
Ocular Surface Disease:
The Villain with 1000 Faces
June 2023
Christopher Putnam, OD, PhD, FAAO

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South Dakota State University
Pacific University Oregon
University of Houston College of Optometry
UMSL Optometry
University of Missouri–St. Louis

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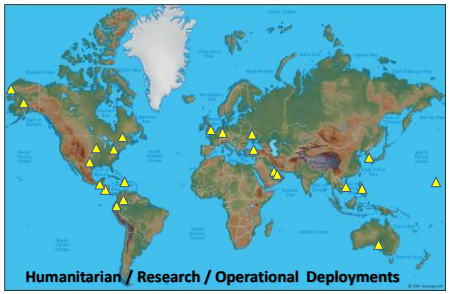
Humanitarian / Research / Operational Deployments

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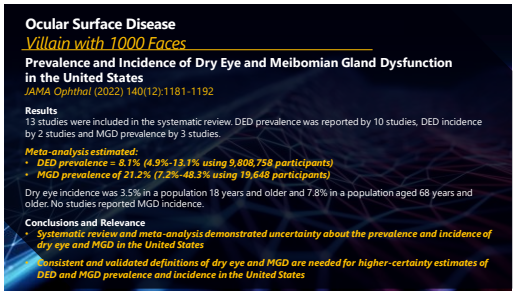
Ocular Surface Disease
Villain with 1000 Faces
Prevalence and Incidence of Dry Eye and Meibomian Gland Dysfunction in the United States
JAMA Ophthal (2022) 140(12):1181-1192
Results
13 studies were included in the systematic review. DED prevalence was reported by 10 studies, DED incidence by 2 studies and MGD prevalence by 3 studies.
Meta-analysis estimated:
DED prevalence = 8.1% (4.9%-13.1% using 9,808,758 participants)
MGD prevalence of 21.2% (7.2%-48.3% using 19,648 participants)
Dry eye incidence was 3.5% in a population 18 years and older and 7.8% in a population aged 68 years and older. No studies reported MGD incidence.
Conclusions and Relevance
Systematic review and meta-analysis demonstrated uncertainty about the prevalence and incidence of dry eye and MGD in the United States
Consistent and validated definitions of dry eye and MGD are needed for higher-certainty estimates of DED and MGD prevalence and incidence in the United States

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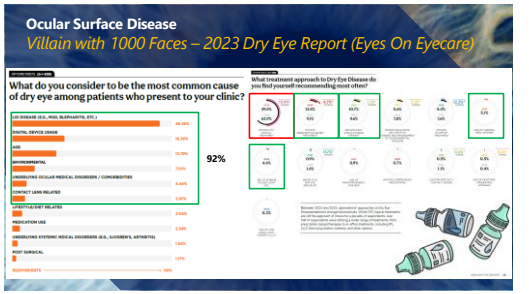
Ocular Surface Disease
Villain with 1000 Faces – 2023 Dry Eye Report (Eyes On Eyecare)
What do you consider to be the most common cause of dry eye among patients who present to your clinic?
92%

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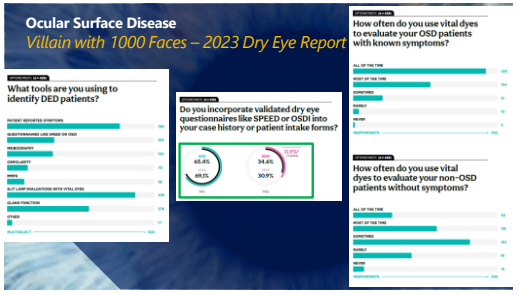
Ocular Surface Disease
Villain with 1000 Faces – 2023 Dry Eye Report
What tools are you using to identify DED patients?
Do you incorporate validated dry eye questionnaires like SPEED or OSDI into your case history or patient intake forms?
How often do you use vital dyes to evaluate your OSD patients with known symptoms?
How often do you use vital dyes to evaluate your non-OSD patients without symptoms?

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Ocular Surface Disease
Villain with 1000 Faces – 2023 Dry Eye Report (Eyes On Eyecare)
TID SCRUB

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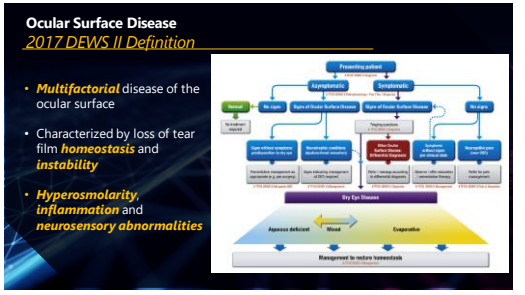
Ocular Surface Disease
2017 DEWS II Definition
Multifactorial disease of the ocular surface
Characterized by loss of tear film homeostasis and instability
Hyperosmolarity, inflammation and neurosensory abnormalities
Dry Eye Disease
Aqueous deficient
Mixed
Evaporative
Management to restore homeostasis

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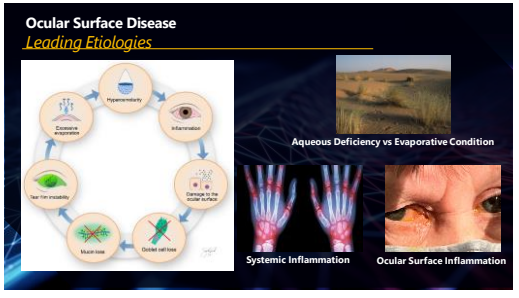
Ocular Surface Disease
Leading Etiologies
Aqueous Deficiency vs Evaporative Condition
Systemic Inflammation
Ocular Surface Inflammation

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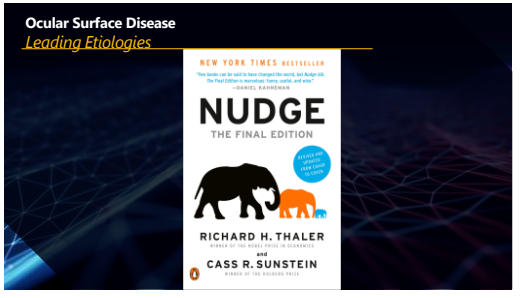
Ocular Surface Disease
Leading Etiologies
NEW YORK TIMES BESTSELLER
NUDGE
THE FINAL EDITION
RICHARD H. THALER
and
CASS R. SUNSTEIN

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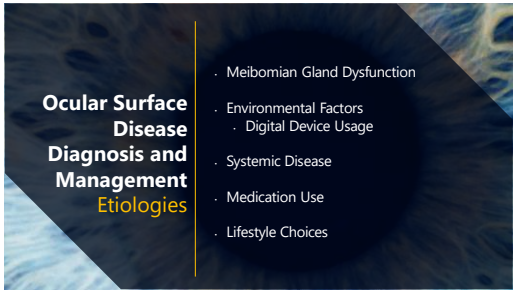
Ocular Surface Disease Diagnosis and Management
Etiologies
Meibomian Gland Dysfunction
Environmental Factors
Digital Device Usage
Systemic Disease
Medication Use
Lifestyle Choices

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Ocular Surface Disease
Leading Etiologies - MGD

MGD: Role of gland dysfunction in dry eye disease
Ophthal (2017) 124 (Suppl 11):S20-S26

Abstract
MGD is an umbrella term that encompasses several meibomian gland disorders ranging from congenital to acquired

- ***Negatively impacts both the quality and quantity of meibum secreted which in affects the ocular surface and TF composition***
- ***Increased evaporation, hyperosmolarity, inflammation and ocular surface damage occur subsequently causing discomfort, visual disruption and dry eye sensation***

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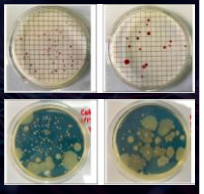
Ocular Surface Disease
Leading Etiologies – Environmental Factors (Indoor)

Association of the Indoor Environment With Dry Eye Metrics
JAMA Ophthal (2020) 138(8): 867-874

Results
97 participants reporting DES symptoms in the moderate range using OSDI score of 31.2. Humidity was associated with worse symptoms and signs, including OSDI score, inflammation, Schirmer score, eyelid vascularity and MGD. Particulate matter of 2.5 μm or less ($PM_{2.5}$) was associated with dry eye metrics when adjusted for demographic characteristics, comorbidities, medications, and interaction variables

- ***1-unit increase $PM_{2.5}$ level was associated with:***
  - ***1.59 OSDI score increase***
  - ***0.39 Schirmer score reduction***
  - ***0.06 increase in inflammation***

Conclusions
- ***Increased particulate matter exposure was associated with worse dry eye metrics***
  - ***Higher humidity increases microbial growth and particulate matter size and mass***



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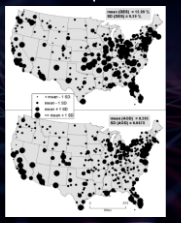
Ocular Surface Disease
Leading Etiologies – Environmental Factors (Outdoor)

Environmental Factors Affect the Risk of DES in a United States Veteran Population
Ophthal (2014) 121(4): P972-973

Table 1. Risk of Dry Eye Syndrome (DES) with Respect to Air Pollution and Weather Conditions

z-Score of	IRR	Robust 95% CI
Log(aerosol optical depth)	1.126*	1.125–1.127
Atmospheric pressure (mbar)	1.131*	1.129–1.133
Wind speed (m/s)	0.938*	0.937–0.939
Relative humidity (%)	0.927*	0.926–0.927
Temperature (°C)	1.008*	1.007–1.010
log(visibility [m])	0.992*	0.992–0.993
Longitude (°)	1.049*	1.048–1.050
Latitude (°)	1.024*	1.022–1.026
Observations (n)	3 343 277	

CI = confidence interval; IRR = incidence rate ratio.
*P < 0.001.



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Ocular Surface Disease
Leading Etiologies – Systemic Disease

Systemic Conditions Associated with Severity of Dry Eye Signs and Symptoms in the Dry Eye Assessment and Management Study
Ophthal. (2021) 128(10): 1384-1392

Methods
535 patients with moderate to severe DED underwent ocular surface examinations and symptom evaluation using standardized protocols at baseline, 6mos and 12mos. Associations of systemic conditions reported as potential DED risk factors with the severity of DED signs and symptoms using the OSDI, 6 DED signs (TBUT, Schirmer testing, NaFL staining, lissamine green staining, tear osmolarity and MGD), and a composite signs severity score were analyzed

Results
Severe DED signs were associated significantly with:
- ***Sjogren's syndrome***
- ***Facial rosacea***
- ***RA***
- ***Smoking history***

Thyroid disfunction, OA, DM, IBS, hypercholesterolemia and hypertension were not associated significantly with DED signs.

Conclusions
Significant DED signs varied by systemic condition, reflecting different DED causes

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Ocular Surface Disease
Leading Etiologies – Medication Use

I. If it causes dry mouth, it causes dry eye
- I. Antipsyetic
- II. Analgesics / Opioids)
- III. Antirheumatic
- IV. Antiarrhythmics
- V. Anticholinergics
- VI. Anxiolytics/ Antidepressants / Antipsychotics
- VII. Antihistamines / Decongestants
- VIII. Antihypertensives / Diuretics
- IX. Antimuscarinics Retinoids
- X. Sedatives / Antipsychotics

I. Polypharmacy (10-yr Relative Risk in patients > 60yo)

I. Antihistamine use	1.24
II. Antianxiety drug use	1.43
III. Antidepressant use	1.44
IV. Diuretic use	1.18
V. Oral steroid use	1.43
VI. Vitamin use	1.30

II. Topical Medications
- I. Beta-blockers
- II. Adrenergic agonists *EMPHASIZE DURATION IS RELEVANT
- III. Cholinergic agents (Vuity)
- IV. Prostaglandins
- V. Allergy agents / Decongestants
- **VI. Preservatives** (BAK)
- VII. Ocular NSAIDs

****Medication-Induced Dry Eye and Dry Mouth May Masquerade as Primary Sjogren's Syndrome***

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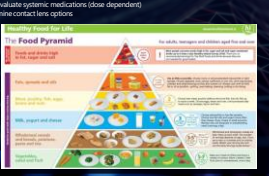
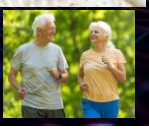
Ocular Surface Disease
Leading Etiologies – Lifestyle Choices

1) Smoking cessation
2) Improved diet
3) Reduced use of digital devices
4) ***Consistance adherence to daily dry eye regimen***
5) Manage environmental factors
6) Improve sleep habits
7) Re-evaluate systemic medications (dose dependent)
8) Examine contact lens options





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Ocular Surface Disease Diagnosis and Management
Measurement and Imaging

- ***Screening Tools***
- Entrance Skills
- Slit lamp Point-of-Care
  - CLIA Testing
  - Detailed Lid Evaluation
  - Schirmer v. Phenol red
  - Vital Dyes
- Smartphone Applications
- Anterior Segment Imaging

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Ocular Surface Disease
Clinical Measurement and Imaging – Screening Tools

Standardized, Comprehensive ROS (Following 2018 AAO PPP)

Ocular History
1) Topical medications
2) Contact lens history
3) Allergic conjunctivitis
4) Ocular surgical history (prior keratoplasty, cataract surgery, keratorefractive surgery)
5) Ocular surface disease (HSV, VZV, ocular mucous membrane pemphigoid)
6) Eyelid / Orbital surgery (punctal occlusion, ptosis repair, blepharoplasty, entropion/ectropion repair, radiation)

Systemic History
1) Systemic medications (anticholinergics, antihistamines, diuretics, hormonies and antagonists, antidepressants, antiarrhythmics, isotretinoin, atropine, beta antagonists)
2) Systemic inflammatory diseases (Sjögren syndrome, GvHD, RA, SLE, Stevens-Johnson syndrome, sarcoidosis, lymphoma)
3) Dermatological diseases (atopy, rosacea, psoriasis, VZV)
4) Neurological conditions (Parkinson disease, Bell's palsy, trigeminal neuralgia)
5) Chronic viral infections (Hepatitis C, HIV)
6) Smoking or exposure to second-hand smoke
7) Trauma (mechanical, chemical, thermal)
8) Non-ocular symptoms: (dry mouth, dental cavities, oral ulcers, fatigue, joint pain/muscle ache, menopause

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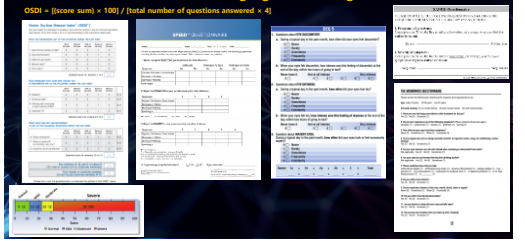
Ocular Surface Disease
Clinical Measurement and Imaging – Screening Tools

OSDI = [(score sum) × 100] / [total number of questions answered × 4]



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Ocular Surface Disease
Clinical Measurement and Imaging – Screening Tools

Comparative Evaluation of 5 Validated Questionnaires as Screening Instruments for DED
JAMA Ophthalmol. (2019) 137(2):228-229

Methods
211 participants were given standardized instructions before administering the OSDI, DEQ-5, McMonnies Dry Eye Questionnaire, SANDE, and SPEED questionnaires in a randomized order. Independent observer evaluated right-eye ocular surface parameters using OCULUS Keratograph 5M and measured the tear film osmolarity of both eyes (TearLab)

TFOS DEWS II DED diagnostic criteria:
- ***Noninvasive TBUT<10sec***
- ***Tf osmolarity ≥308 mOsm/L or interocular difference in osmolarity ≥8 mOsm/L***
- ***>5 corneal staining spots;***
- ***>9 conjunctival staining spots***
- ***Margin staining >2mm in length and >25% in width***

Results
- 69% participants fulfilled the TFOS DEWS II criteria. NITBUT was 8.6 secs, tear osmolarity was 310 ± 12 mOsm/L, interocular osmolarity difference was 8±6 mOsm/L.
- 34% participants exhibited > 5 corneal spots, 51% participants exhibited >9 conjunctival spots, and 46% participants exhibited eyelid margin staining >2mm in length and >25% in width.
- ***Discriminative abilities of the OSDI and SPEED scores were significantly greater than chance.***

Discussion
TFOS DEWS II highlighted the considerable heterogeneity in the study populations, methodologies and reference standards used in previous diagnostic accuracy studies of validated DED questionnaires.

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Ocular Surface Disease
Clinical Measurement and Imaging – Screening Tools

Symptoms of dry eye disease and personality traits
PloS one (2016) 11(11): e0166838

	Mean of the score Low/High	Mean ± SD	DEQS		OSDI	
			r	p-value	r	p- value
Openness	Conventional/ Imaginative	44.25 ± 10.81	0.015	0.913	0.075	0.587
Conscientiousness	Negligent/ Conscientious	45.81 ± 9.88	0.075	0.587	-0.026	0.848
Extraversion	Passive/ Active	48.60 ± 10.66	-0.118	0.391	-0.112	0.414
Agreeableness	Suspicious/ Trusting	49.78 ± 9.18	0.078	0.573	0.09	0.512
Neuroticism	Pessimistic/ Optimistic	44.83 ± 11.93	-0.353	0.008	-0.28	0.039

The Big Five personality traits consist of openness, conscientiousness, extraversion, agreeableness, and neuroticism. Only neuroticism shows a significant correlation to the DEQS ($r = -0.353$, $p = 0.008$), and OSDI ($r = -0.28$, $p = 0.039$). DEQS and OSDI also show a significant correlation ($r = 0.837$, $p < 0.0001$). r: Spearman's correlation coefficient.

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Ocular Surface Disease
Clinical Measurement and Imaging – Screening Tools

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Ocular Surface Disease Diagnosis and Management
Measurement and Imaging

- Screening Tools
- ***Entrance Skills***
- Slit lamp Point-of-Care
  - CLIA Testing
  - Detailed Lid Evaluation
  - Schirmer v. Phenol red
  - Vital Dyes
- Smartphone Applications
- Anterior Segment Imaging

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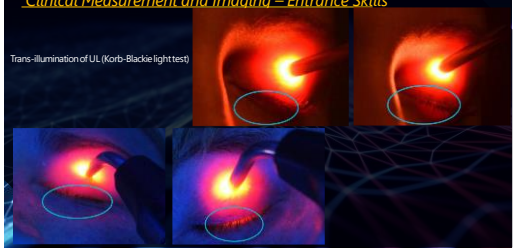
Ocular Surface Disease
Clinical Measurement and Imaging – Entrance Skills

Trans-illumination of UL (Korb-Blackie light test)



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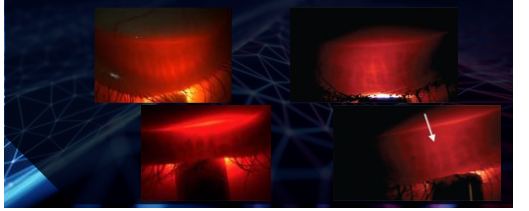
Ocular Surface Disease
Clinical Measurement and Imaging – Entrance Skills

Trans-illumination of LL (gross meibography)



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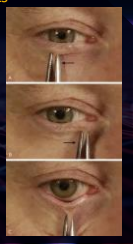
Ocular Surface Disease
Clinical Measurement and Imaging – Entrance Skills

Lower Lid Snap-back test (laxity)
- Pull the lower lid down and away from globe for several seconds
- Note the length of time required before the lower lid returns to its original position
- ***Healthy lid should spring back into original position immediately***
- Graded from 0-4 with a grade of 0 indicating normal and a grade of 4 indicating severe

Medial canthal laxity test
- Pull the lower lid laterally away from the medial canthus and measure punctum displacement
- ***Displacement should only be 0-1mm***
- Graded from 0-4 with a grade of 0 indicating normal and a grade of 4 indicating severe

Lateral canthal laxity test
- Pull the lower lid medially away from the lateral canthus and measure lateral canthal displacement
- ***Displacement should only be 0-2mm***
- Graded from 0-4 with a grade of 0 indicating normal and a grade of 4 indicating severe



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Ocular Surface Disease Diagnosis and Management
Measurement and Imaging

- Screening Tools
- Entrance Skills
- ***Slit lamp Point-of-Care***
  - ***CLIA Testing***
  - ***Detailed Lid Evaluation***
  - ***Schirmer v. Phenol red***
  - ***Vital Dyes***
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- Anterior Segment Imaging

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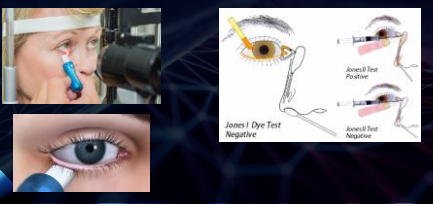
Ocular Surface Disease
Clinical Measurement and Imaging – Slit Lamp Point-of-Care

Meibomian gland evaluator (Tear Science)
Examination of meibum secretion upon blink

Jones I (physiologic)
CTA swab / blow nose

Jones II (non-physiologic)
Punctal dilation + irrigation



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Ocular Surface Disease

Clinical Measurement and Imaging – Slit Lamp Point-of-Care

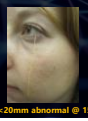
Comparison of Phenol Red Thread Test With Schirmer I Test for the Reproducible Measurement of Tear Production
IOVS (2008) 49(13)

Results
Schirmer data from 16 subjects demonstrated no significant difference when the 3 sets of data were compared.

16 subjects underwent 3 separate PRT tests. No significant difference was found between the 15s vs. 45s tests.

Conclusions
- ***15s PRT test was the most reproducible***
- ***45s PRT test provided the most accurate delineation***

Schirmer <15mm abnormal @ 5min



PRT <20mm abnormal @ 15sec

Does the Phenol Red Thread test and the Schirmer test measure the same thing?
IOVS (2013) 54(15)

Results
When comparing the two recommended measuring times (5 min vs 15 s) no significant correlation was observed.

Significant positive correlation was observed when comparing the two end-points (5 min and 90s)

Conclusions
PRT and Schirmer do not measure the same thing when recommended observation times were used (5min v 15s)

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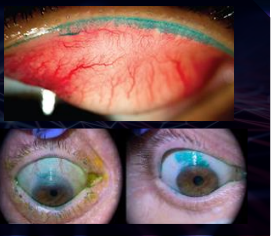
Ocular Surface Disease

Clinical Measurement and Imaging – Slit Lamp Point-of-Care

Vital Dyes
- NaFl with Wratten #12 (cobalt blue)
- Lissamine Green



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Ocular Surface Disease

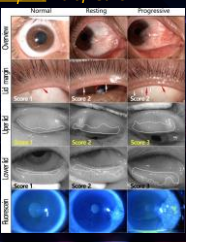
Clinical Measurement and Imaging – Slit Lamp Point-of-Care

Influence of Pterygium on Meibomian Glands and Dry Eye Parameters
OVS (2023) 10:1097

Methods
Pterygium patients and age-matched, healthy volunteers of similar age underwent Schirmer 1, OSDI score, TBUT and ocular surface staining scores. Meiboscores were estimated based on meibomian gland loss rate on infrared meibography (Topcon)

Results
54 eyes with pterygium (Group 1) and 50 control eyes (Group 2) were included.
- ***Schirmer 1 test results and TBUT were lower in Group 1***
- ***OSDI and meiboscores were significantly higher in Group 1***
- ***MG dropletion in 91% of Group 1 and 32% of Group 2***
- ***MG loss region was distributed asymmetrically in 76% of Group 1***
- ***MG asymmetry located adjacent to pterygium in 95% of Group 1***

Conclusions
- ***Overlap of the pterygium location and MGD suggests a direct mechanical relationship***
- ***In pterygium patients, the possibility of MGD and associated evaporative dry eye should be considered***



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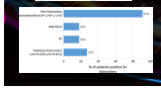
Ocular Surface Disease

Clinical Measurement and Imaging – Slit Lamp Point-of-Care



- **Osmolarity System (TearLab)** [Class I CLIA]
  - Measurement of tear film osmolality
  - ***Non-differential KCS marker***
- **Lactoferrin (Advanced Tear Diagnostics)** [Class II CLIA]
  - Protein produced by the acinar cells of the lacrimal gland
  - ***Differential KCS marker***
- **IgE (Advanced Tear Diagnostics)** [Class II CLIA]
  - ***Presence of ocular allergen***
- **InflammaDry (RPS)** [Class I CLIA]
  - ***Detection of inflammatory marker MMP-9***
  - Qualitative marker
- **AdenoPlus® (RPS)** [Class II CLIA]
  - FDA-approved with CLIA-waiver
  - ***In vivo detection of adenoviral antigen***
- **Sjo® Test**
  - RF and ANA
  - ***SS-A and SS-B with immune markers PSP-1, CA-6 and SP-1***

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Ocular Surface Disease

Clinical Measurement and Imaging – Slit Lamp Point-of-Care

https://www.cms.gov/Medicare/CMS-Forms/CMS-Forms/downloads/cms116.pdf

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Ocular Surface Disease

Clinical Measurement and Imaging – Slit Lamp Point-of-Care

Link between Tear Instability and Hyperosmolarity in Dry Eye
IOVS. (2009); 50(8): 3671-3679.

Results
TF led to an average discomfort rating of 6/10 and sensations of burning and stinging which occurred with hyperosmolar solutions that required 800 to 900 mOsM/kg to generate the same discomfort levels reported during tear break-up. MAPK was activated at 600 mOsM/kg of transient hyperosmolar stress.

Conclusions
Link suggesting that hyperosmolar levels in the tear film may transiently spike during tear instability resulting in corneal inflammation and triggering sensory neurons.

Muro 128 = corneal hyperosmolarity

Evidence of central sensitization in DES and neuropathic-like ocular pain complaints: incomplete response to topical anesthesia and generalized sensitivity to evoked pain
Br J Ophthal (2017) 101(9): 1238-1243.

Results
DED symptoms and NOP symptoms were higher in subjects with persistent ocular pain after anesthesia. Most DED signs were not related to persistent pain. When considering persistent pain as a gold standard for central sensitization within the corneal pathway, ***intensity of ocular pain ratings, OSDI and sensitivity to light provided the most robust relationships***

Conclusions
Individuals with DED symptoms and persistent ocular pain after topical proparacaine more frequently report NOP-like symptoms and demonstrate increased sensitivity to evoked pain.

Proparacaine pain abatement = peripheral
Proparacaine pain persistence = centralization

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Ocular Surface Disease Diagnosis and Management Measurement and Imaging

- Screening Tools
- Entrance Skills
- Slit lamp Point-of-Care
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  - Schirmer v. Phenol red
  - Vital Dyes
- ***Smartphone Applications***
- Anterior Segment Imaging

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Ocular Surface Disease

Clinical Measurement and Imaging – Smartphone Applications

Evaluation of the SVOne: a handheld, smartphone-based autorefractor

OVS (2015) 92(12): 1133

Methods

Refractive error was assessed both with and without cycloplegia in 50 visually normal, young adults. Further, to assess repeatability of the instruments, the entire procedure was repeated in a subgroup of 10 subjects.

Results

- No significant difference was observed between the mean values of spherical equivalent for the different techniques.
- ***Retinoscopy and subjective refraction showed the best repeatability for pre-cycloplegic and post-cycloplegic measurements, respectively.***
- Significant correlations were observed between the subjective findings and the other four techniques.

Conclusions

The handheld aberrometer provides measurements of refractive error in normal, young individuals that are not significantly different from other subjective and objective procedures.

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Ocular Surface Disease

Clinical Measurement and Imaging – Smartphone Applications

Reliability and clinical applicability of a novel tear film imaging tool

Clin Exp Ophthalmol (2021) 259: 1935–1943

METHODS

264 videos of TBUT were randomly selected and analyzed by two masked observers and a third investigator using the automatic software application. Subjective evaluation was conducted only once on an online software designed for this protocol where videos were presented in random masked order. Automatic evaluation based on color and texture analysis was performed by automatic NITBUT measurement in the region of interest as time elapsed

RESULTS

Statistical difference between observer 1 and 2 evaluations whereas data provided by the ***software showed no significant differences from those of the observers***. Similar results to the whole data set analysis were obtained when the sample was reassessed only considering mean BUT values ≤15 seconds.

CONCLUSIONS

Acceptable clinical results for the software application designed to objectively measure the NITBUT

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Ocular Surface Disease

Clinical Measurement and Imaging – Smartphone Applications

Characteristics and Risk Factors Associated With Diagnosed and Undiagnosed Symptomatic Dry Eye Using a Smartphone Application

JAMA Ophthal (2020) 138(1): 58-68

Results

DryEyeRhythm data were collected on demographics, medical history, lifestyle, subjective symptoms, and disease-specific symptoms, using the OSDI and the Zung Self-Rating Depression Total of 899 participants with diagnosed DED and 2395 participants with undiagnosed symptomatic DED completed all questionnaires and their data were analyzed.

Risk factors for ***symptomatic vs asymptomatic DED***

- **female sex (OR 1.99)**
- **allergies (OR: 1.35)**
- **mental illnesses (OR 1.87)**
- **current contact lens use (OR 1.27)**
- **extended screen exposure (OR 1.55)**
- **smoking (OR 1.65)**

Risk factors for ***undiagnosed vs diagnosed symptomatic DED***

- ***male sex (OR: 0.55)***
- ***mental illnesses (OR: 0.50)***
- ***ophthalmic surgery (OR 0.41)***
- ***contact lens use (OR 0.64)***

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Ocular Surface Disease Diagnosis and Management Measurement and Imaging

- Screening Tools
- Entrance Skills
- Slit lamp Point-of-Care
  - CLIA Testing
  - Detailed Lid Evaluation
  - Schirmer v. Phenol red
  - Vital Dyes
- Smartphone Applications
- ***Anterior Segment Imaging***

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Ocular Surface Disease

Clinical Measurement and Imaging – Anterior Seg Imaging

Corneal epithelial thickness profile in DED

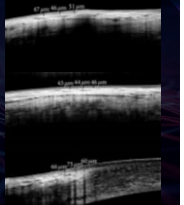
Eye (2020) *34*(5): 915-922

Results

DED patients had a highly irregular corneal epithelial surface compared with controls. Epithelial thickness profile variance (EIF) and range were significantly higher in DED as compared with controls (5.79 vs. 0.77 and 7.6 vs. 4.6 μm). Both parameters were highly significantly correlated with questionnaire scores (EIF: $r = 0.778$; range: $r = 0.737$). ***Treatment and follow-up showed a statistically significant reduction in epithelial thickness profile variance and range of treated patients***

Conclusions

- ***DED patients have irregular epithelial surface that can be quantified using UHR-OCT generated corneal epithelial maps.***
- ***Epithelial thickness profile range and variance correlate accurately with symptoms and could be used to follow-up patients and response to treatment.***



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Ocular Surface Disease

Clinical Measurement and Imaging – Anterior Seg Imaging

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Ocular Surface Disease

Clinical Measurement and Imaging – Anterior Seg Imaging

Quantitative analysis of morphological and functional features in Meibography for MGD: Diagnosis and Grading

EClinicalMed (2021) 40: 1011-1019

Design

256 subjects with DED symptoms and 56 healthy volunteers underwent complete ocular surface examination. Symptomatic subjects were classified into MGD group and symptomatic non-MGD group. An automatic MGs analyzer was used to obtained multi-parametric measurements in meibography images including the MGs area ratio (GA), MGs diameter deformation index (DI), MGs tortuosity index (TI), and MGs signal index (SI).

Findings

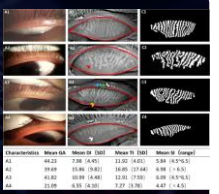
When consider age, sex, ocular surface condition together, the estimated ORs were: DI=1.62, SI=24.34, TI=0.76 and GA=0.86 for MGD. The

- ***Combination of DI-TI-GA-SI showed an AUC 0.82 for discriminating MGD from symptomatic subjects.***

Merging DI-TI-GA showed the highest AUCs in distinguish MGD severities.

Interpretation

- ***MG area ratio, diameter deformation, tortuosity and signal intensity could be considered promising biomarkers for MGD diagnosis***



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Ocular Surface Disease

Clinical Measurement and Imaging – Anterior Seg Imaging

TearScience LipiView II Ocular Surface Interferometer ***(Johnson & Johnson Vision)***
- Real-time visualization of lipid layer to evaluate the dynamic response of lipids to blinking

TearScience LipiScan Dynamic Meibomian Imager ***(Johnson & Johnson Vision)***
- Dynamic illumination offers an enhanced view of meibomian gland structure in ~ 10sec

Ocular Keratograph 5M ***(Oculus)***
- Advanced corneal topographer with a built-in real keratometer and a color camera optimized for external imaging

Meibox ***(Bon Medical Solutions)***
- Portable slit lamp-mounted, cloud-based infrared non-contact camera captures black and white external images of MG

MK2 ***(Shaffer Vision Solutions)***
- First high-definition, cloud-based, portable and slit compatible ocular camera and meibographer

IDRA Ocular Surface Analyzer ***(SBM Sistemi)***
- Comprehensive diagnostic system for high-quality tear film analysis

LacryDiag ***(Quantel Medical)***
- Performs four noncontact examinations (interferometry, noninvasive tear breakup time, tear meniscus, and meibography) in 4 minutes

HD Analyzer ***(Keeler)***
- Measures total optical quality, accounting for light scatter caused by pathologies

Systane iLux ***(Alcon)***
- Portable imager to visualize blocked meibomian glands

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Ocular Surface Disease

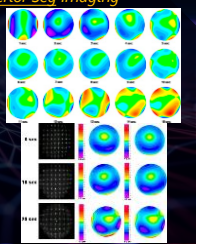
Clinical Measurement and Imaging – Anterior Seg Imaging

Systematic Review on the Association Between Tear Film Metrics and Higher Order Aberrations in DED and Treatment

Ophthal and Therapy (2021) 11: 35–67

Review was to first determine if an association between tear film metrics and HOAs exists and second to determine if the treatment of dry eyes can improve tear film metrics and HOAs together.

- ***Clear evidence demonstrating that DED and HOA are associated and the tear film is one of the most important factors in this relationship***
- ***Direct correlation between tear film metrics and HOA.***
- ***Improvements in HOAs with dry eye interventions provide further evidence to support the intricate relationship***
- Further research is still required in the realm of clinical application as ***dry eye interventions vary across patient severity and treatment modality***



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Ocular Surface Disease Diagnosis and Management

Treatments and Algorithms

- In-office
  - Unhealthy Eyelids vs. MGD
  - Laxity
  - Chronic desiccation
- Pharmacologic
- Homework
- Lifestyle
- Targeted Treatment
  - Root Cause vs. Sequela
  - Episodic vs. Chronic

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Ocular Surface Disease

Clinical Treatments and Decision Algorithms – Lids / Lashes

Rubric for Effective Therapy
- Dirty Eyelids (Comprehensive Cleaning- BlephEx, NuLids, microapplicators)

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Ocular Surface Disease

Clinical Treatments and Decision Algorithms – Lids / Lashes

Telangiectasia | <- Both -> | Lid Margin Irregularity

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Ocular Surface Disease

Clinical Treatments and Decision Algorithms – Lids / Lashes

- Mastroda paddle (Ocusoft)
- Collins Expressor (Collins)
- Davis Foreign body spud (Miltex)

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Ocular Surface Disease

Clinical Treatments and Decision Algorithms – Lids / Lashes

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Ocular Surface Disease

Clinical Treatments and Decision Algorithms – Lids / Lashes

***Demodex* blepharitis: clinical perspectives**

Clin Optom (2018) 10:57-63

Demodex folliculorum and *Demodex brevis* infest the human eye and, in excess, can be associated with wide range of anterior segment findings

- ***Implicated in anterior and posterior blepharitis, blepharoconjunctivitis and blepharokeratitis***
- ***Demodex infestation remains underdiagnosed***
- ***Epithelial hyperplasia and reactive hyperkeratinization along with follicular distention and misdirected lashes***
- ***Definitive diagnosis can be made with lash sampling***
- ***Primary treatment modalities:***
  - ***Hypochlorous solution 0.2%***
  - ***Tea tree oil***
  - ***Lotaliner 0.25% (pending FDA approval)***

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Ocular Surface Disease

Clinical Treatments and Decision Algorithms – Thermal

LipiFlow (J&J)
- Heat + Pressure
- 1st FDA device
- ~$850/session x 1

iLux (Alcon)
- Heat + Pressure
- Hand-held
- ~$600/session x PRN

TearCare (Sight Sciences)
- Heat
- ~$650/session x 1

MiBo (MiBo Medical)
- Heat
- Manual massage during procedure
- ~$300/session x 3

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Ocular Surface Disease

Clinical Treatments and Decision Algorithms – IPL

OptiLight (Lumenis)
- 1st FDA-approved IPL device (**Apr 2021**)
  - Reduced inflammation / telangiectasia
  - Improve TBUT
  - Improved MG function
  - Decreased Demodex infestation
- λ: 530-650nm & 900-1200nm with >600nm most effective for MGD
- ~$400/session x 4

E.Eye (ESW Vision)
- Not FDA-approved
  - "Micro-gradient temperature changes to parasympathetic nerves releasing NT affecting MG"
  - Improved MG function
- ~$200/session x 4

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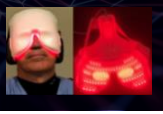
Ocular Surface Disease
Clinical Treatments and Decision Algorithms – LLLT

Equinox (Marco) and Epi-C Plus (Marco)

Effect of low-level light therapy in patients with dry eye: a prospective, randomized, observer-masked trial.
Sci Rep (2022) 12(1): 3575

Low-level light therapy in the treatment of meibomian gland dysfunction
ARVO Journal (2020)

Intense pulsed plus low-level light therapy in meibomian gland dysfunction
Clin Ophthalmol (2021) 15: 2803-2811



Equinox (Marco)
- Not FDA approved
- PBM procedure
- λ: 633nm
- ~$150/session x 4

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Ocular Surface Disease
Clinical Treatments and Decision Algorithms - RF

Radio Frequency Versus Thermal Pulsation for MGD : Split-Faced Randomized Dry-Eye Treatment Pilot Study
2017 ASCRS Symposium and Congress

Methods
10 patients with MGD with OSD were followed after randomized manual massage of the eyelids using the Pellevé Wrinkle Reduction System (thermaLid Procedure) in 1 eye and a standard LipiFlow procedure performed the same day in the fellow eye at 1 and 3mos. Response was assessed by the Korb MGD Evaluator, tear lipid layer, TBUT, ocular surface staining, Marx Line grading, osmolarity and Schirmer's testing. Symptoms were assessed by the SPEED and OSDI.

Results
Function of the MG improved significantly from baseline to 3 months and was not statistically different between thermaLid and Lipiflow treated eyes at 3 months, as measured by MG grading, wax plug scoring, SPEED and OSDI scoring. A significant change in conjunctival staining was found after both thermaLid and Lipiflow treatments at the 1-month time point but not the 3-month time point.

Conclusion
thermaLid's efficacy was similar to Lipiflow in reducing wax plugging, improving the number of functioning MGs and reducing conjunctival staining in MGD-related DED

Pellevé Wrinkle Reduction System
***thermaLid**

~$500/session x 4

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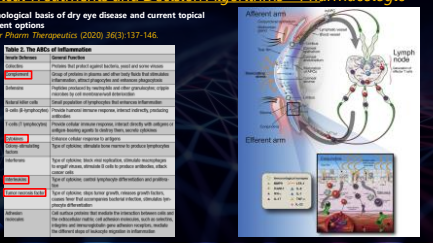
Ocular Surface Disease
Clinical Treatments and Decision Algorithms – Pharmacologic

Immunological basis of dry eye disease and current topical treatment options
J Ocular Pharm Therapeutics (2020) 36(3):137-146.



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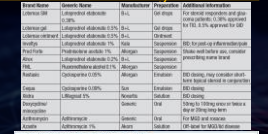
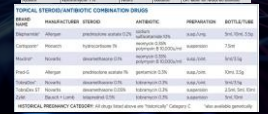
Ocular Surface Disease
Clinical Treatments and Decision Algorithms – Pharmacologic





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Ocular Surface Disease
Clinical Treatments and Decision Algorithms – Pharmacologic

Bringing biologics to eye health: Regenerative medicine for inflammatory disorders
Ophthal Times Europe (2022; 18(3)

- Include a vaccines, blood and blood components, allergenics; somatic cells, gene therapy, tissues and recombinant therapeutic proteins
- Isolated from a variety of natural sources, typically proteins from humans, animals or microorganisms and can also consist of sugars, nucleic acids or a combination
- Acellular and complex and, because they are not a pharmaceutical product, they are less likely to produce adverse effects in patients
- Ability to promote healing without scarring is a significant benefit in the treatment of DED and other corneal disorders

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Ocular Surface Disease
Clinical Treatments and Decision Algorithms – Pharmacologic

Antibiotic treatment for DED related to MGD and blepharitis – Review
Ocular Surface (2022)

Results
Oral and topical antibiotics appeared to have short-term positive effects on signs and symptoms of blepharitis and MGD-related DED. However, these improvements often reverted upon cessation of treatment. ***The need for repeated treatments and mild adverse events were common.***

Conclusions
Current evidence suggests that patients with blepharitis or MGD-related DED experience short-term benefits of antibiotics (azithromycin, doxycycline, minocycline)

Varenicline Solution Nasal Spray: Review in DED
Drugs (2022) 82(14):1481-1488

Data Synthesis
FDA approved for the treatment of DED in 2021 and demonstrated a ***statistically significant improvement in outcomes related to basal tear film production as measured by a Schirmer test score*** in data from phase 2 and 3 clinical trials. Tyrvaya was well tolerated with minimal ocular side effects (sneezing, coughing, throat/nasal irritation)

Conclusions
IN varenicline stimulates nicotinic cholinergic receptors and basal tear film production through the CN V parasympathetic nerve pathway. There is ***no evidence to support the long-term remission of DED symptoms with IN varenicline as seen with anti-inflammatory modulators***

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Ocular Surface Disease

Clinical Treatments and Decision Algorithms – Pharmacologic

Systematic review of the effect of Ω-3 supplements on MGD

Therapeutic Adv Ophthal (2020) 12

Results

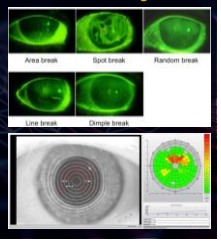
Database search yielded to one RCT and six clinical trials through the MEDLINE of a total of 350 participants for the systematic review and meta-analysis study.

- ***Ω-3 group had a positive effect on MGD protection demonstrated by the NaFl-TBUT score compared with the placebo group (OR=8.72)***

Data suggest that the odd ratios of the Ω-3 group to control group increased the likelihood of the improved TBUT in the treatment group

Conclusions

- ***Moderate daily dose of Ω-3 may be a beneficial therapeutic for MGD***
- ***Underscores the value of NITBUT compared with invasive NaFl-TBUT***



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Ocular Surface Disease

Clinical Treatments and Decision Algorithms – Pharmacologic

Efficacy of Ω-3 Fatty Acid Supplementation for Treatment of Dry Eye Disease: A Meta-Analysis of Randomized Clinical Trials

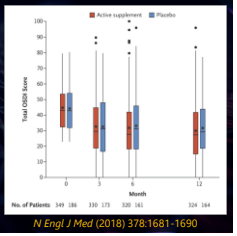
Cornea (2019) 38(5):565-573

Results

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

Conclusions

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



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

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Ocular Surface Disease

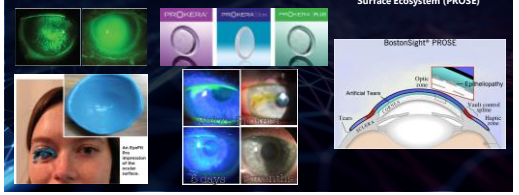
Clinical Treatments and Decision Algorithms – Therapeutic

Severe Desiccation or Neurotrophic keratitis (NK)

Scleral lenses

Prokera (Biotissue)

BostonSight Prosthetic Replacement of the Ocular Surface Ecosystem (PROSE)



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Ocular Surface Disease

Clinical Treatments and Decision Algorithms – Homework

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Ocular Surface Disease

Clinical Treatments and Decision Algorithms – Lifestyle

Impact of lifestyle intervention on DED in office workers: RCT

J Occup Health (2018) 60(4): 281-288

Methods

Prospective interventional RCT study with definite and probable dry eye disease were enrolled and randomized to an intervention group (n=22) and a control group (n=19). The intervention aimed at ***modifying diet, increasing physical activity, and encouraging positive thinking***. The primary outcome was change in DED. Secondary outcome was change in disease parameters, including dry eye symptoms, as assessed using the Dry Eye-Related Quality of Life Score, corneal and conjunctival staining scores, TBUT and Schirmer test results.

Results

A total of 36 participants (intervention group, 17; control group, 19) completed the study. The number of definite dry eye disease diagnoses decreased from four to none.

- ***DES score showed a significant decrease in the intervention group***
- ***Staining scores, tear break-up time, and Schirmer test results did not differ significantly between groups***

Conclusions

- ***1-month lifestyle intervention employed in this study improved dry eye disease status among office workers with considerable decrease in subjective symptoms***

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Ocular Surface Disease

Targeted Treatment – Root Cause vs. Sequela + Episodic vs. Chronic

Underlying systemic disease?
Current medication regimen?
Environmental factors?
Personality traits?

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Ocular Surface Disease
Take Home Points

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Ocular Surface Disease
Take Home Points

TYPE	MANAGEMENT	
EPISODIC	Tear supplements / lubricants	*Consider composition of available agents (lipid-based, products that restore the mucin layer, overall)*
	Ocular	*Hot compresses, lid hygiene, moisture chamber glasses, modifications to CL wear (switch to daily disposables)*
	Non-ocular considerations	*Environmental (ambient humidity, air movement, computer use), systemic medications and supplements, alcohol, smoking, hormonal status, sleep apnea*
CHRONIC		**Episodic management** +
	Short-term	*Topical corticosteroid*
	Long-term	*Topical cyclosporine*
	Supportive	*Essential fatty acids*
		Oral tetracycline / macrolide, lacrimal occlusion, meibomian gland (MG) expression (in-office), sleep masks/ lid taping
RECALCITRANT	Ocular	*Scleral lenses, filament removal, autologous serum eye drops, amniotic membranes, tarsorrhaphy, other surgical techniques*
	Systemic	*Secretagogue, systemic immunosuppressive therapies*

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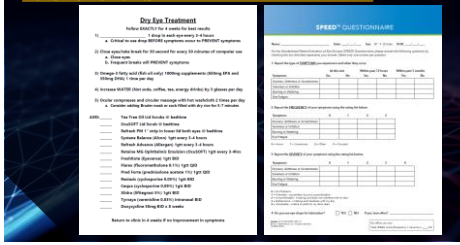
Ocular Surface Disease
Take Home Points



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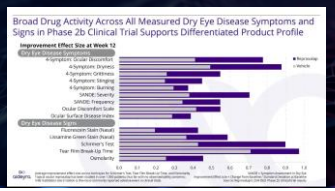
Ocular Surface Disease
What's next? - Reproxalap

- FDA has accepted the New Drug Application for topical ocular reproxalap ***(Feb2023)***
- First-in-class, small-molecule modulator of RASP (reactive aldehyde species) used for treatment of DED signs and symptoms



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Ocular Surface Disease
What's next? – Lotaliner 0.25%

Approximately 45% of patients with blepharitis have concomitant Demodex infestation

- TP-03 (Tarsus Pharmaceuticals) would be the first FDA-approved for Demodex blepharitis
  - Solution paralyzes by selectively hindering parasite-specific γ-aminobutyric acid chloride channels.
- Demonstrated safety, tolerability, and efficacy in reducing collarettes and mite density in ~28 days
- After 43 days of treatment, study group achieved:
  - ***clinically meaningful collarette cure (81% v. 23%)***
  - ***complete collarette cure (44% vs 7%)***
  - ***mite eradication (68% vs 18%)***
  - ***erythema cure (19% vs 7%)***

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Ocular Surface Disease
What's next? – NovaTears + Ω-3

DED MGD patienmts tend to have lower levels of polyunsaturated fatty acids in their tear film

- NOV03 (Bausch + Lomb) is a water-free eye drop that combines perfluorohexyloctane with Ω-3 fatty acid esters, which positively influence evaporation and oxidative stress resistance
- Demonstrated a clinically and statistically significant ability to improve DED signs and symptoms after QID treatment x 8 weeks
  - Corneal NaFl staining and MGD scores improved significantly at 8 weeks compared with baseline and no adverse events were reported

FDA New Drug Application received: Sep2022
Prescription Drug User Fee Act (PDUFA) date 23June2023.

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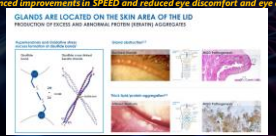
Ocular Surface Disease

What's next? – AZR-MD-001

- Ophthalmic keratolytic (Azura Ophthalmics) may be able to loosen blockages and improved meibum secretion in the upper and lower eyelids in patients with MGD.
  - Prevents protein buildup and blockage by promoting healthy oil production
    - Similar product used in dandruff shampoos and utilized for in-office use only as a sporadic maintenance measure
- During the phase 2b study, patients with MGD applied AZR-MD-001 0.5% to their lower eyelid twice weekly qhs
  - During the 3-month study, the medication met its co-primary endpoints of improved Meibomian Glands Yielding Liquid Secretion and OSDI scores
  - ***Patients experienced improvements in SPEED and reduced eye discomfort and eye dryness***



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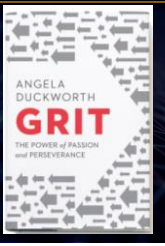

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Questions?

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