

Not a Dry Eye in the House: the true story of a dry eye sufferer

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Overview

- ▶ **Patient Impact:**
 - ▶ Dry Eye Disease can be miserable—same utility score as angina
 - ▶ tale of three amazing ladies
- ▶ **Pathophysiology:**
 - ▶ Dry Eye Disease is a chronic, self-perpetuating downward spiral
 - ▶ Think: Donald Trump, the shameless self-promoter.
- ▶ **Causes:**
 - ▶ Dry Eye Disease is multifactorial
 - ▶ think Wagon Wheel, not linear
- ▶ **Treatment:**
 - ▶ Dry Eye Disease is treatable and the options are expanding
- ▶ **Case Studies:** Apply what we have learned

Patient Impact

- ▶ Suffering—golden, rewarding opportunity to relieve suffering
 - ▶ Utility scores
- ▶ Quality of Life: activities, work, lifestyle, family, stigma
 - ▶ Estimated costs: \$55 Billion total US burden. \$18,000 in lost productivity/year/severe pt
 - ▶ #3 reason for eye clinic visit (AAO 2011 survey #1 Refractive error, #2 Cataract)
- ▶ Prevalence:
 - ▶ 14-33% of US population has Dry Eye in some form or degree
 - ▶ 52.7% of Contact Lens wearers (Scaffidi and Korb)
 - ▶ 20-40% of patients in any given clinic day
- ▶ Vision: fluctuating VA, repeat MRs, repeat SCL fittings, unhappy premium IOL patients

Measures: OSDI, IDEEL, SPEED questionnaires

Why Are We Seeing So Much Dry Eye?

- ▶ Hormones—menopause, andropause, hormone replacements
- ▶ Diet—proinflammatory, leaky gut syndrome. Paleo diet helpful?
- ▶ Age
- ▶ Awareness
- ▶ Electronic devices
- ▶ Better diagnostics
- ▶ Effective treatments are now available

A Tale of Three Amazing Ladies

1. JB—60 year old female presenting with intolerable dry eyes, worsening since early menopause at age 38
2. HG—48 year old female presenting with red, burning and stinging eyes and intolerable air travel
3. LC—22 year old Nursing student from Anchorage with SCL intolerance and eye pain during her hospital shifts

Pathophysiology

- ▶ Immunology Nerd Heaven
- ▶ Dysfunctional, chronic, self-perpetuating downward spiral. Aberrant activation of natural defenses against pathogens.
- ▶ Bron et al Vicious Circle/Egocentric Broken Record/Death Spiral
 - ▶ Hyperosmolarity—inflammatory molecules—damage—early TBUT—increasing hyperosmolarity
- ▶ DEWS Report—more complicated explanation
- ▶ Natural History—Bron et al. *Ocular Surface* 2009 7:78-92
 - ▶ Aqueous Deficient Dry Eye—
 - ▶ 34% of the problem but 94% of the Products are directed here
 - ▶ Evaporative Dry Eye—Lipid Deficiency (Evaporative Dry Eye)
 - ▶ 65-85% of the Problem, but only 5% of Products address this

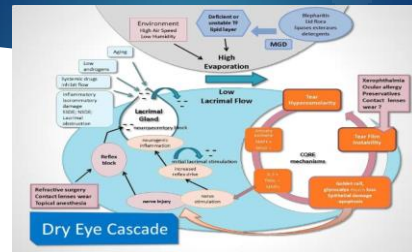
Temp et al. *Cornea* 2012, 31 (3):472-479

The Evolution of Dry Eye Disease



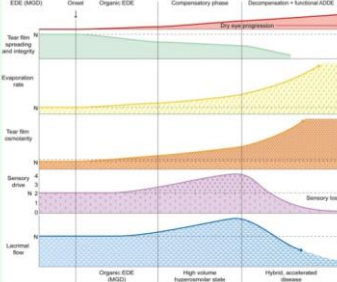
It is likely that with time the disease becomes self-perpetuating

Boss, MGD A-2 Slide



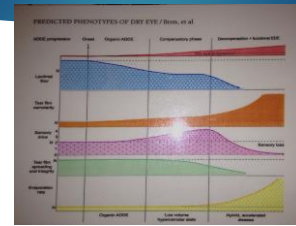
DEWS Report 2007

PREDICTED NATURAL HISTORY OF EVAPORATIVE DRY EYE



Boss et al., Ocul

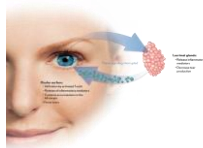
Aqueous Deficiency Dry Eye Natural History



Boss Ocular Surface 2009 7:75-92

Pathophysiology—Sleeping Giants, Paul Revere and Donald Trump

- Dry Eye is believed to have an inflammatory component, even if not clinically evident^{1,2}
- Inflammation is present in all severity levels and can cause decreased tear production¹⁻⁴



1. Belmont et al. Cornea, 2006; 2. Stern et al. Asian J Ophthalmol, 2005; 3. Nelson et al. Adv Ther, 2000; 4. Stern et al. Cornea, 1998; 5. Phylipides et al. Dry Eye and Ocular Surface Disorders, 2004.

Multifactorial: What causes Dry Eye?

- ▶ Environment—indoor or outdoor
- ▶ Lifestyle
- ▶ Mechanical—nocturnal lagophthalmos
- ▶ Allergies—seasonal, perennial, acute, chronic
- ▶ Medications—know your options
- ▶ Systemic Disease—later talk
- ▶ Neurotrophic—diabetic, post-herpetic
- ▶ Surgery—refractive surgery (LASIK, PRK), cataract surgery, cosmetic surgery

Environmental

- ▶ Humidity
- ▶ Temperature
- ▶ Wind: Nature
- ▶ Wind: Man-made
 - ▶ Office buildings
 - ▶ Big box stores
 - ▶ Airplanes
 - ▶ Forced air heating in homes
 - ▶ Fans in the bedroom
- ▶ AAO poster 2013: 400,000 US Veterans. Risk Factors for dry eye: #1 pollution, #2 high altitude, low humidity, higher winds

Lifestyle

- ▶ Work—Microsoft Valley. Puget Sound is tech heavy, computer use heavy
- ▶ Play/Sport—sunscreens (UV) and wind jacket (wrap around design) for your eyes. Sports sunglasses.
 - ▶ 7-eyes sunglasses (\$\$\$). Harley-Davidson stores, <http://www.7eye.com>.
 - ▶ Onion goggle design (\$20 at www.bedbathandbeyond.com).
- ▶ Diet
 - ▶ Inflammatory foods may lead to Leaky Gut Syndrome
 - ▶ Paleo diet
- ▶ Contact lenses
 - ▶ AV Oasys the most common lens I see used in young patients with Dry Eye.
 - Design problem leading to limbal stem cell deficiency?



Mechanical

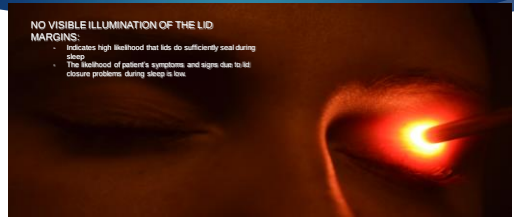
- ▶ Lid malposition—entropion, ectropion, lagophthalmos, exophthalmos
- ▶ Nocturnal lagophthalmos
 - ▶ Tremendously under diagnosed problem. Must address this.
 - ▶ Light leak at interpalpebral fissure when eyes "closed" and muscle light placed at superior sulcus
- ▶ Altered Blink Pattern
 - ▶ Computer—Time after Time (exposed cornea after TBUT, but prior to next blink)
 - ▶ Parkinson's—decreased frequency, incomplete, weak
- ▶ Altered Blink Mechanics
 - ▶ Floppy Eyelid Syndrome —Highly correlative (85-95%) with Obstructive Sleep Apnea. Picking up on this saves lives! High levels of MMP-9

Monica et al. SIO 2013 11(11) 1287-90

Complete Seal

NO VISIBLE ILLUMINATION OF THE LID MARGINS:

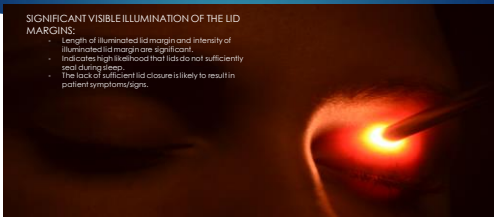
- Indicates high WetRead that lids do sufficiently seal during sleep.
- The WetRead of patient's symptoms and signs due to lid closure problems during sleep is low.



Incomplete Seal

SIGNIFICANT VISIBLE ILLUMINATION OF THE LID MARGINS:

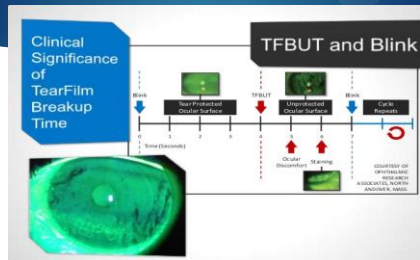
- Length of illuminated lid margin and intensity of illuminated lid margin are significant.
- Indicates high WetRead that lids do not sufficiently seal during sleep.
- The lack of sufficient lid closure is likely to result in patient symptoms/signs.



Easy Fix for Nocturnal Lagophthalmos

- ▶ www.eyebeco.com
- ▶ Silicone night shields plus lubricants (e.g. Refresh PM) solves the ongoing desiccating insult.
- ▶ Specifically designed for CPAP users, Sjogren's patients, nocturnal lag





Prescription Medications that Contribute to Dry Eye Disease

- ▶ Ocular Surface October 2011
 - ▶ Laminated medication list
- ▶ Broad categories of offending medications:
 - ▶ **Boo Hoo:** anti-depressants e.g. tricyclics, SSRIs
 - ▶ **Koo Koo:** anxiolytics, benzodiazepines, anti-psychotics
 - ▶ **Hi Hoo:** anti-hypertensives HCTZ and Beta Blockers most offenders. Suggest switching to CCB or ACE-I. Low cost generics in less offending classes.
 - ▶ **When Hoo:** hormone supplementation (70% increased risk), hormone manipulation or blockade (Lupron, Tamoxifen, aromatase inhibitors, Spinaloctone).
 - ▶ **You Hoo:** Cialis and Viagra

Systemic Diseases Associated with Dry Eye Disease

- ▶ Diabetes—neurotrophic Dry Eye. Loss of feedback of lacrimal functional unit
- ▶ HIV—direct infiltration of lacrimal gland
- ▶ Cancer—chemotherapeutics, hormone receptor blockers, radiation
- ▶ Thyroid Disorders—hyperthyroidism, hypothyroidism
- ▶ Autoimmune Disease
 - ▶ #1 Rheumatoid Arthritis
 - ▶ #2 Sjögren's Syndrome—11.6% of patients in a Dry Eye Referral Center prospective study

Mathews and Akpek EPOS Poster 2013

Dry Eye is the Most Common Presenting Symptom of Sjogren's Syndrome

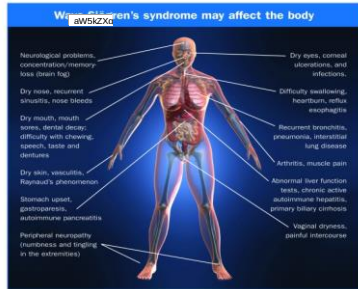
- ▶ **Prevalence:**
 - ▶ 4 million Americans, but only 1 million are diagnosed
 - ▶ Average time to diagnosis 4.7 years. 11.6% of patients in a Dry Eye Clinic prospective study (Apek)
- ▶ **Symptoms:**
 - ▶ Dry eyes, dry mouth, dry vagina
 - ▶ Fatigue, poor energy (Venus Williams, diagnosed in 2012—psychological impact)
 - ▶ Chronic bronchitis, chronic sinusitis, dental problems
 - ▶ Joint pain, joint swelling, rashes
 - ▶ **Lymphoma in 5% of Sjögren's patients (44x higher than controls)**

Dry Eye is the Most Common Presenting Symptom of Sjogren's Syndrome

- ▶ **Interval time from symptom onset to diagnosis:**
 - ▶ Average interval 5 years: lost time, lost tissue
 - ▶ Venus Williams: 2 years
- ▶ **Clinical suspicion:**
 - ▶ Dry eye findings out of proportion to risk factors
 - ▶ Family history of any autoimmune or Rheumatologic disorder
 - ▶ ROS
- ▶ **Testing:**
 - ▶ Traditional blood testing for SSA and SSB fraught with 33% false negative rate
 - ▶ New biomarkers detects Sjogren's syndrome much earlier and more efficiently

Ocular Complications of Sjogren's Syndrome

- ▶ Fourteen-year Retrospective Study 183 patients at a Sjogren's Institute.
- ▶ **One-third had extra glandular ocular findings**
- ▶ **Half of those had significant, vision-threatening disease:**
 - ▶ Conjunctiva: cicatrizing conjunctivitis
 - ▶ Corneal: ulcer, infiltration, melt, perforation
 - ▶ Uveitis: anterior, posterior, retinal vasculitis
 - ▶ Optic Nerve: optic neuritis
- ▶ Three minute Sjog test—early diagnosis and treatment might prevent these outcomes. Be proactive (e.g., the time to treat HTN is upon detection, not after the CVA).



In Office Sjogren's Syndrome Test

- ▶ Dramatically improves the sensitivity and specificity of Sjogren's syndrome testing.
 - ▶ Old SSA and SSb—33% false negative rate
 - ▶ New proprietary markers are a dramatic improvement in our ability to test for SS
 - ▶ SP-1 greatest specificity and sensitivity for early SS
 - ▶ Early detection—avoids tissue
 - ▶ Three minute test in clinic. Techs can do the finger stick (but not ODs in WA state). Patients readily participate with the blood collection. Results in 1-2 weeks.
 - ▶ Rheumatology consult
 - ▶ Systemic treatment benefits patient and makes Dry Eye treatment easier for the patient and ophthalmologist



Neurotrophic

- ▶ Infectious:
 - ▶ HSV, VZV, EKC
- ▶ RGP and SCL use:
 - ▶ Decreased corneal sensation. Disrupts the normal surface-lacrimal functional unit feedback loop
- ▶ Very high hyperosmolarity:
 - ▶ Corneal nerves increase in firing rate with increasing osmolarity until a certain tipping point, they stop firing (ARVO 2013)
- ▶ Autologous serum and ProKera helpful in this situation

Surgically Induced Dry Eye

- ▶ LASIK/PRK: Neurotrophic. LASIK-induced Neurotrophic Epitheliopathy (Wilson)
- ▶ Cataract surgery: chronic pain syndromes (pt C8)
- ▶ Acutely interrupts the anti-inflammatory signals (eg. Barry Manilow) from a healthy cornea:
 - ▶ VIP
 - ▶ Substance P

Diagnostic Aids to Clinical Exam

- ▶ Osmolarity: Tear Lab
- ▶ Stability: LipiView
- ▶ Meibomian Gland morphology: Meibomography
 - ▶ Oculus Keratograph
 - ▶ Tear Science—HDLT. High Definition Laser Transillumination
- ▶ Topography:
 - ▶ IOL calculations—dry eye induced topographical irregularities can change IOL calculations by 2 diopters! Start Dry Eye treatment 2-6 weeks before pre-op biometry (Trotter)

Tear Lab—know the Osmolarity

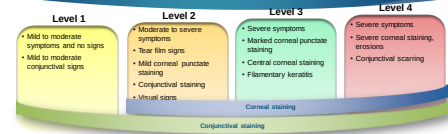
- ▶ Osmolarity is an independent driver of inflammation (DEWS 2007)
- ▶ As osmolarity increases, corneal nerve firing increases up to a point
- ▶ Asymmetric readings is characteristic of Dry Eye
- ▶ Values improve as treatment improves normal tear production
- ▶ 308 mOsm/L cut off for severe dry eye
- ▶ Sneak in from the side and verbally distract the patient to avoid reflex tearing and artificially low readings



Treatment—cyclosporin is the foundation

- **Characteristics:**
 - Pregnancy category C
 - Non-detectable in the bloodstream (HPLC <0.1 ng/ml)
 - Steroid-sparing, macrophage-function sparing, low side effect profile approach to long term management of chronic inflammation
- **ITE Guidelines**
 - Cornea 2006 Delphi panel of 17 Dry Eye Experts from around the world
 - Consensus on diagnosis, staging and treatment
 - Easy categorization
 - Used in study designs
 - Easy to dove tail current practice patterns based on emerging research

Use Dry Eye Consensus Guidelines Classify Patient Severity Level and Direct Treatment



- Experts recommended cyclosporin for Level 2, 3, and 4 patients whose tear production is decreased by ocular inflammation due to Chronic Dry Eye¹
- Punctal plugs are not recommended until Level 3¹

10

Medical Treatment

- **Environmental controls—**
 - lower computer screen—decrease surface area of evaporation
 - no vent air—tape off ducts
 - desktop humidifier—\$50 miracle from Amazon.com Air-O-Swiss
- **Control allergy and co-morbid conditions**
 - Blepharitis—AzaSite, **NO BABY SHAMPOO** Scrubs (formaldehyde, detergent)
 - Rosacea—topicals, doxycycline, IPL
- **Lubricants**—preservative free, gels, ointments, night shields (Bucky neoprene shield or Onyx Silicone shield www.eyescca.com)
- **Fish Oil**—Triglyceride formulation superior bioavailability (70% more)
 - Beware nardic and poor quality fish oils (taste and chew test, thyroid test)
 - Nordic Naturals Ultimate Omega—cod-liver fish oil that everyone else tries to imitate
 - Avoid Flax Oil (100 calories intake for only 10 calories benefit due to poor conversion from ALA to DHA and EPA in the gut)

Medical Treatment--continued

- **cyclosporin 0.05% (Restasis)**—cornerstone and foundation. Steroid-sparing. Macrophage-function sparing.
- **loteprednol etabonate (Lotemax Gel)**—superior product, 70% less BAK, glycerol and propylene glycol for superior lubrication. The corneas I see at the 6-8 week follow up have less staining.
- **Doxycycline**—low dose has potent anti-inflammatory activity (anti MMP-9 activity). Generic ok (doxycycline hyclate 50 mg QD x 6 months). Oracea is helpful but \$\$\$
 - Pitfalls: gut dysbiosis, yeast vaginitis, solar hypersensitivity, headaches, pseudotumor cerebri (papilledema with normal LP opening pressure and normal analysis)

Medical Treatment--continued

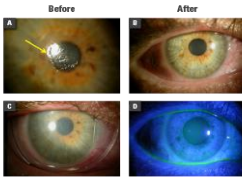
- Autologous Serum
 - Leiter's Pharmacy—high shipping costs
 - Local lab and Kelley-Ross Compounding Pharmacy
- Compounding Pharmacy
 - Topical testosterone/progesterone
 - Topical DHEA

Procedural Treatment of Dry Eye

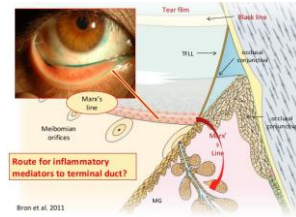
- Punctal Plugs or Cautery—
 - Avoid plugs, especially in uncontrolled inflammation and in patients with any seasonal or perennial allergy.
 - Think habitat restoration. Fresh mountain stream, not a Frog Pond!
- ProKera
- Amniotic membrane grafting
- Tarsorrhaphy—temporary tape, 2 week sutured, permanent
- Maskin Probing
- LipiFlow—finally something useful for MGD
 - MGD is 65-85% of the Problem, but only 5% of Products address this

ProKera—self retaining amniotic membrane contact lens

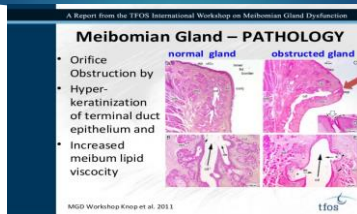
Dry Eye Syndrome, Exposure Keratopathy



Secondary MGD—Mechanism



MGD Histology



Maskin Probing for MGD

- ▶ Painful, awkward
- ▶ Anesthetics cause significant keratitis
- ▶ Mechanically dilating the duct obstructions
- ▶ Traumatic to meibomian glands and surrounding tissues

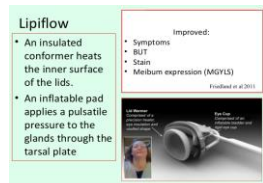
LipiView and LipiFlow

- ▶ Assess the degree of meibomian drop out and atrophy
- ▶ Assess the quality and quantity of the oil layer of the tear film by interferometry (oil slick appearance)
- ▶ Spa-like treatment
- ▶ 10-15 minute in office procedure

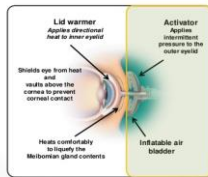


LipiFlow

- ▶ 10-15 minutes in office
- ▶ Comfortable procedure
- ▶ Eyes feel "lubricious"



LipiFlow® Mechanism of Action



Overview

- ▶ **Patient Impact:**
 - ▶ Dry Eye Disease can be miserable—some utility score as angha
 - ▶ Role of three amazing ladies
- ▶ **Pathophysiology:**
 - ▶ Dry Eye Disease is a chronic, self-perpetuating downward spiral
 - ▶ Think Donald Trump and Olympic Pan Figure Skating
- ▶ **Causes:**
 - ▶ Dry Eye Disease is multifactorial
 - ▶ Think Wagon Wheel, not linear
- ▶ **Treatment:**
 - ▶ Dry Eye Disease is treatable and the options are expanding
- ▶ **Case Studies:** Apply what we have learned

A Tale of Three Amazing Ladies

- ▶ 1. JB—60 year old female presenting with intolerable dry eyes, worsening since early menopause at age 38.
 - ▶ Chronic dry eye that worsened over the years. ITF stage 3.
 - ▶ Significant improvement over 4 years with Restasis, Lotemax, Oracea (long acting doxycycline), scleral fitted RGP's, 7 eyes, onion goggles, autologous serum and LipiFlow.
- ▶ 2. HG—48 year old female presenting with red, burning and stinging eyes and intolerable air travel
 - ▶ Family history: father had 'autoimmune disease' and two paternal aunts had Lupus. Severe seasonal allergies. Treating with ITF level 3 interventions. LipiFlow successful in adding relief.
 - ▶ Sjog test came back positive. Rheumatology consult pending.
- ▶ 3. LC—22 year old Nursing student with SCL intolerance and eye pain during her hospital shifts
 - ▶ Environment (AK childhood, hospital work) SCL overuse. Responding to medications. Sjog testing pending. Incomplete blinker and nocturnal lagophthalmos. Moisture chambers.

Conclusions

- ▶ Dry eye is a chronic, multifactorial, self-perpetuating disease that must be addressed. Turn an immunopathologic dysfunction into an immunotolerant harmony.
- ▶ History
- ▶ Medications
- ▶ Lifestyle
- ▶ Patient Education
- ▶ Treatments/Medicines
- ▶ Procedures

Future of Dry Eye

- ▶ **New medications**
 - ▶ **Lifitegrast**: LFA-1 blockade. Prevents T-cell modulation. Very rapid onset of action in treating dry eye. Very high safety profile.
 - ▶ CF-101: an anti-inflammatory steroid. First-in-class small molecule targeting the A3 adenosine receptor
 - ▶ EGP-437: corticosteroid solution tailored for iontophoresis
 - ▶ Mucin Secretagogues: Diquafosol approved in Japan
- ▶ **New Devices:**
 - ▶ Blephasteam—France, Belgium
 - ▶ High Definition Laser Transillumination—exquisite definition of meibomian gland anatomy. Somewhat like an OCT for the meibomian glands.
- ▶ **New Approaches**
 - ▶ Biochemical manipulation of meibum production
 - ▶ Cytokine profiling to tailor the anti-inflammatory approach
 - ▶ Autologous Stem Cell Therapies/PRP

Thank you

- ▶ Laura M. Periman, MD
- ▶ Redmond Eye Clinic
- ▶ 16150 NE 85th Street, Suite 206
- ▶ Redmond, WA 98052
- ▶ www.redmondeyeclinic.com
- ▶ 425 885 3574 clinic
- ▶ 425 881 0230 fax
- ▶ 206 234 9846 cell
- ▶ lperiman@comcast.net