Topiramate (Topamax) and Vision

- Uses: anticonvulsant, migraine prevention, bipolar disorder, obesity, OCD, IIH, neuropathic pain, essential tremor, post-herpetic neuralgia, and other esoteric uses.
- Topiramate is a sulfa derivative (like CAI’s)
- Idiosyncratic ciliochoroidal effusion is the most common ocular side effect, and most always results in a myopic shift with or without increased IOP
- This rare event usually occurs within 2 weeks of initiation (or doubling) of dosing
- First described in 2001 – 70% are female
- Tx: D/C the medicine; use (PRN) beta-blocker, brimonidine, or, in refractory case, oral prednisone or IV methylprednisolone. Also, instill cycloplegic agent, and do not use pilocarpine.

Clinical Ophthalmology. January 2012

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Qsymia: Potential for Decreased Weight and Increased Risk of Angle Closure

- New drug for weight loss patients who are overweight or obese and also have at least one weight-related condition such as high blood pressure, diabetes or high cholesterol.
- Combination of two older drugs
  - Phentermine (appetite suppressant)
  - Topiramate (feeling of satiation)
- Lesser dosages of each component drug tend to act synergistically
- On average, patients lose about 10% of their body weight over one year
- Marketed by Vivus Inc (Mountain View, California)
- FDA approval July 17, 2012

Tafluprost Ophthalmic Solution

- FDA approved February 2012
- First “preservative-free” prostaglandin
- Reduces IOP similarly to the other prostaglandins
- Dosage: once daily, preferably in the evening
- Most common side-effect – conjunctival hyperemia
- Available in unit dose containers
- Marketed as Zioptan 0.0015% ophthalmic solution by Akorn

Simbrinza – (brinzolamide 1.0% and brimonidine 0.2% combination)

- Combination drug without a beta blocker where both ingredient drugs are dosed the same (b.i.d.)
- Combines 1% brinzolamide (Azopt ophthalmic suspension) with 0.2% brimonidine
- Offers a wide range of treatment possibilities due to its strong efficacy and ability to decrease elevated IOP by 21- 35%
- Marketed by Alcon under the brand name Simbrinza suspension
**Are Generics OK?**

“The more recent (since 1992) ophthalmic generics are approved according to strict criteria for sameness and are expected to behave in the same manner as the innovator.”

*Reference: Ophthalmology, June 2012. Editorial by W. Chambers, MD of the FDA*

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**Trimethoprim with Polymyxin B**

- Trimethoprim, a non-antibiotic antibacterial
  - Bacteriostatic and broad spectrum
  - Inhibits bacterial dihydrofolate reductase
  - Effective against most common ocular pathogens, except pseudomonas species
  - Excellent for bacterial infections in children
  - Haemophilus influenzae and streptococcus pneumoniae

- Polymyxin B is a highly effective gram – bactericidal drug
- Available as a 10 ml solution (Polytrim and generic)

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**Aminoglycosides**

- Bactericidal
- Inhibits protein synthesis
- Effective against most commonly encountered gram positive and gram negative bacteria
- Available in both solution and ointment form
  - Gentamicin - toxic/allergic reactions do occasionally occur. Pregnancy category C. (visit www.ferapharma.com for free samples)
  - Tobramycin - resistance, toxic and allergic reactions rare (Pregnancy category B)

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**Antibiotic Susceptibilities**

- “The efficacy of aminoglycosides has been well-documented in endophthalmitis.”
- As the use of topical fluoroquinolones has increased, so have the number of reports documenting an increase in bacterial resistance.
- “The 4th generation fluoroquinolones evaluated did not provide much greater coverage than the earlier generation fluoroquinolones.”
- To guard against resistance, eye doctors are discouraged from using antibiotics with EKC, and prophylactic use before intravitreal injections.

*Reference: Ophthalmology, August 2014*

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**Evolving Fluoroquinolone Resistance**

“Fourth-generation fluoroquinolones are significantly more expensive than generic traditional antibiotic eyedrops such as gentamicin sulfate and polymyxin B sulfate/trimethoprim, which have been shown to cover endophthalmitis isolates at least as well . . . “Given the frequent and increasing resistance, subtherapeutic penetration, and higher cost compared with other antibiotic eyedrops, the widespread perioperative and periprocedural use of fourth-generation fluoroquinolone antibiotic eyedrops should be reevaluated.

*Reference: Archives of Ophthalmology, December 2012*

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**Drugs and Antibiotic Resistance**

- Study: 200 patients - - 90% Gm+, 10% Gm –
- Least susceptible: penicillins (17%) and erythromycin (48%)
- Highest susceptible: gentamicin (94%), tobramycin (90%), tetracycline (91%)
- Intermediate susceptible: moxifloxacin and gatifloxacin (75%)
- About half of Gm+ were methicillin resistant
- “The fluoroquinolones are failing to cover 20% or more potential pathogens; additionally, we found that fluoroquinolones may cover 1 but not all CNS strains present in a patient. One should therefore entertain alternatives to fluoroquinolones. Indeed, given the overall 90-plus percent susceptibility rate, one should perhaps consider instead the aminoglycosides.”

*Reference: AJO, January 2013*
Antimicrobial Resistance

• Staph. Epi. was the most common pathogen in this study
• 97% of all isolates were sensitive to gentamicin
• Fluoroquinolone resistance ranged from 32% to 40%
• “The high prevalence of fluoroquinolone-resistant organisms among ocular and nasal flora in our patient population raises concern with regards to the usefulness of topical fluoroquinolones as the best first-line agent in the setting of ophthalmic prophylaxis and for empiric use in acute ophthalmic infectious processes.”

Reference: AJO, December 2011

Preventing Eye Infections (Intravitreal Injections)

• Kill time for Betadine (povidone iodine) 15-120 seconds...at any concentration!
• Anaphylaxis to iodine does not exist!
• “Topical moxifloxacin .5% had no additional effect on reducing conjunctival bacterial counts beyond the effect of 5% povidone iodine alone.”
• “Preinjection antibiotics either before the day of injection or immediately prior to injection are not generally recommended.”
• Gentamicin was vastly more effective than fluoroquinolones


Antibiotics and Intravitreal Injections

• Preoperative and postoperative antibiotics might have a negative impact on the safety of the procedure because, with repeated injections, patients develop ocular surface bacteria that are antibiotic-resistant.
• Topical antibiotics before the day of injection did not reduce conjunctival bacterial counts more than the immediate pre-injection use of povidone-iodine
• In spite of this knowledge, 27% of surveyed retina specialists continue to use pre-injection antibiotics and 63% use post-injection antibiotics.


Implications of Azithromycin and Fluoroquinolone Use

• “The repeated use of azithromycin or fluoroquinolone antibiotics significantly alters the composition of conjunctival flora by increasing the percentage of S. epidermidis.”
• “Resistant strains of S. epidermidis emerge rapidly after antibiotic exposure and possess co-resistance to other classes of antibiotics.”
• “The high percentage (75%) of baseline resistance to azithromycin may have allowed resistant S. epidermidis strains to readily out-compete other flora.”
• “The practice of long-term or repeated use of azithromycin for blepharitis may therefore select for not only azithromycin-resistant but also doxycycline-resistant strains of S. epidermidis.”

Oph. May 2013

A Novel Fluoroquinolone - Besifloxacin

• A unique bi-halogenated quinolone
• New chemical entity: An 8-chloro fluoroquinolone
• NOT used systemically – only available in U.S.
• Relative resistance-proof:
  No oral counterpart
• FDA-approved medication: Bacterial conjunctivitis
• FDA-approved treatment protocol: tid for 7 days
• Pediatric approval: ages 1 and older
• Preserved with 0.01% BAK (Durasite vehicle)
• Marketed as Besivance 0.6% ophthalmic suspension by B&L Pharmaceuticals – 5 ml

2009 ARMOR Surveillance All S. aureus (n= 200)

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>MIC Range</th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt;</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt;</th>
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<tr>
<td>Besifloxacin</td>
<td>≤0.008 – 4</td>
<td>0.03</td>
<td>1</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>≤0.008 – 64</td>
<td>0.06</td>
<td>8</td>
</tr>
</tbody>
</table>

39% of ocular S. aureus isolates were MRSA
38% of ocular S. aureus isolates were FQ-resistant

Haas et al. Presented at ARVO, Fort Lauderdale, FL, May 2-6, 2010. Abstract #O965. % resistance based on oxacillin and ciprofloxacin breakpoints.
Chloramphenicol Revisited

- More than 50% of the world uses chloramphenicol as a first-line agent in the treatment of conjunctivitis
- It is OTC in many countries
- Approximately a one in 2 million chance of blood dyscrasia
- “If American medicine continues to tilt towards more socialized care and some medications are not available based on cost alone, drugs like chloramphenicol eye drops could be considered as a viable treatment option.”

Reference: AJO, September 2013

Antibiotics - Systemic

- Penicillins
- Cephalosporins
- Tetracyclines
- Macrolides
- Fluoroquinolones

Consult Drug Facts & Comparisons (www.drugfacts.com)

Amoxicillin/Clavulanic Acid (Augmentin)

- Clavulanic acid enables amoxicillin to be bactericidal against common gram positive pathogens
- Useful in treating soft tissue infections
- Cannot use if patient is allergic to penicillin
- Tx: 250, 500 & 875 (generic) or 1000 mg (branded only) tablet q 12 hrs x 7-10 days
- Can be taken with meals

Cephalexin (Keflex)

- Cephalexin - 1st generation cephalosporin
- Effective against most gram positive pathogens
- All cephalosporins share a 1-2% cross-sensitivity to PCN (true allergy to PCN)
- Usual dosage: 500 mg bid x 1 week
- Useful in soft tissue staph infections, such as internal hordeola, preseptal cellulitis, etc.

Options for True Penicillin Allergy Patients

- 2nd or 3rd generation cephalosporin
- Sulfamethoxazole/trimethoprim (Bactrim or Septra)
- A fluoroquinolone (Levofloxacin)
- Doxycycline
- Erythromycin

Allergic Reactions to Cephalosporins

- Widely used to treat outpatient infections
- 19 of “more than a million” patients experienced allergic reactions
- “Almost 66,000 patients who received cephalosporins had previously documented allergies to penicillin, and 3,300 had previous reports of cephalosporin allergies.”
- “New reports of allergies to cephalosporins were entered for 0.5% of men and women.”

Reference: J. Allergy and Clinical Immunology. March 15, 2015.
The Tetracyclines

- Tetracycline, doxycycline, minocycline
- Doxycycline most commonly used
- Advantages over tetracycline
  - Maintenance dose 20-100 mg daily
  - Can be taken without regard to meals
- Contraindicated in pregnancy, nursing mothers, under age 8; photosensitivity warning
- Indications in primary eye care
  - Meibomianitis (chronic inspissated glands)
  - Adult inclusion conjunctivitis (chlamydia)
  - Recurrent corneal erosion

Doxycycline

- Most commonly used
- Advantages over tetracycline
  - Maintenance dose 20-100 mg daily
  - Can be taken without regard to meals

Oracea

- Doxycycline 30 mg immediate release and 10 mg delayed release beads (once daily 40 mg capsule)
- First and only oral therapy approved by FDA to treat rosacea
- Works by controlling inflammation
- Recommended to take in morning with a full glass of water
- Contraindications and side effects similar to tetracyclines (photosensitivity and yeast infections not observed in clinical trials).
- Marketed by Galderma

Systane Tears

- Anterior uveitis
- Tricyclic antidepressants
- Adjunctive therapy for dry eye

Medical Approach to RCE

- Small study – limited follow-up
- 100 mg doxycycline per day for 1 month and Lotemax q.i.d. for 1 month
- Results: Curative in almost all cases
- An alternative (or adjunctive) to ASP or conventional therapies

Oral Doxycycline and Pterygial Angiogenesis

- UV light is a known trigger for pterygenesis and progression
- Doxycycline (and corticosteroids) can inhibit neovascularization
- Perhaps pterygium management can be augmented with 50 mg P.O. doxycycline daily for many weeks or many months after (or concurrent with) topical loteprednol q.i.d. for 1 month, the b.i.d. for 2 months


Minocycline, MGD, and Dry Eye

- “Lid hygiene plus minocycline showed significant improvements in clinical signs and remarkable changes in fatty acid composition.”
- “There is no agreement on the ideal dosage of minocycline.”
- “Our study showed remarkable benefit with 50 mg oral minocycline twice daily for two months without any fatal complications.”
- “To obtain meaningful patient satisfaction and favorable clinical results we should consider minocycline as a first-line therapy for the treatment of moderate and severe MGD.”

AJO, December 2012

Azithromycin - (Zithromax)

- Used for soft tissue infection; heavy prescribing has resulted in much resistance
- Drug of choice for chlamydial infections
- Dosage for chlamydial eye infection - four 250 mg capsules or two 500 mg capsules for one day or a single dose of a 1,000 mg suspension
- Zmax is a 2,000 mg oral suspension
- 1.0% AzaSite ophthalmic solution by Akorn
A NEW INSTRUMENT & METRIC
STANDARDIZED DX EXPRESSION FOR MG FUNCTIONALITY

Concept: An active—functional meibomian gland should yield liquid secretion = MGYLS

Korb & Blackie—Cornea 2008

THREE DIAGNOSTIC QUALIFIERS
1. Standard force to mimic force of blink ≈ 1.0 gram/mm² (0.3 PSI)
2. Application ≤ 15 seconds
3. Secretion must be liquid (MGYLS)

A new metric allowing standardized expression for diagnosis & quantification of MG functionality

SUMMARY—NEW PARADIGM

“It is important to note that MGD, a condition of MG obstruction, may be the leading cause of dry eye syndrome throughout the world”

TFOS 2008, Report to Professions, 2011

- Lipid deficiency & not aqueous deficiency is usually the catalyst for DRY EYE & inflammatory cascade
  In contrast to conventional models and treatment
- MGD and MG OBSTRUCTION may be obvious or non-obvious, most frequently non-obvious
- Dx of MG functionality requires expression—new metrics
- Treatment of MGD with new technology can treat obstruction improving meibomian gland function to effectively treat dry eye disease & CL intolerance

MG Scraping in Treating DES

- Anatomic alterations at the mucocutaneous junction may inhibit proper meibum flow to the tear film
- “It is notable that a single debridement procedure improved comfort and MG function.”
- “Hypothetically, early and frequent debridement of the MCJ and lid margin could prevent or delay the cascade of increased osmolarity, tissue desiccation, and ultimately inflammation and tissue damage simply because of mechanical barriers to oil entering the tear film.”


(continued)

Bactrim or Septra

- Drug of choice for MRSA infections
- Combination of 160 mg of trimethoprim and 800 mg of sulfamethoxazole
- Rule out true sulfa allergy
- Sig: Take 1 or 2 DS tabs p.o. bid x 7-10 days
- Note that the standard strength of these drugs is “double strength” (DS)
- If sulfa-allergic, then doxycycline 100 mg used bid for 7-10 days
- Both are old, generic, and highly-effective
### Ester vs Ketone Corticosteroids

<table>
<thead>
<tr>
<th>Ester</th>
<th>Ketone</th>
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<tbody>
<tr>
<td>Loteprednol</td>
<td>Prednisolone</td>
</tr>
<tr>
<td>Fluorometholone</td>
<td>Dexamethasone</td>
</tr>
<tr>
<td>Medrysone</td>
<td>Rimexolone</td>
</tr>
<tr>
<td>Difluoroprednisolone</td>
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</table>

**Difluprednate 0.05% (Durezol)**

- “There is increased bioavailability and dose uniformity resulting from the formulation of difluprednate as an emulsion, rather than a suspension.”
- Steroid-induced hypertension seen in 8% of the normal population, and is more common in patients with glaucoma.
- Steroid-induced hypertension is “generally not seen until 3 to 6 weeks of corticosteroid use.”
- “Difluprednate was shown to provide better results compared with prednisolone acetate…”
- “We believe the effects seen are the result of the greater anti-inflammatory potency of difluprednate.”

*AJO, October, 2011*

### Lotemax Gel

- A new and improved gel drop formulation of ester-based loteprednol corticosteroid
- This eye drop possesses “adaptive viscosity”
- Provides clear vision in a gel drop delivery system
- No shaking required!
- pH of 6.0-6.5 vs 5.3-5.6 in the suspension
- 70% less BAK than Lotemax suspension
- No increased IOP vs vehicle in phase III study
- FDA approval: post-operative pain and inflammation
- Marketed by B&L as Lotemax Gel in a 5 gm bottle


### Loteprednol Ophthalmic Ointment

- The only ester-based steroid ointment available
- It is a 0.5% concentration and preservative-free
- FDA-approved: Post-operative inflammation and pain
- Numerous “off-label” clinical uses: dry eye, allergy, corneal transplant protection, blepharitis, GPC, chronic uveitis, stromal immune herpetic keratitis, Thygeson’s SPK, RCE, augmentation of steroid eyedrop therapy in acute, advanced uveitis or episcleritis, following Betadine EKC Tx, contact dermatitis, and other inflammatory conditions as indicated
- Available in a 3.5 gm ophthalmic tube as Lotemax 0.5% ophthalmic ointment by B&L

### Long-Term FML Use After PKP

“In summary, we found that the prolonged use of 0.1% fluorometholone was beneficial for the prevention of rejection after PKP. Because no adverse consequences associated with the use of the eye drops were noted, we recommend continuing the use of low-dose corticosteroids, even in non-high-risk cases.”

*Reference: Oph, April 2012*

*M & T: If such prolonged use of a ketone-based steroid is safe and effective, it would stand to reason that long-term use of loteprednol would be even safer. This has clear implications for long-term use in dry eye-related ocular surface inflammation.*

### Children and Steroids

- “A tapering regimen of FML for ocular surface disease in children constitutes a safe anti-inflammatory treatment option to avoid steroid-induced glaucoma.”
- “These patients may need prolonged treatment with FML to control the inflammation, a tapering regimen may help avoid steroid-induced glaucoma.”
- No study had an increased IOP above 19mmHg.

*Reference: BJO; 2011, 95 (11), Pp 1531-1533*

*M&T Commentary: We would be much more comfortable using an ester-based corticosteroid such as loteprednol with these patients.*
Non-ophthalmic steroid: ointment/cream/lotion

- Triamcinolone - moderate potency steroid
- Available in cream, ointment and lotion (0.5%, 0.1%, 0.025%)
- Our favorite: the 0.1% cream

Reference: Drug Facts and Comparisons

Systemic Prednisone

- Most common Rx’d systemic corticosteroid
- Common initial dosage 40-60 mg
- Available generically in both tablets and DosePaks (5 or 10 mg at 6 or 12 day course)
- Questions to ask before prescribing?
  - Diabetic?
  - Peptic Ulcer Disease?
  - Tuberculosis?
  - Pregnant?

Dry Eye Syndrome

- Common presenting problem
- Symptoms: burning, gritty-sandy feeling, foreign body sensation, and/or tearing or watering
- Diagnosis: Good History, decreased lacrimal lake, decreased BUT, Lissamine Green staining
- Treatment: Frequent use of preservative-free artificial tears; anti-inflammatory medications, punctal plugs, oral doxycycline/minocycline, oral omega-3 fatty acids
- Patient education is vitally important to maximize care

Correlation of Tear Osmolarity and Dry Eye Symptoms

“Conclusions
In this nonclinical population, no significant correlation was found between tear osmolarity as measured with the TearLab instrument and ocular symptoms as reported on the DEQ-5 or with tear osmolarity and a Gestalt self-assessment of dry eye. Self-assessed subjects were often missed by osmolarity testing.”

Reference: Optometry and Vision Science, February 2014

The Value of Tear Osmolarity as a Metric in Evaluating the Response to Dry Eye Therapy in the Clinic and in Clinical Trials

"There was no correlation (among 186 patients) between longitudinal change in osmolarity (as measured by the Tear-Lab osmometer) and changes in either corneal fluorescein staining or in patient symptoms, 2 widely accepted outcome measures in dry eye disease."  
"Our data demonstrate that nearly half the patients who had improved symptoms showed increases in tear osmolarity and the other half showed decreases in tear osmolarity."

Reference: Amparo F et al. AJO. April 2014

The Value of Tear Osmolarity as a Metric in Evaluating the Response to Dry Eye Therapy in the Clinic and in Clinical Trials

“We presented data on subgroups based on osmolarity cut-points (308 mOsm/L and 314 mOsm/L) and still observed no correlation between changes in osmolarity and either symptoms or staining; and we also presented data on a number of disparate sub-groups based on various cut-points and reported consistent results; no correlation between change in osmolarity with change in either corneal staining or symptoms.”

Reference: Amparo F et al. AJO. April 2014
**Immunoassay for Dry Eye Inflammation**

- Extracellular matrix metalloproteinase (MMP-9) is a quantifiable marker of ocular surface inflammation in dry eye disease.
- MMP-9 levels >40ng/ml are strongly associated with dry eye disease.
- InflammaDry is a ten minute, in-office assay of MMP-9 with a sensitivity of 85% and a specificity of 94%.
- MMP-9 levels increase proportionally to the longevity and severity of the dry eye disease.
- Corticosteroids > doxycycline > cyclosporin inhibit MMP’s.
- InflammaDry is available from www.rpsdetectors.

**Lipid-Based Artificial Tears (For Evaporative Dry Eye)**

- Vast majority of dry eye patients have MGD.
- Meta-stable emulsions are optimum Tx.
- Rapidly provides a protective lipid barrier.
- Reduces harmful evaporation to prevent tear loss.
- Replenishes the complete tear film.
  - Systane Balance emulsion (10 ml) – Alcon
  - Refresh Optive Advanced (10 ml) – Allergan
  - FreshKote (15 ml Rx) – Focus Labs
  - Retaine MGD - OCuSOFT

**Aqueous-Based Artificial Tears (For Aqueous Deficient Eye)**

- Relatively uncommon cause of dry eyes.
- Aqueous-based solutions are optimum Tx.
- Rapidly provides ocular surface hydration.
- Main ingredients commonly include:
  - Cellulose
  - Glycerin
  - Polyethylene Glycol
  - Propylene Glycol
  - Soothe Xtra Hydration (15 ml) – B&L
  - Systane Ultra (15 ml) – Alcon
  - Optive (15 ml) - Allergan
  - Blink (15 ml) – AMO
  - FreshKote (15ml) – Focus Labs

**Inflammation and Dry Eye**

“The tear film can be destabilized by decreased tear production, delayed clearance, or altered tear composition, ultimately leading to inflammation and exacerbating tear film instability.”

Reference: AJO. March 2014

“Because inflammation plays a central role in the pathogenesis of DED, anti-inflammatory therapies have become a mainstay of treatment.”

Optometry Times, September, 2013

**Dry Eye Diagnosis: “Symptoms”**

“Dry eye disease remains a largely symptomatic diagnosis, without a single diagnostic test.”

Reference: AJO, March 2015. P 470

**Dry Eye Milestones**

“So why does clinical dry eye disease still seem so hard to treat?”

Reference: Advanced Ocular Care, May/June 2013

**Melton and Thomas answer:**

Because clinicians have failed to embrace the “pulse-dosing” of loteprednol!
Perspective on Therapeutic Approaches

- "... it is clear that many patients with DED do not show a consistent therapeutic response to topical cyclosporin A, and... some patients experience bothersome adverse effects (eg, burning or irritation) that impair medication tolerability."
- "Clinical trials have demonstrated the efficacy of topical corticosteroid treatment at diminishing symptom severity and minimizing ocular surface staining."
- "Repetitive short-term pulsatile administration of topical corticosteroids is a promising method of harnessing their beneficial effects, while minimizing the risk of adverse events."

Archives of Ophthalmology, January 2012

Tear Dysfunction Perspectives

- "Over the past decade there has been a trend towards increased use of anti-inflammatory therapies to improve comfort, corneal smoothness, and barrier function."
- Corticosteroids, doxycycline, and EFA's have been found to decrease production of a variety of inflammatory mediators and improve corneal epithelial disease.

AJO, December 2011

FDA Draft Guidance on Generic Eye Drug

"... the U.S. Food and Drug Administration proposed allowing companies to apply for marketing approval of generic versions of Restasis based on laboratory tests, not on human clinical trials.

The FDA said in its proposed guidance that conducting a study in humans to test whether the drugs are essentially equivalent would not be feasible or reliable due to the 'modest efficacy' of Restasis."

(Reuters) by Toni Clarke on June 24, 2013

Alternative Supplementation

- Orally administered omega-3 essential fatty acids
- May take 4-6 months to obtain a significant clinical effect
- Liquid formulations are available for those patients who have difficulty swallowing large capsules.

Vascepa (icosapent ethyl)

- FDA-approved prescription product containing only the Omega-3 fatty acid EPA.
- Used along with low-fat, low-cholesterol diet to help reduce triglyceride levels in adults with severe (>500 mg/dL) hypertriglyceridemia without raising LDL (bad) cholesterol
- Most commonly reported side effect is arthralgias. The effect of VASCEPA on patients at risk for pancreatitis, cardiovascular mortality and morbidity has not been determined.
- Pregnancy category C
- www.vascepa.com
Epanova (omega-3-carboxylic acids)

- First FDA approved prescription omega-3 in free fatty acid form
- A new treatment option for adults with severe hypertriglyceridemia (triglyceride levels 500 mg/dL or higher)
- There are currently two other prescription formulations of omega-3 supplements on the market: Lovaza and Vascepa

Supplemental Therapeutic Approaches in Dry Eye Disease (DED)

- “Most of the available evidence suggests that administration of omega 3 EFAs can lessen DED severity.”
- Regarding omega 3 EFAs, “… more evidence is needed to identify the most efficacious forms and doses.”
- “The evidence implicating inflammation in pathogenesis of DED has opened new avenues for the treatment of this complex disorder. The successful application of anti-inflammatory medications in the treatment of DED provides hope for the millions of individuals who daily experience this deleterious condition.”

*Archives of Ophthalmology, January 2012*

Non-Steroidal Anti-Inflammatory Drugs

- Inhibition of prostaglandin synthesis is the mechanism of action.
- They specifically inhibit the action of cyclooxygenase, an enzyme vital to prostaglandin synthesis.
- Prostaglandins are powerful mediators of inflammation.
  - Acular (Ketorolac 0.5%) by Allergan and generic
  - Acular LS (Ketorolac 0.4%) - Allergan
  - Acuvail (Ketorolac PF 0.45%) - Allergan
  - Ocufem (Flurbinprofen 0.03%) by Allergan and generic
  - Profenal (Suprofen 1%) by Alcon and generic
  - Voltaren (Diclofenac 0.1%) by Novartis and generic
  - Bromday (Bromfenac 0.09%) by B+L
  - Nevanac (Nepafenac 0.1%) by Alcon

Nepafenac Ophthalmic Suspensions

- Nevanac 0.1% AND Ilevro 0.3%
- Indication: Treatment of pain and inflammation associated with cataract surgery
- Nevanac is dosed tid; Ilevro, once daily
- Ilevro is to be prescribed the day before surgery, the day of surgery and then 14 more days
- BAK 0.005%, pH 6.8, pregnancy category C, pediatric use down to age 10
- Marketed by Alcon as Ilevro 0.3% ophthalmic suspension 1.7 ml in a 4 ml bottle

Bromfenac Ophthalmic Solutions

- Bromday 0.09% and Prolensa 0.07% (22% less concentration)
- Indication: Treatment of pain and inflammation associated with cataract surgery
- Both are dosed once daily
- Both are prescribed the day before surgery, the day of surgery and then 14 more days
- BAK 0.005% BAK pH 7.8, pregnancy category C, pediatric use down to age 18
- Marketed by B&L at Prolensa 0.07% ophthalmic solution 1.6 ml and 3 ml in a 7.5 ml bottle

Anti-infective/Anti-inflammatory Combinations

<table>
<thead>
<tr>
<th>Prednisolone</th>
<th>Dexamethasone</th>
</tr>
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<tr>
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<tr>
<td>Pred-G</td>
<td>TobraDex(ST)</td>
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<td>Loteprednol</td>
<td>Zylet</td>
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<tr>
<td>Zylet</td>
<td>Hydrocortisone</td>
</tr>
<tr>
<td>Cortisporin</td>
<td></td>
</tr>
</tbody>
</table>
**Neomycin, Polymyxin B, and 0.1% Dexamethasone**

- Excellent coverage against most bacteria
- Effective suppressor of inflammation
- Has been a time honored work horse in medical eye care
- Guard against aminoglycoside reactions and IOP increase by limiting use to <1 week
- Now a relatively obsolete combination
- Marketed as Maxitrol ophthalmic suspension and generically

**Tobramycin and Dexamethasone**

- Excellent coverage against most ocular pathogens with minimal concern of aminoglycoside toxicity
- Effective suppressor of inflammation
- Guard against prolonged use with dexamethasone
- Marketed as TobraDex Suspension and Ointment (tobramycin 0.3% and dexamethasone 0.1%) by Alcon, (suspension available generically)
- Also available as TobraDex ST (tobramycin 0.3% and dexamethasone 0.05%) by Alcon

**Tobramycin 0.3% and Loteprednol etabonate 0.5%**

- Excellent coverage against most ocular pathogens with minimal concern of aminoglycoside toxicity
- Safe, effective suppressor of inflammation
- Ideal adjunctive pulsed therapy for staphylococcal blepharitis
- Available in 5, and 10 ml bottles
- Marketed as Zylet Ophthalmic Suspension by B&L Pharmaceuticals

**Advanced Lid and Lash Cleansers**

- New eye care cleansers for lids, lashes, periorbital skin with extremely low toxicity
- Can be used for blepharitis, meibomitis, and other conditions of eyelids or eyelashes which often cause inflammation and discomfort
- Effective against broad range of pathogens usually found on the lids and lashes
  - Avenova (0.01% hypochlorous acid) by NovaBay
  - iLast (0.2% hyaluronic acid) by Paragon
  - HypoChlor (0.02% hypochlorous acid) by OCuSoft

**Loteprednol Effects on Dry Eye Disease**

- “Eyelid scrubs with warm compresses alone are sufficient to modulate the inflammatory process in moderate to severe MGD.”
- Systemic doxycycline has been effective in treating moderate to severe MGD
- Compared with eyelid scrubs with warm compresses alone, additional application of topical 0.5% loteprednol significantly decreased inflammation. There was noticeably improved BUT, corneal and conjunctival fluorescein staining, lid margin abnormality, meibum quality, expressibility, ocular irritation symptoms, and MGD stage.

**Loteprednol Effects on Dry Eye Disease**

- Using 0.5% loteprednol qid for one month was sufficient to control ocular surface inflammation
- “No cases showing a significant increase of IOP were detected.”
- “Pflugfelder and associates reported no clinically significant changes in IOP in any patient who received topical loteprednol 4 times daily for 1 month.”
- Summary: Loteprednol can provide greater anti-inflammatory effects and clinical benefits through reduction of ocular surface inflammation without serious adverse events.
Treatment of Blepharitis-Related Dry Eye

- “Antibiotic/steroid combination agents can play an important role in a rational, stepwise dry eye treatment plan.”
- “These drugs do not appear to alter meibomian gland secretions. However, they can effectively reduce both bacterial proliferation and inflammation of the lid margins.”
- Treat with “…combination antibiotic/steroids as needed on a pulsed basis as part of a long-term treatment plan for recalcitrant or recurrent blepharitis.”

Reference: Refractive Eyecare, December 2011

Obviously, in chronic conditions, an amino-glycoside combined with loteprednol would be the wisest choice.

Cliradex for Demodex

- A derivative of Tea Tree Oil ingredients
- Terpinen-4-ol (T4o) is the most demodexicidal
- For cleansing the face and eyelid skin
- Has a transient slight stinging, menthol-like sensation
- If ocular contact, rinse with saline or artificial tear
- Must keep eyes closed, and allow to air dry for 1 minute
- Try this once daily for 6-8 weeks (bid if severe)
- Available from BioTissue, Doral, Fl
- See www.cliradex.com for more information

Resistance and Unnecessary Antibiotic Use

- “Now that we know that unnecessary treatment fosters resistance, and resistance has become a significant threat to our patients, we cannot simply prescribe for any conjunctivitis on the grounds that it may be bacterial. Fortunately, there is now a test available that will detect adenovirus, the most common cause of viral conjunctivitis.”
- Dr. McDonald is referring to the RPS Adenodetector (www.RPSdetectors.com)

Reference: M. McDonald, Refractive Eyecare, September 2011

AdenoPlus™

- Convenient in-office, 10 minute immunoassay
- Detects all known serotypes of adenovirus
- Clinical Laboratory Improvement Amendment (CLIA) waived
- Has sensitivity of 90% and specificity of 96%
- Adenoviral infection is commonly a clinical diagnosis
- Helpful for challenging cases, and for primary care physicians
- CPT code 87809QW
- www.adenoplus.com

Clinical Perspective on AdenoPlus Immunoassay

- Adenovirus can cause: nonspecific follicular conjunctivitis, PCF, acute hemorrhagic conjunctivitis, and EKC
- Clinical diagnostic accuracy ranges from 40-70%
- AdenoPlus is a rapid in-office assay having 90-95% sensitivity and specificity
- AdenoPlus results correlates with disease infectivity (i.e. the intensity of the positive result line is directly proportional to the amount of antigen present)
- “In addition to the typical management strategy for adenovirus conjunctivitis, 2 novel treatments, topical povidone iodine and ganciclovir gel, have become more widely used.”
- www.nicox.com

Reference: JAMA-Oph, January 2013

Povidone - Iodine 5% ophthalmic solution

- Broad spectrum microbicde
- Indicated for “irrigation of the ocular surface”
- “Off label” use: Tx adenoviral keratoconjunctivitis
  - Anesthetize with proparacaine
  - Instill 1 or 2 drops of NSAID
  - Swab or rub excess over eyelid margin
  - After 1 minute, irrigate with sterile saline
  - Instill 1 or 2 drops of NSAID
  - Rx steroid qid x 4 days
- No reports in clinical trials of adverse reactions.
- Marketed as Betadine 5% ophthalmic prep solution (30 ml opaque bottle) by Alcon surgical
- CPT 99070 supply code
**Treatment Options - Ocular Allergy**

- Artificial Tears
- Mild Vasoconstrictors
- Decongestant / Astringents
- Vasoconstrictor / Antihistamines
- Antihistamines
- Antihistamine / Mast Cell Stabilizers
- Mast Cell Stabilizers
- Non-steroidal Anti-inflammatories
- Mild Corticosteroids
- Systemic Antihistamines
- Potent Corticosteroids
- Homeopathic Formulations

**Antihistamine/Mast Cell Stabilizer**

- Highly selective H1 receptor blockers with prolonged receptor binding
- Good mast cell stabilization
- All bid dosing, except Pataday and Alcaftadine qd

<table>
<thead>
<tr>
<th>Drug</th>
<th>Strength</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olopatadine</td>
<td>0.1%</td>
<td>(Patanol) (5 ml)</td>
</tr>
<tr>
<td></td>
<td>0.2%</td>
<td>(Pataday) (2.5 ml)</td>
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<tr>
<td></td>
<td>0.7%</td>
<td>(Pazeo) qd (2.5 ml)</td>
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<tr>
<td>Beopotastine</td>
<td>1.5%</td>
<td>(Bepreve) (5, 10 ml)</td>
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<tr>
<td>Epinastine</td>
<td>0.05%</td>
<td>(Elestat and generic) (5 ml)</td>
</tr>
<tr>
<td>Alcaftadine</td>
<td>0.25%</td>
<td>(Lastacaft) qd (3 ml)</td>
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<tr>
<td>Azelastine</td>
<td>0.05%</td>
<td>(Optivar and generic) (6 ml)</td>
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<tr>
<td>Ketotifen</td>
<td>0.025%</td>
<td>(generic and OTC)</td>
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<tr>
<td></td>
<td></td>
<td>(Claritin Eye) (5 ml)</td>
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<td></td>
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<td>(Zyrtec Itchy Eye) (5 ml)</td>
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<tr>
<td></td>
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<td>(Zaditor) (5 ml)</td>
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<td></td>
<td></td>
<td>(Alaway) (10 ml)</td>
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<tr>
<td></td>
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<td>(Refresh) (5ml)</td>
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<tr>
<td></td>
<td></td>
<td>(TheraTears) (5 ml)</td>
</tr>
</tbody>
</table>

**Non Pharmacological Treatment of Ocular Allergy**

- "The use of ATs as a control has been shown to have a drug effect of up to 50% to 70%, and this is considered to be a placebo effect. Because ATs may produce a real physical effect in the bonding of allergens to the ocular surface, this mechanism cannot be considered purely as placebo."
- "For occasional sufferers, such self-management, with reduced risks of drug interactions and patient expense, should be considered."

_Ophthalmology. January 2014_

**Intranasal Steroids for Ocular Symptoms in Allergic Rhinitis**

- In a randomized trial, intranasal steroids relieved both nasal and ocular symptoms.
  - Because intranasal steroids are the most effective medications for allergic rhinitis symptoms (especially congestion), guidelines recommend them as first-line agents for moderate-to-severe disease
  - As many as 85% of patients with seasonal allergic rhinitis also have ocular symptoms
  - For these patients, many clinicians prescribe oral antihistamines or ocular products rather than (or in addition to) intranasal steroids

Reference: _journalwatch.com, June, 2010_

**Anti-Viral Medicines**

- These are anti-herpetic drugs and are ineffective against the various adenoviral serotypes -

<table>
<thead>
<tr>
<th>Topical</th>
<th>Oral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trifluridine</td>
<td>Acyclovir</td>
</tr>
<tr>
<td>Ganciclovir</td>
<td>Valacyclovir</td>
</tr>
<tr>
<td>Zirgan</td>
<td>Valtrex</td>
</tr>
<tr>
<td>Viroptic</td>
<td>Famciclovir</td>
</tr>
<tr>
<td>Zovirax</td>
<td>Famvir</td>
</tr>
</tbody>
</table>
Topical Antiviral Options

### Trifluridine
- Old drug
- Indiscriminate expression
- Potentially toxic
- More frequent dosing
- Refrigerate until opened
- Solution (7.5 ml bottle)
- Viroptic and generic

### Ganciclovir
- New drug
- Infected cell-specific
- Minimally toxic
- Less frequent dosing
- No refrigeration needed
- BAK preserved
- Gel (5 gram tube)
- Zirgan by B+L

Valacyclovir vs. Acyclovir for Recurrent HSV

“One-year suppression therapy with oral valacyclovir (500-mg tablet daily) was shown to be as effective and as well-tolerated as acyclovir (400-mg tablet twice daily) in reducing the rate of recurrent ocular HSV disease.”


Study on Stromal HSK

- OD response rate, 6% - MD response rate 15%
- ALL: 95% treated epithelial keratitis correctly
- For stromal immune keratitis
  - 54% OD correct
  - 74% MD correct
  - 82% corneal subspecialist correct
- Correct = topical steroids with antiviral cover
- Correct use of oral antiviral prophylaxis for recurrences
  - 51% - OD, 60% - MD, 62% corneal subspecialist correct
- “Training” was most significant determining factor

**Reference:** Letters – Arch. Oph., December 2010

Preventing HSV Disease Recurrences

- Patients being treated with oral antiviral therapy were 9 times less likely than untreated patients to develop recurrent keratitis
- Recurrence rates: 27% at 1 year
  - 50% by 5 years
  - 57% by 10 years
  - 63% by 20 years
- Stromal disease is more likely to recur than epithelial disease
- Length of prophylaxis: Generally 5 disease-free years

**Reference:** Arch. Oph. January 2012

Pediatric Herpes Simplex Disease

- Herpes simplex virus (HSV) and herpes blepharoconjunctivitis (HSB) frequently misdiagnosed
- Recurrence of HSV more common in children (50%) than adults
- 30% of patients with HSK initially misdiagnosed
- Suspect HSV keratitis in recurrent unilateral keratoconjunctivitis with corneal neovascularization and decreased corneal sensation
- Peds patient HSV shows severe inflammation and stromal keratitis; in adults, most common manifestation is dendritic keratitis
- Tx: Oral ACV

**Reference:** Ophthalmology, October 2012 (Lin, Pavan-Langston, Colby)

Treatment and Prophylactic Dosages for Acyclovir in Children

<table>
<thead>
<tr>
<th>Age</th>
<th>Treatment Dose Thrice Daily</th>
<th>Prophylactic Dose Twice Daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants (up to 18 mos)</td>
<td>100 mg (2.5 ml)</td>
<td>100 mg (2.5 ml)</td>
</tr>
<tr>
<td>Toddlers (18 mos-3 yrs)</td>
<td>200 mg (5 ml)</td>
<td>200 mg (5 ml)</td>
</tr>
<tr>
<td>Young children (3-5 yrs)</td>
<td>300 mg (7.5 ml)</td>
<td>300 mg (7.5 ml)</td>
</tr>
<tr>
<td>Older children (6 yrs and older)</td>
<td>400 mg (10 ml)</td>
<td>400 mg (10 ml)</td>
</tr>
</tbody>
</table>

**Reference:** Ophthalmology, October 2012
Zostavax

- Vaccine for prevention of shingles in adults age 50 and older
- Marketed by Merck as Zostavax and is given as a single dose by injection
- Anyone who has been infected by chicken pox (more than 90% of adults in US) is at risk for developing shingles
- Contraindicated if Hx of allergy to gelatin, neomycin; Hx of acquired immunodeficiency states; pregnancy
- In landmark Shingles Prevention Study, Zostavax reduced risk of developing shingles by 51% (4 yrs of follow-up)
- Duration of protection after vaccination unknown

References: www.cdc.gov/vaccine/vpd-vac/shingles; FDA News Release, March 24, 2011 "FDA approves Zostavax vaccine to prevent shingles in individuals 50 to 59 years of age."

Zoster Disease: Young (<60) vs Old (>60)

- Overall peak incidence of HZO: 50-59 years of age
- Because of childhood chickenpox immunization, there will be an increased incidence of younger people developing HZ for a few decades
- Younger: secondary inflammation "flares" (pseudodendrites, keratouveitis) more common
- Older: neurotrophic keratitis in about 25%, therefore need to enhance tear film function
- Long-term oral antiviral and corticosteroid therapy may be indicated in many HZO patients

Reference: Ophthalmology, November, 2011

Antiviral Treatment for VZD

- Unlike stromal keratitis and uveitis, the dendriform lesions do harbor active virus, and respond to oral and topical antiviral therapy
- Such "late dendriform keratopathy" occurs in 2-10% of patients after HZO
- While corticosteroids are commonly used to treat the sequela of HZO, if the tissues do not respond as expected, perhaps trying a seven day course of oral antiviral could be tried.


Impact of Zostavax Vaccination: per one million vaccine recipients

- Could prevent:
  - 300,000 outpatient visits
  - 375,000 medication prescriptions
  - 9,700 emergency department visits
  - 10,000 hospitalizations
- "Shingles is a disease with potentially devastating systemic and ocular consequences and physicians, including ophthalmologists (optometrists) and primary care doctors, can and should recommend this vaccine to eligible patients."

Reference: AJO, May 2013

Zostavax Efficacy: How Long?

- "After 10 years, vaccination lost most of its power"
- "Efficacy against HZ incidence fell from 46% in year 7 to 14% in year 10 and was negligible among 1470 participants who were followed for the 11th year."
- "Vaccination at age 60 is unlikely to confer protection for the duration of a person’s life."
- We foresee new public health recommendations advising re-vaccination after about 8 years. This certainly sounds prudent to us.