


# Glaucoma and Dry Eye (Ocular Surface Disease)

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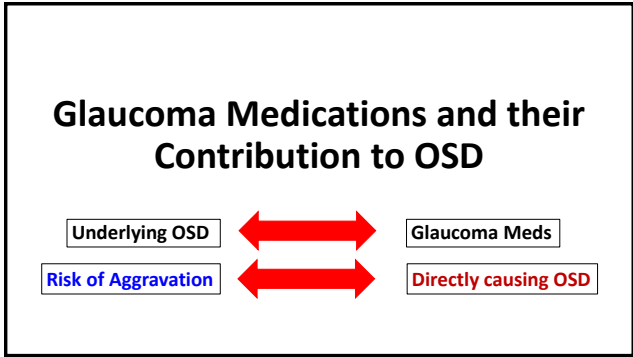
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## OSD is Just Like Glaucoma?

- A chronic disease that increases with age
- Definitions of the disease vary
- Signs of the disease often do not match the symptoms and vice versa
- Affects Quality of Life
- Diagnostic tests are variable, not always repeatable and often inconclusive
- Treatment regimens are variable and often not fully/solely effective
- Majority of patients are non-compliant



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## Best Article Title Ever!



**Preservatives in eyedrops: The good, the bad and the ugly<sup>1</sup>**  
Christophe Baudouin<sup>1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100</sup>, Anne-Laure Llabre<sup>10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100</sup>, Hong Jiang<sup>10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100</sup>, Anne Bailey<sup>10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100</sup>, Françoise Brignole-Baudouin<sup>10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100</sup>

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## The Ocular Surface




**IN CONCLUSION**

It would be useful if the evidence supports to suggest the notion that BAK in therapeutic eye drops is a potential and significant glaucoma risk factor and cause of OSD. Every doctor who prescribes BAK eye drops should be aware of this risk. The use of BAK eye drops should be avoided in patients with OSD. The use of BAK eye drops should be avoided in patients with OSD. The use of BAK eye drops should be avoided in patients with OSD.

Noecker R, Miller KV. 2011;9(3):159-162.

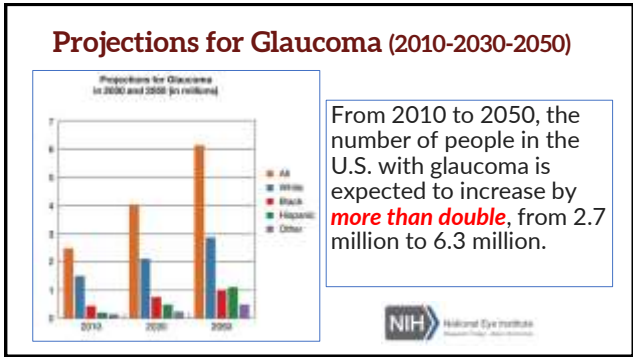
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## Key Reason why this matters: ~-6.5 IOP lowering

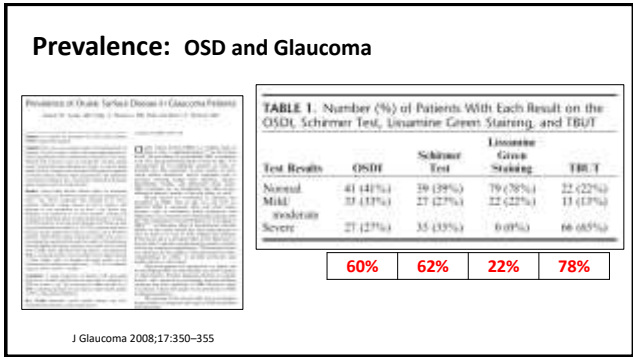


- The mean IOP in these patients significantly decreased from 23.75mmHg before OSD treatment to:
  - 15.15mmHg (-36.2%; P=0.0001) after 3m
  - 15.45mmHg (-34.9%; P=0.01) after 11m
- The mean number of IOP-lowering drugs also significantly decreased by almost one drop from 3.7 to 2.8 drops after treatment (P=0.01).
- All our observations also showed ocular surface improvement. The Oxford score significantly decreased from a mean 1.7±0.67 before treatment to 0.4±0.51 (-76.5%; P<0.001) and
  - conjunctival hyperemia significantly decreased
- All patients received preservative-free artificial tears and performed eyelid care.
  - 5 patients received topical PF NSAID
  - 1 patient received cyclosporine

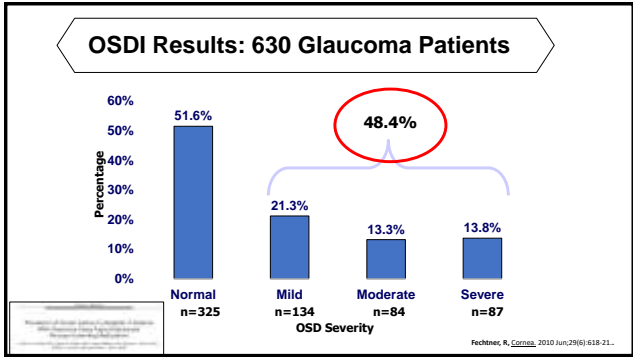
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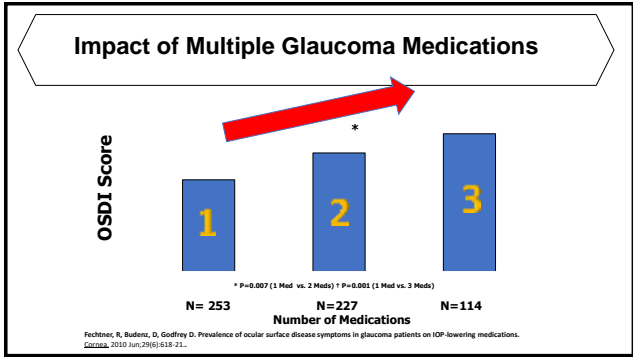
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### PGAs and BAK

**In Vitro Comparison of Cytoprotective and Antioxidative Effects of Latanoprost, Travoprost, and Bimatoprost on Conjunctiva-Derived Epithelial Cells**

Juan-Marc Guzmán,<sup>1,2,3</sup> Christophe Baudouin,<sup>1,2,4</sup> Patrice Bar,<sup>1,4</sup> André Parfitt,<sup>1</sup> Jean-Michel Fernot,<sup>1,4</sup> and Françoise Bigosio-Bambauer<sup>1,4</sup>

**RESULTS.**  
Cellular viability decreased as BAK concentration increased.

IOVS, December 2005, Vol. 46, No. 12

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### OSD Amongst Glaucoma Patients Reaffirmed in Many Studies (#720 articles in 35 yrs)

- ~60% Total (30% mild/mod; 30% mod/severe)
- Glaucoma medications can be associated with toxicities to the ocular surface,
  - most often due to the nature of the preservative included in the medication; however,
- the incidence of toxicity can be mitigated by the use of preservative free medications, decreased preservative medications, or treatment of dry eye disease.

Zhang X, Vadootker S, Munir WM, Saeedi O. Ocular Surface Disease and Glaucoma Medications: A Clinical Approach. *Eye Contact Lens*. 2019 Jan;45(1):11-18. doi: 10.1097/

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ORIGINAL ARTICLE

### Prevalence and risk factors for ocular surface disease among patients treated over the long term for glaucoma or ocular hypertension

Christophe Dechaux<sup>1</sup>, Jean-Paul Ribaud<sup>2</sup>, Jean-Philippe Meunier<sup>1</sup>, Philippe de Saadeh<sup>3</sup>, Jean-François Riviere<sup>4</sup>, Mehdi Jaber<sup>5</sup>, Stéphane Rouze<sup>6</sup>

• Classified into 3 groups, according to their total scores on an OSD Survey:

- Group A: score = 1-4 **49%**
- Group B: score = 4-10 **30%**
- Group C: score = 10-30 **21%**

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### Associated Risk Factors for OSD

	Patients with an ocular surface score from 1 to 4 (group A) are the reference group		Patients with an ocular surface score from 4 to 10 (group B)		Patients with an ocular surface score from 11 to 30 (group C)	
	OR	95% CI	OR	95% CI	OR	95% CI
Age, y (reference: <60 years)						
60-70	1.76	1.03-3.07	1.76	0.91-3.81		
>70	1.00	1.11-3.26	3.13	1.54-6.37		
Number of active drugs (reference: monotherapy)						
Bimodality	1.08	0.85-1.88	1.26	0.65-2.51		
Tertiary	2.43	1.25-4.73	3.29	1.48-7.28		
ICP >18 mmHg (reference: <16 mmHg)	1.03	0.79-1.84	3.04	1.0-4.66		
Glaucoma severity (reference: moderate/severe)						
reference: moderate/severe	1.44	0.80-2.54	3.30	1.68-6.58		
Concomitant ocular surface disease (reference: no)	5.76	2.52-12.17	13.93	5.83-32.58		
Modification of the treatment in the past due to ocular surface intolerance (reference: no)	3.98	1.78-8.87	7.66	4.12-15.30		

Eur J Ophthalmol 2013; 23 (1): 47-54

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### Ocular Surface Disease in Glaucoma Patients

Christophe Dechaux<sup>1</sup>, Jean-Paul Ribaud<sup>2</sup>, Jean-Philippe Meunier<sup>1</sup>, Philippe de Saadeh<sup>3</sup>, Jean-François Riviere<sup>4</sup>, Mehdi Jaber<sup>5</sup>, Stéphane Rouze<sup>6</sup>

**Conclusion**

Ocular surface disease in the glaucoma patient population is now widely recognized. Signs and symptoms of ocular surface disease should be addressed to maximize patient compliance and quality of life. Several PF drop alternatives are now available in addition to therapy that targets dry eye disease used concomitantly with glaucoma therapy. Novel drug delivery systems on the horizon will hopefully lessen the burden of ocular surface disease, but until then, ophthalmologists are creatively devising strategies to make patients more satisfied with their treatment and safely bridge them to surgery when needed.

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• Alternatives to topical meds:

- **Bitmatoprost SR**
  - Intercameral placement of PGA
  - Approved for 1x application
  - 10 mcg elutes over 4 months
  - 40-50% of patients did not need additional Tx at one year
  - ~30% No Tx at 2 years
- **Selective Laser Trabeculoplasty**

24-Month Phase III Clinical Trial of Bitmatoprost Sustained-Release Implant (Bitmatoprost SR) in Glaucoma Patients. Drugs (2020) 80:167-179

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### DEWS II iatrogenic report

• Interestingly, a recent survey showed that almost **38% of glaucoma patients were using tear substitutes, more than half of which were preserved.**

• This finding illustrates the lack of knowledge on the iatrogenic cause of DED in glaucoma, employing an additive strategy to manage DED consisting of treatments to alleviate symptoms without considering the cause and the illogical use of preservative-containing eyedrops.

Gomes JAP, et al. Ocul Surf. 2017 Jul;15(3):511-538. doi: 10.1016/j.jtos.2017.05.004.

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### Quality of Life

**CONCLUSIONS:** OSD is more common in patients with increasing glaucoma severity and is associated with poorer glaucoma-related QoL and higher exposure to SAs.


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### OSD, Glaucoma and Quality of Life (QOL)

National Eye Institute-Visual Function Questionnaire (NEI-VFQ) 25 and the Glaucoma Symptom Scale (GSS) questionnaires

**Conclusions:**

- Many patients present an OSD related to therapy, and this affects their quality of life.
  - The use of fixed combinations to reduce surface exposition and of benzalkonium chloride-free formulations should be encouraged to reduce and contain the onset or worsening of this secondary condition in glaucoma patients.
- The GSS has shown a good relation to signs and should be routinely used to evaluate the impact of OSD on the quality of life.




Rossi GC, et al. Ocular surface disease and glaucoma: how to evaluate impact on quality of life. J Ocul Pharmacol Ther. 2013 May;29(4):390-4.

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### Signs and Symptoms of Ocular Surface Disease: The Reasons for Patient Dissatisfaction with Glaucoma Treatments


- Cross-sectional study in 793 treated and stabilized glaucoma patients to assess patient satisfaction and local tolerability of their treatment
- Even if patients report to be highly satisfied, they may still have signs and symptoms of local intolerance to their therapy, possibly requiring a treatment change.



Clinical Ophthalmology 2020;14:3675-3680

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### How happy are glaucoma patients? Survey instrument:



n=793

Clinical Ophthalmology 2020;14:3675-3680

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### Survey Results

- The vast majority (93.7%) of patients was satisfied or very satisfied with their treatment in terms of tolerability and only 6.3% were dissatisfied.
- However, ophthalmological examination showed a high frequency of ocular signs:
  - conjunctival hyperemia (32%), OSD (42.5%) and positive conjunctival staining (10.3%)
- Additionally, patients reported symptoms upon instillation (31.4%) and between instillations (57.3%)
- 25.1% of patients were using tear substitutes.
  - All signs and symptoms were significantly associated with patient dissatisfaction.

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### Conclusion


- Based on these results, we believe that it is important to question patients about any tolerance issues associated with their topical glaucoma treatment.
- Even if patients report to be highly satisfied, they may still have signs and symptoms of local intolerance to their therapy, possibly requiring a treatment change.

Stalmans I, Lemij H, Clarke J, Baudouin C; GOAL study group. Signs and Symptoms of Ocular Surface Disease: The Reasons for Patient Dissatisfaction with Glaucoma Treatments. Clin Ophthalmol. 2020 Oct 30;14:3675-3680.

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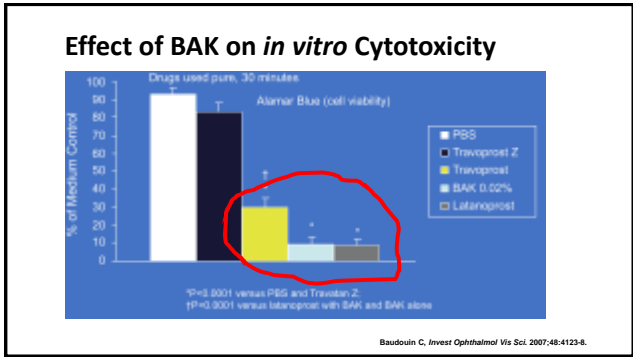
### Compliance Component

- "A major cause of intolerance or poor tolerance to glaucoma medication is the ocular surface changes created by treatment."
  - Detry-Morel M. Side effects of glaucoma medications. Bull Soc D'elge Ophthalmol. 2006;27-40.



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### When is BAK Use Most Problematic?

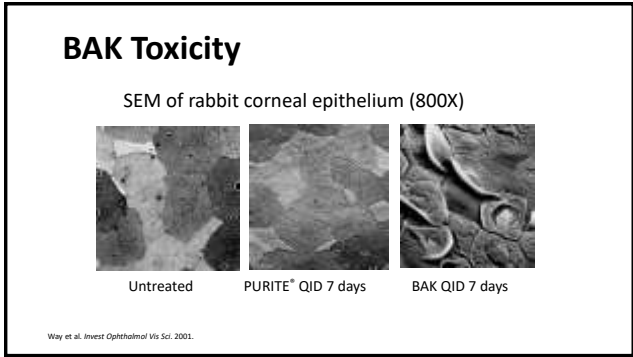
- **High BAK Concentration: Cell Death is Dose-Dependent.**<sup>1,2,3</sup>
  - High Concentration in a Single Drop or Due to The Accumulation of Dose With Multiple Drops.
- **Treatment of Chronic Ophthalmic Diseases, such as Glaucoma, with BAK Containing Medications.**
  - Longer Duration of BAK Exposure → Increased Corneal Epithelial Cell Lysis.<sup>3</sup>

1. Neuberth R. Ophthalmic preservatives: Considerations for long-term use in glaucoma patients with dry eye or glaucoma. *Review of Ophthalmology (journal online)* 2003 June. Available from: [http://www.wegnet.com/2003/06/06/00000002\\_article.htm](http://www.wegnet.com/2003/06/06/00000002_article.htm) accessed June 5, 2006.

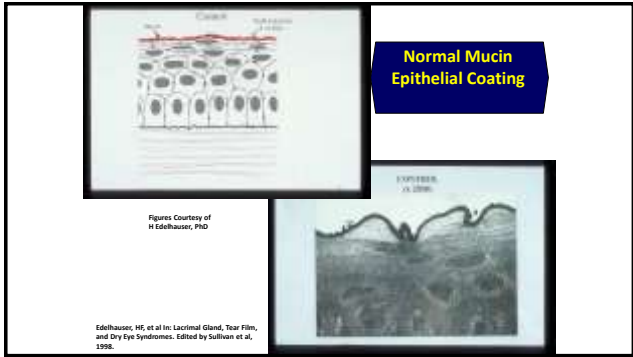
2. De Santis Jean M, et al. Expression of CD40 and CD 40 ligand in the human conjunctival epithelium. *Current Eye Res.* 2000;29:85-94.

3. Chu SK, et al. Corneal epithelial cellular dysfunction from benzalkonium chloride (BAK) in vitro. *Exp Eye Res.* 2004;32:180-184.

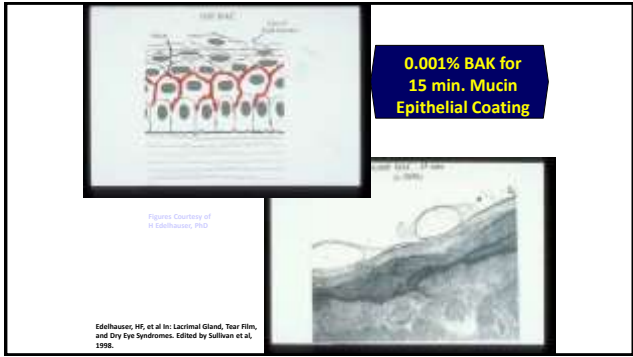
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### Review Article

#### Conjunctival Goblet Cells, the Overlooked Cells in Glaucoma Treatment

Hee-Jeong Park, MD, PhD, J. Ronald A. Marmor, MD, PhD, The P. Schiner MD-PhD Center for Ocular Health, Johns Hopkins University School of Medicine, Baltimore, MD, USA; J. Ronald A. Marmor, MD, PhD, and Victor J. Arora, MD, PhD

- Goblet Cells essential to mucin layer
- Findings indicate that patients treated with antiglaucomatous drugs containing preservatives and patients treated with multiple antiglaucomatous eye drops may have decreased GCD, thus being at risk of surgical failure when treated with filtration surgery.
- Preservative Free glaucoma medications help to reverse this.

J Glaucoma. 2019 Apr;28(4):325-333

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### SUMMARY Implications for Glaucoma Therapy

- Chronic therapy with BAK preserved medications can:
  - Promote development of dry eye and OSD
  - Increase risk of:
    - Corneal/Ocular SEs and complications
    - Symptoms potentially leading to decreased Compliance

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### BAK: The Need for Alternatives

**ISSUES:**

- Glaucoma patients:
  - Elderly (decreased tear secretion)
  - Multiple topical medications (both for glaucoma and for concurrent ophthalmic diseases)
  - May undergo filtering surgery (impact on healing)
- Tolerability (and consequent negative impact upon patient compliance)
- There is a significant need for alternatives
- BAK-free formulations:

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### BAK % in current Medications

**PGAs:**

• Latanoprost 0.005%	0.02% BAK
• Bitmatoprost 0.01%	0.02% BAK
• Latanoprostene bunod	0.02% BAK
• Bitmatoprost 0.03%	0.005% BAK

As reported on Package Insert

**All Others BAK:**

- Netarsudil
  - 0.015%
- Azopt
  - 0.01%
- Timolol sol
  - 0.01%
- Cosopt
  - 0.0075%
- Simbrinza
  - 0.003%

Higher  
↓  
Lower

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### Treatment Options Section:

#### How can I help my patient now?

- Select BAK Free and/or Preservative Free Glaucoma Medications
- Use Preservative Free Artificial Tears

➔ Reducing total BAK can improve/minimize OSD signs/symptoms.

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### Preservative Free Formulations



Packaged in unit dose vials

- Timolol
- Dorzolamide/Timolol Fixed Dose Combination (FDC)
- Tafuprost
- Latanoprost (Canada)

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### Timolol PF

- Preservative Free
- Unit dose vials
- 0.25 and 0.5%
- Long time available option for PF
- Frequently high cost w/o coverage
  - Good Rx = \$570/month (May 2022)
  - B+L has Patient Assistance Program

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### Timolol PF




- Preservative-free eye drops have a significant advantage over preserved drops in that they essentially eliminate the potential for preservative-induced toxicity and associated adverse effects.
- This results in improved ocular tolerance, patient comfort, and thus compliance.
- Patients who cannot tolerate the effects of preservatives may skip doses of preserved drops in order to avoid discomfort or discontinue medical therapy all together.
- By maintaining patient compliance, preservative-free drops have the potential to improve outcomes in patients with glaucoma.

Clinical Ophthalmology 2013;7:2131-2135

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### Dorzolamide/timolol FDC Preservative Free

- dorzolamide HCL - timolol maleate
  - 2%/0.5% solution
- Preservative Free, Unit dose vials
  - BID dosing
  - 25-30% IOP reduction (monotherapy)
  - COPD and other beta blocker contraindications
- Similar indications for OSD patients where BAK toxicity is a concern



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### Clinical studies on dorzolamide/timolol PF



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### Preservative Free: Tafluprost (Zioptan)

- A Preservative Free prostaglandin analog
  - Introduced in **2003**
  - Tafluprost 0.015%
  - Single use vial delivery
- Similar Efficacy to latanoprost
- Same PGA side effects:
  - Iris/Periorbital Pigmentation, Hyperemia, Deepening Orbital Sulcus, etc.



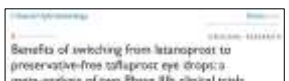

Clinical Ophthalmology 2013;7:901-910

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### Tafluprost vs. Latanoprost

**Conclusion:**

- This meta-analysis confirmed that **IOP remained at the same level** after replacing benzalkonium chloride-preserved latanoprost eye drops with preservative-free tafluprost eye drops.
- Preservative-free tafluprost significantly decreased the symptoms and signs of ocular surface disease and outperformed latanoprost in drop comfort and treatment preference.




Uusitalo H, Egorov E, Kaarniranta K, Astakhov Y, Ropo A. Clin Ophthalmol. 2016 Mar 15;10:445-54. doi: 10.2147/OPTH.S91402. PMID: 27041987; PMCID: PMC4801127.

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### Tafluprost vs. Latanoprost

**Efficacy:**

- "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




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### Taflopust PF in OSD

**Conclusion:**

- Preservative-free taflopust was better tolerated than the commercially available formulation of latanopust in patients who were recruited to the study because exhibiting symptoms / signs of ocular surface side-effect during atanoport treatment at the baseline visit.
- It is suggested that the high concentration of BAC in the latanopust formulation negatively affects the tolerability and that patients with ocular surface side effects may benefit from switching to a preservative-free prostaglandin preparation such as taflopust.



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### Zioptan: Decreased Osmolarity Switch from Latanopust

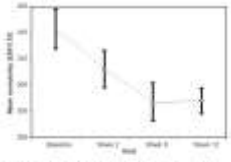


Figure 1 Mean (standard deviation) osmolarity (mOsm/kg) in patients switching from Latanopust to Zioptan.

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### Zioptan: IOP, Symptoms

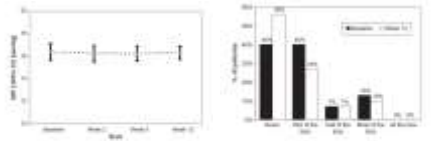


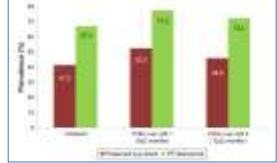
Figure 1 Mean (standard deviation) IOP (mmHg) at Baseline, Week 1, Week 2, and Week 3.

Figure 2 Mean (standard deviation) OSDI scores at Baseline, Week 1, Week 2, and Week 3.

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### Latanopust PF

Better tolerance of preservative-free latanopust compared to preserved glaucoma eye drops: the 12-month real-life FRSE study



Prevalence of patients with no conjunctival hyperemia at inclusion, follow-up visit 1, and follow-up visit 2.

In conclusion, this first real-life study confirmed the clinical benefit of PF latanopust and its better local tolerance over preserved eye drops over a sustained period of 12 months. PF latanopust provided a significantly higher patient satisfaction, thus potentially allowing improvement in the patient's daily life.

Clinical Ophthalmology 2018;12:2399-2407

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### Preserved Versus Preservative-Free Latanopust for the Treatment of Glaucoma and Ocular Hypertension: A Post Hoc Pooled Analysis

**Conclusion:**

- This post hoc pooled analysis confirmed the findings of the individual studies that PFL is as efficacious at reducing IOP as PCL but better tolerated.
- After switching to PFL, there was twice the improvement in the OSD composite score. PFL was twice as effective at reducing ocular hyperemia and other ocular signs.
- These findings suggest that PFL has features that may improve patient compliance, thereby potentially improving the IOP-lowering efficacy on a long-term basis.

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### Monoprost

- **Preservative Free Latanopust (Canada, not US)**
  - Introduced in 2017
  - Latanopust 0.0005%
  - Single use vial delivery
- **Same PGA side effects:**



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### Potential New Products

U.S. National Library of Medicine  
ClinicalTrials.gov

Prospective, Double-masked, Randomized, Multi-center, Active-controlled, Parallel-group, Second-Stage Study Assessing the Safety & Order Hypothesis Efficacy of TC-002 Ophthalmic Solution Compared to Latanoprost Ophthalmic Solution 0.005% in Subjects With Elevated Intraocular Pressure (TC-002-01)

View Study | All Sites | Top Study

View Study | Study Dates | View Study

Prospective, Double-masked, Randomized, Multi-center, Active-controlled, Parallel-group, Second-Stage Study Assessing the Safety & Order Hypothesis Efficacy of TC-002 Ophthalmic Solution Compared to Latanoprost Ophthalmic Solution 0.005% in Subjects With Elevated Intraocular Pressure (TC-002-01)

ClinicalTrials.gov Identifier: NCT04583308

TC-002 is a potential new product for the treatment of glaucoma. It is a microdosed formulation of latanoprost, a prostaglandin analog. The study is designed to evaluate the safety and efficacy of TC-002 compared to latanoprost 0.005% in subjects with elevated intraocular pressure.

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### PF Bitmatoprost in Multi-Dose Bottle

#### Aequus Announces Canadian Filing of NDS for Preservative - Free Glaucoma Medication

PF Bitmatoprost is a potential new product for the treatment of glaucoma. It is a prostaglandin analog. The study is designed to evaluate the safety and efficacy of PF Bitmatoprost compared to latanoprost 0.005% in subjects with elevated intraocular pressure.

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### Microdose latanoprost: Piezoelectric microdosing technology

Latanoprost with high precision, piezo-print, microdose delivery for IOP lowering: clinical results of the PG21 study of 0.4 µg daily microdose

Clinical Ophthalmology 2018:12 2451-2457

The image shows a piezoelectric microdosing device and a clinical study abstract. The abstract discusses the results of the PG21 study, which evaluated the efficacy of a 0.4 µg daily microdose of latanoprost in lowering intraocular pressure (IOP) compared to a standard 0.005% latanoprost solution. The microdosing technology is described as having high precision and being suitable for IOP lowering.

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### Reduced volume:

- Typical Eye Drop:
  - Excessive volume means excessive drug and preservative
- Microdosing:
  - Less drug loss and medication dilution.
  - Increased bioavailability to the eyes.
  - Reduced local drug reactions.
  - User friendliness may increase compliance with ocular dosing regimens.
  - Systemic drug absorption and related side effect risk are decreased

The image compares a typical eye drop (40µl) with a microdose (5µl). A bar chart shows that microdosing results in higher bioavailability compared to a typical eye drop. The chart compares the bioavailability of a typical eye drop (40µl) and a microdose (5µl) in terms of drug concentration in the eye. The microdose shows a significantly higher concentration of drug in the eye, indicating increased bioavailability.

Clinical Ophthalmology 2018:12 2451-2457

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### Another way to reduce the BAK load?

- The capacity of the human eye is 7-10 µl
- Nanodropper significantly reduces drop volume by over 60% on average
- Never produces drops less than 10 µl

https://nanodropper.com/

The image shows a comparison between a current eye drop and a nanodropper. The nanodropper is shown to produce a much smaller drop volume than a standard eye drop. The nanodropper is a small, handheld device that can be used to deliver precise, small volumes of eye drops.

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### No published data yet:

CLINICAL TESTING Multiple Non-Inferiority Clinical Trials Scheduled for 2022

The image shows a screenshot of ClinicalTrials.gov search results for nanodropper trials. The search results show several clinical trials that are scheduled for 2022. The trials are designed to evaluate the safety and efficacy of nanodropper technology compared to standard eye drops.

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## BAK Free Formulations

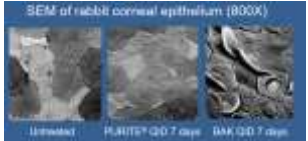
Use an alternative preservative to BAK, packaged in standard multidose vials

1. Brimonidine
2. Travoprost
3. Latanoprost

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### Brimonidine with Purite (Alphagan P)

- Brimonidine 0.1%
  - Frequent adjunct to PGA
  - TID dosing per FDA label
  - Lower risk of "allergy" vs. higher concentrations
    - ~10%
- PURITE
  - stabilized oxychloro complex
  - is a preservative that is effective at low concentrations
  - Non-toxic to epithelial cells



- Brimonidine 0.15% (generic)
- POLYQUAD
- Brimonidine 0.2%
- 0.05% BAK


Way WA. Invest Ophthalmol Vis Sci. 2001;42(4):539

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### Travoprost BAK Free (Travatan Z)

Generic+ Brand

#### Ionic Buffer System



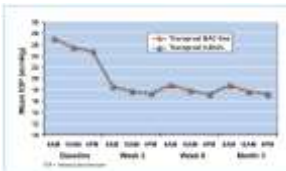
- Boric acid in ionic buffered solution
- Generic (Mylan, Apotex)
- Note:
  - Generics are not always low priced

Travatan Z (travoprost) - First-time generic  
[https://professionalknowledge.com/publications/library/the-generics-travatanz\\_2019-1220.html](https://professionalknowledge.com/publications/library/the-generics-travatanz_2019-1220.html)

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### Travoprost w/ and w/o BAK

**No difference in IOP efficacy:**



Latanoprost with BAK, travoprost with BAK, and BAK alone have significant cytotoxic effects on human conjunctiva-derived cells and are associated with apoptosis. IOP lowering agents with alternative preservatives instead of BAK will most likely have fewer ocular surface adverse effects than agents containing BAK.


In Vitro Studies of Antiglaucoma Prostaglandin Analogues: Travoprost with and without Benzalkonium Chloride and Preserved Latanoprost  
 (Shenoy S, et al. J Glaucoma. 2007;16(11):1001-1007)

Lewis RA, Katz G, Weiss MJ, et al. Travoprost 0.004% with and without benzalkonium chloride: a comparison of safety and efficacy. Journal of Glaucoma. Invest Ophthalmol Vis Sci. 2007;48:4123-4128


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### Travoprost with SofZia preservative

**Had reduced OSD signs:**



**Minimal Difference vs. latanoprost:**



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### Latanoprost with potassium sorbate (2018)

- Xelpros™ is a new latanoprost 0.005% ophthalmic emulsion
  - developed by Sun Pharmaceuticals Advanced Research Center (SPARC, Ltd)
- Does not contain BAK
- Supplied as a sterile, isotonic, buffered aqueous emulsion of Latanoprost
  - pH of approximately 7.0
  - Uses sorbate based preservative system
- Also uses a microemulsion (swollen micelles) technology for releasing the constituents which then supplements tear film components.

- Efficacy:
  - Similar IOP reduction to latanoprost with BAK
    - Medical Information Sun Pharmaceutical Industries, Inc.
- Corneal and OSD Effects
  - Have not been studied nor reported
- Thus, theoretical benefits only

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**Clinical Ophthalmology** | **ELSEVIER**

**ORIGINAL RESEARCH**

**Effect of benzalkonium chloride-free latanoprost ophthalmic solution on ocular surface in patients with glaucoma**

**Conclusion:** Results indicate that switching from BAK-containing latanoprost to BAK-free latanoprost resulted in significant improvements in TBUT, OSDI score, and inferior corneal staining score, and measurable reductions in conjunctival hyperemia score. Furthermore, BAK-free latanoprost was well tolerated with only mild-to-moderate and self-limiting AEs. BAK-free latanoprost appears to be effective in protecting ocular surface integrity in glaucoma patients but further studies are needed to confirm this beneficial effect.

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**Latanoprost BAK Free** • Potassium sorbate isotonic, sterile, buffered emulsion

**Primary Efficacy Endpoint**  
Average TBUT

**Secondary Efficacy Endpoint**  
OSDI evaluation

SUN-MED-SRD-XEL-004\_MED-US-XP50004\_Xelpros\_OcularSurfaceStudy\_Final\_22Feb2019\_Approved

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**Does travoprost/latanoprost without BAK really help OSD?**

**Conclusion:** Results indicate that switching from BAK-containing latanoprost to BAK-free latanoprost resulted in significant improvements in TBUT, OSDI score, and inferior corneal staining score, and measurable reductions in conjunctival hyperemia score. Furthermore, BAK-free latanoprost was well tolerated with only mild-to-moderate and self-limiting AEs. BAK-free latanoprost appears to be effective in protecting ocular surface integrity in glaucoma patients but further studies are needed to confirm this beneficial effect.

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**travoprost 0.003% + Polyquad vs travoprost 0.003% + BAK**

**FIGURE 2.** Effect on intraocular pressure (IOP) in patients with glaucoma treated with travoprost 0.003% + polyquad or travoprost 0.003% + BAK. Data are presented as mean (95% CI) and 95% confidence intervals.

JAMES H. WATKINS, PETER S. HILBERG, MATTHIAS WAGNER, JOHN M. LIM, DAVID WITKIN, AND JAMES G. BRADY. *Investigative Ophthalmology and Visual Science* 2015;56(12):266-274.

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**Glaucoma Medications with BAK alternative or Preservative Free formulations**

<p><b>BAK Free</b></p> <ul style="list-style-type: none"> <li>Brimonidine with Purite (Alphagan P)</li> <li>Travoprost with Sofiza preservative (Travatan Z)</li> <li>Latanoprost with potassium sorbate preservative (Xelpros)</li> </ul>	<p><b>Preservative Free (PF)</b></p> <ul style="list-style-type: none"> <li>Timolol PF (Timoptoc Oducose)</li> <li>Dorzolamide/Timolol FDC PF (Cosopt PF)</li> <li>Tafuprost PF (Zioptan)</li> </ul>
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**New(er) and Commonly Recommended Artificial Tears**

**Three Goals:**

- Avoid generic brands
- Avoid ATs with Preservatives
- Do not hinder glaucoma medication use

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**Trehalose/hyaluronate eyedrops. (Thea Pharma)**  
 Preservative-free extended relief and ocular surface protection (Multi-dose bottle)

- **Povidone**
  - the active ingredient to enhance viscosity and provide moisturizing and lubricating properties;
- **Trehalose**
  - a disaccharide that provides ocular bioprotection, osmoprotection and rehydration
- **Hyaluronic acid**
  - a component of tear film with the ability to lubricate – can bind 1000x more water than its weight.

• Aragona P, et al. Sci World J. 2014;2014:717835.  
 • Chiambaretta F, et al. Eur J Ophthalmol. 2017;27(1):1-9.  
 • Liu Z, et al. Invest Ophthalmol Vis Sci. 2020;61(10):26.  
 • Schmidt D, et al. Cornea. 2015;34(4):421-426.

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**Efficacy and safety of hyaluronic acid and trehalose**

- Increased tear thickness to 240 minutes from one application,
  - 6 times longer than hyaluronic acid alone
- Provided a majority of patients with greater improvement in scores on the Ocular Surface Disease Index compared with hyaluronic acid alone
- Decreases ocular surface inflammation; and
- Relieves symptoms including blurred vision, stinging and itching.

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**Decreases Inflammatory Markers**

Figure 4. Tear levels of interleukin (IL)-1 $\beta$  (upper left), IL-6 (upper right), and IL-8 (bottom) are graphed, at baseline (V0-V1) and endpoint (V3).

Clinical Ophthalmology 2018:12

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**Alcon OTC**

- **Systane® Complete PF**
  - Nano-droplet technology
  - **NOW Preservative Free**
  - **Multi-Dose Vial**
- **Systane® NightTime**
  - PF
  - Ointment; 3.5 g tube
  - Active ingredients: mineral oil (3%), white petrolatum (94%)
  - Inactive ingredient: anhydrous liquid lanolin (3%)

Silverstein S, Yeu E, Tauber J, et al. Symptom Relief Following a Single Dose of Propylene Glycol-Hydroxypropyl Guar Nanoemulsion in Patients with Dry Eye Disease: A Phase IV, Multicenter Trial. Clin Ophthalmol. 2020;14:2167-2177.  
 Rangrajeev R, Kellison H. Pre-clinical evaluation of a novel hydroxypropyl-guar phospholipid nanoemulsion-based artificial tear formulation in models of corneal epithelium. J Ocul Pharmacol Ther. 2019;35(1):32-37.  
 Kellison H, Rangrajeev R. Pre-clinical evaluation of a novel phospholipid nanoemulsion based lubricant eye drops. Poster presented at ARVO 2017, Baltimore, MD.

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**Allergan OTC**

- **Refresh® Relieva PF**
  - Repairs and protects the eyes from the harmful effects of Dry Eye
  - Treats the signs and symptoms of Dry Eye while delivering improved comfort and clarity of vision
  - Safe to use with contact lenses
  - Low-blur drop
  - Active ingredients: carboxymethylcellulose sodium 0.5%, glycerin 0.9%
- **Refresh Liquigel®, Refresh Celluvisc® (PF)**
  - Soothing gels
  - Long-lasting
  - Active ingredient: Moisturizing relief
  - Soothing relief
  - Active ingredients: carboxymethylcellulose sodium (1%)
- **Refresh P.M.®, Refresh Lacri-Lube®**
  - **PF ointment**
  - Nighttime dryness and exposure
  - Active ingredients: mineral oil (42.5%), white petrolatum (57.3%)

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**Bausch + Lomb OTC**

- **Soothe® PF**
  - Long lasting lubrication
    - Relieves dryness and prevents further irritation
  - Sensitive eyes
  - Active ingredients: glycerin (0.6%), propylene glycol (0.6%)
- **Soothe® NightTime Ointment**
  - Overnight relief
  - Gentle
  - Active ingredients: mineral oil (20%), white petrolatum (80%)

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### Santen (Eyeveance)

- FRESHKOTE® Preservative Free (PF)**
  - The active ingredients in FRESHKOTE PF are a patented polymer blend with a unique ratio of polyvinyl alcohol and povidone
- MUCOAGUEOUS LAYER**
  - Polyvinyl Alcohol (2.7%)<sup>1-3</sup>
- LIPID LAYER**
  - Povidone (2.0%)<sup>1,2</sup>
- HIGH ONCOTIC PRESSURE**
  - Unique Ratio Blend<sup>1,2</sup>



US Ophthalmic Review, 2007,3:38-41

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### "It takes a Village"

- Modify environmental/external factors
  - Vaporizer/humidifier
  - Visual breaks and blink awareness for digital devices
  - Ointment at night with CPAP machines and humidifier
  - Bruder Mask
- Modify oral medications if possible with PCP






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### The Dry Eye Cocktail- Tools in our Clinical Arsenal

- Autologous Tears
  - Vital Tears
- Amniotic Membrane
  - Dehydrated with large diameter BCL
  - Cryopreserved Self Retained
- Soft BCL
- Scleral lens
- Tarsorrhaphy




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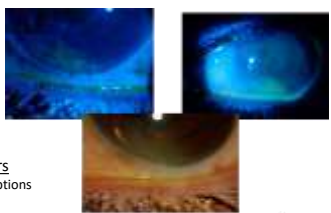
### Importance of Educating Glaucoma Patients

- Patients are perceived as high maintenance
  - Fluctuating VA in already compromised VA from glaucoma
  - Light sensitive when we need more light if Low Vision
  - Patients frustrated and decrease in quality of life
- Can affect compliance and adherence in maintaining glaucoma therapy
- Important to stress the following:
  - Dry Eye does not go away
    - Flares and regresses depending on above factors
  - If severe, can take months to improve
    - Prescribed regimen must be followed
    - High maintenance disease=High maintenance regimen
      - Consistent treatment needed for resolution
  - When improved, requires maintenance plan for long term success.

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### My Typical Approach

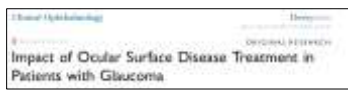
- Glaucoma Patient
  - New or established
- History
  - Specific for dry eye symptoms
  - Questionnaire if necessary
- Thorough slit lamp
  - TBUT, Stain, Lissamine green, etc.
- With Positive Findings or Risk Factors
  - Review Medications and Treatment Options
  - Patient Education
  - Reduce the Preservative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



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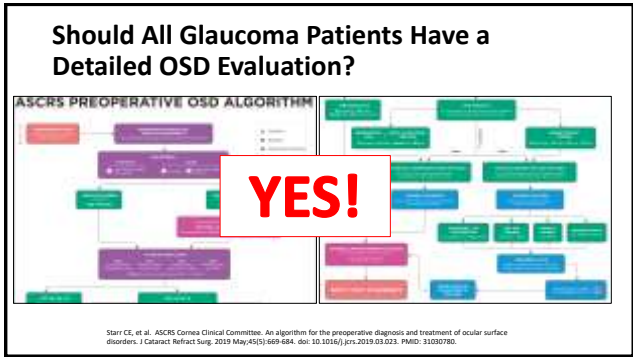
### How long to see improvement?

- 19 Patients with OAG, treated for >6m. No change in glaucoma medications.
- Comprehensive Treatment for OSD with:
  - Eyelid hygiene using a gel twice a day, fluorometholone acetate 0.1% (one drop at night), preservative-free lubricant every 2 hrs, omega 3 and flaxseed oil capsule 2g a day, and oral doxycycline.
- @ 1-3 months, Statistically significant improvements were found in:
  - BCVA, OSDI score (p<0.0001), bulbar conj. redness and fluorescein staining
- Interestingly: (?)
  - After treatment, mean IOP reduced 1.4 mmHg and 1.6 mmHg from baseline in OD and OS
  - And an IOP reduction ≥2 mmHg was observed in 58% of the eyes after treatment



Mylla Bosso AL et al  
Clin Ophthalmol. 2020 Jan 14;14:103-111.

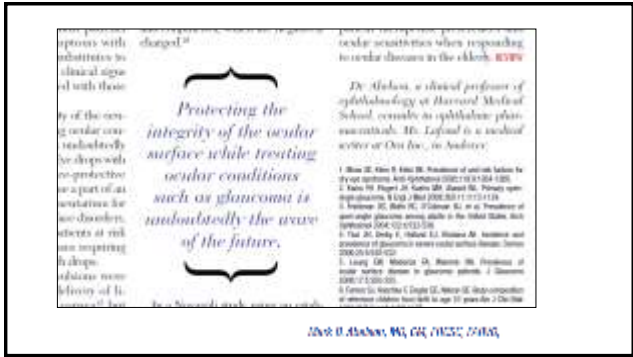
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- ### Summary
- Do preserved glaucoma medications have a deleterious effect on superficial eye tissues? **Yes**
  - Are preservatives like BAK deleterious? **Yes**
  - Are the changes dose/time dependent ? **Yes**
  - Are the changes reversible? **Yes**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

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