. Manufacturer

4. Lot #  
5. DIN #/NPN #

6. Country of purchase  
   - Canada  
   - United States  
   - Other (specify) __________

7. Where it was purchased/obtained  
   - Pharmacy  
   - Grocery store  
   - Internet  
   - Other (specify) __________

8. Product start date (yyyy-mm-dd)  
9. Product end date (yyyy-mm-dd)

At the time of the side effect, specify:

10. Dosage (strength and quantity)  
11. Frequency (e.g. twice daily)  
12. How the product was taken (e.g. by mouth)

13. What was the product prescribed/taken for? __________

14. Did use of the product stop after the side effect appeared?  
   - Yes  
   - No

15. If the product was stopped did the side effect stop?  
   - Yes  
   - No  
   - Does not apply

16. Was the product restarted after the side effect stopped?  
   - Yes  
   - No  
   - Does not apply

17. If the product was restarted, did the side effect return?  
   - Yes  
   - No  
   - Does not apply

18. Likelihood that the product caused the side effect  
   - Certain  
   - Probably/Likely  
   - Possible  
   - Not available/Unable to assess  
   - Unlikely  
   - Unrelated

19. Other health products taken at the time of the side effect, excluding treatment (length of use, timelines, etc.) __________

---

* As per the Treasury Board of Canada Secretariat: Government Security Policy.

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Management of each individual patient entails thorough and detailed attention to all issues including ADRs of treatments.
OSD and Glaucoma

Glaucoma and OSD

• Tsai et al found the incidence of glaucoma in a retrospective analysis of 108 patients with severe OSD was 20.4% (13.6%-60%)
• Overall prevalence of glaucoma in patients with severe OSD is 65.7% (42.9% to 88.4%)
  – A significantly higher prevalence of glaucoma was noted in patients with severe OSD than population
  – Warrants increased attention to treatment of OSD and glaucoma

In patients with glaucoma that Leung et al studied
  • 59% had dry eye symptoms in at least one eye (OSDI), with 27% severe
  • 61% had decreased tear production (Schirmer, at least one eye); 35% with severe deficiency
  • 65% showed severe decrease in tear quality
  • 78% decreased TFBUT
  • 22% corneal/conjunctival lissamine green staining


Ocular Surface Disease in patients with Glaucoma

- How much OSD is in our patients who have glaucoma?
- Is there something in the eyedrop bottles contributing to OSD?
- Are some topical meds better than others?
- What is the relationship between the number of medications used and the OSD?

- Does the OSD affect the adherence to treatment?
- Do we treat the OSD in those patients with glaucoma differently to those patients without?
  - How aggressive do we get in treating the OSD?
- Is IOP affected by OSD?
  - “OSD Exacerbated Glaucoma”
- Other treatment options without drops?
OSD and Glaucoma

Glaucoma and OSD

• **OSD and glaucoma frequently coexist.**
  – Topical anti-glaucoma medications have been shown to cause OSD and can lead to conjunctival inflammation, shortening and shrinkage
  – Worst case scenario – equivalent of ocular cicatricial pemphigoid (OCP) termed Drug-induced cicatricial conjunctivitis and pseudopemphigoid
  – IVCM is showing us the way….

• **Glaucoma is more prevalent in patients with OSD.**
  – Tsai et al found the prevalence of glaucoma in patients with severe OSD to be 65.7%.
  – Fechner found 48.4% (384/605) had an OSDI score indicating either mild (n = 134, 21.3%), moderate (n = 84, 13.3%), or severe (n = 87, 13.8%) OSD symptoms.

WATERLOO
OPTOMETRY & VISION SCIENCE

Tsai JH, Derby E, Holland EJ, Khatana AK.
Incidence and Prevalence of Glaucoma in Severe Ocular Surface Disease. Cornea 2006;Volume 25, Number 5.

Leung EW, Medeiros FA, Weinreb RN.
OSD and Glaucoma

Glaucoma and OSD

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OSD and Glaucoma

Glaucoma and OSD

- The number and frequency of preserved eyedrops increases the risk and severity of OSD
  - Numerous reports of prolonged use of BAK-preserved topical ocular medications may exacerbate symptoms and signs of OSD
  - Adverse effects on the conjunctiva and cornea include
    - Induction of subclinical inflammation, Reduction of corneal epithelial barrier function; Destabilization of the tear film; Overall higher incidence of patient complaints of dryness and irritation
    - More later! (IVCM)
  - Each additional BAK-containing eyedrop was associated with an approximately 2 times higher odds of showing abnormal results on the lissamine green staining test (adjusted for age, sex)
    (odds ratio = 2.03; 95% confidence interval: 1.06 to 3.89; P = 0.034)
  - BAK exerts its damaging action mainly through a direct cytotoxic mechanism, accentuated by the cumulative effect of repeated administrations of preserved eyedrops
Prevalence of OSD in patients with Glaucoma

101 patients, cross-sectional

OSDI

LG

IVCM can be used in DED to evaluate morphologic changes of the ocular surface

- Corneal superficial/wing/basal epithelial cell density and area, stromal keratocyte density, endothelial cell density; and nucleocytoplasmic ratio in conjunctiva
- Corneal nerve fiber density, beadings, nerve tortuosity, nerve reflectivity
- Inflammatory cell density in the cornea, goblet cell, microcyst
- Meibomian gland acina (unit density, unit longest diameter, unit shortest diameter, and inflammatory cell density
- Lacrimal gland structure, and inflammatory cell density
IVCM may be useful for structural parameters to correlate with the functional OSDI assessments in the evaluation of ocular surface toxicity associated with topical A/G therapy

Significant microstructural alterations in eyes treated with topical A/G therapy

Topical A/G therapy noted significantly higher OSDI scores compared to controls
Table 1. Demographic features and clinical test results of normal age-matched control and topical A/G therapy groups

<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th>A/G treatment group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyes, n</td>
<td>20</td>
<td>30</td>
<td>–</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>2/8</td>
<td>5/11</td>
<td>–</td>
</tr>
<tr>
<td>Age, years</td>
<td>65.50±14.52</td>
<td>69.00±9.06</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>OSDI score</td>
<td>8.72±6.32</td>
<td>32.06±28.50</td>
<td>0.002</td>
</tr>
<tr>
<td>TBUT, s</td>
<td>12.00±2.56</td>
<td>4.1±2.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Schirmer 1 test, mm</td>
<td>13.5±5.5</td>
<td>6.5±4.5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Age and OSDI score are expressed as means ± standard deviation. OSDI, Ocular Surface Disease index; TBUT, tear film break-up time.
**Fig. 6.** Subbasal nerve fiber characteristics imaged by IVCM: control group versus A/G treatment group. Data presented as means ± standard deviation. *p < 0.05. **a** Subbasal nerve fiber density. **b** Subbasal nerve fiber tortuosity in grades 0–4. **c** Subbasal nerve fiber reflectivity in grades 0–4.
Fig. 3. Representative images for corneas of normal age-matched control eyes (top row) and the eyes receiving chronic A/G topical therapy (bottom row), illustrating epithelial and neuroinflammatory changes in glaucomatous eyes under chronic topical therapy. a, e Epithelial wing cell layer. b, f Epithelial basal cell layer. c, g Sub-basal nerve plexus. d, h Dendritic cells along subbasal nerve fibers.
The contribution of preservatives ...BAK
# Preservatives and Examples

<table>
<thead>
<tr>
<th>Preservative</th>
<th>Example of medication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DETERGENTS</strong></td>
<td></td>
</tr>
<tr>
<td>BAK (benzalkonium chloride)</td>
<td>e.g. XALATAN, LUMIGAN, TIMOPTIC, etc</td>
</tr>
<tr>
<td>BDD (benzododecininium bromide)</td>
<td>Timoptic XE</td>
</tr>
<tr>
<td>Chlorbutanol</td>
<td>TobraDEX ung</td>
</tr>
<tr>
<td>Polyquad (polyquaternium-1)</td>
<td>e.g. IZBA, Tears Naturale 2, Optifree express</td>
</tr>
<tr>
<td>Cetrimonium chloride</td>
<td>Civigel</td>
</tr>
<tr>
<td><strong>OXIDATIVE</strong></td>
<td></td>
</tr>
<tr>
<td>sofZia</td>
<td>Travatan Z</td>
</tr>
<tr>
<td>sodium perborate (GenAqua)</td>
<td>Genteal</td>
</tr>
<tr>
<td>stabilized oxychloro-complex (Purite)</td>
<td>Refresh Tears, Alphagan-P</td>
</tr>
</tbody>
</table>
Glaucoma and OSD

Role of preservatives

- **Complaints**
  - Reduced with PF formulations

- **Epithelium (cornea + conj)**
  - Significant difference in SPK in patients on preserved versus PF anti-glaucoma therapy (25% vs 9% and 19% vs 9%)
  - Abnormal morphology (electron microscopy); infiltrates
  - BAK > SofZia > Polyquad
  - Hyperosmolar TF potentiates the toxicity of BAK

- **Neurotoxicity**
  - Decreased stromal NFL density
  - Decreased sensitivity (BAK)

- **TM cells**
  - BAK reduced cell viability compared to SofZia, Polyquad

- **Endothelium**
  - Decreased survival in BAK

- **Flare in AC**
  - BAK

# Preservatives in Glaucoma Medications

<table>
<thead>
<tr>
<th>BAK</th>
<th>Drug</th>
<th>Oth. preserv</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.005%</td>
<td>brimonidine 0.2% (ALPHAGAN)</td>
<td>Arrested growth at 0.0001% BAK</td>
<td>brimonidine 0.005% (ALPHAGAN P)</td>
</tr>
<tr>
<td></td>
<td><em>bimatoprost 0.03%</em> (LUMIGAN)</td>
<td>BDD 0.012%</td>
<td>timolol 0.5% (TIMOPTIC XE)</td>
</tr>
<tr>
<td></td>
<td>levobunolol 0.5% (BETAGAN)</td>
<td>sofZia</td>
<td>travoprost 0.004% (TRAVATAN Z)</td>
</tr>
<tr>
<td>0.0075%</td>
<td>dorzolamide 2.0% (TRUSOPT)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>dorzolamide/timolol (COSOPT)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.010%</td>
<td>brinzolamide 1.0% (AZOPT)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.015%</td>
<td>betaxolol 0.25% (BETOPTIC S)</td>
<td>Apoptosis at 0.01% BAK</td>
<td></td>
</tr>
<tr>
<td></td>
<td>timolol (TIMOPTIC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>travoprost (TRAVATAN)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.02%</td>
<td>latanoprost (XALATAN)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>bimatoprost 0.01%</em> (LUMIGAN RC)</td>
<td>Necrosis at 0.05% to 0.1% BAK</td>
<td></td>
</tr>
</tbody>
</table>

BAK preservative is an increasing problem at higher doses – cell death is noted to be dose dependent due to either:

- High concentration applied to tissues
- Frequency of dosing causing accumulation

Longer duration of BAK exposure leads to increased corneal cell lysis.
Multiple eyedrops and symptoms (OSDI)

- OSDI scores in patients using multiple IOP-lowering medications.
- Mean OSDI on 1 drop was 12.9; 2 drops 16.7; 3 drops 19.4.

When to go PF?
# Considerations for PF Tx

Most relevant antecedents in patient assessment when considering a chronic, preservative-free topical ocular therapy

<table>
<thead>
<tr>
<th>Antecedents</th>
<th>Conditions/factors</th>
</tr>
</thead>
</table>
| Demographics and occupational factors | Aging  
Female sex  
Professional users of screen/video displayers |
| Systemic conditions                | Collagen vascular diseases  
Rheumatoid arthritis  
Wegener granulomatosis  
Systemic lupus erythematosus  
Autoimmune diseases  
Sjögren syndrome associated conditions |
| Systemic treatments                | Antidepressants  
Antihistamines  
Beta-blockers  
Cholino-mimetics  
Nasal decongestants  
Oral contraceptives  
Postmenopausal estrogen therapy  
Retinoic acid |

<table>
<thead>
<tr>
<th>Antecedents</th>
<th>Conditions/factors</th>
</tr>
</thead>
</table>
| Ocular conditions                  | Ocular surface disease  
Dry eye  
Chronic/recurrent corneal, conjunctival, or lid disorders  
Surgical procedures  
Periocular skin disorders |
| Ocular topical therapy             | Previous use of preserved treatments  
Ocular hypertension and glaucoma  
Ocular surface diseases  
Intraocular inflammatory diseases  
Documented intolerance/allergy |
| Symptomatology                     | Recurrent discomfort  
Intermittent visual disturbances  
Tear film instability |
Decision algorithm re: consideration for PF treatment

- Apply fluorescein
- Symptomatic?
- Is filamentary keratitis present?
- Marked corneal staining?
- TFBUT <5s?
- PF-treatment to be considered
- PF-treatment highly recommended

SUMMARY: Ocular Surface Disease in patients using BAK-preserved drops

- Preserved glaucoma medications show adverse effects on the surface of the eye in some individuals
- BAK causes adverse effects on the ocular surface
- These changes are \textit{time} as well as \textit{dose} dependent
- These ocular surface changes may be \textit{reversible}
- These issues are important clinically in many patients, especially those with pre-existing OSD
Other manifestations...
Glaucoma and OSD

Allergic manifestations

- Topical anti-glaucoma treatments primarily affect: **conjunctiva** (hyperemia, chemosis) and **periorbital areas** (lid edema, periorbital erythema or eczema, and itching)
- IgE type I HS or delayed type IV HS due to either the pharmaceutical and/or the preservatives
  - **B-blockers** (11 – 13% contact dermatitis)
  - Brimonidine (9 and 11.5% in two long-term studies)
  - Dorzolamide (3% dermatitis; 4% conjunctivitis)
  - Prostaglandins uncommon (1.5% on latanoprost)
Glaucoma and OSD

Other manifestations

• **Pseudopemphigoid**
  – cicatrizing conjunctivitis mimics ocular mucous membrane pemphigoid (MMP)
  – Associated with long-term topicals (28%), usually *multiple* agents (97%); usually a z *beta-blocker* (87%)

• **Recurrent HSK**
  – *latanoprost, bimatoprost, and travoprost* in case reports
  – May promote viral shedding

• **Corneal decompensation**
  – *Dorzolamide* perhaps potentiated previous decreased endothelial function from intraocular surgery

• **Vernal-like keratoconjunctivitis**
  – *Brimonidine* (single case report) characterized by tarsal or limbal papillae, superior limbal Horner Trantas Dots and superior tarsal follicles resolved after d/c
OSD and Glaucoma

Glaucoma and OSD

**Role of preservatives**

- BAK is reported to produce severe changes in epithelial cells (microvilli loss, disruption of plasma membranes, and desquamation of the top 2 cell layers)
- Drops more BAK result in greater damage to the cornea/conjunctiva
  - Reducing BAK exposure by switching from preserved to preservative-free medication or reducing the number of eye drops containing BAK leads to a significant reduction in the clinical signs of OSD
- Henry et al evaluated the effect of changing to preservative-free g. travoprost 0.004% from prior use of preserved prostaglandin therapy with either generic latanoprost 0.005% or bimatoprost 0.03%. The study concluded that not only was there a *clinically and statistically significant improvement in OSD symptoms and signs* but there was also a *statistically significant reduction in the mean IOP* (P < 0.0001).


OSD and Glaucoma

Glaucoma and OSD

- **Raised IOP has been noted in OSD**
  - Possible mechanisms of raised IOP in OSD (Tauber et al)
    - Severe inflammation in patients with OCP (ocular cicatricial pemphigoid) using anti-glaucoma medications, as compared with patients with OCP but without glaucoma, suggesting that anti-glaucoma medications provoke inflammation
  - Elevated IOP in OCP may be due to vascular etiologies, inflammation of the trabecular meshwork and inflammation and scarring of the episclera and sclera may change outflow facility


“OSD Exacerbated Glaucoma”

A novel term to describe those patients with severe **OSD** who also have have **glaucoma that is refractory to medical therapy**

...also more likely to have compromised success during glaucoma filtering procedures (inflammation and scarring of the conjunctiva)
Ocular Surface Disease Exacerbated Glaucoma: Optimizing the Ocular Surface Improves Intraocular Pressure Control

Ruchika Batra, MRCOphth, Rajen Tailor, MRCOphth, and Shabbir Mohamed, FRCSEd

Purpose: To describe a series of 4 patients with inadequately controlled primary open angle glaucoma and ocular surface disease (OSD) in whom a combination approach was used to manage the OSD resulting in improved intraocular pressure (IOP) control.

Patients and Methods: A retrospective review of the clinical notes of 4 patients referred to a tertiary surgical glaucoma service was performed. At the initial visit, measures to control the OSD were employed in all patients; twice-daily lid hygiene measures, a 3-month course of 50 mg daily oral doxycycline, topical carmellose sodium (celluvisc) 0.5% 4 to 6 times daily, and preservative-free equivalents of topical antiglaucoma medications as deemed appropriate, depending on the perceived severity of the OSD.

Results: Patients were reviewed for a maximum of 24 months after intervention. In all patients, treatment resulted in a marked symptomatic and clinical improvement in the ocular surface with a reduction in hyperemia, meibomian gland dysfunction, and superficial keratopathy. A reduction in the IOP also occurred in all patients, obviating the need for glaucoma drainage surgery during the study period.

Conclusions: Patients with severe OSD often have glaucoma that is refractive to medical therapy. Furthermore, the surgical success of glaucoma filtering surgery is compromised in patients with scarring and inflammation of the conjunctiva. The term we postulate is “OSD exacerbated glaucoma.” This is the first study to suggest that the use of a combination approach comprising medical treatment to manage the OSD in patients with primary open angle glaucoma may lead to an improvement in the IOP control and the management of glaucoma.

Key Words: glaucoma, ocular surface disease, ocular surface inflammation, preservative

(J Glaucoma 2014;23:56–60)
“OSD Exacerbated Glaucoma”

- 4 patients with inadequately controlled POAG and OSD in whom a combination approach was used to manage the OSD resulting in improved IOP control

- TREATMENT at first visit:
  1. twice-daily lid hygiene measures,
  2. 3-month course of 50 mg daily oral doxycycline,
  3. topical carmellose sodium (celluvisc) 0.5% 4 to 6 times daily, and
  4. Oral doxycycline
  5. (PF-equivalents of topical antiglaucoma medications appropriate)
  6. (no change to active ingredient of IOP lowering medication(s))

- Patients reviewed for 24 months (max) after intervention
"OSD Exacerbated Glaucoma"

- There was marked symptomatic and clinical improvement in the ocular surface after treatment
  - A reduction in hyperemia, MGD, SPK was documented for all patients
- VF/ONH were unchanged over the study period

- A reduction in the IOP also occurred in all patients, obviating the need for glaucoma drainage surgery during the study period.
<table>
<thead>
<tr>
<th>Case</th>
<th>Range of IOPs 1 y Before Referral (mm Hg)</th>
<th>IOP at Presentation to Tertiary Glaucoma Clinic (mm Hg)</th>
<th>Intervention</th>
<th>Posttreatment IOP (mm Hg) at No. Months (mo) After Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R 15-20, L 15-20</td>
<td>R 28 on August 19, 2002, L 19 on October 19, 2001</td>
<td>Hot compress BD Punctal plugs g. celluvisc 0.5% 4-6× per day Doxycycline 50 mg OD 3 mo g. timolol + dorzolamide combination preservative-free BD both eyes g. latanoprost noce both eyes (as before)</td>
<td>R 13 R 10 R 8 R 9 L 13 L 11 L 11 L 9 3 mo 8 mo 14 mo 19 mo</td>
</tr>
<tr>
<td>2</td>
<td>R 24-30, L 24-28</td>
<td>R 26 on April 23, 2002 L 28 on May 6, 2008</td>
<td>Hot compress BD g. celluvisc 0.5% 4-6× per day Doxycycline 50 mg OD 3 mo Left cataract surgery Glaucoma medication unchanged</td>
<td>R 16 R 14 R 15 L 16 L 10 L 14 3 mo 9 mo 17 mo</td>
</tr>
<tr>
<td>3</td>
<td>Unknown</td>
<td>R 20 L 19</td>
<td>Hot compress BD g. celluvisc 0.5% 4-6× per day Doxycycline 50 mg OD 3 mo g. bimatoprost noce R + L g. timolol 0.5% preservative-free BD R + L g. dorzolamide preservative-free BD R + L</td>
<td>R 12 R 12 R 15 L 13 L 12 L 15 3 mo 8 mo 12 mo</td>
</tr>
<tr>
<td>4</td>
<td>R 16-30, L 16-26</td>
<td>R 34 L 36 on April 8, 2002 L 20</td>
<td>Hot compress BD g. celluvisc 0.5% 4-6× per day Doxycycline 50 mg OD 3 mo g. timolol + dorzolamide combination preservative-free BD both eyes g. travoprost BAK-free noce R + L</td>
<td>R 18 L 18 2 mo</td>
</tr>
</tbody>
</table>

BAK indicates benzalkonium chloride; BD, twice daily; IOP, intraocular pressure; OD, once daily.
“OSD Exacerbated Glaucoma”

• In all cases, the management of the OSD resulted in improvements to the IOP control
• It seems that glaucoma therapy causes OSD and that severe OSD in turn exacerbates glaucoma.
• The authors suggest a combination approach comprising aggressive management of the OSD may lead to an improvement in the IOP control while improving the ocular surface
Diurnal?

IOP history:
BP?

Xalatan, switched to generic
**Canada Vigilance Adverse Reaction Reporting Form**

Report of suspected adverse reactions to marketed health products in Canada

**See instructions and information on adverse reaction reporting and confidentiality on Page 2.**

Complete all mandatory items, marked by a *, and provide as much information as possible for the remaining items.

---

### A. Patient Information

<table>
<thead>
<tr>
<th>1. Identifier</th>
<th>01897</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Age</td>
<td>67</td>
</tr>
<tr>
<td>3. Sex *</td>
<td>Female</td>
</tr>
<tr>
<td>4. Height</td>
<td>5'1&quot;</td>
</tr>
<tr>
<td>5. Weight</td>
<td>185 lbs</td>
</tr>
</tbody>
</table>

### B. Adverse Reaction

1. **Outcome attributed to adverse reaction (Select all that apply)**
   - Death
   - Life-Threatening
   - Hospitalization
   - Hospitalization - prolonged
   - Other: **ocular irritation**

2. Reaction date (yyyy-mm-dd) | 2012-01-16
3. Report date (yyyy-mm-dd)    | 2012-05-08

4. **Describe reaction or problem**
   - Increase in ocular surface irritation (extreme redness)

---

### C. Suspected Health Product(s)

1. **Name**: Proscar
   - Male Pattern Baldness, Proscar

---

### D. Reporter Information

1. **Name, occupation, address, telephone number**
   - Dr. Lisa Bock, Optometric, 600 University Ave West, Hamilton, ON, L8S 3G1
   - 519-888-4633

2. **Health professional?** | Yes |
3. **Reported to manufacturer?** | Yes | No 

---

**Gastro**

---

**WATERLOO**

**OPTOMETRY & VISION SCIENCE**

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As per the Treasury Board of Canada Secretariat Government Security Policy.

A program of MedEffect™ Canada

HC Pub. 100251 (January 2011)
Medically Necessary Brands
“No Substitutions”

• The ministry will provide reimbursement of a higher cost interchangeable product only when a patient has experienced a significant adverse reaction with a lower-cost interchangeable drug product.

• The practitioner must:
  – Specify on the prescription — “No Substitution” (full words, “no subs” is insufficient, as is a tick box)
  – complete, sign and forward to the pharmacist a Health Canada - Canada Vigilance Reporting Form (pharmacist can provide this or get it on-line)
Do we treat OSD differently if a person is also being treated for glaucoma?
Glaucoma and OSD

Interventions

• Consider preservatives..... Including FC
Adrenomimetics

**brimonidine 0.2, 0.15%** *(0.10% US only)*

**brimonidine 0.2%**
(old ALPHAGAN)

*generics* are available

- BAK 0.05% (!)
- Vehicle PVA
- pH 6.3-6.5
- ADRs 10-30%

**brimonidine 0.15%**
(ALPHAGAN-P)

*generics* are available

- Reduced conc. brimonidine
- Purite 0.005%
- pH 6.6-7.4
- ADRs 10-20%
# Adrenomimetics

**brimonidine 0.2, 0.15% +/- PURITE vs ALPHAGAN**

## Systemic Treatment related ADRs

<table>
<thead>
<tr>
<th></th>
<th>0.15% + purite</th>
<th>0.2% + purite</th>
<th>ALPHAGAN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>&gt;5%</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI: <strong>oral dryness</strong></td>
<td><strong>5.3%</strong></td>
<td>9.4</td>
<td>10.4%</td>
</tr>
<tr>
<td><strong>1 – 5%</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system: <strong>headache</strong></td>
<td><strong>2.4%</strong></td>
<td>1.8</td>
<td>1.8</td>
</tr>
<tr>
<td>General: <strong>asthenia (lethargy)</strong></td>
<td><strong>1.6%</strong></td>
<td>2.1</td>
<td>4.2</td>
</tr>
<tr>
<td>Resp/Thoracic/Mediastinal: <strong>rhinitis</strong></td>
<td><strong>1.1%</strong></td>
<td>0.5</td>
<td>0.3%</td>
</tr>
</tbody>
</table>
IZBA
(travoprost 0.003%)

- 25% less drug
- Reduced IOP to an equivalent extent as TRAVATAN Solution at all on therapy visits and time points
- An improved safety profile with IZBA
- Hyperemia was observed in 11.8% of patients on IZBA compared with 14.5% for patients using TRAVATAN
- POLYQUAD (polyquaternium-1) is an polycationic anti-microbial preservative and does not function like a detergent (like BAK)

WATERLOO
OPTOMETRY & VISION SCIENCE

5. Data on file, Alcon Inc.
TRUSOPT
(PF dorzolamide 2%)

4 pouches of
15 x 0.2mL single use pipettes
(Purdue makes this in Canada)

COSOPT
(PF timolol 0.5% + dorzolamide 2%)

4 pouches of
15 x 0.2mL single use pipettes
(Purdue makes this in Canada)
SAFLUTAN (or ZIOPTAN)  
(tafluprost 0.0015%)

• PRESERVATIVE FREE FP agonist prostanoid  
• q.d. dosed at night  
• Was to be called Saflutan, as in UK/Spain etc, but changed to Zioptan in U.S. (Feb.2012)  
• Canada (Purdue) was to be Saflutan  
  – Purdue has Trusopt, Cosopt, Timoptic and Timoptic XE
MONOPROST
(PF latanoprost 0.005%)

- Canada’s first PF prostaglandin
- Approved October 2017
- Single-dose containers (0.2 mL; 1gt / eye)
- 5x single-dose containers in individual paper-aluminium sachets
  (Groups of 6 or 18 per box; i.e., 30 or 90 single-dose containers)
- Non-medicinal ingredients include:
  - carboxer 974 P, disodium edetate, macrogol 4000,
    macrogolglycerol hydroxystearate 40, sodium hydroxide (to
    adjust pH), sorbitol, and water for injection

http://www.labticianthea.com/about-
labtician-thea/
TIOPEX

(PF timolol 0.1%)

- In UK, not yet approved in Canada
- Single-dose containers (0.2mL; cannot re-cap; 1gt/eye, ie. q.d.)
- Compared it to b.i.d. timolol and noted that this was 10X decrease in amount of timolol administered with 90% reduction in systemic absorption
- Non-medicinal ingredients – carbomer and PVA to increase contact time

http://www.labticianthea.com/about-labtician-thea/
Glaucoma and OSD

Interventions

• ATs, lubricating gel, ointment
  – Consider allergic component, as well as MGD etc.
• Low risk steroids on a short-term basis (watch IOP, BAK)
• Supporting evidence for topical cyclosporine, none yet with lifitegrast
  – More study for glaucoma-related OSD
• If OSD is not improving, further consider ocular allergy (d/c and trial a different class of medications)
• If sensitivity to multiple meds, allergy to BAK should be suspected; prescribe BAK-free or PF
  – BUT… BAK-free drugs may cost 2–10X more…
    e.g. timolol in PF individual dose ampules costs ~27X;
    e.g. ~$275US for generic prostaglandin vs $1100 for BAK-free
Cyclosporin in patients with glaucoma after LT use of topical anti-glaucoma medications

- 6 month treatment with cyclosporin, noted statistically significant improvement in:
  - Tear production (Schirmer)
  - TBUT
  - Conjunctival and corneal staining
  - OSDI
  - Corneal sensation

Table 1 Ocular surface evaluation parameters and corneal sensitivity pre/post cyclosporine therapy

<table>
<thead>
<tr>
<th>Study group</th>
<th>Pre-CsA treatment</th>
<th>Post CsA treatment</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schirmer’s test (mm)</td>
<td>7.28 ± 3.48</td>
<td>10.78 ± 2.593</td>
<td>(0.003)</td>
</tr>
<tr>
<td>TBUT (s)</td>
<td>8.67 ± 3.01</td>
<td>12.24 ± 1.83</td>
<td>(0.007)</td>
</tr>
<tr>
<td>Conjunctival staining scores</td>
<td>3.38 ± 1.93</td>
<td>1.50 ± 0.718</td>
<td>(0.00)</td>
</tr>
<tr>
<td>Corneal staining scores</td>
<td>5.19 ± 1.82</td>
<td>1.81 ± 0.78</td>
<td>(0.098)</td>
</tr>
<tr>
<td>OSDI</td>
<td>30.63 ± 14.61</td>
<td>14.76 ± 6.06</td>
<td>(0.007)</td>
</tr>
<tr>
<td>Corneal sensations (cm)</td>
<td>4.64 ± 0.46</td>
<td>4.94 ± 0.39</td>
<td>(0.002)</td>
</tr>
<tr>
<td>Controls</td>
<td></td>
<td>12.86 ± 1.93</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>11.80 ± 1.88</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.84 ± 0.46</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.10 ± 0.58</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.02 ± 3.84</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.07 ± 0.37</td>
<td></td>
</tr>
</tbody>
</table>

Pre-CsA, parameters before cyclosporine therapy.
Post CsA, parameters after cyclosporine therapy.
Ophthalmic Compounding

• Many formulations can be compounded
  – e.g. steroids, antibiotics etc.
  – Sterile conditions
  – Limited shelf life (max 7 days)
Ophthalmic Compounding

**Autologous serum**

- 6-10 times per day depending on severity of condition
- Add hyaluronate for viscosity, contact time, and ocular surface healing properties
Compounded formulations

- **OMNI** - Ocular Science, has 503 A status
  - patient-specific compounding pharmacy
  - combinations of latanoprost and timolol, but have all 4 glaucoma agents (timolol/brimonidine/dorzolamide/latanoprost) in one bottle
  - Also have p/o Cataract formulation (pred phosphate/ketorolac/gatifloxacin qid x 2 weeks, then bid x 2 weeks), LASIK formulation, etc.

- **Simple drops** - Imprimis is a 503 B compounding pharmacy
  - manufactures preservative-free glaucoma formulations
## Simple Drops™

No more juggling multiple bottles
Simplify with one Simple Drops™

### SINGLE DROP
- **LAT™**
  - Latanoprost – 0.005%
  - Bottle: 5mL

### DUO DROP
- **TIM-LAT™**
  - Timolol – 0.5%
  - Latanoprost – 0.005%
  - Bottle: 5mL

### TRIPLE DROP
- **TIM-BRIM-DOR™**
  - Timolol 0.5%
  - Brimonidine 0.15%
  - Dorzolamide – 2%
  - Bottle: 10mL

### QUAD DROP
- **TIM-BRIM-DOR-LAT™**
  - Timolol – 0.5%
  - Brimonidine – 0.15%
  - Dorzolamide – 2%
  - Latanoprost – 0.005%

---

LAT-DS™
- Latanoprost
- Double Strength – 0.010%
- Bottle: 5mL

BRIM-DOR™
- Brimonidine – 0.15%
- Dorzolamide – 2%
- Bottle: 10mL

TIM-DOR-LAT™
- Timolol – 0.5%
- Dorzolamide – 2%
- Latanoprost – 0.005%
- Bottle: 5mL

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Accessed Jukn.2019
So, what’s new in treatment?
Other options?

- Nonadherence rates in glaucoma have been reported to vary from 24% to 59%.
- Reasons for nonadherence include:
  - forgetfulness, side effects, lack of affordability, difficulty administering drops, complicated medication schedules, poor understanding of the disease, and poor patient–doctor communication.
- Moderate-to-severe ocular surface disease is present in 71% of patients receiving triple drop therapy; PF treatments add additional cost.
- Reported that SLT is more cost-effective than a prostaglandin, if accounting for realistic adherence rates.
Novel considerations in Management

**Medical therapies**
- Existing drugs; changing practice patterns
  - Decreasing trabeculectomies with prostaglandin introduction
- Combination products
- *New meds*
- *New drug delivery systems*

**Surgical**
- Trabeculectomy
- Cataract surgery
- Combined procedures
- Laser therapies
- MIGS
- other
With all this talk of MIGS and novel treatments, are topical eyedrops for glaucoma going to be obsolete?
New Drug Delivery?
Drug Delivery to the eye

• Drug delivery to targeted ocular tissues has been a major challenge to ocular scientist, for decades
• Administration of drug solutions as topical drop with conventional formulations was associated with certain drawbacks which initiated the introduction of different carrier systems for ocular delivery
• Tremendous efforts are being put into ocular research toward the development of safe and novel drug delivery strategies that will improve adherence and QoL
  – *in vivo* performance of conventional formulations
  – Nanotechnology, new techniques, devices and their applications in drug delivery
A typical eyedrop is three to four times the size of the liquid capacity of the average human eye. Most of the drop is often wasted. (Craig Chivers/CBC)

... Allisa Song, 26, a medical student from Seattle, wanted a more immediate solution "I was thinking, how do we circumvent these drug companies who won't budge?"

So she and three friends, all with biomedical or engineering backgrounds, came up with a plastic adapter that screws onto the tip of any bottle and turns those wasteful blobs of eye medicine into a precise, little 9.4-μl drop... the Nanodropper, extends the life of a one-month supply of drops to three or four months.

https://apple.news/AiFqiR3hKQwGHBpMDBBCOTw
Health benefits of smaller droplets

**Decreased side effects**
Overdosing can cause adverse side effects that range from minor annoyances such as foul taste and smudging makeup to serious systemic effects on heart health such as causing bradycardia and arrhythmias.

**Improved treatment efficacy**
Clinical studies demonstrate that smaller eyedrops are just as safe and efficacious as traditional droplets. Studies have also shown that larger droplets irritate the eye, eliciting a tearing, blink, and drain reflex that dilutes the medicine. By abrogating this reflex, smaller droplets deliver a more efficacious treatment.

**Limited preservative exposure**
Eyedrop medications contain preservatives that ensure the sterility of the contents of the bottle. Reducing droplet size will minimize patient exposure to these potentially toxic preservatives.

**Improved treatment adherence**
By reducing many of the top complaints arising from over-sized drops and minimizing the adverse side effects, the Nanodropper is removing multiple barriers to patient adherence. We hope to help maintain productive doctor-patient relationships and promote eye health by making consistent treatment a pragmatic long-term option for our customers.

**Decreased rate of adverse events in the elderly**
By improving treatment adherence through the elimination of the financial barrier to expensive prescription medication, the Nanodropper is improving numerous aspects of patient life.

“Glaucoma patients who go untreated...run the risk of worsening vision loss and increased likelihood of requiring surgical intervention...Vision loss from glaucoma has been associated with an increase in the rates of falls, depression,...reduced physical activity, and nursing home admissions.” -American Glaucoma Society
SMART. PRECISE. BRILLIANT.

Eyenoiva is a clinical stage, ophthalmic biopharmaceutical company transforming the delivery of therapeutics for the treatment of prominent eye diseases, such as glaucoma, dry eyes, allergic eye disease and many others. Eyenoiva's breakthrough piezo-dispersion and microdosing technology enable a portfolio of first-in-class, next-generation, micro-therapeutics for the eye designed to reduce ocular and systemic toxicity and improve the risk-benefit profile of both new and existing therapeutics.

At Eyenoiva, we believe that when it comes to your eyes, smaller is better.

Microdrops: smaller is better!

Eyenoiva is leading the charge in how eye care is delivered with its microtherapeutic technology. Eyenoiva’s microdrops and high-precision microdosing are designed for more efficient and gentler treatments for the eye with the delivery of 80% less unnecessary drug and preservatives.

Beat the Blink

Don’t wait for the drop to fall. Fast piezo-print delivery ensures microdrops gently coat the ocular surface at the speed of your blink, avoiding inconveniences such as overflow down the cheek and into the nose.

Pixel-sharp precision for your eyes

Eyenoiva is bringing ocular drug delivery into focus. Our proprietary solution uses piezo-print electronics and microfluidics to generate tiny droplets for high-precision delivery of eye therapies. Applying high-resolution inkjet technology towards the development of microtherapeutics for the eye, Eyenoiva can achieve gentle and precise micro-dosing at 6-8 µL volumes – a dosing far less than the traditional eye drops which overdose the eye with 30-50 µL and often lead to adverse side effects such as redness, irritation and pain.

Smart technology: be smart... eye-smart!

Eyenoiva’s intelligent electronic system is one of the first smart technologies to enter FDA clinical trials for ophthalmic use. Smart sensors and mobile cloud connectivity can help patients and physicians stay on top of treatment plans.

https://eyenoiviabio.com/?cmp=apple_news_cbc_news
Intracanalicular Implants
Ocular Surface Inserts
Drug-Delivering CLs

External

Intraocular Depot Implants
Nanoliposomes
Microparticles

Internal
Glaucoma devices in the Pipeline

• Clinicians may be on the verge of another exciting era of delivering medications to the target tissue in unique ways
• Benefits: reduced preservatives and ocular surface irritation, adherence but…
• Need to be accessible to most patients, risk of endophthalmitis, must be quick to administer, low risk, cost-effective, comfortable etc.

• External eye delivery
  - Implants (intracanalicular), contact lenses, ocular insert
• Internal eye delivery
  - More than 6 are being investigated with prostanoids alone!
    • Nanoliposome drug delivery for latanoprost (single SC injection; 3 months)
    • Microparticle-encapsulated dorzolamide to deliver SC

WATERLOO
OPTOMETRY & VISION SCIENCE
External eye delivery

**Implants (intracanalicular), contact lenses, ocular insert**

Internal eye delivery

*More than 6 are being investigated with prostanoids alone!*

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Figure 1. A range of sustained-release drug delivery innovations are in various stages of development.
OTX-TP

travoprost sustained release

- Lacrimal insert (intracanalicular depot)
- Composed of PEG hydrogel + microparticles of travoprost
- Sustained release (up to 3 months) of drug to lower IOP
- Advantages: are potential for improved adherence, and NO preservative!
bimatoprost SR
Sustained-release Ring

- Topical ocular insert
  - Rests in the fornices
- Up to 6 months of prostaglandin analogue
bimatoprost SR
Sustained-release Implant

• Intracameral injection
  (pre-filled single-use applicator)

• Advantages:
  – Reduces ocular ADRs
  – Adherence
  – Located closer to the site of action

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OPTOMETRY & VISION SCIENCE
Thanks!
Ocular Surface Disease and Glaucoma

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Thanks!

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Ocular Health Clinic
Ocular Surface Disease and Glaucoma

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Clinical Professor
Ocular Health Clinic

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Thanks!