Medical Therapy for Glaucoma
Current Status

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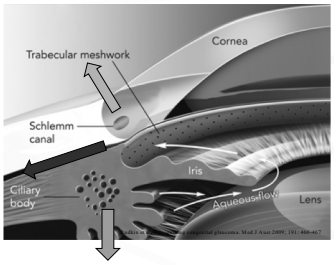
Glaucoma Center of San Francisco,
Glaucoma Research and Education Group

Financial Disclosure
Consultant: Netra Systems, Inc

Trabecular outflow
- Pilocarpine

Uveoscleral outflow
- Prostaglandins
- Alpha agonists



Aqueous inflow
- Beta blockers
- Alpha agonists
- CAIs

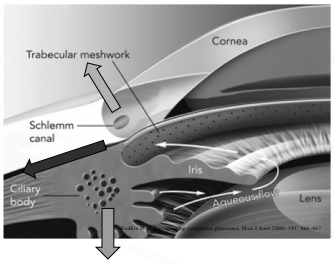
Latanoprostene bunod | Netarsudil

FDA approval Nov 2017 Dec 2017

NEW

Trabecular outflow
- Pilocarpine
- **Latanoprostene bunod**
- **Netarsudil**

Uveoscleral outflow
- Prostaglandins
- Alpha agonists



Aqueous inflow
- Beta blockers
- Alpha agonists
- CAIs

Latanoprostene bunod

- Latanoprost + Nitric oxide donating component (butanediol mononitrate)
- Dual mechanism of action
  - Latanoprost increases uveoscleral flow
  - NO relaxes TM and increases trabecular outflow
- QHS dosing

Latanoprostene bunod

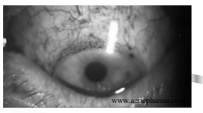
- Efficacy: IOP reduction of 8-9 mm Hg (30 to 33%) in OAG/OHTN (pooled phase-3 study findings, Weinreb et al. J Glaucoma 2008)
- Side effects
  - Similar to latanoprost
  - Stinging

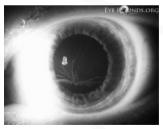
Netarsudil

- RhoKinase inhibitor
- Multiple mechanisms of action
  - Increases trabecular outflow by relaxing TM
  - Reduces episcleral venous pressure
  - Reduces aqueous production
- QHS dosing
- Efficacy: IOP reduction of 3.3 to 5.0 mm Hg (15 to 19%) in 2 phase 3 trials (ROCKET-1 and 2)

Netarsudil

- Side effects
  - Hyperemia: 53%, mostly mild and reported by investigator (not by patient)
  - Subconjunctival hemorrhages: 17%
  - Cornea verticillata: 20%
    - First noted at 4 weeks
    - Most resolved upon discontinuation





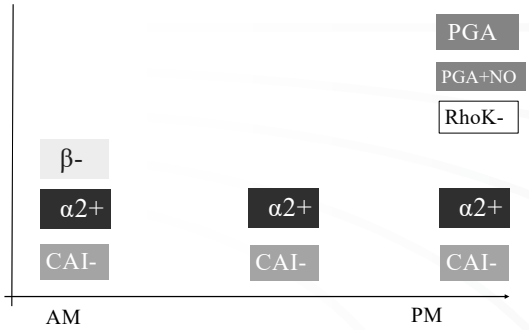
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208254Orig1s000SumR.pdf

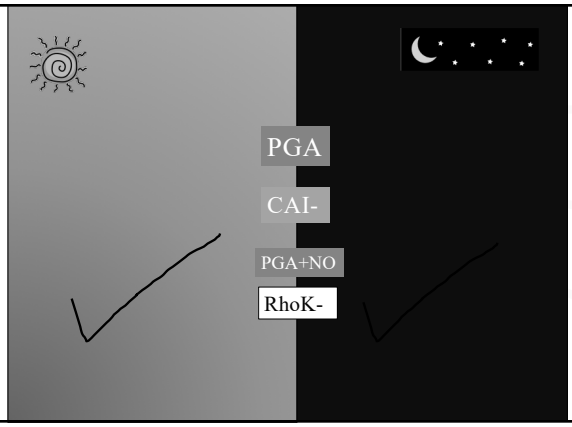
Netarsudil – Phase 3 pooled data

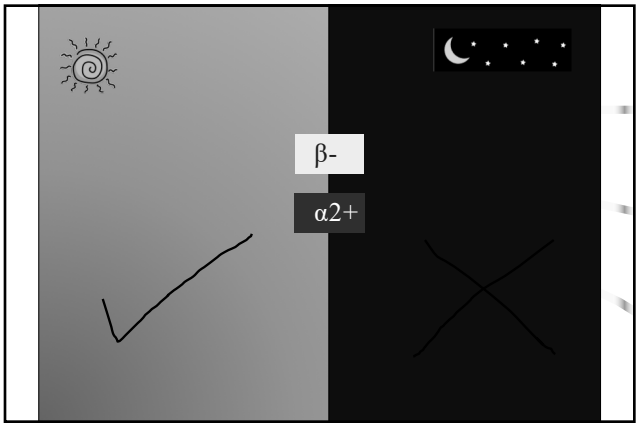
- Discontinuation rate:
  - From all adverse events (mostly ocular): **19%**
  - Due to conjunctival hyperemia: **6%**
  - Due to cornea verticillata: **4%**
  - Due to blurry vision: **1.5%**

https://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/dermatologicandophthalmicdrugsadvisorycommittee/ucm579731.pdf

Frequency of administration







Choosing first line therapy

- Effective
- Good side effect profile
- Inexpensive
- Once a day dosing
- 24 hour IOP control

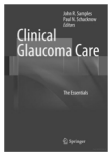


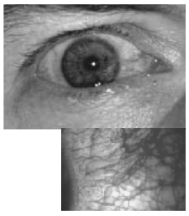
Table 23.5 Intraocular pressure-lowering effects of glaucoma medications based on a meta-analysis of 28 randomized clinical trials through 2003

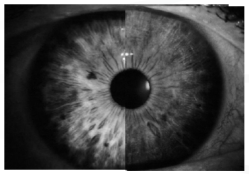
IOP-lowering effects of common glaucoma medications		
	Peak IOP (%)	Trough IOP (%)
Betaxolol	−23	−20
Timolol	−27	−26
Dorzolamide	−22	−17
Brinzolamide	−17	−17
Brimonidine	−25	−18
Latanoprost	−31	−28
Travoprost	−31	−29
Bimatoprost	−33	−28

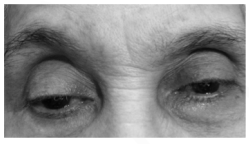
Van der Walk R, et al. IOP lowering effects of all commonly used glaucoma drugs: a meta-analysis of RCTs. Ophthalmology. 2005;112:1177-85

Prostaglandins

- Most common first line therapy
- Lower IOP by ~ 30%
- Once a day dosing (qHS)
- Effective day and night
- Few systemic side effects

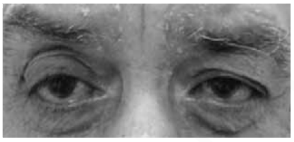






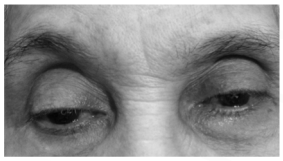
Prostaglandin associated periorbitopathy

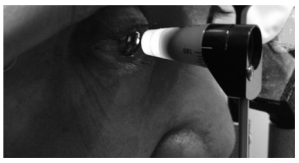
- Upper lid ptosis
- Deep upper lid sulcus
- Involution of dermatochalasis
- Periorbital fat atrophy
- Mild enopthalmos
- Inferior scleral show
- Tight eyelids
- Prominent lid vessels



Pasquale L. Prostaglandin associated periorbitopathy. Glaucoma Today Summer 2011.

Topical medications – 15 years





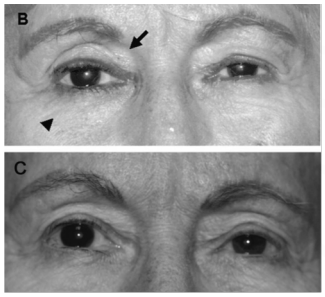
OD 17, 19
OS 18, 20

OD 12, 10
OS 10, 11

Periorbital Changes Associated With Topical Bimatoprost

Theodoros Filippopoulos, M.D.*†, Jayter S. Paula, M.D., Ph.D.†, Nurhan Torun, M.D.‡, Mark P. Hatton, M.D.§, Louis R. Pasquale, M.D.*, and Cynthia L. Grosskreutz, M.D., Ph.D.*

Ophthalmic Plastic and Reconstructive Surgery
Vol. 24, No. 4, pp 302–307 ©2008



Bimatoprost 0.03% OD for 4 years

3 months after switching from Bimatoprost to Brimonidine 0.2%

Beta blockers

- Alternative to PGAs as first line therapy
  - Concerns regarding side effects of PGAs
  - Inflammatory glaucoma
  - Pregnancy
  - Children

Beta blockers

- IOP reduction is 20-25%
- Once a day dosing (qAM)
- Not effective at night
- Few local side effects

Systemic side effects

- Cardiovascular
  - Bradycardia
  - Hypotension
  - Decreased AV conduction
- Pulmonary
  - Bronchospasm
  - Reduced exercise tolerance
- Central nervous system
  - Depression
  - Fatigue
  - Confusion
  - Sleep disturbance
- Sexual dysfunction

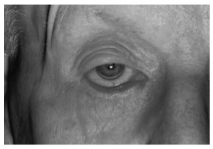
Alpha agonists and CAIs

- Disadvantages when used as first line agents
  - Must be taken 2-3 times a day
  - Relatively lower efficacy
  - Trough effect = IOP fluctuations
  - Alpha agonists not effective at night

Drug-Induced Ectropion

What Is Best Practice? *Ophthalmology 2007;114:362–366*

Vijay Hegde, MRCOphth,[1] R. Robinson, FRCOphth,[2] F. Dean, FRCOphth,[2] H. A. Malelhill, FRCSI,[1] H. Ahluwalia, FRCOphth[2]



- N = 13
- Dorzolamide 53%
  Brimonidine 23%
- Ectropion resolved partially or completely on discontinuing offending agent + topical steroid

Simbrinza

Courtesy Andrew Iwach MD

Ophthalmol Ther (2018) 7:211–215
https://doi.org/10.1007/s40123-018-0136-8

COMMENTARY

"Doctor, I have a Sulfa Allergy": Clarifying the Myths of Cross-Reactivity

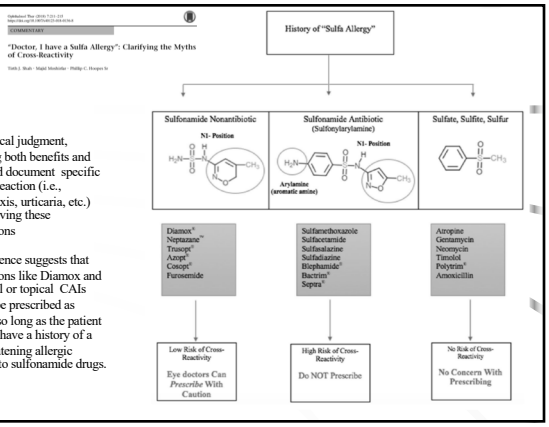
Tirth J. Shah · Majid Moshirfar · Phillip C. Hoopes Sr

- "Sulfa" drugs
  - Sulfonamide antibiotics
  - Sulfonamide non-antibiotics
  - Sulfur element - sulfate, sulfite

'Sulfa'

- Sulfonamide antibiotics and non-antibiotics differ in chemical structure and theoretically should not cross-react
- BUT, patients allergic to sulfonamide antibiotics are more likely to have future allergic reactions regardless of specific medication type

  - Strom BL et al. NEJM 2003. Patients with h/o allergy to sulfonamide antibiotics were more likely to react to sulfonamide non-antibiotics AND even more likely to react to penicillin
  - Guedes JB et al J Ocul Pharm Ther Jun 2013. Patients with a self-reported history of sulfa allergy had significantly more ocular adverse reactions after the initiation of any of the topical antiglaucoma medications when compared to those patients with no reported allergies. Self-reported sulfa-allergic patients had similar rates of adverse reactions to topical CAIs compared with topical prostaglandin analogues.



- Use clinical judgment, weighing both benefits and risks, and document specific allergic reaction (i.e., anaphylaxis, urticaria, etc.) before giving these medications
- The evidence suggests that medications like Diamox and other oral or topical CAIs should be prescribed as needed, so long as the patient does not have a history of a life-threatening allergic reaction to sulfonamide drugs.

Newer options for first line therapy

- Latanoprostene bunod and Netarsudil
  - Advantages:
    - May help maintain the physiological aqueous outflow pathways
    - Convenient dosing
  - Disadvantages
    - Cost/Access
    - Netarsudil: Side effects/Lower efficacy

Adjunctive treatment

- Many glaucoma patients require more than one medication to adequately lower IOP
  - OHTS, 40% required 2 or more meds by year 5
  - CIGTS, 75% required 2 or more meds after 2 years of treatment
- With PGA monotheraphy, consider trying a different PGA before adding another medication

Choosing adjunctive therapy

- Additional IOP lowering
- Other factors
  - Side effects
  - Impact on adherence
    - Dosing schedule
    - Cost

Adjunctive therapy to PGAs

- Beta blockers
  - Easy once daily dosing schedule
  - Poor nocturnal IOP control
- Rho Kinase inhibitor
  - Easy qd dosing
  - Diurnal and nocturnal IOP control
- Topical CAIs
  - At least BID
  - Diurnal and nocturnal IOP control
- Brimonidine
  - At least BID
  - Poor nocturnal IOP control

Choosing adjunctive therapy to PGA

- All classes of medications are effective when added to PGA
- Added medication is usually less effective than monotherapy with the same drug

Tabet et al. A review of additivity to PG Analogs:Fixed and unfixed combinations. Survey of Ophthalmology. Nov 2008
Tanna et al. Meta-analysis of efficacy and safety of ….with prostaglandin analogs. Archives of Ophthalmology July 2010

Meta-analysis of the Efficacy and Safety of α_2-Adrenergic Agonists, β-Adrenergic Antagonists, and Topical Carbonic Anhydrase Inhibitors With Prostaglandin Analogs

Angelo P. Tanna, MD; Alfred W. Rademaker, PhD; William C. Stewart, MD; Robert M. Feldman, MD

Arch Ophthalmol. 2010;128(7):825-833

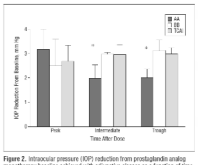


Figure 2. Intraocular pressure (IOP) reduction from prostaglandin analog monotherapy baseline achieved with adjunctive classes as a function of time after dosing. Error bars indicate the upper limits of the 95% confidence intervals. Asterisks indicate that the α_2-adrenergic agonist (AA) group achieved statistically significantly less IOP reduction compared with the β-adrenergic antagonist (BB) and topical carbonic anhydrase inhibitor (TCAI) groups at intermediate and trough times.

- Mean IOP reduction of ~3mm Hg
- Alpha agonists less effective at trough than beta blockers/CAIs

New medications versus latanoprost

- Latanoprostene bunod
  - Mean diurnal IOP 1.23 mm Hg lower (VOYAGER study)
- Netarsudil
  - Average IOP 1.8mm Hg lower (Mercury 2 study)

First line and adjunctive therapy

- No one-size-fits-all algorithm
- Treatment has to be individualized for each patient

Medical therapy during Pregnancy and Lactation

Table 1. FDA's classification of glaucoma medications

FDA Class	Description	Glaucoma medications
A	Strong evidence of safety based on human studies	None
B	Varying and/ or contradictory human and animal study data	Brimonidine
C	Side-effects shown in animal models but few or no human studies	Beta blockers
		Carbonic anhydrase inhibitors
		Prostaglandin analogues
D	Human studies showing risk to fetus	None
X	Strong evidence of birth defects in humans	None

Salim S. Glaucoma in pregnancy. Curr Opin Ophthalmol 2014,25:93-97

Beta blockers in pregnancy/lactation

- Category C (side effects shown in animal studies, inadequate human studies)
- Most common first choice in pregnancy
  - Frequently used by obstetricians to treat pregnancy-induced hypertension
  - Long-standing experience
- Consider lower concentration and gel forming solution
- American Academy of Pediatrics has approved use during lactation

Carbonic Anhydrase Inhibitors

Pregnancy

- No reports of adverse effects with topical CAIs
- Avoid oral CAIs
  - Sacrococcygeal teratoma
  - transient renal tubular acidosis in neonates

Lactation

- Acetazolamide approved by American Academy of Pediatrics
  - Level in breastmilk 1/3rd of plasma level

Brimonidine in pregnancy/lactation

- Only Class B drug (No risk in animal studies, inadequate human studies)
- Avoid near-term and during nursing
  - CNS effects on infants
    - Severe hypotension and apnea

Prostaglandin analogs

- Generally avoided since this class of medications is used to induce labor
- ? Safe to use in pregnancy
  - Systemic dose with topical use extremely low
  - Case series of 11 women exposed to latanoprost*
    - No adverse effects on pregnancy or neonatal outcome
- No data to guide use during lactation

*DeSantis et al, AJO August 2004

Considerations in chronic medical therapy

Preservatives

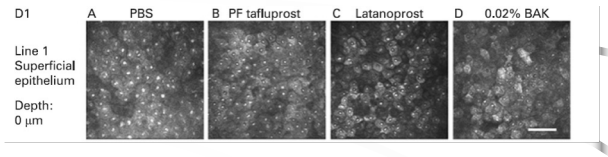
Prevalence of Ocular Surface Disease in Glaucoma Patients

Eamon W. Leung, MD, Felipe A. Medeiros, MD, PhD, and Robert N. Weinreb, MD

J Glaucoma 2008;17:350–355

- Cross-sectional study of glaucoma patients on medical therapy
- **60%** reported symptoms of OSD (OSDI questionnaire)
- More BAK containing drops associated with higher odds of abnormal lissamine green staining

Preservatives



Liang H, Baudouin C et al. BJO 2008
Conjunctival and corneal reactions in rabbits…

Non-BAK preservatives

PURITE®

SofZia ®

Brimonidine 0.1%

Travoprost 0.004%

Non-BAK preservatives

PURITE®

Brimonidine 0.1%

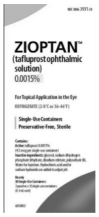
SofZia ®

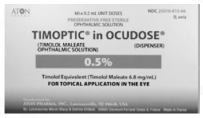
Travoprost 0.004%

Potassium Sorbate

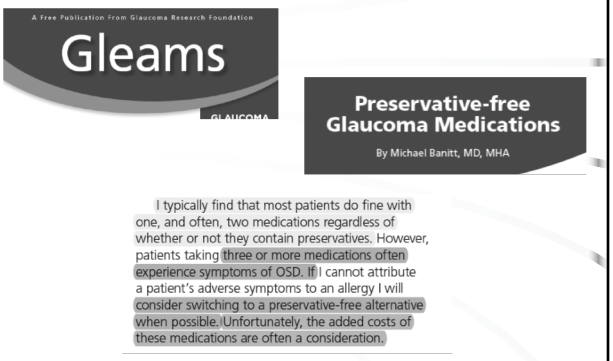
Latanoprost 0.005%

Commercially available preservative free medications





Compounded formulations



Combination medications

Considerations in chronic medical therapy

Adherence

Nov/Dec 2016

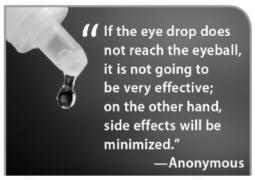
THE ADHERENCE PROBLEM

Its scope and strategies for its reduction.

BY HENRY D. JAMPEL, MD, MHS

Not all patients obtain their first prescription for eye drops, many do not regularly refill them,[1] and some who have a bottle in hand do not use it with prescribed regularity.[2] These problems are compounded by patients who run out of eye drops before their insurance plan allows them to obtain a refill and by the inability of others to safely hold a bottle half an inch over their eye and then successfully squeeze it to deliver medication to the cornea, sclera, or conjunctiva.[3]

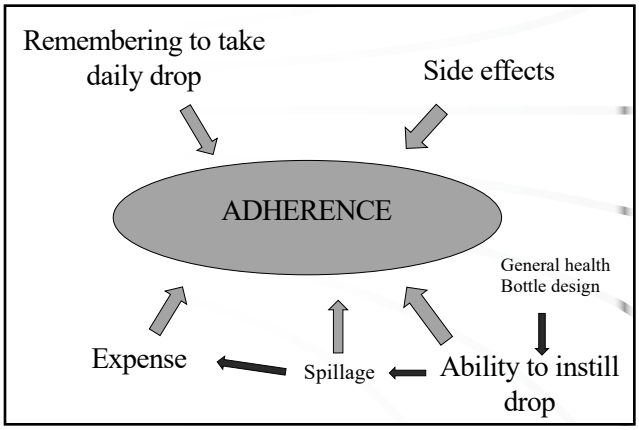
For all of these reasons, poor adherence to prescribed topical IOP-lowering therapy is a problem but certainly not a new one. Kass and colleagues informed the glau-



Adherence

- Based on several studies, the adherence rate for glaucoma therapy is ~ **60%** Schwartz G, Glaucoma Today July/Aug 2014
- Various ways of measuring adherence
  - Electronic monitoring: ~ 20% with poor compliance
  - Prescription records: only 56% of days of therapy could be accounted for by medication supply dispensed
  - Medical chart review: Only 67% remained persistent 12 months after starting therapy

Reardon G, Kotak S, Schwartz GF.Objective assessment of compliance and persistence……a systematic review. *Patient Preference and Adherence*. Sept 2011



The Most Common Barriers to Glaucoma Medication Adherence

A Cross-Sectional Survey

Paula Anne Newman-Casey, MD, MS,[1] Alan L. Robin, MD,[1,2] Taylor Blachley, MS,[1] Karen Farris, PhD,[3] Michele Heisler, MD, MPA,[4,5] Ken Resnicow, PhD,[4] Paul P. Lee, MD, JD[1]

Ophthalmology *Volume 122, Number 7, July 2015*

- N = 199 patients on 1 or more glaucoma meds
- 61% cited MULTIPLE barriers
- 30% of those with poor adherence cited EACH of the 11 barriers as important

Barriers to Glaucoma Medication Adherence
Beliefs about glaucoma, skepticism that glaucoma will cause vision loss
Beliefs about glaucoma medications, skepticism that glaucoma medications will mitigate vision loss
Poor self-efficacy
Poor knowledge about glaucoma
Mistrust of physician
Difficulty with eye drop administration
Medication cost
Medication-induced side effects
Forgetfulness
Difficulties with the medication schedule
Life stress

Identifying non-adherence

- Open-ended questions:

"What difficulties are you having with your drops?"
versus
"Are you having difficulties with your drops?"

"How often do you miss your drops?"
versus
"Do you miss your drops?"

Schwartz G, Glaucoma Today July/Aug 2014

Enhancing Glaucoma Patients' Adherence to Prescribed Medical Therapy

BY GAIL F. SCHWARTZ, MD

THE KEY POINTS RELATED TO NONADHERENCE

- relying on the doctor for all glaucoma-related information
- lack of concern regarding vision loss
- difficulty taking medication when away from home
- not keeping appointments (shown in several studies in addition to the Glaucoma Adherence and Persistency Study [GAPS][1-4])
- "skipping" versus "forgetting"
- no complaints of burning or stinging
- cost
- not white
- dependence on samples
- concern about side effects
- not wanting others to notice his or her eyes, such as with hyperemia

1. Friedman DS, Quigley HA, Gelb L, et al. Using pharmacy claims data to study adherence to glaucoma medications: methodology of the Glaucoma Adherence and Persistency Study (GAPS). *Invest Ophthalmol Vis Sci*. 2007;48:5052-5057.
2. Friedman DS, Nordstrom B, Mozaffari E, et al. Glaucoma management among individuals enrolled in a single comprehensive insurance plan. *Ophthalmology*. 2009;116:1500-1504.
3. Schwartz GF, Platt R, Reardon G, et al. Accounting for restart rates in evaluating persistence with ocular hypotensives. *Ophthalmology*. 2007;114:648-652.
4. Kosoko O, Quigley HA, Vitale S, et al. Risk factors for noncompliance with glaucoma follow-up visits in a residents' eye clinic. *Ophthalmology*. 1998;105:2105-2111.

Improving adherence

- Simplified dosing regimens
- Written instructions
- Watch patients administer drops
- Reminders (calls/apps)
- Involve family members
- Ask about side effects
- Ask about cost
- Associate medication use with activities the patient never misses
- Regular education
- Frequent follow-ups to reinforce importance of adherence

RESEARCH REPORT

Feasibility, Patient Acceptability, and Preliminary Efficacy of a Culturally Informed, Health Promotion Program to Improve Glaucoma Medication Adherence Among African Americans: "*Glaucoma Management Optimism for African Americans Living with Glaucoma*" (GOAL)

Laura E. Dreer[1], Cynthia Owsley[2], Lisa Campbell[2], Liyan Guo[1], Andy Wood[1] and Christopher A. Girkin[3]

Current Eye Research, Early Online, 1–9, 2015

Feasibility of motivational interviewing delivered by a glaucoma educator to improve medication adherence

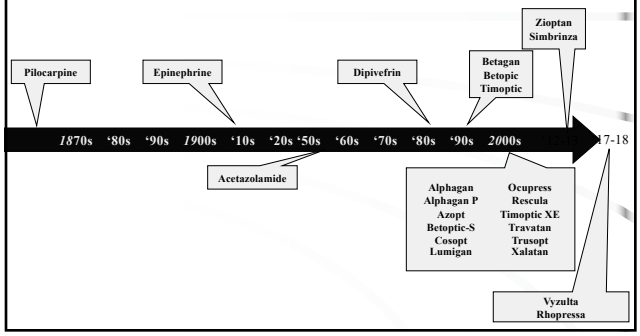
Paul P. Cook[1] Robert W. Bremer[2] Aj Ayala[3] Malik Y. Kahook[2]

Clinical Ophthalmology 2010:4 1091–1101

Interventions Improve Poor Adherence with Once Daily Glaucoma Medications in Electronically Monitored Patients

Ophthalmology 2009;116:2286–2293

Glaucoma Therapeutic Option Timeline



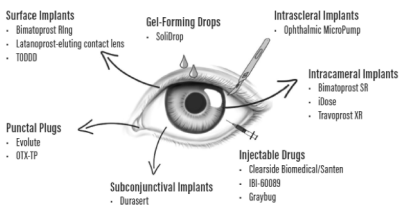
Better drug delivery devices needed to improve patient outcomes

Ocular Surgery News U.S. Edition, May 10, 2014
Richard L. Lindstrom, MD

1953

While on a sales call in West Texas, Robert Alexander and a local physician create and patent the DROP-TAINER® eye drop dispensing bottle, now standard for eye care products.

Glaucoma Today May/June 2018



AMERICAN ACADEMY OF OPHTHALMOLOGY

Ophthalmology 2016;123:1685-1694

Six-Month Intraocular Pressure Reduction with a Topical Bimatoprost Ocular Insert

Results of a Phase II Randomized Controlled Study

James D. Brandt, MD,[1] Kenneth Sall, MD,[2] Harvey DuBiner, MD,[3] Robert Benza, MD,[4] Yair Alster, MD,[5] Gary Walker, PhD,[3] Charles P. Semba, MD[3]

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Ocular retention rate of insert

- 93% at 3 months
- 89% at 6 months

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	Bimatoprost Patients (n = 64)	Timolol Patients (n = 66)
Ocular TEAE		
Patients with any ocular TEAE	29 (45.3)	23 (34.8)
Ocular TEAE ≥5%		
Eye discharge	10 (15.6)	9 (13.6)
Conjunctival hyperemia	9 (14.1)	3 (4.5)
Punctate keratitis	8 (12.5)	4 (6.1)
Eye pruritus	7 (10.9)	2 (3.0)
Ocular discomfort	4 (6.3)	2 (3.0)

- Bimatoprost insert showed ~20% IOP reduction sustained for 6 months
- Timolol provided 0-1.5mmHG more IOP reduction than BIM insert

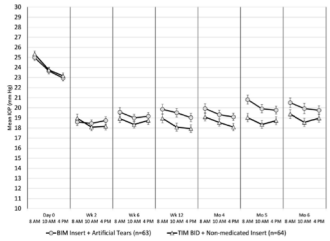


Figure 4. Graph showing the mean intraocular pressure (IOP) at each time point in a study of a bimatoprost (BIM) insert plus artificial tears compared with timolol 0.5% ophthalmic solution (TIM) and a nonmedicated insert (observed data; full analysis set population). Diurnal washout IOPs are shown at day 0 (D0) followed by diurnal IOPs at 8 AM, 10 AM, and 4 PM at weeks (Wk) 2, 6, and 12 and at months (Mo) 4, 5, and 6. BID = twice daily.

Mean IOP reduction from baseline: 3.2 to 6.4mm HG for bimatoprost insert, 4.2 to 6.4 mm HG for timolol

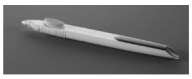
Intracameral versus surface delivery

- Intracameral delivery is more invasive but lower drug concentration is required which reduces side effects

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

American Journal of Ophthalmology March 2017

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



28G applicator
Drug concentration 6 to 20 µg

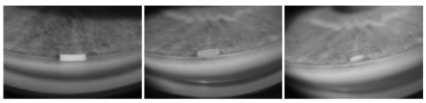


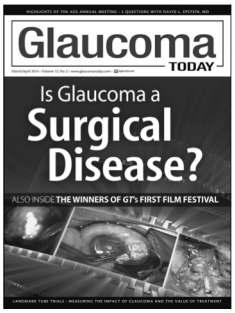
FIGURE 3. Gonioscopic photographs of bimatoprost sustained-release implant 10 µg in the anterior chamber of an eye of a representative patient diagnosed with open-angle glaucoma at (Left) 2 weeks, (Center) 9 months, and (Right) 12 months after injection.

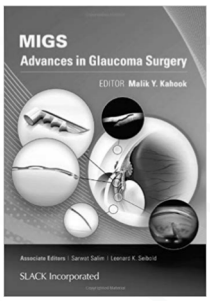
Bimatoprost SR

- IOP lowering efficacy similar to topical bimatoprost 0.03%
- IOP lowering lasted for 6 months in 71%
- Side effects
  - Usually occurred within 2 days of injection and were transient
  - Conjunctival hyperemia occurring after 2 days was greater in the topical bimatoprost group (17.3% vs. 6.7%)

Patient attitudes towards sustained delivery devices – Acceptance rates

- Survey in Singaporean Chinese subjects Chan HH et al. J Glaucoma Sept 2015
  - Punctal plugs: 63%
  - Intracameral implant: 57%
  - Punctal plugs preferred over subconjunctival or intracameral routes.
- U.S. based survey (67% Caucasian) Wang BB Digit J Ophthalmol Sept 2018
  - Triple combination drop: 85%
  - Periocular ring insert: 31%
  - Intracameral implant: 30%





Summary

- Most glaucoma patients will be treated medically
- Many options available
  - treatment must be tailored to the individual
- Limitations of the 'eyedrop' model are well recognized