Systemic Treatment of Dry Eye

Tracy Doll, O.D., F.A.A.O.
Pacific Dry Eye Solutions Coordinator
Located within Pacific University College of Optometry Pacific EyeClinic
Beaverton, Oregon
503-352-1699
Disclosure Slide

• I have been a paid “dry-eye consultant” for Allergan
• I have not been paid to endorse any product/technology
Ocular Surface Dryness is...

- A chronic condition
- A progressive condition
- A debilitating condition
Debilitating

- Foreign Body Sensation
- Redness
- Burning
- Stinging
- Reflex Tearing/”Crying”
- Fatigue
- Blur
Ocular Surface Dryness Categories

- Evaporative (EDE)
  - Meibomian Gland Dysfunction (MGD)
- Exposure
  - Poor Blinking
  - Nocturnal Lagophthalmos
  - Mechanical
Ocular Surface Dryness Categories

- Inflammatory (IDE)
  - Underlying Systemic Disease
  - Chronic Dryness leading to localized "auto-immune-like" response

- (Infective)
  - (Blepharitis)
Bottom line: they all work together

• It’s very rare that my patients experience an isolated category of dry eye disease
• Chicken or egg?

• As ocular surface dryness is multifactorial, it needs to be treated with multiple treatment modalities
There is no magic pill

• Systemic options should be combined with topical/ mechanical / anti-inflammatory treatments
Oral treatment for Dry Eye

- Omega-3 Fatty acids
- Doxycycline
- Azithromycin
- Salogen/Evoxac
Omega -3 Fatty Acids

- Humans do not make PUFAs intrinsically
- Must consume them in diet

- There are three major types of omega-3 fatty acids
  - α-linolenic acid (ALA)
  - eicosapentaenoic acid (EPA)
  - docosahexaenoic acid (DHA)

- Once ingested, the body converts ALA to EPA and then to DHA
- DHA is the most readily usable by the body, followed by EPA
Why Omega-3’s Work

• EPA and DHA are important precursors potent anti-inflammatory lipids called resolvins (Rvs) and protectins (PDs)

• Omega 3’s also smooths meibum secretions by making lipids more liquefied versus solid
Omega-3 Dietary Sources

• ALA:
  • flaxseeds, walnuts, pecans, hazelnuts, kiwifruit
  • Algae
  • Sea buckthorn oil

• EPA/DHA:
  • Cold water fishes (salmon, tuna, and herring), krill
  • Krill may be better at lifting mood?
  • Marine microalgae
FISH vs. PLANT

• Which is superior?
• ALA sources (plant) must first be converted to EPA
  • 3 independent reactions
• EPA then to DHA
  • 2-4 more reactions
Ethyl-Ester Format vs. Triglyceride

TG- Triglyceride
- Naturally occurring
- Costly - must find higher quality sources of marine life
- Better sources are needed to insure lack of contaminants
- More bio-availability of EPA and DHA in the body as detected in blood stream of human subjects and organs of animal models

EE- Ethyl ester
- Processed
- Less Expensive - Can refine lower quality fish oil to generate
- Removes contaminants (heavy metals)
- Needs extra processing by the liver to remove the ester component - to get the EPA/DHA out, this can lead to "fish-burp"
- The addition of lecithin which is a fat emulsifier reduces the fish-burp
- The Rx format of this for systemic hyperlipidemia does not interfere with omeprazole, warfarin or avorstatin

• There is clinical evidence for both forms that show effectivity in treating dry eye conditions.
• Take into consideration liver /gastro-intestinal status of the patient
How much to take: Monotherapy

• Monotherapy with fish-oil is recommended in the therapeutic range similar to what is recommended for inflammatory conditions
  • Between 1000-3000mg daily
  • What really counts is level of EPA/DHA found in the supplement.
  • Look for at least 600mg of combined EPA + DHA per each 1000mg (1g) capsule
Prescription Omega-3

- **LOVAZA**
  - Each 1-gram capsule of LOVAZA contains at least 900 mg of the ethyl ester format of omega-3 fatty acids sourced from fish oils
  - 465mg of EPA and 375mg of DHA
  - Suggested dose is 4 capsules daily

- **Vascepa**
  - Only contains EPA - 1 gram
  - Suggested dose is capsules daily

Cost of Rx Omega-3 = $$$
Not Yet Released

• Epanova
  • Triglyceride Rx form of Omega-3
  • Not yet available in the US

• Omtryg
  • Generic Lovaza
The Wrong Omega-6

- Avoid: Linoleic acid (LA)
  - Promotes inflammation on its pathway to arachidonic acid (AA)
    - AA is the precursor for the synthesis of the biologically active eicosanoids, the prostaglandins (PGs), thromboxanes (TXs), and leukotrienes (LTs)
  - LA: Particularly in vegetable oils (corn, soybean, peanut), grains
  - AA is easily found in American Diet:
    - Animal fats (chicken, eggs, beef, pork)- higher in organs
    - Grains
  - If we can’t get rid of LA, we need to create competition AA
The Competition: The Right Omega-6

• Go for: Gamma Linoleic acid (GLA)
  • GLA is converted to an anti-inflammatory substance called dihomo-gamma linolenic acid (DGLA) before GLA becomes AA.

• DGLA incorporates into the cell membrane faster than AA

• Diets enriched in GLA result in an alteration in the ratio of membrane arachidonate (immediate precursor is AA) to DGLA.

• Leads to creation of less inflammatory eicosanoids

• It also leads to the creation of a tear production-stimulating eicosanoid: prostaglandin E₁
Dietary Sources of GLA

• GLA is found mostly in rarer plant-based oils:
  • Hard to come across these easily in diet
  • Borage seed, evening primrose, acai berry, hemp and black currant seed oils
• The body needs help promote the conversion of GLA to DGLA
  • Magnesium, Zinc, Vit C, Vit B3.
  • Careful about vitamin deficiencies

• No Black Currant Seed Oil for anyone with ASA allergy
Balancing the Omegas

- Omega-3 and Omega-6 PUFAs compete for incorporation into cell membranes.
- Omega-3 PUFAs will compete with the enzymes that convert AA into the biological eicosanoids. It stops DGLA from becoming AA!

- Need at least 1:1 ratio of omega-3 to 6 to reduce inflammation in the body.
- One study showed that women with lower than a 1:15 omega-3:omega-6 ratio had a 2.5 x greater prevalence of dry eye.

- Take Aways:
  - Get the right Omega-6 PUFAs in the body: GLA
  - Get a combo dose of anti-inflammatory action by using omega-3 and 6
Formulations

- Different combinations of the omegas, vitamins and minerals have yielded improvement of signs and symptoms in the literature.
- The combinations have shown success with lower levels of fish oil
- EZ Tears (ONIT study)
- Maxitears
- HydroEye
<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Amount</th>
<th>Timing</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creuzot et al, 2006</td>
<td>71</td>
<td>Omega 3: 196 mg EPA/14 mg DHA Omega 6: 41 mg GLA/ 63 LA</td>
<td>6 months</td>
<td>Increased Schirmer’s, TBUT (not stat significant) Decreased corneal staining lissamine (not stat significant) Symptom improvement (nearly stat significant)</td>
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<td>Larmo et al, 2010</td>
<td>45 tx, 41 placebo</td>
<td>2 g of Sea Buckthorn oil Omega 3: 150mg Omega 6: 245mg Also Vit A, E, K, Omega- 7, Omega-9</td>
<td>3 months</td>
<td>Decreased osmolarity, Decreased symptoms: redness, burning</td>
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<tr>
<td>Brignole-Baudouin et al, 2011</td>
<td>61 tx, 66 placebo</td>
<td>Omega 3: 427.5 mg EPA /285 mg DHA Omega-6: 15mg Also Vit A, B6, B12, C, E, lecithin, zinc</td>
<td>3 months</td>
<td>Reduce the expression of the inflammatory marker in the conjunctival epithelium: HLA-DR &amp; CD11c Symptom improvement: burning, dryness, FB sensation, photophobia, stinging Improvement in BUT, corneal staining, Schirmer</td>
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<tr>
<td>Wojtowicz et al, 2011</td>
<td>36</td>
<td>Omega 3: 450 mg EPA/ 300 mg DHA and 1000 mg flaxseed oil- Also Vit E Thera Tears</td>
<td>3 months</td>
<td>Reduced symptoms Increased tear production and volume</td>
</tr>
<tr>
<td>Bhargava R, et al, 2013</td>
<td>264 tx, 254 placebo</td>
<td>Omega 3: 325mg EPA / 175mg DHA Daily In CL wearers</td>
<td>3 months</td>
<td>Increase in Schirmer and TBUT Decrease in symptoms</td>
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<td>Kangari, et al, 2013</td>
<td>33tx, 31 placebo</td>
<td>Omega 3: 360 mg EPA / 240 mg DHA</td>
<td>1 month</td>
<td>Increased TBUT and Schirmer’s Decrease in OSDI Score</td>
</tr>
<tr>
<td>Sheppard et al, 2013</td>
<td>38</td>
<td>Omega 3: 100mg EPA/ 70mg DHA Omega 6: 1570mg Also Vit A, B6, C, E and magnesium, lecithin -HydroEye</td>
<td>6 months</td>
<td>Decrease OSDI Score Maintained corneal surface smoothness Halted the number of inflammatory biomarker on conjunctiva (HLA-DR, CD11c integrin)</td>
</tr>
<tr>
<td>ONIT Study 2015</td>
<td>67</td>
<td>Omega 3:EPA 590mg/DHA 440mg Omega 6:900mg Also Vit A Vit D3, E, Tumeric, Green Tea Extract -Ez Tears</td>
<td>3 months</td>
<td>Increase: 38% OSDI, 45% TBUT, 50% Tear Meniscus Height Decrease: 33% in corneal staining, 50% decrease in corneal redness, lid inflammation</td>
</tr>
<tr>
<td>Korb, et al, 2015</td>
<td>13 tx, 13 placebo</td>
<td>Omega 3: EPA 528mg/DHA278mg Also Vit E, lid scrubs and lipid drop vs. warm compress</td>
<td>3 months</td>
<td>Increased in amount of secreting MG Improved Speed Scores/OSDI</td>
</tr>
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Doxycycline

- A tetracycline generic that has gotten very expensive ($$$)
- Low chronic does vary from 20mg to 100mg
- Initial dose 100-200mg daily x 1 month
- Tapered dose moves on from there
- Action is NOT due to its antimicrobial properties
  - Inhibits lipase, reduces free fatty acid production
  - Anti-inflammatory (MMP, phospholipase A2, collagenase)
Doxycycline

• Recall side effects and patients who are NOT candidates
  • Pregnancy/ pediatrics
  • Light sensitivity
  • Gastric upset
• Consider highly in patients with concurrent rosacea and seborrhea- related condition
• Recommend a good probiotic to go alongside
Case Report: Watch the Skin

History:
• 16 yo female with red, irritated eyes
• Medical History: acne, otherwise unremarkable
• Meds: none, denies sexual activity/ oral contraceptives
• Ocular History: eyelid “Bumps” that would appear in different locations in her eyelids. The last one was 1 month prior to the visit, treated with hot compresses
• Hobbies: hanging out with friends
Case Report: Watch the Skin

- Refraction: varies with a blink, but via retinoscopy: bilateral -0.50DS
- External: severe acne
- Lids/Lashes: moderate scurf, telangiectasia, multiple capped meibomian glands, low tear meniscus
- Cornea: mild PEE of lower 1/3 of the cornea bilaterally
- Reduced TBUT <5 seconds
- MGYLS: <5 glands on both inferior lid margins

https://www.epainassist.com/skin/acne-or-acne-vulgaris
Case Report: Watch the Skin

• Diagnosis: MGE with mild bleh
• Treatment strategies:
  • Least → Most invasive
  • Least → Most expensive
• Home therapy x 1 month: Fish Oil 1000mg, hot compresses, tea-tree oil- based lid scrubs yielded very little symptomatic relief
Advanced Diagnostics: Watch the Skin

• Meibography (left): Grade 2 gland loss of inferior eyelids, Grade 1 duct dilation

Example Healthy Glands: Should extend ¾ length of the eyelid
Advanced Diagnostics: Watch the skin

- LLT: Varies greatly from visit to visit, showing instability
  - OD: 86nm to as low as 27nm
  - OS: 93nm to as low as 27nm
- Incomplete Blink Measurement:
  - OD: 7/8 blinks incomplete
  - OS: 7/7 blinks incomplete
- NIKBUT:
  - 3.44s
  - 3.82s
Watch the Skin: Treatments

• In-office meibomian gland hand-expression, performed with cotton-tip applicators, Arita forceps, Mostrada paddle: yielded hard tooth-paste secretions, with patient difficulty tolerating treatment pain

• Two-month follow-up after expression (due to patient schedule), combined with continued lid therapy, and added Omega-3s and blink therapy yielded:
  • Mild improvement in symptoms
  • NIKBUT up to 5.74s OD and 6.98s OS
  • No return of chalazia/ hordeola
  • BUT still felt dry with vision fluctuations
Now what: Watch the Skin

• Lid hygiene, blinking, Omega-3 fatty acids and in-office gland expression are not enough to help this teenager

• Then there is this acne problem....
Doxycycline to the Rescue: Watch the Skin

• Once again confirmed lack of sexual activity and strongly educated on the risk of damage to an unborn baby should she become sexually active
• Educated on risks for stomach upset (take with food)
• Educated on risks for sun-sensitivity (wear sunscreen)
• Started on 100mg BID (total of 200mg) for 2 weeks
Doxycyline Treatment: Watch the Skin

• Patient returned with **dramatically** improved symptoms: SPEED Q down to 6
• Did admit to getting sunburn due to NOT wearing sunscreen as recommended
• There were a few capped glands, so hand expression was again performed and much better tolerated with yellow oil secretions this time.

• Tapered down to 50mg BID for 2 more weeks, then 50mg qd for 2 more weeks
• Then down to 20mg for 2 months
Current status: Watch the Skin

• 20mg maintenance dose
• White eyes
• No more vision fluctuations with stable low minus rx
• No more chalazion recurrences
• Facial acne is about 10% of face instead of 90%- only noticeable on the cheeks
• Increased NIKBUT: Now up to 5.83s OD and 8.09s OS
• Repeated gland expression with clear oil and reported as half as painful as initial expression
• Scheduled for 6 month check-in
Azithromycin is the new Doxy?

- 2014 study published BJO showed that oral azithromycin may actually be superior than doxycycline for MGD
  - 5 day azithromycin treatment (500mg qd on day 1, followed by 4 days of 250mg qd) regimen compared to a 1 month doxycycline 200mg qd
- Both groups showed equal symptom improvement BUT azithromycin yielded
  - Less surface staining and conjunctival redness
  - Less gastrointestinal side effects at second visit, 4% compared to 26%
  - Not in the study, BUT azithromycin is MUCH less in cost ($)

Bye bye Flora

• The Z-Pack is a wide spectrum antibiotic that will take out much of the flora of the digestive and genitourinary tract
• Warn female patients about the risk of yeast infections
• Always Rx with a probiotic
  • Still can’t eat enough yogurt to fully replace and much is lost in the stomach acid of the gut
Salagen

• Pilocarpine HCL
• Rx’d for Sjogrens patients to help combat dry mouth, but also can increase tear production
• A cholinergic agonist
• Side effects: Sweating, NV&D, rhinorrhea, increased salivation, increased urination, dizziness, miosis, can actually lead to more dryness, if water intake is not increased
Evoxac

- Cevimeline HCL
- Indicated, again, for dry mouth secondary to Sjogrens
- Also a cholinergic agonist
- Similar side-effects to Salagen
The impact of Other Systemic medications

• Many classes of medications can cause dry eye
• A thorough look at the patient’s current medication list can be very enlightening
• I do not recommend telling a patient to discontinue “out-of-scope” medications, but a discussion with the PCP/specialist could be warranted
Medication classes that cause dry eye

- Antihistamines
- Anti-depressants
- Anti-psychotics
- Anti-Parkinson
- Decongestants
- Diuretics
- Beta-blockers
- ORAL CONTRACEPTIVES
- ULCER MEDICATIONS
- INCONTINENCE MEDICATIONS
- RETINOIDS
- CHEMOTHERAPY
The Impact of Systemic Conditions

• Any condition affecting the mucous membranes, tear production or inflammation in the body
  • Sjogren’s Disease
  • Rheumatoid Arthritis
  • Thyroid disease
  • Lupus
  • Diabetes
  • Hormonal changes
The Power of Medical Laboratory Testing

• Depending on scope of practice in the individual state
• May be able to order via PCP/Specialist if warranted

• What to watch for: unexplained/diagnosed joint pain and fatigue, excessive thirst (water-bottle) in combination with punctate corneal erosions.
Sjo Test

- A group of blood tests that check for markers in the blood that are correlated with Sjögrens Syndrome
- No CLIA certification needed if approved by insurance for testing in your office
- More commonly done through independent labs (LabCorp)
  - Medical Lab bills patient directly
- 89% cumulative sensitivity and 78.2% specificity
Sjo Test

- New proprietary markers aimed at **early** disease detection
  - Salivary Protein-1 (SP-1)
  - Carbonic Anhydrase-6 (CA-6)
  - Parotid Secretory Protein (PSP)

- Includes the classic biomarker of ANA (antinuclear antibodies)
  - ANA itself will test positive in 70% of patients with Sjögrens
  - Most often used for suspect SLE patients
  - Could use the ELISA or IFA (titer) to measure

Sjo Test

- Rheumatoid factor (RF)
  - Another classic marker
  - Used for detecting rheumatoid arthritis (RA)
  - 20% of people with RA don’t test positive
  - Positive RF also in 1-5% of healthy people
  - Positive RF with other conditions:
Sjo Test

- Sjögrens Antibodies: SS-A/Ro and SS-B/La
  - More classic, later stage markers
  - A positive result is consistent with connective tissue disease, including Sjögren's syndrome, lupus an/or rheumatoid arthritis
  - SS-B is detected in approximately 15% of patients with Sjögren's Syndrome.
  - SS-B is present only if SS-A is also detected.
  - The presence of both antibodies strengthen the diagnosis of Sjögren's Syndrome.
Sjo Interpretation

• The more markers that test positive, the more likely the patient should seek care with a rheumatologist
• B&L offers an interactive interpretation tool: http://sjodiagnostictool.bausch.com/
Cost of the Sjo

• Medical labs will bill the patient directly
• Portions of this test battery can be out-of-pocket
• Classic biomarkers are often covered by insurance, while the novel biomarkers are not.
• The test will still usually cost the patient even with insurance.
• Not all medical labs can run this test, careful with HMOs
Systemic Treatment: Look –Listen- Feel

• Remember this from your old CPR class?

• **Look** at the medication list, the skin

• **Listen** in case history for joint pain, dry mouth, excessive fatigue

• If you **Feel** like something just isn’t right with the health of the patient, don’t be afraid to order medical laboratory testing.
There is no magic pill

• Systemic options should be combined with topical/mechanical/anti-inflammatory treatments

• For completeness, I’ve added the next slides to demonstrate the complexity of dry eye treatment.
Recommended Home Therapy: Evaporative

***These are possibilities. Each home care regimen depends on the patient’s individual disease state

- Modern Hot Compress and Oil-Based AT for comfort
- Tea-tree oil/ Hypochlorous Acid Based Lid Scrubs
- Blink Exercises/ Training
- Sleep Shields/ Gel or Ung PM/ Evaporative Eyewear
Recommended Home Therapy: Inflammatory

***These are possibilities. Each home care regimen depends on the patient’s individual disease state

- Aqueous-based AT for comfort
- Topical Anti-inflammatory Drops
  - Steroids
  - Restasis (cyclosporine)
  - Xiidra (lifitegrast)
  - Autologous Serum (ASED)
Recommended In-Office therapy

• ***These are possibilities. Each treatment regimen depends on the patient’s individual disease state

• Evaporative:
  • LipiFlow Thermal Pulsation
  • Hand Meibomian Gland Expression
  • Lid debridement

• Inflammatory
  • Amniotic membranes
Systemic Treatment of Dry Eye

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