


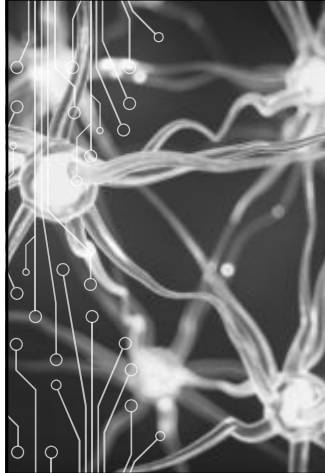
On behalf of Vision Expo, we sincerely thank you for being with us this year.

Vision Expo Has Gone Green!

We have eliminated all paper session evaluation forms. Please be sure to complete your electronic session evaluations online when you login to request your CE Letter for each course you attended! Your feedback is important to us as our Education Planning Committee considers content and speakers for future meetings to provide you with the best education possible.



1



**It's All In Their Head:
Diagnosing
Neurological Related
Eye Conditions**

CECELIA KOETTING OD FAAO DIPABO
UNIVERSITY OF COLORADO SCHOOL OF MEDICINE

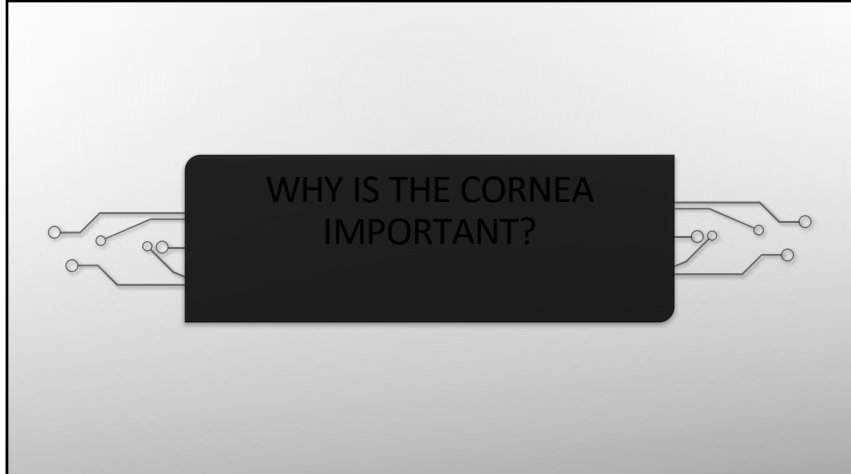
2

CECELIA KOETTING FINANCIAL DISCLOSURES

"All relevant relationships have been mitigated."

• Ocular Therapeutix	• RVL	Glaukos
• Glaukos	• Oyster Point	Avellino
• Horizon	• Allergan	B +L
• Quidel	• Alcon	Iveric
• Eyevance/Santen	• Visus	Aldura
• Ivantis	• Thea	Claris Bio
• Orasis	• Bruder	Aldeyra
• Kala	• Blinkjoy	Twenty Twenty
	• SCOPE	

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**WHY IS THE CORNEA
IMPORTANT?**

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CORNEAL FUNCTION

- Shields the eye from germs, dust, other harmful matter
- Contributes between 65-75% refracting power to the eye
- Filters out some of the most harmful UV wavelengths

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CORNEAL EPITHELIAL CELLS

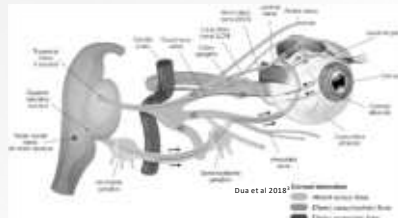
- Corneal integrity and function depends on a constant replenishment of epithelial cells
- Stem cells located in the limbus divide asymmetrically to produce:
 - More stem cells
 - Cells that differentiate into epithelial cells as they migrate out of the limbus
- In the healthy cornea, production of new epithelial cells is sufficient to replace cells lost at the epithelial surface

Mastropasqua L, et al. J Cell Pathol. 2017;232:717-24;2. Adapted from Shaheen R, et al. Surv Ophthalmol. 2014;59:263-85.

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HIGHEST CONCENTRATION OF NERVES

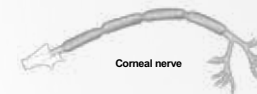
- Healthy cornea contains no blood vessels and is extremely sensitive to pain¹
- Corneal sensory nerves originate from the ophthalmic branch of the trigeminal nerve
- Cornea also receives sympathetic innervation from the superior cervical ganglion



1. Mastropasqua L, et al. J Cell Pathol. 2017;232:717-24;2. Müller LJ, et al. Exp Eye Res. 2003;76:521-42; 3. Dua HS, et al. Prog Retin Eye Res. 2018; doi: 10.1016/j.preteyres.2018.04.003. [Epub ahead of print].

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NERVES, NERVES, NERVES



Job #1: react to injury at the ocular surface by registering pain and irritation and triggering **protective reflexes**, such as **tear production and blinking**¹

Job #2: release neuromediators that provide **trophic support** to corneal epithelial cells and keratocytes^{1,2}

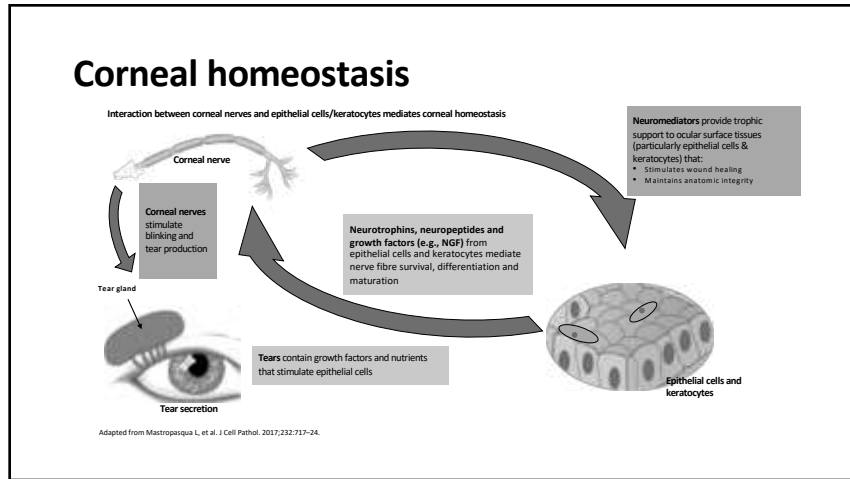
Neuromediators¹

- Substance P
- Neurokinin A
- Calcitonin gene-related peptide
- Acetylcholine
- Cholecystokinin
- Galanin
- Noradrenaline
- Serotonin
- Neuropeptide Y
- Vasointestinal peptide
- Met-enkephalin
- Brain natriuretic peptide
- Vasopressin
- Neurotensin
- Beta endorphin

Images by kind permission of Prof. Dua

1. Mastropasqua L, et al. J Cell Pathol. 2017;232:717-24; 2. Müller LJ, et al. Exp Eye Res. 2003;76:521-42.

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WHAT HAPPENS WHEN HOMEOSTASIS IS LOST?

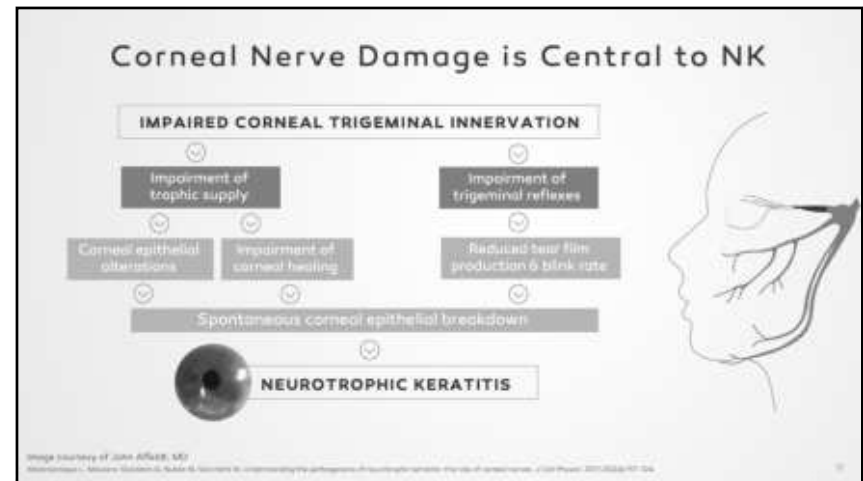
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NEUROTROPHIC KERATITIS

- Rare disease
 - Fewer than 65,000 in the US****
- Degenerative corneal disease caused by damage of the trigeminal corneal innervation
 - Breakdown of epithelium
 - Corneal ulceration

Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. Clin Ophthalmol. 2014;8:571-579.

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ETIOLOGIES ASSOCIATED WITH NK

Ocular <ul style="list-style-type: none"> • Herpes (simplex or zoster) infection • Other infections e.g acanthamoeba • Chemical or physical burn • Abuse of topical anaesthetics • Drug toxicity • Chronic ocular surface injury or inflammation • Ocular surgery • Cataract surgery • LASIK, PRK • PK and DALK • Collagen crosslinking for keratoconus • Vitrectomy for retinal detachment • Photocoagulation for diabetic retinopathy • Postsurgical or laser treatment • Routine laser for proliferative diabetic retinopathy • Contact lenses • Orbital neoplasia • Corneal dystrophies 	Central nervous system <ul style="list-style-type: none"> • Neoplasm • Aneurysms • Stroke • Degenerative CNS disorders • Post-neurosurgical procedures <ul style="list-style-type: none"> - For acoustic neuroma - For trigeminal neuralgia • Other surgical injury to trigeminal nerve 	Systemic <ul style="list-style-type: none"> • Diabetes mellitus • Leprosy • Vitamin A deficiency • Amyloidosis • Multiple sclerosis Genetic <ul style="list-style-type: none"> • Riley-Day syndrome (familial dysautonomia) • Goldenhar-Gorlin syndrome • Mobius syndrome • Familial corneal hypoesthesia
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DALK=deep anterior lamellar keratoplasty; LASIK=laser in situ keratomileusis; PK=penetrating keratoplasty; PRK=photorefractive keratectomy

1. Dua HS, et al. Prog Retin Eye Res. 2018;doi: 10.1016/j.preteyres.2018.04.003.

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MACKIE CLASSIFICATION

STAGE 1 Mild
Punctate epithelial keratopathy (PEK)

STAGE 2 Moderate
Resistant epithelial defect (RED)

STAGE 3 Severe
Corneal ulcer

Some vision loss can potentially be seen in all stages of NK⁵
 If untreated, moderate NK progresses to severe disease with associated risks of profound vision loss resulting from scarring and corneal perforation⁶

1. Dua HS, Sall OG, Maresca EM, et al. Neurotrophic keratopathy. Prog Retin Eye Res. 2018;66:107-131. 2. Semperov F, et al. Neurotrophic keratopathy. Ophthalmologica. 2014;231:191-197. 3. Sachithan M, Lamberti A. Diagnosis and management of neurotrophic keratopathy. Clin Ophthalmol. 2014;8(1):171-176. 4. Maresca E, Galimberti R, Uboldi G. Pediatric atypical keratopathy. Asia J Ophthalmol. 1998;12(4):207-210. 5. Ruiz-Lorenzo RL, Hernandez-Camacho JC, Lopez-Garcia D, Velasco-Usson J, Rodriguez-Garcia A. The molecular basis of neurotrophic keratopathy: Diagnostic and therapeutic implications. A review. Ocul Surf. 2011;Jan;19:224-240.

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CASE #1

- 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.
- 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 OU
 - Previous treatments
 - Amniotic membrane OS (2019, 2020)
 - Punctal cautery (2011) OU
- Med Hx:
 - NIDDM 15 yrs
 - Osteoarthritis
 - Hypothyroid
 - Seasonal allergies
- Meds:
 - Ceterizine
 - Lactulose
 - Tirosint

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CLINICAL EXAM

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

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ASSESSMENT OF CORNEAL SENSITIVITY IS ESSENTIAL TO CONFIRM NK DIAGNOSIS¹

Ocular symptoms
History
Clinical examination and tests

NK suspected

Test corneal sensitivity

Corneal sensitivity tests:²

- Qualitative (touching cornea with cotton thread)
- Quantitative (corneal aesthesiometer)
- Severity of NK related to severity of corneal sensory impairment

Normal → NK unlikely

Reduced → Further tests required

Adapted from 1. Dua HS, et al. Prog Retin Eye Res. 2018;doi: 10.1016/j.preteyeres.2018.04.003. [Epub ahead of print]; 2. Sacchetti M & Lambiase A. Clin Ophthalmol 2014;8:571-9.

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CORNEAL SENSITIVITY TESTING: ESTHESIMETRY

- Qualitative
 - Cotton tip applicator
 - Dental floss
- Quantitative
 - Cochet-Bonnet
 - Non contact esthesiometer

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COCHET-BONNET

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Assessment and safety of the new esthesiometer BRILL: Comparison with the Cochet-Bonnet Esthesiometer

Jessie Méryso-Louvet et al. Eur J Ophthalmol. 2022.

Abstract

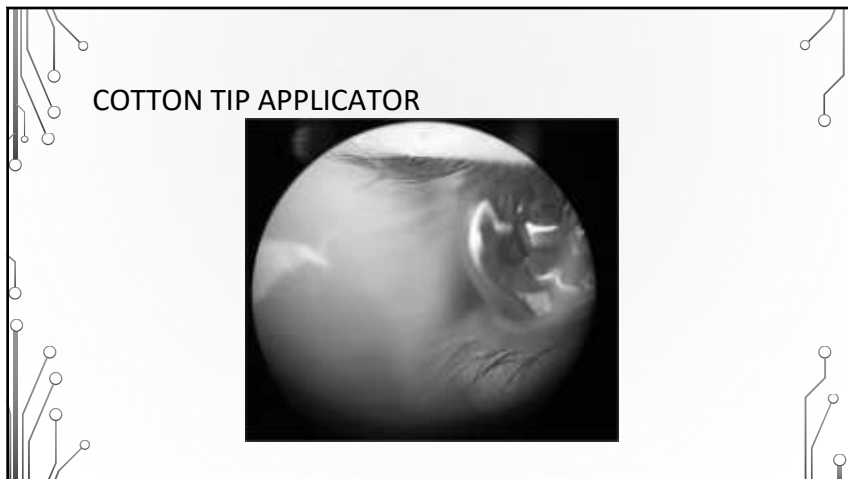
Background: Corneal sensitivity can decrease by several ocular conditions, such as dry eye or refractive surgery, which favor ocular epithelial lesions and is measured using an esthesiometer. The study's primary objective was to demonstrate the efficacy and safety of the non-contact esthesiometer BRILL, which delivers air pulses to the corneal surface to assess corneal sensitivity.

Methods: A single-center, retrospective, nonmasked pilot study was carried out in adult patients, with healthy eyes and/or with pathology. Corneal sensitivity measurements were made in duplicate for both eyes of three consecutive visits. The esthesiometer BRILL was used in all visits, and on the last visit, the contact esthesiometer Cochet-Bonnet was also used. The results of both devices were compared by incorporating these into force values.

Results: 54 subjects with a mean age of 50.43 (SD 16.55, interval 18-87), 77.78% women, were included. Comparing the forces applied by both esthesiometers in the healthy eyes, in the eyes with pathology in all the groups, and in the dry eyes showed significant differences, $p = 0.03603$, $p = 0.00614$, and $p = 0.0001$, respectively.

Conclusion: The BRILL esthesiometer proved to be an effective and safe tool for non-contact assessment of corneal sensitivity with operator-independent repeatability. The measurements had a good agreement and comparable range with the Cochet-Bonnet esthesiometer measurements in healthy and dry eyes but with no interchangeable values. This portable device can help ophthalmologists and optometrists to diagnose eye pathologies that cause decreased corneal sensitivity and to assess the efficacy of therapy and disease progression.

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PROPARACAINE CHALLENGE

- Instill a drop of proparacaine
 - Does the patient still have pain?
 - Yes then the issue is further back in the trigeminal nerve than the eye
 - No then ocular pain is ocular surface related
- Only works on nociceptors on they ocular surface.

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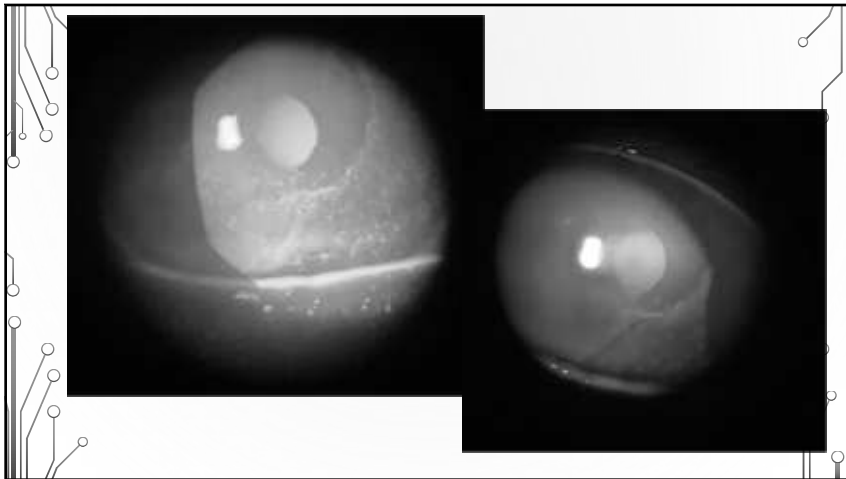
CASE #2

- 57 YOA caucasian male
- CC: Progressive decrease in vision over the last 1 month with sharp change in the last week.
- OHx: CL overwearer (when prompted says he has had to peel them off his eyes the last few months)
- No systemic Hx or medications

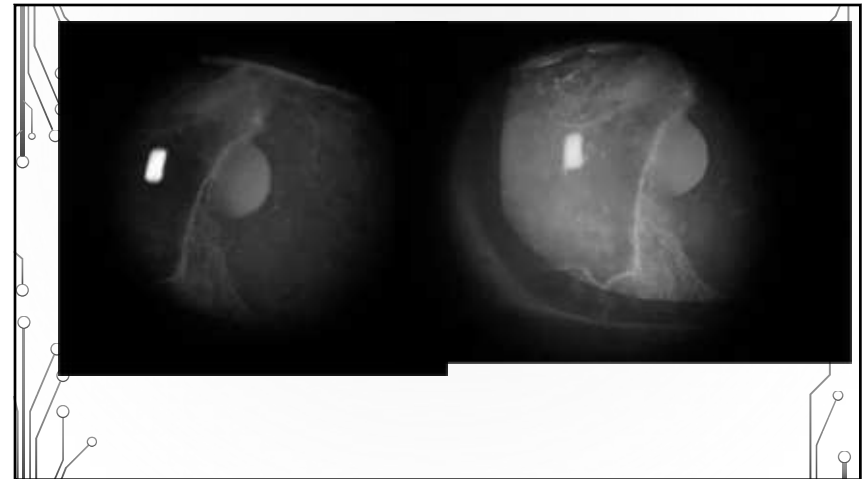
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- BCVA OD: 20/400; OS: HM 5Ft
- IOP App 16mmHg OD and OS
- SLE:
 - OS>OD: 3+ stippling in whorl like pattern, moderate haze with central line (conjunctivalization)

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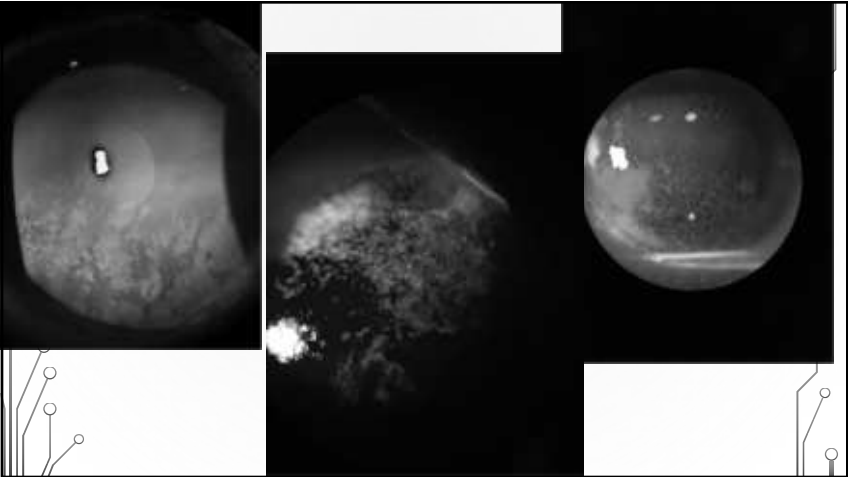
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SLIT LAMP EXAM WITH VITAL DYES ARE IMPORTANT!

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- INITIAL TREATMENT FOR PATIENT
- Topical corticosteroid BID OU
 - Cyclosporine BID OU
 - Hylo Vit A ointment at night
 - PF AT every 2 hours or more

 - Next appointment No Touch

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TREATMENT OF NK

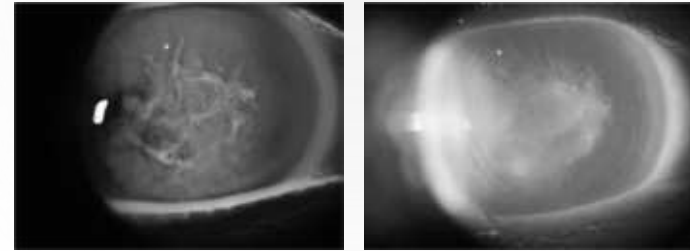
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STAGE 1

- Remove any ocular medication that may be associated with toxicity
 - Preservative free options, tears and ointments
- Treat other associated ocular problems
 - LSCD
 - OSD/DED
 - Exposure keratitis
- Vitamin A ointment
- Amniotic membranes
- Autologous serum or PRP eye drops
 - Growth factors, neuromediators, cytokines, vitamins
 - Steroids
- Recombinant NGF Cenegevine

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NK FROM RCE



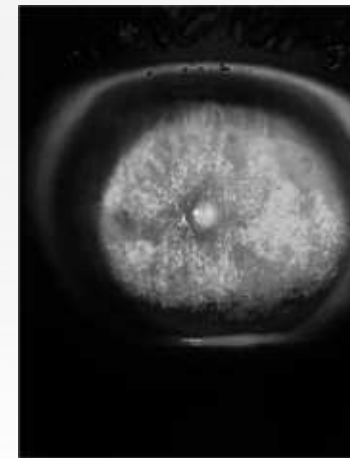
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STAGE 2

- Promote healing of epithelial defect and prevent corneal ulcer
- Monitor patient frequently
- Topical antibiotics
- Bandage contact lens

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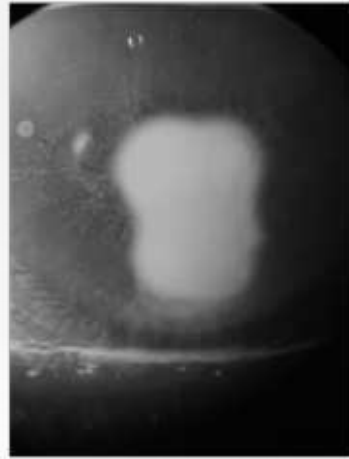
PERSISTENT EPITHELIAL DEFECT



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STAGE 3

- All the above
- Heavy antibiotics
 - Consider fortified
- Will need surgery if perforation



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VITAMIN A OINTMENT

- Vitamin A regulates the proliferation and differentiation of corneal epithelial cells,
 - Preserves conjunctival goblet cells
- Vitamin A is an essential nutrient present naturally in tear film of healthy eyes
- Vitamin A plays an important role in production of the mucin layer



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AMNIOTIC MEMBRANE FOR NK

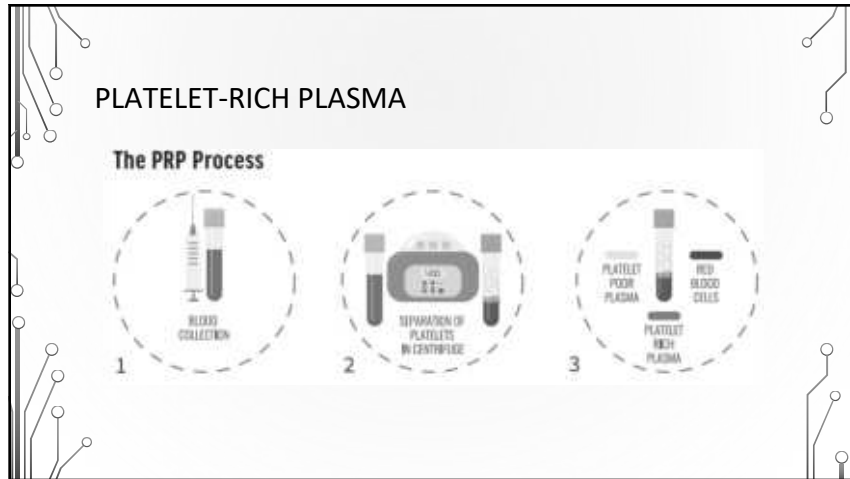
- Khokhar et al 2005
- 30 patients given either amniotic membrane or tarsorrhaphy and bandage CL
- 3 months
 - 10/15 patients receiving tarsorrhaphy or bandage CL had full epithelialization and healing
 - 11/15 patients receiving amniotic membrane tx had full epithelialization and healing

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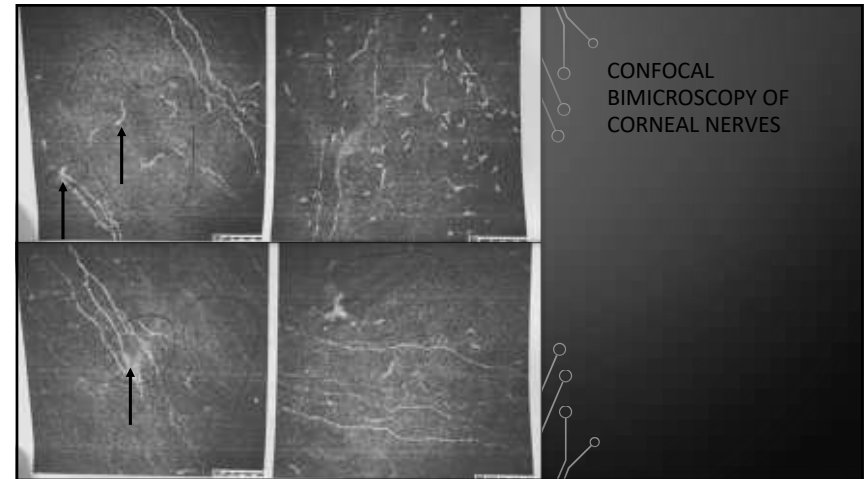
AUTOLOGOUS SERUM TEARS FOR NK

- Matsumoto et al 2004
- Complete healing of all the 14 eyes with NK treated with autologous serum drops and an increase in corneal sensitivity in 64.2% of cases
- The study demonstrated that serum harbors neurotrophins and growth factors to the ocular surface.
- More recent studies confirmed that autologous serum eye drops allowed high rates of corneal healing, and also the improvement of corneal nerve morphology with increased number, length, width, and density

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- ### SURGICAL INTERVENTION
- Tarsorrhaphy
 - LSC transplant
 - Cyanoacrylate glue for small perforations
 - Penetrating keratoplasty
 - Lamellar keratoplasty

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CORNEAL NERVE SURGERY

Direct neurotization

utilizes the supraorbital and supratrochlear branches of the frontal nerve

sensory function of the two nerves overlap over the medial forehead, so harvesting one for a corneal neurotization surgery should theoretically leave adequate residual sensation

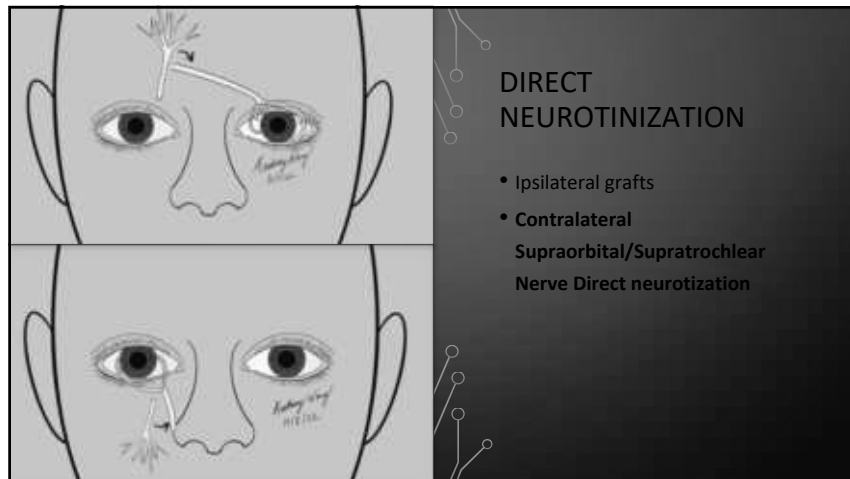
Indirect neurotization

utilizes sural nerve due to accessibility and low risk donor graft site in other neurotization procedures

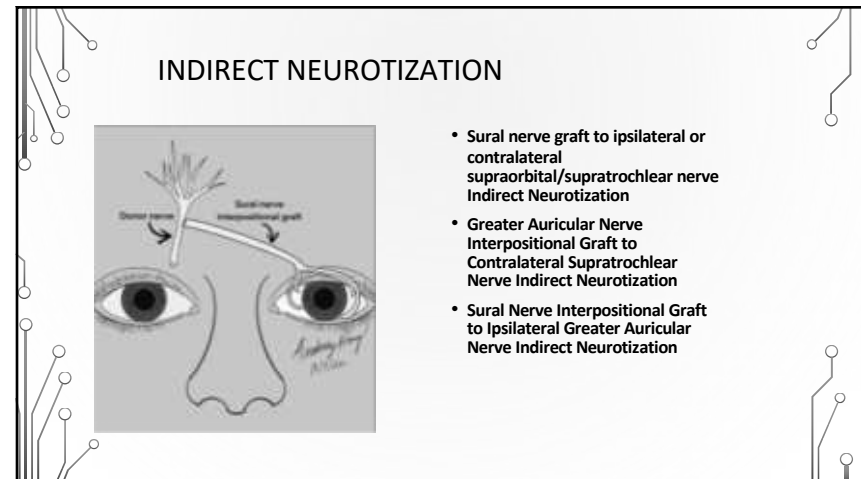
- Provides sensation in calf region of leg and has branches from tibial and common fibular nerve

great auricular nerve has been used in corneal neurotization surgeries and one advantage is its proximity to the recipient site as well as the need to only prepare one surgical field

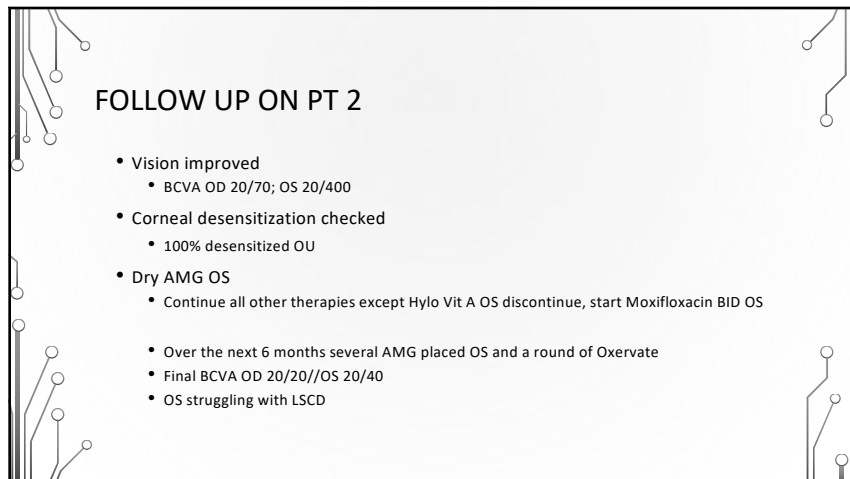
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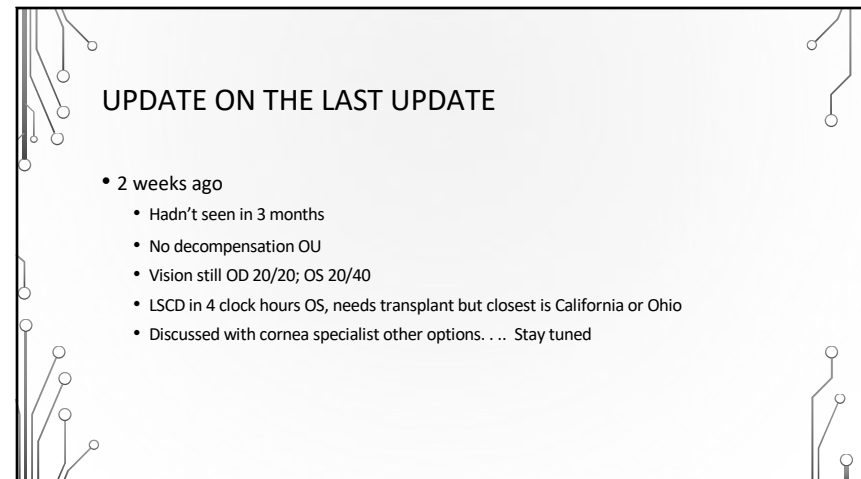
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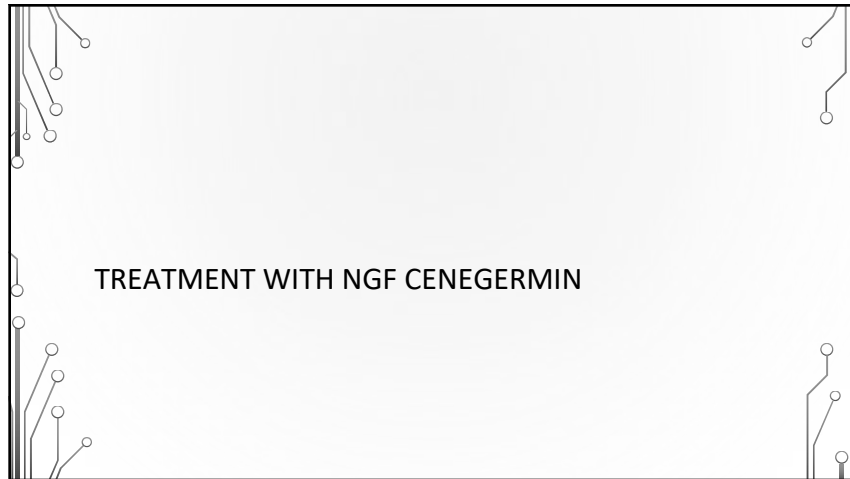
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TREATMENT WITH NGF CENEGERMIN

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

Neurotrophic keratitis (NK) is a result from impaired trigeminal corneal innervation

Endogenous NGF maintains corneal integrity by three mechanisms

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

Mastropasqua et al. (2017) | Cell Physiol 232:737-24

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

- 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

Bonini S, Lambase 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.

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PIVOTAL STUDIES OVERVIEW

	REPARO ¹ (n=156)	NGF0214 ² (n=48)
Geography	Europe	USA
Design	3 treatment arms*: vehicle, cenegermin 10 mcg/mL, cenegermin 20 mcg/mL	2 treatment arms: vehicle, cenegermin 20 mcg/mL
Course of Therapy	8 weeks	8 weeks
Duration of follow-up	48 weeks	24 weeks
Uni/bilateral disease	Unilateral	Unilateral and bilateral
Endpoints	Complete corneal healing[†] at Week 8 (based on a post-hoc analysis [‡])	Complete corneal healing[†] at Week 8
	Primary analysis was <0.5 mm maximum diameter of fluorescein staining in the lesion area at Week 4	

*The formulation that was tested in study NGF0214 included the antioxidant methionine and is the final formulation that is marketed. More than one study was conducted with the final commercial formulation. No difference in safety was seen in any of the trials.
[†]Defined as 0.0 mm maximum diameter of fluorescein staining in the lesion area) and no persistent staining in the rest of the cornea.
[‡]FDA approval was based on complete corneal healing defined as absence of staining of the corneal lesion and no persistent staining in the rest of the cornea after 8 weeks of treatment.
 Please see Important Safety Information in this presentation and a Dompé representative for Full Prescribing Information.

1. Bonini S, Lambase 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. 2. Plugfelder SC, Massimo-Gostardo M, Paves VL, et al. Topical Recombinant Human Nerve Growth Factor (Cenegermin) for Neurotrophic Keratopathy: A Multicenter Randomized Vehicle-Controlled Pivotal Trial. *Ophthalmology*. 2020;127(1):16-26.

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TRIALS INCLUDED A DIVERSE POOL OF PATIENTS REPRESENTATIVE OF NK

REPARO Study ^{1,2}			NGF0214 Study ^{1,2}		
	OXERVATE (n=52)	Vehicle (n=52)		OXERVATE (n=24)	Vehicle (n=24)
Primary NK diagnosis*, no. (%)			Primary NK diagnosis*, no. (%)		
Stage 2 (moderate)	27 (51.9)	28 (53.8)	Stage 2 (moderate)	15 (62.5)	18 (75.0)
Stage 3 (severe)	25 (48.1)	24 (46.2)	Stage 3 (severe)	9 (37.5)	6 (25.0)


*Based on Mackie classification.

The formulation that was tested in REPARO (Study NGF0212) did not include the antioxidant methionine and is not the final formulation that is marketed as OXERVATE. Methionine is an excipient added to the commercial formulation to improve its stability. More than one study was conducted with the final commercial formulation. No difference in safety was seen in either of the trials. Please see Important Safety Information in this presentation and a Dompé representative for Full Prescribing Information

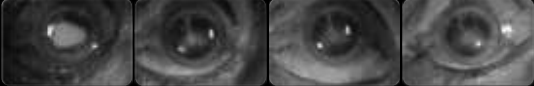
1. Borry S, Lambiano A, Ramo P et al. Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis. *Ophthalmology* 2018;125:3332-3343. 2. Pflugfelder SC, Massaro-Giordano M, Pense V, et al. Topical Recombinant Human Nerve Growth Factor (Cenegegan) for Neurotrophic Keratopathy: A Multicenter Randomized Vehicle-Controlled Phase III Trial. *Ophthalmology*. 2020;127(1):142-50. 3. Drug Approval Package: OXERVATE (Cenegegan) (SAs). Accessdata.fda.gov. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/761094Orig1s000201R.pdf. Published 2018. Accessed November 13, 2018.


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PRIMARY EFFICACY MEASURE: COMPLETE CORNEAL HEALING




Original Endpoint (EMA)¹:
<0.5 mm lesion staining





Revised Endpoint (FDA)²:
0 mm staining in lesion area;
no other residual staining



1. Data on file: NGF0212 (REPARO) CSR
2. Data on file: NGF0214 CSR

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ROCK SALT TO THE EYE

- 40 YOA White Female
- Got rock salt in her OS 2 years previously in NYC when walking around outside her hotel.
- Pain and light sensitivity still present and persistent.
 - No improvement with aggressive dry eye treatment
 - Only improvement is with sun glasses and photochromatic CL

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WHAT'S REALLY GOING ON HERE?

- Corneal sensitivity
 - 100% sensitivity OD; 50% sensitivity OS
- Started on topical cenegegan Q2hr x 8 weeks
 - Improvement to approximately 70% sensitivity OS

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NEUROPATHIC CORNEAL PAIN

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- Persistent ocular pain
 - Burning
 - Increased light sensitivity
 - Increased sensitivity to wind
 - Shooting pains from one or both eyes
- May be present WITH or WITHOUT ocular surface abnormalities

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WHAT CAUSES THIS?

- Suggested that there is an initial insult to the eye causing chronic nerve abnormality
- The initial trigger may be any of the following:
 - trauma (e.g., corneal abrasion, radiation therapy)
 - chemical exposures (e.g., preservatives in topical medications, chemical burns, systemic chemotherapy)
 - infection (e.g., herpes simplex virus, herpes zoster virus)
 - eye surgery (e.g., refractive, cataract, glaucoma, and retinal surgery)
 - systemic disease (e.g., autoimmune or inflammatory conditions, diabetes, fibromyalgia)
 - other neurological disease (e.g., trigeminal neuralgia, migraine)

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ARVO Annual Meeting Abstract | June 2021

Topical Recombinant Human Nerve Growth Factor Improves Outcomes in Murine Model of Neuropathic Corneal Pain

Brendan Henry, Dasha L. Harris, Fangfang Qiu, Cecilia Chang, Taylor Joseph-Racot, Nathan Henrich

Author Affiliations & Notes

Investigative Ophthalmology & Visual Science June 2021, Vol. 62, 842, 844

SHARE TOOLS

Abstract

Purpose: Since its discovery, nerve growth factor (NGF) has sparked widespread interest in possible therapeutic utility across neurologic diseases. NGF and other neurotrophic factors are upregulated in neuropathic pain, although their precise role remains to be fully understood. Herein, we assess the possible therapeutic benefits of recombinant human NGF (rhNGF) in the olfactory nerve lesion model of neuropathic corneal pain.

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STUDY METHOD

- Adult Male mice underwent ciliary nerve ligation to induce NCP
- Treated with 6 10uL drops/day of 0.02mg/mL rhNGF or vehicle
- Outcomes @ day 7,10,14:
 - corneal fluorescein stain
 - Cochet-Bonnet esthesiometry
 - L-metnhol for assessment of pain by paw wipe response
- Day 14 trigeminal ganglia were removed and analyzed for neurotrophic factors and cytokines

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RESULTS

- Did not alter the corneal fluorescein staining or the corneal sensitivity in either group
- Reduction in several neurotrophic factors in the treatment group vs the vehicle only
 - No increase in pro-inflammatory cytokines
- **Findings suggest that topical rhNGF treatment improves pain outcomes in our neuropathic corneal pain and warrant future studies in the clinic**
- **Topical rhNGF treatment alters expression of neurotrophic factors, but not pro-inflammatory cytokines within the TG**

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FUTURE TREATMENTS

Study	Eyes (no.)	Treatment	Posology	Onset-treatment interval (days)	Complete healing	Healing time (days)
Alfa et al ¹	11	RGTA	1x/on alternate days	>15	72.7%	60.9
Arvola et al ²	6	RGTA	1x/on alternate days	45	33%	56
Dunn et al ³	9	Thymosin beta-4	4x/day	>42	67%	45
Nishida et al ⁴	9	SP and IGF1	4x/day	141	89%	13.3
Yamada et al ⁵	26	SP and IGF1	4x/day	96	73%	10.5
Lambiasi et al ⁶	14	NGF	Every 2 h for 2 days, then 6x/day	45	100%	21
Bonini et al ⁷	45	NGF	Every 2 h for 2 days, then 6x/day	38	100%	22.8/26.6 ⁸
Lee et al ⁹	27	Nicergoline (oral)	10 mg 2x/day	>60	85%	15.6

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FUTURE TREATMENTS

Topical Insulin Drops

Trefoil (TTHX1114) in studies for endothelial disease and neurotrophic keratitis

OK-101- Neuropathic pain-Phase 2 studies

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PEARLS

- When you've thrown the kitchen sink at a dry eye patient and its not better, check the corneal sensitivity
- Stain without pain, check corneal sensitivity
- Pain without stain, check NaFl with wratten filter or LG AND check corneal sensitivity
- NK is classified as a rare disease, but its more likely that its just under diagnosed

SO, Don't lose your nerve, CHECK CORNEAL SENSITIVITY!!

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QUESTIONS?

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THANK YOU!



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