Latest Updates

Dry Eye Disease & Omega 3

Alice T. Epitropoulos, MD
The Eye Center of Columbus
Clinical Assistant Professor
The Ohio State University

Alice T. Epitropoulos MD

Disclosures

Speaker & Consultant

Alcon/Novartis
Allergan/Abbvie
AMO/J&J/TearScience
Bausch & Lomb
Dompe
EyeVance
Kala Pharmaceuticals
OTX
Oyster Point
Physician Recommended Nutriceuticals
SUN Ophthalmics
Tarsus
TearLab Corp

Consultant

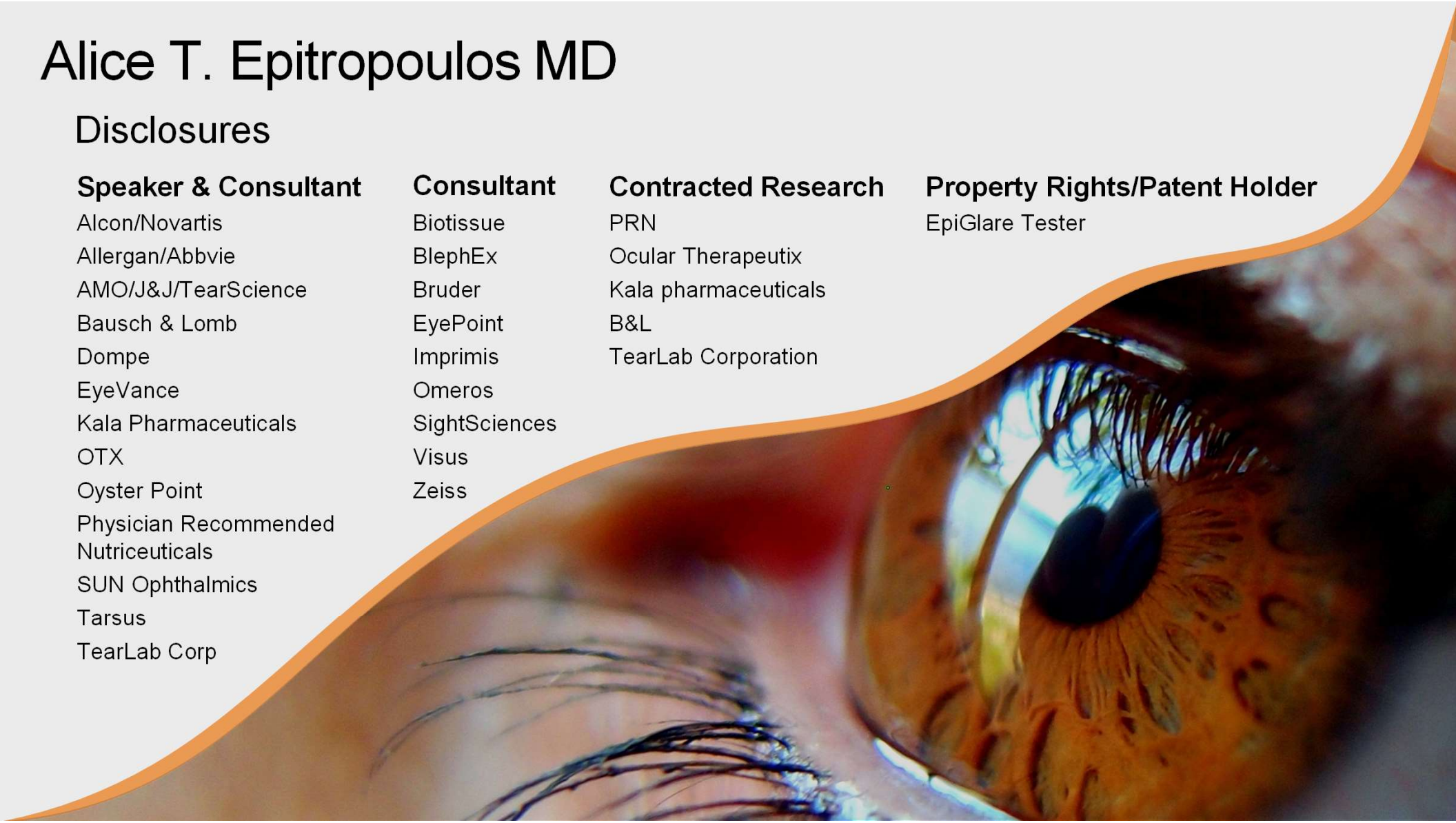
Biotissue
BlephEx
Bruder
EyePoint
Imprimis
Omeros
SightSciences
Visus
Zeiss

Contracted Research

PRN
Ocular Therapeutix
Kala pharmaceuticals
B&L
TearLab Corporation

Property Rights/Patent Holder

EpiGlare Tester



Dry Eye Disease

One of the Most Common Reasons Patients Visit an ECP[1]

344 M  WORLDWIDE ESTIMATE OF DED2

30 M  DED SYMPTOMS REPORTED BY US ADULTS[3,4]

16 M  DIAGNOSED WITH DED[5]

1.5 M  TREATED WITH A PRESCRIPTION[6]

DRY EYE DISEASE IS UNDER-DIAGNOSED AND UNDER TREATED

1. Nichols KK et al. Inv Ophthalmol & Vis Sci. 2016;57:2975-2982.
2. 2016 Dry Eye Products Market Scope Report: A Global Market Analysis for 2015-2021. Market Scope. 2016:1-213.
3. Paulsen AJ et al. Am J Ophthalmol. 2014;157(4):799-806.
4. US Census Bureau. Annual estimates of the resident population for selected age groups by sex for the United States, States, Counties, and Puerto Rico Commonwealth and Municipios: April 1, 2010 to July 1, 2014. Available at: https://factfinder.census.gov/faces/tableservices/jsf/pages/productview.xhtml?src=bkmk. Accessed May 4, 2018.
5. Data on file. 6. Steinberg D et al. Equity Research Americas. May 18, 2017:1-38.

Questionnaire

SPEED

SPEED Questionnaire

Name: _____, _____ Date: ___/___/_____
(Last) (First)

DOB: ___/___/_____ Sex: M F

Report the type of **SYMPTOMS** you experience and when they occur:

SYMPTOMS	AT THIS VISIT		WITHIN PAST 72 HRS		WITHIN PAST 3 MONTHS	
	YES	NO	YES	NO	YES	NO
Dryness, Grittiness or Scratchiness						
Soreness or Irritation						
Burning or Watering						
Eye Fatigue						

Report the **FREQUENCY** of the above-checked symptoms as Never, Sometimes, Often or Constant using the numbering system below:

SYMPTOMS	0	1	2	3
Dryness, Grittiness or Scratchiness				
Soreness or Irritation				
Burning or Watering				
Eye Fatigue				

0 = Never, 1 = Sometimes, 2 = Often, 3 = Constant

Report the **SEVERITY** of your Symptoms using the rating list below:

SYMPTOMS	0	1	2	3	4
Dryness, Grittiness or Scratchiness					
Soreness or Irritation					
Burning or Watering					
Eye Fatigue					

0 = No problems
1 = Tolerable – not perfect but not uncomfortable
2 = Uncomfortable – irritating but does not interfere with my day
3 = Bothersome – irritating and interferes with my day
4 = Intolerable – unable to perform my daily tasks

Do you use drops and/or ointment? _____ What drops do you use?_____

OSDI

Ocular Surface Disease Index© (OSDI©)[2]

Ask your patients the following 12 questions, and circle the number in the box that best represents each answer. Then, fill in boxes A, B, C, D, and E according to the instructions beside each.

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?	4	3	2	1	0
2. Eyes that feel gritty?	4	3	2	1	0
3. Painful or sore eyes?	4	3	2	1	0
4. Blurred vision?	4	3	2	1	0
5. Poor vision?	4	3	2	1	0

Subtotal score for answers 1 to 5 (A)

Have problems with your eyes limited you in performing 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	N/A
6. Reading?	4	3	2	1	0	N/A
7. Driving at night?	4	3	2	1	0	N/A
8. Working with a computer or bank machine (ATM)?	4	3	2	1	0	N/A
9. Watching TV?	4	3	2	1	0	N/A

Subtotal score for answers 6 to 9 (B)

Have your eyes felt uncomfortable in any of the following situations *during the last week?*	All of the time	Most of the time	Half of the time	Some of the time	None of the time	N/A
10. Windy conditions?	4	3	2	1	0	N/A
11. Places or areas with low humidity (very dry)?	4	3	2	1	0	N/A
12. Areas that are air conditioned?	4	3	2	1	0	N/A

Subtotal score for answers 10 to 12 (C)

Add subtotals A, B, and C to obtain D
(D = sum of scores for all questions answered) (D)

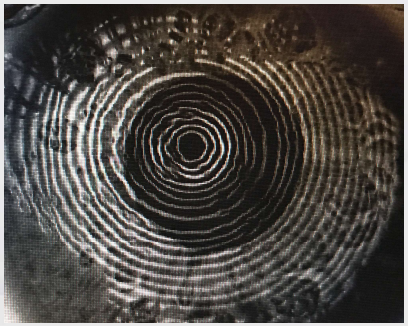
Total number of questions answered
(do not include questions answered N/A) (E)

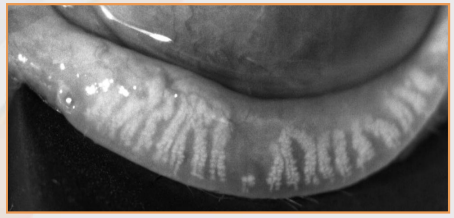
Please turn over the questionnaire to calculate the patient's final OSDI© score.

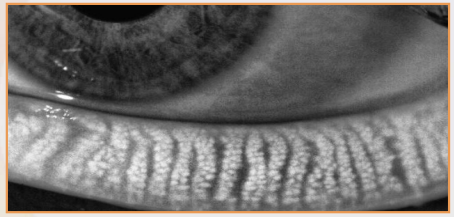
Current Options Diagnosing & Evaluating Dry Eye

Point of Care Testing

- Tear osmolarity
- MMP-9 testing
- Interferometry
- Dynamic illumination of MGs
- Advanced corneal topography







Empower Technicians to perform POC

- Tear Osmolarity & MMP9
  - Before any eye drops
- Meibography
- Improves ability to diagnose and classify OSD

InflammaDry

Detects MMP9

Inflammatory Marker - elevated in tears of patients with DED!

85% Sensitivity[2]

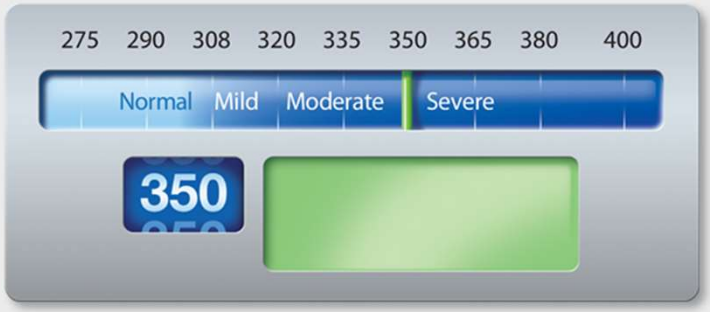
94% Specificity[2]

Chotikavanich S, de Paiva C, Quan Li D, et al. Production and activity of matrix metalloproteinase-9 on the ocular surface increase in dysfunctional tear syndrome. Invest Ophthalmol Vis Sci; 2009

Tear Osmolarity

Evaluates dry eye severity & therapeutic response

- OSD
- Hyperosmolarity
- Unstable Tear Film



JOURNAL OF
CATARACT &
REFRACTIVE SURGERY

Effect of tear osmolarity on repeatability of keratometry for cataract surgery planning

Alice T. Epitropoulos, MD, Cynthia Matossian, MD, Gregg J. Berdy, MD, Ranjan P. Malhotra, MD, Richard Potvin, OD

SETTING: Three clinical practices.

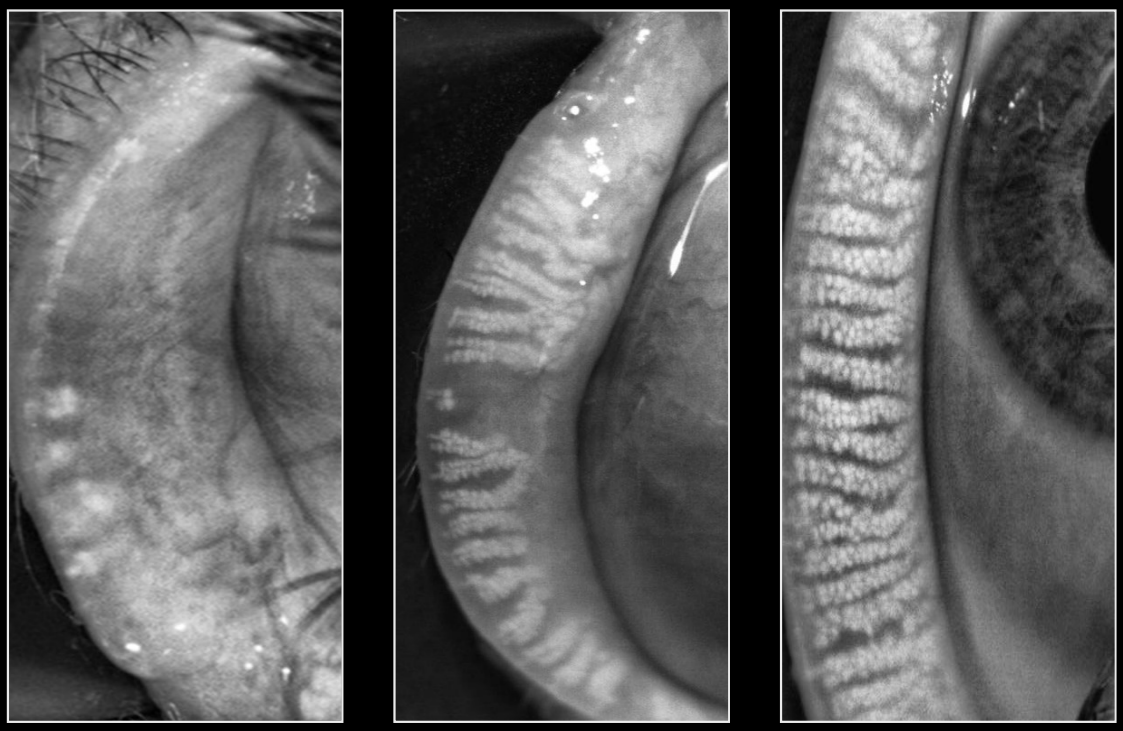
DESIGN: Observational prospective nonrandomized study.

METHODS: Subjects were prospectively recruited based on tear osmolarity (Tearlab Osmolarity System); that is, osmolarity more than 316 mOsm/L in at least 1 eye (hyperosmolar) and osmolarity less than 308 mOsm/L in both eyes (normal). The baseline K value was measured, and a second measurement was taken on the same instrument (IOLMaster) within 3 weeks of the first. Variability in average K, calculated corneal astigmatism using vector analysis, and intraocular lens (IOL) sphere power calculations were compared between groups.

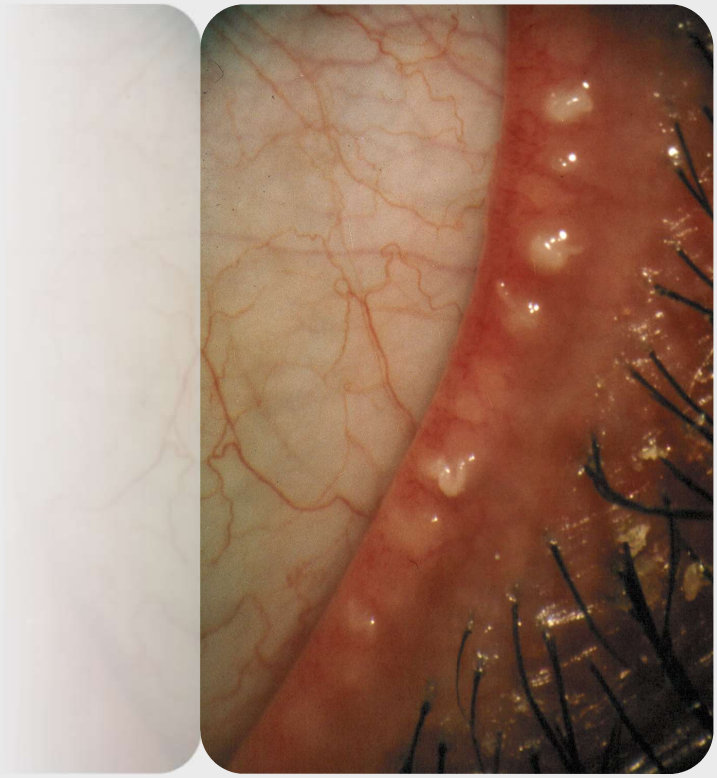
RESULTS: The hyperosmolar group (50 subjects) had a statistically significantly higher variability in the average K reading ($P = .05$) than the normal group (25 subjects) and a statistically significantly higher percentage of eyes with a 1.0 diopter (D) or greater difference in the measured corneal astig-

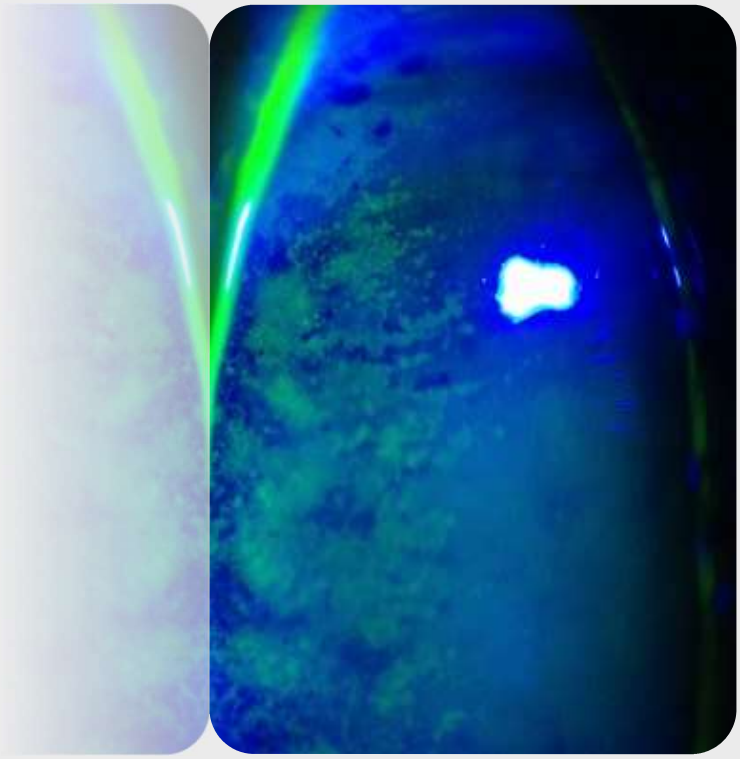
CONCLUSIONS: Significantly more variability in average K and anterior corneal astigmatism was observed in the hyperosmolar group, with significant resultant differences in IOL power calculations. Variability was not significantly different when subjects were grouped by self-reported dry

Screen for MGD

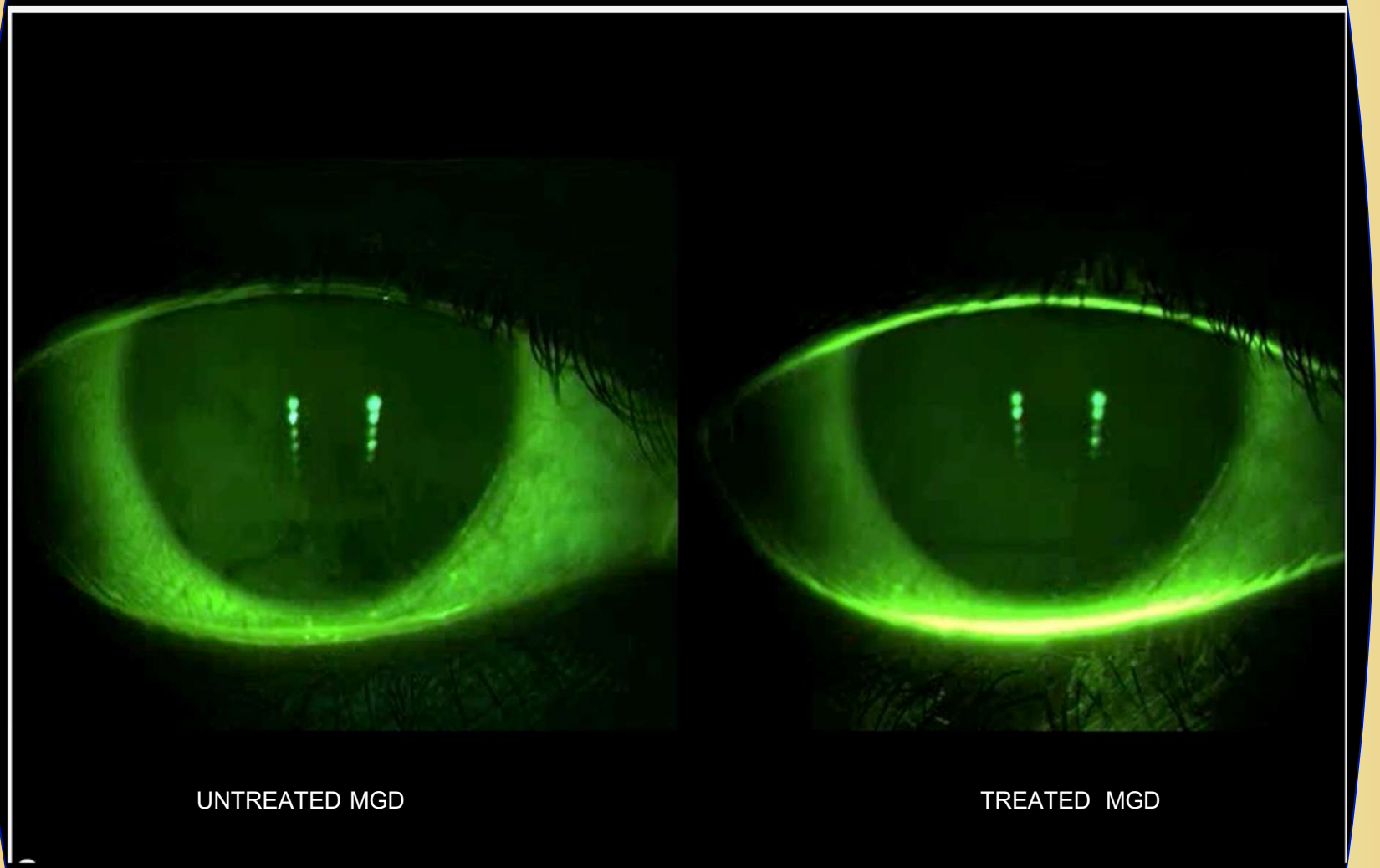


Careful slit lamp biomicroscopy





Evaporative Dry Eye - MGD



Identify Influential Factors that may exacerbate DED

Visual Tasking
(e.g. PC use)

Systemic Medications
(e.g. anti-histamines)

Alcohol
(e.g. beer)

Arid Conditions
(e.g., Midwest)

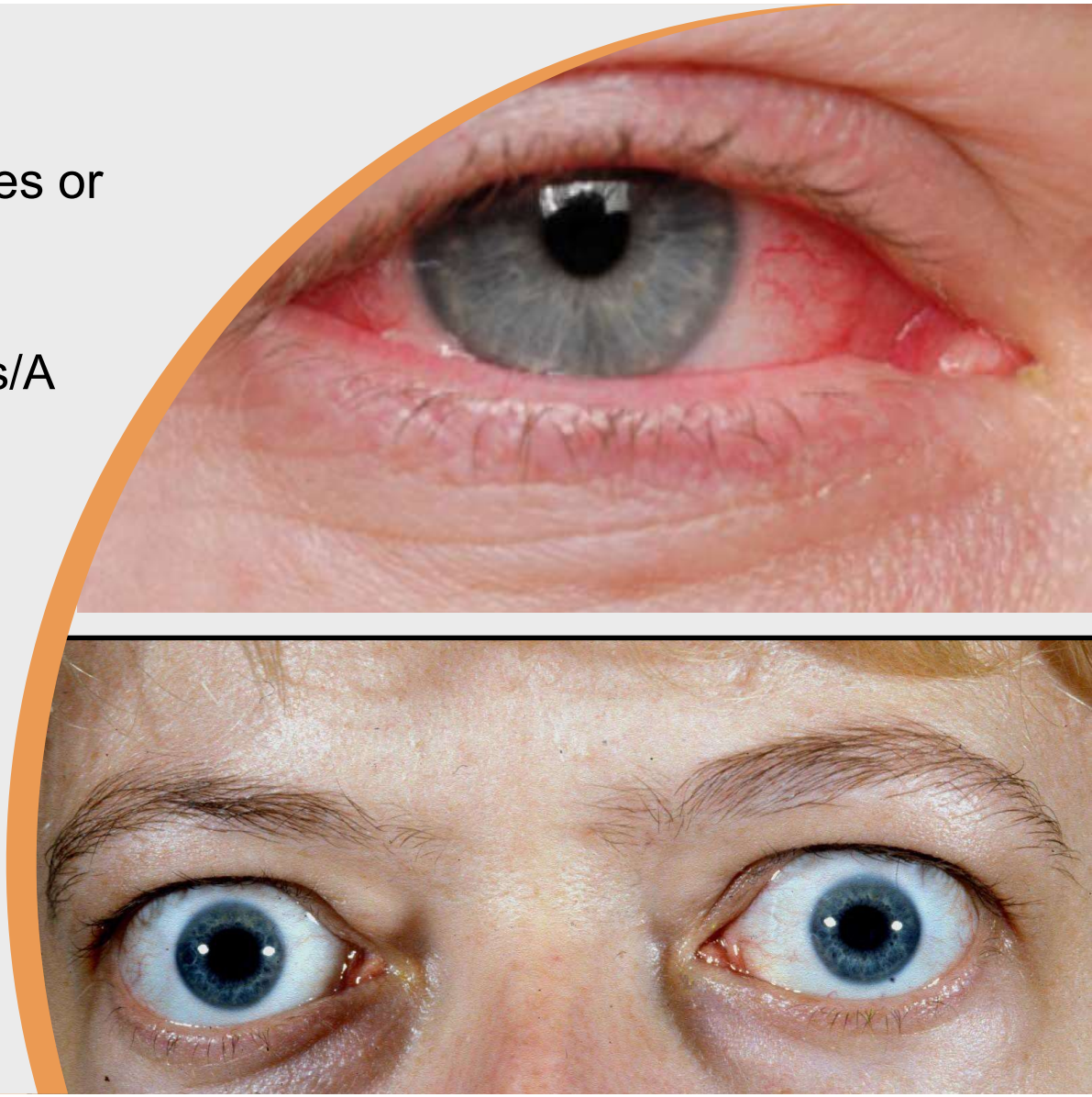
Windy Environments
(e.g., AC, forced heat)

Pollutants
(e.g., exhaust, smog)

Identify

other underlying high-risk diseases or medications?

- Thorough medication history
  - Antihistamines/Decongestants/Antidepressants
  - Eye drops – ***GLAUCOMA!!!***
- Systemic history
  - Sjogren's (Sjo test)
  - Rheumatoid
  - Rosacea
  - Thyroid dysfunction
  - Lupus
  - Hormonal changes



Treatment Options Today…

Therapeutic approach making headway

Current Therapies

- Omega-3 supplements
- Cyclosporine
- Lifitigrast
- Steroids
- Lid cleansers
- Oxervate – NK
- Serum Tears

In-office therapies

- Microblepharoexfoliation
- Thermal pulsation
- iLux
- Tear Care
- Maskin probing
- IPL
- Punctal occlusion
- Amniotic membrane

…In the Future

Pipeline

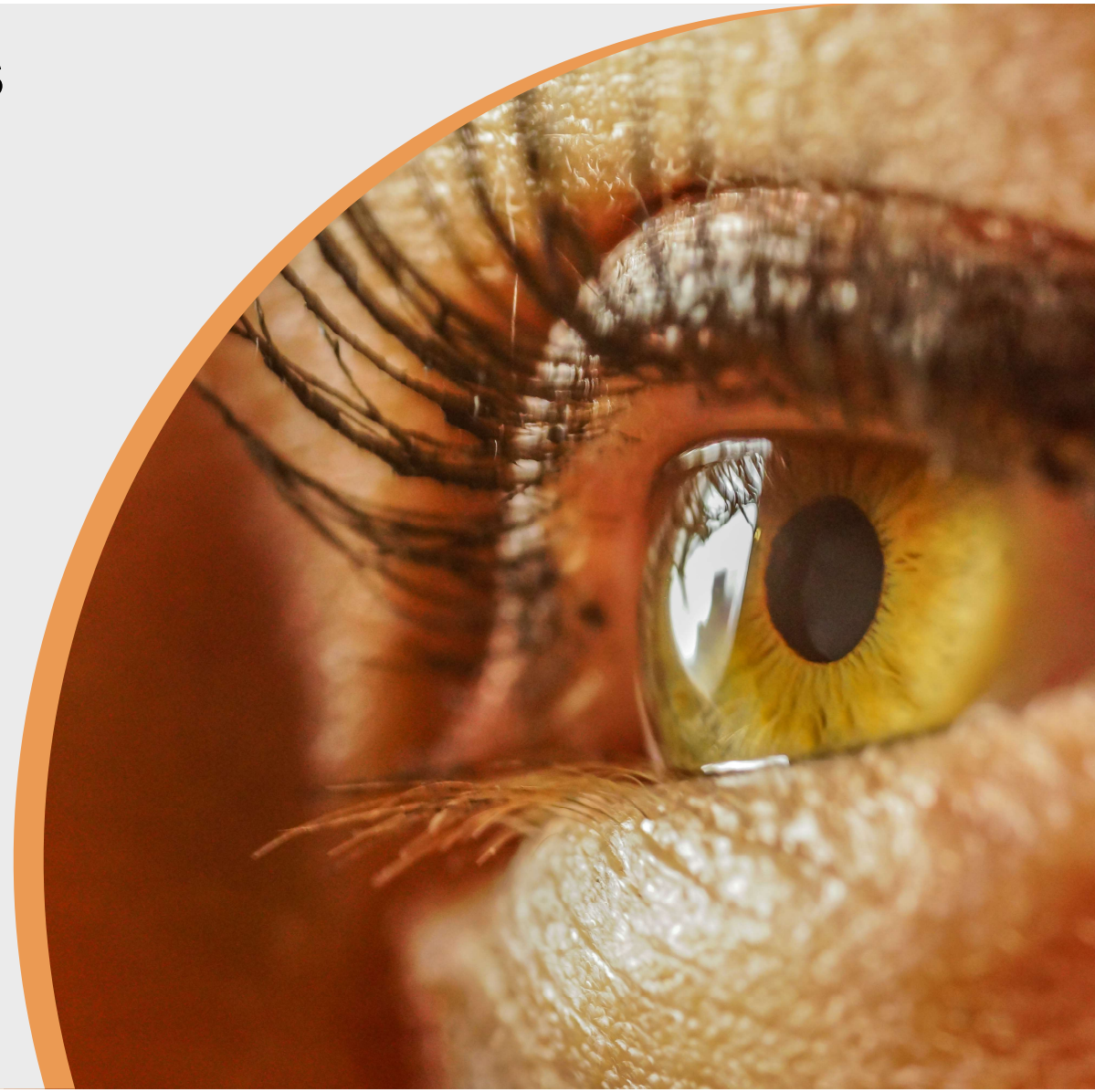
In Development

- AZR-MD-001 (Azura)
- OC-01 Nasal Spray (Oyster Point)
- TP-03 (Tarsus)
- Intracanalicular punctal plugs
- Lacripep (synthetic peptide of lacritin
- Novaliq's CyclASol A
- Topical Spironolactone
- Mucous Secretagogues
  - MIM-D3
  - Rebamipide
- Amniotic drops
- Devices
  - Ocular Iontophoresis

Bring Tears to Your Eyes

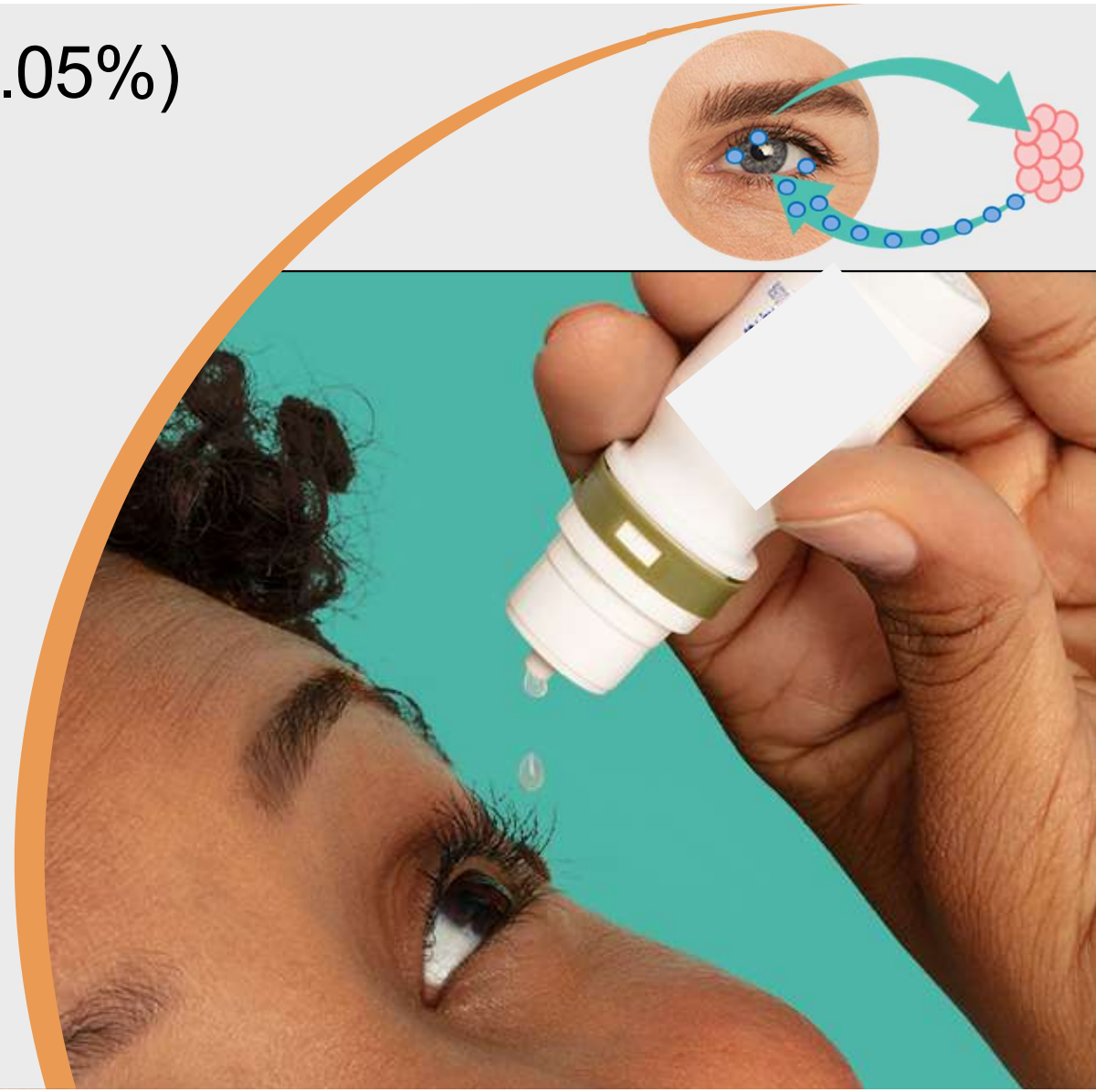
Anti-Inflammatory Agents

PRIMARY GOAL:
Reducing inflammation in treatment of mild, moderate and advanced DED



Restasis (Cyclosporine 0.05%)

- Inhibits T-Cell activation
- Clinical trials
  - Increased tear production
  - Reduced corneal staining
  - Increased goblet cell density
  - Reduced reliance on artificial tears
  - Less likely to progress[1]
  - Improved visual acuity (Donnenfeld)[2]



Cequa (Cyclosporine 0.09%)

- Novel nanomicelle formulation improves delivery of cyclosporine A
  - improved therapeutic penetration and efficacy
  - Well tolerated, mild AE's
  - Significant improvement tear production & ocular surface integrity

Xiidra (Lifitegrast)

Small-molecule Integrin Antagonist

Indication

- Approved to treat both signs & symptoms of DED
- Results seen as early as 2 weeks[1]
- Might be used together with Cyclosporine for greater effectiveness

1Semba CP, Gadek TR. Development of lifitegrast: a novel T-cell inhibitor for the treatment of dry eye disease. Clin Ophthalmol. 2016;10:1083-1094-

Xiidra (Lifitegrast)

LFA-1 and ICAM-1 binding is central to the immunological response

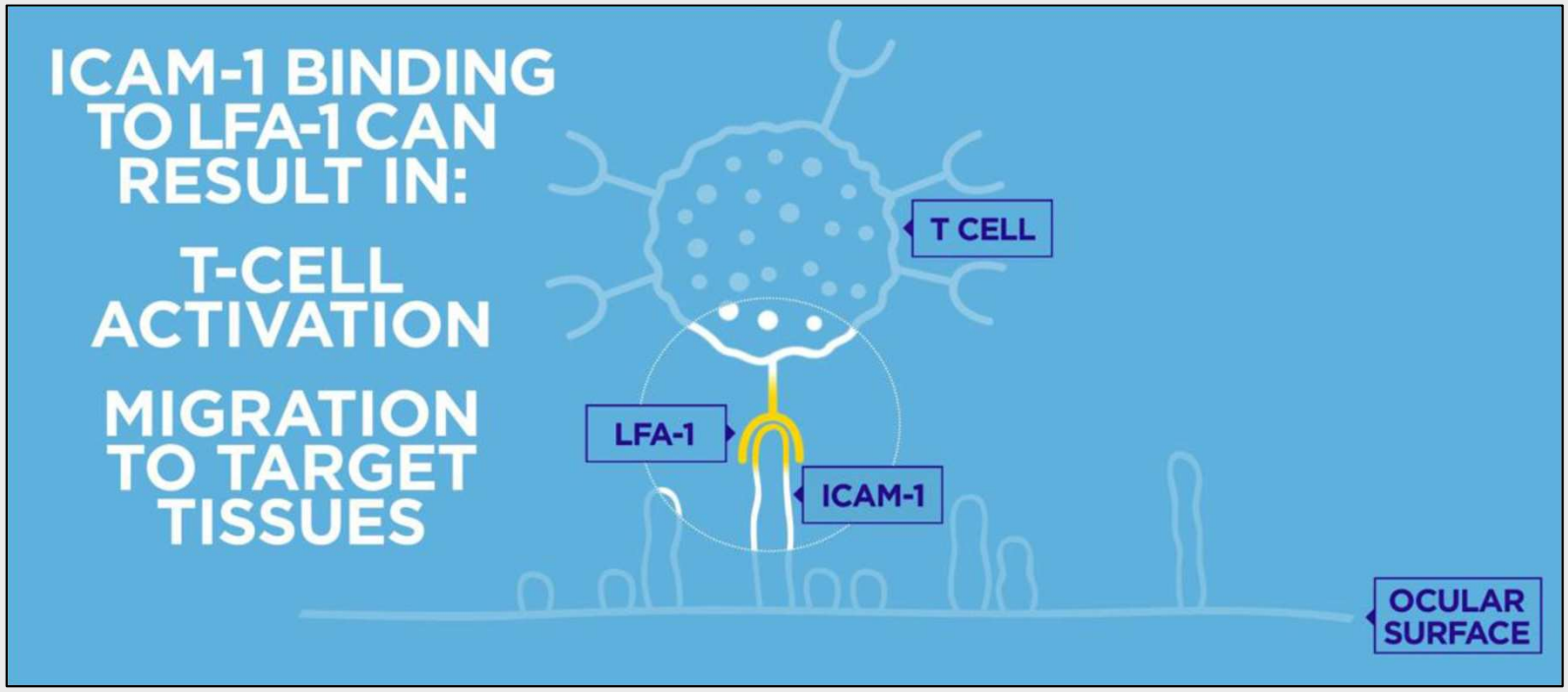


Image courtesy Shire

Xiidra (Lifitegrast)

LFA-1 and ICAM-1 binding is central to the immunological response

Indication

- By Blocking ICAM-1/LFA-1 interaction, lifitegrast may prevent
  - T Cell activation
  - Migration
  - Cytokine release

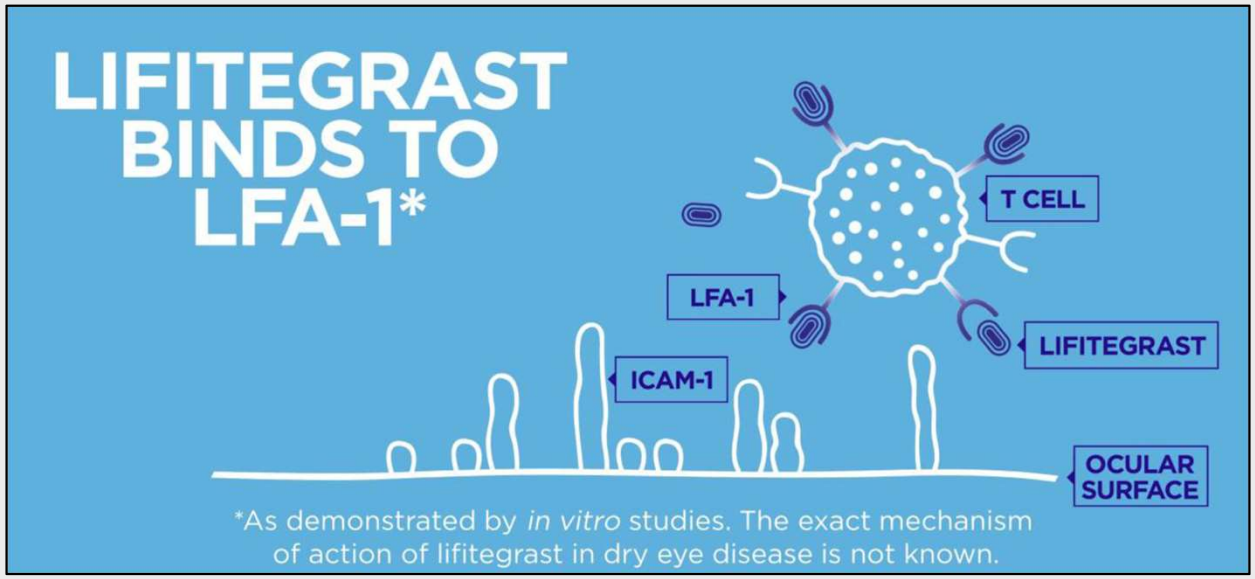
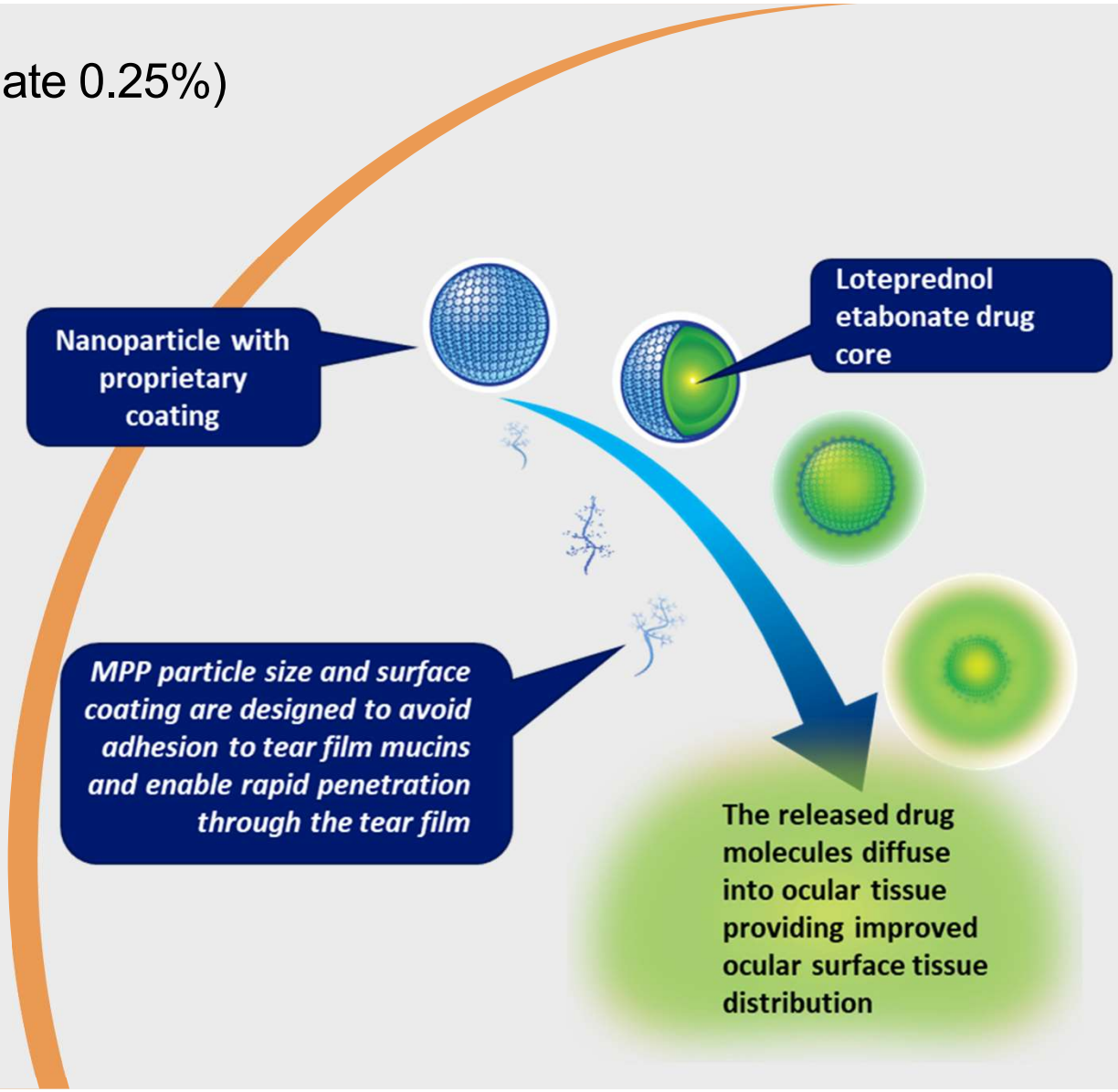


Image courtesy Shire

EYSUVIS (Loteprednol etabonate 0.25%)

Newest Option

- Nano-suspension of Loteprednol etabonate (LE)
  - Ester steroid designed to avoid steroid related side effects
  - Formulated with proprietary (MMP) vehicle
  - Nanotechnology allows rapid penetration through ocular tissues
- Temporary relief of signs and symptoms of dry eye disease



1Semba CP, Gadek TR. Development of lifitegrast: a novel T-cell inhibitor for the treatment of dry eye disease. Clin Ophthalmol. 2016;10:1083-1094-

OXERVATE™

(cenegermin)

- Recombinant human nerve growth factor FDA approved August 2018
- First drug approved for the treatment of Neurotrophic keratitis
- Treatment one 8-week cycle
- Developed by Dompé pharmaceuticals,

Bonini S, Lambiase A, Rama P *et al.* Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis. *Ophthalmology* 2018;125:1332-1343.

AMERICAN ACADEMY OF OPHTHALMOLOGY®

Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis

*Stefano Bonini, MD,[1] Alessandro Lambiase, MD, PhD,[2] Paolo Rama, MD,[3] Francesco Sinigaglia, MD,[4] Marcello Allegretti, PhD,[4] Wendy Chao, PhD,[4] Flavio Mantelli, MD, PhD,[4] for the REPARO Study Group**

Purpose: To evaluate the safety and efficacy of topical recombinant human nerve growth factor (rhNGF) for treating moderate-to-severe neurotrophic keratitis (NK), a rare degenerative corneal disease resulting from impaired corneal innervation.

Design: Phase II multicenter, randomized, double-masked, vehicle-controlled trial.

Participants: Patients with stage 2 (moderate) or stage 3 (severe) NK in 1 eye.

Methods: The REPARO phase II study assessed safety and efficacy in 156 patients randomized 1:1:1 to rhNGF 10 μg/ml, 20 μg/ml, or vehicle. Treatment was administered 6 drops per day for 8 weeks. Patients then entered a 48- or 56-week follow-up period. Safety was assessed in all patients who received study treatment, whereas efficacy was by intention to treat.

Main Outcome Measures: Corneal healing (defined as <0.5-mm maximum diameter of fluorescein staining in the lesion area) was assessed by masked central readers at week 4 (primary efficacy end point) and week 8 (key secondary end point) of controlled treatment. Corneal healing was reassessed post hoc by

Oxervate

Up to 72% of patients achieved complete corneal healing;
80% of healed patients were recurrence free after 1 year*

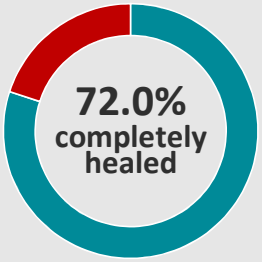
After 8 weeks of treatment,
6 times daily

In the majority of patients across two clinical studies OXERVATE™ (cenegermin ophthalmic solution 0.002%) was well tolerated and more effective than vehicle in promoting complete corneal healing of moderate or severe NK.

Study NGF0212 (REPARO) (N=52 per group)

European patients with NK in one eye

NCT01756456

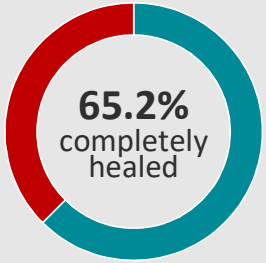


Vehicle response rate 33.3%

Study NGF0214 (N=24 per group)

U.S patients with NK in one or both eyes

NCT02227147



Vehicle response rate 16.7%

Of patients who healed after one 8-week course of treatment…

80%

Remained healed for one year*

*Based on REPARO, the study with longer follow-up

Image courtesy Shire

American diet appears to be a major contributor to MGD

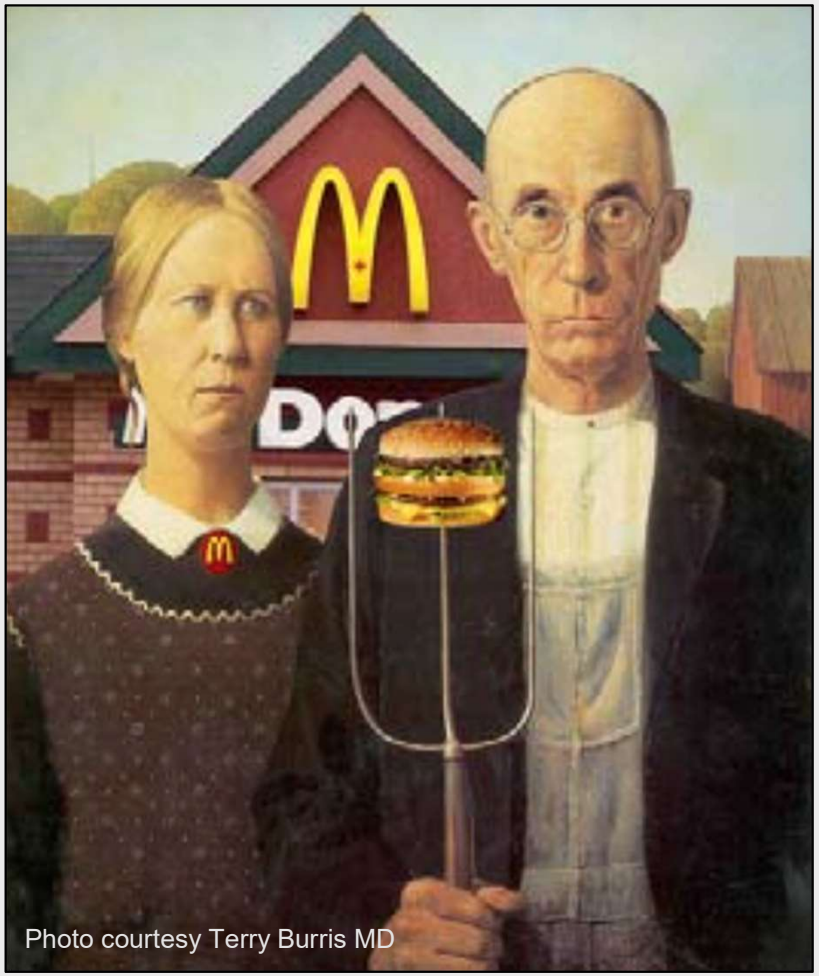
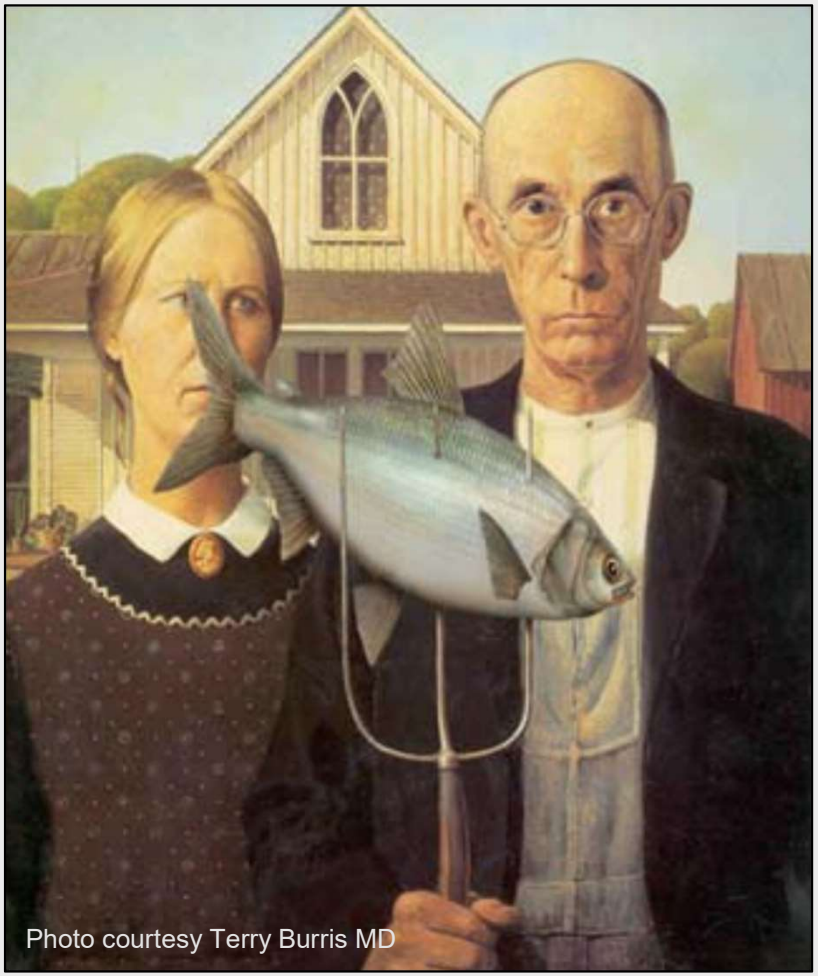


Photo courtesy Terry Burris MD

The Solution?
“Let food be thy Medicine”



Hippocrates

Treatment of Ocular Surface

Neutraceuticals – Omega 3

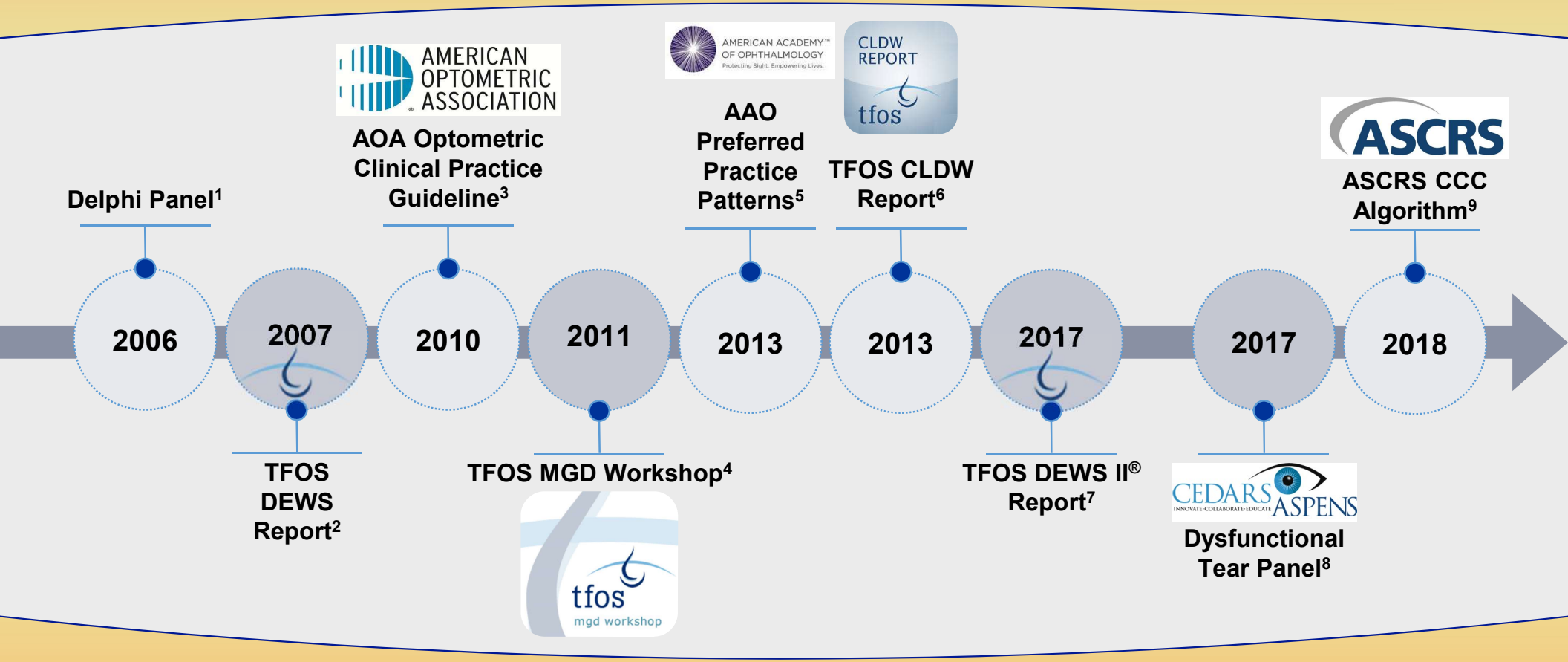
- Decrease inflammation; increase quality of tear film[1]
- Reduction of dry eye symptoms[1]
- Faster epithelial healing & visual recovery with PRK[2]
- Regeneration of corneal nerves[3]

1. Epitropoulos, Alice T, Donnenfeld, Eric D., et al., Effect of Oral Re-esterified Omega-3 Nutritional Supplementation on Dry Eyes. Cornea 2016 Sep: 35(9): 1185-1196

2. Ong NH, Epithelial healing and visual outcomes of patients using omega-3 oral nutritional supplements before and after photorefractive keratectomy: a pilot study Cornea.2013 Jun;32

3. He J,Bazan HE.Omega-3 fatty acids in dry eye and corneal nerve regeneration after refractive surgery. Prostaglandins Leukot Essent Fatty Acids.2010;82(4-6):319-325.

Experts Have Weighed In On Frameworks For Approaching DED



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2. Research Subcommittee of the International Dry Eye WorkShop. Ocul Surf. 2007;5(2):179-93.
3. Optometric Clinical Practice Guideline. 2010.
4. Nichols KK. Invest Ophthalmol Vis Sci. 2011 Mar; 52(4): 1922–1929.
5. American Academy of Ophthalmology Cornea/External Disease Panel. San Francisco, CA: American Academy of Ophthalmology; 2013.
6. Nichols JJ et al. Invest Ophthalmol Vis Sci. 2013;18;54(11):1-6.
7. Nelson JD et al. Ocul Surf. 2017;15(3):269-275.
8. Milner MS et al. Curr Opin Ophthalmol. 2017;27 Suppl 1:3-47.
9. Kim T. ASCRS Annual Meeting; April 13-17, 2018; Washington, DC.

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Am J Clin Nutr. 2005 October ; 82(4): 887–893.

The relationship between dietary n-3 and n-6 fatty acids and clinically diagnosed dry eye syndrome in women [1,2,3]

Biljana Miljanović, **Komal A. Trivedi**, **M. Reza Dana**, **Jeffery P. Gilbard**, **Julie E. Buring**, and **Debra A. Schaumberg**

Abstract

Background: Dry eye syndrome (DES) is a prevalent ocular condition, but information on risk or protective factors is lacking.

Objective: We aimed to determine the association between dietary intake of n-3 and n-6 fatty acids and their ratio and the presence of DES.

Design: Of the 39,876 female health professionals in the Women's Health Study (WHS), we studied cross-sectionally 32,470 women aged 45 to 84 years who provided information on diet and DES. We assessed intake of fatty acids by a validated food frequency questionnaire, and DES using self-reports of clinically diagnosed cases. Of the sample, 1546 (4.7%) subjects reported a clinical diagnosis of DES. We used logistic regression models to estimate the odds ratios (OR) and 95% confidence intervals (CI) to describe the relationships of fatty acid intake with DES. We analyzed the association between consumption of fish and DES in a similar way. **Results:** After adjusting for demographic factors, hormone therapy, and total fat intake, the OR (CI) for the highest versus lowest fifth of n-3 fatty acids was 0.83 (0.70-0.98), P[trend]=0.05. A higher ratio of n-6/n-3 fatty acid consumption was associated with significantly increased risk of DES, OR (CI) =2.51 (1.13-5.58) for >15/1 versus <4/1 (P[trend]=0.01). In addition, tuna consumption was inversely associated with DES (OR=0.81, CI=0.66-0.99 for 2-4 113 g (4 oz) servings/week, and OR=0.32, CI=0.13-0.79 for 5-6 servings/week versus ≤1 servings/week; P[trend]=0.005).

Conclusion: These results suggest that a higher dietary intake of n-3 fatty acids is associated with a decreased presence of DES in women. These findings are consistent with anecdotal clinical observations and postulated biological mechanisms.

CORNEA
The Journal of Cornea and External Disease

CLINICAL SCIENCE

OPEN

Effect of Oral Re-esterified Omega-3 Nutritional Supplementation on Dry Eyes

Alice T. Epitropoulos, MD, Eric D. Donnenfeld, MD,† Zubin A. Shah, MPH,‡ Edward J. Holland, MD,§ Michael Gross, MD,‡ William J. Faulkner, MD,§ Cynthia Matossian, MD,¶ Stephen S. Lane, MD,‖ Melissa Toyos, MD,** Frank A. Bucci, Jr, MD,†† and Henry D. Perry, MD†*

Purpose: To assess the effect of oral re-esterified omega-3 fatty acids on tear osmolarity, matrix metalloproteinase-9 (MMP-9), tear break-up time (TBUT), Ocular Surface Disease Index (OSDI), fluorescein corneal staining, Schirmer score, meibomian gland dysfunction (MGD) stage and omega-3 index in subjects with dry eyes and confirmed MGD.

Methods: This was a multicenter, prospective, interventional, placebo-controlled, double-masked study. Subjects were randomized to receive 4 softgels containing a total of 1680 mg of eicosapentaenoic acid/560 mg of docosahexaenoic acid or a control of 3136 mg of linoleic acid, daily for 12 weeks. Subjects were measured at baseline, week 6, and week 12 for tear osmolarity, TBUT, OSDI, fluorescein corneal staining, and Schirmer test with anesthesia. MMP-9 testing and omega-3 index were done at baseline and at 12 weeks.

Results: One hundred five subjects completed the study. They were randomized to omega-3 (n = 54) and control group (n = 51). Statistically significant reduction in tear osmolarity was observed in omega-3 group experienced a significant reduction in MMP-9 positivity versus control group (67.9% vs. 35.0%, $P = 0.024$) and OSDI scores decreased significantly in omega-3 (-17.0 ± 2.6) versus control group (-5.0 ± 2.7, $P = 0.002$).

Conclusions: Oral consumption of re-esterified omega-3 fatty acids is associated with statistically significant improvement in tear osmolarity, omega-3 index levels, TBUT, MMP-9, and OSDI symptom scores.

Key Words: dry eyes, omega-3 fatty acid, tear osmolarity, re-esterified omega-3, meibomian gland dysfunction

(*Cornea* 2016;0:1–7)

Dry eye disease (DED) is a common, yet complex, multifactorial progressive condition that can lead to visual loss, damage to the ocular surface, discomfort, and overall reduction in quality of life.[1,2] Meibomian gland dysfunction (MGD) results in inadequate and dysfunctional lipid production, which leads to evaporative DED.[3] MGD has also recently been shown to be a sign of hypercholes-

Study Design & Subject Selection

Neutraceuticals – Omega 3

Multi-center, Prospective, Interventional, randomized, Double-Masked, placebo-controlled

105 subjects completed the study randomized

- 54 in treatment group received 2 gms reesterified omega 3
- 51 in placebo group

Conclusion PRN Results

Primary:

Met both sign & symptom endpoints prospectivley

Significant improvement

- OSDI symptom scores (greater than 50% decrease)
- Tear osmolarity (19 mOsm/L decrease)
- MMP9 positivity
- Omega 3 index levels
- TBUT

CORNEA
The Journal of Cornea and External Disease

CLINICAL SCIENCE

Long-term Supplementation With n-6 and n-3 PUFAs Improves Moderate-to-Severe Keratoconjunctivitis Sicca: A Randomized Double-Blind Clinical Trial

John D. Sheppard, Jr,†‡ Ruhi Singh,§ Andrew J. McClellan,‖ Mitchell P. Weikert,‖ Stephen V. Scoper,*‡ Thomas J. Joly,*‡ Walter O. Whitley,‡ Ekta Kakkar,¶ and Stephen C. Pflugfelder§‖¶*

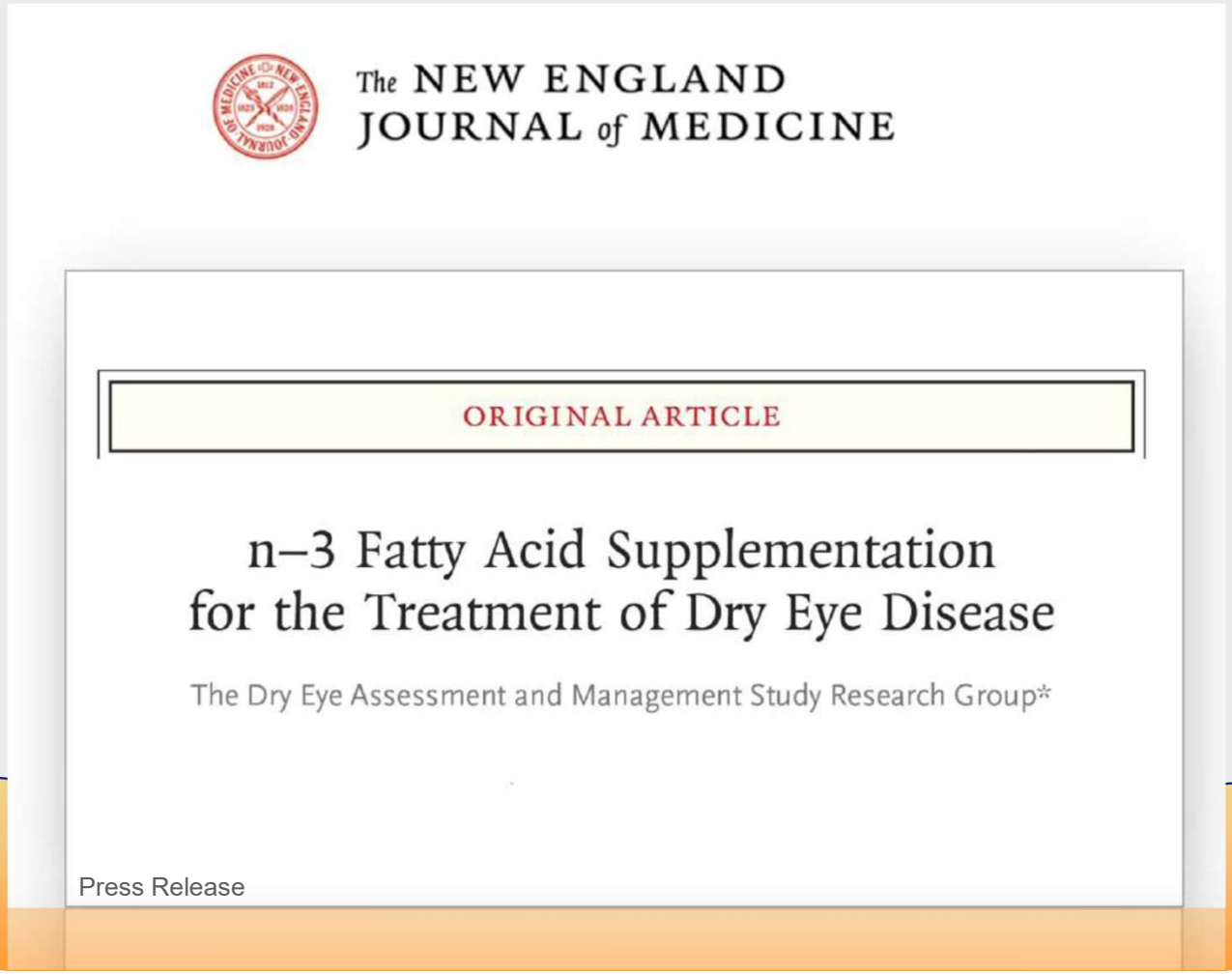
Purpose: Supplementation with gamma-linolenic acid (GLA) and omega-3 (n-3) polyunsaturated fatty acids (PUFAs) has been found to decrease the production of disease-relevant inflammatory mediators that are implicated in the pathogenesis of chronic dry eye. This study evaluated the effect of a supplement containing both GLA and n-3 PUFAs on signs and symptoms of moderate-to-severe keratoconjunctivitis sicca in postmenopausal patients.

Methods: This multicenter, double-masked placebo-controlled clinical trial enrolled 38 patients (both eyes) with tear dysfunction who were randomized to supplemental GLA + n-3 PUFAs or placebo for 6 months. Disease parameters, including Ocular Surface Disease Index, Schirmer test, tear breakup time, conjunctival fluo-

subjects (0.37 ± 0.03, n = 15) than placebo (0.51 ± 0.03, n = 16) at 24 weeks (P = 0.005). Placebo treatment also significantly increased HLA-DR intensity by 36% ± 9% and CD11c by 34% ± 7% when compared with supplement treatment (n = 19 per group, P = 0.001, 24 weeks). Neither treatment had any effect on tear production, tear breakup time, or corneal or conjunctival staining.

Conclusions: Supplemental GLA and n-3 PUFAs for 6 months improved ocular irritation symptoms, maintained corneal surface smoothness, and inhibited conjunctival dendritic cell maturation in patients with postmenopausal keratoconjunctivitis sicca. ***Clinical Trial Registration***—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00883649.

DREAM Study



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

n–3 Fatty Acid Supplementation for the Treatment of Dry Eye Disease

The Dry Eye Assessment and Management Study Research Group*

Press Release

DREAM Study

U.S. Department of Health & Human Services

NIH National Institutes of Health
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NEWS RELEASES

Friday, April 13, 2018

Omega-3s from fish oil supplements no better than placebo for dry eye

NIH-funded study finds omega-3 fails to yield beneficial results in the clinic.

DREAM Objective

To evaluate the safety and effectiveness of omega 3 supplementation in relieving the symptoms of moderate to severe DED

- 535 subjects
  - 3 grams omega-3

    vs
  - 5 grams olive oil placebo

DREAM Study Flaws

Major flaws in the design/conclusion of the DREAM Study

1. Uncontrolled study
2. Selection Criteria
3. Olive oil Placebo
4. Omega-3's DID work

Uncontrolled Study - “Real World”?

Subjects allowed to use wide variety of other therapies

- Artificial tears & gels (79.4%)
- Cyclosporine drops (38%)
- Warm soaks (22.9%)
- Lid scrubs or baby shampoo (16%)
- **Omega-3 Up to 1200 mg per day**
- Systemic meds that cause dryness
- Systemic steroids
- Other immune suppressive agents

Uncontrolled Study - “Real World”?

Subjects not controlled for changes in treatment regimen

Tx compared to Baseline	Omega 3	Placebo
Stopped ≥1 treatment	53%	57%
No change	25%	22%
Changed ≥ 1 Treatments	12%	13%
Added Treatments	10%	8%
% Subjects changed treatments	**75%**	**78%**

DREAM Deficiencies

Selection Criteria

DEWS I

"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"

DREAM Deficiencies

Selection Criteria

Only 6% of patients met a more focused traditional definition of dry eye disease

- **osmolarity** of at least 312m Osm /mm in at least one eye
- **mild MGD** in **both** eyes

Olive Oil Placebo was NOT neutral

3 grams of omega-3 (vs.) 5 grams of olive oil (1 tsp)

Oil VS Oil

Placebo – Olive oil

placebo /plə'si:boʊ/ *noun*

Save

plural **placebos**

Learner's definition of PLACEBO

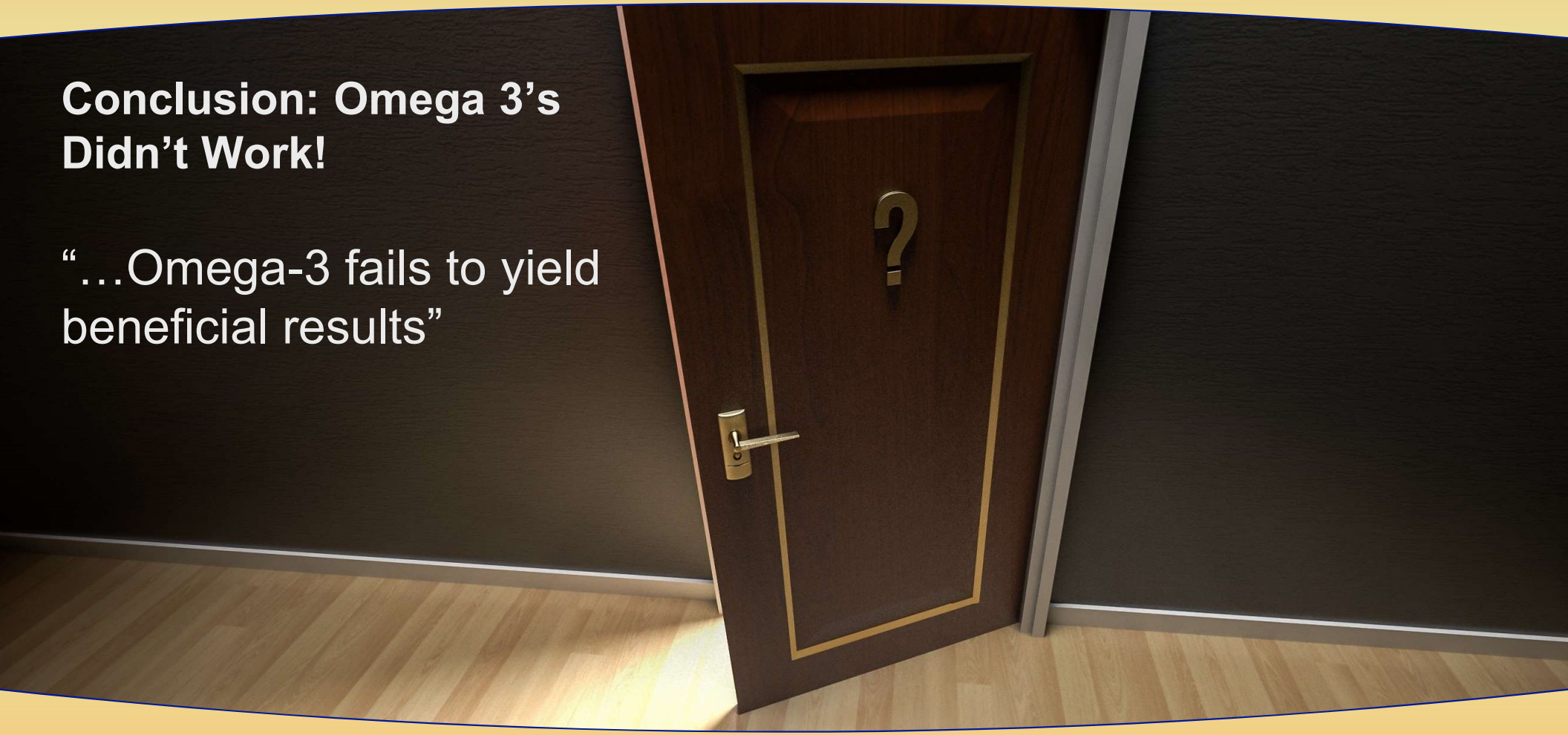
[count] *medical*

: a pill or substance that is given to a patient like a drug but that has no physical effect on the patient

DREAM Deficiencies

Conclusion: Omega 3's Didn't Work!

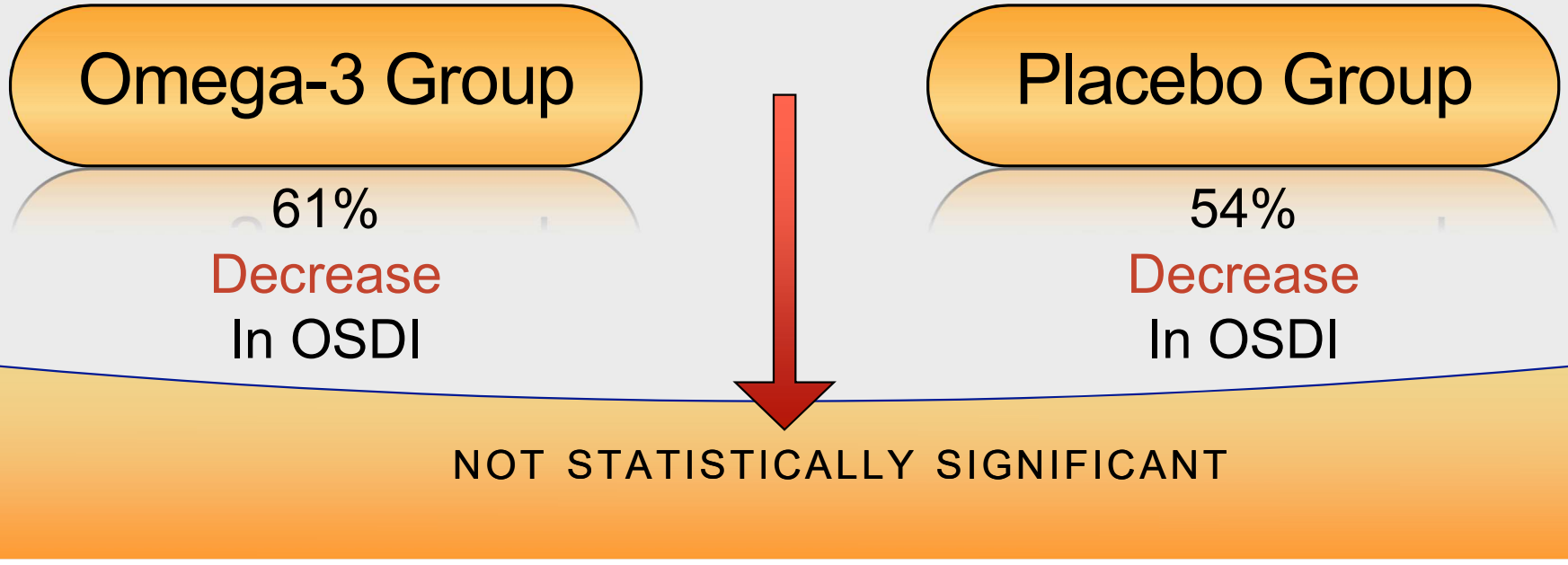
"…Omega-3 fails to yield beneficial results"



DREAM Deficiencies

Conclusion: Omega 3's DID Work!

- RESULTS of the DREAM TRIAL
- Significant improvement in dry eye signs and symptoms in both groups



Meta Analysis – *Cornea* 2019

Purpose:

To Assess whether omega-3 fatty acid (FA) supplementation is more efficacious than placebo in amelioration of signs and symptoms of dry eye disease.

Conclusion:

This meta-analysis provides evidence that omega-3 FA supplementation significantly improves dry eye symptoms and signs in patients with dry eye disease. Therefore, our findings indicate that omega-3 GA supplementation may be an effective treatment for dry eye disease.

CLINICAL SCIENCE

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

Giuseppe Giannaccare, MD, PhD, Marco Pellegrini, MD, Stefano Sebastiani, MD, Federico Bernabei, MD, Matilde Roda, MD, Leonardo Taroni, MD, Piera Versura, BSD, and Emilio C. Campos, MD

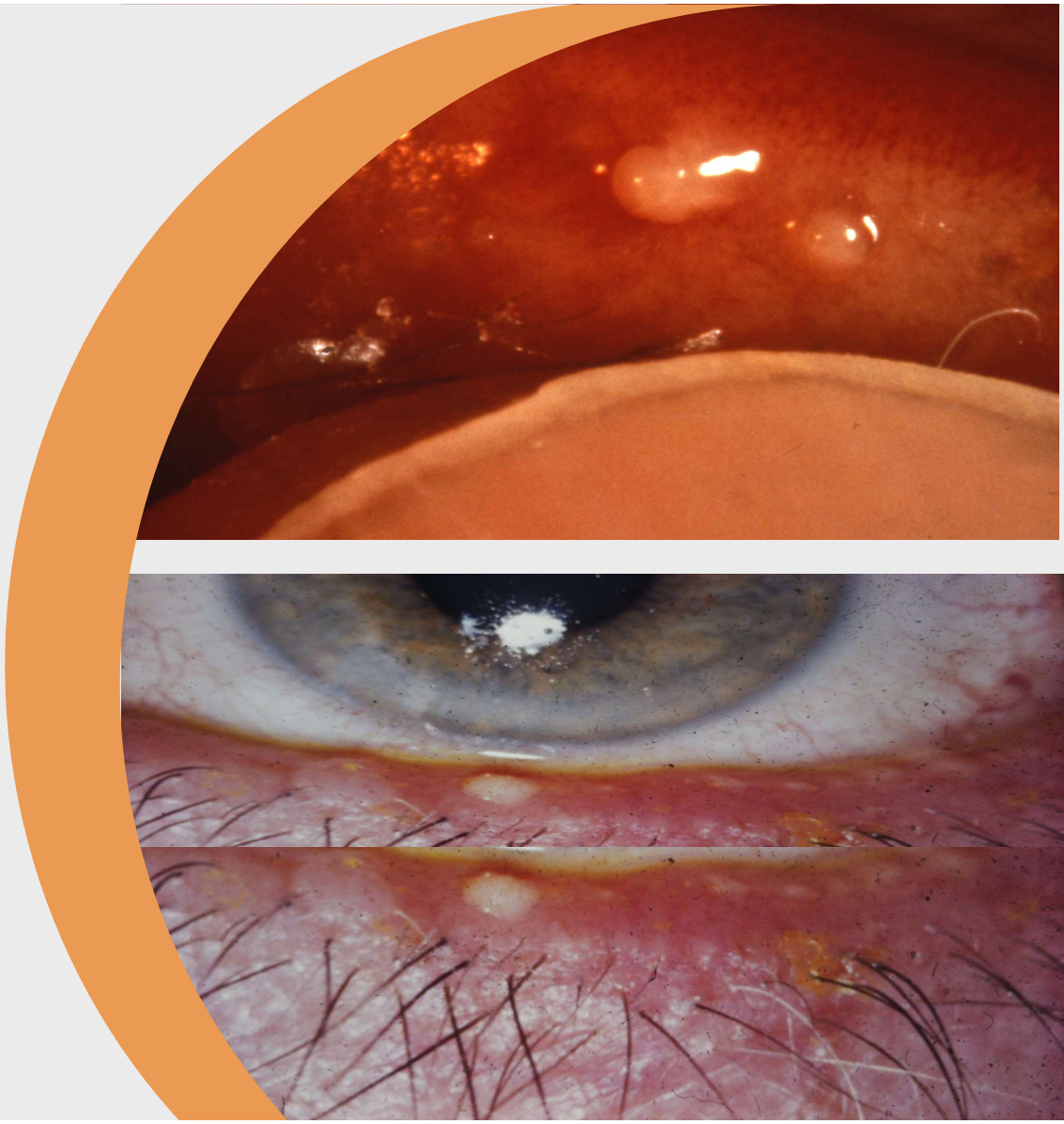
Dry eye disease (DED) is a common, multifactorial disease of the tear film and ocular surface that causes ocular discomfort and visual disturbance, affecting the patient's quality of life and restricting daily activities and work productivity.[1,2] Ocular surface inflammation is believed to have a central role in the pathogenesis of DED.[3] The mainstay of DED therapy is instillation of tear substitutes to moisten and lubricate the ocular surface. However, this therapy provides temporary symptomatic relief but does not address the inflammatory process that underlies the disease. Topical corticosteroids target ocular surface inflammation, but their use is limited by potential long-term adverse effects. On the other hand, topical cyclosporine A is an alternative option to overcome the above-mentioned side effects, but the limited efficacy and the lack of market availability in some countries represent important limitations to its use.[4]

Omega-3 fatty acids (FAs) are essential polyunsaturated FAs, which need to be obtained from dietary sources because humans are unable to synthesize them in vivo. They exist as both short (alpha-linolenic acid) and long-chain [eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)] subtypes. Walnuts, soy beans, flaxseed, and linseed oil constitute common vegetable sources of short-chain omega-3 FAs. On the other hand, the long-chain omega-3 FAs are found in high concentrations in oily fish and may be produced within the body through desaturation/elongation of short-chain FAs.[5]

Essential FAs are the precursors for synthesis of eicosanoids, that is prostaglandins, thromboxanes, and leukotrienes, which play important roles in the inflammatory cascade. The antiinflammatory properties of omega-3 FAs are determined by competitive enzyme inhibition with

Think MGD 1st!!

- 86% of dry eye patients have an MGD component[1]
- Pure aqueous deficiency is uncommon
- MGD is progressive
- All dry eye should be considered to have a significant MGD component until otherwise proven

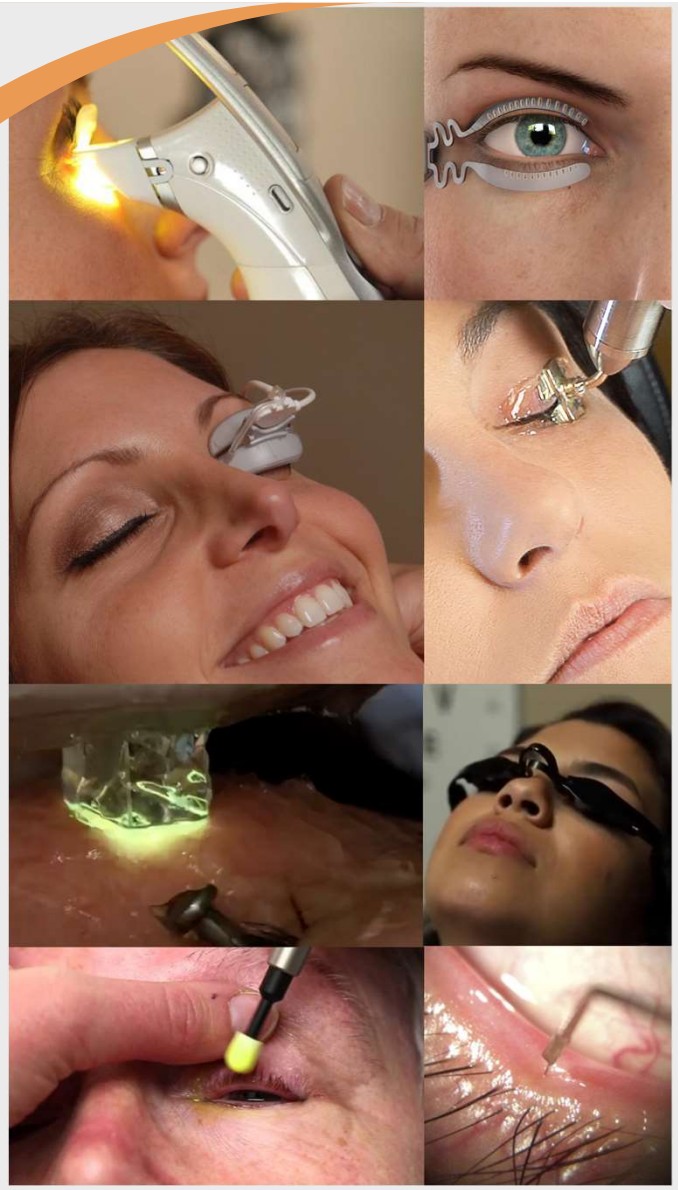


MGD is taking some Heat!!
In-office treatment options

3 step approach MGD

- Lid margin hygiene
  - Microblepharoexfoliation
- Removal of obstruction
  - Lipiflow thermal pulsation
  - iLux
  - TearCare
  - MiBo Thermaflow
  - Thermal I-Touch
  - Maskin Probing
- Reduction/elimination inflammation
  - Intense pulsed light therapy

Most effective when treated earlier before atrophy/dropout



Jones L et al. TFOS DEWS II Management and Therapy Report. Ocul Surf 2017l 15(3)L 580-634

Microblepharoexfoliation (MBE)

Treatment of Lid Disease

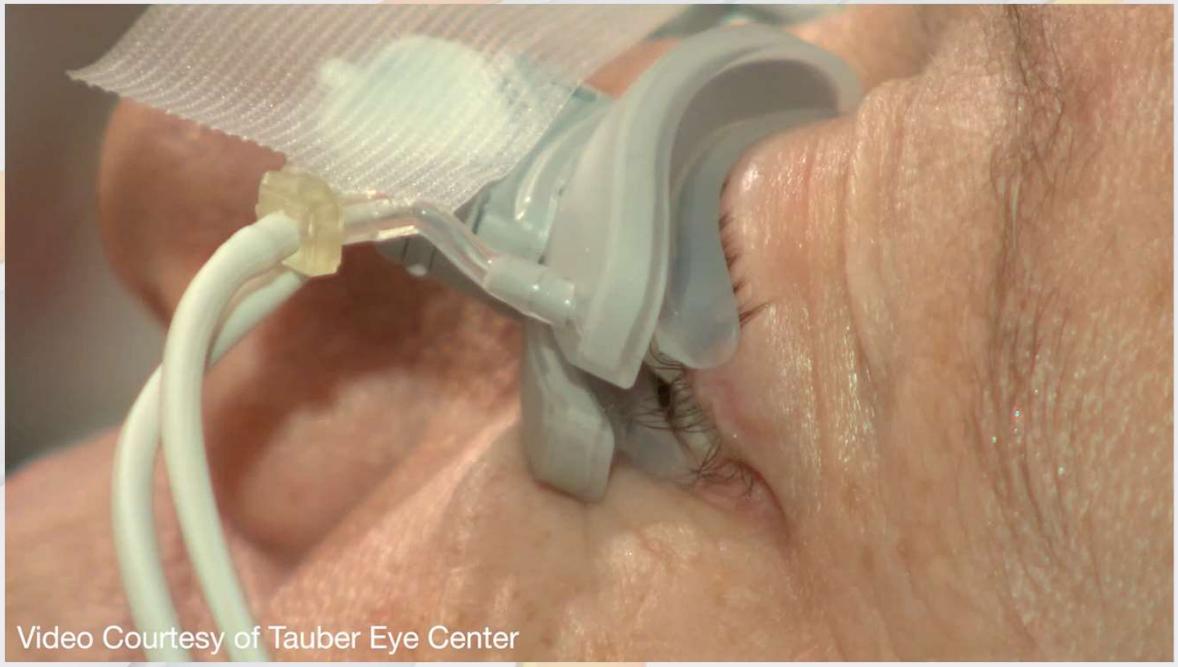
- Mechanical debridement removes biofilm
  - Reducing bacteria & demodex that contributes to inflammation and obstruction of MG's
  - Biofilm analogy plaque around teeth & gums

Rynerson JM, et al. *Clin Ophthalmol.* 2016;doi:10.2147/OPTH.S114674.

Lipiflow Thermal Pulsation

Treatment of Lid Disease

- Combination of heat and Vectored pulsation applied to posterior and anterior eyelid to unclog obstructed MG's
- FDA approved in 2011
- Device applies heat, massaging & unclogging glands
  - Allowing meibum to be secreted into tear film
- 12 minute in-office treatment
- Long term efficacy with single treatment
  - Effectiveness up to 3 years after single tx[1]
- Conventional treatments ineffective - do not address MG obstruction



Greiner JV. *Eye Contact Lens*. 2016;42(2):99-107.

iLux

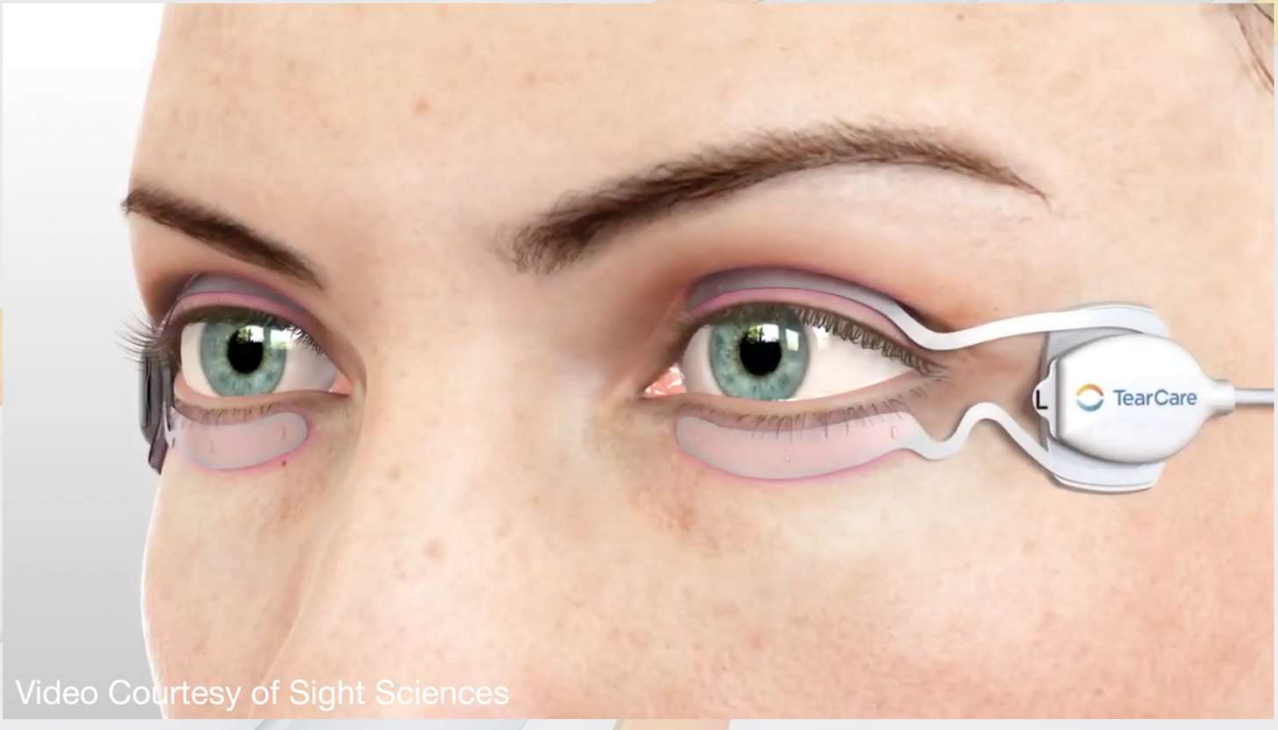
Treatment of Lid Disease

- Handheld thermal device
- Focally applies heat via light source to obstructed glands
- Unique - direct visualization of glands thru magnifier with ability control heat and expression

TearCare

Treatment of Lid Disease

- Applies heat to the external lid 15 minutes
- Patients can blink normally
- followed by manual expression
- disposable



Mibo Thermoflow

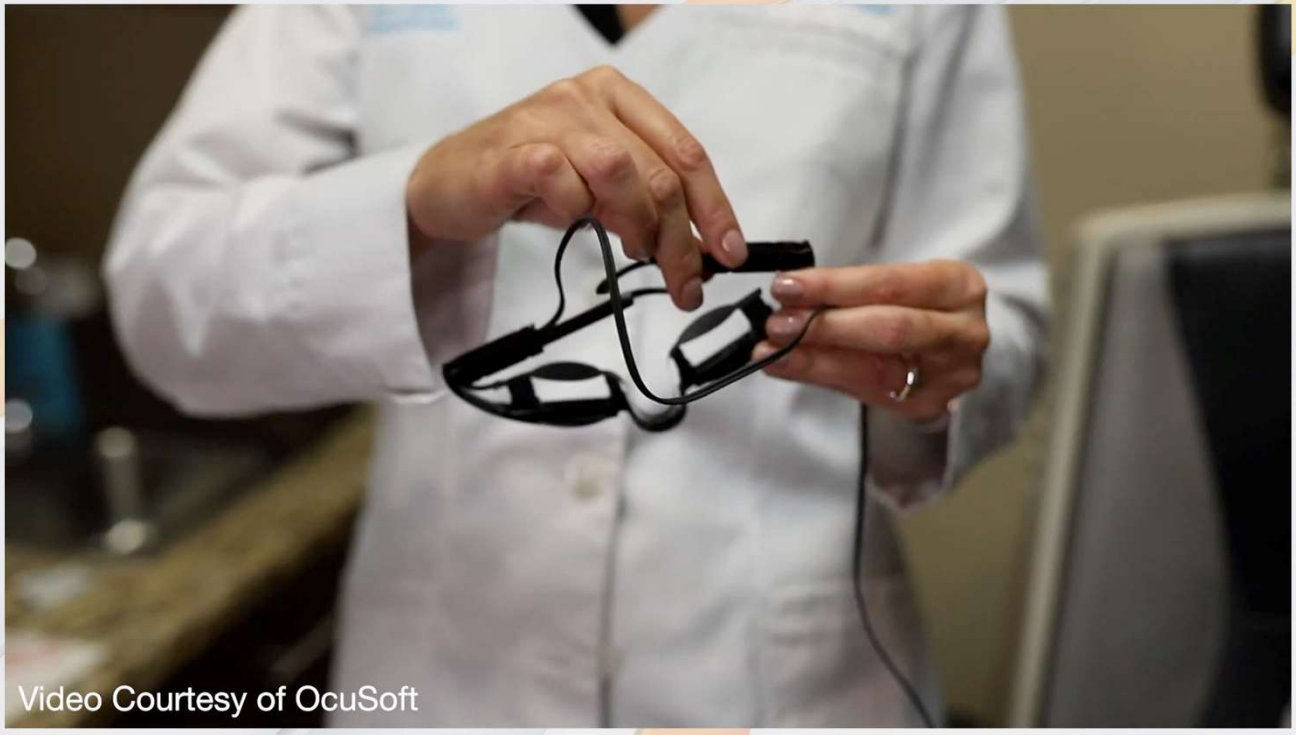
Treatment of Lid Disease

- Delivers heat (108 degrees) tarsal conjunctiva
- Non disposable
- Adjustable treatment settings

Thermal 1-Touch & EyeXpress

Treatment of Lid Disease

- Hands-free, goggle system
- Delivers heat to all 4 lids simultaneously
- Non disposable
- Adjustable heat settings



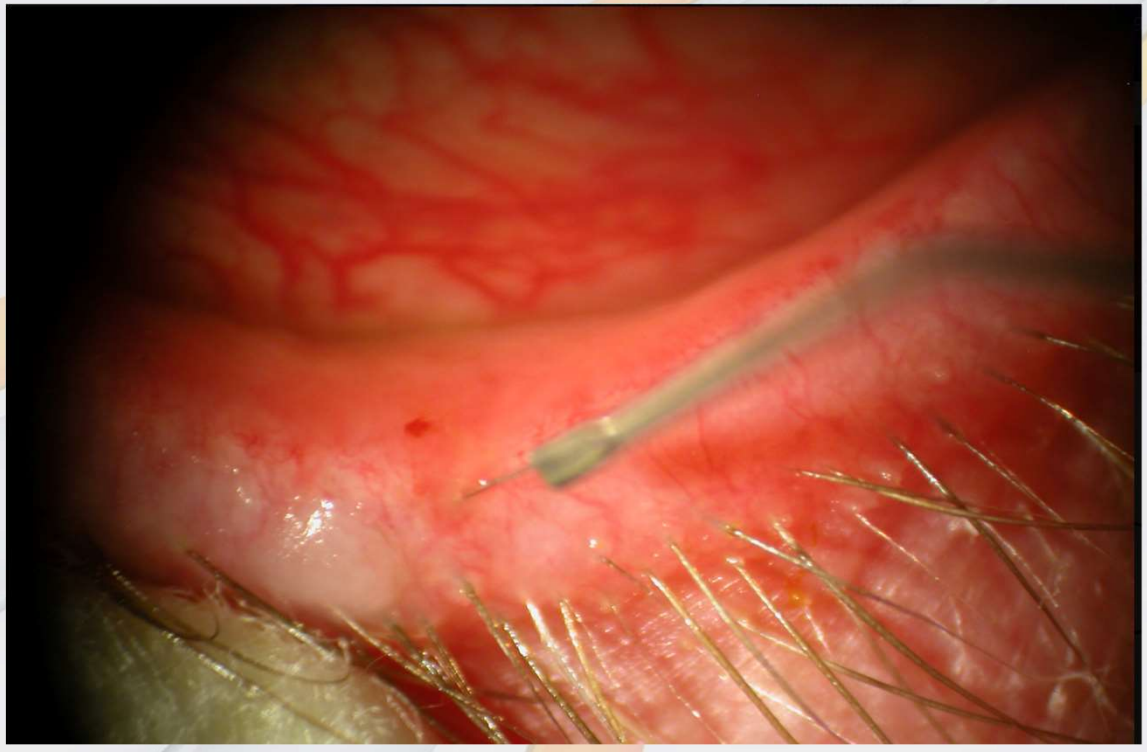
Manual MG Expression Therapeutic

Treatment of Lid Disease

Maskin Probing

Treatment of Lid Disease

- Relieves obstructed MG's by mechanically dilating glands under local anesthesia[1]
- Sometimes uncomfortable for patients
- Maskin probe (microcannula)
- Relieving obstruction improves flow of meibum



IPL Treatment

Intense Pulsed Light

- Non laser light source
- Originally developed for dermatology
- Adopted for use rosacea and MGD[1]
- Uses certain wavelengths of light – targets abnormal blood vessels
  - Reducing inflammation
- Reduces bacterial load and demodex[2]

1.Toyos R, et al. *Photobiomodul Photomed Laser Surg*. 2019;doi:10.1089/photob.2018.4599.

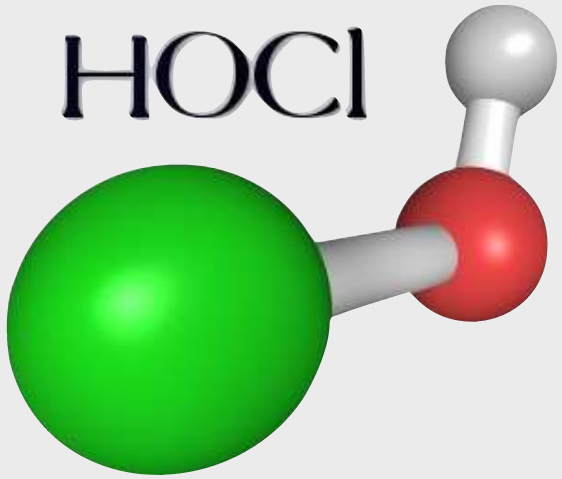
2. Suwal A, Hao JL, Zhou DD, Liu XF, Suwal R, Lu CW. Use of Intense Pulsed Light to Mitigate Meibomian Gland Dysfunction for Dry Eye Disease. *Int J Med Sci*. 2020;17(10):1385-1392. Published 2020 Jun 1. doi:10.7150/ijms.44288

Lid Hygiene

Hypochlorous Acid or Tea Tree Oil

Uses

- Blepharitis
- Dry Eye (MGD)
- Preoperative hygiene
- Before/After contact lens wear
- Demodex



Punctal Occlusion

Treatment of Lid Disease

Specifics

- Re-Establish health tear film first
- Wait until MMP-9 is negative

Dry Eye Pipeline

The Next Generation of Therapies

Pipeline for MGD

The Next Generation of Therapies

- AZR-MD-001 (Azura Ophthalmics)
  - promotes breakdown disulfide bonds slow production of keratin & stimulate Meibum production
- NOV03 - 100% perfluorohexyloctane (Novaliq/B&L)
  - Water-free, preservative-free formulation based on EyeSol technology for EDE/MGD
  - Drops are only 10 microns in diameter
- 0C-01 nasal spray - (Oyster Point Pharma)
  - selective nicotinic acetylcholine receptor agonist stimulates trigeminal nerve in nasal cavity to improve natural tear production including lipids and mucins
- Diquafosol (DQS)
  - P2Y2 receptor agonist

Pipeline for MGD

The Next Generation of Therapies

- TP-03 (Tarsus) Demodex
- Phase 2a/2b MARS study
  - Well tolerated
  - Efficacy treating Demodex
  - Persisting effect 90 days

Intracanalicular Punctal Plug

NOT FDA APPROVED

(low dose dexamethasone)

Specifics

- FDA approved to treatment ocular inflammation & pain after ocular surgery
- Delivery system via punctal plug
- Sustained release to the ocular surface for up to 30 days

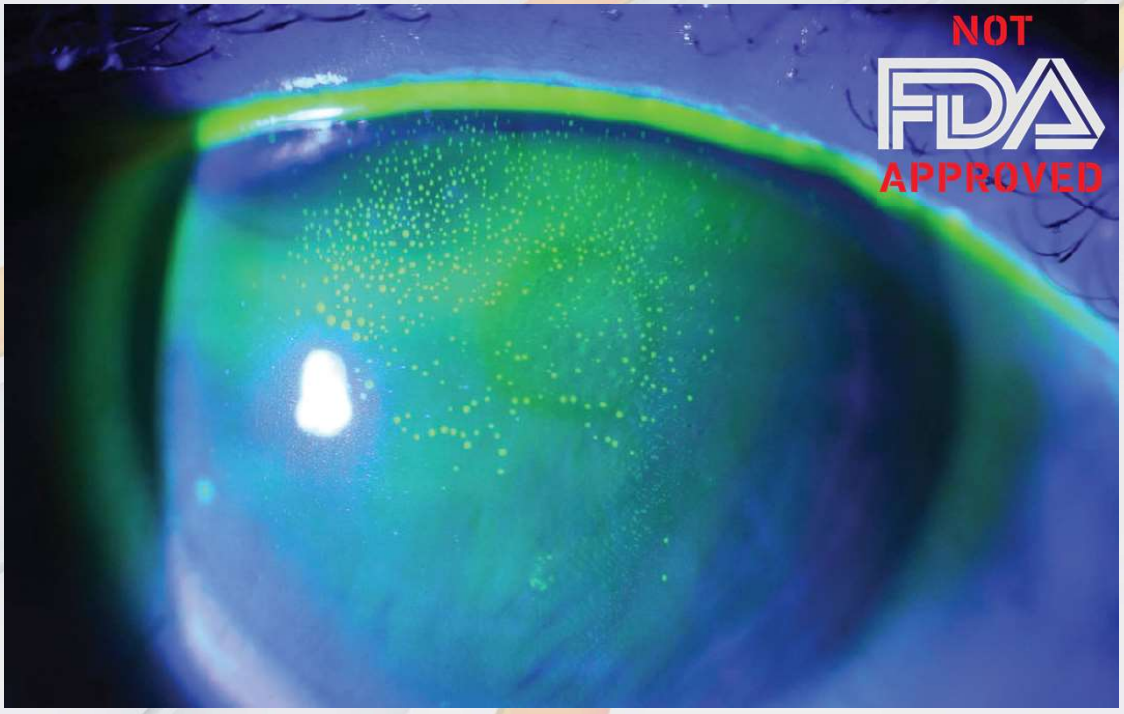
Potential Uses

- Allergic conjunctivitis
- Dry eye

Lacripep

synthetic peptide of lacritin

- Fragment of Lacritin protein
- Thought to be reduced in DED & Sjogren's
- Clinical expectations: promote basal tearing & restore normal fluorescein staining
- Phase II clinical trials in patients with Sjogren's



Summary

- High prevalence of MGD resulting in chronic DED
- Early identification and treatment is key
- Educate patients on importance of treating
- Incorporating advanced office-based treatments greater chance successfully managing this chronic disease and improving long term outcomes