Clinical Potpourri
Off-Label Medication Use in Primary Care Optometry

June 2023

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Financial Disclosures

- None

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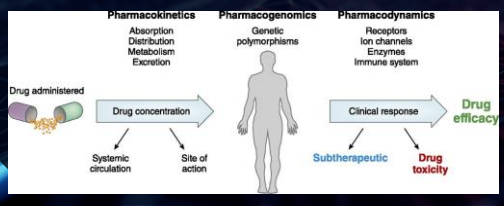
Pharmacokinetics vs. Pharmacodynamics



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Food and Drug Administration

- Approval Process
- Timelines and Milestones
- Barriers to Entry

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FDA Approval Process

- FDA is a public-health agency whose 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)
- When a drug is approved, the FDA issues a label that describes and defines:
  - Specific medical indication
  - Dose
  - Dosage form
  - Side effects
  - Chemical structure.

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FDA Approval Process

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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 who received 151,305 incident prescribed drugs were assembled from primary care clinics using EMR documentation of treatment indications and treatment outcomes. Prescriptions were followed up from the date of the prescription to the date the drug use was discontinued, end of treatment or the end of follow-up.

RESULTS

3484 ADEs were found with an incidence rate of 13.2 per 10,000 person-months. The rate of ADEs for off-label use was higher (19.7) than that for on-label use (12.5). Off-label use lacking strong scientific evidence had a higher ADE rate (21.7) compared with on-label use

- ***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**

***** In reality, 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***

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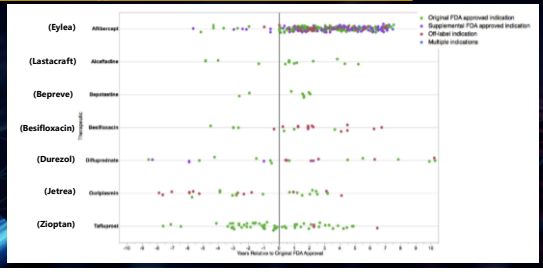
On-Label and Off-Label Clinical Studies of FDA–Approved Ophthalmic Therapeutics

Ophthalmology (2020)



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Proper Use of Off-Label Medications

- Off-Label Defined
- Investigational Use
- Informed Consent
- Insurance Carrier Criteria

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Off-Label Use Defined

- **Any use of a drug not listed on the label is considered off-label to include:**
  - Utilizing an approved drug for a condition or indication other than the condition for which it is approved
  - Prescribing approved drug at different dose, frequency or route of administration than specified in the label
  - Treating pediatrics when the product is approved to treat adults
- **Although the FDA label has important marketing implications, *use of an approved product is not restricted by the FDA to the limitations of the label***
  - Providers are allowed to use FDA-approved drugs in the treatment of a specific patient as medical practice
- **FDA recognizes that off-label use of drugs by providers is often appropriate and may represent the standard of care**
  - ***Example:*** Intravitreal antibiotic use for reduction of post-operative endophthalmitis incidence reduction despite the fact that no FDA-approved drugs for endophthalmitis prophylaxis exist

*****Legal implications of off-label use primarily involves risk management***

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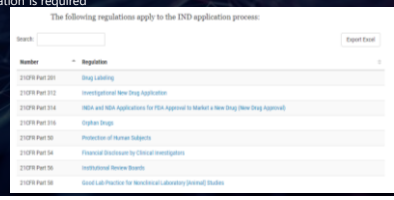
Investigational Use

- **Investigational use suggests the use of an approved drug in the context of a clinical study protocol**
  - If primary intent is to develop information about drug safety or efficacy or if the off-label use involves a route of administration, dosage level, subject population or other associated risks with the use of the drug, submission of an Investigational New Drug application is required



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Informed Consent

- **FDA approval status does not necessarily define appropriate medical practice nor regulate medical practice**
  - Medical practice is the therapeutic relationship between a physician and an individual patient and this decision must fall within the standard of care

SAMPLE INFORMED CONSENT TEMPLATE FOR A DRUG OR DEVICE

When a drug or device is approved for medical use by the FDA, the manufacturer produces a label to explain its use. Once a device/medication is approved by the FDA, physicians may use it off-label for other purposes if they are well-informed about the product, base its use on firm scientific method and sound medical evidence, and maintain records of its use and effects.

[State purpose of the off-label drug/device.]

[State alternatives to the off-label drug or device.]

[State known complications and side effects of the off-label drug/device.]

I understand that [state drug/device] was approved by the FDA for [state approval purpose/conditions]. Nevertheless, I wish to have [state treatment/procedure] performed on my eye/used in my eye and I am willing to accept the potential risks that my physician has discussed with me. I acknowledge that there may be other, unknown risks and that the long-term effects and risks of [state drug/device] are not known.

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Insurance Carrier Criteria

- Question then becomes "when does off label drug use become the standard of care?"
  - Answer depends on who is defining the standard of care.
  - Payers may use specific definitions of the standard of care to establish coverage determinations based upon supporting authoritative literature, expert consensus, scientific rationale and national medical practice patterns.

Off-label use of U.S. FDA approved drugs as prescribed by a physician to treat chronic, disabling, or life-threatening illnesses ***may be considered medically necessary*** when approved by the FDA for at least one indication, **AND** one of the following:

- Is recognized in one of the following prescription drug reference compendium for treatment of the indication for which the drug is prescribed
  1. Thompson Micromedex Drug Dex Compendium (Drug Dex);
  2. American Hospital Formulary Service Drug Information (AHFS DI);
  3. National Comprehensive Cancer Network's Drugs and Biologics Compendium;
  4. The United States Pharmacopoeia-Drug Information; **OR**

**** MUST supported by qualified clinical research in peer-reviewed scientific literature specific for treatment of the indication for which the drug is prescribed***

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Godfather of Off-Label Use

- Bevacizumab (Avastin)

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Off-Label Medication Use

Bevacizumab (Avastin)

- FDA-approved for treating various cancerous tumors both alone and in combination with other cancer treatments
- *MOA: Selectively binds circulating VEGF, thereby inhibiting the binding of VEGF to its cell surface receptors. This inhibition leads to a reduction in microvascular growth of tumor blood vessels and thus limits the blood supply to tumor tissues.*
- Commonly used off-label to treat retinal vascular diseases, especially nvAMD including NVM formation as a result of myopic degeneration and POHS and DME
- ***"Management of exudative conditions with Avastin has been embraced by the ophthalmologic profession without definitive guidelines from clinical trial data.*** The reality is that Avasin really is the larger molecule of the FDA-approved version, Lucentis. Off-label use gives the patient the opportunity to utilize the medication at fraction of the cost of the FDA-approved version. The benefits have been shown to be equal and short of any side-effects."

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Comparative Study of Intravitreal Bevacizumab (Avastin) versus Ranibizumab (Lucentis) in the Treatment of nvAMD

Ophthalmologica (2009) 223:370-375

Methods

Primary outcome measures were:
- BCVA
- CFT assessed by SD-OCT

Results
- Bevacizumab group included 184 injections (mean 4.7 per eye)
- Ranibizumab group included 187 injections (mean 5.5 per eye)
- Mean logMAR BCVA at 1 month improved by 0.18 in the bevacizumab group and by 0.13 in the ranibizumab group
- Mean CFT decreased 7.7% in the bevacizumab group and 5.9% in the ranibizumab group

Conclusions
- Bevacizumab and ranibizumab treatments resulted in similar gains in BCVA and reduction in CFT
- ***Intravitreal bevacizumab appears to be as safe and effective as intravitreal ranibizumab*** in the treatment of exudative AMD

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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%)*

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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

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Fourth Generation Fluoroquinolones: New Weapons in the Arsenal of Ophthalmic Antibiotics

Am J Ophthalmol (2002)133:463– 466.

METHODS:
Minimum inhibitory concentrations (MICs) of 93 bacterial endophthalmitis isolates were determined to CIP, OFX, LEV, GAT, and MOX using E-tests. The National Committee of Clinical Laboratory Standards (NCCLS) susceptibility patterns and the potencies of the MICs were statistically compared.

RESULTS:
With in vitro tests, Staph aureus isolates that were resistant to CIP and OFX were statistically most susceptible to MOX. Coagulase (-) Staphylococci resistant to CIP and OFX were statistically most susceptible to MOX and GAT. Strep viridans were more susceptible to MOX, GAT, and LEV than CIP and OFX. In general, MOX was the most potent FQ for gram (+) bacteria while CIP, MOX, GAT, and LEV demonstrated equivalent potencies to gram (-) bacteria.

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

Microorganism	Total	Gatifloxacin	Moxifloxacin	Levofloxacin	Ciprofloxacin	Ofloxacin
		Susceptibility				
	N	N (%)	N (%)	N (%)	N (%)	N (%)
Gram positive						
Coagulase-negative Staphylococcus	30	30 (100)	30 (100)	18 (60.0)	18 (60.0)	15 (50.0)
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 viridans group	1	1 (100)	1 (100)	0 (0)	0 (0)	1 (100)
Total gram-positive microorganisms	30	30 (100)	30 (100)	27 (81.8)	28 (87.8)	26 (84.0)
Gram negative						
Pseudomonas sp	7	7 (100)	7 (100)	5 (71.4)	6 (85.7)	5 (85.7)
Moraxella sp	3	3 (100)	3 (100)	3 (100)	3 (100)	3 (100)
Other gram-negative microorganisms *	8	8 (100)	9 (100)	6 (75.0)	7 (87.5)	7 (87.5)
Total gram-negative microorganisms	18	18 (100)	19 (100)	14 (80.4)	17 (94.4)	17 (94.4)
Grand Total	51	51 (100)	51 (100)	41 (80.4)	46 (90.2)	43 (88.2)

* Bordetella sp (1), Haemophilus sp (2), Pseudomonas aeruginosa (1), Proteobacter sp (1), Moraxella osloensis (1), and Chlamydia sp (1).

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.***

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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 Epstein–Barr virus. We investigated the *in vitro* anti-HAdV activity of Ganciclovir ophthalmic gel, 0.15% (Virgan®) ganciclovir in several common types currently inducing keratoconjunctivitis.

Results
The 50% cytotoxic concentration of ganciclovir was 212 mg/mL. The 50% effective concentration of ganciclovir obtained by real-time PCR ranged between 2.64 and 5.10 mg/mL. A significant inhibitory effect of ganciclovir on adenoviral proliferation was found in all types in a dose-dependent manner. The selectivity index of ganciclovir ranged between 41.6 and 80.3.

Conclusion
- Ganciclovir showed ***significant inhibitory activity against HAdV3, 4, 8, 19a and 37 which induce EKC***
- Results indicate that ***ganciclovir is a possible candidate for the treatment of HAdV keratoconjunctivitis***

Table 1 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

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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. EKC occurred bilaterally in 40 participants (66%). Single eye from each participant was included for analysis. Time elapsed before treatment was 2.1 (1.46) days and recovery rate within 1wk of treatment was 77%. Twenty-eight participants (46%) recovered within a 1wk after the onset. Application of PVP-I was sustained until recovery or completing a 7-day trial in 79%. No severe ocular or systemic adverse effects have been reported related to this treatment.

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

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?**

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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 by
  - 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 applied compresses to each eye for 10min BID x 14d
- Treatment group used Azasite BID x 2d then QD x 12d

RESULTS

At visit 2, Azasite group demonstrated significant improvements in MGD, MG secretions and eyelid redness as compared with the compress group. In the Azasite, MGD resolved completely in 3 patients and MG secretion returned to normal in 2 patients. Furthermore, a 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 in treating the signs and symptoms of posterior blepharitis

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	-1.482	0.132	NS
Lacrimation	Mean±SD Range	1.0 ± 0.79 0 – 3	1.43 ± 0.77 0 – 3	-2.349	0.036	S
Burning	Mean±SD Range	1.40 ± 0.72 0 – 2	1.63 ± 0.61 0 – 3	-1.277	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 ± 0.81 0 – 2	0.97 ± 0.87 0 – 2	-2.080	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 ± 0.80 0 – 3	2.30 ± 0.55 1 – 3	-3.611	0.011	S
Lid collarettes	Mean±SD Range	0.90 ± 0.88 0 – 3	1.37 ± 0.89 0 – 3	-1.336	0.187	NS
MG secretion	Mean±SD Range	1.83 ± 0.70	2.03 ± 0.56	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 ± 0.85 1 – 3	0.551	0.584	NS

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

Topical Azithromycin (Azasite 1%)

JUNE 17, 2015 5:11PM

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, U.S. authorities announced on Wednesday. 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.

The lawsuit said that 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. Lawsuit stated:

- ***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%)

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Off-Label Medication Use

Topical corticosteroids

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 Internalization	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 Sodium Phosphate	Inflamase Forte	4	NA	NA	600

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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 gene expression involving inflammation, angiogenesis, oxidative stress and apoptosis***

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

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Topical 0.1% prednisolone lowers nerve growth factor expression in KCS patients

Ophthalmology (2006) *113*(2):198-205

Methods

Prospective, double-masked, comparative RCT utilizing 41 KCS patients and 23 matched controls. subjects. Baseline tear NGF levels were measured using enzyme-linked immunosorbent assays. KCS patients received 0.1% prednisolone drops in one eye and 0.1% hyaluronic acid drops in the other TID for 28 days. Impression cytology and immunostaining for NGF on conjunctival epithelium were performed on both groups.

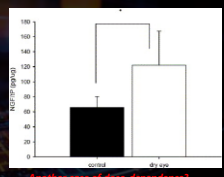
Results

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 such 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 0.1% prednisolone. Ocular surface NGF may play an important role in ocular surface inflammation processes associated with dry eyes.



Another case of dose-dependence?

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Off-Label Medication Use

Duflurprednate 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 gene expression involving inflammation, angiogenesis, oxidative stress and 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 than on prednisolone acetate were cleared of A/C cells on day 21 (71% vs 55%)
- Treatment withdrawals were higher with prednisolone acetate than diflupredrnate (20% vs 7%)
- Study discontinuation due to lack of efficacy was also higher with prednisolone acetate than diflupredrnate (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, DES and CME
- DME

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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 in type 1 and type 2 diabetics. 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.

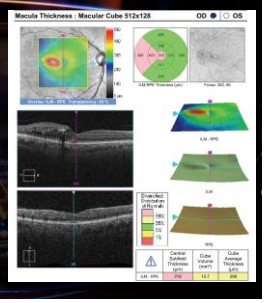
Results:

A total of 39 eyes met criteria and 87% had follow up at 1 month, 77% had follow up at 3-6 months

- ***4-wk CMT: 35% improvement / 35% worsened / 26% failed***
- ***3-month CMT: 40% improved / 23% worsened / 7% failed***

Conclusions

Our project demonstrates a ***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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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

42

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

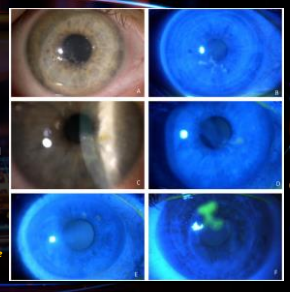
Acta Ophthalmologica Vis Sci (2019) 97.2:e194-e198

Methods
38 eyes of 33 patients with HSK were randomly assigned to receive either 2% Cs-A or 1% prednisolone acetate eye drops. 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 of 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



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Peer-Reviewed Off-Label Medications

- **Mucolytic agents (acetylceysteine)**
- **Anti-Glaucoma**
  - α-adrenergic Agonists
  - Carbonic anhydrase inhibitors
  - Beta-blockers
  - Prostaglandin analogues
  - Rho-kinase inhibitors

44

Off-Label Medication Use

*Mucolytic Agents (Mucomyst** 10% or 20%)*

FDA-approved as:
- Mucolytic agent in bronchiopulmonary conditions

MOA: *Decreasing free radicals and inhibition of inflammatory factors*

*****NAC** is thought to increase GSH concentrations by replenishing intracellular cysteine levels*

Off-label uses identified in the literature:
- vernal and giant papillary conjunctivitis
- filamentary keratitis
- Reduction in pterygium progression

*****Prepared for topical ocular use by diluting the commercial preparation to 2% to 5% with artificial tears***

45

Effect of N-Acetylcysteine in conjunctival pterygium

IOVS (2019) 60:6247

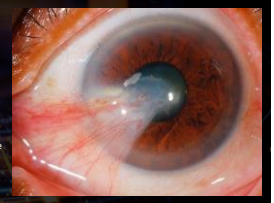
Methods
This study included 15 eyes with primary pterygia undergoing surgical excision and were divided into 3 groups:

- Group I was treated with NAC 600mg orally
- Group II with topical application of NAC 10%
- Group III, as a control without treatment

Postoperatively, pterygium specimens were examined by to evaluate histopathologic characteristics including vascular density, stromal elastosis, stromal fibrosis, inflammation and changes in epithelium.

Results
Group I: Abundant goblet cell hyperplasia, epithelial lymphocytic exocytosis with perivascular stromal infiltrate and scarce solar elastosis
Group II: Pterygia showed little goblet cell hyperplasia, exocytosis, little elastosis and all perivascular infiltrate
Group III: Hyperplasia, perivascular infiltrate, moderate goblet cell hyperplasia and all had elastosis

Conclusions
NAC ocular instillation reduces the inflammatory, epithelial hyperplasia and development / recurrence of pterygium useful in the therapeutic management



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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

47

Upper Eyelid Resposne to Topical 0.5% Aproclonidine

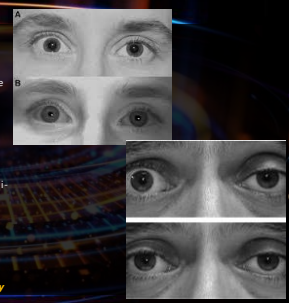
Ophthal Plast Reconstr Surg (2018) 34:13-19

Methods
100 self-reportedly normal subjects received a 1-time administration of topical 0.5% apraclonidine in each eye. Digital photographs were taken at baseline and then 30 and 45 minutes following apraclonidine instillation. Marginal reflex distance was determined via image analysis of acquired digital photographs. The horizontal corneal diameter was used as a constant measurement scale in each photograph.

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 an increase in i-marginal reflex distance at 30 minutes
- Of the 100 subjects, 85% had a bilateral increase in i-marginal reflex distance, 4% had a bilateral decrease and 11% had a unilateral increase with a contralateral decrease

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



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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

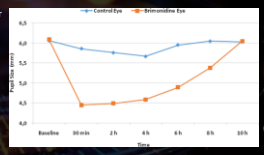
49

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
Six patients with significant night-vision complaints after refractive surgery were enrolled in this study after other treatable causes of night-vision difficulty such as residual refractive error and dry eye were excluded. LCVA over a range of contrasts (1.25% to 25%) and small letter contrast sensitivity were tested at photopic and mesopic luminance levels, with and without a standard glare source. Measurements were repeated 1 hour and 1 month after the use of brimonidine tartrate.

Results
One hour after using brimonidine tartrate 0.15% solution, patients had significant improvement in LCVA, LCVA with glare and CS. After 1 month of treatment, all 6 patients reported subjective improvement in night vision and there was a significant difference in performance in mesopic LCVA and mesopic LCVA with glare. The mean pupil size before brimonidine tartrate ophthalmic solution 0.15% was 6.4±1.1mm and 1 hour after instillation had decreased to 4.5±1.3mm



Conclusions
Improved contrast sensitivity and acuity and decreased night-vision difficulty for up to 1 month in patients with significant complaints after refractive surgery

50

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, choroidemia and chemotherapy toxicity
- CSC

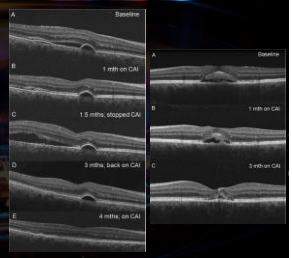
51

Topical carbonic anhydrase inhibitor efficacy in reducing duration of chronic CSC

Translational Vision Science & Technology (2020) 9(13):6

Methods
Prospective, nonrandomized, controlled intervention study of patients with chronic CSC of at least 3 months duration. Controls were observed without active intervention, whereas treated cases were treated with topical dorzolamide for 3 months. The study end points were change in CMT, change in BCVA and proportion of eyes achieving complete resolution of SRF)

Results
Patients who received topical CAI had greater reduction in CMT (−146μm) compared to observed controls (−45μm) at 3 months. A higher proportion of treated patients achieved complete resolution of SRF compared to observed controls (78% vs. 40%) at 3 months. However, change in 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***

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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

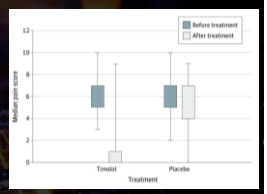
53

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 with placebo
- ***40% patients found β-blockers very effective while only 4% of placebo patients did***



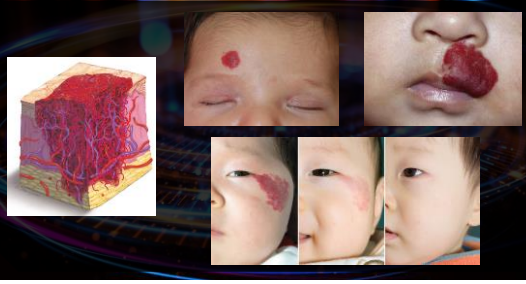
Conclusions
Topical timolol 0.5% is an effective abortive treatment for some patients with migraines

- Vital component: ***Instillation OU at the first sign of an aura or migraine and a second set within 15 minutes***

54

Topical Timolol Maleate Treatment of Infantile Hemangiomas

Pediatrics (2016) *138*(3): 1-11.



55

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

56

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

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

Methods

Multicenter, randomized placebo-controlled clinical trial enrolling 50 nvAMD patients who had persistent exudation despite intravitreal anti-VEGF injections at 4-week, 5-week or 6-week intervals. Patients were randomized to use dorzolamide-timolol or artificial tears for the study duration. Anti-VEGF interventions were continued at the same intervals.

Results

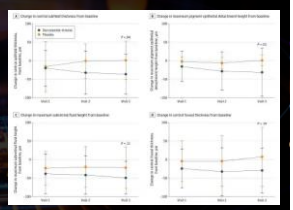
All 27 patients assigned to dorzolamide-timolol and 23 assigned to placebo were analyzed for the primary outcome. Mean (SD) age was 78.4±7 years. Mean baseline logMAR VA was 0.361± 0.26

Dorzolamide-timolol vs placebo at 3 months:

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

Conclusions

Dorzolamide-timolol in patients with nvAMD with persistent exudation resulted in anatomic but not visual acuity improvements



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Off-Label Medication Use

Prostaglandin Analogue (Lataprost 0.005%)

FDA approved for:

- Treatment of elevated IOP in OHTN or POAG

MOA: Increases the uveoscleral outflow of the aqueous through relaxation of ciliary smooth muscles

- Cytoskeletal alteration in the shape of cells
- Remodeling of the uveoscleral extracellular matrix of by increased MMP

Off-label uses identified in the literature:

Skin re-pigmentation combined with fractional laser (CO_2 and Er:YAG)

58

Laser Treatment of Hypopigmentation in Scars: Review

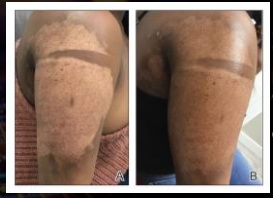
Dermatologic Surgery (2022) *48*(2): 201-206

Results

Search on PubMed and on Oxford Academic was conducted with additional relevant literature obtained from reference lists. Treatment regimens that address hypopigmentation within scars were reviewed. A combination of nonablative fractional or ablative fractional laser treatment with topical prostaglandin analogue with or without topical retinoid were found to result in superior repigmentation.

Conclusion

Ultraviolet laser can achieve modest repigmentation; however, results are short-lived and require continued re-treatment. Modest improvement in pigmentation is seen with non-ablative fractional laser or ablative fractional laser alone and ***enhanced repigmentation is demonstrated when combining fractional laser resurfacing with topical application of synthetic prostaglandin analogues and other known modulators of melanogenesis***



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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 trabecular meshwork route; however, the exact mechanism is unknown.*

Off-label uses identified in the literature:

DME management
Corneal endothelial dysfunction (Fuchs dystrophy)

60

Rho-Associated Kinase Inhibitor eye drop treatment as possible medical treatment for Fuchs Corneal Dystrophy

Cornea (2013) 32(8):1167-1170

Methods

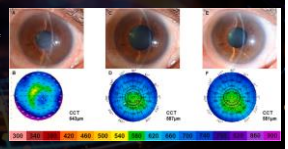
A 52-year-old male with a diagnosis of late-onset Fuchs corneal dystrophy was referred to our hospital as a candidate for keratoplasty. BCVA was 20/20 in the right eye and 20/63 in the left eye. Multiple guttae were observed in both eyes. The right cornea was clear, but the left showed severe central edema, with a central corneal thickness of 703μm. The patient was treated by a corneal endothelial denudation in the prepupillary region followed by the topical administration of a selective ROCK inhibitor, Y-27632, as eye drops for 1 week. Follow-up of 24 months is reported.

Results

Corneal clarity recovered and BCVA improved to 20/20 two weeks after the treatment. At 6 months, vision had improved to 20/16 and central corneal thickness measured was 568μm, significantly lower than its pretreatment value. Endothelial function and vision have been well maintained up to the most recent observation, 24 months after the treatment. The average corneal endothelial density in the central and peripheral cornea was 1549±89 and 705±61.1 cells/mm²

Conclusions

Use of ROCK inhibitor eye drops as an 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-lycine****
- ***AREDS2****
- ***Chromium****
- ***Beta-carotene****
- ***Acetyl hexapeptide-4 (argireline)***
- ***Ω-3 FA****
- ***MacuHealth****
- ***VitreousHealth****
- ParaSym Plus Eyes
- N-acetylcarnosine (Can-C)
- Lanosterol

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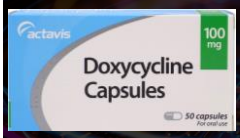
Off-Label Medication Use

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
- Prophylaxis of malaria

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

64

Treatment of recurrent corneal erosion syndrome using the combination of oral doxycycline and topical corticosteroid

Clin Exp Ophthal (2008) *36*(1):8-12

Methods

Retrospective single-observer case series involving 21 patients with RCE who were treated at a community-based clinic and received oral doxycycline 50 mg BID and topical FML 0.1% TID for at least 4 weeks.

Results

At 8 weeks, 15/21 patients (71%) were symptom free. All but one of these patients reported an improvement in symptoms. Of those patients not lost to follow up, 15/18 patients (83%) and 11/15 patients (73%) denied any symptoms suggestive of relapse at 6 and 12 months, respectively. Among the patients in remission was one who had responded poorly to other treatments including ocular lubricants, epithelial debridement, serum eyedrops, anterior stromal puncture and PTK.

Conclusion

- ***Combination of oral doxycycline and topical corticosteroid is the first treatment option when conservative management with ocular lubricants fails***
- ***May help patients with recurrent corneal erosion syndrome who have failed other forms of treatment.***

	Treatment	Example	Indication	Recovery Period	Effectiveness	Prophylaxis Qualities
Medical	Lubrication	Artificial tears with NSAIDs and antibiotics	Acute attack	Short	Low	Mild
		Lacri-Lube or Muro 128 with NSAIDs and antibiotics	Chronic episodes	Short	Low	Mild
	Punctal occlusion	Collagen or silicone punctal plugs	Failed lubrication	Short	Moderate	Moderate
	Bandage soft contact lens	Focus Night & Day or Kontur	Failed lubrication and punctual occlusion	Long	Moderate	Risk
	Combination therapy	Oral tetracyclines, topical corticosteroids, lubrication	Failed lubrication and punctal occlusion	Short	High	High
Surgical	Anterior stromal micropuncture	—	Failed aggressive medical therapy; lesions off visual axis	Medium	Moderate	Mild
	Superficial keratectomy	—	Failed aggressive medical therapy; lesions on visual axis	Long	High	Mild
	Phototherapeutic keratectomy	—	Failed aggressive medical therapy; patients with nonadaptrophic RCES	Long	High	Mild

65

Topical azithromycin and oral doxycycline therapy of MGD: Comparative clinical and spectroscopic study

Cornea (2013) *32*(1):44

Methods

Signs of MGD were evaluated with a slit lamp and symptoms were measured by the response of subjects to a questionnaire. Meibum lipid-lipid interaction strength, conformation and phase transition parameters were measured using Fourier transform infrared spectroscopy

Results

Topical therapy with azithromycin and oral therapy with doxycycline relieved signs and symptoms and restored the lipid properties of the MG secretion towards normal

- ***TF lipids were brought closer to normal with azithromycin treatment than doxycycline treatment***

Both doxycycline and azithromycin treatment restored the levels of the relative areas of resonance to normal levels.

Conclusions

- ***MOA of doxycycline may be different than that of azithromycin in MGD therapy***
- ***Carotenoids restoration in conbination with azithromycin and doxycycline treatment restored TF stability and resolve DED S/S***

Azithromycin and Doxycycline group at pretreatment and in all follow up

	Azithromycin		Doxycycline		p value
	Mean	SD	Mean	SD	
Pre-treatment					
Symptoms	7.50	1.26	7.60	1.35	0.704
Sign	8.70	1.28	8.38	1.87	0.321
Total	16.20	2.01	16.18	2.39	0.964
1st Follow up					
Symptoms	2.36	1.27	2.50	1.29	0.587
Sign	3.22	1.20	2.84	1.27	0.127
Total	5.58	2.19	5.34	2.13	0.581
2nd Follow up					
Symptoms	0.82	0.69	0.76	0.77	0.683
Sign	2.08	0.63	2.04	0.80	0.783
Total	2.92	0.96	2.80	1.30	0.603
Last Follow up					
Symptoms	0.62	0.23	0.62	0.40	0.701
Sign	1.22	0.76	1.30	0.78	0.608
Total	1.84	1.09	1.92	1.08	0.714

66

Off-Label Medication Use

Oral Atorvastatin 40mg and 80mg

FDA approved for:

- Risk reduction of MI, stroke and angina in patients with multiple risk factors including CHD and CHF
- Reduce elevated total-C, LDL-C, apo B and TG levels and increase HDL-C in adult patients

MOA: *Competitively inhibits 3-hydroxy-3-methylglutaryl-coenzyme A reductase decreasing cholesterol production in the liver and increasing LDL-C receptors*

Off-label uses identified in the literature:

- Decreased AMD risk features
- Reduced progression of DR

**Consider adding Co-Q_{10}*
- Decreased muscle wasting in statin users

67

Effects of lipid-lowering agents on DR: Meta-analysis and systematic review

Int'l J Ophthal (2018)11(2):287

METHODS

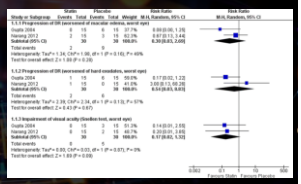
Search of PubMed, Embase and Cochrane Library Central Register of Controlled Trials and abstracts from main annual meetings. The primary endpoint was the progression of DR, and the secondary endpoints included vision loss, development of DME and aggravation of hard exudates.

RESULTS

Results revealed that lipid-lowering drugs were associated with reduced risk in DR progression [OR=0.77] and may have protective effect on DME compared to placebo However, no significant differences in the worsening of vision acuity and hard exudates were found between the lipid-lowering drugs and the placebo

CONCLUSION

- ***Lipid-lowering agents show a protective effect on DR progression and might be associated with reduced risk in the development of DME***
- ***Lipid-lowering agents have no effects on vision loss and hard exudates aggravation***



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Off-Label Medication Use
Oral Prednisone

FDA approved as an:

- Anti-inflammatory or immunosuppressive agent for certain allergic, dermatologic, gastrointestinal, hematologic, ophthalmologic, nervous system, renal, respiratory, rheumatologic, specific infectious diseases or conditions and organ transplantation

MOA: *Decreases inflammation via suppression of the migration of polymorphonuclear leukocytes and reversing increased capillary permeability and suppressing expression of inflammatory mediators*

Off-label* uses identified in the literature:
Oral treatment of ON

69

Effect of Treating Acute Optic Neuritis With Bioequivalent Oral vs Intravenous Corticosteroids: RCT

JAMA Neurology (2018) 75.6): 690-696

Methods

- Single-blind RCT with 6-month follow-up was conducted at a single tertiary care center
- Patients 18 to 64 presenting within 14 days of acute optic neuritis onset without any recovery at time of randomization and without history of optic neuritis in the same eye, were screened.
- Inclusion criteria included BCVA of 20/40 or worse and corticosteroids deemed required
- 55 participants were enrolled and randomized. Analysis was unadjusted according to intention-to-treat principle

Interventions

Participants were randomized 1:1 to the IV methylprednisolone (1000-mg) or oral prednisone (1250-mg)

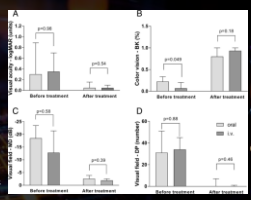
Results

At 1 month and 6 months:

- P100 latency in between IV group and oral group showed no significant difference between groups
- BCVA recovery showed no significance between the groups at 1 or 6 months
- Low-contrast BCVA showed no significance between the groups at 1 or 6 months

Conclusions

Bioequivalent doses of oral corticosteroids may be an alternative to IV corticosteroids to treat acute ON



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Off-Label Medication Use
Oral Metformin

FDA approved as an:

- Antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes lowering both basal and postprandial plasma glucose

MOA: **1) decreases hepatic glucose production**
2) decreases intestinal absorption of glucose
3) improves insulin sensitivity by increasing peripheral glucose uptake and utilization

Off-label* uses identified in the literature:
Diabetes prevention
AMD mitigation
Stargardt disease*
- ClinicalTrials.gov Identifier: NCT04545736
- Estimated completion date: Aug 2026

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Association of Metformin Use With AMD: Case-Control Study

JAMA Ophthal (2021) 139(3):302-309

Conclusion

Dose-dependent metformin use was associated with reduced odds of developing AMD with the greatest benefit at low to moderate doses. When looking only at patients with diabetes, we saw a preservation of the dose-dependent decrease in the odds of patients developing AMD. ***Metformin DOES NOT appear to be protective in patients with diabetes AND coexisting diabetic retinopathy***. This study suggests that ***metformin may be useful as a preventive therapy for AMD*** and provides the basis for potential prospective clinical trials.

Metformin and risk of AMD in individuals with type 2 diabetes: a retrospective cohort study

Br J Ophthal (2022) doi:10.1136/bjophthalmol-2021-319641

Conclusion

No evidence that metformin was associated with risk of AMD in primary care patients requiring treatment for type 2 diabetes

****On-going Clinical Trials:***

Investigation of Metformin in Pre-Diabetes on Atherosclerotic Cardiovascular OuTcomes (VA-IMPACT)
Metformin in Longevity Study (MILES)

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Off-Label Medication Use
Oral Lisinopril

FDA approved as an:

- Antihyperglycemic agent which improves glucose tolerance in patients with DMII lowering both basal and postprandial plasma glucose

MOA: *Inhibits ACE resulting in the suppression of the renin-angiotensin-aldosterone system leading to decreased vasopressor activity and to decreased aldosterone secretion activity and to decreased aldosterone secretion*

Off-label uses identified in the literature :
Decreases progression of DR
Migraine prophylaxis

75

Effect of lisinopril on progression of retinopathy in normotensive people with type 1 diabetes

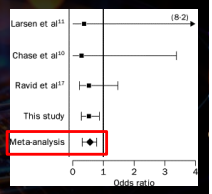
Lancet (2008) 351(9095):28-31

Methods

During a 2-year randomized double-blind placebo-controlled trial, baseline retinal photographs were compared to follow-up (24 months) in patients aged 20–59 in 15 European centers. Patients were not hypertensive and were normoalbuminuric (85%) or microalbuminuric. Retinopathy was classified from photographs on a five-level scale (none to proliferative).

Findings

Proportion of patients with retinopathy at baseline was 65% in the placebo group and 59% in the lisinopril group. Retinopathy progressed by at least one level 13% of patients on lisinopril and 23% of patients on placebo (OR: 0.50). Lisinopril also decreased progression by two or more grades and progression to proliferative retinopathy. Treatment reduced retinopathy incidence



Interpretation

Lisinopril may decrease retinopathy progression in non-hypertensive patients who have type 1 diabetes

76

Off-Label Medication Use
Oral Sildenafil

FDA approved as an:

- Indicated for the treatment of erectile dysfunction

MOA: *Selective inhibitor of cGMP-specific phosphodiesterase (PDE-5). Penile erection involves relaxation of the corpus cavernosum, an event mediated by NO and cGMP. The biological actions of cGMP are terminated by phosphodiesterase enzymes and PDE-5 is the major cGMP metabolizing enzyme*

Off-label* uses identified in the literature include:
Increased choroidal perfusion
Mitigation of AMD and CSC

78

Treatment of Macular Degeneration with Sildenafil: Results of a Two-Year Trial

Ophthalmologica (2018) *240*(1):45-54

Methods

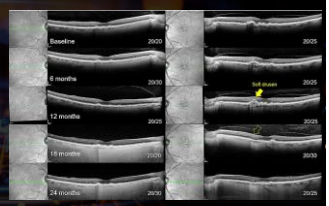
Sildenafil was prescribed to treat participants with macular degenerations or macular dystrophies measured by spectral-domain optical coherence tomography, color fundus photography, enhanced depth imaging, and best-corrected visual acuity.

Results

No change in calcified drusen was noted. Vitelliform-type soft drusen were not substantially changed. A participant with Best vitelliform macular dystrophy had a significant improvement in vision as well as in photoreceptor and ellipsoid layers.

Conclusions

- Supports sildenafil as a safe treatment for age-related and vitelliform macular degenerations
- Thickened Bruch's membrane reduces the beneficial effect of perfusion increase but all eyes appear to benefit from PDE6
- ***Maintenance or improvement in the PR layer may be the most significant result of sildenafil and is consistent with PDE6 inhibition.***



79

Off-Label Medication Use
Oral Levodopa

FDA approved as an:

- Treatment of Parkinson's disease, post-encephalitic parkinsonism and symptomatic parkinsonism

MOA: *Levodopa is the metabolic precursor of dopamine (able to cross the blood-brain barrier) and is converted to dopamine in the brain.* ***Mechanism in Parkinson's disease symptom treatment***

Off-label uses identified in the literature include:
Reduction of nvAMD

80

Levodopa Positively Affects nvAMD

Am J Med (2021) 134:122-128

METHODS

In an open-label pilot study, in patients with newly diagnosed nAMD and naïve to anti-VEGF injections (Cohort-1), the effects of carbidopa-levodopa on vision and anatomic outcomes were evaluated for 4 weeks. Patients were followed 5 months with ascending levodopa doses. Patients previously treated with anti-VEGF injection therapy (Cohort-2) were also treated with ascending levodopa doses and evaluated for 6 months.

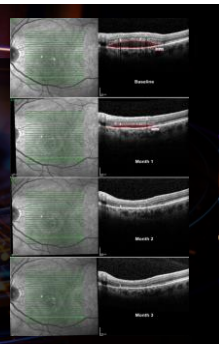
RESULTS

Levodopa was safe, well tolerated, and delayed anti-VEGF injection therapy while improving visual outcomes

- ***1st month: SRF decrease by 29% without anti-VEGF treatment***
- ***6 months: SRF decrease was sustained with a mean frequency 0.38 injections/month***
- ***BCVA improved by 4.7 letters in Cohort-1 and 4.8 letters in Cohort-2***
- ***52% reduction in the need for anti-VEGF injections in Cohort-2***

CONCLUSIONS

pharmacological targeting with levodopa for the treatment of nAMD in future studies



81

Off-Label Medication Use
Oral Minocycline

FDA approved as an:

- **Arestin (subgingivally)** – adjunct to scaling and root planning procedures in adult periodontitis
- **Minocin (IV)** – treatment of susceptible microorganisms and alternative to PCN
- **Solodyn (oral)** – primary therapy in acne vulgaris
- **Amzeeq (topical)** – treatment of non-nodular inflammatory lesions in moderate to severe acne vulgaris

MOA: *Inhibition of bacterial protein synthesis resulting in bacterial stasis*

Off-label* uses identified in the literature include:
Treatment of acute ischemic stroke

82

Minocycline for acute stroke treatment: a systematic review and meta-analysis of RCT

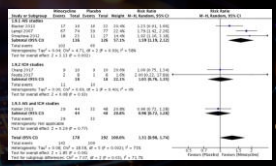
J Neurology (2018) 265:1871-1879

Methods

Literature search across major databases to identify all RCTs that reported following efficacy outcomes among acute stroke patients treated with minocycline vs. placebo: National Institute of Health Stroke Scale, Barthel Index, and modified Rankin Scale scores. Additional safety, neuroimaging and biochemical endpoints were extracted. We pooled mean differences (MD) and risk ratios (RR) from RCTs using random-effects models.

Results

We identified 7 RCTs comprising a total of 426 patients. Of these, additional unpublished data was obtained on contacting corresponding authors of 5 RCTs. In pooled analysis, minocycline demonstrated a favorable trend towards 3-month functional independence (RR=1.31) and 3-month BI (MD=6.92). In AIS subgroup, minocycline was associated with higher rates of 3-month mRS-scores of 0–2 (RR=1.59) and 3-month BI (MD=12.37) whereas reduced the 3-month NIHSS. ***Minocycline administration was not associated with an increased risk of mortality, recurrent stroke, myocardial infarction and hemorrhagic conversion.***

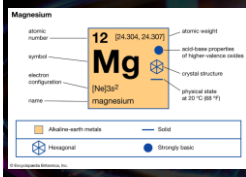


Conclusions

Although data is limited, ***minocycline demonstrated efficacy and seems a promising neuroprotective agent in acute stroke patients, especially in AIS subgroup***. Further RCTs are needed to evaluate the efficacy and safety of minocycline among ICH patients.

83

Off-Label Medication Use
Magnesium



Supplement not regulated by FDA

MOA: *Cofactor in >300 enzymatic pathways that regulate protein synthesis, muscle and nerve function, blood glucose control, and blood pressure regulation. Required for energy production, oxidative phosphorylation, and glycolysis.*

Off-label uses identified in the literature:

- Reduction of benign myokymia
- Muscle cramps

84

Will Hypomagnesemia Induce Benign Eyelid Myokymia?

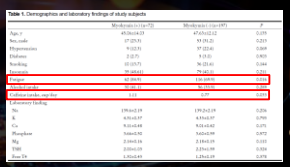
Korean J Health Promotion (2021) *21*(4):129-133

Methods

Cross sectional study on 72 patients with myokymia and 197 controls. Investigated fatigue, sleep quality, alcohol, smoking, caffeine use, and exercise data by interview. Analyzed laboratory data including magnesium, calcium, phosphate, thyroid hormone in serum

Results

Demographic characteristics between the patients with myokymia and controls showed no significant differences in age, gender, smoking, and alcohol history. Fatigue and poor sleep quality were significantly higher in the myokymia group than control group. However, any laboratory results including magnesium showed no significant differences between two groups

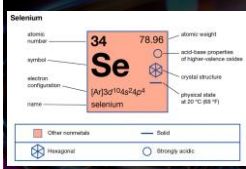


Conclusions

- ***Eyelid myokymia was not related to the serum magnesium level nor was TSH, free T4, calcium or phosphate***
- ***Only fatigue and sleep quality were shown the relationship with eyelid myokymia.***

85

Off-Label Medication Use
Selenium



Supplement not regulated by FDA

MOA: *Required for antioxidant function and metabolism of thyroid hormones responsible for conversion of T4 to T3 and stability of TSH production in the hypothalamic-pituitary axis*

Off-label uses identified in the literature:

- Proptosis reduction in thyroid eye disease

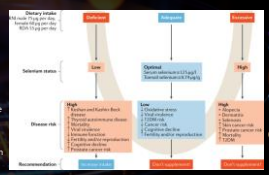
86

Selenium supplementation for patients with Graves' hyperthyroidism (GRASS trial): study protocol for RCT

Trials (2013) 14(1):119

Methods

- Randomized, blinded, multicenter clinical trial including patients ≥18 years or older with a diagnosis of active Graves' hyperthyroidism within the last two months
- 492 participants, randomized (1:1) to two tablets of 100μg selenium once daily for the 24-month intervention period versus placebo tablets once daily
- 1° outcome is the proportion of participants with anti-thyroid drug treatment failure at 24 months
- 2° outcomes are: 1) thyroid-specific quality of life during the first year
  2) TSH-receptor antibody levels at 18/24 months
  3) Hyperthyroid and ocular symptoms at 12/24 months



Results

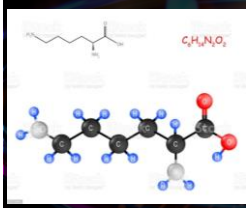
- Both FT4 and FT3 decreased more in the selenium group than the control, while the TSH level increased more in patients receiving selenium supplementation. Anti-TSH receptor antibody level was significantly lower in patients receiving selenium supplementation. The percentages of patients with normal anti-TSH receptor antibody level at 6 months was also significantly higher in the selenium group (19.0 vs. 0 %). Kaplan-Meier survival curve showed selenium supplementation had significantly higher rate of remission than controls.

Conclusions

- ***Selenium supplementation can enhance the effect of anti-thyroid drugs in patients with Graves' disease.***

87

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

89

Comprehensive Safety Assessment of L-Lysine Supplementation from Clinical Studies - Systematic Review

J Nutr (2020) 150(Supp 1): 2561S–2569S

Methods

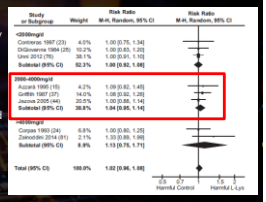
PubMed, Cochrane Library, Ichushi Web, and EBSCOhost search using the relevant keywords, "L-lysine" and "clinical trial" was conducted. To investigate all adverse events observed during intervention trials, we included all intervention studies with orally ingested L-lysine without restricting background factors, environment, study designs, and sample sizes.

Results

Identified 71 articles that included 3357 study subjects. The L-lysine doses ranged from 16.8 to 17.5 g/d, and the dosing period ranged from 1 to 1095 d. The observed adverse events were mainly subjective gastrointestinal tract symptoms; however, the risk analysis for incidence of gastrointestinal symptoms was not statistically significant (RR=1.02)

Conclusion

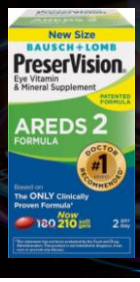
The provisional ***no-observed-adverse-effect level in healthy human subjects*** was based on gastrointestinal symptoms and ***identified at 6000 mg/d.***



90

Off-Label Medication Use

AREDS2 Formulation



Supplement not regulated by FDA

Proposed MOA:

AREDS2 high-dose antioxidants and zinc may slow the progression of AMD in part through the attenuation of endothelial inflammatory events within the choroid and may affect both angiogenesis and endothelial-macrophage interactions

Off-label uses identified in the literature:

- IMT2 treatment

91

Off-Label AREDS 2 Supplementation for the Treatment of Macular Degeneration in Non-Proliferative Idiopathic Type 2 Macular Telangiectasia

Clinical Ophthalmology (2021) 15:1133

Methods

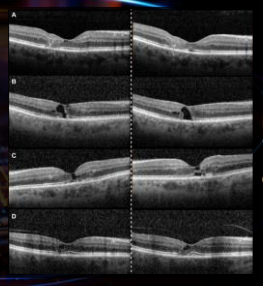
Single-center retrospective, comparative study of 82 IMT2 eyes treated with AREDS2. The study analysis consisted of a non-comparative arm and a comparative arm (27 AREDS2 and 42 untreated eyes). Primary outcomes were BCVA and OCT anatomical characteristics at 24 months.

Results

- ***BCVA mean difference was greater for untreated eyes @ 24mos***
- ***AREDS2 eyes had EZ loss compared to untreated eyes***
- ***Untreated eyes had worse BCVA @ 24mos***
  - ***Increases in EZ loss among untreated eyes were only significant for eyes with worse baseline BCVA***

Conclusion

Off-label AREDS2 supplementation in non-proliferative IMT2 may prevent anatomical and visual deterioration in a subset of eyes



92

Off-Label Medication Use

Chromium

Supplement not regulated by FDA

Proposed MOA:

Essential nutrient involved in the metabolism of glucose and serum lipoproteins

- *Increased insulin binding to cells*
- *Increases insulin receptor density*
- *Activation of insulin receptor kinase leading to enhanced insulin sensitivity*

Off-label uses identified in the literature:

- Adjunctive benefit in anti-VEGF therapy

93

Effect of Chromium in DME Management: Interventional Comparative Case Series

J Ophthalmic Clin Res (2021) 8:83

Methods

Patients received the supplementation with or without chromium for 4 months and were followed for six months. BCVA, CFT, HbA1c, and the frequency of IVB injection were compared. From 129 eligible patients, 90 patients involved in this study and completed the six months' follow-up period. 51 of them were in chromium and 39 were in the control group.

Results

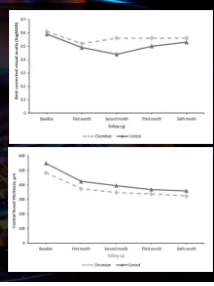
BCVA improved significantly from baseline in all follow-up points in both groups for all visits compared to baseline but there was no significant difference between groups. The linear mixed model analysis showed that the mean CFT reduction was not significantly different between both groups in four follow-up visits.

Conclusions

HbA1C and the average number of IVB injections were significantly lower in the chromium group. Chromium supplementation did not affect the visual acuity or central foveal thickness.

**** Optivision capsule contained vitamin C (75mg), Vitamin E (12.5mg), Lutein (10mg), Zinc (7.5mg), *Chromium (50mcg)*, Selenium (35mcg) and Vitamin A (5000IU)**

****Control supplement contained zero chromium***



94

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

95

Serum Vitamin A Levels in Patients with Chalazion

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

Abstract
The study involved a total of 107 subjects (52 patients with chalazion and 55 control healthy subjects). Patients were further divided into four subgroups based on the type of chalazion: single, multiple, primary, and recurrent. Blood samples were collected and the serum was tested for levels of vitamin A using HPLC. The 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) doi: 10.1097/OPX.0000000000001887

Methods
The study included 180 subjects (90 patients with chalazion and 90 control healthy subjects) with an average age of 4.13 ± 2.01 years old, and 47.8% of whom were females. Serum samples were collected and used to measure the levels of vitamin A.

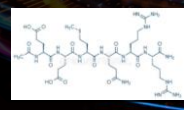
Results
The average serum vitamin A levels in patients with chalazion (0.54 ± 0.15 μmol/L) were significantly lower than in their control counterparts (0.60 ± 0.15 μmol/L). The percentage of ***vitamin A deficiency in chalazion group (52.2%) was much higher than the control counterparts (28.6%)***.

Conclusions
Low serum vitamin A was significantly associated with chalazion in children. The serum 25(OH)D level exhibited no correlation with chalazion.

96

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

97

Synthetic hexapeptide (Argireline) with antiwrinkle activity

Int J Cosmetic Sci (2002) 24(5): 303-310

Abstract
Botulinum neurotoxins (BoNTs) represent a revolution in cosmetic science because of their remarkable and long-lasting antiwrinkle activity. However, high neurotoxicity limits their use. Hexapeptide Ac-EEMQRR-NH(2) (argireline) was identified as a result of a rational design program

- ***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* oral toxicity nor primary irritation at high doses
- ***Findings support argireline as biosafe BoNT alternative***

98

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
- Enhanced MP deposition

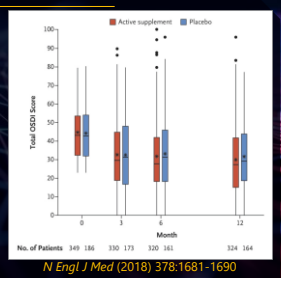
99

Efficacy of Ω-3 Fatty Acid Supplementation for Treatment of Dry Eye Disease: Meta-Analysis of RCT

Cornea (2019) 38(5):565-573

Results
17 RCTs involving 3363 patients were included and compared placebo, Ω-3 FA supplementation decreased dry eye symptoms and corneal NaFl staining and increased the TBUT and Schirmer test values. No evidence of publication bias was observed, and sensitivity analyses indicated the robustness of results obtained.

Conclusions
- ***Ω-3 FA supplementation significantly improves dry eye symptoms and signs in patients with DED***
- ***Findings indicate that Ω-3 FA supplementation may be an effective treatment for DED***



N Engl J Med (2018) 378:1681-1690

100

Off-Label Medication Use

MacuHealth

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

101

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

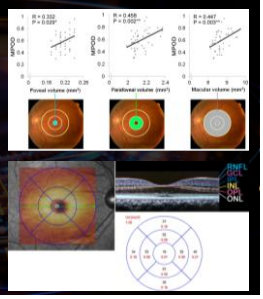
In meta-analysis of 22 publications, MPOD was found to be significantly correlated with:

- ***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.***



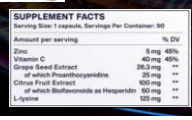
102

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

103

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

TVST (2021) 10(12)

Methods

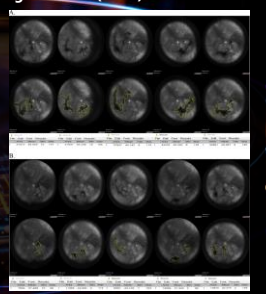
61 patients with symptomatic vitreous floaters were randomized to consume daily, the active supplement consisting of 125 mg L-lysine, 40 mg vitamin C, 26.3 mg *Vitis vinifera* extract, 5 mg zinc, and 100 mg *Citrus aurantium* or placebo for 6 months. Change in visual discomfort from floaters was the primary outcome measure. Secondary outcome measures included 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*** and an insignificant increase in vitreous opacity areas in the placebo group.
  - ***Significant improvement in photopic functional contrast sensitivity*** in the active group after supplementation

Conclusions

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



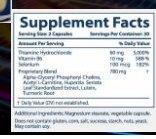
104

Off-Label Medication Use
Parasym Plus Eyes

Supplement not regulated by FDA

Proposed MOA:

acetylcholine release via the parasympathetic lacrimal nerves that stimulate lacrimal gland



Supplement Facts

Serving Size: 2 Capsules — Servings Per Container: 30

Amount Per Serving		% Daily Value
Thiamine Hydrochloride	50 mg	3,350%
Vitamin B6	10 mg	588 %
Selenium	100 mcg	182%
Proprietary Blend	700 mg	†
Alpha-Glycerylphosphorylcholine, Acetyl-L-Carnitine, Huperzia Serrata Extract, Ginkgo Biloba Extract, Lutein, Turmeric Root		

† Daily Value (DV) not established.

Additional Ingredients: Magnesium stearate, vegetable capsule. Does not contain gluten, corn, soft, sucrose, starch, nuts, yeast. May contain soy.

Off-label uses identified in the literature:**

- Stimulation of the lacrimal glands and enhanced tear production

105

Restoring Acetylcholine Levels for Nicotinic and Muscarinic Receptors

Published on https://vagusnervesupport.com/dry-eye-disease/

Abstract

To test the hypothesis that DED is a local manifestation of systemic inflammation due to reduced release of acetylcholine, an OTC supplement patented to stimulate the postganglionic vagus nerve or the ***nicotinic receptors**** on the organs served by the vagus nerve (Parasym Plus Eyes™) was used for dry eye symptoms.

An initial group of 18 patients with dry eye were selected to participate in a double-blind placebo-controlled study using Parasym Plus Eyes™ or a placebo (both oral capsules). Ocular Surface Disease Index (OSDI®) scores, corneal staining, and Tear Breakup Time (TBUT) were evaluated before treatment and one month later.

	Treatment group:	Placebo group:
Corneal staining:	92%	60%
OSDI score:	83%	40%
Improved TBUT:	75%	60%

Results of treatment were strongly positive. A larger study is warranted and is currently being completed. Importantly, comments by patients included ***systemic improvements, including normalization of bowel movements and dramatically improved cognition and short-term memory***.

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Off-Label Medication Use
Can-C (N-acetylcarnosine)

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

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[a,c] (n = 39)	0.41 ± 0.05[a] (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[a] (n = 37)	0.38 ± 0.05[a] (n = 37)

Conclusions

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

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Off-Label Medication Use

Lanosterol

Supplement not regulated by FDA

Proposed MOA:

Amphipathic molecule enriched in the lens synthesized by a key cyclization reaction of a cholesterol synthesis pathway.

- Lanosterol was loaded into a lipid-polymer hybrid nanoparticles to enhance can corneal penetration

Off-label uses identified in the literature:**

- Cataract prevention and reversal

**Pet-formulation ONLY+*

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Lanosterol reverses protein aggregation in cataracts

Nature (2015) 523:607-611

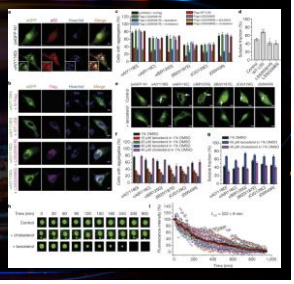
Abstract

Human lens is comprised largely of crystallin proteins assembled into a highly ordered, interactive macro-structure essential for lens transparency and refractive index. Disruption of protein interactions will alter this structure, exposing hydrophobic surfaces, with consequent protein aggregation and cataract formation.

Lanosterol is an amphipathic molecule enriched in the lens. It is synthesized by lanosterol synthase (LSS) in a key cyclization reaction of a cholesterol synthesis pathway.

Treatment by lanosterol significantly decreased preformed protein aggregates both in vitro and in cell-transfection experiments.

Lanosterol is a key molecule in the prevention of lens protein aggregation and points to a novel strategy for cataract prevention and treatment.



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Peer-Reviewed Off-Label Medications

Central serous chorioretinopathy treatment

- **Mineralcorticoid antagonist**
- **Antimycobacterials**
- **Melatonin**

- **Case Report**

111

Off-Label Medication Use

Central Serous Chorioretinopathy

Mineralcorticoid antagonists

- Eplerenone (Inspra) – selective aldosterone receptor antagonist (K^+ sparing diuretic)
  - Mineralocorticoid receptor is involved in human ocular chorioretinopathy. *J Clin Invest* 122.7 (2012): 2672-2679
    - 4 patients using 25mg QD x 1 week then 50mg QD x 1-3 months
    - Significant reduction in SRF, CRT and intraretinal cystic formation
  - Mineralocorticoid receptor antagonism treatment of chronic central serous chorioretinopathy: a pilot study. *Retina* 33.10 (2013): 2096-2102
    - 13 patients using 25mg QD x 1 week then 50mg QD x 1-3 months
    - Significant reduction in SRF, CRT and BCVA at 1 month and 3 months
- Spironolactone (Aldactone) – less selective aldosterone receptor antagonist (K^+ sparing diuretic)
  - Spironolactone in the treatment of central serous chorioretinopathy–a case series. *Clin & Exp Ophthal* 252.12 (2014): 1985-1991
    - 18 subjects using 25mg BID X 1-3 months
    - Significant improvements in SRF, CRT and BCVA at 3 months

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Off-Label Medication Use

Central Serous Chorioretinopathy

Antibiotics

- Rifampin (Rifampicin)
  - Oral Rifampin treatment for long-standing chronic central serous chorioretinopathy. *Clinical & Exp Ophthal* 254.1 (2016): 15-22
    - 12 subjects (14 eyes) using 300mg BID x 3 months
    - Significant improvements in BCVA, CRT, choroidal thickness. SRF reduced in 9 eyes and resolved in 4 eyes.
  - Rifampin for treatment of central serous chorioretinopathy. *Invest Ophthal & Vis Sci* 52.14 (2011): 2137-2137
    - Retrospective evaluation of 5 subjects using 300mg BID x 3 months
    - 3 subjects showed decreased CRT and 2 remained unchanged while 3 subjects showed no BCVA improvement and 2 subjects improved >3 lines
  - Oral rifampin utilization for the treatment of chronic multifocal central serous retinopathy. *Brit J Ophthal* 96.1 (2012): 10-13
    - Patient with chronic CSR and persistent SRF x 2 years completely resolved using oral rifampin 300mg BID x 1month
      **cytochrome P450 induction is thought to favorably alter the metabolism of endogenous steroids

Circadian-rhythm hormone

- Melatonin (melatonin receptor 1 + 2 agonist)
  - Therapeutic benefit of melatonin in refractory central serous chorioretinopathy. *Eye* 29.8 (2015): 1036-1045
    - 8 subjects using 3mg melatonin TID x 1 month
    - Significant improvements in BCVA and CRT with 3 subjects showing complete resolution

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Central Serous Chorioretinopathy

• Case Report

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Central Serous Chorioretinopathy

Case Report

- 39YO Caucasian male presented for difficulty focusing with OD at distance and near x 1 week
  - Appreciated changes in color vision perception in OD compared to OS and metamorphopsia OD
  - Denied recent injuries or trauma, flashes/floaters, contact lens wear, recent illness or travel outside country
- LEE: >2 years ago @ civilian practice
- FMHx: unremarkable
- PMHx: unremarkable
- (-) current medications
- (+) H/O smoking 2-3 packs/d
- NKDA

Distance VAsc
OD: 20/100 PH: 20/80 and OS: 20/20 OS
Pupils: ERRL (-) APD OD, OS
EOM: FROM OU w/ (-) pain
CVF: FTFC OU
Amiser grid: Distortion inferior ¾ OD and (-) scotoma or distortion OS
PIP I: 10/14 OD and 14/14 OS
GAT: 16mmHg OD and 18 mmHg OS

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Central Serous Chorioretinopathy

Case Report

SLE
- L/L – unremarkable OD, OS
- Conj - unremarkable OD, OS
- Cornea - unremarkable OD, OS
- A/C – unremarkable OD, OS
- Iris - unremarkable OD, OS
- Lens - unremarkable OD, OS

DFE
- C/D – 0.40/0.40 OD, OS w/ healthy neuroretinal rim and distinct margins OD, OS
- ***Macula – Significant elevation extending temporally from ONH OD*** / unremarkable OS
- Vessels – 2/3 A/V ratio OD, OS
- Vitreous – Trace syneresis OD, OS
- Periphery – (-) H/T/B OD, OS

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Central Serous Chorioretinopathy

Case Report #1

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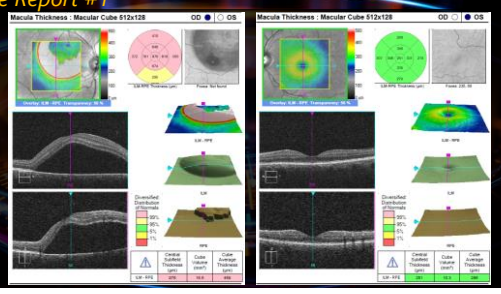
Central Serous Chorioretinopathy

Case Report #1



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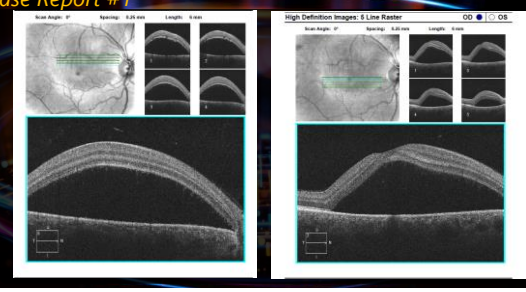
Central Serous Chorioretinopathy

Case Report #1



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Central Serous Chorioretinopathy

Case Report #1

- Due to the almost 1000um of elevation, a phone call was made to Okinawa ophthalmology clinic
  - ***Murphy's Law:*** Both ophthalmologists off-island for the holiday season for the next 2 weeks.
- Referral management recommended consult with Tripler Army Medical Center. A phone call was placed to ophthalmology on-call at the Tripler Army Medical Center happened to be a retinal specialist (***anti-Murphy's Law?***)
  - Reviewed the patient's medical record, current encounter and all photos and testing performed
  - Recommended 2 capsules of rimfampin 300mg BID for 30 days and F/U after finishing therapy
    - Suggested FA at that time if there was no improvement
  - Patient's PCM was notified of the treatment and the patient was scheduled for F/U in 30 days

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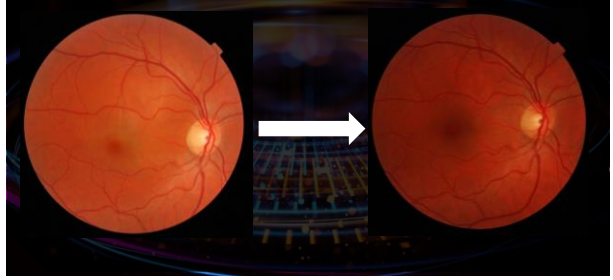
Central Serous Chorioretinopathy

Case Report #1



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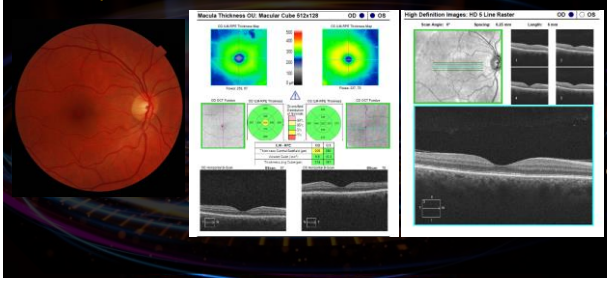
Central Serous Chorioretinopathy

Case Report #1



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Central Serous Chorioretinopathy

Case Report

Distance VAsc
OD: 20/30 and OS: 20/20 OS
Amlser grid: (-) scotoma or distortion OD, OS
PIP I: 12/14 OD and 14/14 OS
GAT: 15mmHg OD and 15mmHg OS

SLE
- L/L – unremarkable OD, OS
- Conj - unremarkable OD, OS
- Cornea - unremarkable OD, OS
- A/C – unremarkable OD, OS
- Iris - unremarkable OD, OS
- Lens - unremarkable OD, OS

DFE
- C/D – 0.40/0.40 OD, OS w/ healthy neuroretinal rim and distinct margins OD, OS
- ***Macula –unremarkable OD, OS***
- Vessels – 2/3 A/V ratio OD, OS
- Vitreous – Trace syneresis OD, OS
- Periphery – (-) H/T/B OD, OS

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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*

***** Mesopic effects during driving?***
***** Myopic shift?***
***** RD in susceptible eyes?***

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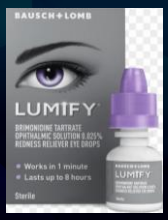
Take Home Points
Optometric Off-Label Use Can Become On-Label



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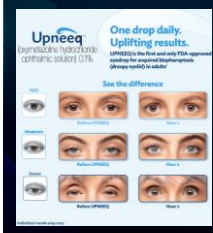
Take Home Points
Optometric Off-Label Use Can Become On-Label



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 0.05% (Restasis)**
  - **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
- Parasym Eyes 2 capsules BID x 4 weeks**
  - Dry eye disease

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Limitations…

- Optometry is typically outside an integrated healthcare setting
  - Private practice
  - Corporate settings
- Off-label medication use may not be standard of care
- Adverse reactions to off-label medication use can expose the provider to liability

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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
- Off-label medication use can reduce need for more invasive therapies
- PCM teaming embraces integrated medicine

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What's next?

- Evidence-based off-label therapy
  - Off-label medication use should be pharmacologically sound and backed by research
  - Pilot data drives larger scale, RCTs that can fundamentally change how medications are utilized
- Off-label algorithms
  - Clinical Findings
  - Drug Class
  - Dosage / Duration
  - Recommended follow-up and testing

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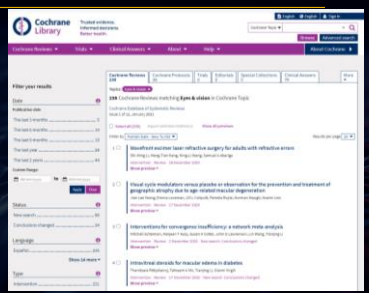
https://www.cochrane.org/evidence



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https://www.epocrates.com/

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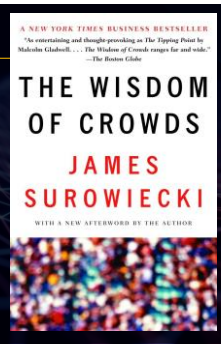
"Paradoxically, the best way for a group to be smart is for each person in it to think and act as independently as possible."

– James Surowiecki



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Questions?

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