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Addressing the Neurotrophic and Neuropathic Surface
COPE#81826-TD


Dr. Walter Whitley

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
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Host: Dr. Elise Kramer



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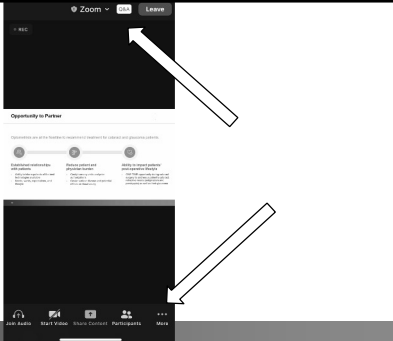
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Speaker Bio –

Walter Whitley, OD, MBA, FAAO serves as the Director of Professional Relations and Education at Virginia Eye Consultants in Norfolk, VA and Regional Medical Director for Eyecare Partners, LLC. Dr. Whitley's practice encompasses ocular surface disease, glaucoma, surgical co-management and clinical research. He is a nationally recognized author and lecturer and serves as co-chief medical editor for Modern Optometry, contributing editor for the Review of Optometry and co-medical editor for Dry Eye Coach. Dr. Whitley is the Immediate Past Chair of the American Academy of Optometry Anterior Segment Section and a past president of the Virginia Optometric Association where he has been recognized as the 2012 Young Optometrist of the Year, the 2015 Legislative Keyperson of the Year and the 2020 Optometrist of the Year.





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NP 46 YOWF Presents for Dry Eye Evaluation

- Blurry vision which has been fluctuating OU. Constant and significant. Very lights sensitive and found the only drops that provide relief steroids but brand not covered by insurance. Eyes are so dry they feel like the lids are sticking to the surface of the eye. Using PF Aqs but did not find relief with those...wants new glasses. Previous discussions of punctal cauterly
- Oc Hx - Hx of plugs that have fallen out multiple times. Most recent plugs causing extreme irritation.
 - Loteprednol etabonate 0.5% BID OU
 - Intolerant to cyclosporine 0.05% and lifitegrast 5%
- Med hx: Thyroid disease, HTN
- Meds: Clonidine, levothyroxine
- Allergies: NKMA

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*What Questions Do
You Want to Ask?*

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Clinical Examination

- BCVA OD 20/20 OS 20/25
- SLE:
 - 1+ telangiectasia, Cloudy secretions OU
 - 1+ papillae OU
 - TBUT 4 / 6 sec
- MMP-9
 - OD Mild +
 - OS Neg
- Tear Osm:
 - 279/284

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Next Steps?? Additional Tests?

Diagnosis??

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Corneal Anatomy

- Most richly innervated structure in the body
 - Densely supplied by sensory and autonomic nerve fibers
- Sensory nerves (the vast majority) come from the ophthalmic division of the trigeminal
 - Possess both sensory and efferent functions
 - Mechanical, thermal and chemical stimulation usually is perceived as pain

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Corneal Sensitivity Changes

- Age considerations
- Contact lenses
- Ocular surface disease
- Previous infections

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TFOS DEWS II Definition

*“Dry eye is a multifactorial disease of the ocular surface characterized by a **loss of homeostasis** of the tear film, and accompanied by **ocular symptoms**, in which tear film **instability** and **hyperosmolarity**, ocular surface **inflammation** and damage, and **neurosensory abnormalities** play etiological roles.”*

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Corneal Nerve Structure and Function in Patients With Non-Sjögren Dry Eye: Clinical Correlations

- Mean corneal sensitivity was significantly lower in the NSDD group as compared with the control group ($P = 0.014$).
- NSDD patients have both structural and functional alterations of subbasal corneal nerves and these changes are related to the severity of dry eye.

Antoine Labbé¹ 2013 ARVO

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The Relationship between Subbasal Nerve Morphology and Corneal Sensation in Ocular Surface Disease

- Corneal sensitivity was significantly decreased in dry eye and glaucoma patients compared with controls. The density and number of subbasal corneal nerves were also significantly decreased in dry eye and glaucoma patients compared with controls.

Labbe 2012 IOVS

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What's Happening in Dry Eye?

- Sensory nerves may adapt to irritation by decreasing the frequency and intensity of action potentials
- With time this elevates pain threshold, and stronger stimuli is needed to evoke corneal sensation for basal and reflex tearing
- Corneal hypoaesthesia likely plays a role in the pathogenesis of tear deficiency

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Refractive Surgery Considerations

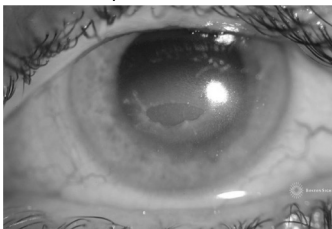
- Several studies showed that nasal or superior LASIK flaps had no effect on corneal sensation
- Transient light sensitivity syndrome

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What is NK?

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Neurotropic Keratitis Definition



- Degenerative corneal disease
- Damage to the trigeminal nerve (cranial nerve V)
- Loss of corneal sensation
- Breakdown of the corneal epithelium
- Impaired corneal healing
- Persistent epithelial defect → corneal ulceration → stromal melting and perforation

Hallmark: decreased sensation, decreased or no pain


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How many cases of NK do you see in a week?

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Neurotropic Keratitis

NK is Classified as a Rare Disease




- Rare/orphan disease (ORPHA137596)¹
 - Affects ≤ 5 individuals in 10,000
- NK Prevalence difficult to determine^{1,2}
 - Estimated to be < 1.6/10,000
 - Best data are based on extrapolation from the most common conditions associated with NK
 - Herpes simplex keratitis: 6% develop NK
 - Herpes zoster keratitis: 12.8% develop NK
 - Postsurgical nerve damage: 2.8% develop NK

1. Dua HS, et al. Prog Retinal Eye Res. 2018;66:307-333.
2. Saari S, et al. Oculop Surg. doi:10.1016/j.ajo.2019.11.038

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Differential Diagnosis

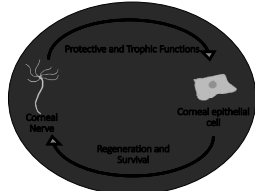
- **Loss of corneal sensation = NK**
- **Neuropathic pain (corneal neuralgia, keratoneuralgia)**
 - Pain without stain
 - Pain in response to minimal or even no stimulus
- **Diseases with overlapping features of NK; can lead to NK if corneal sensation is affected^{1,2}**
 - Dry eye disease
 - Contact lens-related disorders
 - Blepharitis
 - Exposure keratopathy
 - Stem cell deficiency
 - Topical drug toxicity
 - Mild chemical injury



1. Dua HS, et al. Prog Retinal Eye Res. 2018;66:307-333.
2. Sachithan A, et al. Clinical Ophthalmology. 2014;8:573-578

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Corneal Innervation




- The cornea is the most sensitive and densely innervated tissue in the human body^{1,2}
- Corneal innervation is essential. Corneal epithelial cells act in a mutually supportive relationship with corneal nerves¹⁻⁴
 - Corneal nerves: maintain corneal integrity
 - Protective functions: blinking and tearing
 - Trophic support: neuropeptides (eg, substance P) promote epithelial cell proliferation, migration, adhesion
 - Epithelial cells: neurotrophic factors (neuronal extension and survival)
- Corneal nerve damage = loss of corneal sensation, epithelial breakdown, poor healing^{1,2}

1. Sheha H. Clinical Ophthalmology. 2019;13:1973-1980.
2. Versura P, et al. Eye and Brain. 2018;10:27-45.
3. Duan H, et al. Prog Retinal Eye Res. 2016;66:107-131.
4. Saad S, et al. Ocular Surf. doi:10.1016/j.prs.2019.11.008.

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Etiology



- INFECTIOUS^{1,2}**
 - Herpes (simplex, zoster)
 - Leprosy
- IATROGENIC^{1,2}**
 - Trauma to ciliary nerves by laser treatment and surgery
 - Corneal incisions
 - LASIK
- SYSTEMIC DISEASE^{1,2}**
 - Diabetes
 - Multiple sclerosis
 - Vitamin A deficiency
- CORNEAL DYSTROPHIES^{1,2}**
 - Lattice
 - Granular
- TOXIC^{1,2}**
 - Chemical burns
 - Carbon disulfide exposure
 - Hydrogen sulfide exposure
- TOPICAL MEDICATIONS^{1,2}**
 - Anesthetics (abuse)
 - Timolol
 - Betaxolol
 - Sulfacetamide
 - Diclofenac sodium
 - Ketorolac
- MISC^{1,2}**
 - CTL
 - Increasing age
 - Dark eye color
 - Adie syndrome
 - Limbic stem cell failure (chronic)
- FIFTH-NERVE PALSY^{1,2}**
 - Trigeminal neuralgia surgery
 - Neoplasia (acoustic neuroma)
 - Aneurysms
 - Facial trauma
 - Congenital
 - Riley-Day syndrome
 - Goldenhar-Gorlin syndrome
 - Mobius syndrome
 - Familial corneal hypesthesia

1. Duan H, et al. Prog Retinal Eye Res. 2016;66:107-131.
2. Medscape. Neurology. Available from: https://reference.medscape.com/doc/1118889-000000.

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Case Example

- The 84 year old, AA female presents for 3-4 month DES check (no touch) and MMP-9 testing. Pt has a h/o DES and POAG mild OU. Pt states OS>OD has some itching. Pt states she has only been using her cyclosporine 0.05% and AT's. She never picked up fluoromethalone drops and is not using AT's ointment or a heat mask.

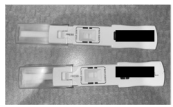
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- Ocular Hx:**
 - Dry eye syndrome – 10+ yrs
 - Herpes stromal keratitis OS
 - Inactive – Last episode 2020
 - Anterior scleritis OS
 - Inactive
 - POAG - Mild OU
 - Pterygium sx OU
 - Phaco / istent OU
 - Previous treatments
 - Amniotic membrane OS (2019, 2020)
 - Punctal cautery (2011) OU
 - PGA OU
- Med Hx:**
 - NIDDM 15 yrs
 - Osteoarthritis
 - Hypothyroid
 - Seasonal allergies
- Meds:**
 - Ceterizine
 - Lactulose
 - Levothyroxone

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Clinical Exam

- Lids / Lashes – Clear and good position
- Conjunctiva – tr injection OU
- Cornea
 - OD 2+ Inf SPK
 - OS Dense SPK, 1+ K edema
- A/C – Deep and Quiet
- PCIOL OU
- IOP – 11 mmHg OU
- K Sensitivity – OD Normal OS Reduced



Anything else we should add???

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Do you test for K sensitivity?

If so, how?

Central vs. S/I/N/T/C??

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Corneal Sensation

- Greatest in the central cornea (elderly patients - more sensitive in the periphery)
- Drops rapidly as distance increases from the limbus
- Falls with increasing age
- Is not affected by iris color
- More sensitive in the temporal limbus than the inferior limbus
- Reduction has been reported in diabetes type 1 and type 2

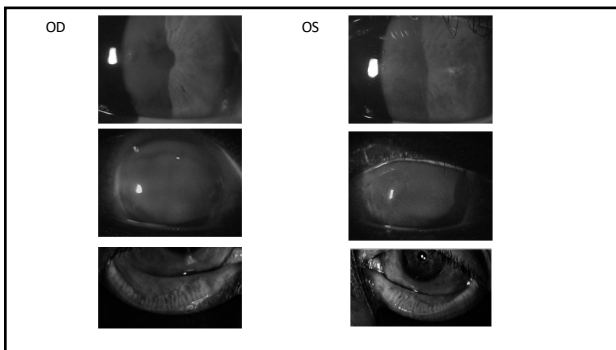
Fauliner WL, Varley GA. Corneal diagnostic techniques. In: Kachmer JH, Mannix MJ, Holland EJ, eds. Cornea, 2nd ed. Vol. 1 Philadelphia: Elsevier/Mosby; 2005:229-235. External Disease and Cornea, Section 8: Basic and Clinical Science Course, AAO, 2010.

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Corneal Sensitivity Testing



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Neurotrophic Keratitis: Classification

Mackie classification

- Stage I is characterized by hyperplasia and/or irregularity of the epithelium, evolving to punctate keratopathy, corneal edema, neovascularization, stromal scarring.
- Stage II is defined by a recurrent or persistent epithelial defects or a PED without stromal thinning.
- Stage III: stromal involvement leads to corneal ulcer, melting and perforation

Mackie IA. Neuroparalytic keratitis. Current Ocular Therapy. Philadelphia, PA: WB Saunders; 1995:452-4.

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Neurotrophic Keratitis: Etiology

1. Infectious: HSV, VZV, leprosy
2. CN V palsy
 - Surgery for trigeminal neuralgia, neoplasia (acoustic neuroma), aneurysm, facial trauma, congenital, familial dysautonomia (Riley-Day syndrome), Goldenhar-Gorlin syndrome, Möbius syndrome, familial corneal hypesthesia

- Topical medications: anesthetic abuse
- Iatrogenic: LASIK/PRK, corneal incisions (RK, AK), contact lens wear, scleral bands, vitrectomy and photocoagulation to treat diabetic retinopathy^{1,2}
- Chemical and physical burns
- Systemic: DM, multiple sclerosis, Vit A deficiency
- Increasing age, chronic DED³

1. Baratz PJ. JAMA ophthalmology 2014;132:750-2.
2. Tinley CO. Eye 2009;23:1819-23
3. Ocul Surf. 2007 Apr;5(2):79-92.

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Endogenous nerve growth factor (NGF) and its role in NK:

impaired trigeminal corneal innervation

- ↓ Lacrimation and blink reflex
- ↓ Epithelial cell vitality, metabolism, mitosis
- ↓ Epithelial trophism and repair
- ↑ Stromal and intracellular edema
- ↓ Microvilli
- ↓ Development of the basal lamina

Mastropasqualetti et al (2007) J Cell Physiol 202:717-24

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Endogenous NGF Maintains Corneal Integrity By Three Mechanisms

Endogenous nerve growth factor acts through specific high-affinity (ie, TrkA) and low-affinity (ie, p75NTR) nerve growth factor receptors in the anterior segment of the eye to support corneal innervation and integrity.¹

SHOWN IN PRECLINICAL MODELS²

- CORNEAL INNERVATION**: NGF plays a role in nerve function and stimulates the regeneration and survival of the sensory nerves.^{2,3}
- TEAR SECRETION**: NGF binds receptors on lacrimal glands and promotes sensory-mediated reflex tearing secretions.⁴
- CELL PROLIFERATION AND DIFFERENTIATION**: NGF stimulates proliferation, differentiation, and survival of corneal epithelial cells.⁵

1. Muthipappa S, Maresio-Giovanetti G, Huber M, Sacchetti M. Understanding the pathogenesis of neurotrophic keratitis: the role of corneal nerves. *J Cell Physiol*. 2017 Apr;232(4):737-744. 2. Miller LJ, Wu Y, et al. 3. Torres JM. Corneal nerve dysfunction, corneal dryness, and keratitis. *Surv Eye Res*. 2009 May;28(5):511-40. 4. Sacchetti M, Lombardo M. Diagnosis and management of neurotrophic keratitis. *Cornea*. 2016;35(7):8-16. 5. Choi J, Lee H, et al. Nerve Growth Factor in the Development and Adult Cornea. *Invest Ophthalmol Vis Sci*. 2010;51(16):1633-1644.

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Severity-Based Therapy

Stage	Therapy
1	<ul style="list-style-type: none"> Preservative-free artificial tears formulations Punctal occlusion Hydrogel contact lens (consider large diameter) Recombinant human NGF (rhNGF; cenegeim) Serum/plasma/platelet rich plasma
2	Supportive therapies plus: <ul style="list-style-type: none"> rhNGF Scleral lens (± serum/plasma) Amniotic membrane Botulinum induced ptosis, tarsorrhaphy
3	<ul style="list-style-type: none"> rhNGF Keratoplasty + scleral lens, tarsorrhaphy, neurotization

Sacchetti M, Lombardo M. Diagnosis and management of neurotrophic keratitis. *Clin Ophthalmol*. 2016;35(7):8-16. Shekhani N, Tighe S, Vlaham C, Nayak V. Update on corneal eye drops in the treatment of neurotrophic keratitis. *Clin Ophthalmol*. 2020;13:1073-1080. Published Oct 7, 2020.

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Serum /Plasma Therapy

- Serum/plasma have reported efficacy as primary or adjunct therapy
- Reported success of serum alone (20-50% concentration) ranges from 71 to 100% within 90 days (Guadilla et al. Arch Soc Esp Offalmol 2013; Jeng and Dupps Cornea 2009; Pflugfelder AJO 2006)
- Umbilical cord serum may be more effective and has higher concentrations of substance P and NGF than peripheral blood serum (Yoon KC et al. *Ophthalmology* 2007)
- Epithelial defect healed in 97.4% of stage 2-3 NK after 11 weeks of plasma rich in growth factors (PRGF) (Sanchez-Avila RM et al. *Int Ophthalmol* 2018)
- Serum can be used safely in combination with SIH CL. No inflammation or CL deposits were observed (Choi JA ECL 2011)

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Amniotic Membrane

- Randomized clinical trial reported healing of refractory neurotrophic ulcers with conventional therapy (lubrication plus BCL or tarsorrhaphy) or amniotic membrane transplant (AMT). Healing rates were similar in the 2 groups: 67% with conventional therapy and 73% with AMT (Khokhar S et al. *Cornea* 2005)
- AMT was also equivalent to autologous serum (AS) in healing neurotrophic ulcers: 70% for AS and 73% for AMT (Turkoglu E et al. *Semin Ophthalmol* 2014)
- Multilayer AMT recommended for deep ulcers and Descemetocoeles (Kruze F et al. *Ophthalmology* 1999)

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Scleral Lenses

- Use of fluid filled scleral contact lenses for treatment of NK initially reported decades ago (Romero-Rangel et al. *AJO* 2000)
- Non-healing corneal epithelial defects with BCL healed without recurrence in all 9 eyes treated with PROSE scleral lens (Ling J et al. *Am J Ophthalmol* 2013)
- Overnight wear (with close monitoring) may accelerate healing (Lim P et al. *AJO* 2013)

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Corneal Neurotization

- Corneal sensitivity restored after sural nerve grafts (Elbaz et al. *JAMA Ophthalmol* 2014)
- Free sural nerve graft was coapted end-to-side with supratrochlear nerve and the distal portion of the nerve was separated into fascicles that were distributed around the limbus
- Corneal sensitivity, measured pre- and post-op with the Cochet-Bonnet esthesiometer, returned to normal after 5 months

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Treatment

- Continue:
 - Cyclosporine 0.05% BID OU
 - Heat Mask
- Stop
 - Oral ceterizine
- Order
 - Cenegermin 20 mcg/mL – Patient to call once meds come in to review meds / demo proper usage
 - Ceterizine ophth sol BID OU
- Follow Up
 - 3-4 months glaucoma / Dilate OCT - G

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cenegermin-bkbj 20 mcg/ml was approved by FDA in August 2018

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

Objectives: To evaluate the safety and efficacy of topical recombinant human nerve growth factor (hNF) for healing 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.

Interventions: The REPAIR group 8 study received 0.02% (20 mcg/mL) hNF in 100 microliters (10 µL) of vehicle. Treatment was administered 6 drops per day for 8 weeks. Patients from control and vehicle groups received vehicle. Safety was assessed in all patients who received study treatment.

Primary Objective: To measure the proportion of patients who achieved complete corneal healing at week 8.

Main Outcome Measures: Corneal healing (defined as ≥ 3 -mm minimum diameter of fluorescein staining of the cornea being seen) compared between control (vehicle) and treatment (hNF) groups at week 8.

- Approved for the treatment of neurotrophic keratitis in adults and children age 2 and older
- Available for ordering since January 2019
- Developed by Dompé pharmaceuticals, available through specialty pharmacy

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Dosing and Administration

Every 2 hours instill 1 drop of (cenegermin-bkbj) ophthalmic solution 0.022% in the affected eye(s)

Apply 6 times daily

Continue for 8 weeks

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Study Conclusions

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

50 clinical trial sites in Europe and the U.S.

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

European patients with NK in one eye

NCT01756456

72.0% completely healed

Vehicle response rate 38.8%

Study NGF0214 (N=24 per group)

U.S. patients with NK in one or both eyes

NCT02271447

65.2% completely healed

Vehicle response rate 38.7%

Of patients who healed after one 8-week course of treatment... **80%** Remained healed for one year*

*Based on REPAIR, the study with longer follow-up.

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9/1/22
85yo AAF Presents for Blurry Vision OD

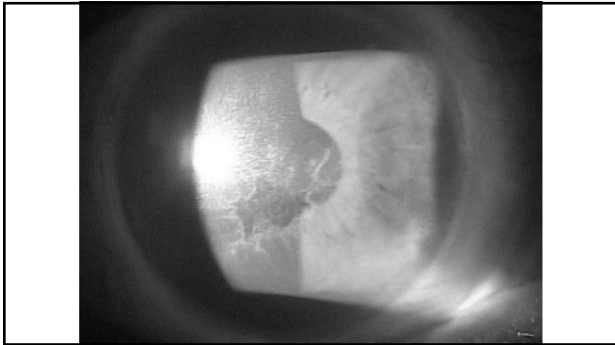
- 7-10 day cornea check / OCT-M / BCL removal
- Oc Hx:
 - K abrasion 8/23/22
 - OTHN
 - ERM OD
 - CME OD
 - Phaco OD 7/28/22
 - RD Repair OD, Cataract OS
- Oc Meds: Moxifloxacin TID OD, Difluprednate QID OD, ketorolac QID OD, timolol BID OD, Brimonidine BID OD

- Med Hx: HTN, Bladder cancer
- Meds: acetaminophen, fexofenadine HCL, ASA, sucralfate, doxycycline 100mg qd, piroxicam, fluticasone propionate, gabapentin, indapamide, nifedipine, omeprazole, valacyclovir, Vit C

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- BCVA OD: 20/80-2 PH: NI
- SLE:
 - 1+K edema / 2mm V x 5mm H epith defect
 - Rare cell
 - PCIOL – 1+ PCO
- What's Next?

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Future Treatments for NK

- Matrix regenerating therapy
- Thymosin β 4
- Substance P / Insulin like growth factor-1
- Nicergoline
- Varenicline
 - Stage 1 OC-10
 - Stage 2 and 3 - C-101 AAV-NGF

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Somebody Help Me

- NP 29 yowf presents for significant dry eyes. Eyes are always in pain, burning, gritty and feels like sand paper. Currently using serum tears 50% qid ou and would like to get serum tears 75%.
- Oc Hx: 8 years
- Med Hx: ADHD, Hypothyroid
- Meds: Nortriptyline, synthroid
- What questions do you want to ask?

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Previous Treatments

- Omega III – stopped on her own – NI
- Cyclosporine BID OU – stopped after 1 month / made eyes worse
- Prednisolone QID OU – stopped due to NI
- Plugs – 3 month plugs all puncta / NI
- Lifitegrast BID OU – stopped after 2 mos / made eyes worse
- Loteprednol 0.2% - NI
- Doxycycline 100 mg BID po – stopped after 2 weeks
- Erythromycin ung – NI
- Neomycin/polytrim/dexamethasone ung – NI
- Multiple preservative free drops

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Any Other Tests??

Diagnosis??

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Causes of NCP

- Trauma
- Chemical exposures
- Previous infection
- Eye surgery
- Systemic disease
 - Autoimmune or inflammatory conditions
 - Depression
 - Diabetes
 - Fibromyalgia
- Other neurological disease
 - Trigeminal neuralgia
 - Migraine

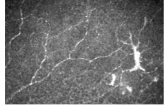


Photo Courtesy of Scott Hauswirth, OD

Moshirfar M, Benstead EE, Sorrentino PM, et al. Ocular Neuropathic Pain. [Updated 2022 Aug 22]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan.

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Diagnosis of NCP

- No universal criteria for dx
- Case history
- Initial triggers for pain
- Time course
- Alleviating and exacerbating factors
- Treatment history
- Symptoms - Topical lubricants provide no / minimal relief
- Clinical Exam
 - Pain without stain
 - Topical anesthetic relief
- Confocal Microscopy


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Neuropathic Pain

- Treatment to either:
 - Regenerate nerves
 - Reduce inflammation that makes nerves more sensitive
- Treatment Options
 - Serum tears
 - Steroids
 - Amniotic membrane
 - Neurostimulation
 - Blue filter glasses
 - Systemic neuro-modulatory therapies
 - Biologics

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Differentiate Your Practice – Advanced Treatments



Patient Name:
DOB:
Date:

Disp: *Autologous Eye Serum 20%*
Sig: *Instill one drop OU QID*

Refills: 8

Signature:
Lic #:

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Autologous Serum

- Blood drawn via 18 gauge needle – 40 mL blood collected into blood tubes
- Blood set aside to clot at room temperature for two hours, then centrifuged at 5600 rpm for 10 minutes
- Serum filtered to remove fibrin strands before mixing with saline
- Typically start with 20% AS up to 50%
- Unopened bottles stored in freezer up to 3 months; open bottles in refrigerator for 48 hours
 - Potential for safe refrigerator storage for up to 1 month

Source: Review of Oculometry

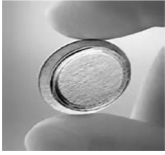
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Benefits and Pitfalls of Autologous Serum


<p><u>Benefits</u></p> <ul style="list-style-type: none"> • Preservative free and innately allergy free • Adverse events rare • Improvement in symptomology • Demonstrated improvement in staining (Tsubota – SS pts) 	<p><u>Complications</u></p> <ul style="list-style-type: none"> • Cost – no insurance coverage • Frequent blood draw • Availability of labs to make ASED • Strict handling
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Amniotic Membranes / Amniotic Membrane Extract Eye Drop (AMEED)



Cryopreserved Membranes



Dry Membranes



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Pros and Cons of Amniotic Membrane Modalities

<p>Cryopreserved</p> <ul style="list-style-type: none"> • Self-retaining on cornea • Higher levels of regenerative complex HC-HA/PTX3 • Shorter storage life – requires refrigeration • Potential discomfort from symblepharon ring <ul style="list-style-type: none"> • Avoid with filtering procedures 	<p>Dehydrated</p> <ul style="list-style-type: none"> • Longer storage life – room temperature • No ring = better comfort • Frequent slippage • Requires bandage lens to maintain position
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*****For all amniotic membranes, RCTs limited**

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Hindawi
Journal of Ophthalmology
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https://doi.org/10.1155/2017/6404918



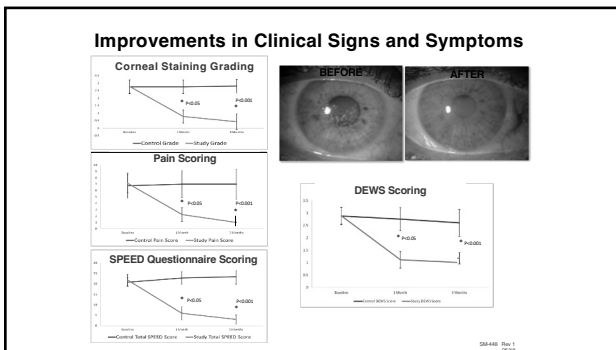
Clinical Study

Corneal Nerve Regeneration after Self-Retained Cryopreserved Amniotic Membrane in Dry Eye Disease

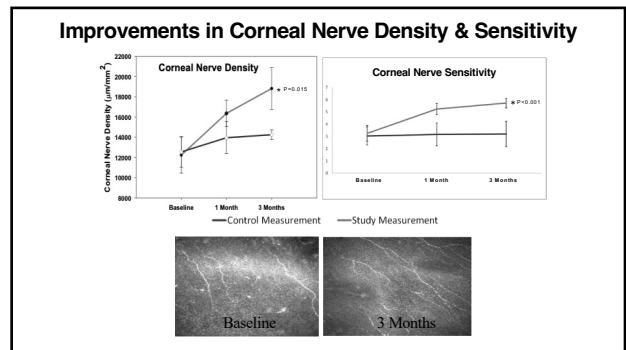
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Amniotic Membrane Extract Eye Drop (AMEED)

- Amniotic cytokine extract (ACE) for the treatment of ocular surface disease.
 - Cryopreserved amniotic eye drops contain more than 120 cytokines, growth factors and anti-inflammatory molecules to modulate and restore balance to the tear film
- Regener-Eyes
 - Sterile, acellular biologic made from 771 anti-inflammatory cytokines, and growth factors

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Future Insights on Neuropathic Corneal Pain

- Antiepileptics
 - Topiramate
 - Lamotrigine
 - Carbamazepine
- Analgesics
 - Mexiletine
 - Naltrexone
- Transcutaneous electrical nerve stimulation (TENS)
- Botulinum toxin type A

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Gabapentin

- Used for suppressing exaggerated pain and seizures
- Glutamate is also involved in transmitting pain signals in the brain and nervous system
- Gabapentin reduces the release of glutamate
- Recently failed study for ocular pain control after PRK (JCRS)
- Dosage 300 mg BID to QID

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Gabapentin and NCP

- Ongun N, Ongun GT. Is gabapentin effective in dry eye disease and neuropathic ocular pain? *Acta Neurol Belg.* 2021 Apr;121(2):397-401. doi: 10.1007/s13760-019-01156-w. Epub 2019 May 27. PMID: 31134508.
- Yoon HJ, Kim J, Yoon KC. Treatment response to gabapentin in neuropathic ocular pain associated with dry eye. *J Clin Med.* 2020;9(11):3765.
- Dario Rusciano, Massimo Dal Monte, Maurizio Cammalleri, Melania Olivieri, Salvatore Pezzino, Paola Bagnoli; EFFECTS OF TOPICAL GABAPENTIN ON OCULAR PAIN AND TEAR SECRETION. *Invest. Ophthalmol. Vis. Sci.* 2021;62(8):1288.

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Efficacy and tolerability of Nortriptyline in the management of neuropathic corneal pain

- **Purpose:** Off-label use of Nortriptyline has been used successfully in the management of non-ocular neuropathic pain – helpful in the management of neuropathic corneal pain (NCP)?
- **Methods:**
 - Retrospective cohort study at the New England Eye Center, Tufts Medical Center, Boston, Massachusetts from July 2015-March 2019
 - 54 patients with NCP with centralized component who were treated with Nortriptyline
 - Centralized NCP:
 - Discordance in clinical signs and symptoms
 - Persistent ocular discomfort/pain after 90s of instillation of 0.5% proparacaine hydrochloride
 - Nortriptyline dosed at 10mg initially and tapered upward to 100mg based on response and tolerability
- Response to treatment measured using Ocular Pain Assessment Survey (OPAS)

Ozmen et al. 2020

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- **Results:**
 - 30 patients included in final efficacy analysis:
 - 40% (n = 12) reported 50% or greater reduction in overall pain score (table 5)
 - Statistically significant reduction in all pain level dimensions (table 6)
 - Statistically significant reduction in many quality of life dimensions (table 7)
 - 19 of 54 discontinued due to side effects:
 - 8 of 19 were included in final analysis and discontinued despite reduction in pain score by 22.4%
 - Lethargy, dry mouth, constipation, nausea, headache, tachycardia, unspecified
- **Conclusion:**
 - Noteworthy pain decrease in patients with centralized component of NCP

Table 6
Results from the questions in pain level dimensions of the Ocular Pain Assessment Survey.

OPAS	Eye Pain Observation	Eye Vision Score	Last Visit Score	Percent Change	p
4	Mean ± SD	7.3 ± 2.2	5.5 ± 2.7	-24.3 ± 16.3	0.008
5	Mean ± SD	2.6 ± 1.2	2.0 ± 1.0	-23.7 ± 10.6	0.019
6	Average	5.7 ± 2.1	3.6 ± 2.1	-37.4 ± 12.6	<0.0001
7	Mean ± SD	7.7 ± 1.7	5.6 ± 2.0	-26.8 ± 16.6	0.003
8	Mean ± SD	4.6 ± 1.6	2.9 ± 1.2	-35.8 ± 16.6	0.0001
9	Average	6.1 ± 2.0	4.2 ± 2.1	-30.5 ± 10.9	0.001

Table 7
Results from the questions in quality of life dimensions of the Ocular Pain Assessment Survey.

OPAS	QoL dimension	Pre Visit Score	Last Visit Score	Percent Change	p
13	Reading/working	4.9 ± 2.3	4.3 ± 2.4	-12.2 ± 10.5	0.007
14	Driving/working	5.3 ± 2.5	3.9 ± 2.5	-26.2 ± 10.7	0.007
15	General activity	5.2 ± 2.4	3.9 ± 2.3	-24.8 ± 12.9	0.003
16	Mood	6.7 ± 2.0	4.9 ± 2.3	-26.8 ± 10.6	0.007
17	Sleep	3.8 ± 2.2	3.3 ± 2.7	-13.1 ± 12.7	0.011
18	Feeling fit	4.5 ± 2.2	4.6 ± 2.0	2.2 ± 10.1	0.668
19	Teaching others	7.6 ± 2.3	5.2 ± 2.5	-31.9 ± 17.6	0.001

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Low-dose Naltrexone (LDN)

- Low-dose naltrexone is effective and well-tolerated for modulating symptoms in patients with neuropathic corneal pain
- Neuropathic corneal pain (NCP) is caused by damage or disease of the somatosensory nervous system that innervates the cornea
- Assess efficacy and tolerability of 4.5mg Naltrexone QD po in refractory NCP patients after 30 days

Dieckmann G, Ozmen MC, Cox SM, Engert RC, Hamrah P. Low-dose naltrexone is effective and well-tolerated for modulating symptoms in patients with neuropathic corneal pain. *Ocul Surf.* 2021 Apr;20:33-38.

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Study Outcomes

- End Points: Decreased Ocular Pain Score and Increased Quality of Life Score
- Side effects of LDN: vivid dreams, headache, stomach ache
- LDN decreased OPS by 49.22%

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What About Botox?

- Cross-sectional retrospective study evaluated the effect of BoNT-A on photophobia and dry eye symptoms in individuals with chronic migraine (CM) and evaluate factors predictive of a positive treatment response.
- 90 patients had chronic migraine (≥ 15 per month) and had failed a trial of at least 2 migraine drugs or had contraindications to these medications.
- Symptom scale from “0” for no photophobia and “10” for the worst photophobia imaginable

Diel RJ, Kroeger ZA, Levitt RC, Sarantopoulos C, Sered H, Martinez-Barrizonte J, Galor A. Botulinum Toxin A for the Treatment of Photophobia and Dry Eye. Ophthalmology. 2018 Jan;125(1):139-140.

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- **Symptom Improvement**
 - The investigators found that the intensity of all 3 sensations—migraine pain, photophobia, and dryness
 - 72.5% of patients reporting improvement in photophobia
 - 29.3% reporting improvement in dry eye symptoms
 - >33% with photophobia improvement rated it as “much better”
 - Older patients reported more relief in eye pain symptoms.
- **Inflammatory action** - researchers believe that calcitonin gene-related peptide (CGRP) may be central to study results.
 - One of the proposed mechanisms in migraine is excessive CGRP release, which leads to neurogenic inflammation, recruitment of inflammatory cells to the site, and an inflammatory environment that does further damage to nerves

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OK-101

- 11/24/22 Investigational new drug application (NDA) with the FDA for the development of OK-101 to treat dry eye disease (DED)
- OK-101 is a lipid conjugated chemerin peptide agonist of the ChemR23 G-protein coupled receptor
- Typically found on immune cells of the eye responsible for the inflammatory response.
- Shown to produce anti-inflammatory and neuropathic pain-reducing activities in mouse models of DED and corneal neuropathic pain, respectively
- Lipid ‘anchor’ contained in the drug molecule to enhance the residence time of OK-101 within the ocular environment

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Take the Holistic Approach!!

- Consider neurologic and psychiatric collaboration
- Pain specialist
- Primary care physician

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Back to Our Initial Patient

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Clinical Examination

- BCVA OD 20/20 OS 20/25
- SLE:
 - 1+ telangiectasia, Cloudy secretions OU
 - 1+ papillae OU
 - TBUT 4 / 6 sec
- MMP-9
 - OD Mild +
 - OS Neg
- Tear Osm:
 - 279/284

Dx: Neuropathic corneal pain
KCS Non-sjogrens

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- Wants loteprednol and the only thing that helps
- Wants new glasses
- What are our options?
- What did I do?

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- ### Treatment and Management
- Loteprednol TID OU until gone
 - Will consider punctal cautery in the future
 - Recommend IPL to optimize ocular surface disease
 - F/u 4-6 weeks with IFD and prescribe autologous serum

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- ### Final Thoughts
- Consider corneal sensitivity
 - Aggressively treat the ocular surface
 - Treat and follow


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Thank You!!

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If you have any questions, you may send an email to wwhitley@cvphealth.com



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Thank you! Please join us for our next COPE events



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