Glaucoma Pharmacology: Old, New and What to Do?

Joseph Sowka, OD
Greg Caldwell, OD

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Medication	Bottle Top Color
Prostaglandin analogue	Light green/Teal
Beta blockers	Yellow or light blue
Carbonic anhydrase inhibitors	Orange
Alpha-adrenergic agents	Purple
Miotics	Dark green
Combination drops	Dark blue
Rho-Kinase	White

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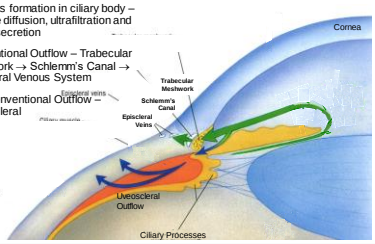
AQUEOUS HUMOR DYNAMICS

IOP – A Complex Homeostasis

- Aqueous formation in ciliary body – passive diffusion, ultrafiltration and active secretion
- Conventional Outflow – Trabecular Meshwork → Schlemm's Canal → Episcleral Venous System
- Non-Conventional Outflow – Uveoscleral



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GLAUCOMA EPIDEMIOLOGY AND TREATMENT

Current Medical Treatments for OAG

↓Aqueous Production	↑ Aqueous Outflow	
	Conventional	Unconventional
β-blocker CAI α_2-agonist	Cholinergic agonist NO-donating PGA RhoKinase inhibitor	Prostaglandin analog NO-donating PGA α_2-agonist

Updated 1/7/18

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PROSTAGLANDINS: OCULAR ADVERSE EFFECTS

- **Hyperemia**
- **Increased iris coloration**
- **Periorbitopathy: skin darkening, Sulcus deepening**
  - Hyperemia is reversible with medication cessation. Iris color changes appear to be irreversible. Periorbitopathy may be reversible if the medication is stopped soon enough, but may indeed be permanent.
- **Hypertrichosis**
- **Punctate keratopathy, dry eye**
- **Uveitis, CME, and dendritic keratitis?**

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PROSTAGLANDINS

- **Prostaglandins are not indicated ideal in secondary inflammatory glaucoma or any clinical entity that has anterior segment inflammation as a component**
- **Prostaglandins are important in that they flatten the diurnal IOP curve as well as giving lingering IOP reduction even as much as 60 hours after dosing. Thus, they are more forgiving of patients that miss dosages.**

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PROSTAGLANDINS

- Xalatan® (latanaprost 0.005%)
  - Generic latanoprost…**APPROVED 3-22-2011**
- Travatan-Z® (travoprost 0.004%)
  - Preserved with Sofzia
- Lumigan® (bimatoprost 0.01%)
- Zioptan ® (tafluprost 0.0015%)- Merck
  - Preservative free
- Vyzulta™ (latanoprostene bunod 0.024%)
  - Approved 11/2/17
  - NO donating PGA

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VYZULTA™ (latanoprostene bunod ophthalmic solution, 0.024%)

- First prostaglandin analog with one of its metabolites being nitric oxide (NO)
- QD dosing
- Dual mechanism of action
  - metabolizes into two moieties, latanoprost acid, which primarily works within the *uveoscleral* pathway to increase aqueous humor outflow, and butanediol mononitrate, which releases NO to increase outflow through the *trabecular meshwork* and Schlemm's canal.
  - Blocks RhoKinase and calcium signaling

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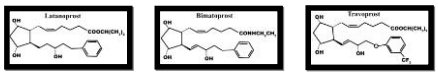

Results of Meta-Analyses of Studies Assessing the Comparative Efficacy of Prostaglandin Analogs

Results of Meta-Analyses of Studies Assessing the Comparative Efficacy of Prostaglandin Analogs

Author/ Reference	Drugs/ Condition	No. of Articles	Sponsor	Relative Efficacy
Denis[42]	Lat/Bim/Trav POAG/OH	9	Alcon	Trav = Bim > Lat
Li[44]	Lat/Bim/Trav POAG/OH	12	Indep	Lat = Bim = Trav
Holmstrom[70]	Lat/Bim/Trav POAG	42	Allergan	Bim > Lat = Trav
van der Valk[145]	Lat/Bim/Trav POAG/OH	27	Indep	Lat = Bim = Trav

Bim = bimatoprost; Indep = independent, no support claimed in the publication; Lat = latanoprost; OH = ocular hypertension; POAG = primary open-angle glaucoma; Trav = travoprost.

Bean GW, Camras CB. Commercially available prostaglandin analogs for the reduction of intraocular pressure: similarities and differences. Surv Ophthalmol. 2008 Nov;53 Suppl1:S69-84.

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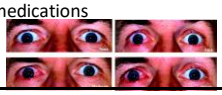
Sorting out the prostaglandins: The XLT study

- The first study performed that simultaneously compared the clinical outcomes associated with the use of latanoprost, bimatoprost, and travoprost
- Compared not only the effectiveness of IOP reduction of the three medications, but also examined the adverse effects and tolerability of the medications



Parrish R, Feldberg F, Shieu WP, and the XLT Study Group. A comparison of latanoprost, bimatoprost, and travoprost in patients with elevated intraocular pressure: A 12-week, randomized, masked-evaluator multicenter study. Am J Ophthalmology 2003; 135 (5):688-703

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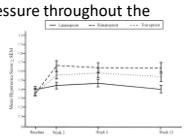
The XLT study

- IOP was significantly reduced from baseline for all three medications.
  - Magnitude of the reduction was not statistically significant between the medications
- There was no significant difference between the medications in the persistence of pressure lowering or for the mean diurnal pressure throughout the study



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"Great, but can you tell me something that maybe I didn't already know?"

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PGA in Chronic Angle Closure Glaucoma

- Mechanism is unknown, but results are impressive
- Aqueous may gain access to CB face/ uveoscleral meshwork via still open part of angle- or another pathway unknown
- PGA have demonstrated pronounced effect in eyes even with complete PAS angle closure
  - –May decrease IOP through uveoscleral tissues other than ciliary face

Kook MS et al. Efficacy of latanoprost in patients with chronic angle-closure glaucoma and no visible ciliary body face. A preliminary study. J Oc Pharm and Therapeutics; 2005; 21(1):75-84

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PGA for chronic angle closure is an exceptional therapeutic option.

Remember that LPI still needs to be performed.

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Autonomics

- **Sympathetic Agents**
  - Adrenergic agonists
    - Sympathomimetic
    - Norepinephrine based
  - Adrenergic antagonist
    - Sympatholytic
- **Parasympathetic Agents**
  - Parasympatomimetics
  - Cholinergic agonists
  - acetylcholine based
  - miotics

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Sympathetics

- Alpha 1
  - Blood vessels of ciliary body: vasoconstriction, which reduces blood flow and aqueous production.
  - Epinephrine-like drugs
- Alpha 2
  - Nerve terminal
- Beta 1
  - Heart: increased
- Beta 2
  - Lungs: relaxed- increased breathing ability
- Beta 1 & 2 on ciliary body
  - Stimulation increases aqueous production
  - Blocking B1 & 2 receptors reduces aqueous production
    - Beta blockers

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Parasympathetics

- Iris: miosis
- Ciliary body: accommodation and trabecular meshwork opening
- Trabecular meshwork: aqueous outflow increase
- Ciliary meshwork (uveal meshwork-uveoscleral pathway)- aqueous outflow decrease

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Parasympathetics

- Glands: increased activity
- Heart: reduced activity
- Blood vessels: vasodilation
- Lung: bronchiole constriction
- Because these organs are more controlled by the sympathetic system, there is less systemic affects by parasympathomimetic drugs than would be expected.
- Gastrointestinal tract: increased motility
- Urinary tract: increased motility

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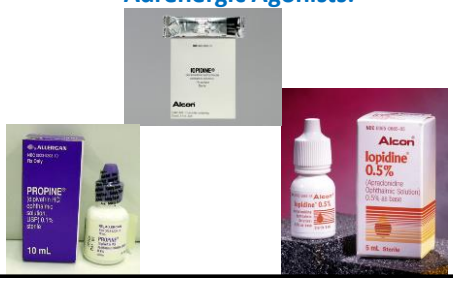
Adrenergic Agonists:



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Adrenergic Agonists:

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Alpha-2 agonists

- Brimonidine acts presynaptically to inhibit release of norepinephrine and reduces adrenergic receptor stimulation. The reduced sympathetic activity in ciliary body reduces aqueous production.
  - Some increase in uveoscleral outflow
- TID dosing
  - Often used initially BID.
  - BID dosing can leave the patient with uncontrolled IOP at certain times of the day.
    - This is significant for monotherapy
  - Patients on polytherapy may be able to get away with BID dosing

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Alpha-2 agonists

- The most significant side effects are drowsiness and fatigue, headache, and dry mouth
- Other side effects:
  - Conjunctivitis (follicular), Blurring, Burning
- Early and late onset Alphagan allergy

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Brimonidine

- No effect on blood pressure, pulse, or pulmonary function
  - Minimal cardiovascular and pulmonary responses- not frankly contraindicated in patients with cardiovascular disease, but use caution in patients with ischemic heart disease or prior MI
- Concurrent use of MAO inhibitors (anti-depressants) are a contraindication to the use of Alphagan
- Does not appear to have IOP lowering effects at night/during sleep

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"Great, but can you tell me something that maybe I didn't already know?"

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Brimonidine

- Crosses blood-brain barrier and has CNS effects
- Adverse effects are most significant in smaller patients and children
- This medication has induced fatigue, drowsiness and even coma in children
- Contrary to what you might have heard, Alphagan is not proven neuroprotective

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Beta Blockers

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Beta Blockers: Contraindications

- Asthma
- Emphysema
- Myasthenia gravis
  - Can worsen myasthenia gravis
- Cerebrovascular insufficiency
- Greater than 1st degree heart block
- Hypotension (<100/60)
- Beta blockers are bad for athletes as it prevents heart rate from exceeding 135 BPM. Athletes cannot train through this block.
- Every patient considered for a topical beta blocker needs baseline blood pressure and resting pulse measurement in addition to review of medical history.

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Beta Blockers: Adverse Effects

- Bradycardia:
  - Slowing of sinus nodal discharge with resultant dose-dependent bradycardia. In most cases, the degree of bradycardia is asymptomatic and does not impact a patient's life.
- Patients using topical beta blockers who develop symptomatic bradycardia -- as manifested by diminished capacity for physical activity or undiagnosed syncope -- likely have coexistent pathology of the sinus AV node or conduction pathways and should be referred to a cardiologist.
  - Problem is not likely solely due to beta blockers

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Beta Blockers

- Topical beta blocker therapy should be avoided in patients with asymptomatic bradycardia and heart block.
  - Patients with symptomatic bradycardia often present with syncope and dizziness, and are identified prior to ophthalmic examination.
- Asymptomatic patients without aerobic conditioning (i.e., athletes) with resting pulse rate under 55 beats per minute should be evaluated by a cardiologist.
  - However, patients with normal resting pulse rates and with no history of syncope or dizziness are unlikely to experience any serious bradycardia effects from topical beta blockers.

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Beta Blockers

- The most significant contraindications are COPD, asthma, emphysema, symptomatic bradycardia, and asymptomatic bradycardia with heart block.
- Beta blockers can be considered in patients with CHF pending approval by the patient's PCP. All other contraindications can be considered 'relative' and beta blockers can be used in many of these situations on a case-by-case basis.
- If a 'contraindication' is present, it doesn't mean that beta blockers (or any medication for that matter) cannot be used, but should be a lesser choice.

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Beta Blockers

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BETA-BLOCKERS

- Timoptic® (timolol maleate 0.25% & 0.5%)
- Timoptic-XE® (timolol maleate gel-forming solution)
- Istalol® (timolol maleate 0.5%)
- Betimol® (timolol hemihydrate 0.5%)
- Betagan® (levobunolol HCl 0.25%)
- Betoptic-S® (betaxolol HCl 0.25% suspension)
  - Beta 1 selective
- Optipranolol® (metipranolol 0.3%)
- Ocupress® (carteolol HCl 1.0%)
  - ISA
  - Residual agonal tone
  - Least likely to affect cardiac system

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"Great, but can you tell me something that maybe I didn't already know?"

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Other Reported Adverse Effects

- *Depression*
- *Loss of diabetic control*
- *Claudication*
- Anxiety
- Fatigue
- Malaise
- Irritability
- Somnolence
- Confusion
- Death
- Palpitations
- *Impotence*
- Diarrhea, nausea, cramps
- *Altered lipid profiles*

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- While there are specific contraindications to the use of topical beta blockers, it appears that much of the propagated fears about this class of medication stems from anecdotal cases reports or sources without sound scientific background.
- There appears to be no support for the induction by topical beta blockers of depression, sexual dysfunction, claudication, prolonged hypoglycemia or hypoglycemic unawareness.
  - Anecdotal reports without controlling for other variables or co-morbidities

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PERSPECTIVE

Systemic Adverse Effects of Beta-adrenergic Blockers: An Evidence-based Assessment

PAUL J. LAMA, MD

• CONCLUSIONS: Many commonly presumed adverse beta-adrenergic blocker effects observed via systemic or ocular administration are not supported by published randomized clinical trials. Wide acceptance of such traditionally purported side effects has been largely due to propagation of isolated case reports and short series as well as personal communication felt to reflect expert opinion. Many more patients may be eligible to use these drugs. Obtaining a careful medical history and checking pulse rate and rhythm in the office should identify the vast majority of patients with potential cardiopulmonary contraindications. (Am J Ophthalmol 2002;134:749–760. © 2002 by Elsevier Science Inc. All rights reserved.)

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Miotics

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Miotics

- Induces ciliary body contraction
- Increases outflow of aqueous through trabecular meshwork (conventional pathway). Tends to decrease outflow through uveoscleral pathway (unconventional pathway).
- 4-8 hrs IOP effect, thus QID dosing
- Oldest anti-glaucoma medication

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Miotics

- Miosis
  - Vision reduction, especially with cataracts
- Field constriction
- Accommodative spasm & myopic shift
- Brow ache from ciliary body contraction
- Globe and orbital pain
- Allergic reactions
- Posterior synechia in some cases
- Retinal detachment due to CB contraction
  - Not common, but be aware of the potential

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"Great, but can you tell me something that maybe I didn't already know?"

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Miotics still have a role today

- Primary angle closure glaucomas
  - Plateau iris syndrome
- Endstage POAG when surgery is not an option
  - Start with 1% BID and work up

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Carbonic Anhydrase Inhibitors

- Sulfonamide non-antibiotic
- Carbonic anhydrase catalyzes the hydration of carbon dioxide to carbonic acid that then dissociates into bicarbonate ions and hydrogen.
- $CO_2 + H_2O \rightarrow CA \rightarrow H_2CO_3 \rightarrow H^+ + HCO_3^-$
- Bicarbonate diffuses into the eye, making it hypertonic in relation to plasma, and fluid flows osmotically into the eye from plasma.

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Carbonic Anhydrase Inhibitors

- Blocking carbonic anhydrase blocks bicarbonate formation - Blocks osmosis into posterior chamber
- Blocks aqueous formation by slowing production of bicarbonate in secretory neuroepithelial cells of ciliary body

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Oral/ Systemic CAIs

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Topical CAIs

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Carbonic Anhydrase Inhibitors

- Dosing label TID, often used BID
- Good additive to PGAs
- Appears to lower IOP at night

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CAI: Contraindications and AES

- Sulfonamide sensitivity**
- Low endothelial cell count
- Blurred vision
- Dysguesia
- Hyperemia
- Corneal edema
- Dry eye
- Dry mouth
- Ocular irritation

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"Great, but can you tell me something that maybe I didn't already know?"

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- While topical CAIs are not thought of as especially good primary agents in adults, they work especially well and are well tolerated in children.
- Topical CAIs are excellent options when IOP reduction is needed in children
  - –In contrast, PGAs tend to not work

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ONCE-DAILY rhopressa® (netarsudil ophthalmic solution) 0.02%

ROCK/Norepinephrine Transporter (NET) Inhibitors

Netarsudil 0.02% (Rhopressa™)- approved 12/18/17

Netarsudil/latanoprost 0.02%/0.005% (Roclatan™)- not yet approved

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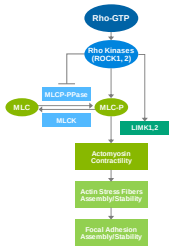
Rho Kinase (ROCK) Inhibition

New Development in IOP Reduction

- Rho activation increases contractility of TM cells
  - Reduces outflow of aqueous humor
- Rho kinase inhibition relaxes TM cells
  - Reduces actin stress fibers/focal adhesions
  - Increases outflow of aqueous humor
- Rho kinase inhibition may also:
  - Increase ocular blood flow
  - Increase retinal ganglion cell survival



Uehata M, et al. *Nature* 1997;389:990-994
Hirata A, et al. *Graefes Arch Clin Exp Ophthalmol.* 2008;246(1):51-59
Wang SK, Chang RT. *Clin Ophthalmol* 2014:8:883-890

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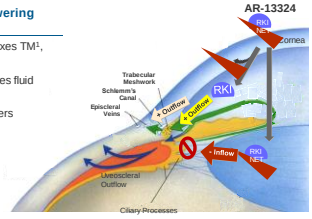
Netarsudil ophthalmic solution 0.02% (ROCK-NET Inhibitor) Triple-Action

3 Identified IOP-Lowering Mechanisms

- ROCK inhibition relaxes TM[1], increases outflow[1,2]
- NET inhibition reduces fluid production[2]
- ROCK inhibition lowers Episcleral Venous Pressure (EVP)[3]



1. Wang SK, Chang RT. An emerging treatment option for glaucoma: Rho kinase inhibitors. *Clin Ophthal* 2014:8:883-890.
2. Wang RF, Williamson JE, Kopczynski C, Serle JB. Effect of 0.04% AR-13324, a ROCK, and norepinephrine transporter inhibitor, on aqueous humor dynamics in normotensive monkey eyes. *J Glaucoma* 2015; 24(1):51-4.
3. Kiel JW, Kopczynski C. Effect of AR-13324 on episcleral venous pressure (EVP) in Dutch Belted rabbits. *ARVO* 2014. Abstract 2900

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Netarsudil ophthalmic solution 0.02%: Rhopressa™ (Rocket 1) Efficacy Results At Different Baseline IOPs

Baseline IOP (mmHg)	Non-inferiority	Numerical Superiority
<27*	Did not meet	Met 2 time points
<26***	Met	Met 4 time points
<25***	Met	Met 7 time points
<24**	Met	Met All 9 time points
<23***	Met	Met All 9 time points

- Per Protocol population (baseline IOP < 27 mmHg)
- Netarsudil did not meet criteria for non-inferiority to Timolol
- Inferiority was driven by a small subset of Netarsudil patients with the highest baseline IOPs

* Primary endpoint
** Pre-specified secondary endpoint
*** Post-Hoc Analysis

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Netarsudil ophthalmic solution 0.02: Rocket 2 study

- Rocket 2 is a 12-month Phase 3 study of Netarsidil vs. Timolol
- The patient group to be used for Rocket 2 primary endpoint analysis was changed with FDA agreement
  - ➢ Primary endpoint analysis will include only patients with a baseline IOP above 20 mmHg and below 25 mmHg
- ➢ Rhopressa QD and BID met criterial for non-inferiority to timolol (baseline < 25 mm)
- Seems to work best at lower/ modest IOP baseline

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Netarsudil ophthalmic solution 0.02% Rhopressa ™

- In two phase III studies, more than half of patients experienced conjunctival hyperemia compared to 8% to 10% of timolol patients.
  - –More complaints of eye redness with Rhopressa.
- 9% and 5% of Rhopressa once-daily patients reported corneal deposits across the two phase III studies compared to 0.4% and 0% of the timolol patients.
- Blurry vision was reported by 7% and 5% of Rhopressa patients compared to 3% and 0.5% of timolol patients in the studies.

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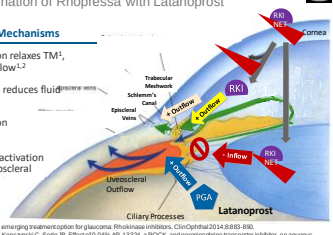
Quadruple-Action (ROCK-NET Inhibitor/latanoprost)- Rocklatan

Fixed Combination of Rhopressa with Latanoprost

4 Identified IOP-Lowering Mechanisms

- ROCK inhibition relaxes TM[1], increases outflow[1,2]
- NET inhibition reduces fluid production[2]
- ROCK inhibition lowers EVP[3]
- PGA receptor activation increases ueoscleral outflow[4]



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3.Kiel JW, Kopczynski C. Effect of AR-13324 on episcleral venous pressure (EVP) in Dutch Belted rabbits. *ARVO* 2014. Abstract 2900
4.Latanoprost prescribing information

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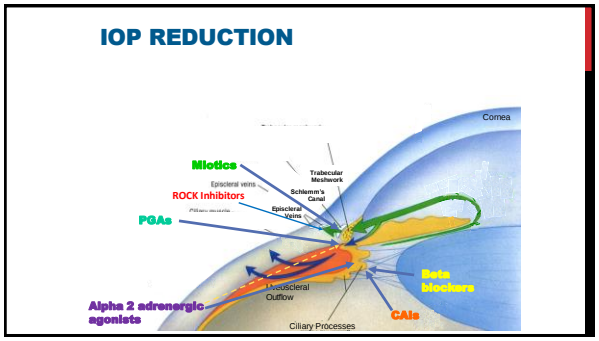

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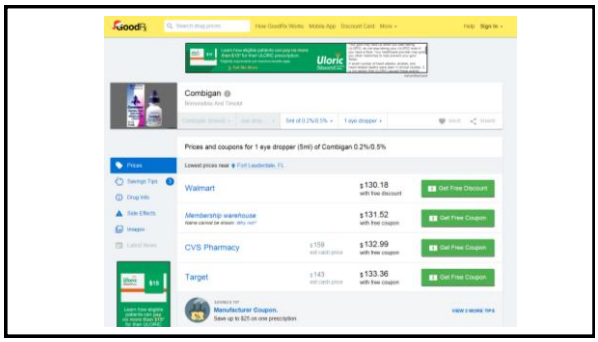

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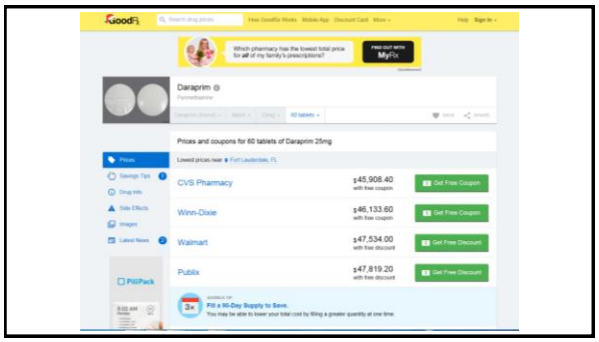

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Medical Management of Glaucoma…

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…has gotten boring

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What is Maximal Medical Therapy and Where Do the New Medications Fall?

- A mutually agreed upon regimen between doctor and patient
  - –Some practitioners will not put patients on any more than two medications and others will use three or four
  - –Patients may be accepting of multiple meds if surgery the next option
    - Laser trabeculoplasty is an option if medications are insufficient
    - Surgery is an option if medications and/or laser fail

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