Dry Eye
Management & Treatment

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Financial Disclosure

I have the following financial interests or relationships to disclose:

- Alcon/ Novartis
- B & L,
- CLAO
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- MC2
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- Santen
- Senju
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- Web MD
- Research to Prevent Blindness
- Martin and Toni Sosnoff Foundation
- NEI
DED Overview

- DREAM Study Results
- New Dry Eye Treatment Options
  - Lids - MGD
  - Anti- inflammatories
  - Tear composition

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The **Dry Eye Assessment and Management Study**

**Patient Population and Treatment**

*Broad spectrum of symptomatic patients with moderate or severe DED*

**REAL WORLD PATIENTS:**

Can continue current treatment

Symptoms for at least 6 months

Signs at screening visit and eligibility confirmation visit

- Supplements – 5 softgels per day
  - Active – 3 gm ω3 per day
    - 2 gm EPA + 1 gm DHA
    - Fish oil concentrate (triglyceride)
  - Placebo - 5 gm olive oil per day
- Identical in size, color, aroma
  - Fish essence added to placebo
  - Lemon essence to both to mask fish odor
- 15 mg Vitamin E as an anti-oxidant
Study Visits and Treatment Assignment

- **Screening**
- **Eligibility Confirmation**
- **Randomization**

**Active ω3**
- 2/3
  - 3 Months
  - 6 Months
  - 12 Months

**Placebo**
- 1/3
  - 3 Months
  - 6 Months
  - 12 Months

535 Subjects
Mean Change in OSDI Score Over Time

Mean Scores of Signs Over Time
DREAM Results

When patients who had moderate to severe dry eye disease despite use of other treatments were randomly assigned to ω3 or placebo supplements, mean values for symptoms and signs improved. However, we found no evidence of a beneficial effect of ω3 supplements on the symptoms and signs DED relative to placebo supplements.

A therapeutic effect of 1 teaspoon of refined olive oil daily is not plausible.¹

Strengths of DREAM

• **Generalizability:** ω3 added to existing treatments in patients who still had symptoms and signs despite Rx – REAL WORLD PATIENTS

• **Comparability of Groups:** Randomization “worked”

• **Compliance:**
  - Drugs delivered to home, even when missed visit
  - High rates of compliance by blood test
  - Missed visit rate < 10%

• **Treatment:**
  - Highest dose (3000 mg) of ω3 in any DED RCT
  - Triglyceride ω3 form more bioavailable than ethyl ester
  - Content verified by an outside laboratory
  - Softgels: active identical to placebo
  - 12 months – reduce seasonality effects
Meibomian Gland Dysfunction

- A leading cause of Dry Eye
- Clinical signs of MGD:
  - Aberrant medium production and/or composition due to:
    - Obstruction of meibomian gland (a)
    - Gland dropout (b)
    - Change in gland secretion (c)
- Patients complaining of repeated ‘styes’
- Characterized by tear film instability and rapid TFBUT

Meibomian Gland Dysfunction - Treatments

Heating & Pressure Devices

- Lipiflow
- Intense Pulsed Light (IPL)
- iLux
- Blephex
- NuLids
- Blephasteam
LipiFlow®, TearScience

- FDA clearance
- Thermal pulsation Device
- 12 minute treatment
- Delivers heat to the inner eyelid and massage to the outside → unblock the flow of lipids from the meibomian glands
- Preliminary evidence: At 3 months-1 year follow-up → improved symptoms and signs (secretions, TBUT)1-5

1Lane SS, et al. Cornea. 2012 Apr;31(4):396-404
2Greiner, JV. Curr Eye Res. 2012 Apr;37(4):272-8
Intense Pulsed Light (IPL), Lumenis or E-eye

Main effect: lower eyelids
Hypothesized mechanism of action:
1) Treat abnormal blood vessels near eyelid to close them off → decrease inflammation
2) Thermal treatment softens the glands and allows to discharge secretions more readily
Some evidence of therapeutic potential but further studies needed\(^1\text{-}^2\)

iLux®, Tear Film Innovations

- Main effect: unblocks Meibomian glands
- Heat & pressure therapy
- 8-12 min treatment
- Handheld Device
- Glands can be viewed via magnifier
  - No clinically significant differences between iLux and LipiFlow with respect to indication for use and device performance.\(^1\)

BlephEx®, Rysurg

- FDA clearance
- Main effect: lid margin debridement
- 6-8 minute treatment
- In-office
- Lasts three to six months before requiring a retreatment
- Evidence of improvement for contact lens wearers through significant reduction in bacterial load on patients’ eyelids

Blephasteam®, Laboratoires Théa

- Main effect: warming goggles that promote fluidization Meibomian glands secretions through heat and pressure
- ESPOIR Study: evidence of significant improvement in symptoms using the visual analogous scale (VAS).
- Expensive device
- Need further studies with larger samples sizes to determine efficacy


NuLids™, NuSight

- Main effect: lid scrub that stimulates Meibomian glands by removing biofilm and scurf that block the opening of the glands
- Doctor-prescribed, In-home treatment
- 60 second daily treatment
- A multi-center clinical study showed evidence of 50% decrease in dry eye symptoms, 65% improvement in TBUT and 81% improvement in Meibomian Gland liquid secretions.¹

¹Schanzlin, Olkowski, Coble, Gross. NuLids II Study, April 2018
TearCare System, Sight Sciences

- First wearable therapeutic eyelid therapy device
- In-office treatment
- 12 minute thermal eyelid treatment followed by expression forceps to manually evacuate residual obstructions
- Evidence from pilot study suggested improved TBUT, corneal and conjunctival staining scored, and dry eye symptoms based on OSDI, SPEED and SANDE.¹
- Further clinical evidence underway

Anti-Inflammatory Pharmaceuticals

**Cyclosporine**

**Main effect:**
- Anti-inflammatory therapy
- Inhibits T-cell maturation
- Decreases pro-inflammatory cytokines
- Upregulates anti-inflammatory cytokines
Cyclosporine A cationic emulsion 0.1% (Ikervis®, Santen)

- Approved in Europe in 2015
- Main effect: prolonged precorneal residence time and improved bioavailability
  - Indicated for patients with severe DED that has not improved using tear substitutes
- Clinical evidence of reduced HLA-DR expression at 6 mo measured through impression cytology; overall greater benefits for patients with Sjögren’s Syndrome.¹

Cyclosporine 0.09% (OTX-101, Cequa™, Sun Pharma)

- FDA Approval Aug 2018
- Highest FDA-approved concentration of cyclosporine A.¹
- Main effect: Increase tear production
- Calcineurin inhibitor.
- Nanomicellar formulation eases entry into corneal and conjunctival cells.
- Two multicenter studies report a statistically significant increase (≥ 10 mm) in Schirmer wetting at 3 mo in patients receiving Cequa™ vs. vehicle.¹

Cyclosporine 0.05% and 0.1% (CyclASol, Novaliq)

- Semifluorinated alkanes formulation better dissolves Cyclosporine A
- Greater penetration than FDA-approved 0.05% Cyclosporine A (Restasis)
- Evidence of decreased corneal and conjunctival staining after 14 days.\(^2\)
- It remains unknown whether greater concentration leads to better results; phase 3 studies are underway.\(^3\)

Cyclosporin with chondroitin sulphate

Klarity- C

Imprimis- compounded chondroitin sulfate
SkQ1

• Main effects: synthesized small molecule targeted to reduce oxidative stress in cell mitochondria
  o Regenerates itself
  o SkQ1 ophthalmic solution is indicated for pathologies of the eye associated with oxidative stress, such as dry eye
  o Approved in Russia (2011) and marketed as Visomitin

• Clinical evidence suggest statistically significant:
  o Decrease in corneal staining
  o Improvements in lid margin redness
  o Improvements in symptoms measured through Ora Calibra™ scales

Steroids - new formulation

- KPI-121 - Kala Pharmaceuticals
- Mucous – penetrating particle (MPP) – nano particles
- Loteprednol -0.25 %
- Better penetration, low dose steroid
- Episodic flare ups of DED
**ADX-102 (Reproxalap, Aldeyra Therapeutics)**
- Small molecule, topical agent
- Traps aldehydes that usually activate inflammatory factors
- Positive clinical evidence of improvement in signs and symptoms of dry eye.

**Thymosin beta 4 (Tβ4)**
- 43-amino acid G-actin binding protein
- Downregulates transcription of inflammatory mediators and promotes corneal epithelial cell migration
- Phase 3 clinical trial with Tβ4 (RGN-259, RegeneRx) showed improvement in signs and symptoms of dry eye through corneal staining, tear production and expression of inflammatory factors.

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Tear Enhancements
Diquafosol Tetrasodium (3% Ophthalmic Solution)

- Currently approved in Japan and South Korea\(^1\)
- Main Effect: Increase tear fluid and mucin secretion on the ocular surface through interaction with P2Y2 receptors in the conjunctiva
- Evidence from clinical trials suggest diquafosol improves corneal staining more effectively than a comparable, sodium hyaluronate solution\(^2\)


Rebapimide
(2% Ophthalmic Solution)

- Currently approved in Japan
- Main Effect: stimulates mucin secretagogue activity in cornea and conjunctiva
- Clinical evidence suggests:
  - Statistically significant Improvement in corneal and conjunctival staining, as well as in quality of life as well as in tear break-up time.\(^1,2\)
  - Potential role in suppressing the expression of inflammatory proteins (Polyl).\(^3\)


TrueTear®, Allergan

• FDA Clearance
• Main effect: intranasal applicator sends electrical currents to nerves that stimulate tear production.
• Evidence of improved Schirmer scores, decreased symptoms and corneal and conjunctival staining at 6 mo. Ocular comfort lasted for 3 hours following neurostimulation.
  - Secondary effect: intranasal application promotes goblet cell mucin secretion which stabilizes the tear film

Gumus K, Schuetzle KL, Pflugfelder SC. Randomized controlled crossover trial comparing the impact of sham or intranasal tear neurostimulation on 654 G.D. Novack et al. / The Ocular Surface xxx (2017) 635e655 conjunctival goblet cell degranulation. Am J Ophthalmol 2017;177:159e68.
Pharmaceutical to stimulate nerves

• Nasal Spray OC-01
• Oyster Point Pharma
• Stimulate natural tears
Amniotic cytokine extract (Ocular Science)

- ACE is a novel drop marketed as Genesis
- Contains various cytokines, growth factor, and anti-inflammatory molecules.
- Effective in a small pilot study.

Amniotic Cytokine Extract Promising in Patients with Dry Eye Disease. MDLinx.
Recombinant human nerve growth factor (Oxervate™ eye drops, Dompé)

- FDA Approval Aug 2018
  - First approved drug for Neurotropic keratitis (NK)—degenerative disease with loss of corneal sensation
  - Topical eye drop
  - Clinical evidence of complete corneal healing in 70% of patients treated with Oxervate after 8 weeks

Perfluorohexyloctane (NovaTears, Novaliq)

- Main effect: prevent evaporative DED by increasing tear film and lipid layer thickness
- Approved in Europe, Australia and New Zealand
- Clinical evidence of increased tear production and tear film stability, as well as significant decrease in OSDI scores and in corneal staining

CrossThiolated Carboxymethyl Hyaluronic Acid Liquid-Gel (Ocular Bandage Gel, EyeGate Pharma)

- Main effects: accelerate corneal healing and reduce corneal staining
  - Indicated for defects due to photorefractive keratectomy (PRK)
  - Indicated for Punctate epitheliopathies (PE) associated with dry eye
- Treatment in development: July 2018 approval to conduct two pilot studies using OBG for PE and PRK
- A first-in-human pilot study (n=39) showed accelerated corneal reepithelialization through slit lamp examination at day 1 after PRK. Further studies needed.¹

Biologic Molecules: Dry Eye Assessment

- **Proteoglycan-4 (Lubricin)**
  - Recently discovered on the ocular surface in the meibomian glands
  - Functions to prevent friction at the cornea-lid interface and has anti-inflammatory properties
  - Commercial lubricin-based lubricants remain scarce
  - Evidence from clinical studies with recombinant human lubricin suggest significant improvement in signs and symptoms of DED through TBUT, corneal staining and eyelid and conjunctival redness.

Why Ocular Biomarkers?

**Surrogate Endpoints**
- None accepted by the FDA or Europe to date
- Validation needed - clear clinical relevance

**Enrichment of Study Population**
- Still regulatory hurdles

**Support mechanism of action of treatment**
- Topical ciclosporin in Europe for Dry eyes
- (Europe, 2015: Ikervis)¹

- SEGMENT THE DRY EYE POPULATION-
- TREAT MORE SPECIFICALLY-Personalize treatment

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1. Ikervis SmPC June 2015, available at [https://www.medicines.org.uk/emc/medicine/30584](https://www.medicines.org.uk/emc/medicine/30584)
Take home pearls

- Fish oil is out!
- Dry Eye – New Treatments:

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<th>Category</th>
<th>Treatments</th>
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<td>BlephEx, LipiFlow, iLux, NuLens, TearCare,</td>
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<td>Blephasteam</td>
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<tr>
<td>Others</td>
<td>NovaTears, Ocular Bandage Gel, NGF</td>
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Thank you!

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