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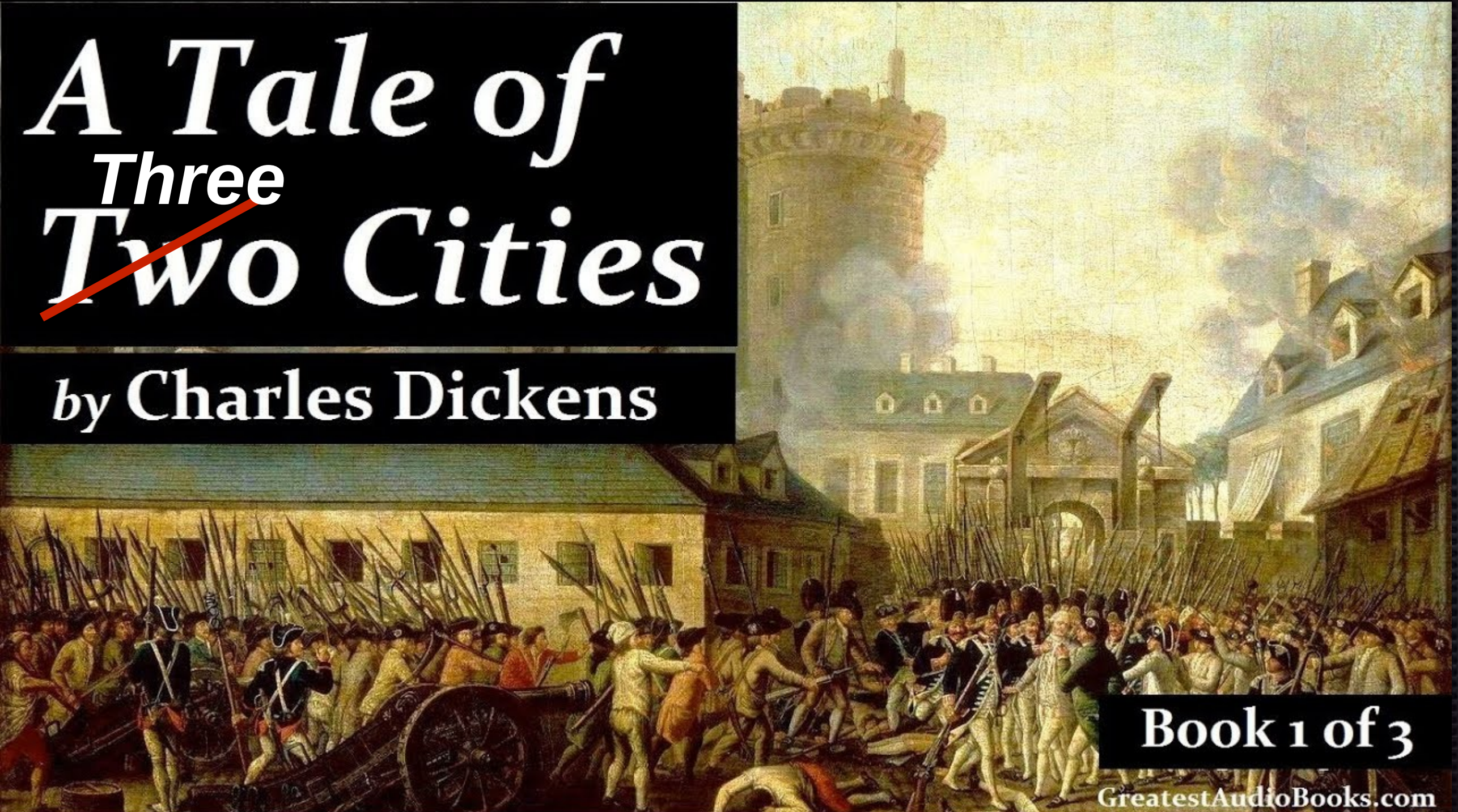
Durham
University

Should preservative free eye drops be first line in glaucoma?

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Honorary senior lecturer
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A Tale of *Three* *Two Cities*

by Charles Dickens



Book 1 of 3

GreatestAudioBooks.com

Preservatives in glaucoma
medications

The tale of 3 components!

Disclosures

- Honoraria: Glaukos, Thea, Santen and Allergan
- Consultancy fees: Thea, Gore, Abbvie, Scope, Alcon and Santen
- Educational grants: J&J, Thea pharmaceuticals and Glaukos

Outline

- What is the culprit?
- Active ingredients vs buffers vs preservatives?
- What about the future?



What is the prevalence of OSD?

- The prevalence of OSD in glaucoma and OHT patients is **approx. 60%** at least in one eye.

Leung EW, Medeiros FA, Weinreb RN. Prevalence of ocular surface disease in glaucoma patients. J Glaucoma 2008;17: 350–355.

What's in a bottle anyway?



Excipients and buffers

Free radicals and the pH of topical glaucoma medications: a lifetime of ocular chemical injury?

D Lockington¹, ECA Macdonald¹, P Stewart²,
D Young³, M Caslake² and K Ramaesh¹

- pH and free radicals in 27 glaucoma drops were measured
- BAK was the commonest preservative found in 70% of the products
- Free radicals ranged from 0 to 4.54 mmol/l

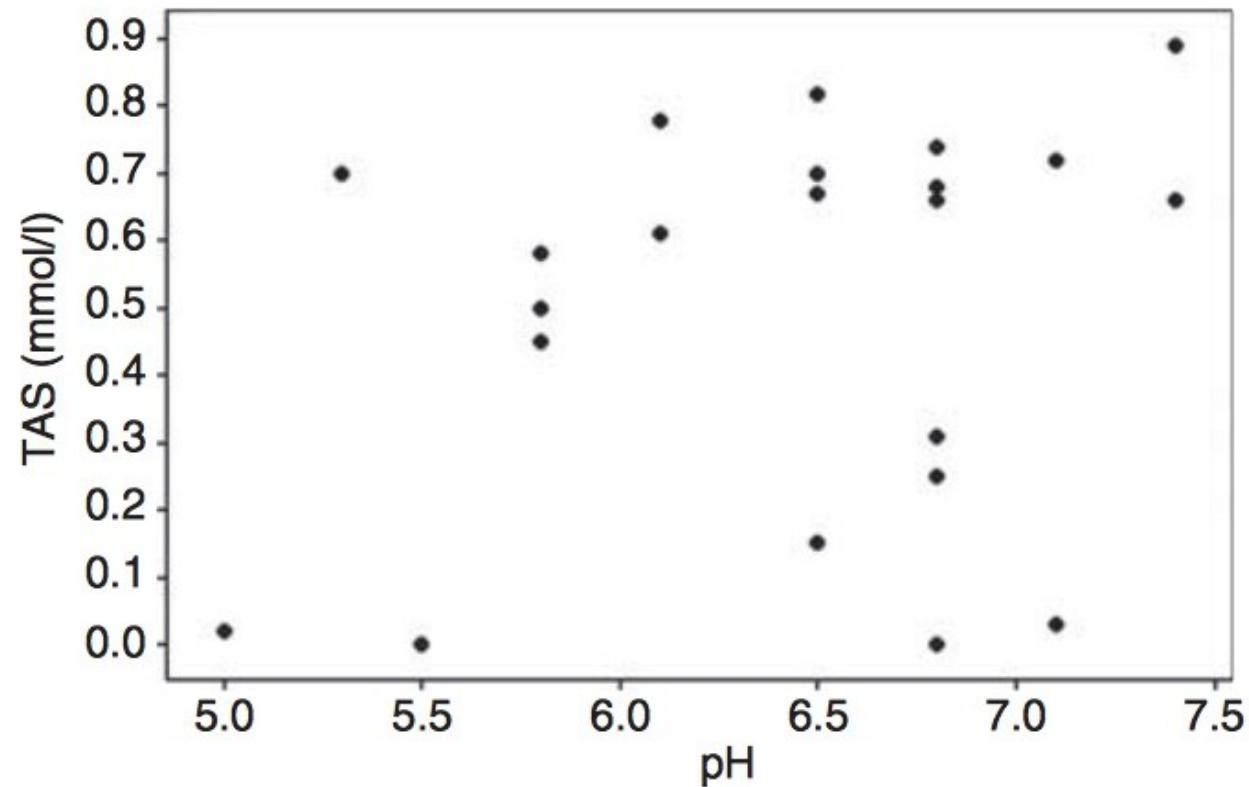


Figure 1 Graph correlating pH with TAS result and showing spread of results. There was no statistical evidence of a direct correlation between free radical concentration and pH ($r = 0.232$, $P = 0.275$).

- pH varied between 4.0 to 7.4
- The excipients play a role in cases of intolerance

Preservatives

- BAK
- PolyQuad
- SofZia

Preservatives

- BAK is an effective disinfectant and detergent which was initially used in RGP contact lenses solutions
- BAK essentially denatures proteins and disrupts the cytoplasmic membranes

- **Higher rate of inflammatory cells** and fibroblasts found in conjunctiva and trabecular tissue of patients receiving polypharmacy as appose to mono therapy

Baudouin C, Pisella PJ, Fillacier K, et al. Ocular surface inflammatory changes induced by topical antiglaucoma drugs: Human and animal studies. *Ophthalmol* 1999;106: 556–563.

Are preservatives necessary to improve efficacy of some glaucoma drops?

Murat Irkec,¹ Banu Bozkurt,² Mehmet Cem Mocan¹

Br J Ophthalmol December 2013 Vol 97 No 12

Preservatives are not necessary to improve
the efficacy of glaucoma drops

ACTIVE CONSTITUENTS VS BAK

Currently available PF glaucoma meds are:

- Latanoprost
- Lumigan
- Cosopt
- Ganfort

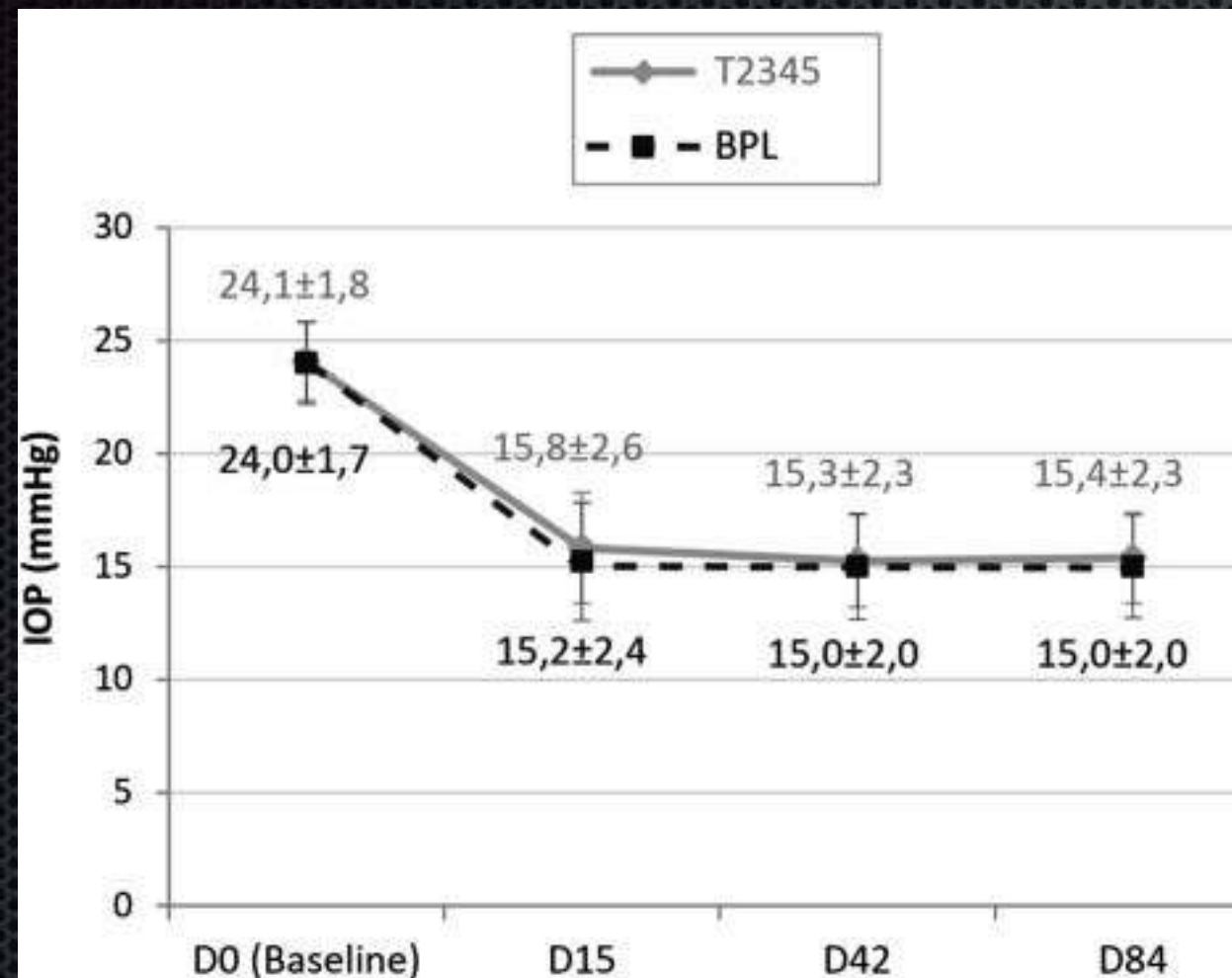


Table 3 Conjunctival hyperaemia score (worse eye) at each visit—safety set

Visit	T2345 (N=213)			BPL (N=189)			Difference between group†
	Hyperaemia score*			Hyperaemia score*			
	2	3–4	5–6	2	3–4	5–6	
D0	36 (17.0)	15 (7.0)	1 (0.5)	38 (20.1)	5 (2.6)	–	ND
D15	42 (20.1)	15 (7.1)	–	50 (26.9)	11 (5.9)	–	p=0.181
D42	31 (14.9)	11 (5.3)	–	41 (22.0)	16 (8.6)	–	p=0.003
D84	34 (16.5)	10 (4.9)	–	40 (21.5)	14 (7.6)	–	p=0.019

Data are number of patients (%). Value shown in bold: p<0.05. ND=not determined.

*The severity of conjunctival hyperaemia was scored using a photographic scale derived from the McMonnies score (2=mild, 3–4=moderate, 5–6=severe).

†Cochran-Mantel-Haenszel stratified by country.

BPL, benzalkonium chloride-preserved latanoprost.

Table 4 Total subjective ocular symptom† score upon instillation—safety set

Visit		T2345	BPL	p Value*
D15	Mean (SD)	0.25±0.81	0.40±0.89	0.085
	95% CI	(0.14 to 0.36)	(0.27 to 0.53)	
D42	Mean (SD)	0.15±0.51	0.41±1.03	0.001
	95% CI	(0.08 to 0.22)	(0.26 to 0.56)	
D84	Mean (SD)	0.18±0.66	0.46±1.05	0.001
	95% CI	(0.09 to 0.27)	(0.31 to 0.61)	

*ANOVA adjusted for country. Value shown in bold: $p < 0.05$.

†Symptoms (pruritus, burning/stinging, blurred vision, sticky eye sensation, eye dryness sensation, foreign body sensation) were graded by the patient according to the following scale: (0)=none, (1)=present but not disturbing, (2)=disturbing, (3)=very disturbing. The total score was calculated as the sum of symptom scores divided by the number of symptoms (thus ranging between 0 and 3).

ANOVA, analysis of variance; BPL, benzalkonium chloride-preserved latanoprost.

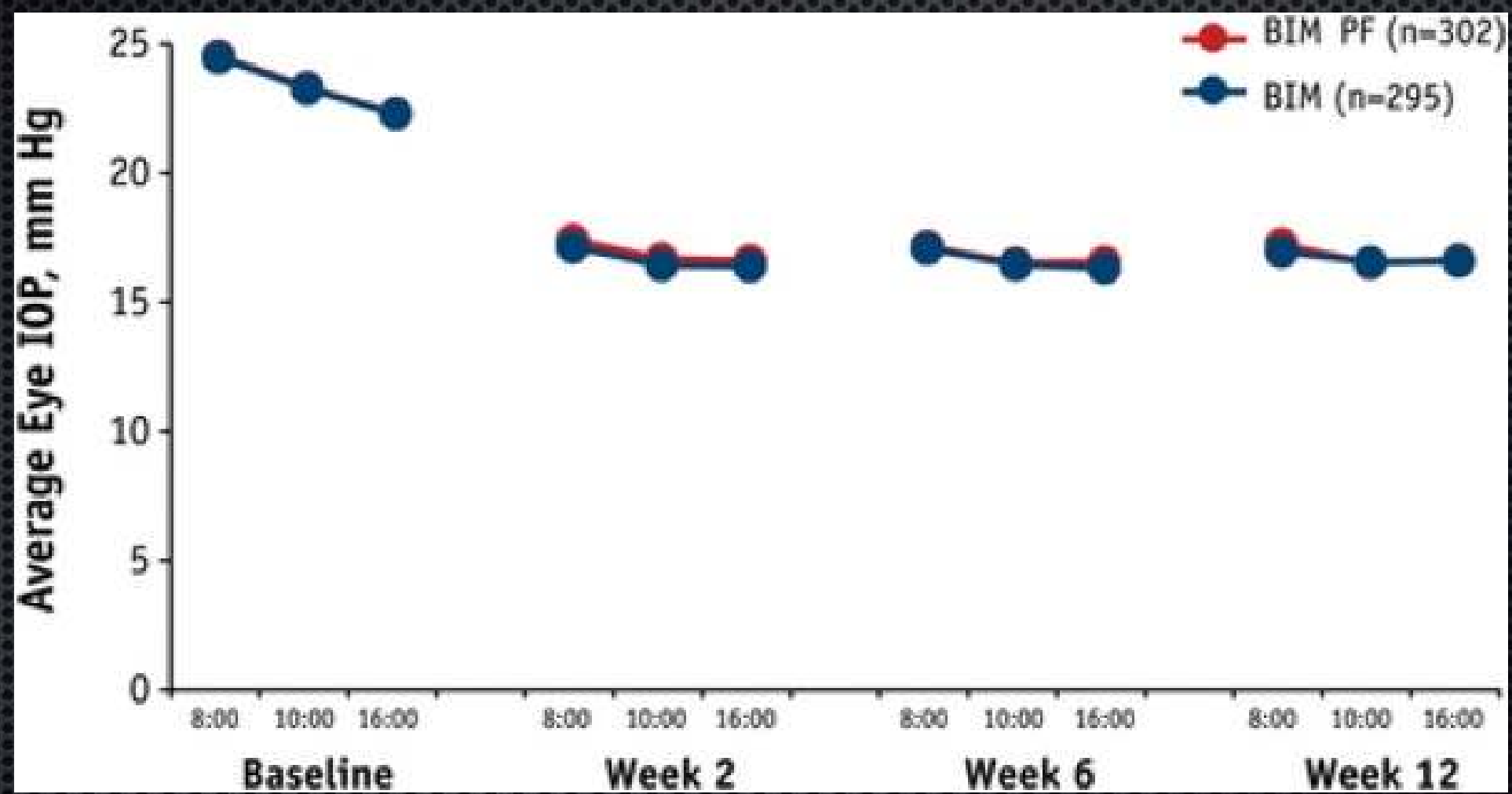
All Symptoms were clumped together!

- The **conjunctival hyperaemia** was used as a proxy for OSD!
- No questionnaire was administered, nor any clinical assessment of ocular surface were reported

- **Bimatoprost 0.03% preservative-free ophthalmic solution versus bimatoprost 0.03% ophthalmic solution (**Lumigan**) for glaucoma or ocular hypertension: a 12-week, randomised, double-masked trial. Day et al. BJO 2013**
- **Bimatoprost 0.03%/timolol 0.5% preservative-free ophthalmic solution versus bimatoprost 0.03%/timolol 0.5% ophthalmic solution (**Ganfort**) for glaucoma or ocular hypertension: a 12-week randomised controlled trial Ivan Goldberg et al. BJO 2014**

Efficacy

- Does BAK affect corneal absorption of drugs?



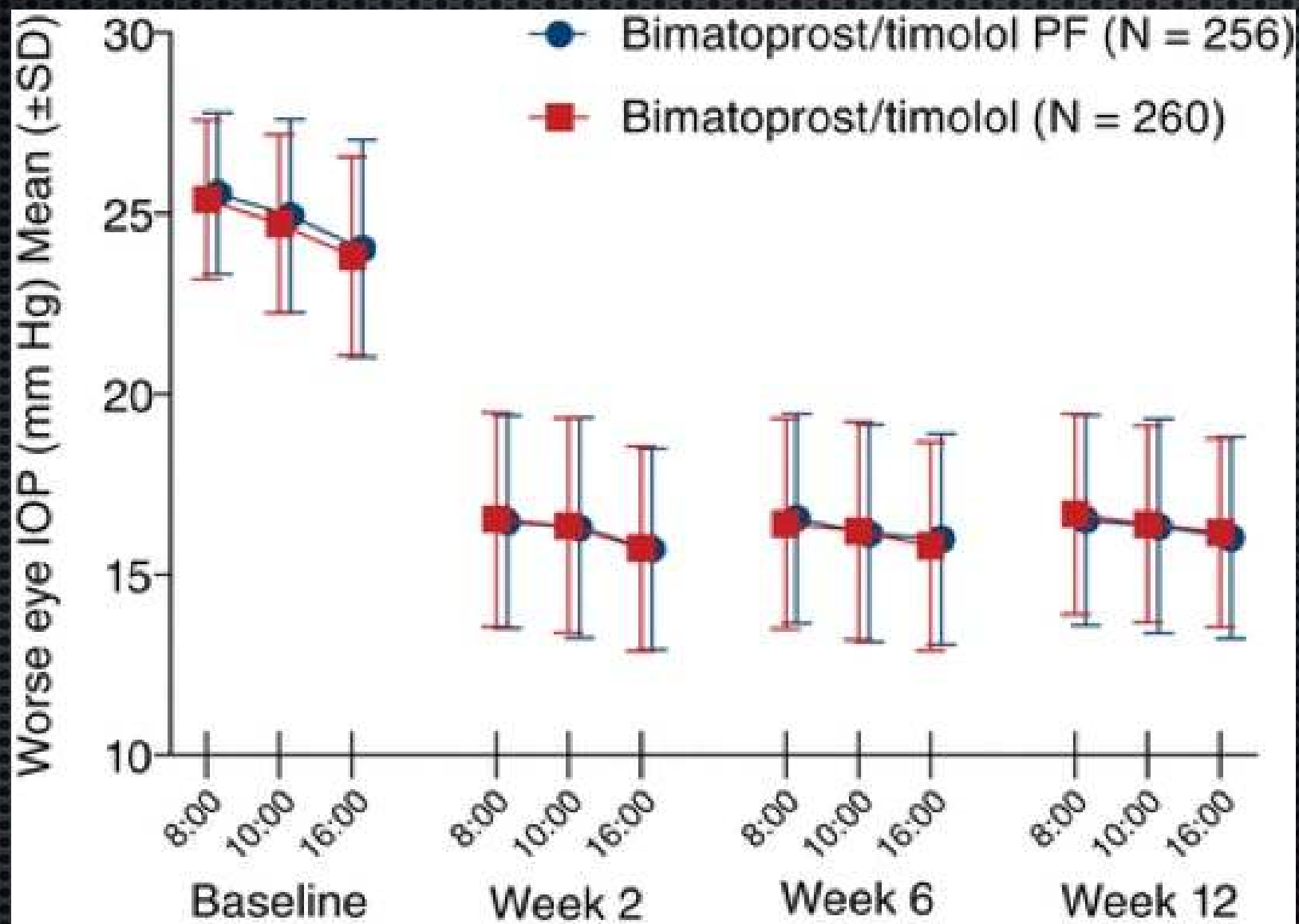
Ocular surface disease

- Is BAK responsible for OSD?

Adverse Event	Preservatives Free (n=301)	With Preservatives (n=295)
Conjunctival Hyperaemia	72 (23.9%)	77 (26.1%)
Mild	53	62
Moderate	19	13
Severe	0	2
Eye pruritis	12	12
Punctate keratitis	9	9
FB sensation	7	2
Dry eye	5	9

Bimatoprost 0.03%/timolol 0.5% preservative-free versus Ganfort for POAG or OHT: a 12-week RCT. Goldberg et al. BJO 2014

- Phase 3, double masked RCT, 55 centres
- POAG/OHT
- Wash-out
- Minimal ocular surface problems
- 1: 1 randomisation



Adverse Event	Preservatives Free (n=278)	With Preservatives (n=282)
Overall	92 (33.1%)	95 (33.7%)
Conjunctival Hyperaemia	59	55
Mild	46	44
Moderate	11	11
Severe	2	0
Eye pruritis	12	5
Dry eye	9	3
Punctate keratitis	8	7
Eye pain	7	5
FB sensation	6	6

Bimatoprost is the most potent & poorly tolerated PGAs*

Lim et al. Ophthalmology. 2008 May. Mechanism of action of bimatoprost, latanoprost, and travoprost

Comparison of the efficacy and tolerability of preservative-free and preservative-containing formulations of the dorzolamide/timolol fixed combination (COSOPT™) in patients with elevated IOP Shedden et al. Graefes Arch Clin Exp Ophthalmology 2012

Equivalent in efficacy and similar tolerability

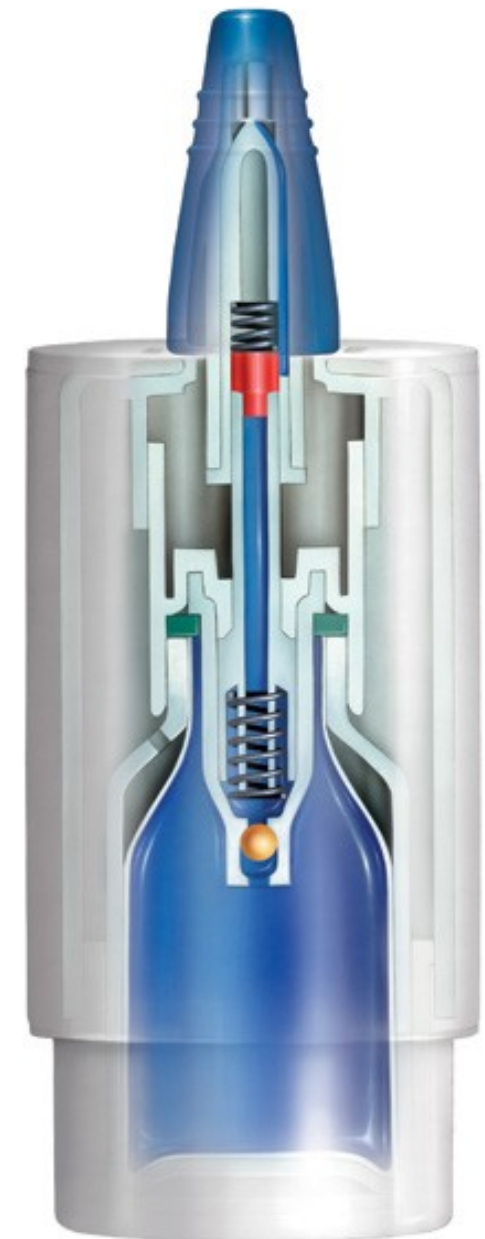
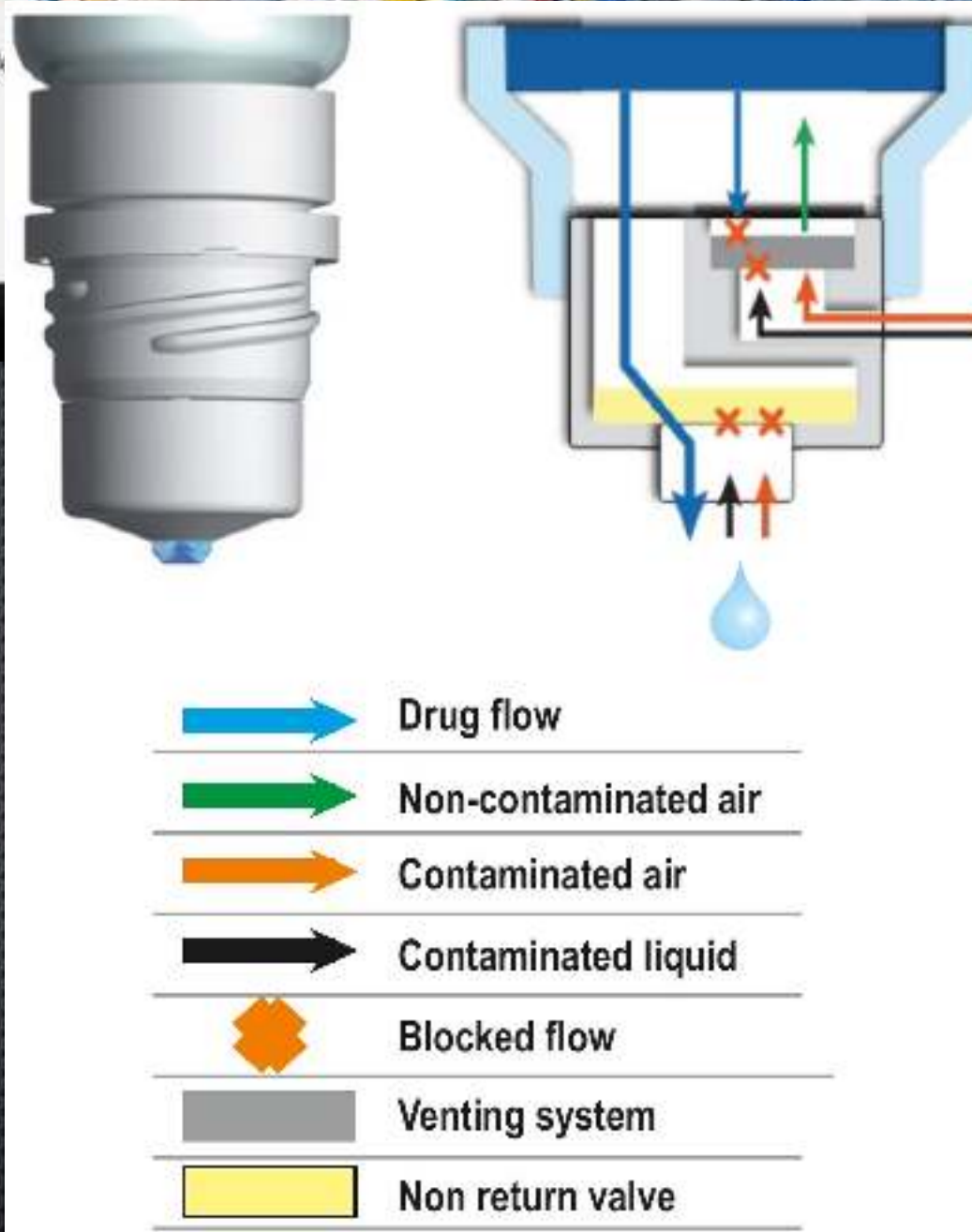
- **Downfalls:**
 - Only one/two glaucoma drop
 - Short duration of studies
 - Excluded patients with significant pre-existing OSD

**No clear evidence of superiority in patients' comfort level
or ocular surface status of preservative-free drops**

Cost

	Preservative-Free	Preserved
Latanoprost	£8.49	£1.62 (generic)
Lumigan 0.03%	£14.36	£9.79 (lumigan 0.01%) generic £11.71 Branded
Ganfort	£17.94	£4.80
Cosopt	£28.00	£8.30

Convenience and waste



BMJ 2013;346-351

Glaucoma

Anthony King,¹ Augusto Azuara-Blanco,² Anja Tuulonen³

- In cases of intolerance to preservatives (e.g. chronic discomfort and redness), one can consider PF drops



European Glaucoma Society
Innovation, Education, Communication, Implementation

5th Edition

TERMINOLOGY and GUIDELINES for GLAUCOMA

The European Medicines Agency (EMA) has suggested that the use of preservatives should be avoided in “patients who do not tolerate eye drops with preservatives” and in those on long-term treatment, or to use “concentration at the minimum level consistent with satisfactory antimicrobial function in each individual preparation”, with a specific indication to avoid mercury containing preparations⁹².

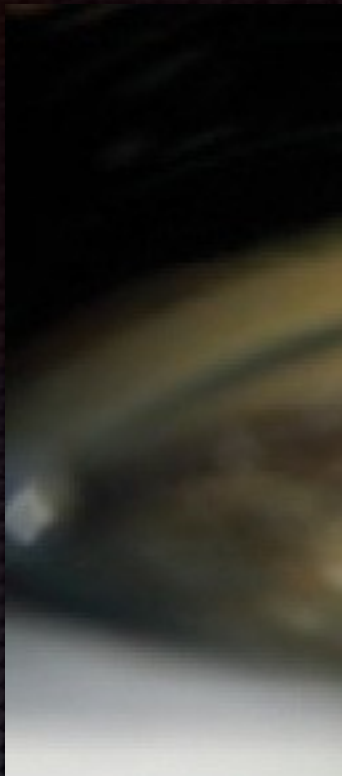
Not all patients are sensitive to preservatives and not all the local side effects observed with topical antiglaucoma medications are induced by preservatives.

Particular attention should be paid to glaucoma patients with pre-existing OSD or to those developing dry eye or ocular irritation over time. This can be done by careful assessment of redness of the eyelid margin, positive corneal and conjunctival fluorescein staining or reduced tear break-up time [I,D].

**Resource impact report:
Glaucoma: diagnosis and management -
partial update (NG81)**

Published: January 2022

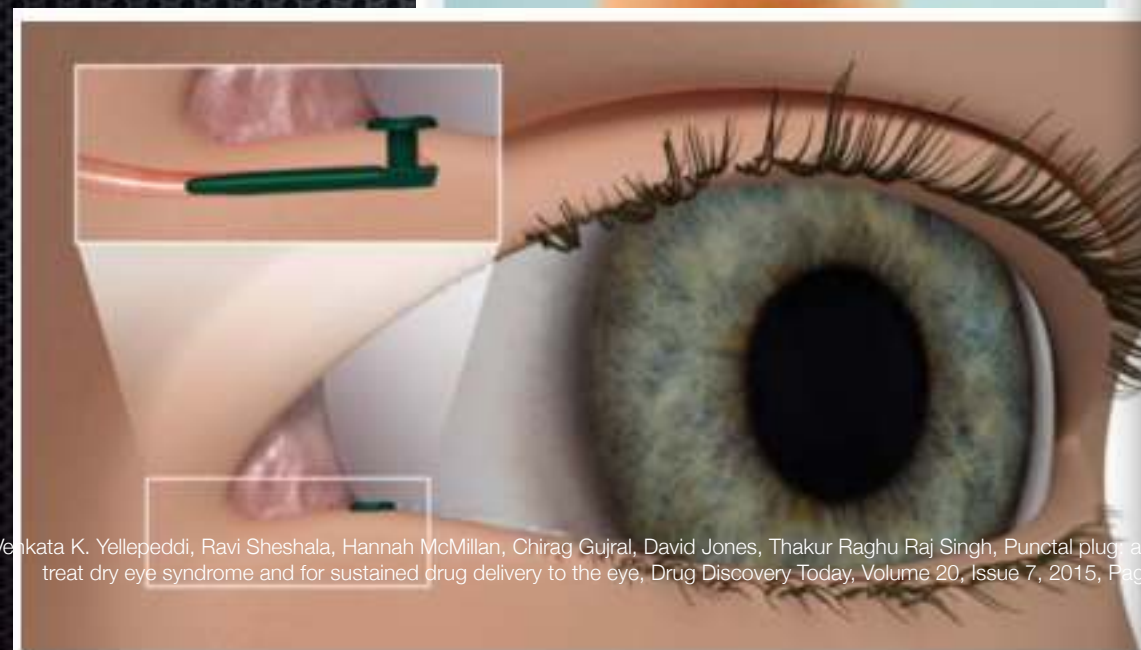
- Offer PF eye drops if there is an evidence of **preservative allergy** or **clinically significant and symptomatic OSD**



Glaukos Corporation's iDose™ Travoprost Achieves Sustained IOP Reduction and Favorable Safety Profile in 12-Month Interim Cohort [press release]. San Clemente, Ca. Glaukos. 1.10.2018.



kuta, Y., Aoyagi, S., Tanaka, Y. *et al.* Creation of nano eye-drops and effective drug delivery to the interior of the eye. *Sci Rep* **7**, 44229 (2017). <https://doi.org/10.1038/srep44229>



Venkata K. Yellepeddi, Ravi Sheshala, Hannah McMillan, Chirag Gujral, David Jones, Thakur Raghu Raj Singh, Punctal plug: a novel device to treat dry eye syndrome and for sustained drug delivery to the eye, *Drug Discovery Today*, Volume 20, Issue 7, 2015, Page 449,

Take-home messages

- Have an individualized approach to each patient
- The less chemicals the better
- In an ideal world you should offer everybody PF (if money was no object!)

Preservatives in glaucoma medication

David W Steven,¹ Pouya Alaghband,² Kin Sheng Lim³

BMJ Journals

British Journal of
Ophthalmology

- Steven DW, Alaghband P, Lim KS
- *British Journal of Ophthalmology* 2018;**102**:1497-1503.

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