

## Topical Pharmacology Rounds

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- No financial disclosures
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### #1) Topical Antibiotics



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### Fourth Generation Fluoroquinolones

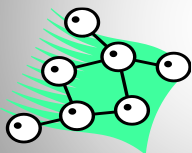
- Gatifloxacin .5% (Zymaxid)
- Moxifloxacin .5% (Vigamox)
- Moxeza
- Besivance
- ? Quixin



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### Fourth generations



- Second generation fluoroquinolones bind only to topoisomerase 4 or DNA gyrase, 4<sup>th</sup> generations bind to both. Therefore not one but two genetic mutations are required for resistance.
- This has certainly helped, but as always, the bugs are figuring it out
- Pediatric use generally down to one year and older

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### ARMOR (antibiotic resistance monitoring in ocular microrg.) study

- Studied 592 ocular isolates
- 200 staph aureus, 144 coagulase negative staph, 75 strep pneumoniae, 73 haemophilus, and 100 pseudomonas
- All susceptibility studies were performed at the same lab

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## ARMOR study

- 39% of staph aureus was MRSA
- 80% of MRSA exhibited Fluoroquinolone resistance
- Besivance proved to show the least resistance across isolates
- Resistance was shown to be a significant problem with multiple drugs and multiple bugs

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## Most recent ARMOR update

- 10 year time period from 2009-2018. Information released in 2020
- 88 sites, 41 states, 6091 isolates
- 1/3 of staph aureus is MRSA
- ½ of CONS is MR
- Increasing resistance to Tobramycin
- ¾ of MR staph is resistant to 3 or more drugs
- 1/3 of strep pneumonia is resistant to Azithromycin
- Pseudomonas and Hemophilus show low resistance across the board
- Besivance still with very low resistance

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## Gatifloxacin

- Zymaxid .5%
- Generic available
- Excellent, broad spectrum agent
- TID for bacterial conjunctivitis
- Original was Zymar, discontinued



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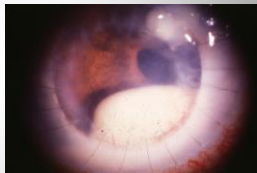
## Moxifloxacin

- Vigamox .5%
- Generic available
- Excellent broad-spectrum agent
- Preservative free
- TID dosing for conjunctivitis
- Moxeza .5%
- Purchased by Harrow Medical
- Different vehicle, and preserved
- Longer contact time, so BID conjunctivitis dosing
- Pediatric use at 4 months and older

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## Besivance

- Besifloxacin .6%
- No generic
- Excellent, broad spectrum agent
- Need to shake
- No oral version, so less problems with resistance
- TID conjunctivitis dosing, pediatric rating down to one year



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## Quixin

- .5% concentration of levofloxacin
- Generic available
- ? 4<sup>th</sup> generation
- Iquix: 1.5%, discontinued.



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## Older Fluoroquinolones

- Ciloxan
- Ocuflor



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## Ciloxan

- .3% Ciprofloxacin, generic available
- Second Generation
- Good gram-negative coverage, adequate pos.
- Weak against Strep, great against Pseudomonas
- White precipitate often seen in bed of ulcer with treatment. Occurs 15% of the time, increases dramatically with age (ph based)
- Has an available ointment

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## Ocuflor

- .3% Ofloxacin : generic
- Second generation
- Good gram-negative, better pos.
- Less effective against Pseudomonas
- Much better tissue penetration than Ciloxan.....present in therapeutic levels in the AC
- Often used as inexpensive but effective prophylaxis with cataract surgery

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## Aminoglycosides

- Tobramycin
- Gentamycin
- Neomycin
- All work by inhibiting bacterial protein synthesis. Are bactericidal
- Highly effective against gram-negative bacteria, especially Pseudomonas
- Effective against gram-positive bacteria but less so with ever increasing resistance

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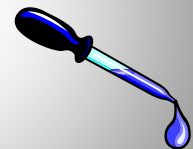
## Aminoglycosides

- Side effects common to the entire class include PEK (epithelial toxicity), potential allergic reactions, and eyelid edema / erythema
- Cost effective due to generic availability (4\$ plans)

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## Tobramycin .3%

- Available generically in drop and ointment form. Ointment (Tobrex) is very expensive!
- More effective and less toxic than Gentamycin
- Less allergic potential than Neomycin
- Tobradex (Tobramycin & Dexamethasone)
- Tobradex ST: lower concentration of dexamethasone (.05%)
- ZyLet (Tobramycin & Loteprednol)
- Pediatric use 2 months and up



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## Gentamycin .3 %

- Available generically in drop and ointment form
- Overall, slightly less effective and slightly more toxic than Tobramycin
- Less allergic potential than Neomycin
- With the arrival of generic Tobramycin, Gentamycin's use dropped off considerably
- Not rated for pediatric use

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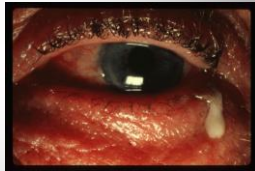
## Neomycin

- Not available as a stand alone drug
- Ointment or drops in combination with other medications. Highest potential for allergy
- Neosporin drops (Neomycin, Polymyxin, Gramacidin)
- Neosporin Ointment (Neomycin, Polymyxin, Bacitracin)
- Maxitrol / Dexacidin (Neo / Poly/ Dexa)

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## Others

- Polytrim
- Erythromycin
- Bacitracin
- Sulfacetamide 10%
- Azasite



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## Polytrim

- Polymyxin-B and Trimethoprim)
- Polymyxin great against gram negative, destroys cell membranes
- Trimethoprim inhibits folic acid synthesis and creates bacteriostasis. Effective against gram-positive and gram-negative except Pseudomonas

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## Polytrim

- Excellent choice in pediatric infections. 2 months and up
- Very effective against Haemophilus and Streptococcus pneumonia which are the most common causes of childhood eye infections.
- Drop form only-generic available
- Good against MRSA (LASIK in susceptible populations)

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## Erythromycin

- .5% ointment only (Ilotycin)
- Bacteriostatic-inhibits protein synthesis
- Good gram-positive, marginal gram-negative
- Not good for active therapy, supportive only
- Prophylaxis for ophthalmia neonatorum, though pediatric rated at 2 months and above



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## Bacitracin

- Ointment only
- Degrades cell walls.....works on gram positive only
- Great against Staph so good choice for blepharitis treatment
- Polysporin ointment (Bacitracin and Polymixin). Good gram pos. and good gram negative from polymyxin

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## Sulfacetamide 10%

- What's old is new again....
- Many of today's bacterial strains have never been exposed
- Resistance is currently actually low
- High allergy rate



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## AzaSite

- 1% Azithromycin in Durasite vehicle
- Approved for bacterial conjunctivitis: Used for MGD too, AIC
- Bacteriostatic, not bactericidal
- Conjunctivitis dosing is BID for two days, QD for five days so nine drops total for treatment course
- Very expensive
- May already be facing considerable resistance due to long time systemic use. Pediatric rated at one year and up

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## #2) Topical Steroids



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## Quick review of topical steroids

- Several topical steroids available for ocular use
- Long track records for many of them with proven efficacy
- Differing levels of activity with differing side effect profiles
- Various clinical niches for different drugs
- Side effects well known.....PSC's (< orals), increased IOP (> orals), etc.

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## Prednisolone Acetate

- Most commonly used topical steroid
- Potent "gold standard" with good mix of effectivity and side effect profile
- .12% suspension (Pred mild)
- 1% suspension (Pred Forte, Omnipred). Econopred no longer exists: replaced by generic Omnipred with smaller molecule.

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## Prednisolone phosphate

- Goes on and off the market in generic form
- Rarely used
- Vasocidin drops in combo with Sulfacetamide
- Used in the SCUT trial

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## Durezol

- .05% Ophthalmic emulsion
- ½ dosing schedule compared to Pred Forte and others
- Generic available at around \$50-\$60
- Very effective against iritis, can be drug of choice
- VERY high propensity to elevate IOP

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## Loteprednol Etabonate



- Site-specific steroids often referred to as “soft steroids”
- .5% (Lotemax) and .2% (Alrex)
- 1% Inveltys by Kala, .38% Lotemax SM, .25% Eysuvis

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## Lotemax

- .5% Loteprednol suspension
- Almost as potent as Pred Forte but very little propensity to elevate IOP or cause PSC's
- In the eye, it binds to the target site and achieves therapeutic effect but then is quickly broken down
- Intrinsic esterases turn the drug into cortienic acid which is an inactive metabolite
- Available in ointment form which is preservative free and as a “gel” forming drop
- Generic of the .5% suspension made by Akorn

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## Lotemax

- This allows for excellent therapeutic effect with a substantially reduced propensity to cause problems
- Penetrates very well
- Potent enough to be used for almost everything except acute iritis / iridocyclitis
- Often “the” choice for chronic intraocular inflammation
- Expensive, but drug program through Walgreens for \$35 copay unless government insurance.

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## Alrex

- .2% Loteprednol
- Similar to Lotemax but not potent enough to treat intraocular inflammation: surface only
- Cost issues: can cost more than Lotemax



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## Inveltys

- 1% Loteprednol
- Purchased by Alcon (Kala originally)
- Approved for post-op inflammation and pain
- Dosed BID

## Lotemax SM

- .38% Loteprednol
- SM for sub-micron technology: improved contact time, much improved AC penetration
- Approved for post-op inflammation and pain
- TID dosing

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## Eysuvis

- .25% Loteprednol
- Approved for 2-week course for dry eye therapy
- Purchased by Alcon from Kala

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## Dexamethasone

- Dexamethasone sodium phosphate or alcohol suspension
- .1% suspension (Maxidex)
- Potent, but tremendous ability to increase IOP
- Frequently used in combination with antibiotics (Tobradex, Maxitrol, Dexacidin)
- Tobradex ST : only .05% dexamethasone

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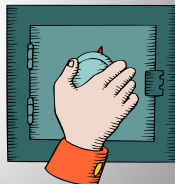
## Fluoromethalone

- Relatively weak, little risk of elevating IOP but limited clinical uses
- .1% ointment (FML)
- .1% suspension (FML and Eflone)
- .25% suspension (FML Forte)
- .1% acetate suspension (Flarex)

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## Combinations

- Maxitrol, Dexacidin
- Pred-G
- Tobradex (has a generic) & Tobradex ST, Zylet
- Blephamide, Vasocidin
- FML-S



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## #3) Topical NSAIDS



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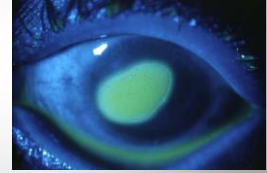
## Ketoralac

- **Acular** LS 0.4% (what does LS stand for?). QID
- **Acuvail** preservative free, unit dose vials. BID
- Original Acular is .5% and it has substantial issues with stinging
- Uses for topical NSAIDS include surface pain, post-operative pain / inflammation, CME
- Generic Acular and generic Acular LS: about \$35
- Acuvail about \$350

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## Diclofenac

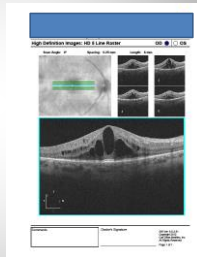
- Diclofenac .1% : branded Voltaren no longer available
- Generically available (earlier generic forms linked to corneal melting)
- QID dosing, cost can be as little as \$10-\$20



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## Nepafanac

- **Nevanac** .1% Nepafanac
- Prodrug
- TID dosing
- Excellent for CME
- Expensive
- **Ilevro** .3% Nepafanac
- QD dosing
- \$250 for 1.7 ml



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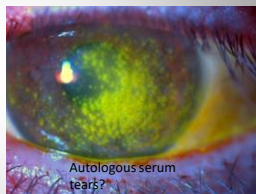
## Bromfenac

- Bromfenac .09% : **Bromday**
- Has a generic: good RX about \$60 for 1.7ml
- QD dosing
- Also **Prolensa** .07%. Decreased PH to increase corneal penetration (1.6 ml and 3ml)
- Also **Bromsite** .075%

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## Immune modulators

- Restasis .05% and generic
- Topical cyclosporin A: Inhibits T-cells
- Emulsion
- Also in multi-dose bottle
- Takes weeks to months for maximum effect
- BID dosing, .1% QD dosing version in Europe
- Possible suppressive use in HSK, HZV, and atopic disease



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## Xiidra

- Lifitegrast (Xiidra) 5%
- Shire (Takeda)- now Novartis
- FDA approval granted in July of 2016
- BID dosing for dry eye
- Not exactly clear how it helps in dry eye, but most likely blocks T-cell adhesion, thus limiting T-cell mediated inflammation.
- Works quicker than Restasis, within about 2 weeks
- \$450.00 / 60 vial carton, can be up to \$600 +

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### Cequa

- Sun pharmaceuticals
- FDA approval in August 2018
- .09% cyclosporine A
- BID dosing
- Nanotechnology for delivery
- Available at special mail order pharmacy at reduced cost to commercially insured patients (no Medicare or Medicaid)
- Also available through traditional pharmacy channels

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### Verkazia

- .1% Cyclosporin emulsion by Santen
- FDA approved for Vernal conjunctivitis @ QID dosing
- Possible off label use for dry eye (similar to European Restasis), other atopic disease, etc.
- \$1500-\$2000!!!!!!!!!!!!



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### Tyrvaya

- Nasal spray
- Varenicline: nerve stimulator to increase tear production
- BID dosing
- Cholinergic agonist
- Works like True Tear device which was discontinued
- Main side effects: sneezing (82% in clinical trials), coughing, throat irritation
- Price of \$500-\$600
- Oral form (Chantix) is a smoking cessation aid

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### #4) Topical Anti-Allergy Medications



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### The OTC players.....

- Ketotofin based mast cell / antihistamine combination products
- Old antihistamine / vasoconstrictor combos
- Vasocon-A, Naphcon-A
- Alaway (CVS has a generic): also a preservative free option
- Pataday once per day (\$19.00 2.5 ml), Pataday twice per day, Pataday extra strength (Pazeo)
- Zaditor
- Caritin Eye
- Refresh Allergy
- Lastacaft (QD)
- Most BID (some QD) for a couple of weeks, then possibly QD chronically

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### Mast Cell Stabilizing / Antihistamine Combination Products

- Prescription drugs.....
- BID dosing
  - Elestat (generic available)
  - Optivar (also generic)
  - Both around \$30, can occasionally have insurance coverage

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## Straight antihistamines

Zerviate

- .24% Cetirizine (Zyrtec)
- Nicox
- Comes in individual vials, but not preservative free
- BID dosing

Bepreve

BID dosing, may help with allergic rhinitis  
10ml bottle

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## Other agents

- Pure mast cell stabilizers
  - Alamast
  - Alocril (BID)
  - Alomide
  - CroloM
  - Opticrom
  - Most are QID dosing

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## #5) Topical Antiviral Agents



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## Viroptic

- HSK Epithelial lesions respond extremely well to topical antiviral therapy. Historical mainstay of treatment is Viroptic (trifluoridine).
- Extremely effective against HSV but very toxic to the cornea. Also, very expensive, even generic

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## Viroptic

- Viroptic is utilized Q 2-3h with an ideal maximum of around nine drops per day (toxicity). Once epithelium heals, decrease to QID for about 1 more week
- Medicamentosa is very common with secondary keratitis but the drug is almost universally effective in treating the infection

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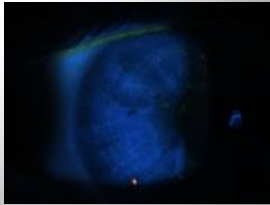
## Zirgan

- Another topical option is Zirgan, a gel forming drop.
- Prolonged contact time, so dosing is less: 5 times per day until the epithelium is intact, then TID for several more days
- Unfortunately, extremely expensive

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## Topical antivirals

- Zirgan has been used in Europe under the name Virgan with a long track record
- Possibly effective against adenovirus as well
- Can work against Zoster dendrites (nothing else does)
- Older agents that are no longer readily available include IDU (Idoxuridine) and Vira-A (vidaribine) ointment



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## Topical antivirals

- Avaclyr 3% acyclovir ophthalmic ointment
- FDA approval Spring of 2019
- FERA pharmaceuticals
- 5 X day until defect healed, then 3 X day for several days
- Never went to market, FDA application withdrawn

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## Treatment alternative

- A viable alternative to topical therapy is the use of oral antiviral agents
- Can be very effective, but may take a while longer to work
- Very, very cost effective if using Acyclovir. Dosing is 800mg TID. Cost of around \$30
- Also available in 200mg pills on most \$4 / \$10 plans. Can run in to issues with supply (need 12 pills per day)

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## Oxervate .002%

- Completely unique agent to treat neurotrophic keratitis
- Dompe out of Italy
- Mimics nerve growth factor proteins
- Dosed 6 X day for 8 weeks



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## Oxervate .002%

- Retail price of around \$12,000 per 8-week supply, but many company programs to help with cost
- Available only through Accredo specialty mail order pharmacy

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## Upneeq .1% (oxymetazoline HCL)

- Unique agent utilized to treat acquired ptosis: elevates eyelid
- Alpha adrenergic agonist
- Non-preserved, comes in individual use vials
- Once per day dosing
- Caution in uncontrolled HTN
- Caution in vascular insufficiency, Sjogrens
- Caution with very narrow angles
- Caution with concomitant MAOI use

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## Upneeq .1%

- Can only prescribe though company's RVL pharmacy
- No insurance filing, all self pay
- 30 vials \$105
- 90 vials \$225

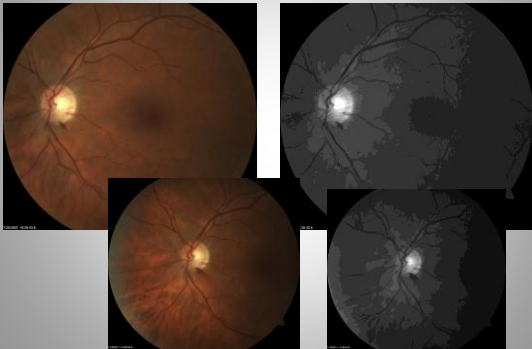
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## Vuity

- Presbyopia treatment
- Onset about 15 minutes, max effect by one hour
- Lasts about 6 hours
- 1.25% pilocarpine
- Improves near and intermediate vision with minimal to no negative impact on distance vision
- Issues with RD with higher myopes and others at risk
- Clinical trials only included patients from 40-55
- Most common side effects are headache / brow ache and injection, decreased vision in scotopic lighting
- Generic pilocarpine (isoptocarpine) still available in 1%, 2%, 4%

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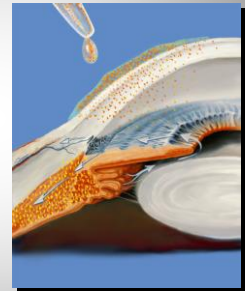
## #6) Topical Glaucoma Medications



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## Prostaglandins

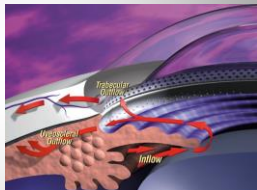
- Four drugs
- Xalatan and generic (also BAK free Xelpros)
- Travatan-Z / generic Travatan
- Lumigan and generic
- Zioptan



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## Prostaglandins

- Work by increasing uveoscleral outflow
- Under normal circumstances uveoscleral outflow in humans accounts for only 10-20% of drainage



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## Prostaglandins

- Very effective
- Can lower IOP 30% and more
- Can get remarkable effects with very high pressures
- First choice for many practitioners
- QD dosing: does not have to be QHS
- Synergistic with other topical meds
- Most synergistic with CAI's and Alpha 2 agonists, seem to be least so with Beta blockers (studies vary)
- Relatively slow onset of action

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### Prostaglandin side effects

- Contraindicated to some degree in.....
- Uveitic and Neovascular glaucoma
- History of uveitis
- History of HSK
- During cataract post-op
- Aphakia
- History of CME
- Mixed colored irises?
- Unilateral Treatment
- Not very helpful with acute angle closure (take too long to work)

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### Prostaglandin side effects

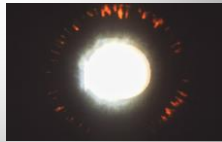
- Can darken mixed colored irises
- Hyperpigmentation of eyelid skin
- Hypertrichosis
- Hyperemia
- "Orbitopathy", ? Lid clicking
- Almost entirely free of significant systemic side effects



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### Xalatan

- Latanaprost .005%
- Generic is available
- Longest track record
- Seems to have the most propensity to change iris color
- Xelpros: BAK free version from Sun pharmaceuticals in India (Potassium Sorbate 0.47%)



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### Xelpros

- Can not just prescribe to any pharmacy
- XelprosExpress program
- Order though one of two specific mail order pharmacies
- Independent of insurance coverage...
- \$55 one month
- \$110 three months
- Can not count toward Medicare D deductible

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### Travatan-Z

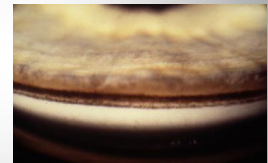
- Travaprost .004%
- Preserved with Sofzia, so less toxicity
- Old original Travatan available generically
- Any blood testing indicated for the patient pictured here?



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### Lumigan

- Bimatoprost .03% (old-generically available) and .01%
- May be slightly more potent than Xalatan and Travatan-Z
- Most prominent side effect profile
- If one does not work, try another?



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## Zioptan

- .0015% Tafluprost
- Preservative free
- FDA approval for OAG and ocular hypertension

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## Latanaprostene Bunod

- Approved by the FDA in late 2017 Nitrous oxide donating molecule
- Vyzulta
- Once per day dosing
- Unique agent that increases both uveoscleral outflow and TM outflow
- Very effective

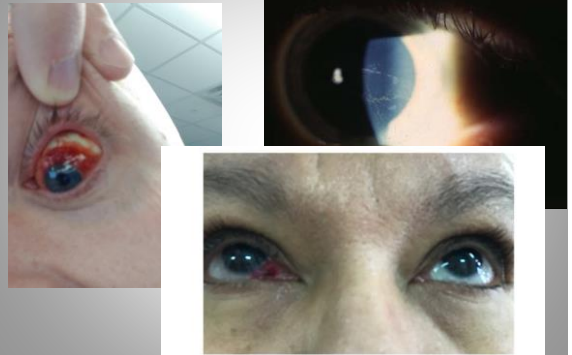
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## Rhokinase inhibitors

- A completely novel drug class for glaucoma
- **Rhopressa**: approved by FDA in late 2017
- **Roclatan**: Rhopressa combined with Latanaprost. Approved by FDA in Early 2019. Over 60% of patients in trials had an IOP decrease of at least 30%
- Can be used to improve endothelial function in Fuch's patients / post surgical edema
- Case reports of benefit in neurotrophic keratitis
- Increases TM outflow
- Lowers episcleral venous pressure so lowers outflow resistance
- Decreases aqueous production
- Substantial redness (53% in trials)
- Vortex keratopathy (20% in trials): can impact vision
- Subconjunctival hemes
- Reticular bullous corneal edema (honeycomb)
- Follicular toxic response similar to Brimonidine, but not common
- Purchased by Alcon from Aerie

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## Rhopressa side effects



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## Beta Blockers

- Many available
- Both .5% and .25%
- Many can be used QD: Can try .25% QAM in mild cases and work up from there
- Decrease aqueous production
- Very, very inexpensive in generic form
- Expect IOP drop of around 25%
- Dose in AM when using QD

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## Beta Blockers

- Timolol / Timoptic .25% and .5% (\$4 / \$10 plans)
- Betagan .25% and .5%
- Betimol .25% and .5%
- Istalol .5%
- Timoptic XE and Timoptic XE PF .25% and .5%
- Most available as generics



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## Beta Blocker contraindications / SE's

- Well known with very long track record.....
- Asthma
- COPD / bradychardia
- Some COPD patients or patients with mild asthma can take Beta Blockers
- Depression
- Impotence
- Effects on cholesterol levels
- Can cause CME post cataract surgery
- Very safe over all

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## Alpha -2 agonists

- Alphagan and Alphagan- P
- Confusing ! Alphagan .2%, Alphagan-P .15%, and Alphagan-P .10%
- .2% and Alphagan-P .15% generically available
- What does the "P" stand for? Purite (preservative in place of BAK)
- Combigan (.2% A and .5% Timolol)
- Simbrinza (.2% A and Azopt)

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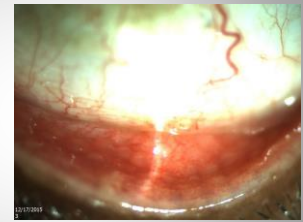
## Alphagan (P)

- Dosed BID; rarely TID
- Expect IOP drop of around 20%
- Work by decreasing inflow and increasing TM outflow
- Now also Lumify (Brimonidine 0.025%) for OTC redness relief. Less chance of rebound hyperemia and tachyphylaxis, selectively constricts veins

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## Alphagan SE's

- Dry mouth
- Hyperemia
- Follicular toxic conjunctivitis
- Fatigue!!!!!!
- Can't use with MAOI's.....but who takes those? Nardil & Parnate



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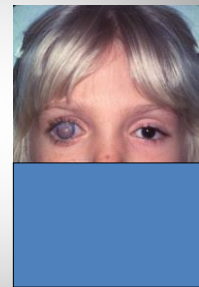
## Topical CAI's

- Two : Trusopt and Azopt
- Relatively safe but not very potent as monotherapy
- Expect IOP drop around 15-20%
- More synergistic with prostaglandins however
- Dosed BID , TID occasionally
- Cosopt is combo drop with Trusopt and Timolol .5%. Has a preservative free version as well
- Trusopt and Cosopt have generics (off and on supply issue)
- New Azopt generic March 2021
- Simbrinza: Azopt and .2% Alphagan combination. Dosed BID-TID. Horrible problem with follicular toxic response. Far more common than with .2% Alphagan alone
- Work by decreasing inflow

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## Topical CAI SE's

- Burning and stinging (especially Trusopt)
- Sulfa allergies (but not a problem for many with systemic allergy, only about 10%)
- Can be hard on corneal endothelium: watch with Fuch's
- Metallic taste



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## Glaucoma treatment during pregnancy and / or nursing

- Many things to consider
- Most important during first trimester due to organogenesis, then again during nursing
- IOP drops naturally during pregnancy



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## Pregnancy / nursing

- Consider no treatment if glaucoma is mild
- Consider SLT
- With drops.....
- Alphagan (pregnancy)
- Beta Blockers (both)
- Prostaglandins while nursing

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## Pregnancy / Nursing

- Alphagan the "safest" based upon category but can cause severe CNS depression and apnea in infants, so D/C shortly before birth
- Many practitioners feel the most safe using beta-blockers, because systemic B-blockers are used for HTN in pregnancy

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## Pregnancy / Nursing

- Avoid prostaglandins (used systemically to induce labor)
- Use NLDO or punctal plugs to minimize systemic absorption in all cases
- Summary: Alphagan or Beta Blocker during pregnancy
- Prostaglandins or Beta Blockers during lactation

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