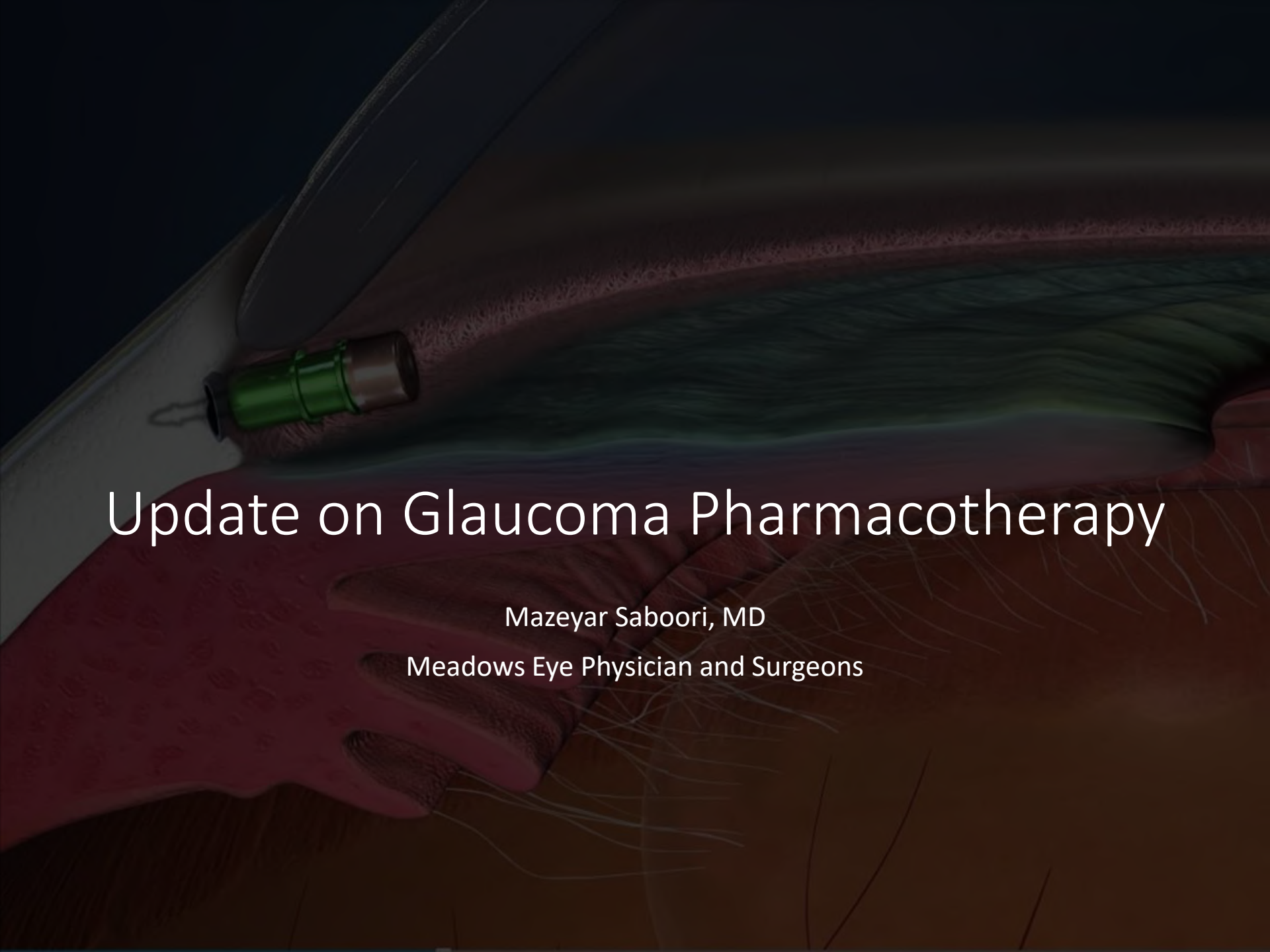


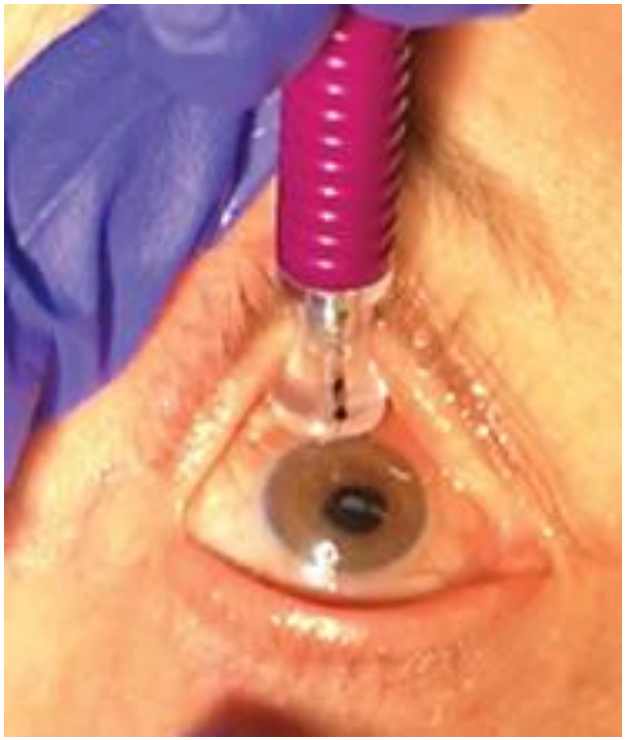
Update on Glaucoma Pharmacotherapy

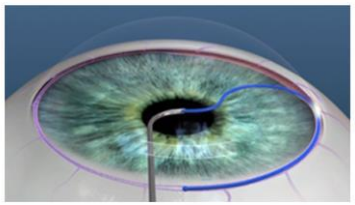
Mazeyar Saboori, MD

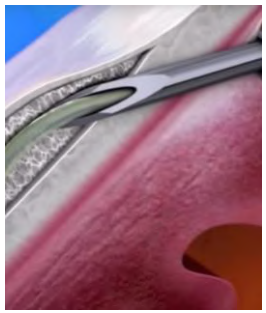
Meadows Eye Physician and Surgeons

Financial Disclosures

- Aerie Pharmaceuticals (faculty)
- Ivantis (consultant)





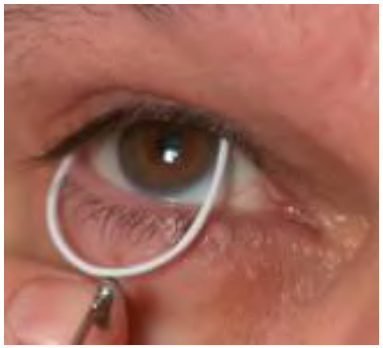


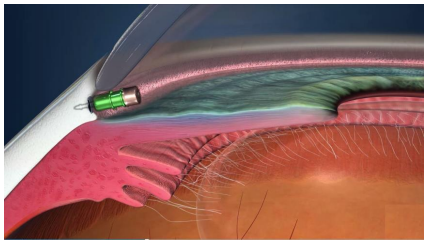
Glaucoma Treatment Options

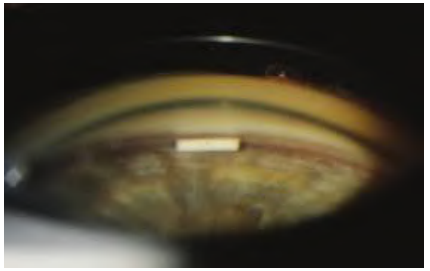
- Cataract surgery
- Hydrus Stent
- iStent
- Kahook Dual Blade
- GATT
- Omni
- XEN gel stent
- Micropulse CPC
- SLT
- Tubes and Trabs

Agenda

- Introduction and background
- Topical IOP lowering medications
- Novel drugs and drug delivery

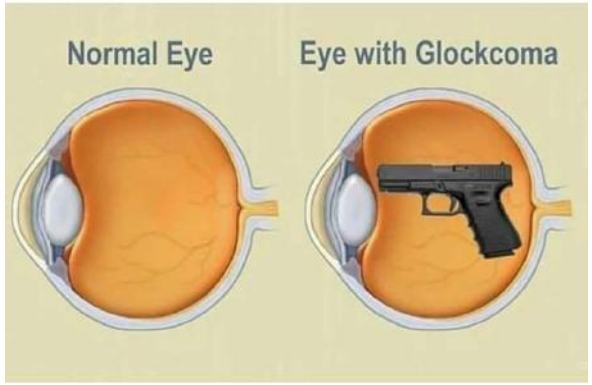






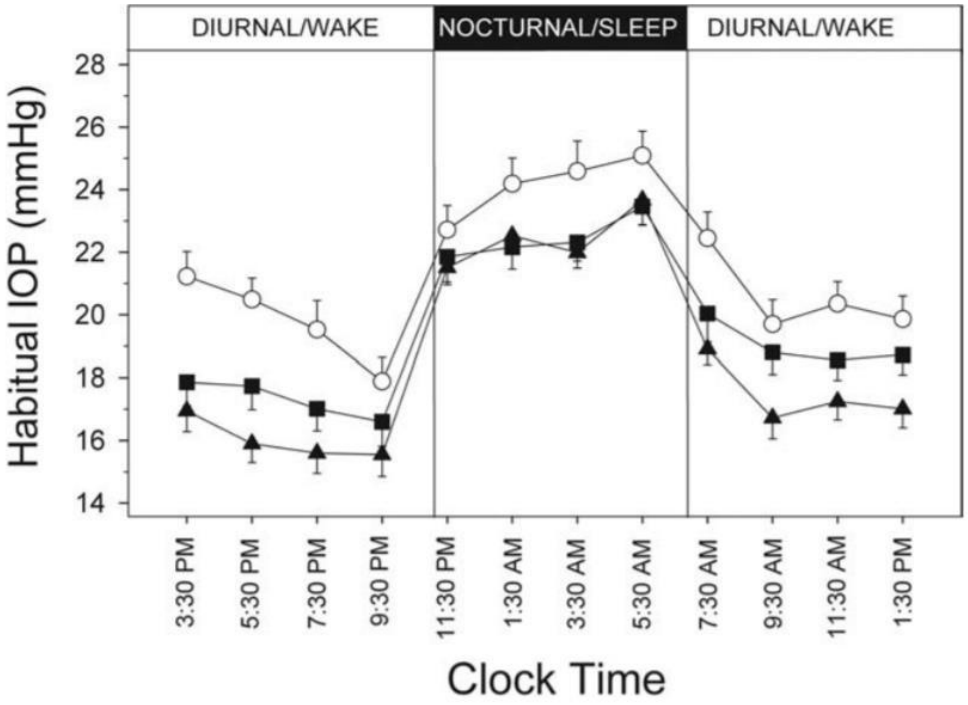
GLAUCOMA

- Global prevalence 3.4%
  - 2.31% in Asia
  - 3.65% Latin America and Caribbean
  - 4.20% in Africa
- Most common cause of irreversible blindness worldwide
- Mainstay of treatment remains IOP lowering
  - Medications
  - Laser
  - Surgery



Diurnal Variation in IOP

- 2-6 mmHg in healthy patients
- 10+ mmHg in glaucoma patients
- 50% decrease in aqueous production during sleep
- Decrease in Uveoscleral outflow at night
- Medications with longer half-lives reduce fluctuations



Goldmann Equation

- IOP = (F/C) + EVP
  - F = aqueous production
  - C = outflow facility
    - Includes both conventional and uveoscleral outflow
  - EVP = episcleral venous pressure

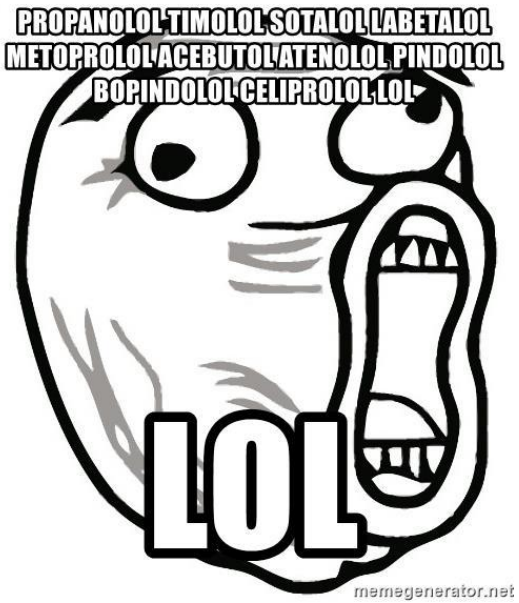
- Lowering of IOP must manipulate F, C, or EVP.

Aqueous Suppressants

- Beta adrenergic antagonists
- Alpha adrenergic agonists
- Carbonic anhydrase inhibitors

Aqueous Suppressants

- Beta adrenergic antagonists
- Alpha adrenergic agonists
- Carbonic anhydrase inhibitors



Beta adrenergic antagonists

- Decrease aqueous production 20-50%
- IOP reduction 20-30%
- Ineffective in lowering IOP during sleep
  - QAM dosing
- Local side effects are mild
  - May exacerbate dry eye
- Systemic side effects are significant
  - Bronchospasm
  - Bradycardia, heart block
  - Hypotension
  - Fatigue, CNS depression
  - Decreased exercise tolerance
  - Decreased HDL
  - Diabetics – decreased glucose tolerance and inability to sense hypoglycemia

Beta Blockers – available formulations

- Timolol
  - 0.5%, 0.25%, PF and gel varieties
- Betaxolol
  - 0.5%, 0.25%
  - $ß_1$ selective, fewer pulmonary side effects
- Carteolol
  - Nonselective beta blocker
  - Intrinsic sympathomimetic activity
- Cosopt (dorzolamide-timolol)
- Combigan (brimonidine-timolol)

Aqueous suppressants

- Beta adrenergic antagonists
- Alpha adrenergic agonists
- Carbonic anhydrase inhibitors

Alpha adrenergic agonists

- Nonselective - epinephrine, dipivefrin
  - No longer used
- α_2 selective
  - Don’t work well during sleep
  - Only glaucoma medication that is pregnancy class B
  - High rate of local side effects, follicular reaction and contact dermatitis
    - Apraclonidine – 40%
    - Brimonidine 0.2% - 15%
    - Brimonidine-purite 0.15% - 10%
  - Systemic side effects
    - Somnolence (elderly, babies)
    - Dry mouth

Alpha adrenergic agonists in children

- Apraclonidine
  - Safe in small children
  - Does not cross blood-brain-barrier

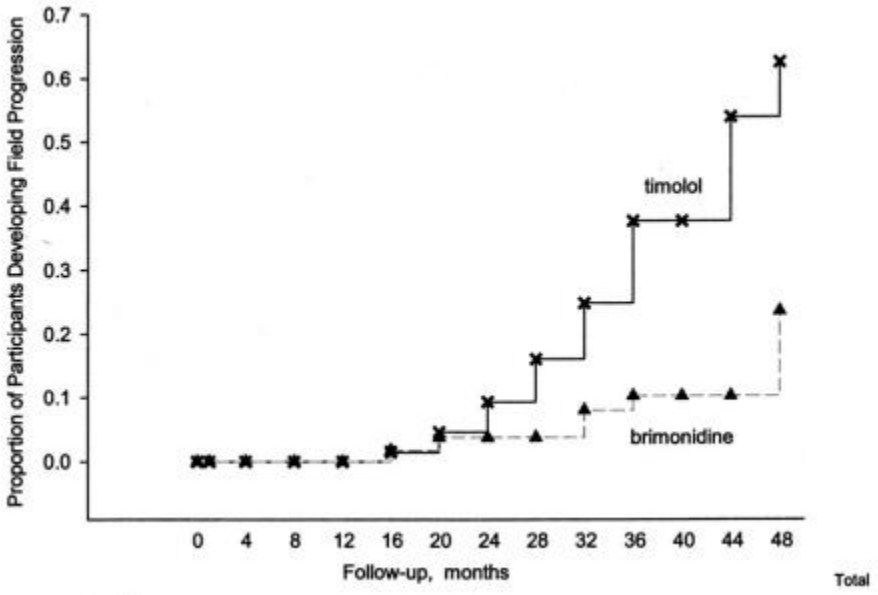
- Brimonidine
  - ABSOLUTELY CONTRAINDICATED IN NEONATES AND SMALL CHILDREN.
  - Causes CNS and respiratory depression, death

Formulations available

- Apraclonidine - 0.5%, 1.0%
- Brimonidine
  - BAK 0.2%
  - Purite 0.15%
  - Purite 0.1%
- Combinations
  - Combigan (brimonidine-timolol)
  - Simbrinza (brimonidine-brinzolamide)

A Randomized Trial of Brimonidine Versus Timolol in Preserving Visual Function: Results From the Low-pressure Glaucoma Treatment Study

THEODORE KRUPIN, JEFFREY M. LIEBMANN, DAVID S. GREENFIELD, ROBERT RITCH, AND STUART GARDINER, ON BEHALF OF THE LOW-PRESSURE GLAUCOMA STUDY GROUP



- 176 patients with NTG (untreated IOP <21) randomized to brimonidine 0.2% BID vs timolol 0.5% BID
- Mean follow up 30 months
- Mean treated IOP similar between groups
- 20% dropout – brim allergy
- Statistically significant different in VF progression at 36m
  - 9.1% in brimonidine group
  - 39.2% in timolol group

AQUEOUS SUPPRESSANTS

- Beta adrenergic antagonists
- Alpha adrenergic agonists
- Carbonic anhydrase inhibitors

Carbonic Anhydrase Inhibitors

- Lower IOP 15-20%
- Conflicting evidence of IOP lowering and aqueous suppression during sleep
  - May be better achieved with TID dosing, higher steady state
- Local side effects
  - Endothelial dysfunction – caution in Fuchs or PBK patients
  - Stinging (worse with dorzolamide compared with brinzolamide)
  - Allergy
- Systemic side effects
  - Bitter taste

Available formulas

- Dorzolamide 2% (Trusopt)
- Brinzolamide 1% (Azopt)
- Simbrinza – brinzolamide-brimonidine
  - Dosage – BID or TID

- Cosopt – dorzolamide-timolol
  - Dosage – BID

Systemic Carbonic Anhydrase Inhibitors

- Acetazolamide (Diamox) 250mg QID, 500mg ER BID
  - Can also be given IV
  - Renal clearance
- Methazolamide (Neptazane) 20-50mg, BID-TID
  - Hepatic clearance, usually better tolerated

Systemic Carbonic Anhydrase Inhibitors

- Bitter or metallic taste, especially carbonated beverages
- Paresthesias
- Lethargy, confusion
- Weight loss
- Hypokalemia (especially if other diuretics are being taken)
- Metabolic acidosis, can lead to compensatory respiratory alkalosis
- Aplastic anemia

Cholinergic Agonists

- Act by muscarinic agonism – contracting the longitudinal ciliary muscle to open the trabecular meshwork
- Increases conventional outflow
- Also affects circular ciliary muscle and pupillary sphincter – accommodation and miosis

Cholinergic Agonists

- Local side effects
  - Miosis
  - Induced myopia – accommodation
  - Risk of retinal detachment, especially myopes
  - Angle closure
    - Lens iris diaphragm shifts anteriorly
- Systemic side effects
  - Cramps, diarrhea
  - Bronchospasm
- Contraindications
  - Extreme high IOP
    - Iris sphincter ischemia reduces effectiveness
  - High myopia
  - Intraocular inflammation
    - Posterior synechia

Cholinergic Agonists

- Indications
  - Peri-operativey for laser iridotomy
  - Plateau iris syndrome
  - Post-operatively for adult goniotomy procedures
  - Occasionally for OAG

Available formulations

- Pilocarpine 1%, 2%, 4%
  - Dosed QID
- Echothiophate iodide 0.125%
  - Dosed BID – very rarely used and often unavailable
  - Can cause cataract in adults, iris cysts in children
  - Can cause prolonged paralysis after administration of succinylcholine

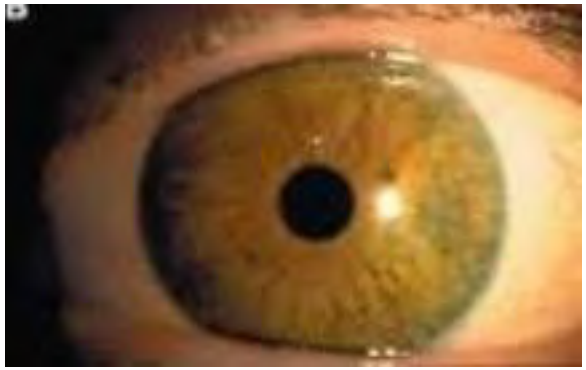
Prostaglandin Analogs

- Most effective of any topical drug class
- First line treatment
- Increase uveoscleral outflow
- Decrease IOP by ~30%
- PGF2α analogs
  - Specifically activate FP receptors
  - Avoids many inflammatory consequences of endogenous PGF2α
  - Improves uveoscleral outflow by altering the extracellular matrix
- Bimatoprost – “Prostamide”

Prostaglandin Analogs

- Local side effects
  - Darkening of iris (rare to affect blue or brown eyes)
  - Periocular skin pigmentation
  - Hypertrichosis
  - Prostaglandin associated periorbitopathy (PAP)
    - Tightening of lids, orbital fat atrophy – reversible
  - Caution in patient with history of HSV keratitis
- Systemic side effects – very rare


A



PGAs and macular edema

Putative Side Effects of Prostaglandin Analogs

Robert A. Schumer, MD, PhD,[1] Carl B. Camras, MD,[2] and Agneta K. Mandahl, MD, PhD[3]

[1]Department of Ophthalmology, Mt. Sinai School of Medicine, New York, New York; [2]Department of Ophthalmology, University of Nebraska Medical Center, Omaha, Nebraska, USA; and [3]Pharmacia Corporation, Stockholm, Sweden

- Review of all published case reports and series of CME associated with PGA's
- 1/131 eyes did not have other risk factors for altered BRB

Effect of prostaglandin analogue use on the development of cystoid macular edema after phacoemulsification using STROBE statement methodology

David J. Hernstadt, MB BS, MPH, Rahat Husain, MB BS, MRCOphth, MD(Res)

- 13 articles included in the study
  - 86,306 eyes in total
  - 4416 on PGA
  - 97 developed CME
- PGA use was not associated with the development of CME at any time point after cataract surgery.
- Possible increased risk if isolated complex surgeries isolated

Association of Postoperative Topical Prostaglandin Analog or Beta-Blocker Use and Incidence of Pseudophakic Cystoid Macular Edema

Colten Wendel, MD, Helena Zakrzewski, MD, MSc,† Bruce Carleton, BSc, PharmD,‡§‖ Mahyar Etminan, MSc, PharmD,* and Frederick S. Mikelberg, MD, FRCSC**

- All adult cataract patients from 2006 – 2016 enrolled in PharMetrics Plus database – diabetics excluded.
  - 508 cases (CME diagnosis)
    - Did not distinguish between routine and complex phacos
  - 5080 controls (age, sex, follow up, surgery matched)
    - Controls did not necessarily have glaucoma

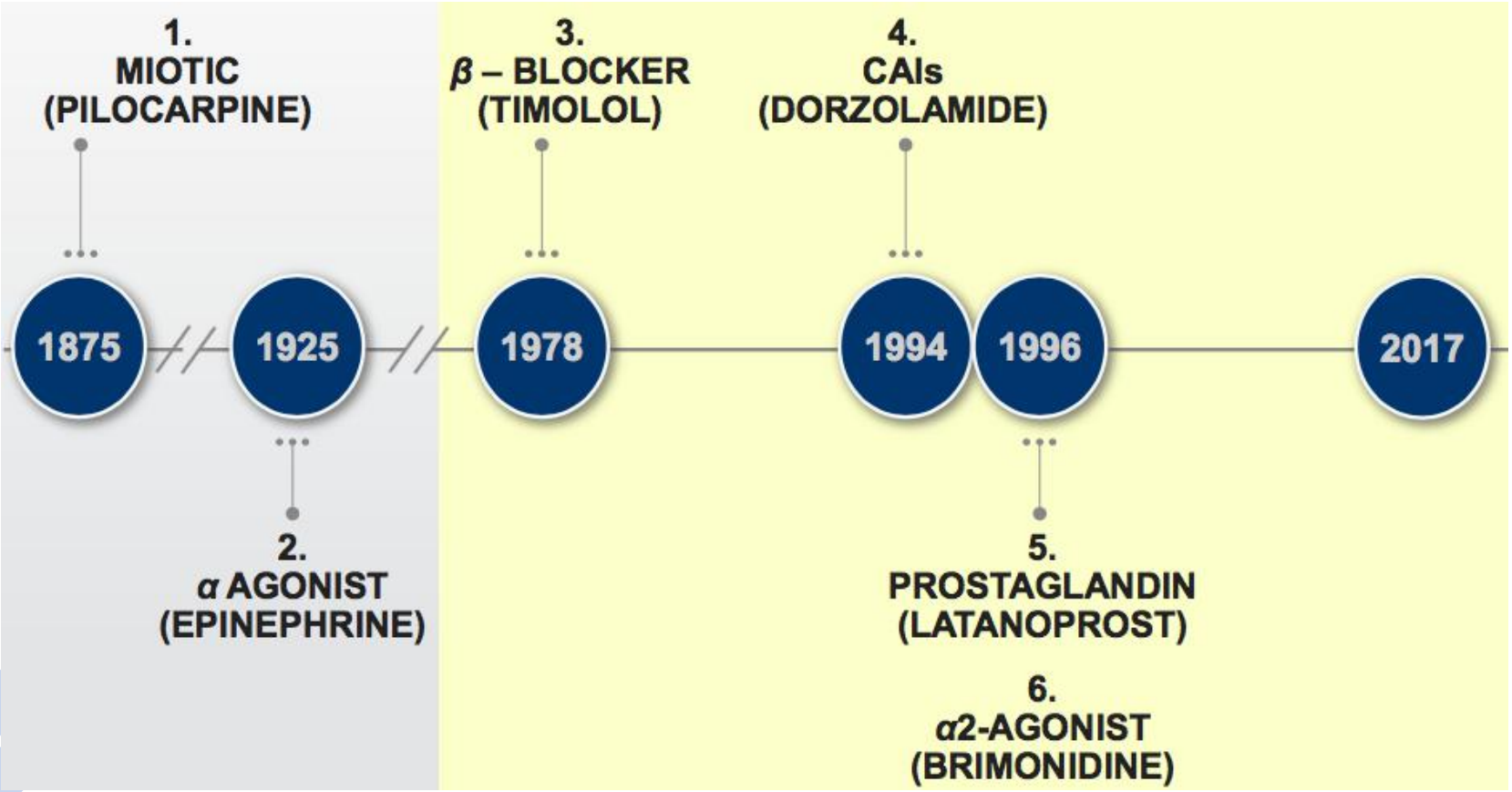
TABLE 1. Current Postoperative Use of Prostaglandin Analogs or Beta-blockers and Incidence of Pseudophakic Cystoid Macular Edema

	Cases (n = 508) [N (%)]	Controls (n = 5080) [N (%)]	RR	95% CI
No current beta-blocker use	489 (96.3)	4999 (98.4)	1.00	Ref.
Current beta-blocker use	6 (1.18)	23 (0.45)	2.64*	1.08-6.49
No current prostaglandin analog use	470 (92.5)	4881 (96.1)	1.00	Ref.
Current prostaglandin analog use	14 (2.76)	79 (1.56)	1.86*	1.04-3.32
No current ranitidine use	501 (98.6)	5030 (99.0)	1.00	Ref.
Current ranitidine use	3 (0.59)	19 (0.37)	1.58	0.47-5.35

Available formulations

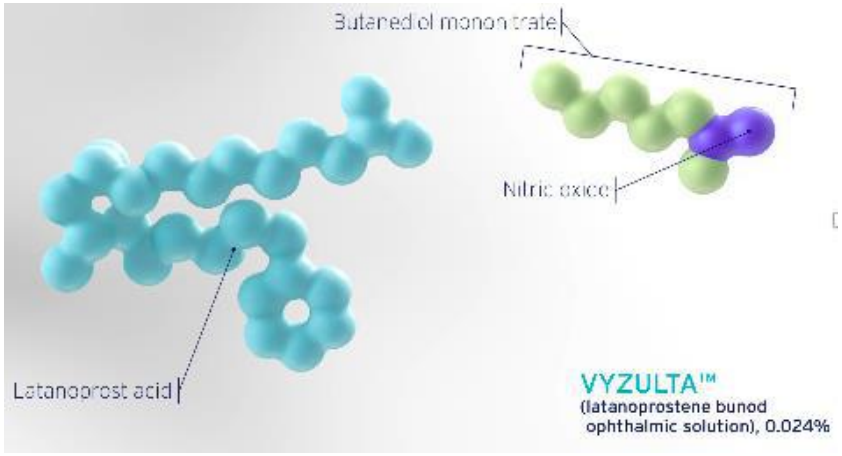
- Latanoprost 0.005% (Xalatan, Xelpros)
- Travoprost 0.004% (Travatan, Travatan-Z)
- Bimatoprost 0.01% (Lumigan)
- Tafluprost 0.0015% (Zioptan)
- Latanoprostene Bunod 0.024% (Vyzulta) Approved Dec 2017
  - Nitric oxide donating moiety theoretically (but as yet unproven) acts to increase conventional outflow.
  - Contains higher concentration of latanoprost
- Dosage
  - QHS

Timeline of Approved Meds



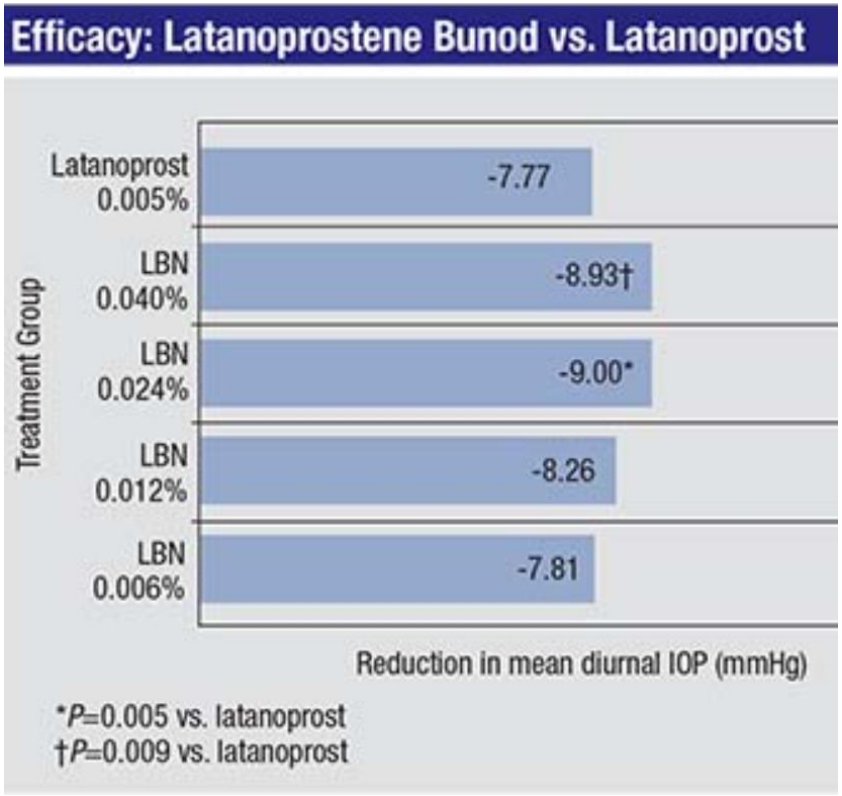
Latanoprostene Bunod

- Dual mechanism of action
  - Latanoprost acid: prostaglandin F2-alpha analogue
    - Increases uveoscleral outflow
  - Butanediol mono-nitrate: breaks down into nitric oxide (NO)
    - NO relaxes cells within the trabecular meshwork
    - Increases outflow through trabecular meshwork and schlemm's canal
    - Mediator in smooth muscle relaxation



VOYAGER Study – Phase 2b Trial

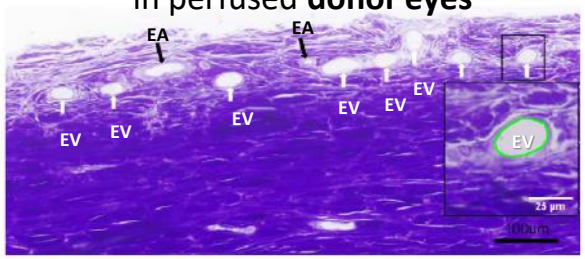
- 413 patients randomized to Latanoprost vs Latanoprostene bunod at varying concentrations
- Dose dependent response with plateau of effect at concentration >0.024%
- Mean reduction in IOP at day 28
  - -9.00 mmHg (34.5%) for latanoprostene bunod 0.024%
  - -7.77 mmHg (29.7%) latanoprost 0.05%
- Adverse reactions
  - 24.1% in LBN 0.024% vs 12.2% in latanoprost
    - Most common: conjunctival hyperemia, pain with instillation

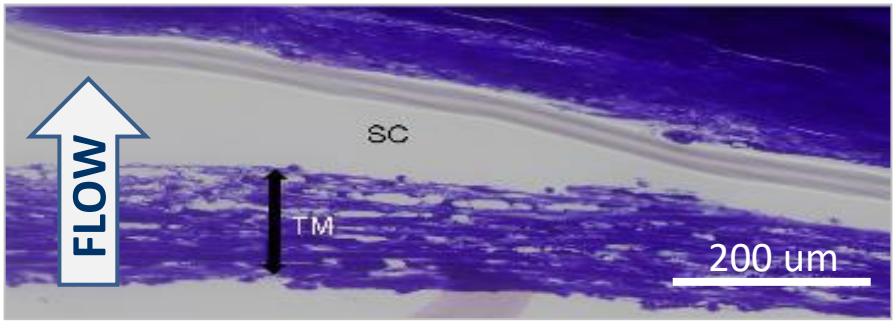


Rho Kinase Inhibitors

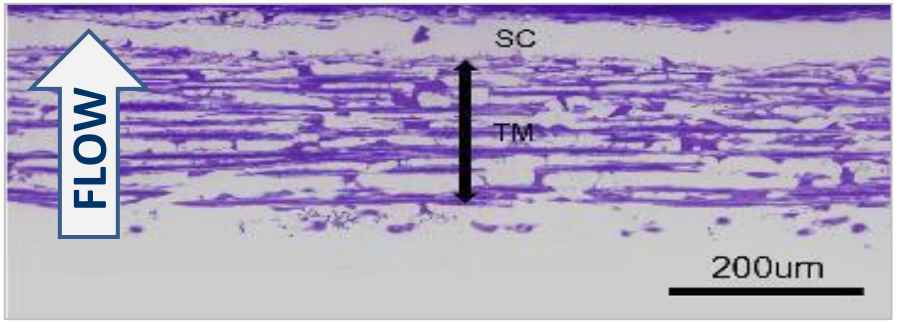
- Rho kinase (ROCK) – increases cell contraction, extracellular matrix production → increased outflow resistance in the conventional outflow pathway
- Netarsudil 0.02% (Rhopressa) – Approved Dec 2017
  - Increases conventional outflow
    - Relaxes TM
    - Lowers EVP (10% decarease)

A **67%** increase in episcleral vein cross-sectional area in perfused **donor eyes**[1]





Control (buffered saline solution)



+ Netarsudil-M1

Netarsudil as Adjunctive Therapy: Similar Efficacy Regardless of Number of Medications Used

Prospective Real World M.O.S.T. Study

Adjunctive Therapy Treatment Group	Baseline	Week 12
Rhopressa + PGA (n=55)		
Mean IOP (mmHg)	21.1	**16.9**
Δ from BL (mmHg)	--	**-4.3 (-20.2%)**
Rhopressa + ≥2 Meds (n=64)		
Mean IOP (mmHg)	20.6	**16.2**
Δ from BL (mmHg)	--	**-4.5 (-20.9%)**

mITT Population. Note: Excludes patients where a prior medication was switched out for Rhopressa

- **Netarsudil MOA defies "law of diminishing returns" common to multi-drug therapy**
- **Netarsudil highly effective at lower baseline IOPs**

Shiuey EJ, et al. Graefes Arch Clin Exp Ophthalmol. 2021 Sep 22. Epub ahead of print.

Netarsudil Highly Effective in Steroid-Induced Glaucoma Patients

- Retrospective chart review at 2 clinical sites
- 27 patients total (32 eyes) on chronic steroid treatment
- **Most patients uncontrolled on 2 – 3 glaucoma medications prior to adding Rhopressa**

Cohort (n)	Mean # Prior Meds	Mean IOP on Prior Meds (mmHg)	Mean IOP post- Rhopressa (mmHg)	Mean ΔIOP (mmHg)
1 (19)	2.7	24.3	**16.4**	**-7.9**
2 (8)	2.4	26.5	**19.5**	**-7.0**

Large IOP Reductions Consistent with Targeting TM Dysfunction

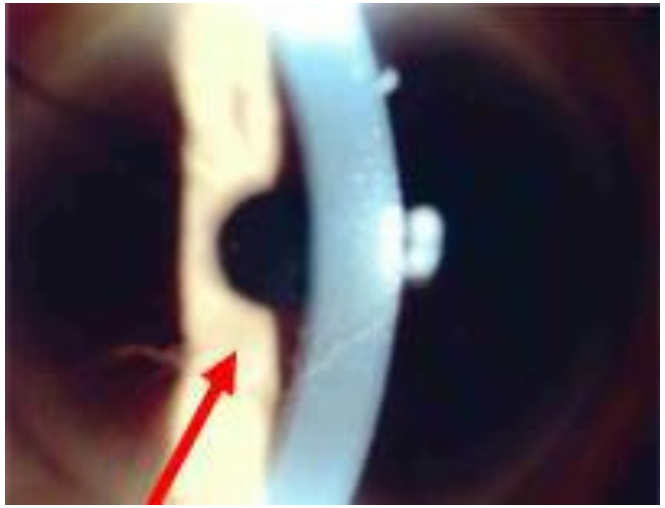
Adverse Events

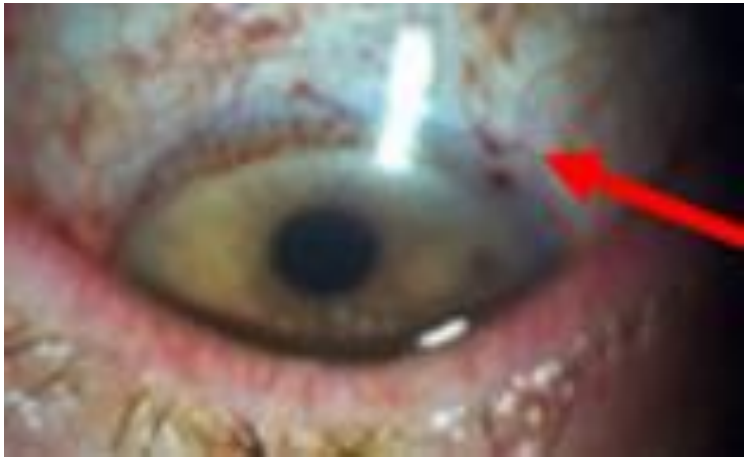
- Most frequent ocular AE was conjunctival hyperemia, most instances of which were mild
  - Led to discontinuation in 6.0% (50/839) of netarsudil-treated patients

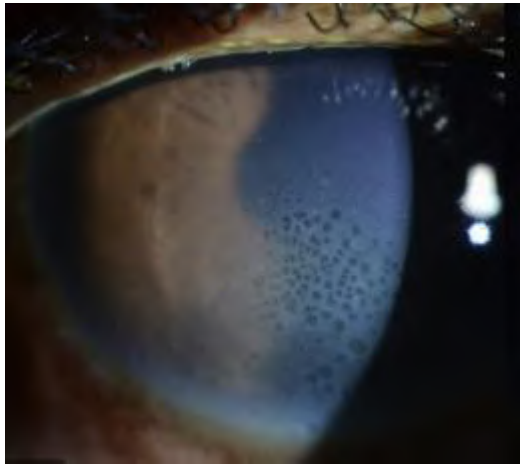
	Once-daily netarsudil 0.02% (n=839)	Twice-daily timolol 0.5% (n=839)
Eye disorders, n (%)		
Conjunctival hyperemia	456 (54.4)	87 (10.4)
Cornea verticillata	175 (20.9)	2 (0.2)
Conjunctival hemorrhage	144 (17.2)	15 (1.8)
Vision blurred	62 (7.4)	12 (1.4)
Lacrimation increased	60 (7.2)	5 (0.6)
Erythema of eyelid	57 (6.8)	6 (0.7)
Visual acuity reduced	44 (5.2)	13 (1.5)
Administration site conditions, n (%)		
Instillation site pain	167 (19.9)	181 (21.6)
Instillation site erythema	76 (9.1)	13 (1.5)
Investigations, n (%)		
Vital dye staining cornea present	79 (9.4)	64 (7.6)

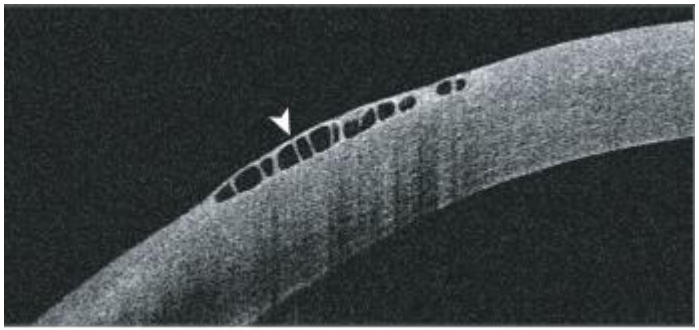
Patients with known contraindications or hypersensitivity to timolol were excluded from Phase 3 studies.

Adverse reactions to Netarsudil









Key Points

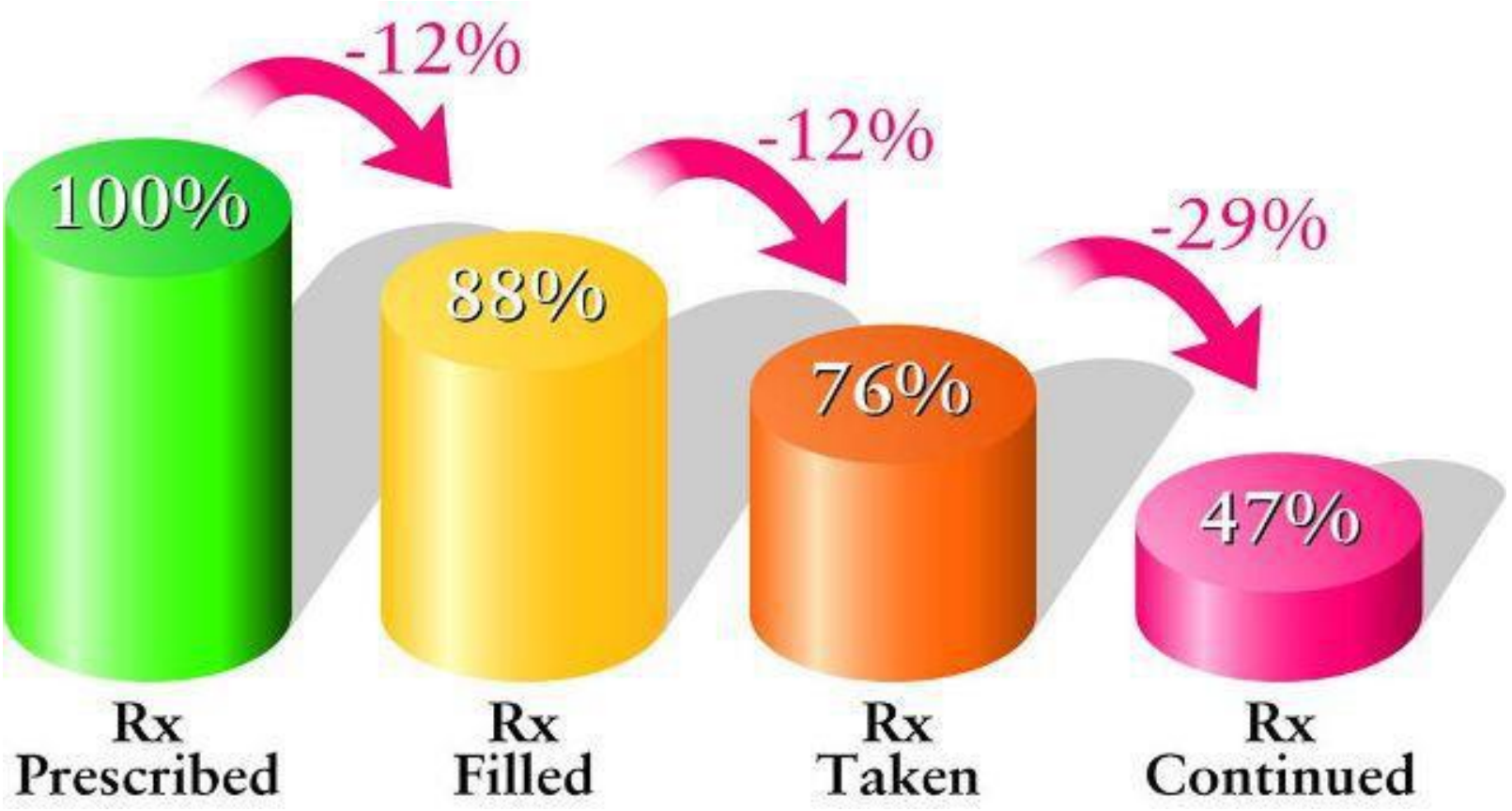
- Preventing disease progression with fewest medications and lowest concentration needed to achieve target IOP (keeping in mind quality of life)
- Change of therapy with a uniocular trial can be helpful to assess efficacy and side effects
- Patient-centered education is key
- When medical treatment is ineffective, initially substitute rather than add medications. May consider stopping treatment to assess efficacy
- When glaucoma is not controlled medically, do not hesitate to move on to surgical intervention

Novel Drug Delivery

- Response to downfalls of eye drops
  - Instillation

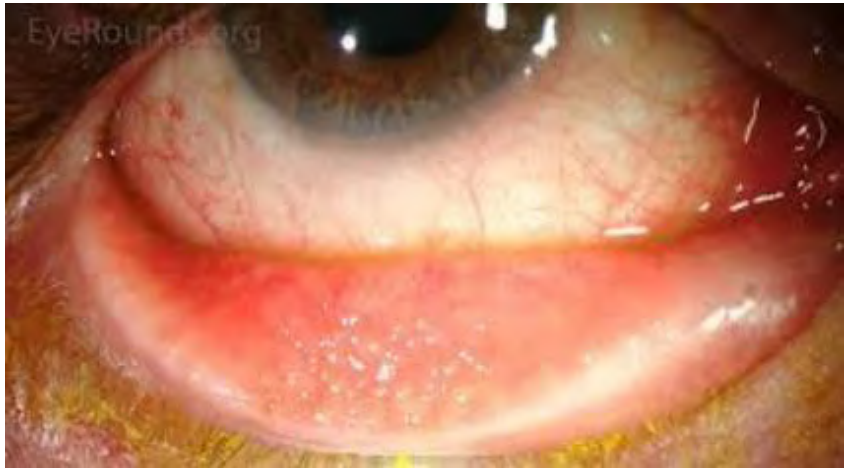
Novel Drug Delivery

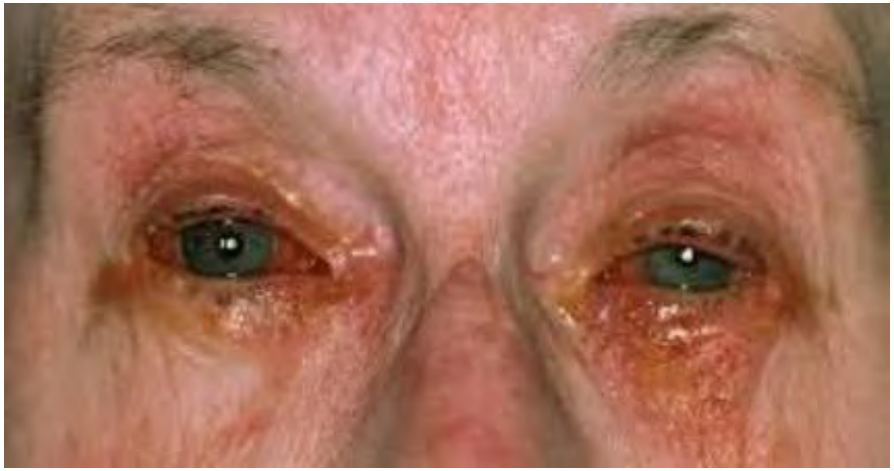
- Response to downfalls of eye drops
  - Instillation
  - Adherence


-12%
-12%
-29%
100%
88%
76%
47%
Rx Prescribed
Rx Filled
Rx Taken
Rx Continued

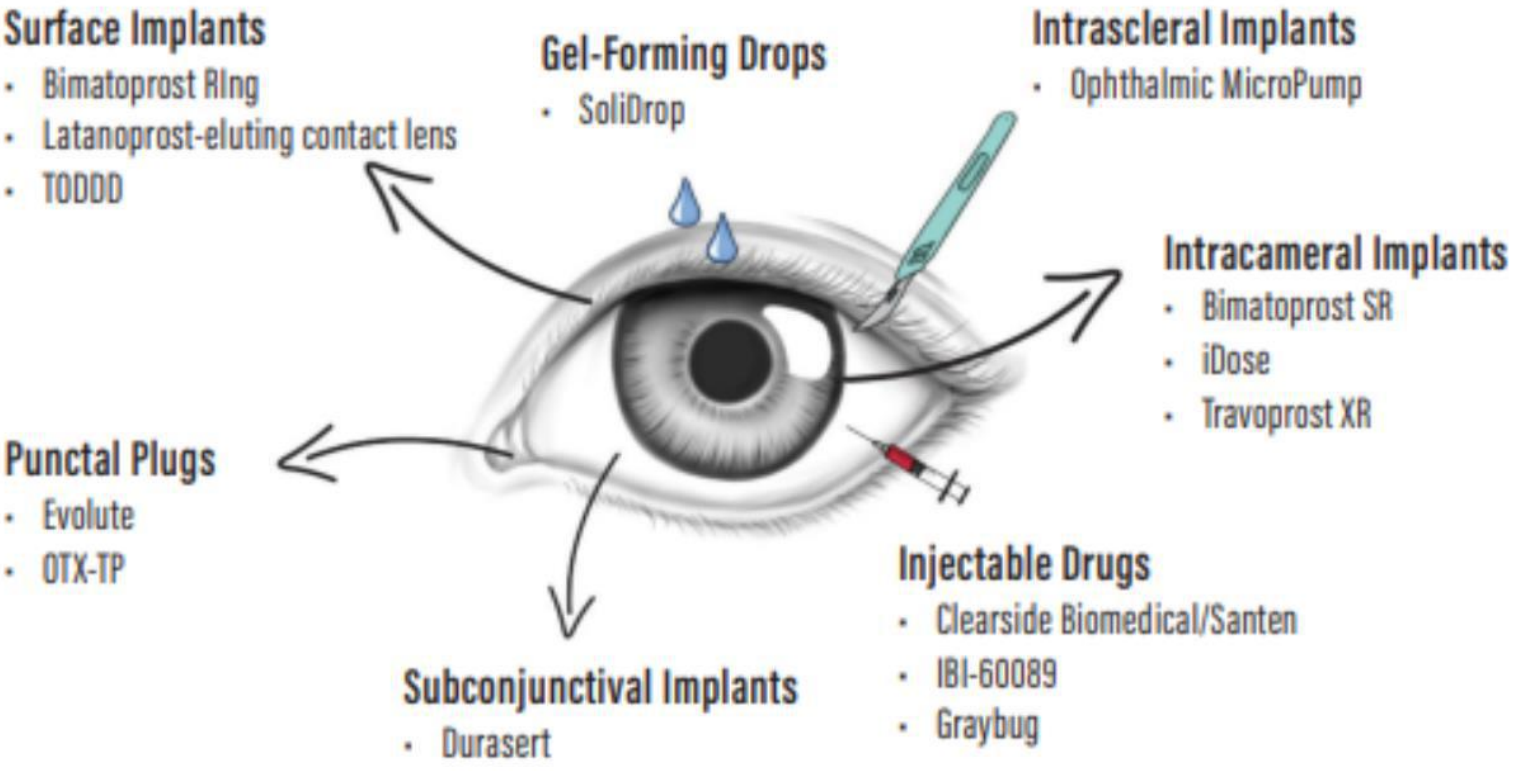
Novel Drug Delivery

- Response to downfalls of eye drops
  - Instillation
  - Adherence
  - Side effects



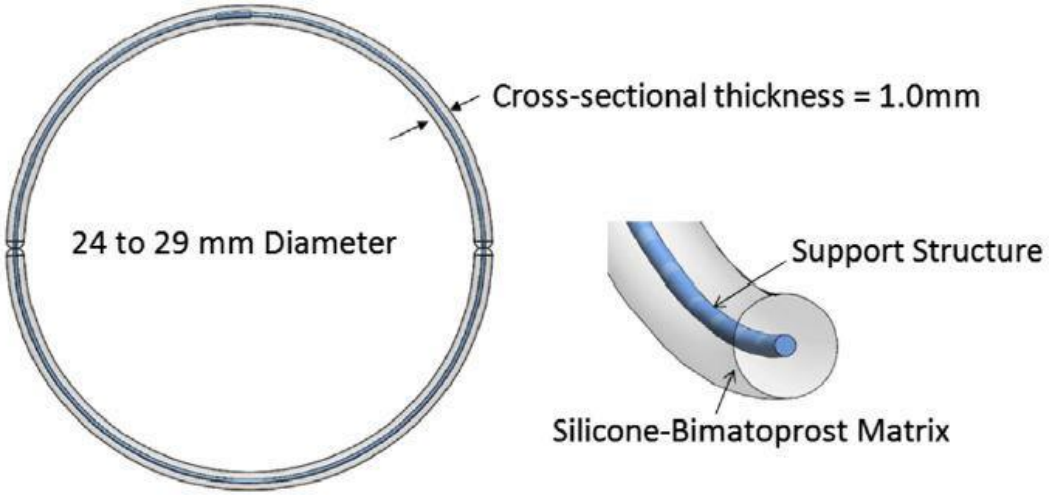


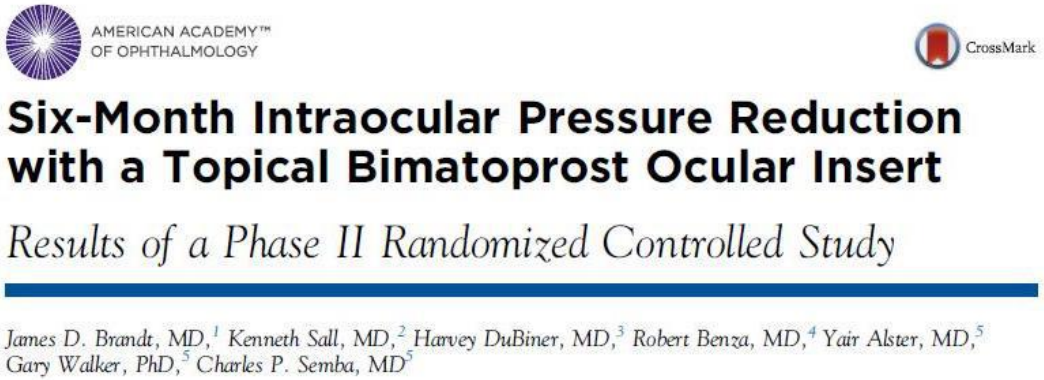
Novel Drug Delivery Systems



Bimatoprost Ring

- Allergan - silicone insert with preservative free bimatoprost





- Bimatoprost ring + AT's BID vs Placebo ring + Timolol 0.5% BID
- 89% retention rate, 94-97% in a follow up study without AT's.
- Hyperemia less than with topical bimatoprost
- Only unique adverse effect was mucoid discharge – 21%

Latanoprost-Eluting Contact Lenses in Glaucomatous Monkeys

Joseph B. Ciolino, MD,[1,2,3] Amy E. Ross, MSc,[1,2,3] Rehka Tulsan, MSc,[1,2,3] Amy C. Watts, OD,[1] Rong-Fang Wang, MD,[4] David Zurakowski, PhD,[3] Janet B. Serle, MD,[4] Daniel S. Kohane, MD, PhD[3]

- Low dose contact lens vs high dose contact lens vs latanoprost solution
- IOP reduction at day 5
  - Latanoprost – 6.6
  - Low dose CL – 6.7
  - High dose CL – 11.1 p=0.015

Latanoprost Eluting Contact Lens

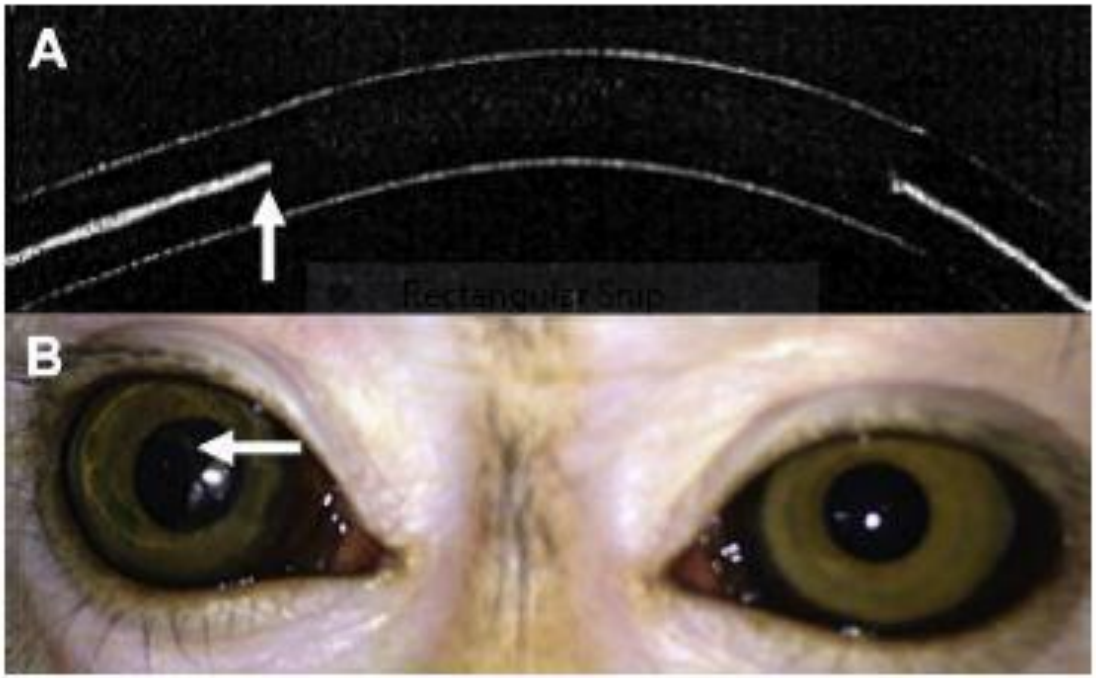
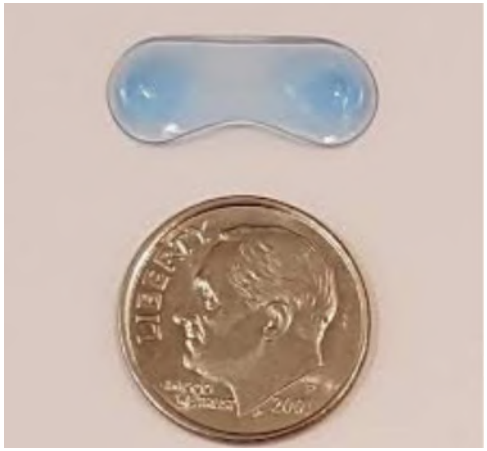


Figure 1. The latanoprost-eluting contact lens. **A**, Representative ocular optical coherence tomography (OCT) image of the cross-section of the contact lens. *Arrow* points to the inner edge of the drug-polymer film within the hydrogel. **B**, Photograph of latanoprost-eluting contact lens on the right monkey eye. The clear central aperture is surrounded by a translucent ring of drug-polymer film. *Arrow* points to the inner margin of the drug polymer film.

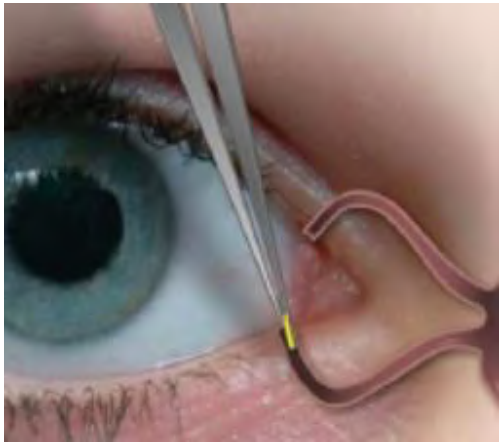
Topical Ophthalmic Drug Delivery Device (TODDD)

- Amorphex Therapeutics
- Soft forniceal implant
- Timolol embedded TODDD sustained therapeutic levels for 180 days



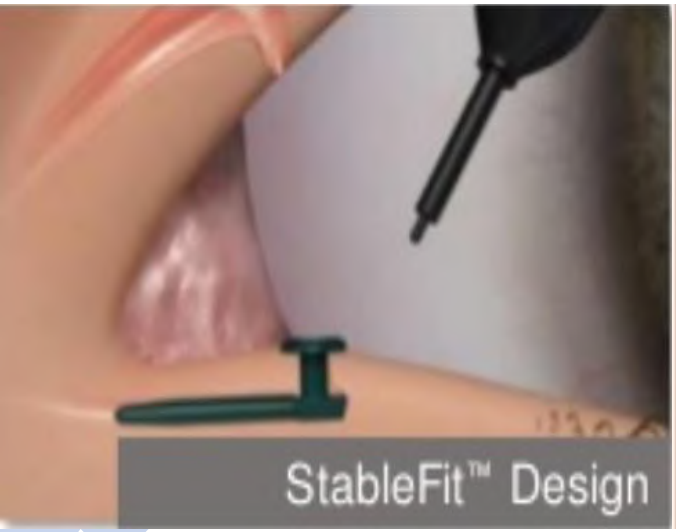
Travoprost Punctal Plug

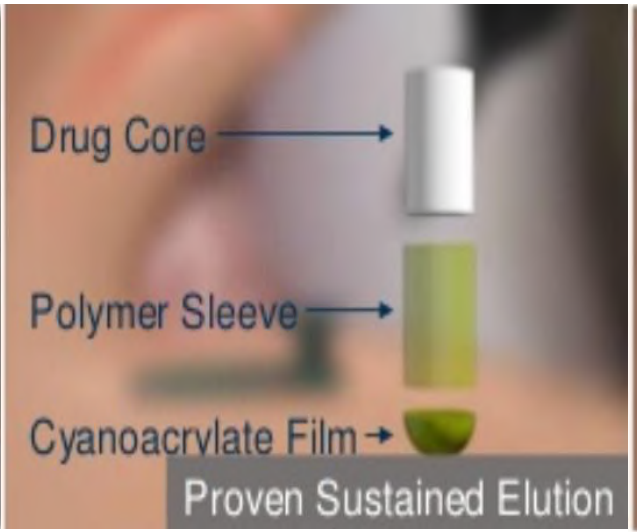
- Ocular Therapeutix (OTX-TP)
- Absorbable hydrogel punctal plug containing travoprost
- 90 day duration
- Same platform as Dextenza – FDA approved 12/2018



Evolute Punctal Plug

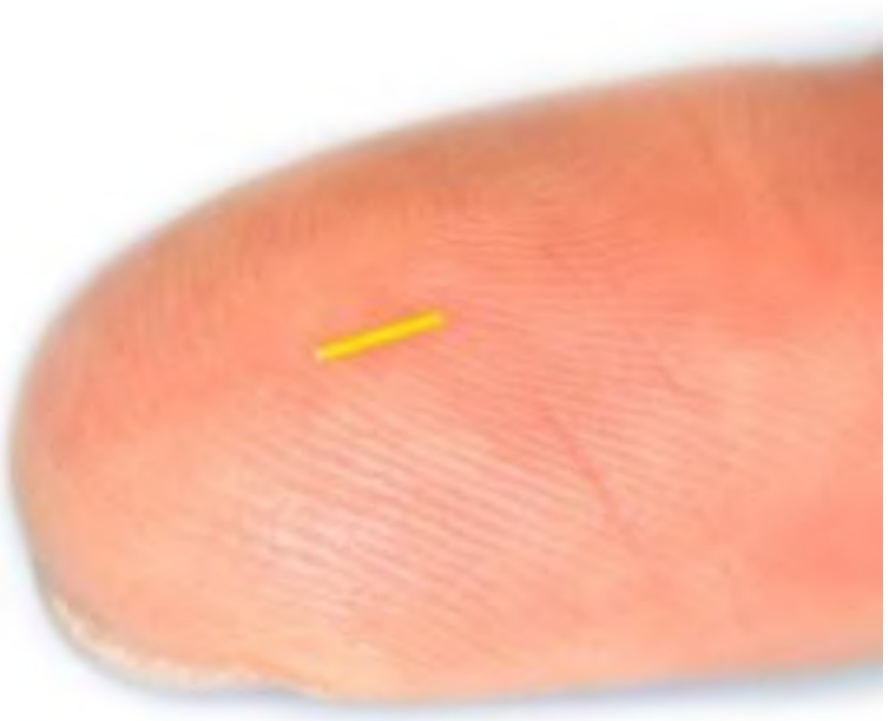
- Mati Therapeutics
- Can be embedded with multiple
- 92%-96% retention at 3 months





Subconjunctival Implants

- Durasert - EyePoint Pharmaceuticals
- 3mm x 0.3 mm transparent biodegradable implant, can be placed at the slit lamp
- Same platform as Iluvien
- Releases latanoprost over 12 months
- Currently in phase 1 and 2 trials



Intracameral Implants

- Bimatoprost SR
- Travoprost SR
- iDose

Bimatoprost SR

- Durysta - Allergan
- Biodegradable implant, 27g needle
- Novadur solid polymer drug delivery system - same technology as Ozurdex

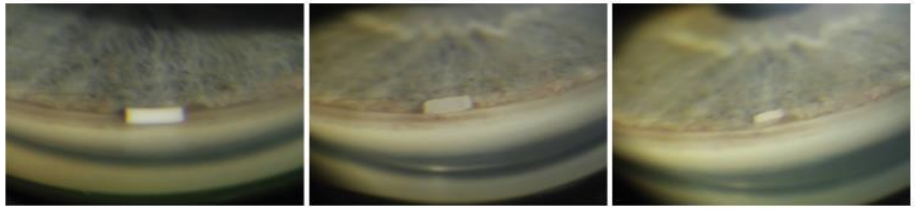


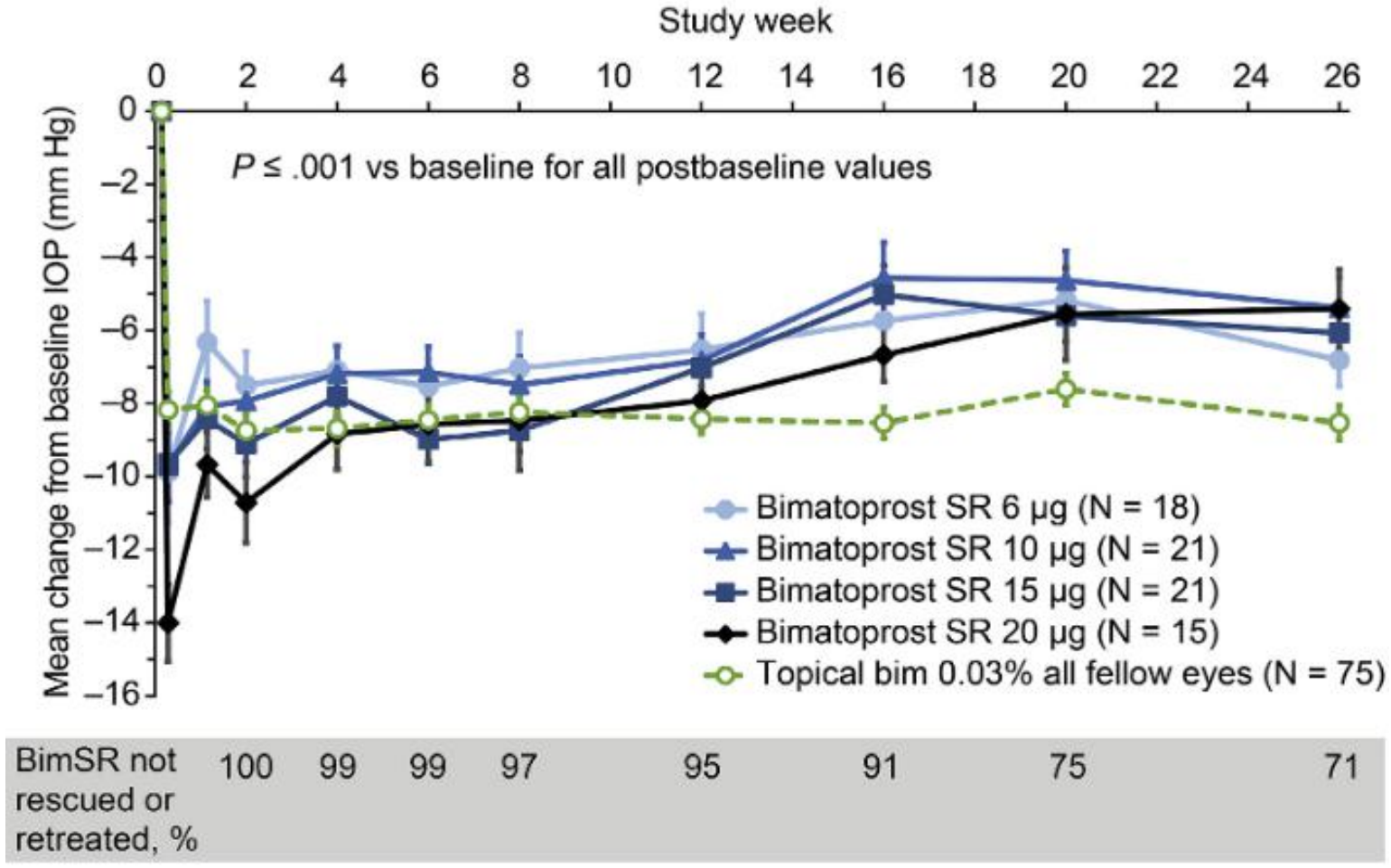
FIGURE 3. Gonioscopic photographs of bimatoprost sustained-release implant 10 µg in the anterior chamber of an eye of a representative patient diagnosed with open-angle glaucoma at (Left) 2 weeks, (Center) 9 months, and (Right) 12 months after injection.

Bimatoprost Sustained-Release Implants for Glaucoma Therapy: 6-Month Results From a Phase I/II Clinical Trial

RICHARD A. LEWIS, WILLIAM C. CHRISTIE, DOUGLAS G. DAY, E. RANDY CRAVEN, THOMAS WALTERS, MARINA BEJANIAN, SUSAN S. LEE, MARGOT L. GOODKIN, JANE ZHANG, SCOTT M. WHITCUP, AND MICHAEL R. ROBINSON, FOR THE BIMATOPROST SR STUDY GROUP

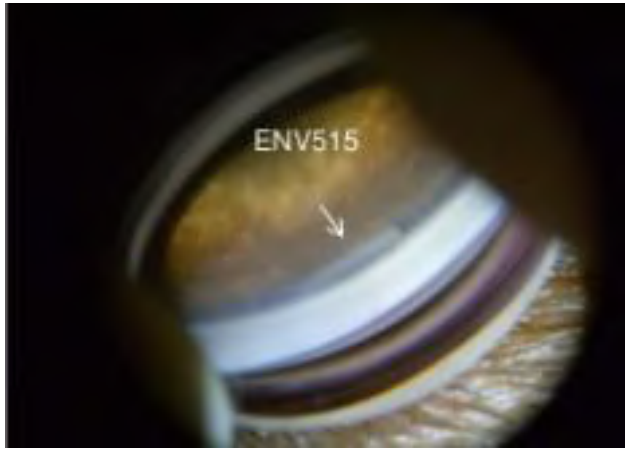
- 75 patients received Bimatoprost SR in study eye, bimatoprost 0.03% topical in fellow eye
- 71% of patients did not require rescue or retreatment at 6 months
- Similar efficacy to topical bimatoprost x 3 months, then effect trails off
- No change in corneal endothelial cell density or corneal thickness

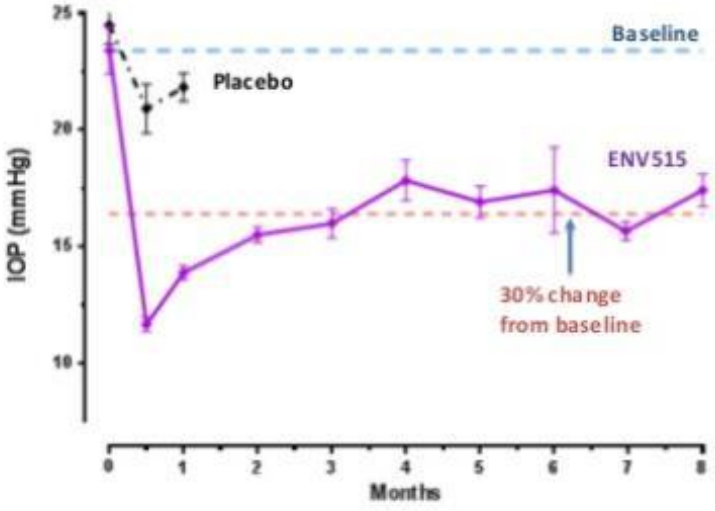
Bimatoprost SR



Travoprost XR

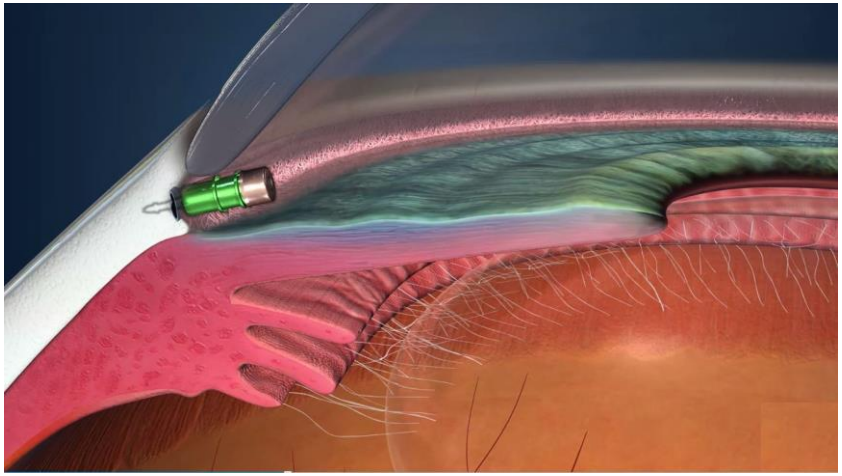
- ENV515 - Envisia Therapeutics
- 25% IOP reduction
- Phase 2a - Noninferiority to timolol x 11 months



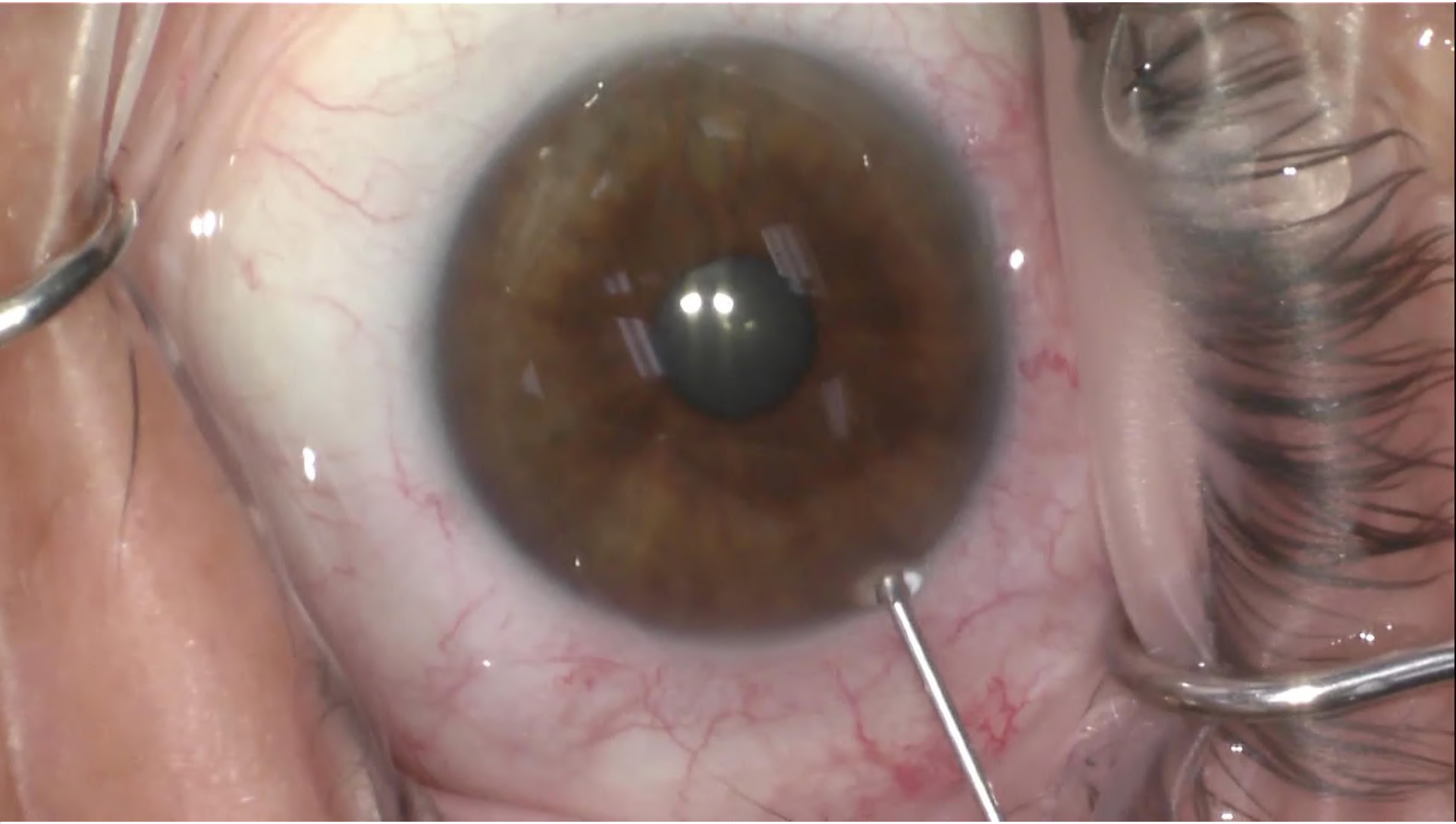


iDose

- Glaukos
- Extended release Travoprost
- Reservoir housed on titanium implant
- Secured within TM
- Reservoir portion can be removed and replaced



iDose

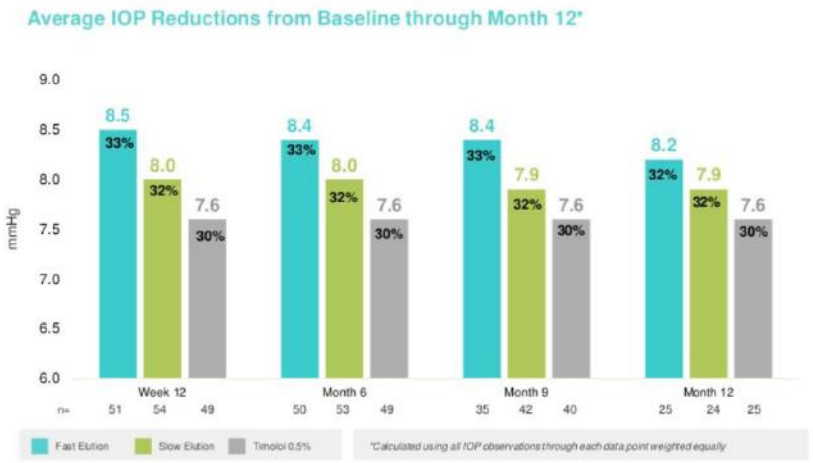


iDose

Phase 2 results show 32-33% IOP reduction at 12 months.

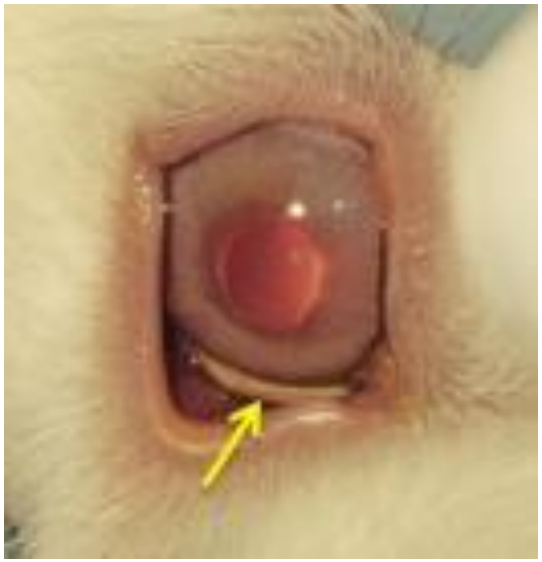
7.9-8.5 mmHG reduction in IOP

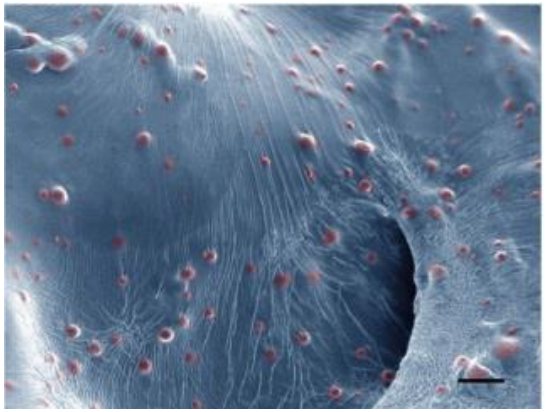
Unlike topical PGAs no hyperemia noted



Gel-Forming Drops

- SoliDrop (Otero Therapeutics)
- Warmth from eye causes drop to become viscous gel
- Sinks to lower fornix to release drug over weeks
- Nondegradable – designed to be removed when next dose placed





Conclusion

- Medical therapy of glaucoma can be effective but burdensome
- New technology on the horizon should help minimize patient burden in medication adherence
- For now the most effective medication is the one that a patient will fill, use, and remember to take.

TABLE 1. 2016 Average PGA Prices for 30-day Supplies and Average PGA Prices in the States With the Highest and Lowest Prices

Drugs	National Average Price ± SD	Least Expensive State (Average Price)	Most Expensive State (Average Price)
Bimatoprost	$107.90 ± 25.19	Arizona ($81.56)	Utah ($181.12)
Latanoprost	$10.16 ± 1.52	Missouri ($9.22)	Maine ($14.36)
Lumigan	$167.30 ± 17.66	New Mexico ($158.29)	Hawaii ($188.83)
Travatan Z	$171.36 ± 19.44	North Dakota ($154.47)	Massachusetts ($193.34)
Travoprost	$92.53 ± 15.14	Washington ($71.93)	Massachusetts ($108.09)
Xalatan	$153.41 ± 15.16	Kentucky ($141.87)	Minnesota ($168.34)
Zioptan	$162.75 ± 13.22	South Dakota ($137.40)	Rhode Island ($171.99)

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