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best education possible.



## The Glaucoma Grab Bag: Practical Guidelines for Effective Glaucoma Therapy

Danica J. Marrelli, OD, FAAO  
University of Houston College of Optometry

### Financial Disclosure

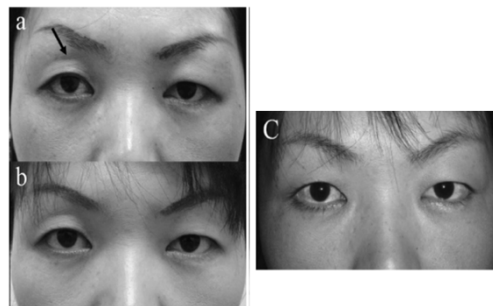
- I have received I have received  
speaking or consulting fees from:
  - Allergan
  - Bausch & Lomb
  - Carl Zeiss Meditec
  - Ivantis
  - Santen

### Prostaglandin Analogs (PGs)

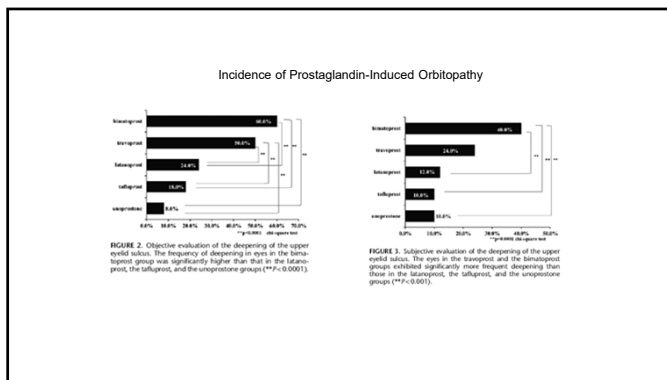
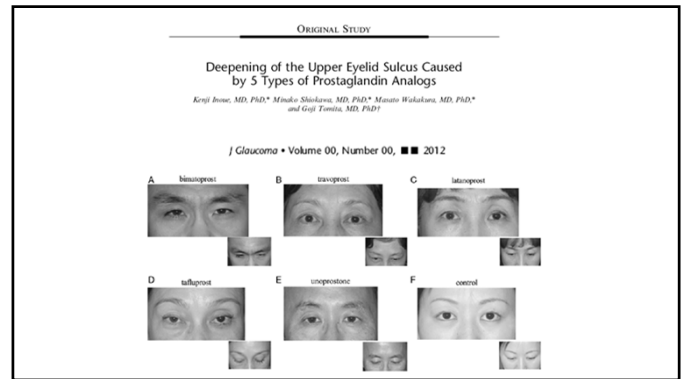
- Mechanism of action: increase uveoscleral outflow
- Effect: excellent (25-35% reduction)
- Dosing: once daily (doesn't matter am/pm)
- Side effects:
  - Minimal systemic
  - Ocular:
    - Hyperemia
    - Hypertrichiasis
    - Hyperpigmentation – iris and periorbital skin
    - Prostaglandin-induced orbitopathy



*Optometry and Vision Science*, Vol. 88, No. 9, September 2011



*Optometry and Vision Science*, Vol. 88, No. 9, September 2011



## Glaucoma - Prostaglandins

- When to Use
  - POAG
  - Pigmentary glaucoma
  - Pseudoexfoliation glaucoma
  - Normal tension glaucoma
  - Ocular Hypertension

## Glaucoma - Prostaglandins

- When to reconsider:
  - Acute rise in IOP
    - Acute angle closure
    - Posner-Schlossman syndrome
    - Post-surgical spike
  - Pt with history of CME or risk of CME
  - Unilateral therapy
  - Pregnancy
  - Uveitic glaucoma (???)
  - Neovascular glaucoma (???)

## UVEITIS

Am J Ophthalmol. 2008 Dec;146(6):876-82.

#### Flare-up rates with bimatoprost therapy in uveitic glaucoma.

Fortuna E, Cevallos-Castellana RA, Bhui P, Doctor P, Foster CS.  
Massachusetts Eye Research and Surgery Institute, Cambridge, Massachusetts 02142, USA.

Environ Int.

Am J Ophthalmol. 2009 Mar;147(3):566. Castellana-Cevallos, Rene A [corrected to Cevallos-Castellana, Rene A].

#### Abstract

**PURPOSE:** To evaluate the rate of flares in patients with uveitic glaucoma treated with topical bimatoprost and to assess its effect on intraocular pressure (IOP) in this subset of patients.

**DESIGN:** Retrospective case series.

**METHODS:** All patients seen at one subspecialty uveitis practice with history of uveitic glaucoma treated with topical bimatoprost were identified and the data collected, which included onset, type, duration of uveitis, onset of secondary glaucoma, and previous therapies for glaucoma. The time of onset of bimatoprost therapy, the IOP, and flare-up rate before and after initiation of treatment with bimatoprost were recorded at one week and one, three, and six months of follow-up.

**RESULTS:** Of the 42 patients (59 eyes) identified, 12 patients had used other topical IOP agents, which were replaced by bimatoprost. Twenty-three patients had not used any IOP agents and bimatoprost was added to their existing anti-glaucoma regimen. Seven patients were newly diagnosed with uveitic glaucoma and were commenced with topical bimatoprost. The rate of uveitis flares while on other anti-glaucoma therapy was 59 per 100 person-years follow-up, while on bimatoprost therapy it was 32.4 per 100 person-years follow-up ( $P = .206$ ). The mean IOP prior to bimatoprost therapy was  $27 \pm 7.3$  mm Hg and after initiation of topical bimatoprost was  $15 \pm 5.5$  mm Hg at the end of six months ( $P < .0005$ ).

**CONCLUSION:** These data suggest that bimatoprost is an effective IOP-lowering agent in patients with uveitic glaucoma in whom the uveitis is controlled on immunosuppressive therapy, and it does not increase the rate of flares of uveitis in these patients.

Br J Ophthalmol. 2008 Jul;92(7):916-21. Epub 2008 May 6.

#### Use of ocular hypotensive prostaglandin analogues in patients with uveitis: does their use increase anterior uveitis and cystoid macular oedema?

Chang JH, McCuskey P, Mossoff T, Ferrante P, Jalaludin B, Lightman S.

Department of Clinical Ophthalmology, Institute of Ophthalmology, Moorfields Eye Hospital, City Road, London, UK.

#### Abstract

**AIM:** A retrospective comparative case series was studied to determine whether the use of prostaglandin (PG) analogues to treat raised intraocular pressure (IOP) in patients with uveitis resulted in an increase in the frequency of anterior uveitis or cystoid macular oedema (CMO).

**METHODS:** 153 eyes of 64 consecutive patients with uveitis and raised IOP treated with a PG analogue at two tertiary referral uveitis clinics were identified over a 3-month period. Control eyes were selected as those uveitic eyes of the same patients, which were treated with topical IOP-lowering agents other than a PG analogue. Pre-treatment IOP was compared with the mean IOP during PG analogue treatment. The frequency of anterior uveitis and CMO during PG analogue treatment was compared with the frequency of these complications in the control eyes during non-PG IOP-lowering treatment.

**RESULTS:** Significant IOP reductions were observed during PG analogue treatment. There was no significant difference in the frequency of anterior uveitis in those eyes treated with PG analogues and those treated with non-PG agents ( $p = 0.87$ , Fisher exact test). None of the 59 uveitic eyes without a previous history of CMO developed this complication. There was no increase in the frequency of visually significant CMO during PG treatment compared with that during non-PG treatment ( $p = 0.19$ , Fisher exact test).

**CONCLUSION:** This study demonstrates that PG analogues are potent topical medications for lowering raised IOP in patients with uveitis and are not associated with increased risk of CMO or anterior uveitis.

© Publication Types, MeSH Terms, Substances

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Search: [Add Citations](#), 2009 Jun 24(16):1775-80. doi: 10.1097/IOA.0b013e318193a33a. Epub 2009 Jun 26.

**Efficacy and safety of latanoprost in eyes with uveitic glaucoma.**

Matsushita M<sup>1</sup>, Saito M<sup>1</sup>, Hara M<sup>1</sup>, Chikama S<sup>1</sup>, Papanicolaou D<sup>1</sup>, Deshpande S<sup>1</sup>.

**Author information**

**Abstract**

**BACKGROUND:** To compare the efficacy and safety of latanoprost against a fixed combination of dorzolamide and timolol in eyes with elevated intraocular pressure (IOP) or glaucoma or anterior or intermediate uveitis.

**METHODS:** Fifty-eight patients with anterior or intermediate uveitis and elevated IOP or glaucoma presented or followed up in the Ocular Inflammation and Immunology Service of General Hospital of Athens were randomly assigned to receive treatment either with latanoprost (30) or with dorzolamide/timolol (28). The main outcome measures were inflammatory relapses and IOP response to treatment.

**RESULTS:** Ten patients (34%) in the latanoprost group and sixteen patients (57%) in the dorzolamide/timolol group experienced relapses of anterior uveitis ( $p = 0.50$ ). There was no statistical difference between the two groups in respect of inflammatory relapses ( $p = 0.21$ ). Twenty-one patients were followed up before starting latanoprost. The number of relapses of anterior uveitis per patient per year before treatment with latanoprost was  $0.52 \pm 1.2$ . The rate of relapses per patient per year after starting latanoprost was  $0.39 \pm 0.7$  for these patients ( $p = 0.030$ ). After 1 year of treatment, intraocular pressure was dropped from  $27.8 \pm 4.4$  mmHg to  $16.8 \pm 5.3$  mmHg ( $p < 0.001$ ) in the latanoprost group and from  $28.2 \pm 4.8$  mmHg to  $22.6 \pm 10.1$  mmHg ( $p < 0.001$ ) in the dorzolamide/timolol group. Four patients during treatment with latanoprost and five patients during treatment with dorzolamide/timolol had no relapses of anterior uveitis.

**CONCLUSION:** Latanoprost is safe and equally effective to a fixed combination of dorzolamide and timolol in the treatment of uveitic glaucoma.

## The Use of Prostaglandin Analogs in the Uveitic Patient

Michael B. Horsley and Teresa C. Chen

Glaucoma Service, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA, USA

Seminars in Ophthalmology, 26(4-5), 285-289, 2011

### SUMMARY

The use of prostaglandin analogs in uveitic patients remains controversial. A causal relationship has yet to be established between prostaglandins and the reactivation of anterior uveitis, the development of cystoid macular edema, or the reactivation of HSK.

Due to the efficacy of prostaglandins in lowering IOP in patients with uveitis and the small likelihood of developing these rare complications, prostaglandin analogs should remain in the treatment algorithm of uveitic glaucoma patients.

## Cystoid Macular Edema \*\*following cataract surgery\*\*

J Ophthalmol. 2010;20(10):1607-10. Epub 2010 Nov 7.

#### Prostaglandin-induced cystoid macular edema following routine cataract extraction.

Agarwal N, Mossad S.

Department of Ophthalmology, University of California, Irvine, CA 92697, USA.

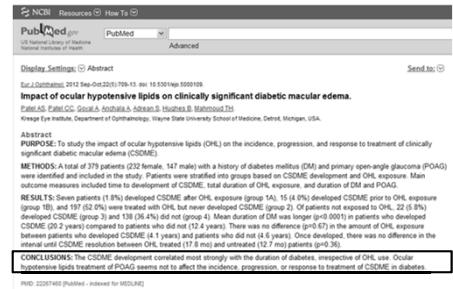
#### Abstract

To our knowledge, we are reporting the first case of a 59-year-old man who developed recurrent CME with three separate trials of three different prostaglandin class drugs following uncomplicated phacemulsification with vitreous lens implantation. Despite multiple reports of individual prostaglandin (PG) analogues being suggested as the cause of CME, there are no recommendations regarding withholding these medications in the perioperative period. Our patient first developed CME (OD) 4 months post uncomplicated cataract extraction. XALATAN (latanoprost) had been started after surgery and discontinued at onset of CME. While off XALATAN (latanoprost), the patient's CME resolved, but his IOP rose. The patient was started on LUMIGAN (bimatoprost) to control the IOP, but within weeks his CME recurred. The patient's CME was again treated and his IOP remained acceptable, but then progressively increased. TRAVATAN (travoprost) was attempted, but he presented with a third round of CME. Definitive conclusions about causal relationships cannot be made without well-designed, prospective clinical trials addressing this issue.

PMID: 21076528 [PubMed - in process] PMID: 21027071 Free PMC Article

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## Clinically Significant Diabetic Macular Edema???

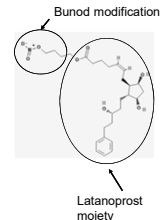


## Glaucoma - Prostaglandins

- **Drugs:**
  - latanoprost (Xalatan® and generic, Xelpros®)
  - travoprost (Travatan-Z® and generic)
  - bimatoprost (Lumigan® 0.01% and generic 0.03%)
  - tafluprost (Zioptan®)
- **How do they compare?**
  - Efficacy
  - Side effects
  - Cost

## Latanoprostene Bunod (Vyzulta®, B&L)

- Latanoprostene = latanoprost
  - Increases uveoscleral outflow
- Bunod modification donates NO
  - Exerts its effect in trabecular smooth muscle
  - Activating cyclic guanosine monophosphate signaling pathway
  - Resulting in trabecular relaxation and increased conventional outflow
- Mechanisms would be expected to be additive



Grant ME, et al. Invest Ophthalmol Vis Sci. 2014;55(15):5055-5015.  
 Sun CC, et al. Invest Ophthalmol Vis Sci. 2010;51(1):1000-1015.

## Latanoprostene Bunod vs Timolol: APOLLO and LUNAR Trials

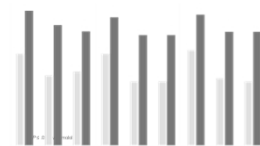
- Study design
  - Randomized (2:1 [LBN:timolol]) phase 3, multicenter, double-masked, parallel-group studies
- 2 treatment groups
  - LBN, 0.024%, qhs
  - Timolol, 0.5%, bid

	APOLLO	LUNAR
Number of subjects	420	387
Mean baseline IOP		
LBN	26.7 mm Hg	26.6 mm Hg
Timolol	26.5 mm Hg	26.4 mm Hg

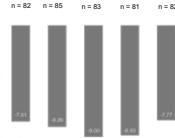
Worthington KL, et al. JAMA. 2014;311(11):1111-1121.  
 Medeiros LA, et al. Arch Ophthalmol. 2014;132(10):1000-1008.

## APOLLO: Efficacy and Safety

- IOP reductions
  - 8 to 9 mm Hg for LBN (n = 264)
  - 6.5 to 7.5 mm Hg for timolol (n = 123)
- Adverse events
  - Similar rates between groups
  - Most common:
    - Eye irritation
    - Conjunctival hyperemia



- N = 413 (intent to treat)
- At highest doses, LBN lowered IOP 1 to 1.5 mm Hg more than latanoprost
- Most common adverse event: pain upon instillation
- Conjunctival or ocular hyperemia:
  - LBN: 7.0%
  - Latanoprost: 8.5%

Weinreb RN, et al. *Br J Ophthalmol*. 2015;99(5):728-745.

- **Mechanism of action:** decrease aqueous production
- **Efficacy:** very good (25-30% reduction)
- **Dosing:** once vs twice daily
- **Side effects:**
  - Minimal ocular side effects
  - **Systemic:**
    - Bradycardia
    - Bronchial constriction
    - \*\* CHECK EXISTING MEDS, VITALS
- **Short term escape & long term drift**

[illegible]

**CONCLUSIONS.** In a studies and in a study did not determine in patients with timolol. (*Invest Ophthalmol Vis Sci* 1999;40:1111-1115)

**CONCLUSIONS.** In agreement with other masked and controlled studies and in conflict with uncontrolled ones, the present study did not demonstrate long-term drift of intraocular pressure in patients with ocular hypertension treated with topical timolol. (*Invest Ophthalmol Vis Sci.* 2001;42:2839–2842)

### Subjects and Methods

The study was designed as a randomized, prospective, double-masked trial comparing typical antipsychotic treatment with placebo treatment in patients with acute schizophrenia and at least one additional risk factor. Acute schizophrenia was defined as chronic EP and current secondarily. Patients were in clinical practice were recruited consecutively between 1991 and 1997. A large majority of the patients (97%) had never been treated with EP before starting drugs before entering the study. Among the 11 patients who had been previously treated, the second treatment was

Investigative Ophthalmology & Visual Science, November 2001, Vol. 42, No. 12  
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- **When to use:**
  - First line therapy for patients with contraindications to prostaglandins
  - Need rapid lowering of IOP
  - Cost (generic is cheap)
  - Added drug for prostaglandin users
    - Different mechanism of action
- **When to reconsider:**
  - Symptomatic bradycardia
  - CHF patient
  - Patient on oral bb (+/-)
  - Normal tension glaucoma

- **Available drugs:**
  - timolol maleate (Timoptic®, Timoptic-XE®, Timoptic PF®, generics, Istalol®)
  - timolol hemihydrate (Betimol®)
  - levobunolol (Betagan® and generic)
  - metipranolol (Optipranolol® and generic)
  - carteolol (Ocupress® and generic)
  
  - betaxolol (generic solution, Betoptic-S®)

- **Mechanism of action:**
  - Decrease in aqueous production
  - Increase in uveoscleral outflow
- **Efficacy:** good (20-25% reduction)
- **Dosing:** tid vs bid
- **Side effects:**
  - **Systemic:**
    - Somnolence
    - Dry mouth
    - Dizziness/fainting
  - **Ocular:**
    - allergy

## Glaucoma - brimonidine

- Allergy:
  - Original brimonidine ® 0.2% generic
    - 30%+ allergy rate
  - Alphagan-P 0.15% (only available in “generic” with Polyquad ® preservative)
    - 20% allergy rate
  - Alphagan-P ® 0.1% (Purite ® preservative)
    - 10-15% allergy rate
  - Combigan ® (0.2%, with 0.5% timolol, BAK)
    - 5% allergy rate (?)
  - Simbrinza® (0.2% with 2% dorzolamide, BAK) -- ??? Allergy rate

## Glaucoma - brimonidine

- When to use
  - Excellent additivity with prostaglandin
  - Good additivity with beta-blocker
  - Rapid IOP lowering (esp in combo)
  - Preservative toxicity/allergy
  - Category B pregnancy (D/C in breastfeeding)
- When to reconsider
  - Monotherapy (dosing)
  - Hx of allergy (any form of brimonidine)
  - CHILDREN (contraindication)

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

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

AMERICAN JOURNAL OF OPHTHALMOLOGY

APRIL 2011

## LoGTS

- Randomized, double-masked clinical trial to compare brimonidine 0.2% vs timolol 0.5% in preserving visual function in normal tension glaucoma patients
  - brimonidine 0.2% bid
  - timolol maleate 0.5% bid
  - Followed with VF every 4 months for minimum of 4 years

## LoGTS

- Results:
  - No significant difference in IOP
  - Significant dropout in brimonidine group (allergy)
  - Significant/dramatic difference in visual field progression
    - 9% for brimonidine group
    - 39% for timolol group
- Question: what does this mean?

## Glaucoma – carbonic anhydrase inhibitors

- Mechanism of action: decreased aqueous production
- Efficacy: excellent (oral – 40-50%+); good (topical – 15-20%)
- Dosing: bid – tid
- Side effects:
  - Topical:
    - Bitter taste
    - Stinging
    - Hyperemia
    - Corneal endothelium

## Glaucoma - CAIs

- When to consider:
  - Good addition to prostaglandin
  - Brimonidine allergy
- When to avoid:
  - Fuchs corneal endothelial dystrophy
  - Pregnancy
  - Sulfa allergy (???)
- Available:
  - Dorzolamide (Trusopt® and generic)
  - Brinzolamide (Azopt®)
  - dorzolamide/timolol (Cosopt®, Cosopt PF®, and generic)
  - dorzolamide/brinzolamide (Simbrinza®)

## Evaluation of Adverse Events in Self-Reported Sulfa-Allergic Patients Using Topical Carbonic Anhydrase Inhibitors

Guilherme B. Guades,<sup>1</sup> Abrar Karan,<sup>1</sup> Hyton R. Mayer,<sup>2</sup> and M. Bruce Shields<sup>2</sup>

**Conclusion:** It may be safe to use a topical CAI in patients who report a history of a sulfa allergy. Patients with medication allergies of any kind may be more likely to develop allergic reactions to other, unrelated drug classes.

**Objective:** To evaluate the safety of topical carbonic anhydrase inhibitors (CAIs) in patients who report a history of a sulfa allergy, systemic, or both) within at least 30 days after receipt of 1 of 4 doses of topical glaucoma medications: CAIs (dorzolamide and brinzolamide), prostaglandin analogs, beta-adrenergic blockers, and alpha2-adrenergic agonists.

**Results:** Patients with a self-reported history of sulfa allergy had significantly more ocular adverse events when the initiation of any of the topical glaucoma medications when compared to those patients with no reported history of sulfa allergy.

**Conclusion:** Patients with a self-reported sulfa allergy and patients who self-reported other, nonocular-related allergies had similar rates of adverse reactions to most of the topical medications. The patients who reported a sulfa allergy who used topical CAIs did not have more adverse reactions compared to those patients who used topical prostaglandin analogs, beta-adrenergic blockers, or alpha2-adrenergic agonists.

**Conclusion:** It may be safe to use a topical CAI in patients who report a history of a sulfa allergy. Patients with medication allergies of any kind may be more likely to develop allergic reactions to other, unrelated drug classes.

## Sulfonamide cross-reactivity: Is there evidence to support broad cross-allergenicity?

NICOLE R. WU AND KARL A. MATUSZAK

**Purpose.** Published and manufacturer-provided data regarding potential cross-reactivity between antibacterial and nonantibacterial sulfonamide agents are reviewed. **Summary.** An estimated 3–6% of the general population is allergic to sulfonamides and thus at risk for type I and other hypersensitivity reactions to sulfamethoxazole and other sulfonamide antibacterial agents. Concerns have been raised that a history of sulfa allergy may be associated with an increased risk of adverse reactions to a wide range of nonantibacterial sulfonamides, including certain antivirals, carbonic anhydrase inhibitors, cyclooxigenase-2-selective nonsteroidal antiinflammatory drugs, loop and thiazide diuretics, and sulfonamides; concerns have also been raised that patients who have experienced an allergic reaction to one nonantibacterial sulfonamide may be at risk for an adverse reaction to others. Structurally, none of the nonantibacterial sulfonamides exhibit both the features shown to be responsible for

sulfonamide reactions (i.e., an N-containing ring attached to the N1 nitrogen of the sulfonamide group and an arginine group at the N4 position), and only two agents (jamprenavir and fosamprenavir) have the latter characteristic. A comprehensive literature search (1966–December 2011) identified nine case reports indicating possible cross-reactivity to sulfonamide medications; however, in most cases, adequate patient testing was not conducted to firmly establish either sulfa allergy or sulfonamide cross-reactivity. The weight of evidence suggests that withholding nonantibacterial sulfonamides from patients with prior reactions to antibacterial sulfonamides or other sulfonamides is not

justified. **Conclusion.** A review of the professional literature and manufacturer-provided data did not find convincing evidence of broad cross-reactivity between antibacterial and nonantibacterial sulfonamide agents. *J Allergy Clin Immunol* 2013;131:1049–54.

## Glaucoma - acetazolamide

- Typically used in emergency/acute situations rather than long term due to systemic side effects:
  - Paresthesia
  - Kidney stones
  - Metabolic acidosis
  - Blood dyscrasia
- Typical use:
  - Post-surgical IOP elevation
  - Acute angle closure (PUPILLARY BLOCK ONLY)
  - Extremely elevated IOP
- Dosing:
  - 250 mg tablets qid (generic)
  - 500 mg time-released capsules (Sequels®, generic) bid

## (NEW-ish DRUG) Rho-Kinase Inhibitors

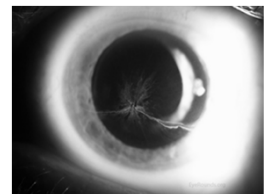
- netarsudil (Rhopressa®, Aerie) FDA approved in December 2017, in pharmacies Spring 2018
  - Inhibits the enzyme Rho kinase
  - Also inhibits norepinephrine transporter (increases adrenergic activity)
- Potentially lowers IOP by 3 mechanisms
  - Increasing trabecular meshwork outflow
  - Reducing episcleral venous pressure
  - Reducing aqueous production (via norepinephrine transporter inhibition)

Wang W, et al. J Glaucoma. 2015;24(12):101–14.

$$\text{IOP} = (\text{PRODUCTION/OUTFLOW}) + \text{EVP}$$

## Netarsudil (Rhopressa®)

- Dosing is once daily (p.m.)
- Side Effects:
  - Hyperemia
    - 50–60% of patients
    - Sporadic
  - Conjunctival hemorrhages (small)
  - Corneal verticillata
    - Intracellular phospholipids
    - Asymptomatic
    - Did not decrease visual function



## Netarsudil (Rhopressa)

- Lowered IOP approximately 5-7 mmHg, irrespective of starting IOP
  - May be best suited for those with lower IOP (?)
- Current development plan is in combination with latanoprost
  - netarsudil, 0.02%, plus latanoprost fixed combination lowered IOP more than latanoprost ( $P < .0001$ ) or netarsudil, 0.02% ( $P < .0001$ ), did in a completed phase 2b trial
  - Hyperemia: 14% latanoprost, 40% netarsudil, 40% fixed combination

## NEW(ish) DRUG!!!! latanoprost + netarsudil (Rocklatan)

- First available fixed combination in US with a pga
- First available fixed combination with once daily dosing (night)
- May be particularly effective in patients with lower starting IOP
- FDA approved March 2019

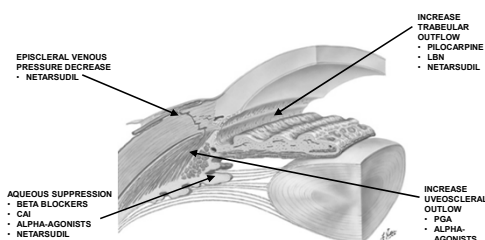
## Glaucoma - pilocarpine

- **Mechanism of action** – increase trabecular outflow
- **Efficacy:** good (25%)
- **Dosing:** qid
- **Side effects:**
  - Accommodative spasm
  - Browache
  - Bronchial constriction
- **Use:** acute angle closure with pupillary block (low concentration)

## Glaucoma - pilocarpine

- **Avoid:**
  - Inflammatory
  - Neovascular
  - “Posterior Pushing” secondary angle closure (ex: topiramate-induced angle closure)

## IOP-Lowering Drugs: Sites of Action



## Fixed Combination Medications

- dorzolamide/timolol (Cosopt® and generic; Cosopt PF®)
  - Bid dosing
- brimonidine/timolol (Combigan®)
  - 5% allergy rate
  - Bid dosing
- brinzolamide/brimonidine (Simbrinza®)
  - First non-beta blocker fixed combination
  - BAK-preserved
  - TID dosing
- Netarsudil/Latanoprost (Rocklatan®)
  - First pga fixed combo in US
  - Qhs dosing



## Other Fixed Combinations

- Imprimis Pharmacy:
  - Compound multiple formulations of off-patent ophthalmics in a multi-dose preservative-free bottle, sell directly to patient (no insurance)
  - Potential Advantages:
    - No preservatives
    - Multiple drugs in one bottle = better adherence
    - Potential cost savings
    - Eliminates third-party dictated prescribing

## Generic Grab Bag

- timolol maleate, other BBs
- latanoprost –or- travoprost – or – bimatoprost 0.03%
- brimonidine 0.15% -or- 0.2%
- dorzolamide
- (dorzolamide/timolol)

### Generic MMT:

- Latanoprost or travoprost or bimatoprost
- Brimonidine 0.15% or 0.2%
- Dorzolamide/timolol combo



### The Making of Generic Medicines

As more ophthalmic drugs become available as generics, what we know about generic requirements will help us make informed decisions when prescribing for glaucoma.

BY ROBERT J. NOCKER, MD, MBA, AND STEVEN T. SIMMONS, MD

- To gain FDA approval, a generic drug must:
  - Contain the same *active* ingredient
  - Be identical in strength, dose form, and route of administration
  - Be bioequivalent (80-120% of branded product)
    - Not the same thing as therapeutic effect
  - Have the same indications for use
  - Meet the same batch requirements for identity, strength, purity, and quality
  - Have a similar shelf life

### The Making of Generic Medicines

As more ophthalmic drugs become available as generics, what we know about generic requirements will help us make informed decisions when prescribing for glaucoma.

BY ROBERT J. NOCKER, MD, MBA, AND STEVEN T. SIMMONS, MD

- We don't know about:
  - Loss of control with long term use
  - Tolerability
  - Efficacy
- Multiple companies can make a generic; differences may not be apparent on bottle
- Cannot know for sure which company the pharmacy will have
- Patient's confidence in generics varies
- Somewhat difficult to understand efficacy due to slow nature of disease

## BAK-free Grab Bag

- Timoptic PF®
- Travatan-Z®, Xelpros® or Zioptan®
- brimonidine 0.15% -or- Alphagan-P® 0.1%
- Cosopt PF®
- BAK-free MMT:
  - Xelpros, Travatan Z, or Zioptan
  - Brimonidine 0.15% or 0.2%
  - Cosopt PF

### Preservative-free Grab Bag

- Timoptic PF ®
- Zioptan ®
- Cosopt PF ®
- (Compounded Drugs)
- Preservative-free MMT
  - Cosopt PF
  - Zioptan

### Medication Follow-Up Questions

1. Is patient using drug?
2. Is patient tolerating drug?
3. Is there a therapeutic effect?
4. Am I reaching target IOP?

### POLLING QUESTION

What do you do if a pga works but is not enough?

- A. Refer for SLT
- B. Refer for consultation
- C. Add a BB
- D. Add brimonidine
- E. Add CAI
- F. Switch to Rocklatan

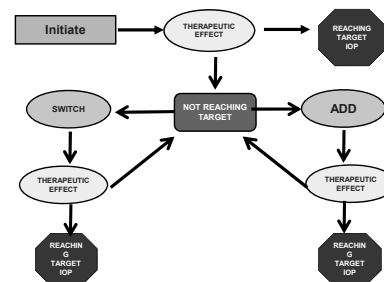
### POLLING QUESTION

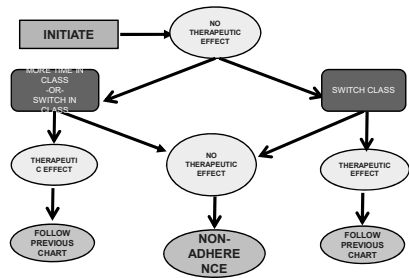
What do you do if a pga is NOT effective?

- A. Refer for SLT
- B. Switch to different pga
- C. Add BB
- D. Add brimonidine
- E. Add CAI
- F. Switch to Rocklatan
- G. None of the above

### TYPICAL DRUG STEPPING

- Start with PGA
  - If good therapeutic effect but NOT reaching target, add timolol, brimonidine, or topical CAI
    - If good therapeutic effect with 2<sup>nd</sup> drug but still NOT reaching target, switch 2<sup>nd</sup> drug to combo
    - \*\*\*Here is where Vyzulta or Rocklatan could work
  - If PGA not having a good therapeutic effect
    - Consider non-adherence; re-try for another month
    - Consider switch to branded if using generic
    - Consider switching class (BB)
      - Can easily switch BB to combo if need additional therapy
  - If multiple meds don't work - COMPLIANCE



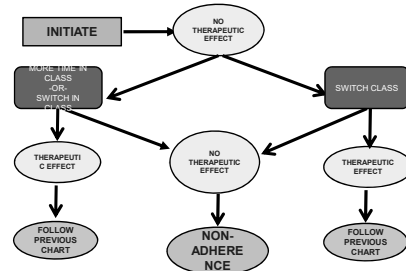


#### Example: Guillermo

- 61yo healthy HM
- High risk ocular hypertension
  - IOPs range 28-32 OD, OS (multiple visits)
  - CCT 500 OU
  - C/D 0.4 OD, OS; normal, no RNFLDO
  - VF normal OU
  - OCT normal OU
- Goal IOP: 20% reduction from highest = under 25mmHg
- Initial therapy: latanoprost qhs OU

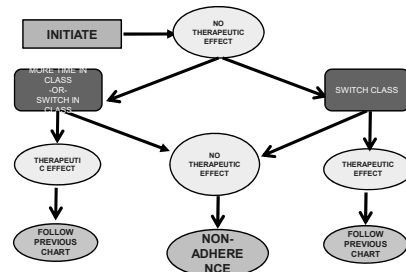
#### Example: Guillermo

- Follow-up:
  1. Is patient using drug? YES, claims excellent compliance
  2. Is patient tolerating drug? YES, minor redness, otherwise fine.
  3. Is there a therapeutic effect? NO – 20% minimum expected from first line med. His IOP on follow-up is 28mmHg
  4. Meeting target? (NO)



#### Example: Guillermo

- Tried additional time: No change in IOP
- Switched to branded: No change in IOP
  - COMPLIANCE CHECK!!!!
    - Pt adamant that he is using properly
    - Observe drop instillation = good technique
- Switched to timolol: IOP 21mmHg OD, 18mmHg OS

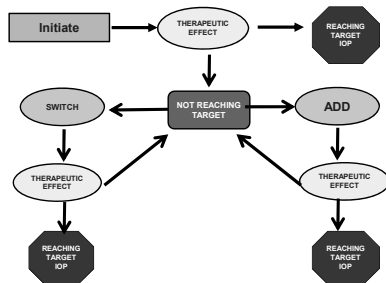


### Example: Natalie

- 62yo Indian female with moderate POAG
  - IOP range 23-27mmHg OU
  - C/D ratio 0.8 OD, OS
  - Mild VF defect consistent with disc appearance
  - Ocular history also includes mild Fuchs corneal endothelial dystrophy
  - Medical history unremarkable
  - GOAL IOP: 35% reduction from highest = 17mmHg or less (mid teens)
  - Initial therapy: latanoprost

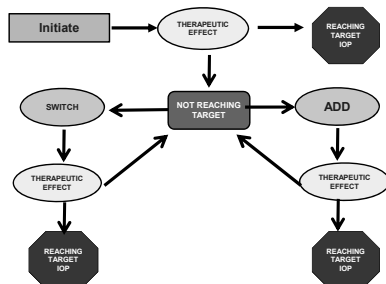
### Example: Natalie

- Follow-up:
  - Is patient using drug? YES, claims excellent compliance
  - Is patient tolerating drug? YES
  - Is there a therapeutic effect? YES – 20% minimum expected from first line med (<21). Pt's IOP on meds = 20
  - Meeting target? NO – Target is 17mmHg or less



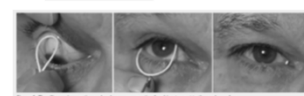
### Example: Natalie

- Choices:
  - Add
    - CAI (but remember Fuch's)
    - BB
    - Brimonidine
  - Switch
    - PGA + timolol
    - Timolol alone
    - Other single or FDC
- We went with brimonidine
  - On return, IOP 18mmHg



### Glaucoma Drugs: What's Next?

- Drug Delivery System (DDS)
  - Contact lens delivery
  - Punctal plug delivery
  - Insertable
  - Injectable
    - Sub-conjunctival
    - Anterior chamber
    - vitreous



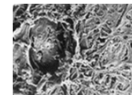


## Where Does Laser Fit In?

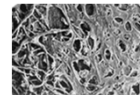
### SELECTIVE LASER TRABECULOPLASTY

- Specially designed laser used to treat pigmented trabecular meshwork cells
- Application of laser is same technique as for Argon Laser Trabeculoplasty (ALT)
- Differences:
  - Very short pulse (3 nanoseconds)
  - Eliminates collateral "burn" damage
  - Mechanism appears to be cytokine-mediated macrophage recruitment
  - Can be repeated

### SELECTIVE LASER TRABECULOPLASTY



ALT



SLT

### SELECTIVE LASER TRABECULOPLASTY

- Post-Op Care
  - Similar to ALT (? Steroid, ? NSAID)
- Complications:
  - Similar to ALT
  - Include:
    - Corneal abrasion
    - Uveitis
    - Scattered PAS
    - Transient IOP rise

"Selective Laser Trabeculoplasty as Primary Treatment for Open Angle Glaucoma" (Archives Ophthalmology July 2003)

- 45 eyes treated with SLT as primary treatment
- Mean IOP decrease: 7.7 mmHg (+/- 3.5)
- 4% non-response to treatment
- 3 eyes required meds at end of 18 month follow up
- Complications: redness, IOP spike

Ayala M, Chen E. Long-Term Outcomes of Selective Laser Trabeculoplasty (SLT) Treatment. *Open Ophthalmol J.* 2011;5:32-4. Epub 2011 May 12.

- Retrospective chart review of 120 eyes of 120 patients undergoing 90° SLT
- Primary measure: time to failure
- Results:
  - Average time to failure: 18 months
  - Success at 12 months: 62%
  - Success at 24 months: 34%
  - Success at 36 months: 28%
  - Success at 48 months: 24%

PubMed  
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Abstract + Send to +

*J Glaucoma*. 2012 Sep;21(7):480-4. doi: 10.1097/IJG.0b013e31821c1c07.

**Selective laser trabeculoplasty versus medical therapy as initial treatment of glaucoma: a prospective, randomized trial.**

Salafut J, Bousquet JC, Kahr A, Moinaux J, Wouff S, Wapetoff G, SLT Trial Study Group

Collaborators (20)

Author information

Abstract

**PURPOSE:** To compare outcomes of selective laser trabeculoplasty (SLT) with drug therapy for glaucoma patients in a prospective randomized clinical trial.

**PATIENTS AND METHODS:** Sixty-nine patients (127 eyes) with open-angle glaucoma or ocular hypertension were randomized to SLT or medical therapy. Target intraocular pressure (IOP) was determined using the Collaborative Initial Glaucoma Treatment Study formula. Patients were treated with SLT (100 applications 300 degrees) or medical therapy (prostaglandin analog). Six visits over 1 year followed initial treatment. If target IOP range was not attained with SLT, additional SLT was the next step, or in the medical arm additional medications were added.

**PRIMARY OUTCOME:** IOP; secondary: number of steps.

**RESULTS:** Sixty-nine patients were treated. Data collection terminated with 54 patients reaching 9 to 12 months follow-up. Twenty-nine patients were in the SLT group, 25 patients in the medical group. Baseline mean IOP for all eyes was 24.6 mm Hg in the SLT group, 24.7 mm Hg in the medical group. Mean IOP (both eyes) at last follow-up was 18.2 mm Hg (6.3 mm Hg reduction) in the SLT arm, 17.7 mm Hg (7.0 mm Hg reduction) in the medical arm. By last follow-up, 11% of eyes received additional SLT, 27% required additional medication. There was not a statistically significant difference between the SLT and medication groups.

**CONCLUSIONS:** IOP reduction was similar in both arms after 9 to 12 months follow-up. More treatment steps were necessary to maintain target IOP in the medication group, although there was not a statistically significant difference between groups. These results support the option of SLT as a safe and effective initial therapy in open-angle glaucoma or ocular hypertension.

PMID: 2194392 (PubMed - indexed for MEDLINE)

ORIGINAL STUDY

Predictors of Success in Selective Laser Trabeculoplasty for Chinese Open-angle Glaucoma

Jacky W.Y. Lee, FRCS Ed<sup>a</sup>, Catherine C.L. Lin, PhD<sup>b</sup>, Jonathan C.H. Chan, FRCS Ed<sup>a</sup> and Jimmy S.M. Lai, MD<sup>a</sup>

*J Glaucoma* • Volume 23, Number 5, June/July 2014

**Aim:** To investigate the determinants of success of selective laser trabeculoplasty (SLT) in Chinese open-angle glaucoma patients.

**Conclusion:** The positive predictors of SLT success included: higher pre-SLT IOP, use of topical CAI, thinner RNFL, and lower day 1 IOP. Using 3 anti-glaucoma medications was associated with failure.

Clinical Study

Baseline Factors Predictive of SLT Response: A Prospective Study

Robin Bruen,<sup>1</sup> Mark R. Leck,<sup>1,3</sup> and Paul Harasymowicz<sup>2</sup>

*Journal of Ophthalmology*  
Volume 2012, Article ID 642869, 5 pages  
doi:10.1155/2012/642869

The results of our study confirm the findings of some other authors that high baseline IOP is a predictor of IOP-lowering response after SLT [19–21]. In addition, our study found that gender, age, and degree of angle pigmentation did not predict response to SLT, which is consistent with much of the other literature on the subject.

In this study, we observed a statistically significant weakening of the IOP-lowering response to SLT in eyes treated with prostaglandin analogue therapy, compared to prostaglandin naïve eyes. This diminished effect of SLT on these patients persisted even when we controlled for baseline IOP and was present at all time points. These findings are consistent with the findings of Latina and De Leon [7], and Kara et al. [10].

Figure 1. Percentage Probability of Success with SLT\*

Pre-SLT IOP (mmHg)	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50
14	28	28	28	28	17	15	13	11	9	8	7	6	5	3	3	3
16	40	36	30	28	25	22	19	16	14	12	10	9	8	5	5	5
18	51	47	40	39	35	31	27	24	21	18	16	13	12	8	7	7
20	63	59	50	50	46	42	37	33	30	26	23	20	17	13	11	11
22	73	69	59	52	57	53	49	44	40	36	32	29	25	19	17	17
24	81	78	66	72	66	64	60	56	52	48	43	39	35	27	24	24
26	87	85	69	80	78	74	71	67	63	59	55	51	46	38	34	34
28	90	86	86	87	85	82	80	77	73	70	66	62	58	49	45	45
30	93	94	95	95	90	88	86	84	80	76	73	70	66	57	53	57
32	97	96	100	94	93	92	91	89	86	81	78	75	71	60	57	58
34	99	97	100	98	96	95	94	92	90	85	80	77	73	60	57	57
36	99	99	100	98	97	96	96	94	94	93	91	90	86	84	84	84
38	99	99	100	99	99	98	98	97	97	96	95	94	90	90	90	90
40	99	99	100	99	99	99	99	98	98	97	97	96	95	94	94	94

\* In this table, the probability of success with SLT is estimated based on the results of 200 SLT patients. A logistic regression model was used to estimate the probability of an SLT patient experiencing an intraocular pressure reduction of at least 20 percent based on his highest recorded pre-SLT IOP and the pre-SLT IOP at the time of SLT.

Mao, Hutnik, et al

PubMed  
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*J Glaucoma*. 2011 Apr-May;20(4):266-70. doi: 10.1097/IJG.0b013e31821c1c07.

**SLT and adjunctive medical therapy: a prediction rule analysis.**

Brosnan J, Jones-Litton K, et al.

Author information

Abstract

**PURPOSE:** To investigate if specific classes of antiglaucoma medications have an influence on selective laser trabeculoplasty (SLT) success.

**METHODS:** This retrospective prediction rule analysis investigated 120 eyes from 120 patients diagnosed with either open angle glaucoma or ocular hypertension, who underwent SLT treatment. Treatment success was defined as ≥20% intraocular pressure (IOP) reduction at 3 and 6 months after the treatment date. Multivariate logistic regression analyses were performed to determine success predictors.

**RESULTS:** Pre-SLT IOP (up to 4 wk before SLT therapy) was the only independent predictor for ≥20% IOP reduction with an odds ratio of 1.30 when controlling for pre-SLT antiglaucoma drops. The area under receiver operating characteristic curve was 0.777.

**CONCLUSIONS:** Topical medications do not adversely, nor favorably, affect SLT success. SLT efficacy is positively associated with the degree of IOP elevation before SLT treatment. Pigmentation of the anterior chamber angle, class of antiglaucoma medications, diabetes, sex, corneal thickness, pseudophakia, diagnosis, washout of eye drops, and previous argon laser trabeculoplasty treatment are not associated with SLT treatment efficacy.

PMID: 20577103 (PubMed - indexed for MEDLINE)



- Newly diagnosed OAG and OHTN (treatment-naïve)
- Two groups:
  - Medicine 1<sup>st</sup>
  - Laser 1<sup>st</sup>
- Compared
  - HRQoL
  - Clinical Efficacy
  - Cost effectiveness
- Followed for 36 mo

## LiGHT Trial

- 356 SLT-1
- 362 Med-1

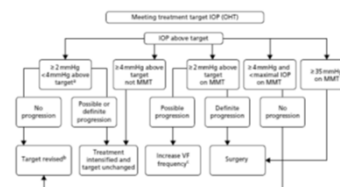


FIGURE 2 Process for escalating treatment in LiGHT. a. On two consecutive visits, b. in per cent, and c. until progression confirmed/definite. If progression required three follow-up visits, maximal IOP above which surgery was offered even without progression or 20 mmHg for LiGHT. Adapted by permission from BMJ Publishing Group Limited. The Laser in Glaucoma and Ocular Hypertension (LiGHT) trial: A multicentre randomised controlled trial comparing patient characteristics, treatment approaches, and outcomes. Li, Jiang, V, Nathanson, K, Hunter, R, Ambler, G, Bunker, C, volume 352, pp 399-403, 2016.

## LiGHT Trial Results

- 91% patients completed 36 months
  - No difference in HRQoL
  - Proportion of patients at target IOP:
    - SLT-1 93% (0 patients requiring surgery)
    - Med-1 91% (11 patients requiring surgery)
  - SLT-1 provided medicine-free treatment for at least 36 months in 74% of group

## SELECTIVE LASER TRABECULOPLASTY

- Consider when:
  - Non-compliance is an issue
  - There are undesirable or intolerable side effects from medications
  - Patient is on maximum tolerated medical therapy (?)
  - Surgical intervention is contraindicated

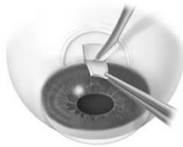
## Is There Another Bag?

## Surgery Indications

- Progressive visual field loss or optic nerve/nerve fiber layer loss despite maximum tolerated medical therapy
- Problems with adherence, allergies, intolerance to medications

## Trabeculectomy

- Goal: Create fistula between anterior chamber and subconjunctival space
- Success is dependent on surgery but also highly dependent on post-surgical care
- Advantages:
  - No devices (\$\$)
  - Can achieve very low IOP
- Disadvantages:
  - Complications up to 40% cases
  - Failure up to 50% at 5 years
  - Cataract formation

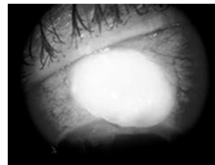


## Filtration Surgery - Complications

- Early
  - Hyphema
  - Inflammation
  - Low IOP
  - IOP spike
    - Deep AC
    - Shallow AC
  - Endophthalmitis (rare in early post-op period)

## Filtration Surgery Complications

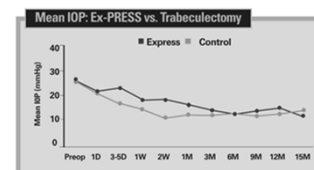
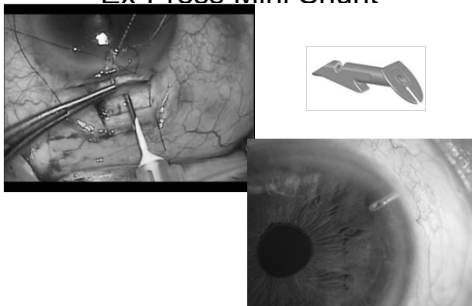
- Late Complications:
  - Bleb leak
  - Hypotony
  - Blebitis/Endophthalmitis
  - Scarring of ostomy



## Alternatives to Trabeculectomy: Ex-Press Mini Shunt

- Non-valved, MRI compatible stainless steel device with 50micron lumen
- Originally placed under the conjunctiva (complications), now placed under a scleral flap
- Lower incidence of hypotony compared to trabeculectomy
- Similar results with fewer early complications

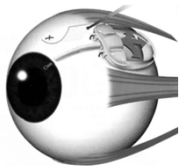
## Ex-Press Mini Shunt





## Alternatives to Trabeculectomy: Tube Shunts

- AKA Glaucoma Drainage Device
  - Historically used in patients with previous trabeculectomy failure or secondary glaucomas
  - Now more common as initial surgical choice
  - TVT study
    - Early post-op complications
      - Tube 21% Trab 37%
    - Late post-op complications:
      - Tube 34% Trab 36%
    - Reoperation for surgical complications:
      - Tube 22% Trab 18%



## Minimally Invasive Glaucoma Surgery (MIGS)

- Aim to lower IOP with a better safety profile than filtration surgery
- Often termed “blebless” surgery
- Generally rapid recovery (same as cataract surgery) with minimal impact on quality of life
- Typically indicated for mild/mod POAG

## Typical MIGS Features

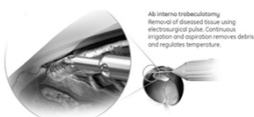
- *Ab interno*
- micro incision
- Minimal trauma
- Efficacy
- High safety profile
- Rapid recovery

## MIGS – Ab Interno

- Usually performed under gonioscopic view, usually through side port incision
- Most commonly performed at the same time as cataract surgery
  - Trabectome OR KDB (TM unroofing with blade)
  - Trabecular microbypass stent (iStent)
  - Xen gel
  - Hydrus
  - Endocyclophotocoagulation (ECP)

## Trabectome

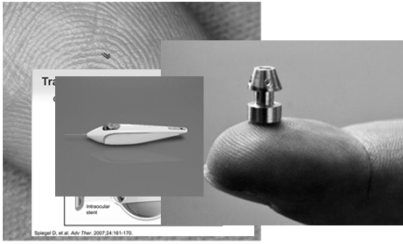
- Bipolar cautery on a handpiece inserted into the AC through the cataract incision
- Ablates and removes a portion of the TM to increase aqueous outflow
- Typical IOP goal is mid-teens
- Complications include hyphema, inflammation
- KDB (similar)



## iStent

- Very small titanium device implanted through TM into Schlemm's canal
- Goal is to improve aqueous outflow through conventional path (bypass TM directly into Schlemm's canal)
- FDA trials compared cataract surgery alone with cataract/iStent; at 12 months:
  - 68% cataract/iStent patients IOP  $\leq$  21 without meds
  - 50% cataract surgery alone IOP  $\leq$  21 without meds
- IOP not lowered as much as with trabeculectomy
- Fewer complications/less hypotony

### iStent



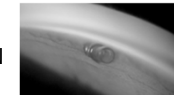
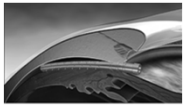
### Xen Gel Stent (Allergan)

- Creates communication between anterior chamber and the subconjunctival space from the inside of the eye



### Other Stents

- CyPass Microstent (Alcon) - WITHDRAWN



- Hydrus Micro Stent (Ivantis)

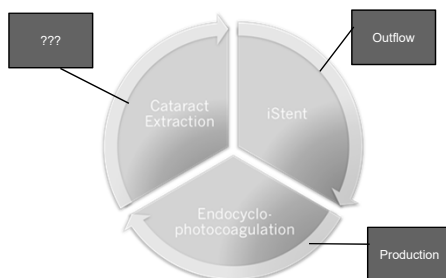
– Schlemm's Canal Scaffold



### Endocyclophotocoagulation

- Endoscopic viewing system with laser, inserted through corneal incision and used to selectively ablate ciliary processes (decrease aqueous production)
- Mean decrease over 2 years = 7.1mmHg
- Not dependent on open angle/TM visualization

### ICE Procedure



### Other Procedures – Ab Externo

- Canaloplasty
  - Circumferential catheterization with suture tensioning of Schlemm's canal

### How Do MIGS Compare to Trab?

- Few reports, somewhat difficult to compare
- Different complications
- Typically less IOP reduction with MIGS than with filtration
- Often seen as an intermediate step in glaucoma management
- Appeal: procedure at same time as cataract surgery

### MIGS – Final Point

- Since MIGS performed at time of cataract surgery, OD must be proactive in seeking surgeon who is experienced and willing to perform
- Don't miss the opportunity!

Thank you for your attention!

DMarrelli@uh.edu