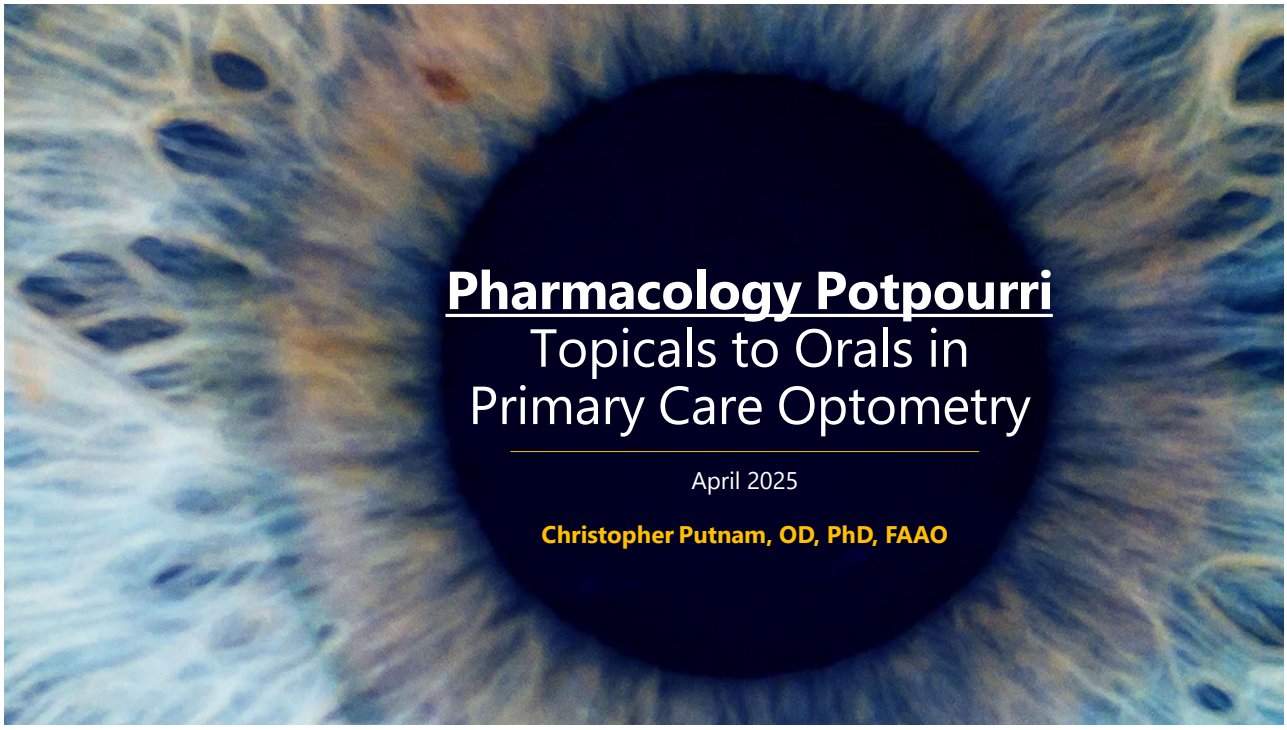


4

Audience Participation

Polling Question #1

In your daily practice, do you currently utilize off-label medication use?

a) **Yes**
b) **No**
c) **Unsure**

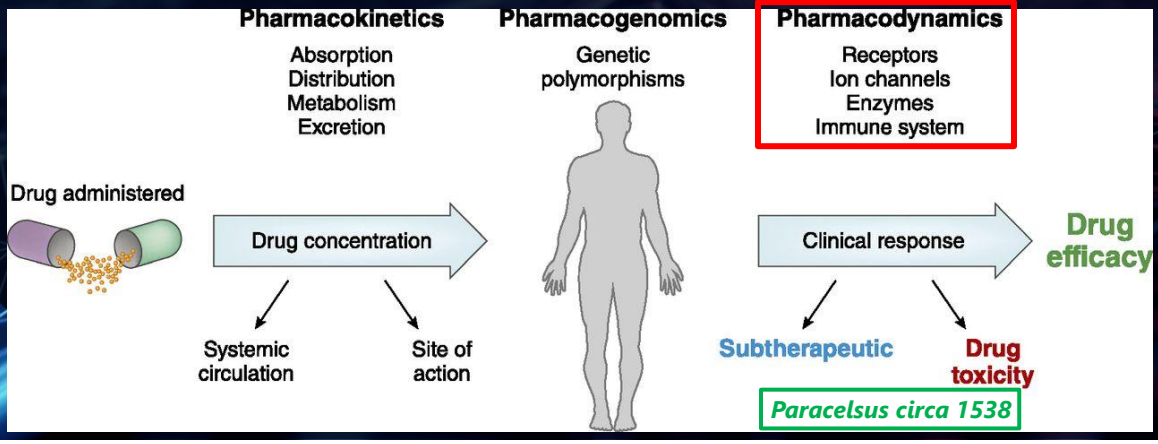
11

You cannot dream of a face you have never seen

- *Stanford University*
- *Boston University*

12

Pharmacokinetics vs. Pharmacodynamics



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Food and Drug Administration

- Approval Process
- Timelines and Milestones
- Barriers to Entry

14

FDA Approval Process

- FDA mission is to oversee the ***use and marketing of regulated medical products***
- 5 Step Approval Process
  - **Preclinical phase -** Basic science
  - **Phase 1 clinical trial -** Establish drug safety in healthy subjects using small cohorts of 20-80
  - **Phase 2 clinical trial -** RCT to assess the drug's efficacy using hundreds of participants (30% success rate)
  - **Phase 3 clinical trial -** Large population trial to test ideal dosage, patient population and other factors
  - **New drug application -** Includes trial data, preclinical information and details on manufacturing process.
    *If FDA accepts the application for review, the agency has 10 months to decide
    *FDA can hold an advisory committee meeting where independent experts assess data and make recommendation
- ***Centers for Medicare & Medicaid Services (CMS) act as basis in National Coverage Determination (NCD)***
- FDA issues a label that describes and defines:
  - ***Specific medical indication***
  - ***Dose***
  - ***Dosage form***
  - ***Side effects***
  - ***Chemical structure***

15

Association of Off-label Drug Use and Adverse Drug Events in an Adult Population

JAMA Intern Med (2016) 176(1):55-63

DESIGN, SETTING, AND PARTICIPANTS

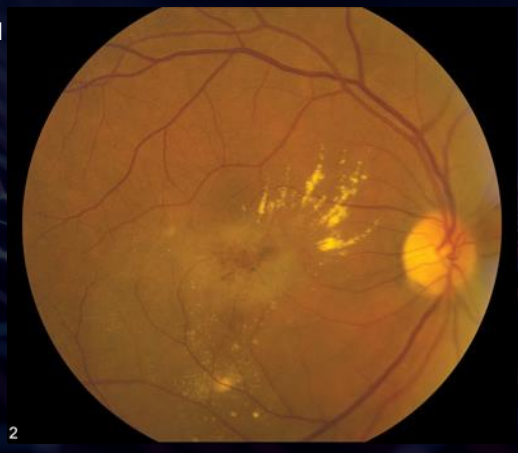
- 46,021 patients receiving 151,305 prescribed drugs were reviewed from primary care clinics using EMR documentation of treatment indications and treatment outcomes

RESULTS

- 3484 ADEs were found with an incidence rate of ***13.2 per 10,000 person-months***
  - Off-label use lacking strong scientific evidence had a higher ADE rate ***(21.7)*** compared with on-label use ***(12.5)***
- ***Off-label use with strong scientific evidence had the same risk for ADEs as on-label use***

CONCLUSIONS

- ***Caution should be exercised in prescribing drugs for off-label uses that lack strong scientific evidence***



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FDA Approval Process

Barriers to Entry

- Executing the trials necessary to get FDA approval can be very costly
  - ***Inexpensive treatments would never recoup high cost of the approval process***
- Running a clinical trial may not be feasible
- FDA approval is very specific and limited
  - ***Beneficial uses of a drug or device evolve over time***

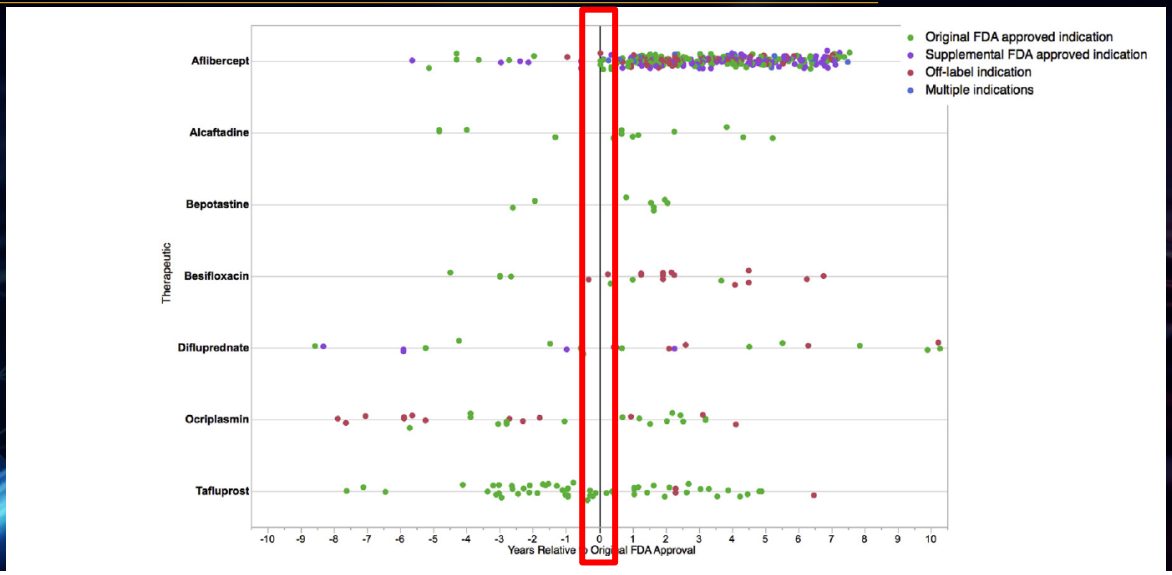
***** Many treatments that have not gone through the FDA-approval process have demonstrated effectiveness and are widely used***
- Quite a few are even standard of care…

***** Many clinical trials reported in the peer-reviewed literature were not done under FDA supervision***
- NEXT SLIDE…

17

On-Label and Off-Label Clinical Studies of FDA-Approved Ophthalmic Therapeutics

Ophthal (2021) 128(2):332-334



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Rules of Engagement (ROEs)

- ***Discussion will center around evidence-based medicine and peer-reviewed literature***
- ***Slides are intentionally information-dense***
  - ***Use as reference***
  - ***Starting point for further peer-reviewed review***
- ***Pharmacology use discussed here is synergistic and adjunctive***
  - ***NOT intended as replacement for standard of care***
- ***Summary slides with Take Home Pearls***
  - ***Medication with dosage / frequency / duration***
  - ***Clinical indications***

23

Off-Label Medication Use

Bevacizumab (Avastin) - Godfather of Off-Label Use

- FDA-approved for treating various cancerous tumors both alone and in combination with other cancer treatments
- ***MOA:*** *Selectively binds circulating VEGF inhibiting cell surface receptors binding*
  - Leads to reduction in microvascular growth and limits blood supply to tumor tissues
- Commonly used off-label to treat retinal vascular diseases including
  - nvAMD
  - NVM formation
  - POHS and
  - DME
- ***"Management of exudative conditions with Avastin was embraced by the ophthalmologic profession without definitive guidelines from clinical trial data"***
- ***Reality:*** Avastin is larger molecule of FDA-approved version Lucentis
  - Off-label use gives patient's opportunity to utilize the medication at fraction of the cost of the FDA-approved version.
  - Benefits have been shown equal and short of any side-effects

25

Treatment burden on patients receiving intravitreal anti-VEGF for nvAMD

Acta Ophthalmologica (2023) 00:1-5

Method

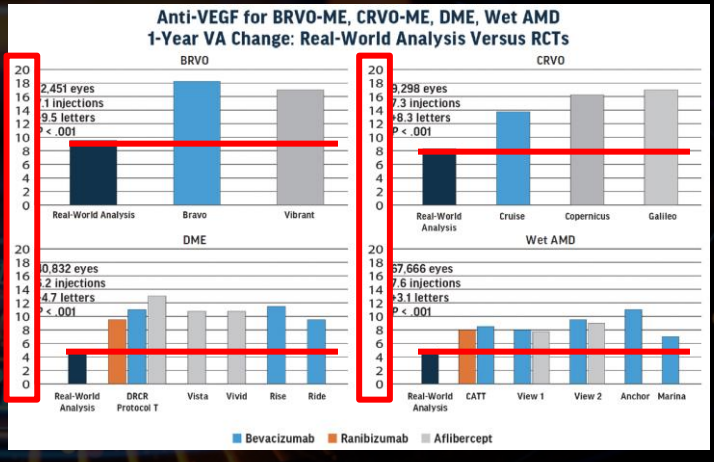
- Patients with ongoing treatment with anti-VEGF for wAMD at a underwent a survey:
  - Time spent receiving treatment
  - Caregiver assistance & transportation
  - Self-rated vision
  - Discomfort, anxiety or transportation problems
  - Number of treatments and treatment intervals

Results

- Study included 93 patients with mean age of 79.9 years
- Mean interval between treatments was 7.3 weeks and 26% had active treatment OU
- ***Patients spent 2.7 hrs/treatment and caregiver assisted in 58% of cases with 19% needing time off***
- ***Significantly lower odds ratio for discomfort + higher self-rated vision with longer treatment intervals***

Discussion

- Anti-VEGF treatment is an effective treatment for nvAMD
  - ***However, relatively short treatment intervals place a considerable burden on patients and care givers time***



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Peer-Reviewed Off-Label Medications

Anti-infectives

- 4th generation fluoroquinolones
- Topical ganciclovir (Zirgan 0.15%)
- Povidone iodine (Betadine 5%)
- Topical azithromycin (Azasite 1%)*

29

Off-Label Medication Use

4th Generation Fluoroquinolones

FDA-approved for:

- Bacterial conjunctivitis

MOA: *Direct inhibition of DNA synthesis by targeting 2 bacterial enzymes (DNA gyrase and topoisomerase) responsible for notching, coiling and sealing during replication*

Off-label uses identified in the literature:

- ***Bacterial keratitis***
- ***Corneal ulcers***
- ***Pre- and post-surgical prophylaxis of infection***

30

4th Generation Fluoroquinolones: New Weapons in the Arsenal of Ophthalmic Antibiotics

Am J Ophthalmol (2002)133: 463-466.

METHODS

- MICs of 93 bacterial endophthalmitis isolates were determined to CIP, OFX, LEV, GAT, and MOX using National Committee of Clinical Laboratory Standards susceptibility patterns

RESULTS

- *Staph aureus* isolates that were resistant to CIP and OFX were statistically most susceptible to MOX
- *Strep viridans* were more susceptible to MOX, GAT, and LEV
- ***MOX was the most potent FQ for gram (+) bacteria***
- ***CIP, MOX, GAT and LEV demonstrated equivalent potencies to gram (-) bacteria***

CONCLUSIONS

- ***4th generation FQs appear to cover bacterial resistance compared to 2nd and 3rd generation FQs***
- ***4th generation FQs were more potent for gram (+) bacteria and equally potent for gram (-) bacteria.***

Table 2. In vitro susceptibility of corneal bacterial isolated to antimicrobial agents

Microorganism	Total N.	Susceptibility: Gatifloxacin N.	Gatifloxacin (%)	Moxifloxacin N.	Moxifloxacin (%)	Lomefloxacin N.	Lomefloxacin (%)	Ciprofloxacin N.	Ciprofloxacin (%)	Ofloxacin N.	Ofloxacin (%)
Gram positive											
Coagulase-negative *Staphylococcus*	22	22	100	22	100	19	86.4	19	86.4	18	81.8
Staphylococcus aureus	5	5	100	5	100	5	100	5	100	5	100
Streptococcus pneumoniae	5	5	100	5	100	3	60.0	5	100	4	80.0
Streptococcus sp *viridians* group	1	1	100	1	100	0	0	0	0	1	100
Total gram-positive microorganisms	33	33	100	33	100	27	81.8	29	87.9	28	84.8
Gram negative											
Pseudomonas sp	7	7	100	7	100	5	71.4	6	85.7	6	85.7
Moraxella sp	3	3	100	3	100	3	100	3	100	3	100
Other gram-negative microorganisms *	8	8	100	8	100	6	75.0	7	87.5	7	87.5
Total gram-negative microorganisms	18	18	100	18	100	14	80.4	17	94.4	17	94.4
Grand Total	51	51	100	51	100	41	80.4	46	90.2	45	88.2

* *Serratia* sp (2), *Haemophilus* sp (2) *Pseudomonas aeruginosa* (1), *Providencia* sp (1), *Morganella morganii* (1), and *Citrobacter* sp (1)

2nd Generation
3rd Generation → levofloxacin
4th Generation

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Off-Label Medication Use

Topical Ganciclovir (Zirgan 0.15%)

FDA-approved for:

- Herpetic keratitis

MOA: *Inhibition of the viral DNA replication by selective polymerase inhibition*

Off-label uses identified in the literature:

- ***Adenoviral keratoconjunctivitis***
  - ***Epidemic keratoconjunctivitis (EKC)***
  - ***Pharyngoconjunctival fever (PCF)***

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Anti-adenoviral effects of ganciclovir in keratoconjunctivitis by quantitative PCR methods

Clin Ophthal (2014) 8:315-320

Purpose

- Ganciclovir has been reported to inhibit CMV, HSV types 1 and 2, VZV and EBV
- Investigated *in vitro* anti-HAdV activity of ganciclovir ophthalmic gel (0.15%) in common serotypes currently inducing keratoconjunctivitis

Results

- ***50% cytotoxic concentration of ganciclovir was 212 mg/mL or 21.2% (Zirgan = 0.15%)***
- ***Significant inhibitory effect of ganciclovir on adenoviral proliferation was found in all types in dose-dependent manner***

Conclusion

- ***Significant inhibitory activity against HAdV3, 4, 8, 19a and 37 which induce EKC***
- ***Possible candidate for the treatment of HAdV keratoconjunctivitis***
- ***However… Zirgan 0.15% 5g tube = ~$450***

Table I Overview of ocular involvement and clinical manifestations with specific adenoviral serotypes[2,8–10,12–14,37,41,99,100,106,110]

Ocular structure	Clinical manifestations	Subtypes involved
Adnexa	Eyelid edema, lacrimal gland enlargement, nasolacrimal duct inflammation	1–5, 7, 8, 19, 37, 53, 54
Conjunctiva	Follicles, hyperemia, edema, petechial hemorrhages, pseudomembranes	1–5, 7, 8, 19, 37, 53, 54
Cornea	Multifocal punctate keratitis, subepithelial infiltrates	8, 19, 37, 53, 54

33

Off-Label Medication Use

Povidone Iodine (Betadine 5%)

FDA-approved for:

- Periocular region preparation and irrigation of the ocular surface and used for the prevention and treatment of skin infections and the treatment of wounds

MOA: *Free form iodine rapidly penetrates microbial cell membranes and oxidizes proteins, nucleotides and fatty acids in the cytoplasm and cytoplasmic membrane.*

Off-label uses identified in the literature:

- ***Adenoviral keratoconjunctivitis***
  - ***Epidemic keratoconjunctivitis (EKC)***
  - ***Pharyngoconjunctival fever (PCF)***

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Treatment of EKC with 2% povidone–iodine

J Ocular Pharm Therapeutics (2012) *28*(1):53-58

Methods

- PVP-I was applied to the affected eyes QID x 1wk. Data collection included history, symptoms and signs at the initial presentation and at 1wk. Main outcomes were the recovery rate within a week of treatment and drug tolerability.

Results

- 61 participants completed the study with bilateral EKC in 40 participants (66%)
- Application of PVP-I was sustained until recovery or completing a 1-k trial in 79%
- Time elapsed before treatment was 2.1 days and recovery rate within 1-wk of treatment was 77%
  - ***28 participants (46%) recovered within 1-week after the onset***
- No severe ocular or systemic adverse effects were reported related to this treatment

Conclusions

- ***Successfully relieved ocular discomfort from EKC in 79% of the study group within 1-wk***

What if you are unsure of the causative organism?

Organism	Medication	Mean (SD)	Minimum	Second Quartile (Median)	Maximum
Bacteria	Povidone–I	9.0 (3.7)	7	7	22
	Antibiotic	8.6 (2.7)	7	7	15
Chlamydia	Povidone–I	14.2 (3.8)	7	14	21
	Antibiotic	14.5 (4.6)	7	14	21
Virus	Povidone–I	8.8 (2.8)	7	7	18
	Antibiotic	9.0 (3.0)	7	7	19

Povidone-Iodine RCT for Infectious Conjunctivitis in Children *(2022)*

- **1.25% povidone-iodine**
  - **Is this dose-dependent?**

35

Off-Label Medication Use

Topical Azithromycin (Azasite 1%)

FDA-approved for:

- Bacterial conjunctivitis
- 1st commercially available ophthalmic formulation of azithromycin

MOA: *Interferes with bacterial protein synthesis by binding to the 50s subunit of the ribosome inhibiting translation of* mRNA

Off-label uses identified in the literature :

- Blepharitis
  - Decreases pro-inflammatory mediators + MMP-9 inhibition

- ***Proprietary mucoadhesive delivery system (DuraSite®)***
  - **Stabilizes and sustains ocular surface release**
  - **Solubilizes drug at a high concentrations**
  - **Slows the drug loss by predictable release over time**

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Efficacy of topical azithromycin ophthalmic solution 1% in the treatment of posterior blepharitis

Adv Therapy (2008) 25:858

METHODS

- 21 patients diagnosed with posterior blepharitis were randomized to receive either azithromycin plus warm compresses (10) or compresses alone (11)
- All patients: Compresses to each eye for 10min BID x 14d
- Treatment group: Azasite BID x 2d then QD x 12d

RESULTS

- ***Azasite group demonstrated significant improvements in MGD as compared to compress group***
  - MGD resolved completely in 3 patients and MG secretion returned to normal in 2 patients
- ***Higher percentage of patients in the Azasite group rated overall symptomatic relief as excellent or good***

CONCLUSION

- ***Azithromycin ophthalmic solution in combination with warm compresses provided a significantly greater clinical benefit than warm compresses alone***
- ***However… Azasite 1% 2.5mL bottle = ~$230***

Comparative study between topical azithromycin versus conventional therapy in treatment of posterior blepharitis causing DED *(2019)*

Second Visit		Azithromycin group No. = 30	Conventional group No. = 30	Test value*	P-value	Sig.
Symptoms						
Foreign body sensation	Mean±SD Range	1.47 ± 0.73 0 – 3	1.73 ± 0.69 0 – 3	-1.452	0.152	NS
Lacrimation	Mean±SD Range	1.0 ± 0.79 0 – 3	1.43 ± 0.77 0 – 3	-2.149	0.036	S
Burning	Mean±SD Range	1.40 ± 0.72 0 – 2	1.63 ± 0.81 0 – 3	-1.177	0.244	NS
Itching	Mean±SD Range	1.40 ± 0.56 1 – 3	1.80 ± 0.76 0 – 3	-2.314	0.024	S
Vision fluctuation	Mean±SD Range	0.63 ± 0.61 0 – 2	0.97 ± 0.67 0 – 2	-2.010	0.049	S
Second Visit		**Azithromycin group No. = 30**	**Conventional group No. = 30**	**Test value***	**P-value**	**Sig.**
Signs						
Lid hyperemia	Mean±SD Range	1.60 ± 0.89 0 – 3	2.10 ± 0.55 1 – 3	-2.611	0.011	S
Lid collarettes	Mean±SD Range	0.80 ± 0.84 0 – 3	1.07 ± 0.69 0 – 3	-1.336	0.187	NS
MG secretion	Mean±SD Range	1.83 ± 0.70 1 – 3	2.03 ± 0.56 1 – 3	1.227	0.225	NS
Conjunctival hyperemia	Mean±SD Range	1.10 ± 0.88 0 – 3	1.57 ± 0.73 0 – 3	-2.231	0.030	S
Frothy discharge	Mean±SD Range	1.50 ± 0.73 0 – 3	1.40 ± 0.67 1 – 3	0.551	0.584	NS

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Off-Label Medication Use – ***Cautionary Tale of Improper Marketing***

Topical Azithromycin (Azasite 1%)

JUNE 17, 2015

Merck to pay ***$5.9 million for misleading marketing*** of pink eye drug

NEW YORK (Reuters) - Merck & Co Inc has agreed to pay $5.9 million to resolve claims that a former unit fraudulently promoted a drug used to treat pink eye for unapproved purposes

- While the FDA had approved AzaSite for treating bacterial conjunctivitis, Inspire sought more revenue by marketing the drug for the non-approved treatment of another eye condition, blepharitis, according to a lawsuit
  - From 2008 through May 2011, Inspire misleadingly marketed to doctors purported anti-inflammatory properties of AzaSite that were not supported by substantial evidence or clinical experience
- ***Marketing caused doctors to prescribe AzaSite for uses not covered by federal healthcare programs, which paid millions of dollars in false claims***

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Peer-Reviewed Off-Label Medications

Anti-inflammatory / Immunosuppressant

- Prednisolone acetate (Pred Forte 1.0%)
- Difluprednate (Durezol 0.05%)
- Topical NSAIDs
- Cyclosporine (Restasis 0.05%)
  (Cequa 0.09%)

39

Off-Label Medication Use

Topical corticosteroids

Corneal Penetration Paradigm

- **Acetate** > Alcohol > Phosphates

Consideration: Treating anterior uveitis or DED?

- ***Reduced corneal penetration reduces risk of***
  - ***IOP increase (short-term)***
  - ***Lenticular changes (long-term)***

ANTI-INFLAMMATORY POTENCY OF TOPICAL OPHTHALMIC STEROIDS

CHEMICAL ENTITY	Common Brand Names	In Vivo Relative Anti-Inflammatory Activity	In Vivo Percent Aqueous Protein Reduction	In Vitro Relative GCR Internaliza-tion	In Vitro Relative Potency
Difluprednate Emulsion	Durezol	60	NA	NA	1,800
Fluorometholone Acetate	Flarex	40	NA	NA	350
Fluorometholone Alcohol	FML Forte	40	80	53	350
Dexamethasone Sodium Phosphate	Maxidex, Decadron	25	90	27	400
Loteprednol Etabonate	Lotemax, Alrex	25	100	100	550
Rimexolone	Vexol	25	NA	NA	300
Medrysone	HMS	4	NA	NA	200
Prednisolone Acetate	Pred Forte	4	110	58	600
Prednisolone Acetate	Generic	4	5	33	600
Prednisolone So-dium Phosphate	Inflamase Forte	4	NA	NA	600

40

Off-Label Medication Use

Topical prednisolone acetate (Pred Forte 1%)

FDA approved for:
- Inflammation of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe
- 1st FDA label received in 1975

MOA: *Disrupt the inflammatory cascade by [1)]immobilizing arachidonic acid, [2)]downregulating cytokine pathways* ***(including the VEGF)****, [3)]stabilizing cell membranes and mast cell granules, [4)]inhibiting leukocyte interaction and slowing [5)]diapedesis.*

Emerging evidence of that corticosteroids also effect:
- ***Inflammatory gene expression***
- ***Angiogenesis***
- ***Oxidative stress***
- ***Apoptosis***

Off-label uses identified in the literature include:
- ***Moderate to severe dry-eye syndrome***

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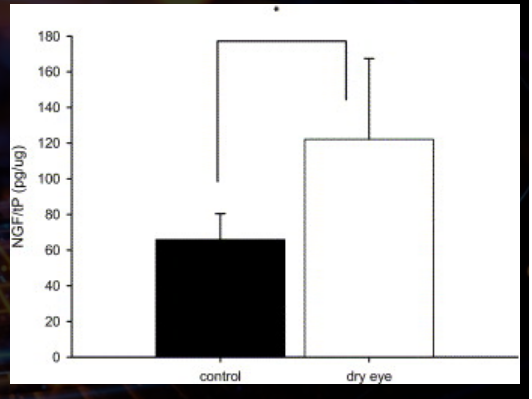
Topical 1% prednisolone lowers nerve growth factor expression in KCS patients

Ophthalmology (2016) *113*(2):198-205

Methods
- Prospective, double-masked, comparative RCT utilizing 41 KCS patients and 23 matched controls. Baseline tear NGF levels were measured using ELISA
- KCS patients received 1% prednisolone drops in one eye and 1% hyaluronic acid drops in the other TID for 28 days

Results
- KCS patients were found to have baseline tear NGF concentrations higher than matched controls
  - In KCS patients, prednisolone treatment for 28 days resulted in a decrease in tear NGF levels, symptom scores and IC scores, whereas
  - ***Hyaluronic acid treatment had no effect***
- ***Measurements taken at both 14 and 28 days indicated that neither prednisolone nor hyaluronic acid treatment affected TBUT or Schirmer values.***

Conclusion
- ***KCS patients showed elevated levels of tear NGF which were decreased by treatment with 1% prednisolone***
- ***Ocular surface NGF may play an important role in ocular surface inflammation processes associated with KCS***



***REDUCED EXPRESSION OF INFLAMMATORY MEDIATORS**

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Off-Label Medication Use

Diflurprednate suspension (Durezol 0.05%)

FDA-approved synthetic steroid indicated for:
- Post-surgical inflammation

MOA: *Disrupt the inflammatory cascade by [1]immobilizing arachidonic acid, [2]downregulating cytokine pathways* ***(including the VEGF)****, [3]stabilizing cell membranes and mast cell granules, [4]inhibiting leukocyte interaction and [5] slowing diapedesis.*

- ***Emerging evidence of that corticosteroids also effect:***
  - ***Inflammatory gene expression***
  - ***Angiogenesis***
  - ***Oxidative stress***
  - ***Apoptosis***

Off-label uses identified in the literature include:
- ***Iritis and uveitis with systemic association (Crohns and IBD)***
- Central retinal ischemic conditions

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Difluprednate 0.05% versus Prednisolone Acetate 1% for Endogenous Anterior Uveitis - Pooled Efficacy Analysis of Two Phase 3 Studies

Ocular Immun and Inflamm (2019) 27(3):484-496

Methods
- Patients received difluprednate alternating with vehicle or prednisolone acetate for 14 days (8 drops/day in both groups), followed by tapering from day 14 to 28. All patients were observed until day 42.

Results
- Patients on difluprednate vs. prednisolone acetate were cleared of A/C cells on day 21 ***(71% vs 55%)***
- Treatment withdrawals were higher with prednisolone acetate than difluprednate ***(20% vs 7%)***
- Study discontinuation due to lack of efficacy was also higher with prednisolone acetate than difluprednate ***(14% vs 0%)***

Variables	Difluprednate group (mean±SD)	Prednisolone group (mean±SD)	*P* (Mann-Whitney *U*-test)
Cells			
ΔCells-3	−8.1±4.9	−9.2±4.6	0.5
ΔCells-7	−10±5.7	−12.4±7.2	0.4
ΔCells-14	−10.2±5.9	−13.3±8.2	0.3
ΔCells-21	−10.2±5.9	−13.3±8.2	0.3
ΔCells-28	−10.3±5.9	−13.2±8.2	0.3
ΔCells-35	−10.3±5.9	−13.2±8.2	0.3
Flare			
ΔFlare-3	−0.8±0.9	−0.9±0.8	0.8
ΔFlare-7	−1.2±0.8	−1.3±0.9	0.8
ΔFlare-14	−1.6±0.7	−1.6±1.08	0.9
ΔFlare-21	−1.7±0.5	−1.9±1.2	0.5
ΔFlare-28	−1.7±0.5	−2±1.2	0.4
ΔFlare-35	−1.7±0.5	−2±1.2	0.4

Conclusions
- ***More difluprednate-treated eyes were quiet following 21 days of treatment and much less likely to be withdrawn from the study because of treatment failure***

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Off-Label Medication Use

Topical Non-steroidal Anti-Inflammatory

FDA-approved for:

- Pain and inflammation associated with cataract surgery

MOA: *Inhibition of cyclooxygenase enzymes (COX-1 or COX-2) activity and disruption in the synthesis of key inflammatory (prostaglandins) and clotting (thromboxanes) mediators*

Off-label uses identified in the literature:

- Allergic conjunctivitis and DES
- ***DME and CME***

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Use of Topical Steroids and NSAIDs in the treatment of Diabetic Macular Edema

Invest Ophthal Vis Sci (2020) 61:4884

Methods

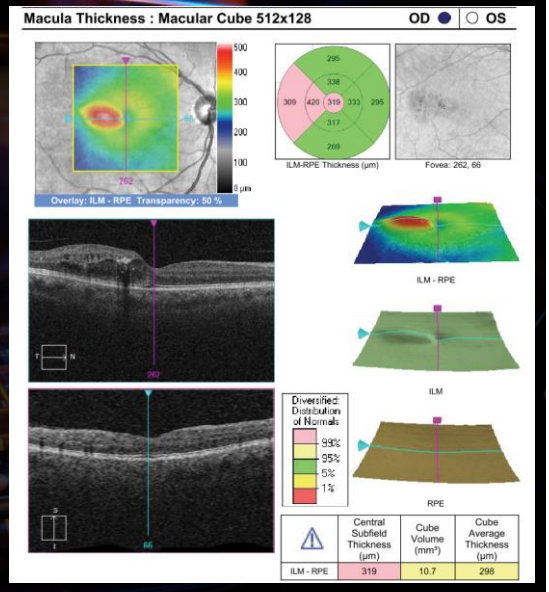
- Retrospective chart review of retina patients were collected for both NPDR and PDR associated with macular edema. Data was collected at baseline, 1 month, and 3-6 months after initiation of therapy. BCVA change, CMT on OCT and degree of retinopathy were documented at each subsequent visit
- ***Treatment failure was defined as worsening of CMT>20µm or involvement of alternate therapy options***

Results

- 39 eyes met criteria
  - 87% had 1-mo follow up
  - 77% had 3-mo follow up
- ***4-week CMT: 35% improvement / 35% worsened / 26% failed***
- ***3-month CMT: 40% improved / 23% worsened / 7% failed***

Conclusions

- ***Viable alternative to intravitreal injections for those patients who are either unable to or choose not to commit to intravitreal injections in the treatment of DME***



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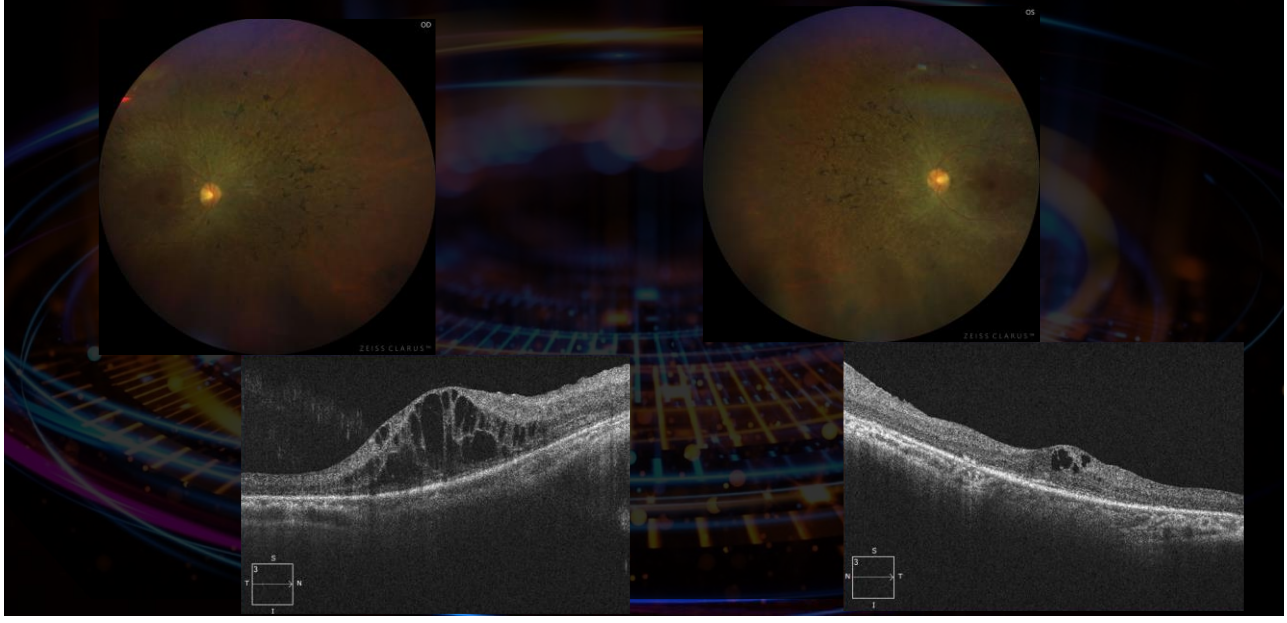
Use of Topical Steroids and NSAIDs in the treatment of Cystoid Macular Edema

Pred Forte 1% QID + Ketorolac 0.4% QID + Dorzolamide 2% TID x 4-12wks



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Off-Label Medication Use

*Topical Cyclosporine (Restasis 0.05% + **Cequa 0.09%**)*

FDA-approved for:

- KCS and DES

MOA: *Calcineurin inhibitors that binds to lymphocytes preventing activation IL-2 which inhibits T-cell-mediated immune response*

Off-label uses identified in the literature:

- Uveitis
- Post-surgical dryness
- Atopic keratoconjunctivitis / vernal keratoconjunctivitis
- PKP rejection prevention
- Thygeson's keratitis
- Superior limbic keratoconjunctivitis (SLK)
- ***Herpetic stromal keratitis***

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Topical cyclosporine-A versus prednisolone for herpetic stromal keratitis: RCT

Acta Ophthalmologica Vis Sci (2019) 97(2): e194-e198

Methods

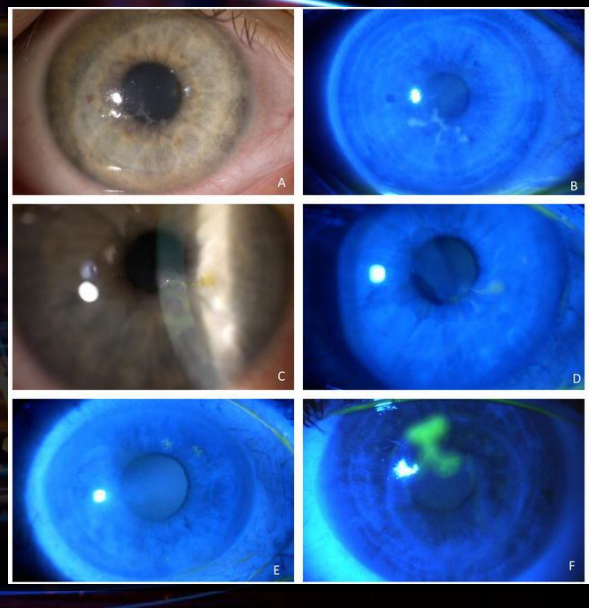
- 38 eyes of 33 HSK patients were randomly assigned
  - ***2% Cs-A***
  - ***1% prednisolone acetate***
  - All subjects received oral acyclovir 400mg BID
- Slit-lamp examination, Pentacam, BCVA and IOP were evaluated at the first visit and 14 and 30 days after the treatment.

Results

- Within-group analysis revealed significant improvement of cornea optical density after 30d treatment in both groups
- ***No significant difference between groups regarding corneal opacity resolution was identified***
- BCVA logMAR significantly improved in both groups after 30d of treatment and analysis between groups did not show a significant difference of BCVA improvement

Conclusions

- ***Cs-A 2% and prednisolone acetate 1% topical eye drops are effective for treatment of HSK***



50

Peer-Reviewed Off-Label Medications

- **Anti-Glaucoma**
  - α-adrenergic Agonists
  - Carbonic anhydrase inhibitors
  - Beta-blockers
  - Prostaglandin analogues
  - Rho-kinase inhibitors

53

Off-Label Medication Use

Alpha-Adrenergic Agonists (Apraclonodine)

FDA approved for:

- Postsurgical IOP control in patients following argon laser trabeculoplasty, argon laser iridotomy or Nd:YAG posterior capsulotomy

MOA: *Reduction of aqueous flow via stimulation of the alpha-adrenergic system*

Off-label uses identified in the literature:

- ***Mild ptosis (including botulism injection-induced)***
- DDx of Horner's syndrome
  - Weak direct action on α-1 receptors with minimal to no clinical effect on normal pupils
  - Horner's patient have α-1 receptor denervation making the pupil dilator hyper-responsive to apraclonidine

55

Upper Eyelid Response to Topical 0.5% Apraclonidine

Ophthal Plast Reconstr Surg (2018) 34:13-19

Methods

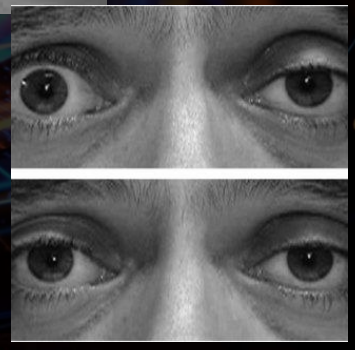
- 100 self-reportedly normal subjects received a 1-time administration of topical 0.5% apraclonidine in each eye
- Digital photographs taken at baseline, 30 and 45 minutes following apraclonidine instillation
- Marginal reflex distance was determined via digital photographs

Results

- Mean increase in i-marginal reflex distance post-administration of 0.5% apraclonidine was +0.70 ± 0.60 mm after 30 minutes and +0.68 ± 0.59 mm after 45 minutes.

- ***Of the 200 total eyelids in 100 subjects***
  - ***91% had i-marginal reflex increase at 30 minutes***

- ***Of the 100 subjects***
  - ***85% had i-marginal reflex increase***
  - ***4% had bilateral decrease***
  - ***11% had unilateral increase with contralateral decrease***



Conclusions

- ***Topical apraclonidine may be a useful off-label alternative treatment for mild upper eyelid ptosis and in eyelid asymmetry***

56

Off-Label Medication Use

Alpha-Adrenergic Agonists (Brimonidine)

FDA approved for:

- IOP reduction in patients with primary open-angle glaucoma or ocular hypertension

MOA: *Reduces aqueous humor production and stimulates aqueous humor outflow through the uveoscleral pathway*

Off-label uses identified in the literature:

- ***Glare***
- Conjunctival hyperemia
- Reduction in ischemic injury following RVO and CSME

57

Effect of brimonidine tartrate 0.15% on night-vision difficulty and contrast testing after refractive surgery

Cataract & Refractive Surg (2008) *34*(9):1538-1541

Methods

- 6 patients with significant night-vision complaints S/P refractive surgery were enrolled in this study after other treatable causes of night-vision difficulty were excluded
- LCVA was tested at photopic and mesopic luminance levels, with and without a standard glare source

Results

- After 1-hour: Patients had significant improvement in LCVA, LCVA with glare and CS.
- After 1 month: All 6 patients reported subjective improvement in night vision with significant difference in mesopic LCVA with and without glare
- ***Mean pupil size before brimonidine 0.15% was 6.0±1mm and 1 hour after instillation had decreased to 4.5±1mm***

Conclusions

- ***Improved contrast sensitivity and acuity and decreased night-vision difficulty***

58

Off-Label Medication Use

Carbonic Anhydrase Inhibitors (Dorzolamide 2%)

FDA approved for:

- Treatment of high IOP due to open-angle POAG or OHTN

MOA: *Catalyzes the reversible reaction involving the carbonic anhydrase isoenzyme and slowed Na^{2+} fluid transport*

Off-label uses identified in the literature:

- CME related to RP, Usher's, choroideremia and chemotherapy toxicity
- ***CSCR***

59

Topical carbonic anhydrase inhibitor efficacy in reducing duration of chronic CSC

TVST (2020) *9*(13):6

Methods

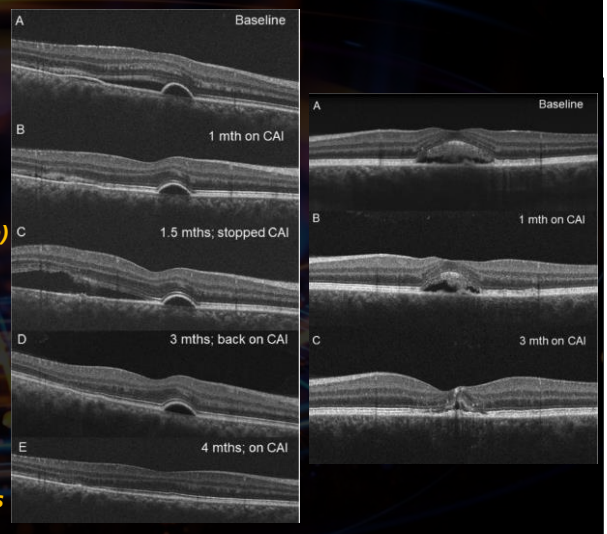
- Prospective, intervention study of patients with chronic CSC of at least 3 months duration
  - Controls were observed without active intervention
  - Treated cases utilized topical dorzolamide for 3 months
- Study end points were change in CMT, change in BCVA and proportion of eyes achieving complete resolution of SRF

Results

- Topical CAI had greater CMT reduction ***(−146µm vs. −45µm)*** compared to observed controls at 3 months
- Higher proportion of topical CAI achieved complete SRF resolution compared to controls ***(78% vs. 40%)*** at 3 months
  - ***BCVA at 3 months was similar in both groups***

Conclusions

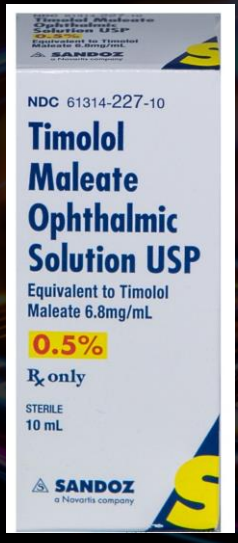
- ***Topical CAI resulted in more rapid reduction of CMT compared to observation***
- ***Topical CAI may be a viable treatment option for patients with chronic CSC***



60

Off-Label Medication Use

Beta-blockers (Timolol 0.5%)



FDA approved for:
- Treatment of elevated IOP in patients with OHTN or POAG

MOA: *β-2 receptors blockade in the blood vessels leads to a decrease in peripheral vascular resistance reducing blood pressure and likely decreases the secretion of aqueous humor in the eye*

Off-label uses identified in the literature:
- ***Migraine management***
- Pediatric hemangiomas

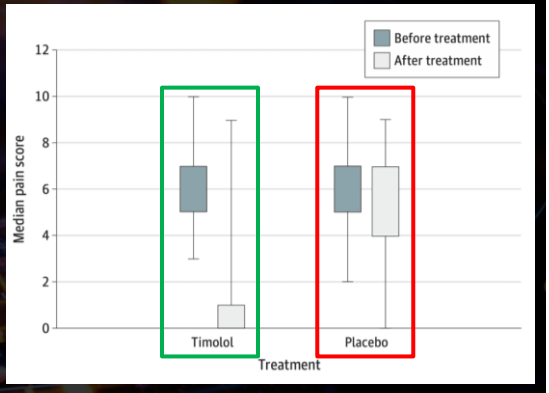
61

Timolol eye drops in the treatment of acute migraine attacks: Randomized crossover study

JAMA Neurology (2018) 75(8), 1538-1541

Results
- Initial enrollment of 26 established migraine patients
- ***2 hours post-instillation:***
  - ***78% of migraines had a severity of none or mild compared to 57% with placebo***.
- Subject-rated overall effectiveness of timolol 0.5% was 2.4 out of 4 compared to 1.4 out of 4 with placebo
  - ***40% of test patients found β-blockers very effective***
  - ***4% of placebo patients found placebo very effective***

Conclusions
- ***Topical timolol 0.5% is an effective abortive treatment for some patients with migraines***
- ***Vital component: Instillation OU at the first sign of an aura or migraine and a second set within 15 minutes***



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Off-Label Medication Use

Beta-2 blocker + CAI (Timolol 0.5% + Dorzolamide 2%)

FDA approved for:

- Reduction of elevated IOP in POAG or OHTN who are insufficiently responsive to beta-blockers.

MOA: *β-2 receptor blockade leads to a decrease in peripheral vascular resistance reducing blood pressure and likely decreases the secretion of aqueous humor in the eye* ***PLUS*** *catalyzes the reversible reaction involving the carbonic anhydrase isoenzyme and slowed Na^{2+} fluid transport*

Off-label uses identified in the literature include:

- ***Reduction of persistent exudation in nvAMD and DME***
- Full-thickness macular holes

64

Effect of adjuvant topical dorzolamide-timolol vs placebo in nvAMD - RCT

JAMA Ophthalmol (2020) 138(5):560-567

Methods

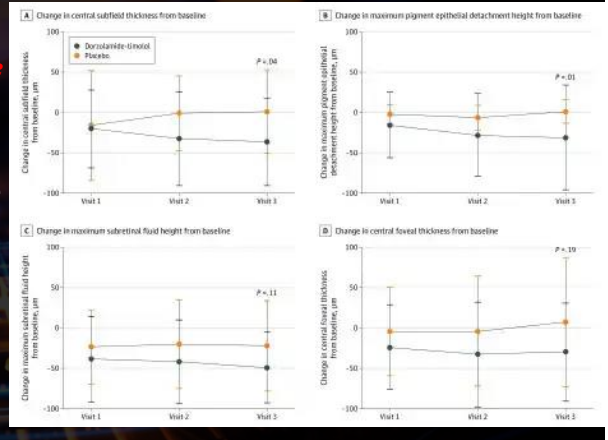
- Multicenter, clinical trial of 50 nvAMD patients with persistent exudation despite intravitreal anti-VEGF injections
- Patients were randomized to use dorzolamide-timolol or artificial tears for the study duration
  - ***Anti-VEGF interventions were continued at the same intervals***

Results

- 27 patients assigned to dorzolamide-timolol and 23 assigned to placebo were analyzed for the primary outcome Mean age was 78 years and mean baseline logMAR VA was 0.36± 0.3

Dorzolamide-timolol vs placebo at 3 months:

- ***Mean change in CFT: −37±54μm vs 3±52μm***
- ***Maximum PED height: −39±65μm vs 1±16μm***
- ***logMAR BCVA change: −2.5±5 vs 0.3±1 letters***



Conclusions

- ***Dorzolamide-timolol in patients with nvAMD with persistent exudation resulted in anatomic but not BCVA improvements***

65

Off-Label Medication Use

Rho-kinase Inhibitor (Netarsudil 0.02%)

FDA approved for:
- Reduction of elevated IOP in patients with POAG or OHTN

MOA: *Believed to reduce IOP by increasing the outflow of aqueous humor through the TM*

Off-label uses identified in the literature:
- DME management
- ***Corneal endothelial dysfunction (Fuchs dystrophy)***

68

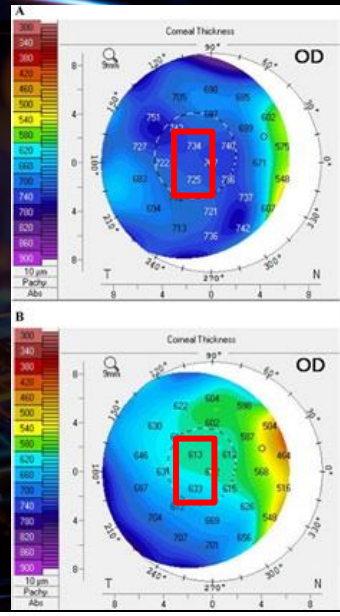
Case Series: Novel Utilization of Rho-Kinase Inhibitor for the Treatment of Corneal Edema

Cornea (2021) 40(1): 116-120

Methods
- 4 patients presenting with visual complaints from corneal edema secondary to endothelial cell dysfunction were treated with topical netarsudil one drop daily in the affected eye

Results
- Corneal clearance observed in:
  - ***Peripheral edema in the setting of iridocorneal endothelial syndrome after 4 week use***
  - ***Edema in the setting of early penetrating keratoplasty graft failure after 2-week use***
  - ***Edema in the setting of chronic penetrating keratoplasty graft failure after 4-week use***
  - ***Corneal clearance was not observed in edema due to pseudophakic bullous keratopathy from previous complicated intraocular lens exchange surgery with placement of an anterior chamber intraocular lens after the use of netarsudil for 12 weeks***

Conclusions
- Addition of topical rho-kinase inhibitor (netarsudil) can result in corneal clearance in variety of cases of endothelial cell dysfunction
  - ***Use of ROCK inhibitor eye drops as alternative to graft surgery for certain forms of corneal endothelial disease***



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Peer-Reviewed Off-Label Medications

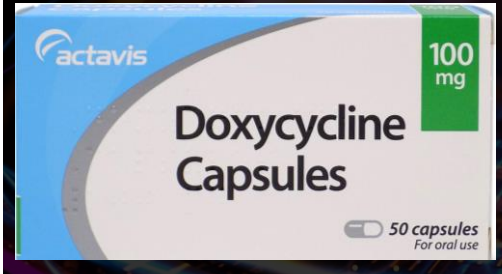
Oral Medications

- ***Doxycycline****
- **Atorvastatin**
- **Prednisone (bioequivalency)**
- **Metformin**
- **Lisinopril**
- **Sildenafil**
- **Levodopa / Carbidopa**
- **Minocycline**
- **Magnesium**
- ***Selenium****
- ***L-lysine****
- ***AREDS2****
- ***Chromium****
- ***Beta-carotene****
- ***Acetyl hexapeptide-4 (argireline)***
- ***Ω-3 FA****
- ***MacuHealth****
- ***VitreousHealth****
- ***Ibuprofen + Acetaminophen****
- **ParaSym Plus Eyes**
- **N-acetylcarnosine (Can-C)**
- **Lanosterol**
- **NuSkin NuColour Nutriol**

72

Off-Label Medication Use

Oral Doxycycline



FDA approved tetracycline-class antimicrobial indicated for:

- Plague due to Yersinia pestis
- Cholera caused by Vibrio cholera
- Trachoma caused by Chlamydia trachomatis
- Inclusion conjunctivitis caused by Chlamydia trachomatis
- Syphilis caused by Treponema pallidum
- ***Malaria prophylaxis***

MOA: *Inhibits bacterial protein synthesis by binding to the 30S ribosomal subunit*

Off-label uses identified in the literature:

- Dry eye syndrome
- Recurrent corneal erosion
- Meibomian gland dysfunction
- ***nvAMD***

73

Oral Doxycycline Reduces the Total Number of Intraocular Bevacizumab Injections Needed to Control nvAMD

Med Hypothesis Innov Ophthalmol. (2017) *32*(1):44

Abstract

- Interventional case series of 28 consecutive patients with nvAMD were treated for 4 months with doxycycline 200mg QD ***(100mg BID)*** after the first intravitreal bevacizumab injection in addition to standard therapy
- After 12 months of follow-up, total number of injections, foveal thickness and visual acuity were compared to those at baseline and of similar studies
- ***Co-treatment with doxycycline resulted in:***
  - ***Lower rates of intraretinal, SRF and leakage***
  - ***No new-onset of macular hemorrhage***
  - ***<5 letter ETDRS reduction***
  - ***Fewer injections (3.14 vs. 5.92)***
  - ***Decreased foveal thickness***

	Values
Age, years	75.5 ± 7.7
Sex, female:male ratio, n (%)	12 (54.5%):10 (45.5%)
Initial lesion size, disc diameter	1.25 ± 0.65
Initial visual acuity score *	28.5 ± 22.57
Initial thickness of the foveal central portion, m	445.14 ± 63.69
Visual acuity score change	7.92 ± 16.89 (P = 0.03)
Foveal thickness change, m	232.68 ± 69.25 (P < 0.001)
Final visual acuity score	36.45 ± 26.66
Final central foveal thickness, micrometer	212.45 ± 29.50
Number of consumed doxycycline tablets	212.5 ± 7.5
Total number of injections in 12 months	3.18 ± 0.79

* based on Early Treatment Diabetic Retinopathy Study (ETDRS) charts

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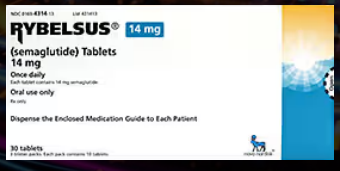
Off-Label Medication Use

IM semaglutide (Ozempic) / Oral semaglutide (Rybelsus)



FDA approved as an:

- GLP-1 (Glucagon-like peptide) agonist to lower blood sugar levels in Type 2 diabetes

MOA: **1) Increases insulin release**
2) Decreases appetite and signals feeling of fullness

Off-label* uses identified in the literature:

- ***Risk reduction in new onset POAG***

84

Glucagon-like peptide 1 receptor agonist use is associated with reduced risk for glaucoma

Br J Ophthal (2023) 107(2):215-220

Methods

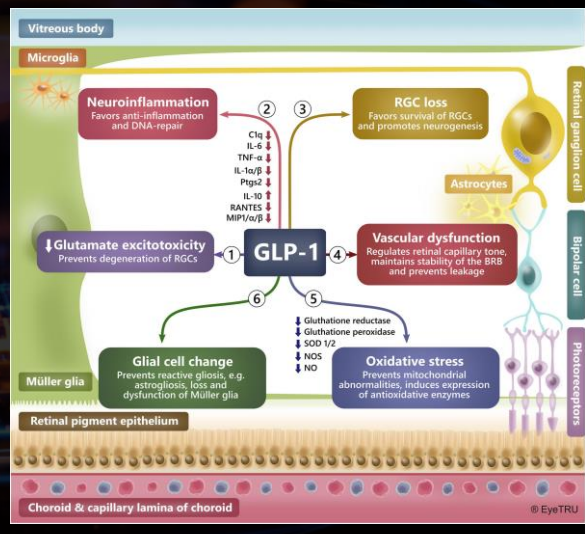
- Retrospective cohort initiated new GLP-1R agonist was matched to patients who initiated a different class of oral diabetic medication.
- Multivariable Cox proportional hazard regression model of association between GLP-1R agonist exposure and a new diagnosis of primary open-angle glaucoma, glaucoma suspect or low-tension glaucoma

Results

- 1961 new GLP-1R agonists sujects matched to 4371 controls
- 10 (0.51%) glaucoma diagnoses present in GLP-1R agonist cohort compared with 58 (1.33%) in the controls
- ***GLP-1R exposure conferred a reduced hazard of 0.56***

Conclusions

- ***GLP-1R agonist showed statistically significant hazard reduction for a new diagnosis of glaucoma***
- Findings support further investigations into the use of GLP-1R agonists in glaucoma prevention



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Off-Label Medication Use

Topical Ivermectin 1%

FDA approved for:

- Strongyloidiasis caused by nematode parasite *Strongyloides stercoralis*
- Onchocerciasis caused by nematode parasite *Onchocerca volvulus*

Proposed MOA:

Binds selectively with high affinity to glutamate-gated chloride ion channels in invertebrate muscle and nerve cells resulting in cell membrane hyperpolarization, paralysis and death of the parasite

<u>Off-label uses identified in the literature:</u>**

- ***Demodex and associated oculocutaneous rosacea***

95

Efficacy of Topical Ivermectin 1% in the Treatment of Demodex Blepharitis

Cornea (2022) 41(4): 427–434

Methods

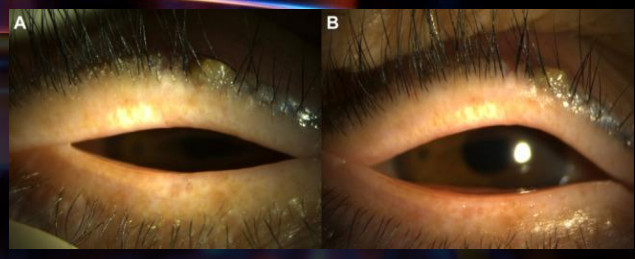
- 102 patients with symptomatic Demodex blepharitis were divided into 2 groups in retrospective case–control study
  - Test group (n=51) applied topical ivermectin 1% cream on the eyelashes for 15 minutes once weekly

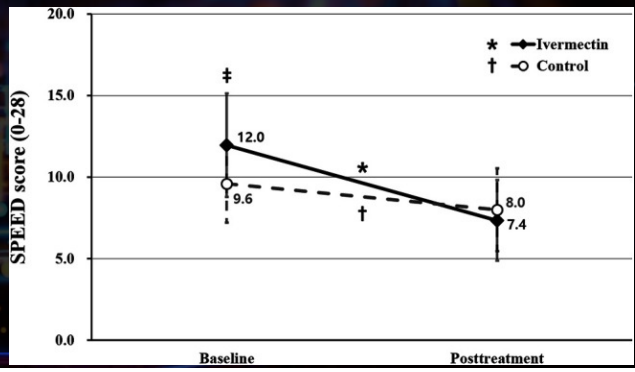
Results

- Mean follow-up periods of the ivermectin and control groups was 15±9 weeks
- SPEED score and eyelid debris grade were significantly improved in both groups during the follow-up
  - ***Eyelid redness/swelling and telangiectasia were significantly improved in the ivermectin group but not in the control group***

Conclusions

- Use of ***topical ivermectin 1% cream x 15min 1X/wk*** had significantly improved symptoms, ocular surface staining, eyelid debris, redness/swelling, and telangiectasia as compared with eyelid hygiene alone





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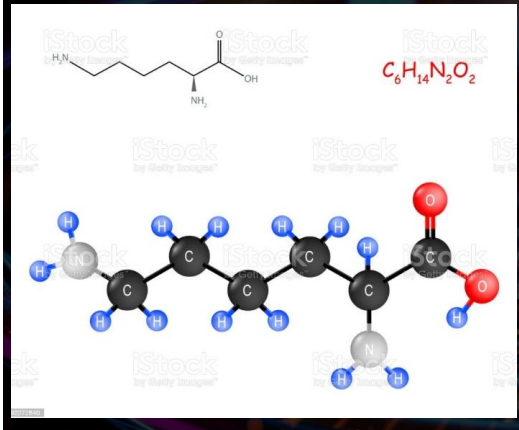
Off-Label Medication Use

L-lysine



Supplement not regulated by FDA

Proposed MOA:

HSV cells synthesize higher levels of arginine and lower levels of lysine than human host cells. Increasing cellular lysine concentrations disrupts HSV's balance between lysine and arginine and inhibits viral replication

Off-label uses identified in the literature :

- ***Adjunctive herpes simplex virus prophylaxis***

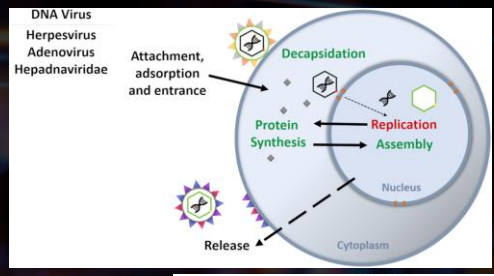
105

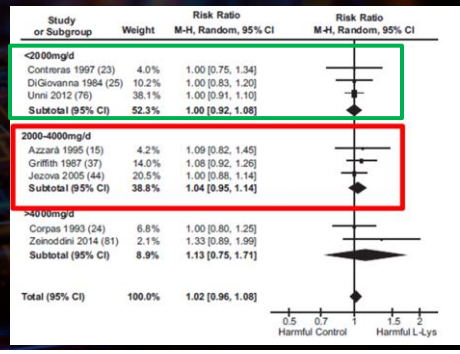
L-lysine: Antagonism with L-arginine in controlling viral infection.

British Journal of Clinical Pharmacology (2022) 88 (11):4708-4723.

Abstract

- Antiviral therapies are not yet able to interfere with a latent virus
  - During infection or viral reactivation, they interfere with the virus adhesion/fusion and viral protein formation
  - L-lysine contributes to the inhibition of these phases by antagonizing arginine, an essential amino acid for some herpesviruses
- Concurrent use of lysine and acyclovir in the treatment of keratitis may have beneficial results by competing with endogenous or exogenous arginine
- ***Dosages range between 1500-3000mg/d***
- ***No observed adverse effect level in healthy human subjects identified at 6000 mg/d.***





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Off-Label Medication Use

Beta-carotene (provitamin A)

Supplement not regulated by FDA

Proposed MOA:

Antioxidant with significant efficacy against the reactive singlet oxygen

- *Scavenger of cell membrane lipophilic radicals*
- *Modulates oxidative modification of LDL*
- *Chelation of oxygen-free radicals inhibiting the peroxidation of lipids.*

Off-label uses identified in the literature:

- ***Treatment and prevention of recurrent chalazion***

112

Serum Vitamin A Levels in Patients with Chalazion

Med Innov Ophthal (2017) 6(3): 63-66

Abstract

- 52 patients with chalazion and 55 control healthy subjects were further divided into four subgroups based on the type of chalazion: single, multiple, primary, and recurrent
- ***Average serum vitamin A levels in patients with chalazion in the age groups of 7-12 and 13-19 years were significantly lower than in their control counterparts***
- ***Serum vitamin A levels in patients with recurrent, multiple chalazia were significantly lower than in patients with primary, multiple chalazia and patients with a recurrent, single chalazion***

Clinical Report: Correlation of Serum Vitamins and Chalazion

OVS (2022) 99(6): 540-543

Methods

180 subjects (90 patients with chalazion and 90 control healthy subjects) with an average age of 4±2 years

Results

- Mean serum vitamin A levels in patients with chalazion (0.54 ± 0.15 μmol/L) were significantly lower than in their control counterparts (0.60 ± 0.15 μmol/L)
- ***Vitamin A deficiency in chalazion group (52.2%) was much higher than the control counterparts (28.6%)***

Conclusions

- ***Low serum vitamin A was significantly associated with chalazion in children***
- ***Serum 25(OH)D level exhibited no correlation with chalazion***

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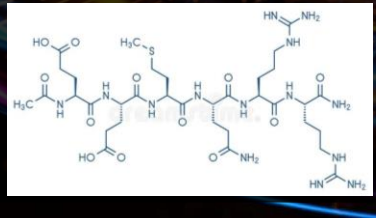
Off-Label Medication Use

Argireline (acetyl hexapeptide-3)



Supplement not regulated by FDA

Proposed MOA:

Inhibition of neurotransmitter release due to hexapeptide interference limiting SNARE complex formation and stability

- *SNAP-25 peptide*

Off-label uses identified in the literature:

- ***Treatment of periorbital wrinkles and festoon formation***

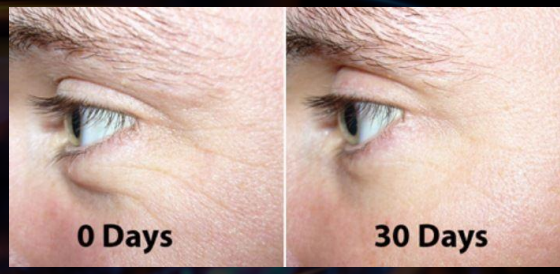
114

Synthetic hexapeptide (Argireline) with antiwrinkle activity

Int J Cosmetic Sci (2022) 24(5): 303-310

Abstract

- Botulinum neurotoxins (BoNTs) possess long-lasting antiwrinkle activity
- ***Skin topography analysis of hexapeptide 10% on healthy volunteers reduced wrinkle depth up to 30% in 30-day treatment***
- ***Argireline significantly inhibited neurotransmitter release with a potency similar to that of BoNT A, although it displayed much lower efficacy than the neurotoxin***
- Peptide did not exhibit *in vivo* toxicity nor primary irritation at high doses
- ***Findings support argireline as biosafe BoNT alternative***



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Off-Label Medication Use

Omega-3 FA

Supplement not regulated by FDA*

Proposed MOA:

- ***Suppressing lipogenic gene expression, increasing beta oxidation of fatty acids, increased expression of lipoprotein-lipase and influencing total body lipid accretion****
- Inhibition of COX activity and its subsequent eicosanoid production ***(leukotrienes and prostaglandins)***
- Inhibition of proinflammatory cytokines ***(TNF-α, IL-1, IL-6)***

Off-label uses identified in the literature:

- ***DED***
- ***AMD***
- Enhanced MP deposition

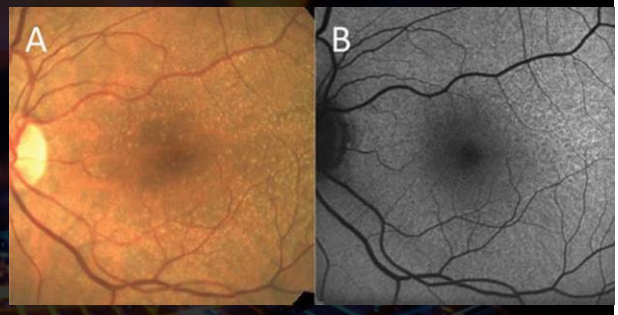
116

Association of plasma Ω-3 fatty acids with early AMD in the Multi-Ethnic Study of Atherosclerosis (MESA)

Retina (2022) doi:10.1097/IAE.0000000000003465

Methods

- 3,772 participants with baseline PUFA measurements and retinal photography were assessed for AMD using a standard grading protocol
- Relative risk was determined associations between PUFA levels and AMD



Results

- ***Significant association between increased DHA+EPA levels and reduced risk for early AMD***
- ***EPA levels alone were not significantly associated with AMD***

Conclusion

- ***Increasing levels of DHA were associated with reduced risk of early AMD in a multi-ethnic cohort***
  - ***First racially diverse study demonstrating an association between Ω-3 PUFAs and AMD risk***

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Regular use of fish oil supplements and course of cardiovascular diseases: prospective cohort study

BMJ Med (2024) doi:10.1136/ bmjmed-2022-000451

Results

- 415,737 participants, aged 40-69 years, enrolled in the UK Biobank study free of cardiovascular diseases were followed for 12 years

- ***(-) CVD***
  - ***HR = 1.13 (Healthy status to atrial fibrillation)***
  - ***HR = 1.05 (Healthy status to stroke)***
- ***(+) CVD***
  - ***HR = 0.92 (Atrial fibrillation to adverse cardiovascular event)***
  - ***HR = 0.85 (Atrial fibrillation to myocardial infarction)***
  - ***HR = 0.91 (Heart failure to death)***

Conclusions

- ***Regular use of fish oil supplements might be a risk factor for atrial fibrillation and stroke among the general population but could be beneficial for progression of existing cardiovascular disease***
- ***HOWEVER…***

3-hour Refrigerator Test

1-hour Styrofoam Test

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Off-Label Medication Use

MacuHealth

MacuHealth

Directions: Take 1 softgel daily, preferably with a meal.

SUPPLEMENT FACTS
Serving Size 1 Softgel

	Amount per serving	% DV
Lutein (L)	10 mg	†
Meso-Zeaxanthin (MZ)	10 mg	†
Zeaxanthin (Z)	2 mg	†

† Daily Value Not Established

Other Ingredients: Sunflower Oil, Gelatin Capsule (Gelatin, Glycerin, Purified Water, Annatto), Marigold Flower Extract, Yellow Beeswax, Tween 80, Soy Lecithin, Ascorbyl Palmitate, d-alpha Tocopheryl Acetate. *CONTAINS SOY

Supplement not regulated by FDA

Proposed MOA:

Preferential accumulation at Henle fiber layer acts as short-wavelength, visible light filter and potent anti-oxidant, free radical scavenger at cellular level

Off-label uses identified in the literature

- Identified link between MPOD
  - ***Photostress recovery***
  - ***Glare disability***
  - ***Contrast sensitivity***

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The association between MPOD and visual function outcomes: systematic review and meta-analysis

Eye (2021) 35(6):1620-1628

METHODS

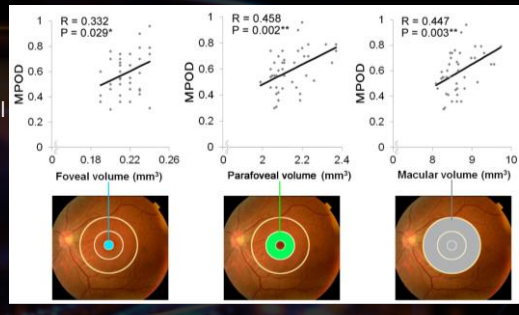
- MEDLINE®, Cochrane, and Commonwealth of Agriculture Bureau abstracts databases were searched for correlations of MPOD and visual function in adults with healthy eyes at all timepoints and all designs. Visual function outcomes reviewed included photostress recovery, contrast sensitivity, visual acuity, glare sensitivity/disability and dark adaptation.

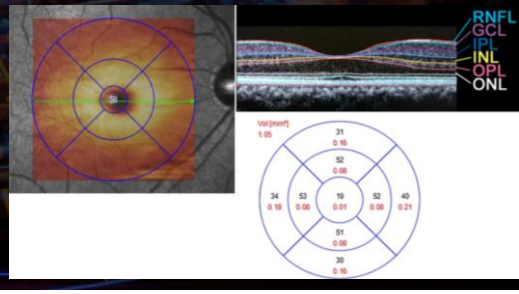
RESULTS

- Meta-analysis of 22 publications, MPOD was significantly correlated with:
- ***Foveal CS with a spatial frequency of 7, 11 and 21 cpd***
- ***Foveal photostress recovery at 10 cpd and 16% contrast***
- ***Foveal glare disability at 460 nm***

CONCLUSIONS

- Identified link between MPOD and visual function with
  1) ***Photostress recovery***
  2) ***Glare disability***
  3) ***Contrast sensitivity.***





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Off-Label Medication Use

VitreousHealth

Supplement not regulated by FDA

Proposed MOA:

Antioxidative and antiglycation micronutrients may mitigate oxidative stress, accumulation of nonenzymatic glycation end-products and decreased vitreous antioxidant capacity

SUPPLEMENT FACTS

Serving Size: 1 capsule, Servings Per Container: 90

Amount per serving		% DV
Zinc	5 mg	45%
Vitamin C	40 mg	45%
Grape Seed Extract	26.3 mg	**
of which Proanthocyanidins	25 mg	**
Citrus Fruit Extract	100 mg	**
of which Bioflavonoids as Hesperidin	60 mg	**
L-lysine	125 mg	**

Off-label uses identified in the literature

- ***Reduction of vitreous degeneration*** leading to decrease visual discomfort and improved contrast sensitivity

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Dietary Intervention With a Targeted Micronutrient Formulation Reduces the Visual Discomfort Associated With Vitreous Degeneration (FLIES)

TVST (2021) 10(12)

Methods

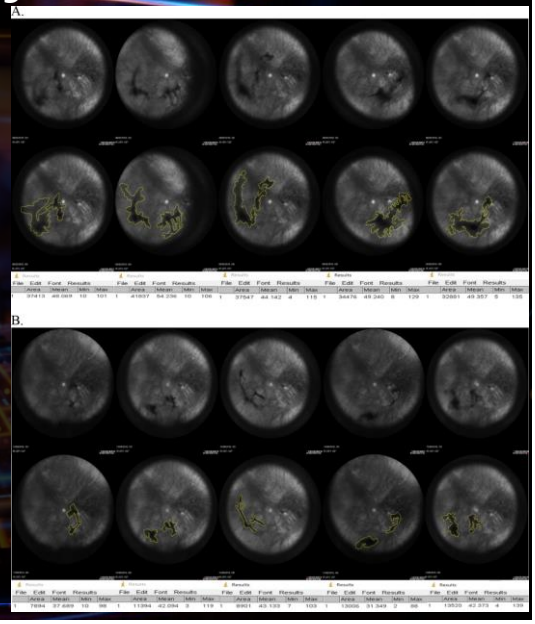
- 61 patients with symptomatic vitreous floaters were randomized to consume VitreousHealth daily or placebo for 6 months
  - 1º outcome measure - Visual discomfort
  - 2º outcome measures - BCVA, photopic CS and quantitative vitreous opacity areas

Results

- Active group reported a significant ***decrease in visual discomfort*** from floaters and placebo group had no significant change in visual discomfort
- ***At 6 months:***
  - ***Significant decrease in vitreous opacity areas in the active group***
  - ***Significant improvement in photopic functional contrast sensitivity in the active group***

Conclusions

- ***Improvements in visual function of patients with vitreous floaters after supplementation confirmed by the decrease in vitreous opacity areas in the active group***



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Off-Label Medication Use

Ibuprofen + Acetaminophen

OTC NSAID + Antipyretic regulated by FDA

Proposed MOA:

Ibuprofen

- Non-selective, reversible inhibition of COX-1 and COX-2

Acetaminophen

- Reduction of COX activity through prostaglandins synthesis inhibition

Off-label uses identified in the literature

- ***Opioid-equivalency analgesic***

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Effect of a single dose of oral opioid and nonopioid analgesics on acute extremity pain in the emergency department: RCT

JAMA (2017) 318(17):1661-1667

Methods

- RCT conducted at 2 urban EDs included 416 patients aged 21-64 years with moderate to severe acute extremity pain
- Participants (104/combination analgesic group) received
  - 400 mg of ibuprofen and 1000 mg of acetaminophen
  - 5 mg of oxycodone and 325 mg of acetaminophen
  - 5 mg of hydrocodone and 300 mg of acetaminophen
  - 30 mg of codeine and 300 mg of acetaminophen

Results

- Of 416 patients randomized, (mean [age, 37±12 years, the baseline mean NRS pain score was 8.7±1.3
- At 2 hours, the mean NRS pain score decreased by:
  - ***4.3 in the ibuprofen and acetaminophen group***
  - ***4.4 in the oxycodone and acetaminophen group***
  - ***3.5 in the hydrocodone and acetaminophen group***
  - ***3.9 in the codeine and acetaminophen group***

Conclusions

- ***No clinically significant differences in pain reduction at 2 hours among single-dose treatment with ibuprofen/acetaminophen vs. opioid/acetaminophen***

	NRS Pain Score, Mean (95% CI)[a]			
	Ibuprofen and Acetaminophen[b]	Oxycodone and Acetaminophen[c]	Hydrocodone and Acetaminophen[d]	Codeine and Acetaminophen[e]
No. of patients[g]	101	104	103	103
Primary end point: decline in score to 2 h	4.3 (3.6 to 4.9)	4.4 (3.7 to 5.0)	3.5 (2.9 to 4.2)	3.9 (3.2 to 4.5)
Baseline score	8.9 (8.5 to 9.2)	8.7 (8.3 to 9.0)	8.6 (8.3 to 9.0)	8.6 (8.2 to 8.9)
Score at 1 h	5.9 (5.3 to 6.6)	5.5 (4.9 to 6.2)	6.2 (5.6 to 6.9)	5.9 (5.2 to 6.5)
Score at 2 h	4.6 (3.9 to 5.3)	4.3 (3.6 to 5.0)	5.1 (4.5 to 5.8)	4.7 (4.0 to 5.4)
Decline in score to 1 h	2.9 (2.4 to 3.5)	3.1 (2.6 to 3.7)	2.4 (1.8 to 3.0)	2.7 (2.1 to 3.3)

	Ibuprofen and Acetaminophen[a]	Oxycodone and Acetaminophen[b]	Hydrocodone and Acetaminophen[c]	Codeine and Acetaminophen[d]
No. of patients	101	104	103	103
Female sex, No. (%)	54 (54)	50 (48)	51 (50)	44 (43)
Age, mean (SD), y	37 (11)	37 (12)	37 (13)	37 (12)
Diagnosis, No. (%)				
Sprain or strain	64 (63)	66 (64)	59 (57)	67 (65)
Extremity fracture	21 (21)	23 (22)	21 (20)	24 (23)
Muscle pain	8 (8)	9 (9)	12 (12)	7 (7)
Contusion	4 (4)	3 (3)	7 (7)	2 (2)
Other	4 (4)	3 (3)	4 (4)	3 (3)
Nonpharmacological ED interventions, No. (%)				
Elastic bandage	39 (39)	37 (36)	23 (22)	36 (35)
Splint	12 (12)	20 (19)	18 (18)	10 (10)
Cast	10 (10)	14 (14)	6 (6)	11 (11)
Ice	7 (7)	11 (11)	10 (10)	4 (4)
Other	11 (11)	5 (5)	15 (15)	16 (16)

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Off-Label Medication Use

Can-C (N-acetylcarnosine) and Lanosterol

Pet-formulation ONLY

Supplement not regulated by FDA

Proposed MOA:

L-carnosine is known to have an antioxidant effect on the cataractous lens, so there is biochemical logic for exploring cataract reversal or progression

- N-acetylcarnosine (NAC) can penetrate the cornea where it is metabolized into L-carnosine

Lanosterol is an amphipathic molecule enriched in the lens synthesized by a key cyclization reaction of a cholesterol synthesis pathway

Off-label uses identified in the literature:**

- Cataract prevention and reversal

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N-acetylcarnosine (NAC) drops for age-related cataract

Cochrane Database Syst Rev (2017) doi:10.1002/14651858.CD009493.pub2

Results

Identified 2 potentially eligible studies from Russia and the US

1) Split into two arms:
   - 6 months with 2-month follow-ups
   - 2 years with 6-month follow-ups
2) 4 months with a data collection point at the start and end of the study only

Total of 114 people were enrolled in these studies with subject ages ranging from 55 to 80 years.

Unable to obtain sufficient information to reliably determine how both these studies were designed and conducted. We have contacted the author of these studies but have not yet received a reply. Studies are assigned as 'awaiting classification' in the review until sufficient information can be obtained from the authors.

Table 8 Mean ± SD of changes (improvement) in visual functions

Treatment group	Visual acuity	Glare radius
9-month follow-up of older subjects with cataract		
Control group	0.90 ± 0.03 (n = 36)	1.53 ± 0.07 (n = 36)
NAC-treated group	1.54 ± 0.05*+ (n = 39)	0.41± 0.05* (n = 39)
9-month follow-up of older adult noncataract subjects		
Control group	0.96 ± 0.03 (n = 35)	1.27 ± 0.05 (n = 35)
NAC-treated group	1.20 ± 0.04* (n = 37)	0.38 ± 0.05* (n = 37)

Conclusions

- ***No convincing evidence that NAC reverses cataract, nor prevents progression of cataract***

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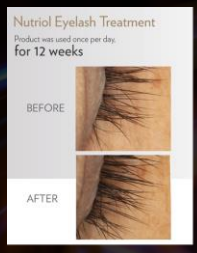
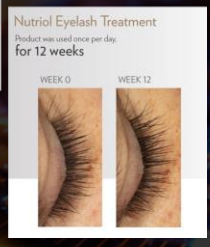
Off-Label Medication Use

Nu Colour Nutriol Eyelash Treatment (Nu Skin)





Supplement not regulated by FDA

Proposed MOA:

Seaweed derivative (Tricalgoxyl) rich in polysaccharides strengthens / lengthens lashes from roots to tips.

Off-label uses identified in the literature:**

- ***Promotes lash growth and thickening***

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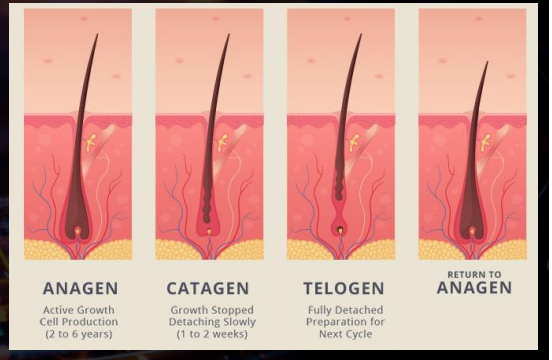
Clinical study of topical mucopolysaccharides & polydeoxyribonucleoprotein therapy in alopecia

J Korean Med Sci (1987) 2(3):157-165

Abstract

- 30 patients with male pattern baldness, alopecia areata and seborrheic alopecia were included in this study. Mucopolysaccarides were applied QOD x 40 days and followed by maintenance therapy of 2x/wk for total of 6 months.
- Concluded that mucopolysaccarides are effective agent for male pattern baldness, alopecia areata and seborrheic alopecia
- ***10 patients with male pattern baldness***
  - ***50% hair regrowth***
  - ***70% decreased hair loss***
- ***13 patients with alopecia areata***
  - ***62% hair regrowth***
  - ***54% decreased hair loss***
- ***7 patients with seborrheic alopecia***
  - ***86% hair regrowth***
  - ***57% decreased hair loss***
- ***Degree of therapeutic success was related to the duration of therapy***



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Peer-Reviewed Off-Label Medications

Central serous chorioretinopathy
- Mineralcorticoid antagonist
- Antimycobacterials

- Case Report

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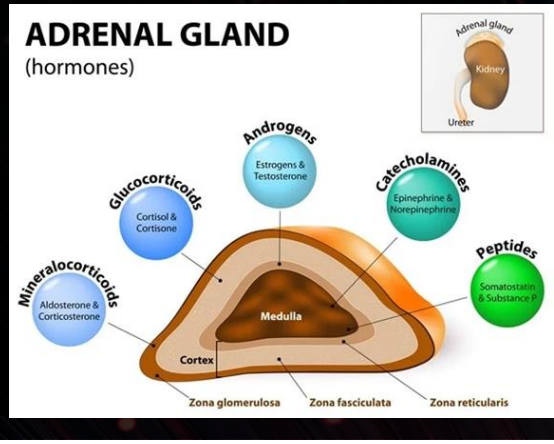
Off-Label Medication Use

Central Serous Chorioretinopathy

- Choroidal pathology
  - Dysautoregulation -> Vascular hyperpermeability -> Accumulation of sub-RPE fluid
  - Pachychoroid spectrum
    - Pachychoroid pigment epitheliopathy
    - Pachychoroid neovasculopathy
    - Polypoidal choroidal vasculopathy
    - ***CSCR***

- Associated with increased levels of adrenal hormones:
  - Glucocorticoids (***Cortisol*** and Cortisone)
  - Mineralocorticoids (***Aldosterone*** and Corticosterone)
  - Androgens (Estrogen and ***Testosterone***)
  - Catecholamines (***Epinephrine*** and Norepinephrine)
  - ***Endogenous + Exogenous***

- Acute (<3-6 months) vs. Chronic (>3-6 months)
  - Non-resolving
  - Recurrent
  - Chronic
  - Inactive



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Central Serous Chorioretinopathy

Clinical Management

- **Case history**
  - ***Obstructive Sleep Apnea (OSA)***
  - ***Cushing's disease***
  - Untreated HTN / Anxiety / Depression
- **Review modifiable risk factors**
  - Corticosteroids (prescribed and naturally occurring)
  - Circadian rhythm disruption (Shift-work, inadequate sleep)
  - Pregnancy (especially 3rd trimester)
- **Acute < 3- 6 months**
  - Consider topical NSAID or CAI treatment x 12 weeks and monitor at 8 weeks
    - (+) improvement: Continue therapy until SRD resolves before discontinuing and monitoring
    - (-) improvement: Consider chronic management ***(BELOW)***
- **Chronic > 3-6 months**
  - Initiate MRA treatment if not contraindicated, obtain baseline serum K^+ levels and monitor at 4 weeks
  - (+) improvement: Continue therapy until SRD resolves before discontinuing and monitoring
  - (-) improvement: Consider alternate MRA and obtain OCTA/FA or ICGA to guide laser treatment
    - Localized, non-central leakage → focal laser
    - Diffuse, central leakage → PDT **[Perspectives & Update on Global Shortage of Verteporfin (2024)** ***Ophthal Therapy]***
      - (+) improvement: Monitor and coordinate additional therapy as needed.
      - (-) improvement: Consider anti-VEGF treatment

Derived from:
- Review of Optometry (2021, 2023, 2024)
- Review of Ophthalmology (2024)
- NIH StatPearls (2023)

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PEER-REVIEWED OFF-LABEL MEDICATIONS

- **Take-Home Points**
- **Opportunities**
- **Limitations**
- **What's Next?**

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Take Home Points
Optometric Off-Label Use Can Become On-Label

FDA approved for:
- Treatment of presbyopia in adults

MOA: *Cholinergic agonist which activates muscarinic receptors located at smooth muscles such as the iris sphincter muscle and ciliary muscle. Activation contracts the iris sphincter muscle and ciliary muscle maintaining some response to light*

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Take Home Points
Optometric Off-Label Use Can Become On-Label

European-approval since mid-1970s
- Treatment of POAG

FDA approval submission (Aug 2024)
- Management of presbyopia

MOA: *Parasympathomimetic miotic agent*
- Muscarinic acetylcholine agonist

****Pupil-selective miotic acting on sphincter muscle with less effect on ciliary muscle***

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Take Home Points
Optometric Off-Label Use Can Become On-Label

FDA approved for:
- Reduction of conjunctival hyperemia as OTC red-eye relief

MOA: *Relatively selective α-2 adrenergic agonist that, at the proposed OTC concentration of 0.025%, has a vasoconstrictive effect*

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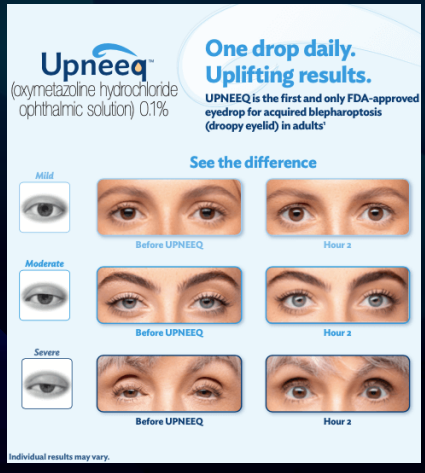
Take Home Points
Optometric Off-Label Use Can Become On-Label



FDA approved for:
- Treatment of acquired blepharoptosis characterized by the abnormal drooping of the upper eyelid that can limit field of vision

MOA: *Direct-acting, relatively selective α-1 adrenergic agonist that targets the Muller's muscle which acts in upper lid elevation*

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Take Home Points
Optometric Off-Label Use Can Become On-Label

FDA approved for:
- Treatment of hypotrichosis of the eyelashes by increasing growth including length, thickness and darkness

MOA: *Precise mechanism of action is unknown; however, the growth of eyelashes is believed to occur by increasing the [1] duration and [2] number of follicles in the anagen (growth) phase*

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Take Home Points
Optometric Off-Label Use Can Become On-Label

FDA approved for:
- Indicated as an aid to smoking cessation treatment - Chantix

MOA: *Binds with high affinity and selectivity at $\alpha_4\beta_2$neuronal nicotinic acetylcholine receptors*

Binding produces agonist activity, while simultaneously preventing nicotine binding to $\alpha_4\beta_2$ receptors

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Take Home Points: Adjunctive Therapy
Optometric Off-Label Use

- Topical ganciclovir 0.15% (Zirgan) QID x 7 days
  - Adenoviral conjunctivitis
- Pred Forte 1% QID + Ketorolac 0.4% QID + Dorzolamide 2% TID x 4-12 wks
  - DME
  - CME
  - RVO
- Pred Forte 1% QID + Timolol 0.5% BID + Dorzolamide 2% TID x 4-12 weeks
  - nvAMD
  - Macular Holes
- Cyclosporine 0.09% (Cequa) QID x 30d or re-epitheliazation
  - HSV stromal keratitis

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Take Home Points: Adjunctive Therapy
Optometric Off-Label Use

- Topical Apraclonidine 0.5% (Iopidine) BID or PRN
  - Mild ptosis
- Topical Brimonidine 0.2% (Alphagan-P 0.15%) BID or PRN
  - Glare
- Timolol 0.5% 2gtts spaced by 15 minutes PRN
  - Acute migraines
- Dorzolamide 2% (Trusopt) TID x 4-12 weeks
  - CME
- Rho-kinase inhibitor 0.02% (Netarsudil) QD x 4 weeks
  - Corneal endothelial injury

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Take Home Points: Adjunctive Therapy
Optometric Off-Label Use

- Oral Doxycycline 100mg BID x 4 weeks
  - RCE
- Atorvastatin 40mg and 80mg
  - High-risk AMD
- Oral Prednisone 1250mg QD x 3 days
  - Optic Neuritis
- Metformin 500mg BID or Glucophage XR 500mg QD x 12 weeks
  - DR and AMD
- Lisinopril 20-40mg QD x 12 weeks
  - DR
- Spironolactone (Aldactone) 25mg BID x 4-12 weeks
- Rifampin (Rifampicin) 300mg BID x 4-12 weeks
  - CSC

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Take Home Points: Adjunctive Therapy
Optometric Off-Label Use

- Selenium 100ug BID x 6 months
  - Proptosis associated with thyroid eye disease (TED)
- L-lysine 1000mg TID x 4 weeks
  - HSV
- AREDS 2 1 capsule BID x 52 weeks
  - IMT2
- Chromium 50mcg BID x 12 weeks
  - Concurrent with anti-VEGF therapy
- Beta-carotene 6mg (10,000 IU) QD [Adults] or 3mg (5,000 IU) QD [Children]
  - Recurrent chalazion
- Topical 1% ivermectin QD x 7 days
  - Demodex and oculocutaneous rosacea

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Take Home Points: Adjunctive Therapy
Optometric Off-Label Use

- **Parasym Eyes 2 capsules BID x 4 weeks****
  - **Dry eye disease**
- **VitreousHealth 1 capsule QD x 6 months**
  - **Vitreal syneresis / floaters**
- **MacuHealth 1 capsules QD x 3-6 months**
  - **Early AMD / DR / Dry Eye Disease**
- **Ω-3 2000mg BID X 3-6 months**
  - **Dry eye disease / Enhancement of retinal carotenoid absorption**
- **Acetaminophen 1000mg + Ibuprofen 400mg**
  - **Moderate to Severe Pain**

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Limitations with Opportunity

- ***Limitations***
  - Optometry is typically outside an integrated healthcare setting
  - Off-label medication use may not be standard of care
  - Adverse reactions to off-label medication use can expose the provider to liability
- ***Opportunity***
  - Off-label, adjunctive therapy can provide meaningful medical treatment during the time between referral and specialist follow-up
  - Off-label medication use can shorten duration and severity of disease condition and reduce need for more invasive treatment
  - PCM teaming embraces integrated medicine

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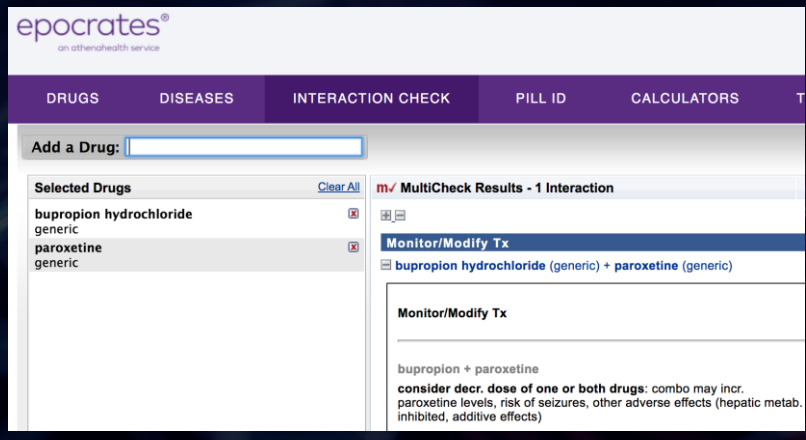
https://www.epocrates.com/



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Questions?

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