

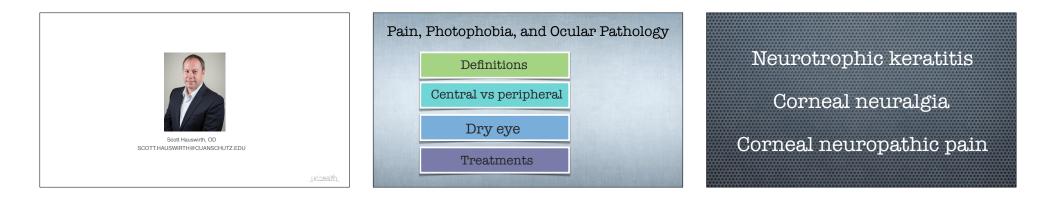
Pain, Photophobia, and Ocular Pathology: What you can do to help your patients

eyemage@mminternet.co

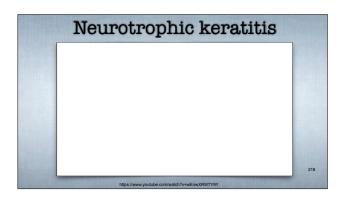
### disclosures

allergan/abbvie bausch health novartis sun pharma kala pharma tarsus pharma hovione scientia silk-tech	sydnexis eyenovia bio laboratoires Th aurinia pharm eyevance phar surface pharn nevakar, inc

visus therapeutics aperta biosciences astareal, inc. azura ophthalmics ideyra therapeutics vyluma ocuphire





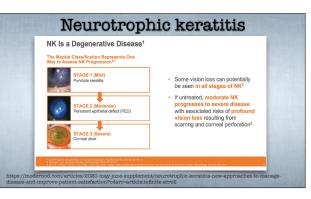


# Neurotrophic keratitis

"Stain without pain"

"A key differentiator is the reduction or total loss of corneal sensitivity...caused by damage to the corneal nerve, which leads to breakdown and poor healing of the epithelium."

Mastropasqua L, Massaro-Giordano G, Nubile M, Sacchetti M. Understanding the pathogenesis of neurotrophic keratitis: the role of corneal nerves. J Cell Physiol. 2017;232(4):717-724. https://knownk.com/about-nk/#what-is-nk



Neurotrophic kerat	titis
--------------------	-------

Discontinue all preservative-containing topical medications	*	*	
vedical management			
Topical preservative-free drops	a	a	a
Topical preservative-free gel drops or ointments			1
Autologous serum drops, human umbilical cord serum, platelet rich plasma	*	•	a
Recombinant human nerve growth factor (cenegermin)	9	a	3
Prophylactic topical preservative-free antibiotics (excluding aminoglycosides)		a	4
Matrix metalloproteinases inhibitors	9	a	a
ion-surgical intervention (i.e., office procedures)			
Corneal therapeutic contact lenses	9	a	b.
Fresh-frozen self-retained amniotic membrane		a	3
Punctal occlusion		a	4
Synthetic (cyanoacrylate) tissue adhesive			a
iurgical intervention (i.e., operating room procedures)			
Tarsorrhaphy		b	a
Amniotic membrane transplant		6	4
Corneal neurotization		9	a
'Treatments rated as potentially optimal, depending on the patient's 'Treatments rated as potentially appropriate, depending on the patie		not noted in the manus	rript)

# FUNDER STATUS <td

### Neurotrophic keratitis

Search		
Drug	Company	Price per month (USD)
1. Myalept	Amryt Pharma	71306
2. Ravicti	Horizon Therapeutics	55341
3. Mavenclad	END Sorono	53730
4. Actimmune	Horizon Therapeutics	52777
5. Oxervate	Dompé	48458
6. Takhzyro	Takeda	45464
7. Daraprim	Vyera Pharmaceuticals	45000
8. Juotapid	Amyrt Pharma	44714
9. Cinryze	Takeda	44141
10. Chenodal	Retrophin	42570

CVS Pharmacy	\$29,162 retail Save 10%	\$26,182.13 with free coupon	GET FREE COUPON
Walgreens	\$29,162 retail Save 9%	\$26,258.94 with free coupon	GET FREE COUPON
Ralphs	\$29,162 retail Save 15%	\$24,656.73 with free coupon	GET FREE COUPON
Costco	\$29,162 retail Save 12%	\$25,418.76 with free coupon	GET FREE COUPON
Rite Aid	\$29,162 retail Save 10%	\$26,030.99 with free coupon	GET FREE COUPON

### Monday Morning Patient Scott Hauswirth, OD

- 71 yo Caucasian female
- 18-month history of dry eye, has seen 8 physicians
  Relatively sudden onset shortly following
- uncomplicated cat sx, gradually worsening
- Primary symptoms: constant burning, moderate photophobia
- Treated with Restasis, Xiidra, ATs, Warm compresses, plugs, steroids, LipiFlow
- <u>"NOTHING HELPS!!"</u>



<u>, coasth</u>







Neurotrophic keratitis Corneal neuralgia Corneal neuropathic pain

# Corneal neuralgia

"Neuralgia is defined as pain in the distribution of a nerve or set of nerves with concurrent signs of nerve damage"

Theophanous, Christos\*; Jacobs, Deborah S.; Hamrah, Pedram Corneal Neuralgia after LASIK, Optometry and Vision Science: September 2015 - Volume 92 - Issue 9 - p e253-e240 doi: 10.1097/097X.0000000000000000652





# Corneal neuralgia

Cornea:

300-600x more sensitive than skin 20-40x more sensitive than dental pulp "Toothache magnified"

### Corneal Innervation

- Cornea is most highly innervated region in the body
- 21,668um/mm<sup>2</sup>
- 7000 nerve terminals per sq mm<sup>1</sup>
- Vast majority (70-80%) unmylenated



1)Muller LJ. Exp Eye Res. May 2003

# Neuropathic pain & dry eye

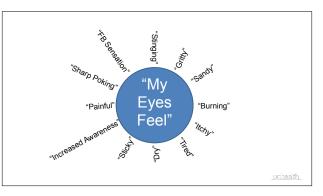
Hyperalgesia-An increased sensitivity to feeling pain and an extreme response to pain. Ex. wind

Allodynia- pain due to a stimulus that does not normally provoke pain (feather touch)

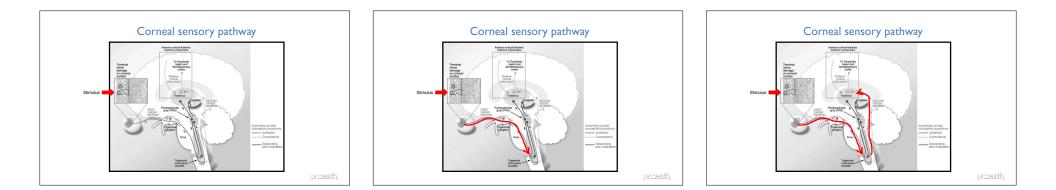
PhotoAllodynia-Photophobia

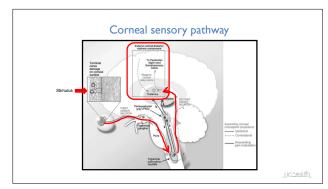
Galor A, Moein HR, Lee C, Rodriguez A, Pelix ER, Sarantopoulos KD, Levitt RC. Neuropathic pain and dry eye. Ocul Surf. 2018 Jan; 16(1):31-44. doi: 10.1018/j.itos.2017.10.001. Epub 2017 Oct 12. FMD: 28031645; FMCD: PMCSF08672.

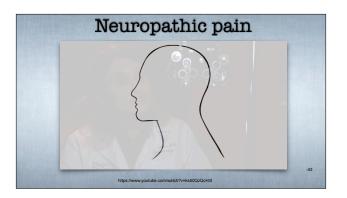








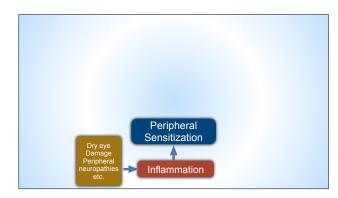




## Neuropathic pain & dry eye

"damage and inflammation...result in peripheral axonal injuries and the release of...inflammatory mediators, potentially resulting in increased sensitivity of peripheral nerves...(peripheral sensitization)"

Dieckmann G, Goyal S, Hamrah P. Neuropathic Corneal Pain: Approaches for Management. Ophthalmology. 2017;124(115):834-847. doi:10.1016/j.ophtha.2017.08.004



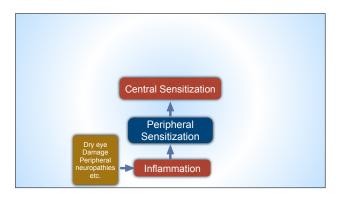
# Neuropathic pain & dry eye

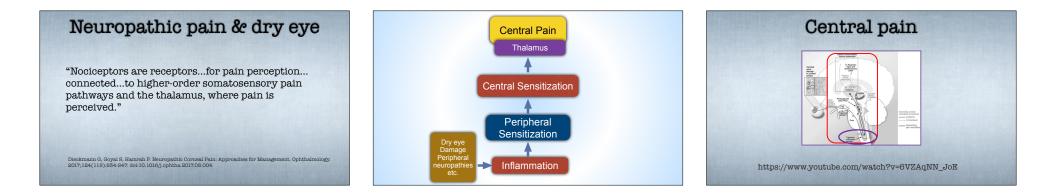
"repeated peripheral nerve injury can lead to central neuronal sensitization"

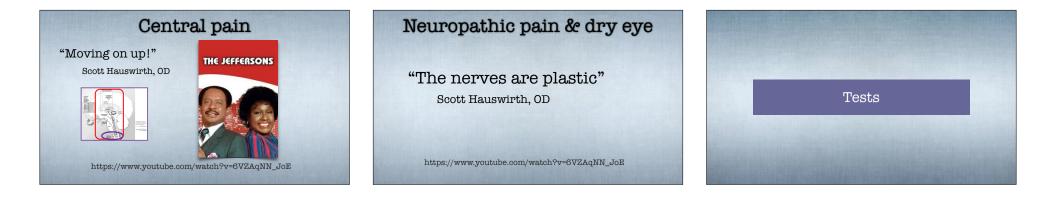
"Over time...can result in central sensitization... central neurons becoming highly responsive to... pain and heightened pain awareness."

Dieckmann G, Goyal S, Hamrah P. Neuropathic Corneal Pain: Approaches for Management. Ophthalmology. 2017;124(118):S34-S47. doi:10.1016/j.ophtha.2017.08.004

Kim J, Yoon HJ, You IC, Ko EY, Yoon KC. Clinical characteristics of dry eye with ocular neuropathic pain features: comparison according to the types of sensitization based on the Ocular Pain Assessment Survey. EMC Ophthalmol. 2020 Nov 13;20(1):485. doi: 10.118/s/12886-020-01733-1. PMID: 53200127; PMID: PMOT92844.









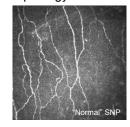
### In-Vivo Confocal Microscopy

- Uses light rays aligned and focused on a tissue by a condenser lens ("con"-"focal")
- · Eliminates scattered light from all planes outside focal point Allows for multiplanar sequential imaging and 3D reconstruction



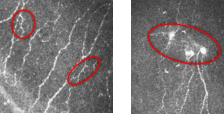
### Alterations in corneal nerve morphology

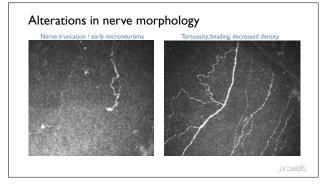
- Decrease in sub-basal nerve plexus density\*
- · Increase in nerve tortuosity
- · Development of nerve beading
- Thickening of nerve trunks
- · Development of corneal microneuromas



Patel & McGhee, BJO 2008

Alterations in nerve morphology







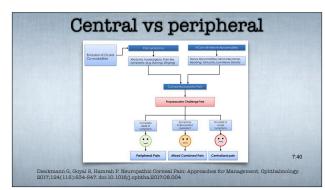
	Sett Story (PSE) is a situation for a for a form           Decide and form (PSE)           Index and form (PSE) <td< th=""></td<>
CYL FARIN RETURN'T AL HOURS Level of apergenerations & BEEET paintum Cyling and aperation and approximation of the second paints of t	Digstright/Relations with other program         Complexity         Units           Digstright/Relations with other program         Complexity         UNA           Digstright/Relations with other program         Complexity         UNA           Digstright/Relations         Digstright/Relations         Complexity         UNA           Digstright/Relations         Digstright/Relations         Complexity         UNA           Digstright/Relations         Digstright/Relations         Complexity         UNA



# Neuropathic pain & dry eye

"Topical anesthetic may be insufficient to alleviate pain in patients with centralized ocular

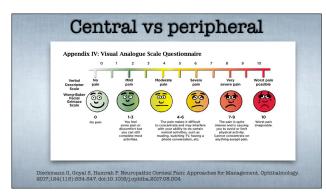
Kim J, Yoon HJ, You IC, Ko BY, Yoon KO. Clinical characteristics of dry eye with ocular neuropathic pain features: comparison according to the types of sensitization based on the Ocular Pain Assessment Survey. BMC Ophthalmol. 2020 Nov 16;20(1):455. doi: 10.1186/s128686-020-01735-1. PMID. 83206127; PMCID: PMC/072924.



### Proparacaine challenge

- 1.Baseline pain reading
- 2.Add drop anesthesia (proparacaine)
- 3.Wait 90 seconds
- 4. Proparacaine pain reading

Dieckmann G, Goyal S, Hamrah P. Neuropathic corneal pain: approaches for management. Ophthalmology. 2017;124(11 Suppl):S34-S47.



### Proparacaine challenge

- 1. Proparacaine reading goes to zero
  - 1. Peripheral NP
- 2. Proparacaine reading less than Baseline, but not zero

Dieckmann G, Goyal S, Hamrah P. Neuropathic corneal pain: approaches for management Ophthalmology. 2017;124(11 Suppl):S34-S47.

- 1. Mixed Central & peripheral
- 3. Proparacaine reading = Baseline 1. Central NP

# Proparacaine challenge

- 1. Baseline = 7, Proparacaine = 0
  - 1. Peripheral NP
- 2. Baseline = 7, Proparacaine = 2
  - 1. Mixed
- 3. Baseline = 7, Proparacaine = 7 1. Central NP

Dieckmann G, Goyal S, Hamrah P. Neuropathic corneal pain: approaches for management. Ophthalmology. 2017;124(11 Suppl):S34-S47.



# Co-morbidities

"DED, infectious keratitis, recurrent erosions...contact lens wear"

"Anxiety, depression, and posttraumatic stress disorders." Dry eye

### **Co-morbidities**

"We believe that patients with signs of DED may also present with symptoms of NCP (neuropathic corneal pain)"

Dieckmann G, Goyal S, Hamrah P. Neuropathic Corneal Pain: Approaches for Management. Ophthalmology. 2017;124(118):S34-S47. doi:10.1016/j.ophtha.2017.08.004

# Neuropathic pain & dry eye

Dieckmann G, Goyal S, Hamrah P. Neuropathic Corneal Pain: Approaches for Management. Ophthalmology 2017;124(115):834-847. doi:10.1016/j.ophtha.2017.08.004

"tear film instability and persistent inflammation can cause... sensitization...repeated peripheral nerve injury can lead to central... sensitization"

Kim J, Yoon HJ, You IO, Ko BY, Yoon KO. Olinical characteristics of dry eye with ocular neuropathic pain features: comparison according to the types of sensitization based on the Ocular Pain Assessment Survey. EMC Ophinhaimol. 2020 Nov 18;20(1):456. doi: 10.1186/s12686-080-01785-1. PMID: 55206127; PMCID: PMC07872844.

### Neuropathic pain & dry eye

"DE symptoms and NOP [neuropathic ocular pain] symptoms were higher in subjects with persistent ocular pain after anesthesia."

Central pain

Crane AM, Feuer W, Felix ER, Levitt EC, McClellan AL, Sarantopoulos KD, Galor A. Evidence of central sensitisation in those with dry eye symptoms and neuropathic-like ocular pain complaints: incomplete response to topical anaethesis and generalized heightend sensitivity to evoked pain. Br J Ophthalmol. 2017 Sep;101(9):1238-1243. doi: 10.1136/hjophthalmol-2016-309658. Epub 2017 Jan 18. PMID: 28100479.



### Neuropathic pain & dry eye

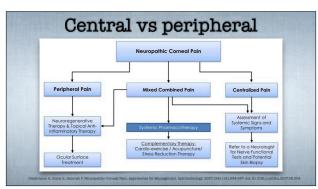
"in our study, 27 out of 33 (81.82%) patients showed mixed sensitization"

Kim J, Yoon HJ, You IC, Ko EY, Yoon KC. Clinical characteristics of dry eye with ocular neuropathic pain features: comparison according to the types of sensitization based on the Ocular Pain Assessment Survey. EMC Ophthalmol. 2020 Nov 18;20(1):456. doi: 10.1186/s12886-080-01735-1. PMID: 53208127; PMCID: PMC7072944.









### Treatment: What to Expect

- Mild peripheral cases difficult to differentiate from typical DE discomfort (continuum)
- Moderate peripheral cases respond well to combination of neuroregen + DE therapy
- Centralized cases (usually with photophobia) will take several months to respond
- -May require management with systemic medications
- -May require more intervention with pain management

### Neuropathic pain & dry eye

"Control / eliminate inflammation and then use your regenerative therapies. The inflammation is what hypersensitizes the nerves in the first place"

Scott Hauswirth, OD

https://www.youtube.com/watch?v=6VZAqNN\_JoE

## Neuropathic pain & dry eye

"Don't prescribe stuff that continues to be an irritant to patients - if they don't tolerate Restasis/Cequa/Xiidra or whatever don't continue to push it, find an alternative"

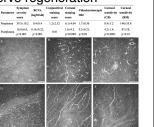
Scott Hauswirth, OD

https://www.youtube.com/watch?v=6VZAqNN\_JoE



### Autologous plasma & nerve regeneration

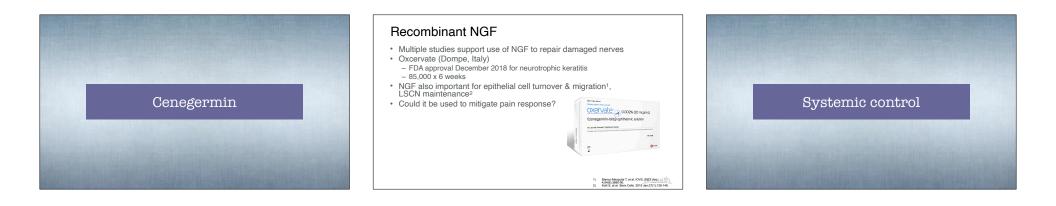
- Rao (Houston) et al. BJO May 2010
- 11 eyes, 6 pts
- Neurotrophic corneas without active disease
   - Punctate keratopathy / persistent epithelial defects included
- Improvements in aesthesiometry
   Increase in mean CND, CNL, CNW, mean # via confocal
- Complete alleviation in 7, significant improvement in 4

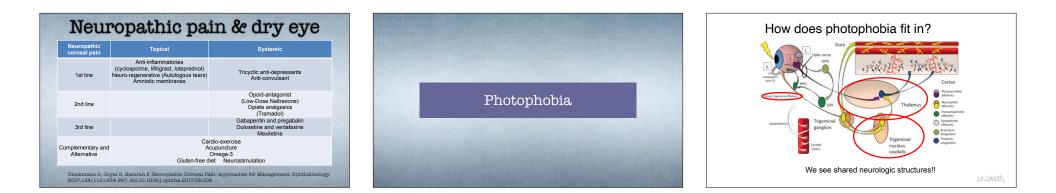








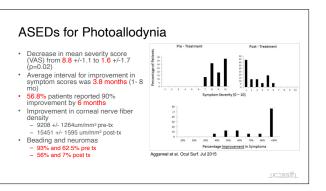




# Neuropathic pain

"[Autologous serum tears] AST restores nerve topography through nerve regeneration, and this correlated with improvement in patientreported photoallodynia"

Aggurard S, Kheirkhah A, Gavalcanti BM, et al. Autologous Serum Tears for Treatment of Photoallodynia in Patients with Corneal Neuropathy: Efficacy and Evaluation with In Vivo Confocal Microscopy. Ocul Surf. 2015;13(3):260-262. doi:10.1016/j.jtos.2016.01.005



### Neuropathic pain

"FL-41 filters out certain wavelengths of blue and green. These colors are thought to be particularly bothersome to patients with light sensitivity. By blocking these wavelengths of light, this filter also improves contrast and sharpness which increases visual acuity."

https://healthcare.utah.edu/moran/optometry/fi41-lenses.php

<section-header><section-header><section-header><section-header><section-header><section-header><section-header><section-header><section-header><section-header><image><image><image><image>

# <section-header>

### Neurostimulation

"Gateway control theory... [neuro]stimulation...from other nerve fibers can block the [abnormal] nociceptive input delivered to higher centers [central pain]"

Dieckmann, Gabriela, et al. "Efficacy of intranasal neurostimulation for peripheral pain among neuropathic corneal pain patients." Investigative Ophthalmology & Visual Science 59.9 (2018): 1806-1806.

## Neurostimulation

"After 3 minutes...71.7% (p<0.01) reduction in pain after [neurostimulation]"

Dieckmann, Gabriela, et al. "Efficacy of intranasal neurostimulation for peripheral pain among neuropathic corneal pain patients." Investigative Ophthalmology & Visual Science 59.9 (2018): 1806-1806.



MDD sharpels	
TRP channels	

Senation	Soma	Channels	Natural Stimuli	Activators
Touch	Mechano	SA (slowly adapting)	Mechanical forces	Mechanical forces
Pain/Heat	Polymodal	TRPA1, TRPV1, TRPV2, SA, ASICs (transient receptor potential, acid sensing)	Noxious Stimuli	Mustard oil, Allcin, Cinnamaldehyde, Capsacin, Piperene
Temperature	Warm	TRPV3, TRPV4	Moderate temp changes	Vanillin, Thymol
Temperature	Cold	TRPM8	Moderate temp changes	Menthol, Eucalyptol

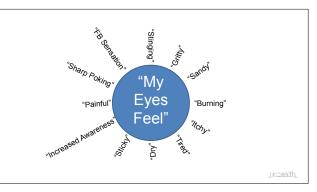
Perghanal formanal Donal root gangtion Spinal cord	TRP channels	TRP channels
	"TRPM8 channels, located on the eyelid and cornea, are cold-sensitive thermoreceptors that play a central role in tear film homeostasis"	"Increased TRPM8 activity increases basal tear secretion and blink rate"
_ucash_	https://aeriepharma.com/rd/ocular-surface-disease/ar-15512/	https://aeriepharma.com/rd/ocular-surface-disease/ar-18512/

# TRP channels

"AR-15512 has been shown to increase the activity of corneal cold thermoreceptor nerve fibers and tear production"

https://aeriepharma.com/rd/ocular-surface-disease/ar-15512/





### Monday Morning Patient Scott Hauswirth, OD

- 71 yo Caucasian female
- 18-month history of dry eye, has seen 8 physicians
- Relatively sudden onset shortly following uncomplicated cat sx, gradually worsening
   Primary symptoms: constant burning, moderate
- photophobia
  Treated with Restasis, Xiidra, ATs, Warm
- compresses, plugs, steroids, LipiFlow
- "NOTHING HELPS!!"



### Monday Morning Patient: Treatment & F/U

- Autologous Serum 50% QID OU (regenerative)
- Pred Forte  $\,$  QID x 1 week, TID x 1 week, BID x 1 week, then QD x 1 week
- Restart Restasis QID OU
- Restart Warm Compress 10-15min once daily
- No systemic medications low centralization

### Monday Morning Patient: 3-mo F/U

- Decrease in VAS from 8 to 5
- Decrease in OPAS
- Notes less sensitivity to wind, light
   Eyes still generally feel "dry" but more bearable
   No real "pain"
- Continue without steroids, +Restasis BID OU
- Continue ATs as needed
- · Patient is very pleased with her results



<u>uchealth</u>

