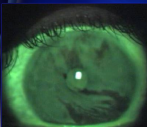


OSD Grand Rounds: Thinking Outside the Box

COPE ID # 24652-AS
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 Private Optometric Practice
 Gadsden, AL

Chief Optometric Editor
 Optometry Times magazine

Changing Paradigms in Dry Eye



FORMER DEFINITION¹

Dry Eye or Keratoconjunctivitis Sicca is a disorder of the preocular **tear film** caused by **tear deficiency or excessive tear evaporation** that results in damage to the interpalpebral ocular surface and is associated with symptoms of ocular discomfort.

Report of the National Eye Institute/Industry Workshop on Clinical Trials in Dry Eye (IAO), 1995, 21:201-30.

Ocular Surface Disease

- The most common clinical problems affecting the ocular surface include:
- Dry Eye Disease
- Blepharitis
- Allergic Eye Disease
- These conditions often co-exist
 - Can share contributing pathology
 - Similar signs and symptoms


Speaker Disclosures

- Alcon Speakers Bureau
- B&L KOL Speakers Bureau
- Inspire Speakers Bureau
- The author has conducted clinical studies for CIBA and Bausch & Lomb

Changing Paradigms in Dry Eye

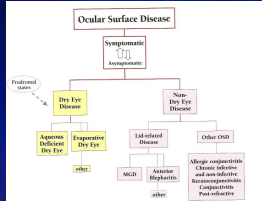
NEW DEFINITION² (Dry Eye Workshop)

Dry Eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by **increased osmolarity** of the tear film and **inflammation** of the ocular surface.



1. U.S. Bhawanji, C. Baum, J. et al. The definition and classification of dry eye disease: Report of the Definition and Classification Subcommittee of the International Dry Eye Workshop (2007). Ocular Surf 2007; 5(2): 75-92.

OSD Etiology & Pathophysiology



Report of Dry Eye Workshop, DEWS 2007 Report, Ocular Surf 2007; 5(2): 111.

- "Dry Eye and Ocular Surface Disease is the one disease process optometry can make all it's own."

Dry Eye Etiology & Pathophysiology

Major Etiological Causes of Dry Eye

Report of the International Dry Eye Workshop, DEWS 2007 Report, Ocular Surf 2007; 5(2): 77.

Why Treat Ocular Surface Disease?

- "many millions" is an accurate generalization
- Can affect most all age groups
- 5% to 35% of persons at various ages have moderate to severe dry eye symptoms *
- Most common reason patients d/c contact lenses
- "It is estimated 40% of ophthalmic visits in the US involve dry eye." ¹

* Ocular Surf 2007; 5(6).

Prevalence of Dry Eye

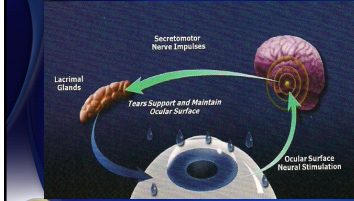
Summary of Studies of Dry Eye Prevalence in the US

Study	N	Age	Criteria	Prevalence	Reference
Wisconsin	3722	48-91	Self-reported	14.4 %	Moss, 2000
Melbourne	926	40-97	>2 signs	7.4%	McCarthy, 1998
Maryland	2520	65-84	Symptoms +1 sign	3.5%	Schein, 1997
Women's Health	39,876	49-84	Severe symptoms or clinical diagnosis	7.8 %	Schaumberg, 2003

Although, percent of individuals who experience signs and symptoms of dry eye at one time or another due to environmental factors = 100%

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Dry Eye Etiology & Pathophysiology



Adapted from Nelson JD et al. Adv Ther 2000; 17: 84-93

Human Tear Osmolarity Recorded in Studies Reported in the Literature

Study	Test	Normal Subjects (n)	KCS (Sum of Subtypes)
McMahon et al.	FPD	304.8 ± 5.033	329.4 ± 5.708
Gilbard et al.	FPD	304.8 ± 8.4 (31)	343 ± 12.3 (36)
Sory and Ball	VP	310 ± 5.7 (6)	—
Gilbard and Farnia	FPD	—	363 ± 7.7 (20)
Furber et al.	FPD	304.4 ± 7.2 (219)	326.6 ± 17 (123)
Fazio	FPD	302 ± 0.95	320.4 ± 0.95
Gilbard	FPD	304.6 ± 3.283	334 ± 1.0 (31)
Madson et al.	FPD	303.6 (0/72)	313.7 ± 1.5 (146)
Updegraves et al. ¹⁴	Con	296.4 ± 30.1 (7)	324 ± 4.1 (16)
Average tear osmolarity	All	302.2 ± 5.7 (835)	326.9 ± 2.1 (621)

Data were recorded in tearing point depression (FPD) and vapor pressure (VP) osmolarity tests in normal subjects and those with all types of keratoconjunctivitis sicca (KCS).

Nelson, et al. Invest Ophthalmol Vis Sci 2006; 47: 4399-4315.

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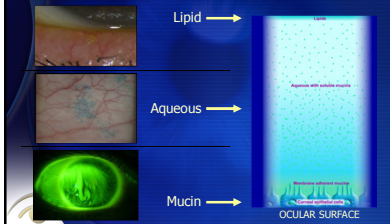
Epidemiology

- Women's Health Study (WHS) & Physician's Health Study
- ~ 3.2 million women & 1.05 million men ≥50 yoa have clinically important dry eye^{2,3}
- 5.7% to 9.8 % of women ≥50 yoa have chronic dry eye²
- Prevalence increases with age

1. Schaumberg et al. Prevalence of dry eye syndrome among US women. Am J Ophthalmol 2003; 136: 319-326.
2. Gilbard et al. Epidemiology of major cornea and ocular diseases. In: The Cornea. Scientific Foundations & Clinical Practice.

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Tear Film



Tear Hyperosmolarity

- "Tear hyperosmolarity is regarded as the central mechanism causing ocular surface inflammation, damage and symptoms, and the initiation of compensatory events in dry eye"¹
- Dry eye patients have higher tear film osmolarity
- Osmolarity is a function of tear flow rate & evaporation
- Hyperosmolarity decreases goblet cell density

1. GES Report. Ocular Surf 2007; 5(1): 86.

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Mostly Consistent - Risk Factors

- Older age
- Post menopausal estrogen therapy
- Smoking 3 and Omega 6 fatty acids
- Medications
- Anticholinergics
- Chronic disease states
- Radiation therapy
- Hemopoietic stem cell transplantation
- Vitamin A deficiency
- Hepatitis C infection

Susceptible - Risk Factors

- Asian race
- Medications
- TCA
- SSRI
- Diuretics
- Systemic steroids
- HEPATIC INFLAMMATION
- Systemic chemotherapy
- ECG and PAF
- Menstruation
- Low humidity environments
- Smoking
- Dietary dysfunction

Protective - Risk Factors

- Cigarette smoking
- Allergies
- Anti cholinergics
- Anesthetics
- Anticholinergics
- Alcohol
- Menopausal
- Acute toxin injection
- Acute
- Oral contraceptives
- Progesterone

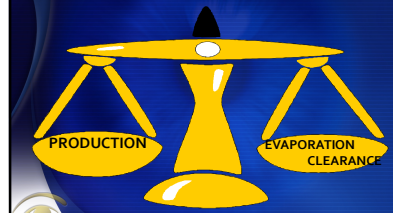
Source: American Academy of Ophthalmology Preferred Practice Pattern: Dry Eye

Dry Eye Etiology & Pathophysiology

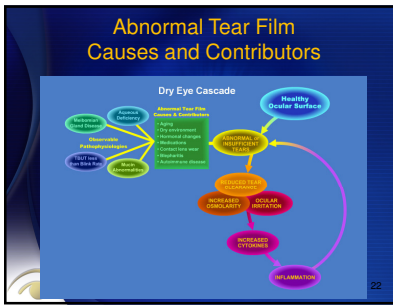
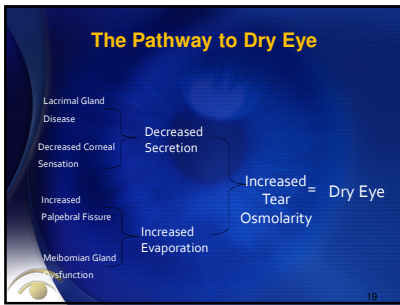
- Mean 10% increase in tear film osmolarity
- Increased expression of HLA class II antigens
- Decreased conjunctival goblet cell density
- Increased conjunctival & lacrimal gland CD4 T-cell infiltration

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Ocular Environment Balance

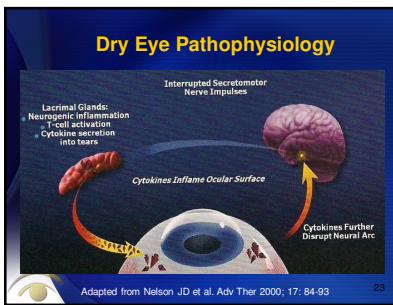
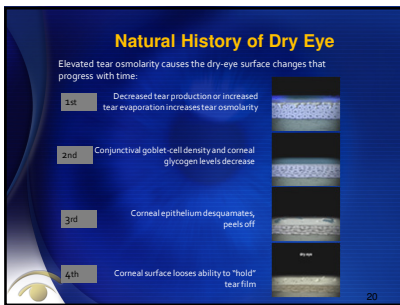


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Patient History

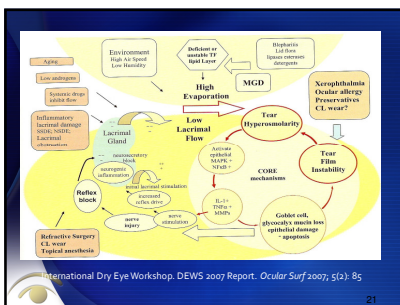
- Dry eye is a symptom-based disease
- Chief complaint !
- Symptoms ≠ signs !



Dry Eye Diagnostic Tools - Symptoms

Ocular Irritation

- Discomfort
- Dryness
- Burning
- Stinging
- Grittiness
- Foreign Body Sensation
- Photophobia
- Light Sensitivity
- Excessive Tearing
- Blurred Vision



Tear Osmolarity & Dry Eye

- Tear osmolarity is considered "the central mechanism causing ocular surface inflammation, damage and symptoms, and the initiation of compensatory events in dry eye."
- Lemp MA. Advances in understanding and managing dry eye disease. *Am J Ophthalmol* 2008; 146 (3): 350-356.

Dry Eye Questionnaires

- Ocular Surface Disease Index (OSDI)
- Rapid, repeatable, and gives a quantifiable result
- Validity has been substantiated by clinical research⁵
- Helpful not only diagnostically, but also as a measure of therapeutic progress

Ocular Surface Disease Index

OSDI: Symptoms, Functions, Environmental Triggers

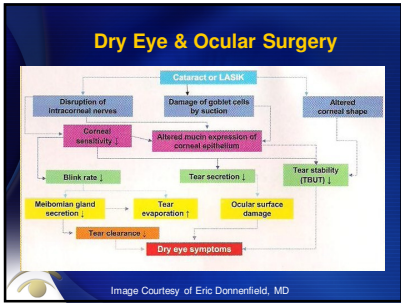
OCULAR SURFACE DISEASE INDEX
Please answer the following questions by checking the box that best represents your answer. Have you experienced any of the following during the last week?

	All of the time	Most of the time	Half of the time	Some of the time	None of the time
1. Eyes that are sensitive to light?					
2. Eyes that are itchy?					
3. Eyes that are watery?					
4. Eyes that are dry?					
5. Eyes that are irritated?					
6. Eyes that are sore?					
7. Eyes that are red?					
8. Eyes that are blurry?					
9. Eyes that are tired?					
10. Eyes that are uncomfortable?					
11. Have you ever had trouble seeing?					
12. Have you ever had trouble seeing at night?					

Influential Medications in Dry Eye

Systemic medications that can dry the eye:

- β-Adrenergic-blocking, Anti-anginals and Anti-hypertensives (e.g. Atenolol, Propranolol)
- Tricyclic Anti-depressants (e.g. Amitriptyline, Doxepin)
- Oral Anti-histamines (e.g. Loratadine, Clemastine, Hydroxyzine)
- Alkylating Immunosuppressives (e.g. Busulfan, Cyclophosphamide)
- Diuretics (e.g. Triamterene)



Dry Eye Questionnaires

- "The best-validated screening definition of dry eye probably comprises these three ??"²
- "How often do your eyes feel dry (not wet enough)?" (constantly, often, sometimes, never)
- "How often do your eyes feel irritated?" (constantly, often, sometimes, never)
- "Have you ever been diagnosed by a clinician as having dry eye syndrome ?"

Patient History

- Chief complaint
- Medications
- History of Refractive Surgery/ Contact Lens Wear

Diagnostic Tools

Environmental Factors

- Visual Tasking - Computer use
- Systemic Medications - Anti-histamines
- Foods/Drink - Alcohol
- Arid Conditions - Southwest
- Windy Environments - Air conditioning, Forced heat
- Pollutants - Exhaust, smoke, smog

Dry Eye & Contact Lenses

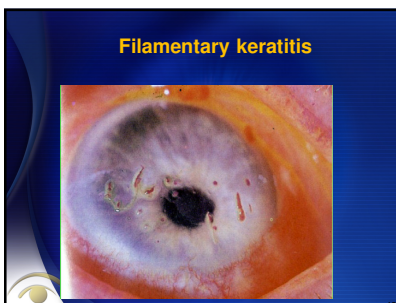
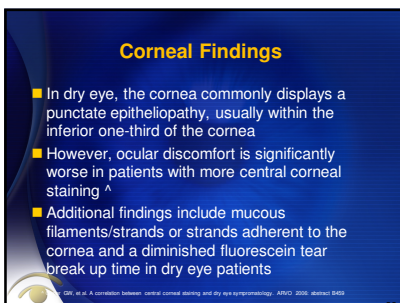
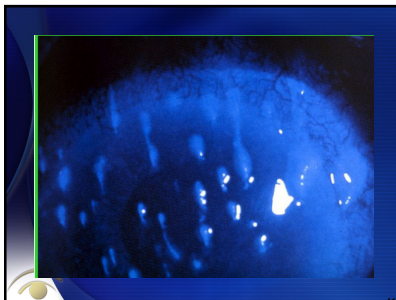
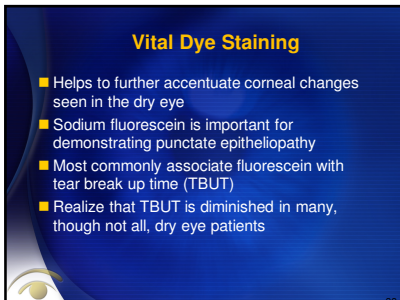
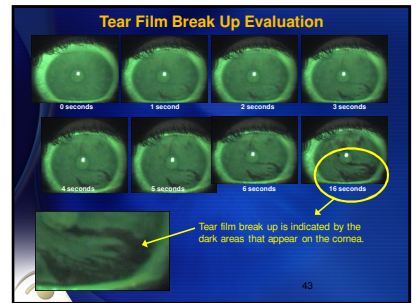
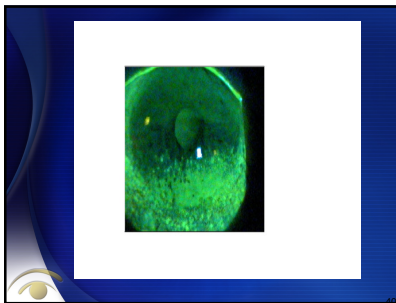
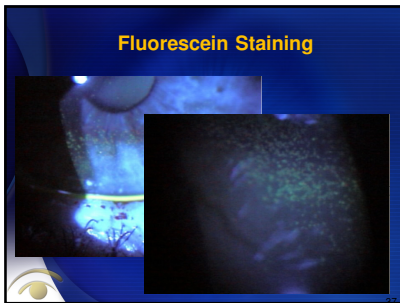
- Single most common complaint among contact lens wearers
- #1 reason patients d/c contact wear
- ~ 34% of patients d/c wear at least once, most frequently because of dry eye symptoms *

DTS Study Group Most Commonly Used Diagnostic Tests

Diagnostic Tests	Respondents Regularly Using Them (%)
Fluorescein staining	100
Tear break-up time	94
Schirmer test	71
Rose bengal staining	65
Corneal topography	41
Impression cytology	24
Tear fluorescein clearance	24
Ocular Surface Disease Index Questionnaire	18
NIHFD-25*	6
Tear osmolarity	6
Conjunctival biopsy	6

*NIHFD-25: National Eye Institute Vision Function Questionnaire-25.

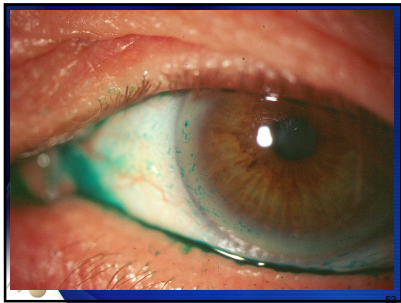
Behrens et al. Dysfunctional Tear Syndrome: A Deeper Approach to Treatment Recommendations. Contact 2006; 25 (8): 900 - 907.



Symptomatic TFBUT (SBUT) or Non-Invasive Tear Break Up Time (NIBUT)

- Improved understanding of TFBUT and its relationship to ocular awareness allows for simple non-invasive test
- Procedure
 1. Obtain a stop watch or clock
 2. Blink 2 times then stare straight ahead
 3. Record time between last complete blink and the first sensation of ocular awareness
 4. This time (in seconds) is the NIBUT

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Vital Dye Staining

- Rose Bengal and Lissamine Green stains reveal damaged areas of epithelium in both the cornea and conjunctiva
- More importantly, these dyes will stain mucin strands and filaments that may be difficult to distinguish otherwise
- No clinical difference between these two dyes



Lissamine Green Staining



But you have to remember...

- " Vital dye staining of the ocular surface, although a measure of damage to the ocular surface, is not specific for dry eye disease, occurs in a substantial percentage of normal subjects and is present in a minority of patients with mild to moderate dry eye disease"

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Tear Volume Testing

- There are few good ancillary tests available for diagnosing dry eye
- One established test specifically for dry eye is tear volume testing via Schirmer strips or phenol red impregnated threads (i.e. ZoneQuick® test)



Interferometry is the Ophthalmoscope of the Lipid Layer

The Schirmer Test

Purpose: Measures quantity of aqueous secretion
Procedure: Filter paper placed under lower eyelid measures volume of tears

Image showing a person's eyes with Schirmer test strips placed under the lower eyelids.

PRTT vs. Schirmer's

- Agreement between the PRTT and Schirmer test was highly significant: 79.8% of subjects had similar quantitative results "
- Drying out the lacrimal meniscus before proceeding to the PRTT provides a highly sensitive & specific method for dry eye diagnosis
- Since the PRTT causes less discomfort and is quicker than Schirmers, it could be used more frequently in a daily practice for the screening of dry eye syndrome "

Quantification of tear film lipid layer thickness (LLT) according to dominant color of interference pattern

Korb DR et al. Tear Film Lipid Layer Thickness as a Function of Blinking. Cornea 1994;13(4): 354-359.

Color	LLT (nm)
Blue	180
Blue/Green	165

Image showing a tear film with interference fringes. A caption below reads: "Wave pattern of predominantly blue color interference fringes; some brown waves are also visible."

Blue interference fringes: thickest visible lipid layer (165-180 nm)

Schirmer vs. Zone-Quick

- The Schirmer test is the preferred quantitative procedure for dry eye research, though it is not as useful clinically
- Schirmer test is somewhat lengthy (5 minutes) & uncomfortable for the patient
- Schirmer results may be quite variable
- Phenol Red Thread Test (PRTT) is much faster (15 seconds) & more comfortable
- PRTT has been shown to be comparable to the Schirmer test in clinical studies.

Other tests used to diagnose dry eyes

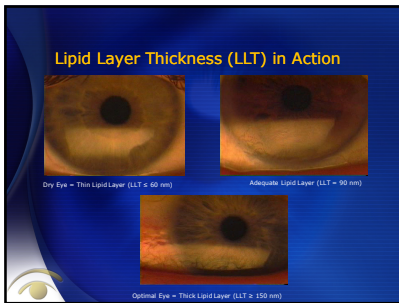
- Osmometers
- Inferometry
- Lactoferrin Microassay

Image showing a lactoferrin microassay kit and an interferometry device.

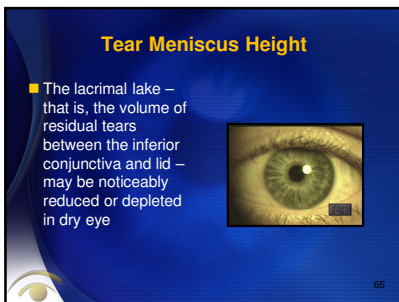
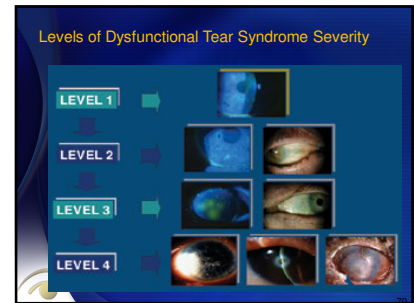
Interferometry - Lipid Layer

Color	LLY (nm)
Blue	180
Yellow	90
White	≤ 60 nm

Image showing two eyes with interference patterns. Arrows point from the table to the corresponding colors in the images.



- "This lack of concordance between signs and symptoms presents a problem not only in the diagnosis of the disease, but also in assessment of severity and in the design of clinical trials to evaluate the clinical efficacy of drugs."
- Michael A. Lemp. Advances in understanding and managing dry eye disease. *Am J Ophthalmol* 2008; 146 (3): 350-356.



Dry Eye Management

- Dry eye is a chronic disease without a cure
- Management is often frustrating for both the patient & the clinician

Therapeutic Approaches

- **Stabilize the tear film** (subjective)
- **Increase lubricity** - decrease coefficient of friction
- **Increase aqueous production**
- **Decrease inflammation**
- Create a more **normal tear film** environment for epithelial healing

Manage a patient's dry eye based on the drop and frequency that best fits their particular form of the condition.

www.eyeserver.com

Which Patients Are Candidates for Therapy?

- No single method for determining if a patient is a candidate for dry eye therapy
- Criteria for starting therapy may include
 - Patient symptoms
 - Corneal & conjunctival staining
 - Decreased TBUT
 - Decreased tear meniscus height
 - Schirmer/ PRTT scores
- Patient symptoms & clinical signs should be considered when deciding on therapeutic intervention

Delphi Panel Consensus for Dry Eye Management

SEVERITY	SIGNS AND SYMPTOMS	RECOMMENDED TREATMENT
1	Mild to moderate symptoms; no signs Mild to moderate conjunctival	Patient counseling, preserved tears, environmental management, use of hypoallergenic products, water
2	Moderate to severe symptoms Tear film signs Mild corneal punctate staining Corneal staining	Unpreserved tears, gels, ointments, cyclosporine A, secretagogues, topical steroids, nutritional support (flax seed oil)
3	Visual symptoms Moderate to severe conjunctival staining Severe corneal staining	Autologous serum eye drops
4	Severe symptoms Severe corneal staining Severe conjunctival staining	PO anti-inflammatory therapy, PO cyclosporine, moisture goggles, scleral lenses, punctal occlusion, tarsal massage

Current OTC Dry Eye Therapy

- Contain various active and inactive agents
- Patients view products as interchangeable
- Differing mechanisms of action and efficacies
- A need exists for clear sub-categories

Qualities of an Ideal Dry Eye Product


- Minimal blur
- Comfort upon instillation*
- Ability of product to spread evenly over the cornea quickly and efficiently
- Prolonged retention time for extended efficacy*
- Objective and subjective improvement in patient signs and symptoms

*Report of the Definition and Classification Subcommittee of the International Dry Eye Workshop (2007), Ocular Surface 2007;5:185.

Advanced Technology

Manufacturer: Alcon, Inc.

- SYSTANE® ULTRA Lubricant Eye Drops
- Active Ingredients: Polyethylene Glycol 400, Propylene Glycol
- Inactive Ingredients: boric acid, HP-Guar, potassium chloride, aminomethylpropanol, purified water, sodium chloride, and sorbitol
- Preservative: POLYQUAD®



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Intelligent Delivery System

Controlled Viscosity in Bottle

Stronger Elasticity in Eye

Sorbitol

Borate competes with Sorbitol for cross-linking Lower Viscosity

Sorbitol Dilution

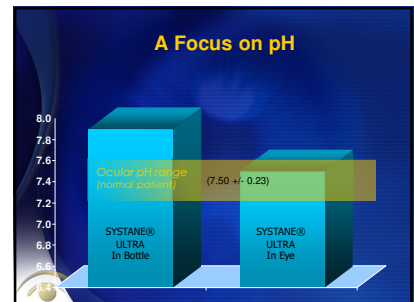
Cross-Links increase as Sorbitol is diluted Increased Elasticity

Categories of Lubricant Eye Drops

- Cellulose Derivative Products
- Glycerin Containing Products
- Oil-Based Emulsion Products
- Polyethylene Glycol and Propylene Glycol Products

Composition Comparison

Ingredients	SYSTANE®	SYSTANE® ULTRA
Polyethylene Glycol	✓	✓
Propylene Glycol	✓	✓
HP-Guar	✓	✓
Boric Acid	✓	✓
POLYQUAD®	✓	✓
Sodium Chloride	✓	✓
Potassium Chloride	✓	✓
Calcium Chloride	✓	✓
Magnesium Chloride	✓	✓
AMP (aminomethylpropanol)	✓	✓
Sorbitol	✓	✓
	7.0	7.9




Challenges with Current OTC Formulations

Current Problems

- Viscosity & Elasticity are out of balance
- ↑ viscosity = ↑ blur
- ↓ elasticity = ↓ corneal retention time

Goal

- Strike a balance between viscosity and elasticity



Mechanism of Action

- HP-Guar, Sorbitol and Borate interact to provide a delivery system to the eye
- The critical mechanism of action elements of SYSTANE® ULTRA Lubricant Eye Drops include:
 - HP-Guar and borate interaction
 - pH
 - Sorbitol
 - Divalent ions in the tears

Multiphasic MOA With Dynamic Structure

- In the bottle
 - Intelligent delivery system
 - Loosely cross-linked droppable gel



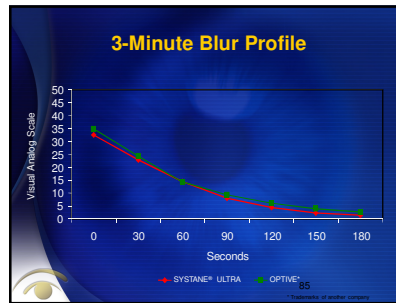
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Multiphasic MOA With Dynamic Structure

Polyethylene glycol 400 (PEG)
 Propylene glycol (PG)
 HP-Guar
 Borate
 Sorbitol

Viscosity decreases Matrix rebuilds and elasticity increases Extended surface protection

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Tear Electrolytes

Normal Electrolyte Concentration in Human Tears (mMol/Liter)	
Na	132
K	24
HCO ₂	32.8
Ca	0.8
Mg	0.61

Lee H, et al. Ophthalmologica 2005; 219 (3): 142-146

Evaluation of Blur SYSTANE® ULTRA Lubricant Eye Drops vs. OPTIVE®

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Int'l Dry Eye Workshop

- For patients with moderate to severe dry eye disease, the absence of preservatives is of more critical importance than the particular polymeric agent used in ocular lubricants.
- Solutions containing electrolytes and/or ions have been shown to be beneficial in treating ocular surface damage due to dry eye.
- Hypo-osmotic artificial tears

Wong, et al. Ocular Surface 2007; 5(2): 165-166

Downsides of TRT

- A plethora of OTC commercial products
- Drugstore.com lists 50 products for "artificial tears"
- Tears have a limited, palliative effect (only lasting 5 minutes in some studies)
- Chronicity of use leads to decreased patient compliance
- Preservatives may have toxic effects on the ocular surface
- Avoid BAK-preserved AT for chronic use

Study Design

- Randomized, double masked, controlled clinical study
- Two period crossover design
- Single drop instillation per period
- 20 patients, previously diagnosed w/dry eye
- Test articles
 - SYSTANE® ULTRA Lubricant Eye Drops
 - OPTIVE® Lubricant Eye Drops

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Osmolarity of Various Artificial Tear Solutions

Product	Osmolarity
TheraTears	181
Refresh Endura	235
Systane	245
OcuFresh	252
Tears Natural Free	266
Bion Tears	279
Moisture Eyes	284
OcuCoat	293
Vision Tears	298
Refresh Plus	318
Similasan Eye Drops #2	334
Viva Drops	334
Similasan Eye Drops #1	341

↑ Hypo-Osmolar
 ↓ Hyper-Osmolar

Wong, Margana, Quintana S, et al. Comparison of osmolarity values of selected ocular lubricants. ARVO 2004, 87

Current Treatment for Dry Eye

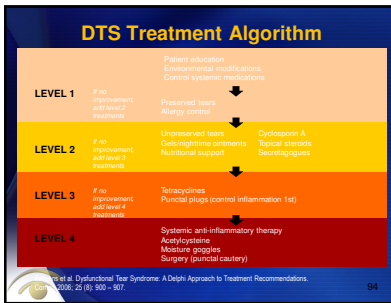
- A majority of patients (74%) do not obtain satisfactory relief from dry eye symptoms with artificial tears
- Many dry eye patients (34%) wish there was an effective therapy available for treating their dry eyes

Gallego-Pohl, Davis and Rife, Allergan

Case Report #1

- 46 y/o WF
- Presents c/o burning, dryness OU x 1 m
- BCVAs = 20/20 OD, OS
- SLEx unremarkable (-) LG or NaFl staining, TBUT 12 sec, PRTT 20 mm/15 sec, normal tear meniscus height

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Environment

- Top 3 intake causes of dry eye?
 - Smoking
 - Caffeine (more than moderate)
 - Diet (low omega 3 intake)

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Summary of the ITF Guidelines for Dry Eye Treatment*

Severity Level	Signs & Symptoms	Recommended Treatment
1	Mild to moderate symptoms and no signs	Patient counseling, preserved tears, environmental mgmt, allergy eyedrops
2	Moderate to severe symptoms; tear film signs; mild corneal punctate staining; conjunctival staining; visual signs	Non-preserved tears, gels, ointments; cyclosporine A, topical steroids, secretagogues, nutritional support (Flaxseed oil)

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Case Report # 1

- Symptomatic dry eye (DTS level 1)

Severity Level	Signs & Symptoms	Recommended Treatment
1	Mild to moderate symptoms and no signs	Patient counseling, preserved tears, environmental mgmt, allergy eyedrops

- Recommend artificial tears, discuss environmental modifications

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Artificial Tears

- The rationale behind artificial tears is straightforward – replenish ocular surface moisture, and wash away accumulated debris, including antigens
- In mild to moderate cases of dry eye, most of these agents work quite well

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Summary of the ITF Guidelines for Dry Eye Treatment*

Severity Level	Signs & Symptoms	Recommended Treatment
3	Severe symptoms; marked corneal punctate staining; central corneal staining; filamentary keratitis	Tetracyclines; punctal occlusion
4	Severe symptoms; severe corneal staining; erosions; conjunctival scarring	Systemic anti-inflammatory therapy; oral cyclosporine; moisture goggles; acetylcysteine; punctal cautery

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Environment

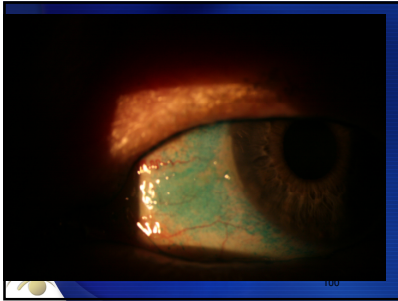
- Air conditioners or heaters
- Airline travel
- Winter months, allergy season
- Exogenous irritants and allergens
- Reading time/Computer use (decrease blink rate)

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Case Report # 2

- 60 y/o WF
- Presents c/o burning & watery eye OU of 6 month duration. Has used "all types of artificial tears" with only minimal symptomatic improvement
- BCVAs = 20/25 OD, OS
- TBUT 4 sec; (+) LG & NaFl staining of cornea + conj
- TM height decreased
- PRTT 5 mm/15 sec OU

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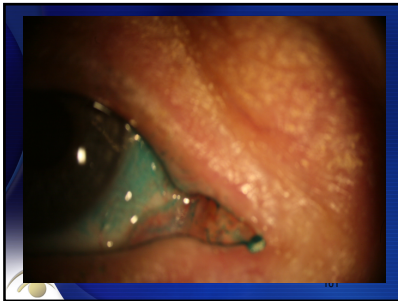
Steroids and OSD

Symptomatic improvement in irritation symptoms in 83% and objective improvement (↓ redness, dye staining) in 80% of 70 patients treated for 2 weeks with non-preserved methylprednisolone

Prabhasawat & Tseng BJO 1998

Ester vs. Ketone Steroids

Loteprednol	→	ester steroid
Prednisolone		ketone steroid
Fluorometholone	→	
Dexamethasone		
Medrysone		
Rimexolone		



Steroid Treatment

- Loteprednol 0.2% (Alrex)
- Loteprednol 0.5% (Lotemax)
- Less side effects - M Abelson 88 patients 35 days
- IOP rise, secondary infection or PSC formation: 0%

Restasis

- Has been shown to increase overall tear volume and goblet cell density in some patients⁶
- Relatively slow onset of action, which can be from three to six months in most patients⁶

Case Report # 2

■ Dx: DTS Level 2

Severity Level	Signs & Symptoms	Recommended Treatment
2	Moderate to severe symptoms; tear film signs; mild corneal punctate staining; conjunctival staining; visual signs	Non-preserved tears, gels, ointments; cyclosporine A, topical steroids, secretagogues, nutritional support (Flaxseed oil)

- Tx: lotemax q.i.d. x 2 wks.
- Restasis b.i.d.
- Recommend nutritional supplements
- Non-preserved artificial tears

Ester vs. Ketone Steroids

- *Ester Steroids* are inactivated by naturally occurring esterases
 - less side effects
- *Ketone Steroids* are not inactivated and have propensity to remain in anterior chamber post breakdown as active metabolites

How Does Restasis™ Work?

- Restasis™ prevents T-cell activation
 - Activated T cells produce inflammatory cytokines that result in:
 - Recruitment of more T cells (Stern et al, IOVS. 2002;43:2609)
 - More cytokine production (Pflugfelder et al, Curr Eye Res. 1999;19:201)

Topical Cyclosporine

- Restasis Ophthalmic Emulsion (Allergan)
 - Useful in long-term mgmt of inflammatory DES
 - BID dosage
 - Cyclosporine A (CsA) 0.05% in castor oil vehicle
 - Mechanism of action:
 - Inhibits activation of inflammatory T-lymphocytes, & induces immune cell apoptosis, stimulating lacrimal gland tear production
 - 3-4 months to achieve clinically significant effect; 6 months for full therapeutic potential
 - 59% Patients achieved improvement from baseline Schirmer scores at 6 months
 - Excellent safety profile

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Expectations for the First Months of Restasis™ Therapy

Statistically significant improvement in signs and symptoms •Drying •Itching •Blurred Vision •Photophobia	Key signs & symptoms continue to improve	Improvement maintained with continued therapy
One Month	Three Months	Six Months

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Asclepius Panel Recommendations

Day 1	Day 14	Day 60
Loteprednol QID	Loteprednol BID	Loteprednol As Needed
Prescription Eye Drops		
Artificial Tears		

Source: Holland EJ et al. Ophthalmology Times 2007; 32: S7-S16.

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Topical Cyclosporine

- Other Safety Results
 - No CSA-related ocular infections
 - No differences in blood chemistry, hematology
 - Including renal and hepatic function
 - No treatment-related changes in IOP, visual acuity, or biomicroscopy (Sall et al, Ophthalmol 2000;107: 631)

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Burning and Stinging

- Not an issue if use Loteprednol simultaneously
- Also long term risks of steroid not an issue as you taper Loteprednol and maintain Restasis

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Nutritional Supplements: Essential fatty acids

- Flaxseed oil (1000 mg bid if tablet form)
- Castor oil
- Fish oils
- Omega-3 fatty acids - linoleic acid

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Topical Cyclosporine

Increased Tear Production in Restasis®-treated Patients

- Schirmer scores increased from baseline for 59% of chronic dry eye patients treated with Restasis®
 - Maximum improvement was 16 mm
- Significantly more Restasis®-treated Patients improved by ≥10 mm vs. vehicle (15% vs. 5%)

Sall et al. Ophthalmol. 2000;107:631

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Topical Loteprednol Improves Patient Compliance and Restasis Efficacy

- Corticosteroids improve tear production by controlling inflammation¹
- Corticosteroids decreases irritation associated with Restasis by 75%²
- Recommend a mild corticosteroid such as loteprednol qid x two weeks & then bid x 2 weeks for patients who complain of irritation with Restasis, high maintenance patients, and patient who want more rapid relief

Marsh, Phugfelder. Ophthalmology 1999
Leopard, ASCRS 2005

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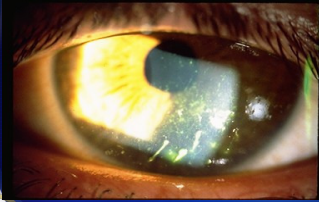
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Nutrient Tx for Dry Eye

- Omega-6 & Omega-3 Fatty acids inhibit the arachidonic acid inflammatory cascade assoc/w dry eye & dry eye assoc/w allergic response
- Nutrients have been shown to increase tear film levels of lactoferrin
- Nutrients enhance production of acetylcholine, which triggers neural reflex loop that stimulates the lacrimal gland to produce aqueous³
- Feher et al, ARVO 2006: Omega-3 polyunsaturated fatty acids (PUFA) & enzyme CoQ10 PO improves dry eye symptoms

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Case Report # 3



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Case Report # 3

Severity Level	Signs & Symptoms	Recommended Treatment
3	Severe symptoms; marked corneal punctate staining; central corneal staining, filamentary keratitis	Tetracyclines; punctal occlusion

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Case Report # 3

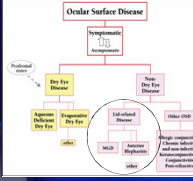
- 76 yo WM
- Presents c/o severe ocular irritation ("burning and stinging") for "several years now"
- Using n/p AT q.2.h. + ung q.h.s. without symptomatic improvement
- "Another doc put me on that new stuff for awhile but it didn't help either"
- Meds: Benicar, Avandia; NKDA

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DEWS Report



According to the DEWS Report:

- Blepharitis is an important subset of Ocular Surface Disease
- Blepharitis often co-exists with Dry Eye Disease
- When a patient presents with both Dry Eye Disease and Blepharitis, treatment targeted at the lids is recommended, in addition to treatment of the Dry Eye

The Report of the International Dry Eye Workshop (DEWS) (2007) pages 92 – 98, 108 – 111

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Case Report # 3

- BCVA 20/30 OD, OS
- TBUT immediate
- TM non-existent
- SPK w/filaments OU / + LG staining of K
- Atrophied meibomian glands OU
- SLEx:

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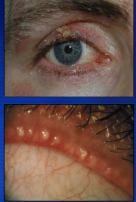
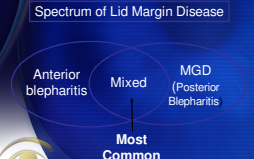
Case Report # 3

- Dx: Filamentary Keratitis OU
- MGD OU
- Tx:
- Debride filaments OU
- Lotemax q.i.d. OU
- Acetylcysteine 10% (mucomyst) q.i.d.
- n/p AT q.2.h. + ung q.h.s.
- Doxycycline 100 mg p.o. q.d. x 2 wks.
- Lid hygiene
- Consider plugs

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The Spectrum of Lid Margin Disease


Although Anterior Blepharitis and Meibomian Gland Disease are distinct entities, they often coexist

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Blepharitis → Definitions

- Anterior Blepharitis
 - Inflammatory condition of outside portion of the eyelids
 - Often secondary to infection, or associated with acne rosacea or seborrheic dermatitis of the scalp or facial areas
- Meibomian Gland Disease (Posterior Blepharitis)
 - Tissue inflammation of the inside portion of the eyelids
 - Associated with altered composition of the meibomian gland secretions, inflammation of local tissue



Traditional Treatments for Blepharitis

- Non-Pharmaceutical Therapy
 - Lid hygiene
 - Warm compresses
 - Commercial lid scrubs
 - Omega 3 nutritional supplements
- Pharmaceutical Therapy
 - Antibiotic ointment
 - Corticosteroids
 - Antibiotic/ corticosteroid combo products
 - Oral tetracyclines




Punctal Occlusion

- Temporary. Initial treatment to monitor response to this therapy
- Permanent
- Cautery

Meibomian Gland Disease (Posterior Blepharitis)

- Involves a change in composition of meibomian gland secretions that leads to inflammation, irritation and an altered tear film
- Signs & symptoms include:
 - Dilated & plugged meibomian gland orifices with "toothpaste" like material
 - Ocular surface disease signs and symptoms (burning, foreign body sensation, contact lens intolerance)
 - Lid and conjunctival hyperemia
 - Thickened lid margin
 - Foamy/soapy tear film
 - Fluctuations in visual acuity



Posterior Blepharitis Treatment

Treatment	Frequency
Antibiotic	
Azithromycin (sulfazone) solution 1% "Drop and massage"	Twice a day for 2 days; THEN once a day in the evening for 28 days
MEIBOMIAN THERAPY	
Lid Cleansing (Commercial lid cleansers)	Twice a day for 2 days; THEN once a day in the evening for 28 days
DIETARY	
Lid Hyperthermia (Warm washcloth 3-5 minutes)	Twice a day for 2 days; THEN once a day in the evening for 28 days
SYSTEMIC	
Oral tetracycline - Doxycycline - Minocycline	Doxycycline 50 mg twice a day or minocycline 50 mg once a day for 2 weeks; THEN 20 mg doxycycline per day for as long as needed
IMMUNOMODULATION	
- Cyclosporine - Corticosteroid	Twice a day for as long as needed Pulse, then taper

If symptoms do not resolve after 30 days, discontinue the antibiotic but continue lid hyperthermia. After 30 days without azithromycin, the full regimen, including azithromycin and lid cleansing, can be restarted for an additional 30 days, if needed. Continue cycle for as long as needed.

Ref: Donnerfeld ED et al. New considerations in the treatment of anterior and posterior blepharitis. Ref Eyecare 2008; 12 (4S):10



Meibomian Gland Disease: Etiology

- Change in composition of meibomian gland secretions that leads to inflammation, irritation and an altered tear film
- Normal secretions convert from unsaturated lipids (that melt at body temperature) to saturated fats
 - Involves degradation of triglycerides to mono- and diglycerides
 - Lipases appear to be involved in this degradation
- The mono- and diglycerides are more solid in composition, leading to obstruction/plugging of the meibomian gland
- The mono- and diglycerides are pro-inflammatory, leading to the inflammation associated with MGD

Restasis vs. Punctal Plugs

- "While punctal plugs increase Schirmer measurement of tear production, cyclosporine is more effective in decreasing the conjunctival staining and need for artificial tears in dry eye patients"
- However, their "use in combination was the most effective in relieving both the signs and symptoms of dry eyes."⁸

SmartPlug®



Systemic Tetracyclines

- Doxycycline or tetracycline for inflammatory dry eye
- Tetracyclines decrease circulating inflammatory mediators
- Promotes comfort and decreased inflammation
- Generally takes 2 or 3 months to see benefit
- Reduce to periostat longer term (20mg doxycycline) bid or qd

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Case Report # 4

- Medications: Diovan p.o. q.d, Naproxen, Plaquenil, carafate; NKDA
- BCVA 20/40 OD, 20/30 OS
- IOP 16 mm Hg OD, OS
- TBUT 2 sec; TM nonexistent; (+) LG & NaFl staining of the cornea & conjunctiva OD, OS; PRTT 2 mm/15 sec.

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Case Report # 4



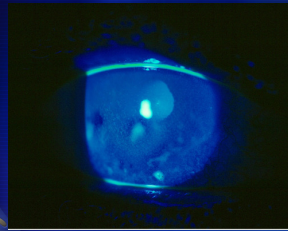
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Doxycycline for OSD

- Reduces enzyme activity of bacteria
 - e.g. lipase activity of staphylococcus
- Accumulation in oil glands
- Anti-inflammatory component

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Case Report # 4



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Case Report # 4

- Dx: Secondary Sjogren's Syndrome
- Tx: Non-preserved AT q.2.h.
- Lotemax q.6 h.
- Discuss punctal occlusion
- Discuss room humidifier
- Recommend Panoptic sunglasses
- Refer to rheumatologist for blood work: ANA, SSA & SSB, RF, ESR, CBC
- Refer to dentist for evaluation

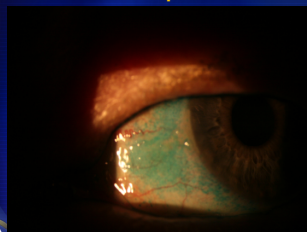
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Case Report # 4

- 70 y/o WF
- Presents c/o "dry eye"; has used artificial tears in the past but not with regularity
- Medical Hx: rheumatoid arthritis, HTN
- Upon questioning, patient states "I have to go with a glass of water in my hands all the time b/c my mouth is so dry."

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Case Report # 4



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Sjogren's Syndrome

- Lymphocytic infiltration of lacrimal & salivary glands
- 0.4% prevalence
- Women > Men (younger women)
- Much lower androgen counts
- Treat underlying immune disorder

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Which of these conditions are Sjogren's patients 46x more likely to develop?

A. Leukemia B. Lymphoma

C. Meningitis D. Cardiac Arrhythmia

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Sjögren's Syndrome KCS

Steroids Effectively Treat KCS
(Marsh, Ophthalmology 1999)

Pre-Steroid

Post-Steroid

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Case Report # 5

- 79 yo WF
- Presents c/o "skim over OU" x 2 months
- Redness, EP, photophobia, tearing OS-OD x 2 w
- Long-standing hx Rheumatoid arthritis w/ Secondary Sjogren's syndrome, currently treated w/ Lotemax + Restasis b.i.d. OU, + N/P AT prn OU. LEEX 2 m.
- CVAs: 20/100 OD, CF @1' OS, PHNI
- SLEx:

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Which of these conditions are Sjogren's patients 46x more likely to develop?

A. Leukemia B. **Lymphoma**

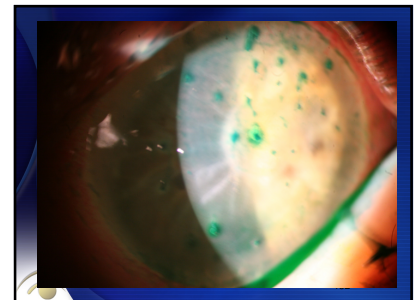
C. Meningitis D. Cardiac Arrhythmia

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Sjogren's Syndrome

- **Medical Treatments: Secretagogues**
 - Salagen 5 mg
 - Pilocarpine tablets
 - Avoid in asthma patients, GI ulcer, acute iritis or narrow angles
 - Evoxac 30 mg – saliva stimulating drug
 - Cevimeline
 - Very effective with a lot less side effects

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Steroids and SS Dry Eye

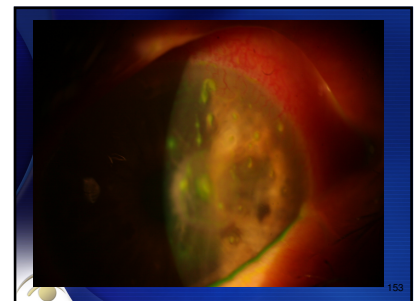
- Moderate (43%) or complete (57%) relief of irritation symptoms accompanied by ↓ corneal NaFl staining and resolution of filamentary keratitis in 21 SS patients treated for 2 weeks with non-preserved methylprednisolone (Marsh & Pflugfelder, 1999)
- Patients often have long lasting relief after 2-week pulse therapy

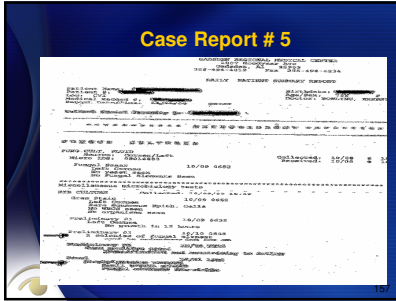
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Panoptx™ "Dry Eye Wear"

- Patented Orbital Seal creates "moisture chamber"
- New study findings demonstrate effectiveness

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- ### Case Report # 6
- 17 yo WM, SDW CL wearer x 4 years
 - Presents c/o itchy, watery eyes of 1 week duration
 - Has used OTC tears & antihistamine/decongestant drops q.i.d. w/ minimal relief
 - No Rx meds; NKDA
 - Entering BCVA w/ specs: 20/20 OD, OS

- ### Case Report # 5
- Dx: Secondary Sjogren's Syndrome
 - Dx: Corneal Ulcer
 - ? Is it infectious
 - Cultures obtained: SBA, Choc, SDA Slant, Broth, Gram stain
 - Vigamox q.h. while awake

- ### Case Report # 5
- Added Natamycin q.h. w.a.
 - Continue vigamox q.h. w.a.
 - Patient totally resolved in 4 weeks
 - Albumin added to artificial tear regimen



Dry Eye & Ocular Infection

Barriers to Infection and Associated Compromising Conditions	
NORMAL BARRIER	COMPROMISING CONDITION
Adequate Tear Film	Dry eye syndrome
Intact Epithelial Surface	Trauma, hypoxia, unusually aggressive pathogen
Tight epithelial-stromal adhesion	Anterior basement membrane dystrophy (ABMD)
Normal immune response	Steroid use, chemotherapy, AIDS, and other immune-suppressing conditions

Source: Wilson SD. Microbial keratitis: An overview of mechanisms and treatment. Topics in Ocular Antinfectives 2009 (4): 4.

- ### 5% Albumin
- Autologous serum is difficult to formulate and expensive. Another Option: 5% albumin
 - "The use of albumin as a protein supplement in artificial tear solutions is a viable approach in the treatment of ocular surface disorders associated with tear deficiency" *
 - Available from Leiter's Pharmacy (www.leiterrx.com 800-292-6773)
 - 30-day shelf life. Keep refrigerated. N/P
- *Shimmura S, et al. Br J Ophthalmol 2003; 87: 1279-1283.





Seasonal Allergic Conjunctivitis

- Signs:
 - Not always present
 - Lid swelling
 - Ptosis
 - Conjunctival hyperemia
 - Chemosis
 - Papillary reaction
 - Follicular reaction

Patanol + Claritin

- Study by Lanier et al. @ University of Texas in 2001
- Compared patient's symptoms and signs in 94 patients randomized to either receiving Claritin alone or claritin with patanol
- Concluded that patanol used in conjunction with claritin provided greater relief of signs and symptoms vs. claritin alone

Case Report # 6

- Dx: Seasonal Allergic Conjunctivitis
- Tx: Pataday q.d.
- Patient education re: decrease CL wearing time. Recommend use of non-preserved artificial tears p.r.n. and cold compresses
- Recommend OTC claritin/zyrtec for rhinitis

Ocular Allergy Management Non-Rx

- Avoidance of allergens, if possible
- Keep car windows closed; use AC
- Avoid outdoor activities, e.g., lawn work or gardening
- Wash hands, face and hair often to remove allergens
- Ice packs/cold compresses
- Lubricants
- DON'T RUB YOUR EYES!

Ocular Allergies – Treatment Pearls

- Though "itching" is the hallmark symptom of ocular allergy, about 1/3 of patients who report "itchy-burnies" will have "burning" as their chief complaint
- When the principal symptom is actually "burning", consider DRY EYE as the diagnosis vs. ocular allergy
- For this reason, always evaluate the lacrimal lake and precorneal tear film volume & function to rule/out dry eye prior to beginning allergy therapy

Incidence of Ocular Allergies by Type of Allergic Eye Disease

■ All Others ■ SAC/PAC

90% - 95% of all ocular allergies are estimated to be SAC/PAC

Nelson M. Allergic Diseases of the Eye. Philadelphia, PA: W.B. Saunders Co. 2000. 165.

Ocular Allergy Management Multiple Mechanism Products

- State of the art broad spectrum products
- Combine mast cell stabilization with direct antihistamine blocking and may possibly have other effects
- Patanol (Olopatadine 0.1%)
- Pataday (Olopatadine 0.2%)
- Zaditor (Ketotifen) – antihistamine w/ so mast cell stabilizing effects. Now OTC
- Elestat (epinastine)
- Do not require loading & can be used throughout allergy season

- OSD = an opportunity to care for a segment of your patient base that may have been overlooked in the past
- OSD = an opportunity profession-wide to lay claim to a disease process we can call all our own!
- Can all provide this service regardless of your practice modality
- OSD = a recognized disease process with it's own CPT-4 code, and thus reimbursable under medical insurance

OSD Is a Disease !!!

- Treat OSD like the disease process it is
- You wouldn't give medications to a glaucoma patient without a thorough workup & appropriate follow -up
- Follow-up with these patients at regular intervals to monitor progress and evaluate therapeutic effects.
- And bill appropriately for your time and expertise !

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Questions? Comments?

- E-mail me: drbowling@windstream.net
ebowling@eyehealthpartners.com
- The presenter has no financial interest in ANY of the products discussed in this presentation. I'm just a poor old country eye doc with 2 kids in college...
- Thanks: Drs. Al Kabat, Paul Karpecki, Milt Hom, Bill Townsend, Chris Snyder

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Thank you!

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