NEUROLOGIC DRY EYE

Jacqueline Theis, OD, FAAO, FNAP

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Financial Disclosures - Dr. Theis

C. Light Technologies - Chief Medical Officer
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Horizon Therapeutics - Advisory Panel
Oculus - Speakers Board
MedEvolve - Speakers Board
Tarsus – Speakers Board
PER – Speakers Board
Abbvie – Advisory Panel
Alcon – Speakers Board, Advisory panel
Dompe – Speakers Board
Zeiss – Advisory panel

All risks have been mitigated

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Course Objectives

- Review the neurosensory pathways of dry eye and the pathophysiological overlap with neuropathic pain and photophobia
- Emphasize the differences between primary dry eye disease from secondary dry eye disease and neuropathic pain
- Discuss how neurosensory dysfunction may affect dry eye treatment and management
- Include neurologic and psychiatric disorders like chronic pain syndrome, TBI, chronic migraine, fibromyalgia, Parkinson's disease, depression, and anxiety

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Dry Eye in my Neuro-Opt Clinic

- Chief complaint: light sensitivity, burning eye pain that started after a MVA
- Previously seen multiple optometrists and ophthalmologists
- Have tried artificial tears, anti-inflammatories, warm compresses, omegas…
- NOTHING is helping

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Defining "Dry Eye"

"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" – TFOS Dews II

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Diagnosis of Dry Eye

Signs

- Unstable osmolarity
- Ocular surface inflammation
  - Conjunctival injection
- Rapid tear film breakup time
- Corneal staining
- Reduced tear production
- Eyelid margin disease
  - Meibomian gland dysfunction
  - Blepharitis
  - Hyperemia
  - Demodex
  - Scurf

Symptoms

- Dryness
- Burning
- Stinging
- Grittiness
- Foreign body sensation
- Discomfort
- Pain sensations
  - Spontaneous
  - Evoked by stimulus- wind or light
    - Hyperalgesia
    - Allodynia

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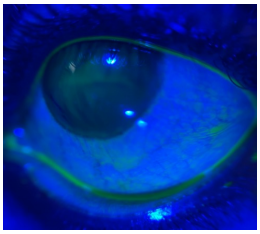
"The tricky part about dry eye is that the signs and symptoms don't match up…."
- Says Everyone… Everywhere… Including the experts…



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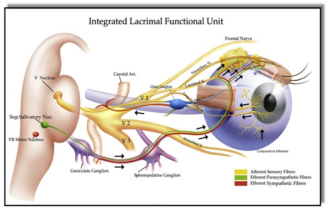
DEWS II Pathophysiology



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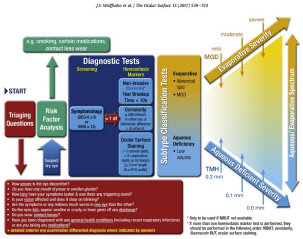
DEWS II Diagnostic Approach: Subtype Classification



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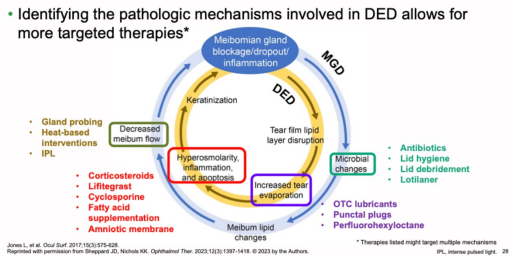
DEWS II – Targeted Treatment

- Identifying the pathologic mechanisms involved in DED allows for more targeted therapies*



Jones L, et al. *Ocul Surf.* 2017;15(3):575-628.
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Treatment

- Majority of optometric treatment is geared towards
  - Lubrication
  - Eyelid hygiene
  - Oral supplementation
- In order to
  - Reduce ocular surface inflammation
  - Re-establish tear film homeostasis

- What happens when your treatment options fail?
- What happens when patients presents with the *symptoms* of dry eye and severe ocular surface pain *without* signs of ocular surface dysfunction and are not getting better with treatment?
- What are the consequences of NOT treating someone with the *signs* of dry eye (ex: punctate keratitis) but no *symptoms?*

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What are you treating?

- As ODs we think to treat the EYE first, but without signs of ocular surface disease – WHAT are you treating?
- What if the SYMPTOMS are secondary to a neurological dysfunction in pain perception?
- What if the SYMPTOMS are actually secondary to an underlying neurologic disease or co-morbidity?

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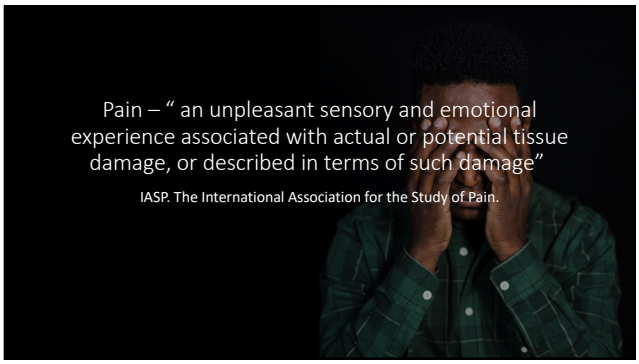

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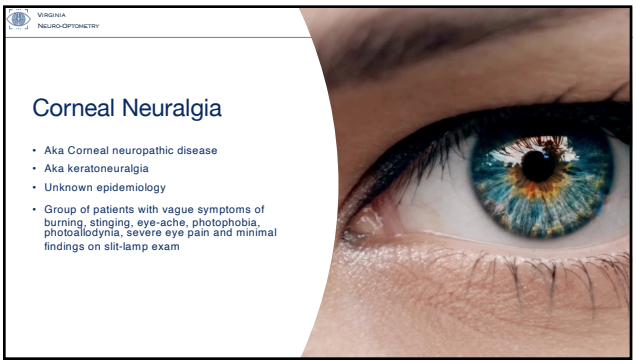

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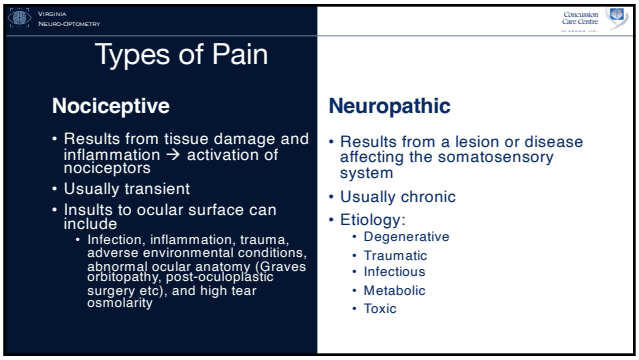

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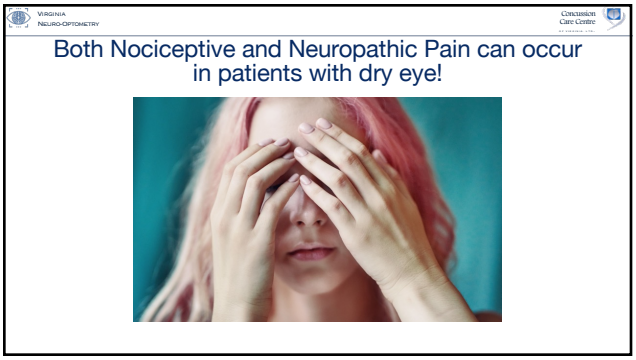

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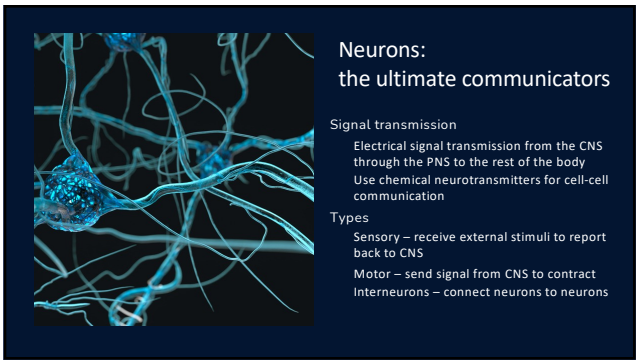

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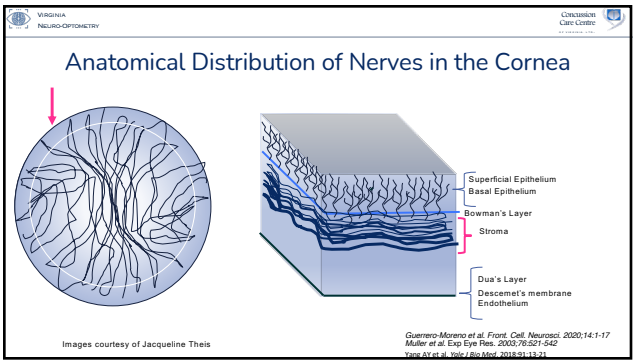

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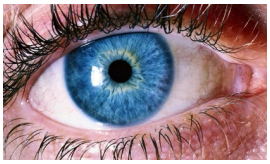
Anatomy of Ocular Neuro-Sensory Pathway

- Corneal branches of nasociliary nerve (branch of V1 – Ophthalmic division of trigeminal nerve) + Sensory nerves in conjunctiva and eyelid have different receptors to nociceptive pain stimuli:
  - Mechanoreceptors – 20%
    - "Touch" – external objects, air pressure, distortion of corneal epithelium by drying ocular surface
  - Polymodal receptors – 70%
    - Heat, cold, chemical/gaseous irritants, bacterial toxins, pH changes
  - Cold receptors – 10%
    - Cooling of surface by solution/air/tear film evaporation or increase of tear osmolarity
    - Maintain ocular surface wetness by regulating basal tear flow and blink rate



Rosenthal P, Borsook D. The corneal pain system. Part I: the missing piece of the dry eye puzzle. Ocul Surf 2012; 10(1): 2–14.
Guthoff RF, Wienss H, Hahnel C, Wree A. Epithelial innervation of human cornea: a three-dimensional study using confocal laser scanning fluorescence microscopy. Cornea 2005; 24(5): 608–613.
Belmonte C, Gallar J. Cold thermoreceptors, unexpected players in tear production and ocular dryness sensations. Invest Ophthalmol Vis Sci 2011; 52(6): 3888–3892.

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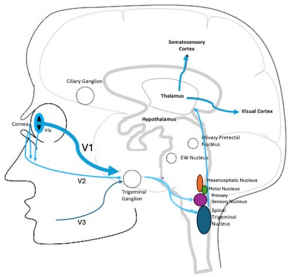
Direct Activation of Trigeminal Afferent Pathway (V1)



- 1st order Trigeminal afferents innervate the conjunctiva, cornea, eyelid → sends signal to **cell body** in Trigeminal nucleus → axons project to the trigeminal brainstem nuclei
  - Spinal trigeminal nucleus
    - Thermoceptive and nociceptive fibers
  - Principal sensory nucleus
    - Fine touch and pressure fibers
- 2nd order neuron: → thalamus
  - Join the contralateral spinothalmic pathway
- 3rd order → Somatosensory cortex
  - Supraspinal centers include somatosensory cortex

Guerrero-Moreno A et al. Front Cell Neurosci. 2020;14:1-17
Yang AY et al. *Yale J Bio Med*, 2018;91:13-21

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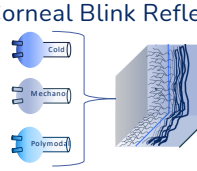
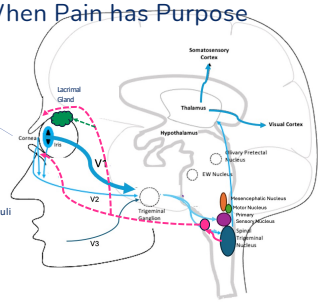
Corneal Blink Reflex – When Pain has Purpose





1) Reflexive Blink
   - Bilateral Symmetric Contraction of Orbicularis Oculi
2) Tear
   - Lacrimal Gland
   - Meibomian Glands

Guerrero-Moreno et al. Front. Cell. Neurosci. 2020;14:1-17
Muller et al. Exp Eye Res. 2003;76:521-542
Yang AY et al. *Yale J Bio Med*, 2018;91:13-21

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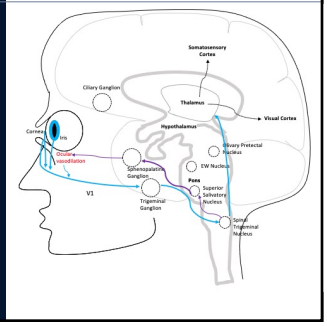
Other 3rd order neuronal pathway

SSN→Sphenopalatine/pterygopalatine ganglion→Parasympathetic activation and uveal vasodilation

Sympathetic dysfunction→ suboptimal pupil control = increased retinal illumination



Albilali A, Dilli E. Photophobia: When light hurts, a review. *Curr Neur Neurosci Rep*. 2018;18:62

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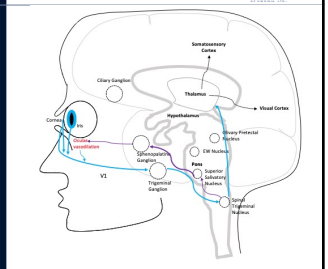
Pain Perception

- Perception of pain is simultaneously modified by descending pain pathways
- Signals transmitted from limbic system and midbrain through the periadequeductal grey to the brain stem and modulated then continue back to the trigeminal subnucleus



Albilali A, Dilli E. Photophobia: When light hurts, a review. *Curr Neur Neurosci Rep*. 2018;18:62

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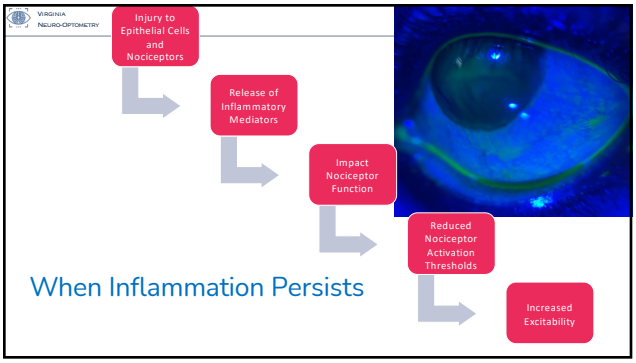
When Inflammation Persists



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Peripheral Pain Sensitization

- Prolonged exposure to painful stimuli → increased responsiveness and reduced threshold of nociceptive neurons in the periphery
- Etiology
  - Local tissue inflammation
    - Bacteria, viruses, fungi
    - Eye injuries
    - Exposure to irritant chemicals or UV
    - Tear evaporation and hyperosmolarity in dry eye disease
  - Peripheral nerve injury
    - Photorefractive surgery
    - Dry eye disease, corneal abrasion
    - Chemical
    - Radiations
    - Diabetes
    - Autoimmune disease
    - Fibromyalgia
    - Herpes Zoster
    - Systemic medications

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Peripheral Sensitization

- No stimulus/OSD but the corneal first order neuron sends signal translating into pain
  - Can occur with nociceptor dysfunction-alterations in ion channel activity
- Can be reversed with resolution of inciting stress
  - (ie treat ocular surface disease)

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Central Sensitization

- Persistent OSD/inflammatory cascade leads to activation of 2nd/3rd order neurons sending signals translating into pain without the signs of OSD
- Often occurs in other pain conditions – depression/anxiety, chronic pain syndrome, TBI, chronic migraine, fibromyalgia

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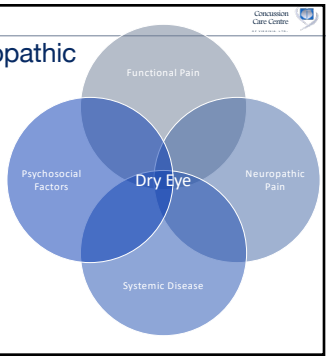
Causes of Corneal Neuropathic Pain and Systemic Associations

- Refractive Surgery
- Sjogren's syndrome
- Herpetic neuralgia
- BAK eye drops
- Accutane
- Chemotherapy
- Radiotherapy
- Depression
- Anxiety
- IBS
- Celiac Disease
- Fibromyalgia



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Dry Eye, TBI, Migraine and Sleep

- Dry eye is common post-TBI
  - a meta-analysis showed that US military veterans with TBI were more likely to have a diagnosis of dry eye(37.2%) compared with their counterparts without TBI (29.1%) (Lee 2018)
- Dry eye is common in Migraine and other pain disorders – chronic regional pain syndrome, fibromyalgia
- Dry eye is common in psychiatric conditions – depression and anxiety
- Dry eye can be caused by sleep deprivation
  - Sleep deprivation compromises the lacrimal gland and induces dry eye within 2 days
  - Staying up all night could induce tear hyperosmolarity and reduce tear secretion
- Sleep apnea is associated with dry eye

Galor A, Feuer W, Lee DJ, Florez H, Carter D, Pouyeh B et al. Prevalence and risk factors of dry eye syndrome in a United States veterans affairs population. Am J Ophthalmol 2011; 152: 377–384 e372
Lee C, Pella E, Levitt R, et al. Traumatic brain injury, dry eye and comorbid pain diagnoses in US veterans. Br J Ophthalmol 2018;102:667–673.
Lee YB, Koh JW, Hyon JY, Wee WR, Kim JJ, Shin YI. Sleep deprivation reduces tear secretion and impairs the tear film. Invest Ophthalmol Vis Sci 2014; 55: 3525–3531
Li S, Ning K, Zhou L, Gan Y, Zhang H, Zhu Y, Zhang L, et al. Sleep deprivation disrupts the lacrimal system and induces dry eye disease. Eye & Ishiko Med. 2018; 97:e451. 1-12

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What do Dry Eye, TBI, Migraine, Fibromyalgia, and Psychiatric Disorders all have in common?

Photophobia!

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Intrinsically Photosensitive Retinal Ganglion cells (ipRGCs)

- Retinal ganglion cell with melanopsin photopigment
  - 1-3% of ganglion cells in the retina
  - Also found in the iris
- Peak activation is at 480nm (between green and blue cones) but can also be stimulated by input from rods and cones
- Send axons to
  - Thalamus (light-pain matrix)
  - Pretectal Nucleus/Edinger-Westphal nucleus (pupillary light response)
  - Hypothalamus/Suprachiasmatic nucleus (circadian rhythm)
- Hypothesis of connections between ipRGCs and TBI symptoms of headaches, ocular pain, light sensitivity and sleep disturbances

Hattar S, Liao HW, Takao M, Berson DM, Yau KW. Melanopsin-containing retinal ganglion cells: architecture, projections, and intrinsic photosensitivity. Science. 2002;295(5557):1065e70
Ellenberger J, Kim B, Castr-Abegar A, Rex TS. Connections between intrinsically photosensitive retinal ganglion cells and TBI symptoms. *Neurology*. 2020;95:826-833
Berson DM, Dunn FA, Takao M. Phototransduction by retinal ganglion cells that set the circadian clock. Science. 2002;295(5557):1070e3
Kawasaki A, Kardon RH. Intrinsically photosensitive retinal ganglion cells. J Neuroophthalmol. 2007;27(3):195e204
Noseda R, Constandil L, Bourgeais L, Chalus M, Villanueva L. Changes of meningeal excitability mediated by corticotrigeminal networks: a link for the endogenous modulation of migraine pain. J Neurosci. 2010;30(43):14420e9
Noseda R, Kainz V, Jakubowski M, et al. A neural mechanism for exacerbation of headache by light. Nat Neurosci. 2010:13(2):239e45

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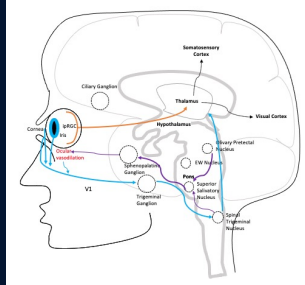
Retino-Thalamo-Cortical Pathway

- Retinal ipRGCs project directly to the thalamus → increased dura-sensitive trigeminovascular neurons →multiple cortical areas (somatosensory and visual)
- Implicated in photophobia that occurs with
  - Migraine triggered by photophobia
  - Exacerbation of headache by light



Albilali A, Dilli E. Photophobia: When light hurts, a review. *Cu*

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Blind patients with migraine

- Intensification of headache by light only perceived by blind migraineurs with an intact optic nerve – who could perceive ambient light illumination but not image formation due to rod/cone degeneration
- Blind migraineurs with optic nerve damage did not have light intensify migraine.
  - Also have fragmented or irregular sleep patterns and deficient pupillary light response
- ipRGCs trigger photophobia in migraine

Moseda R, Kainz V, Jakubowski M, et al. A neural mechanism for exacerbation of headache by light. *Nat Neurosci.* 2010;13:239-245

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Evidence for Tilted Filters - FL41

- Developed in England in the 1980s for fluorescent light sensitivity
- Transmission minimum is 480nm
- Wavelength of light plays a role in the degree of discomfort in Migraine
  - Short (blue) and long (red) wavelengths can be uncomfortable for migraine patients
  - 480nm is particularly triggering in migraine patients
- FL41 is helpful in patients with
  - Migraine
  - Benign Essential Blepharospasm
  - Vestibular dysfunction/migraine

Wilkins AJ, Nimmo-Smith I, Slater AI, Bedocs L. Fluorescent lighting, headaches and eyestrain. Lighting Res Technology. 1989;21:11e8
Blackburn MK, Lamb RD, Digre KB, et al. FL-41 tint improves blink frequency, light sensitivity, and functional limitations in patients with benign essential blepharospasm. Ophthalmology. 2009;116(5):997e1001
Tatsumoto M, Eda T, Ishikawa T, Ayama M, Hirata K. Light of intrinsically photosensitive retinal ganglion cell (ipRGC) causing migraine headache exacerbation. Cephalalgia. 2013;33(8 Suppl):2, (abstract OR-3).

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Not all Filters are the Same

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(Optom Vis Sci 2025;00: 00–00)

CLINICAL TRIAL

OPEN

A randomized crossover trial: The impact of ocular lubrication on migraine severity in persons with dry eye disease and migraine

Nur Amalina Md Isa, MOptom,[1] Arun V. Krishnan, MD, PhD,[2,3] Alessandro S. Zagami, MD,[2,3] Shyam S. Tummanapalli, PhD,[1] Katherine Spira, MD,[2] Eric B. Papas, PhD, FAAO,[1] Azadeh Tavakoli, PhD,[1] and Maria Markoulli, PhD, FAAO[1]*

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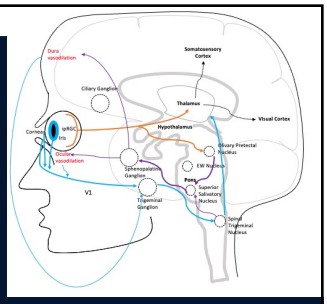
Retino-Pretectal-Parasympathetic – Trigeminovascular Pathway

- ipRGCs project directly to the olivary pretectal nucleus → superior salivatory nucleus →parasympathetic ocular vasodilation →Trigeminal stimulation



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Okamoto K, Thompson R, Tashiro A, Chang Z, Bereiter DA. Bright light produces Fos-positive neurons in caudal trigeminal brainstem. Neuroscience. 2009;160(4):858–64

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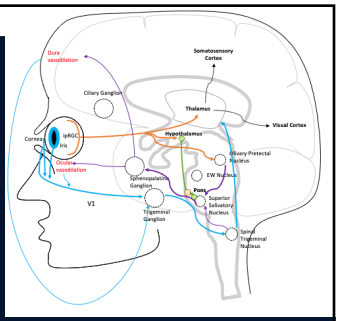
Retino-Hypothalamic-Parasympathetic – Trigeminovascular Pathway

- ipRGCs project directly to the hypothalamus→ superior salivatory nucleus →parasympathetic ocular vasodilation →Trigeminal stimulation



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Okamoto K, Thompson R, Tashiro A, Chang Z, Bereiter DA. Bright light produces Fos-positive neurons in caudal trigeminal brainstem. Neuroscience. 2009;160(4):858–64

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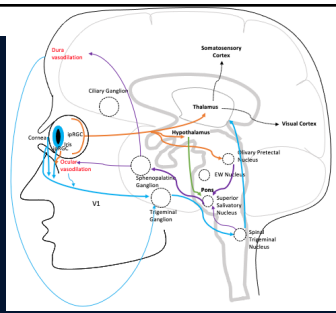
Indirect Activation of Trigeminal Afferent Pathway (V1)

- ipRGCs in the iris/ciliary body→trigeminal afferents



Albilali A, Dilli E. Photophobia: When light hurts, a review. *Curr Neur Neurosci Rep*. 2018;18:62

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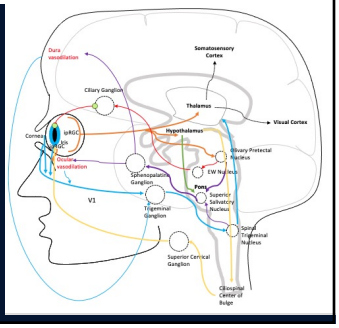
Autonomic Nervous System Dysfunction

- Pupillary Light Reflex is slowed in mTBI (Truong) and migraine
- Non-blast related TBI, subacute phase (Thiagarajan)
  - ↓Average pupillary constriction velocity
  - ↓ Maximum constriction velocity
  - ↓ Average dilation velocity
  - ↓ Maximum diameter
  - ↓ Amplitude of constriction
- Blast-related TBI, subacute phase (Capo)
  - ↓ Constriction latency
  - ↓ Constriction velocity
  - ↓ Dilation velocity
  - ↓75% dilation recovery time
- Migraine
  - ↓ Constriction latency
  - ↓ Dilation velocity
- Slowed dilation dynamics and reduced maximum pupillary diameter → sympathetic deficiency
- Slowed constriction dynamics → parasympathetic deficiency



Capo-Aponte JE, Urosevich TG, Walsh DV, Temme LA, Tarbett, AK. Pupillary light reflex as an objective biomarker for early identification of blast-induced mTBI. *Journal of Spine* 2013;S4:004
Thiagarajan P, Ciuffreda, K.J. Pupillary responses to light in chronic non-blast induced mTBI. *Brain Injury*. 2015;29(12):1430-1435
Truong, J.Q., Ciuffreda, K.J. Influence of refractive error on pupillary dynamics in the normal and mild traumatic brain injury (mTBI) populations. Brain Inj. 2016, 30, 1378–1389

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Case: 54yo Caucasian male

- Chief Complaint: Right eye pain– dry, sandy, watering right eye only.
  - Started immediately after concussion 12/2020 – he was on an elevator and fell ~9ft to the floor. Fell on top of a ladder and hit the left side of his head.
  - Has persistent neck/brain injury complaints

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Assessment of Ocular Surface Pain

Indirect

- Slit lamp exam with vital dyes
  - Fluorescein – corneal epithelial breakdown
  - Lissamine green – devitalized cornea and conjunctival surface
- Tear break up time
- Tear osmolarity
- Schirmer's (lacrimal gland function)

Direct

- Esthesiometer
  - Cochet-Bonnet (contact)
  - Belmonte (noncontact)
  - Cotton wisp or dental floss

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How to differentiate pre-clinical DED and non-OSD neuropathic pain?

- Neuropathic ocular pain more likely to be chronic
- Pain descriptors in survey – burning, tingling, electric
- Exaggerated pain response to normal stimuli
  - Photoallodynia - subtype of photophobia
  - Hyperalgesia
- The Proparacaine Challenge
- In Vivo Confocal Microscopy

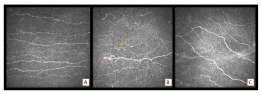

Figure 1.
Representative in vivo confocal microscopic pictures A) Normal cornea of a patient showing subbasal plexus of nerves. B) Patient with corneal pain showing decrease in nerve density, increased tortuosity (yellow arrow) and beading (orange arrow). C) Same patient exhibiting increase in nerve density, less tortuosity and disappearance of beading 8 weeks of lotemax and autologous serum tears treatment.

Image from Goyal S, Hamrah P. Understanding Neuropathic Corneal Pain-Gaps and Current Therapeutic ApproachesSemin Ophthalmol. 2016; 31(1-2): 59-70

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Clinical Assessment

Slit Lamp Exam (raw data)	• Tear Lake (no dye) • Eyelid assessment (Symmetric? Blepharitis? MGD? Basal blink rate) • Cornea (Epi defects? Scars? stromal swelling? Opacification?) • Conjunctiva (Injection? Chemosis? Pingueucla?) • Tears (Saponification? Tear Lake?)
Corneal/Tear Assessment (Vital Dyes)	• Fluorescein – Corneal epithelial breakdown • Staining • Tear Break Up Time • Lissamine Green – devitalized conjunctival surface • Rose Bengal
Lacrimal Gland Function (w/o anesthetic)	• Schirmer's Test • Tear osmolarity
Corneal Sensitivity Testing	• Esthesiometer - contact or noncontact • Cotton wisp or dental floss
Lacrimal Gland Function (w/ anesthetic)	• Recheck tear lake • Schirmer's Test • Recheck tear lake • Proparacaine Challenge
Extra	• Corneal Cultures if Epithelial defect • Confocal microscopy

45

The Proparacaine Challenge

- Central vs Peripheral Pain
  - 0.5% proparacaine will attenuate peripheral corneal pain but not central pain or referred cervicogenic pain
  - pain but not central pain

46

Visual Symptoms in Nek Pain/Whiplash Injury

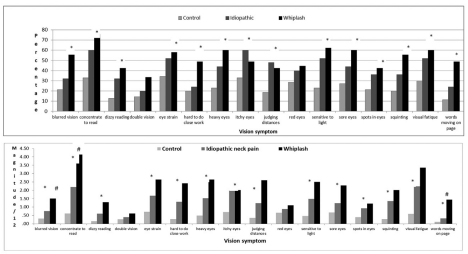
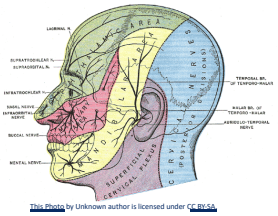


Fig. 1. A. Percentage of subjects in each group who reported each visual symptom regardless of magnitude. B. Average magnitude of each visual symptom for each group. The magnitude score out of 12 was formulated by the product of the frequency (1–3) and intensity rating (1–4) for each symptom. *indicates where there was a significant difference ($P < 0.05$) between control ($N = 70$) and the neck pain subjects ($N = 70$). #indicates where there was a significant difference ($P < 0.05$) between the idiopathic neck pain ($N = 25$) and the whiplash group ($N = 45$).

Treleaven J, Takasaki H. Characteristics of visual disturbances reported by subjects with neck pain. Man Ther. 2014 Jun;19(3):203-7. doi: 10.1016/j.math.2014.01.005. Epub 2014 Jan 27. PMID: 24521926.

47

Is it the Neck? Pathophysiology



This Photo by Unknown author is licensed under CC BY-SA.

Nerves from the cervical spine converge onto the trigeminocervical nucleus along with the trigeminal nerve, which shares pathoanatomy with the eye patterns

Slide courtesy of Sara Etheredge DPT

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Pathophysiology

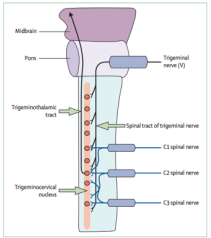

IMAGE FROM: Conidi F. The Role of the Cervical Spine in Sports Concussion and Post Traumatic Headache : Physiological and Anatomical Correlates. 2014. Semantic Scholar

Most studies support this theory for C3 and above, however, anastomosis between the spinocervicothalamic tract and the TCN may provide an avenue for lower cervical levels to refer along the trigeminal nerve.

Slide courtesy of Sara Etheredge DPT

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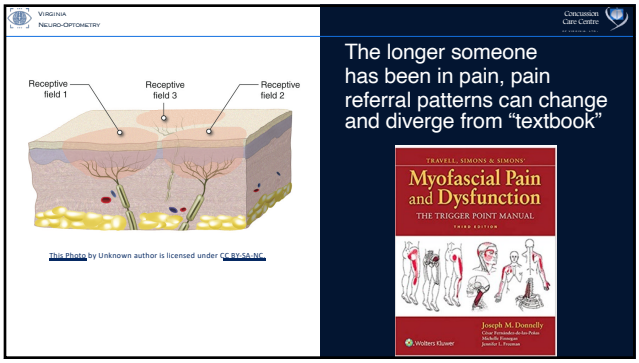

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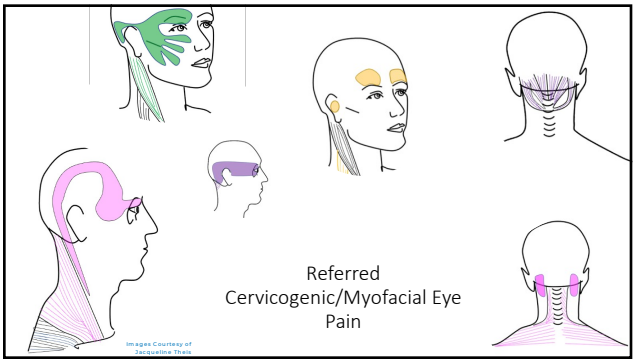

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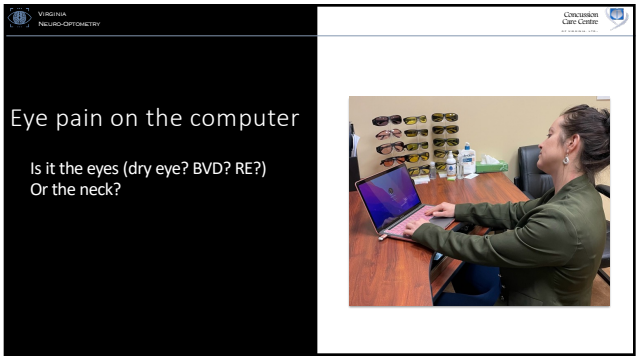
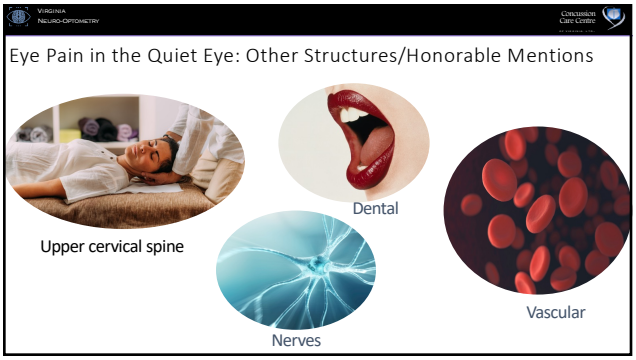


52



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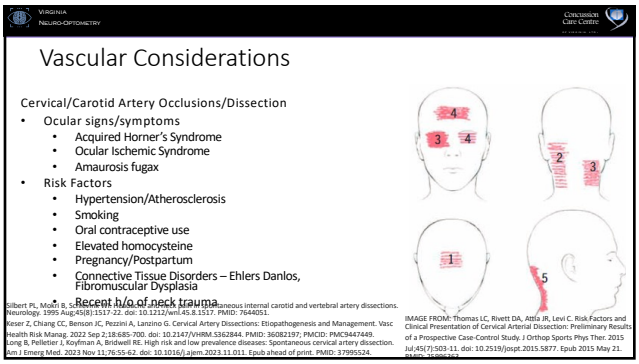

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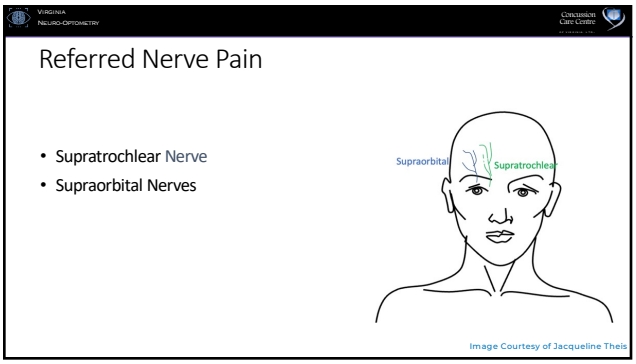
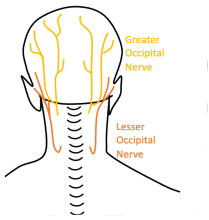


55

Referred Nerve Pain: Greater and Lesser Occipital Nerves



- Location of Pain:
  - Back of head
  - Neck
  - Scalp
  - Forehead
  - BEHIND THE EYES
- Type of Pain:
  - Burning, hot, electric like, intense, stabbing, brief or chronic
- Additional Symptoms:
  - vision impairment/ocular pain (67%)
  - tinnitus (33%)
  - dizziness (50%)
  - nausea (50%)
  - congested nose (17%)

Image Courtesy of Jacqueline Theis

56

Occipital Neuralgia: headache caused by irritation to the greater or lesser occipital nerve

(+) Pillow Sign:

Pain elicited with lying on a pillow in supine with hyperextension or rotation of the head

When To Consider:

- Migraine
- Neck trauma
- Descriptor of pain

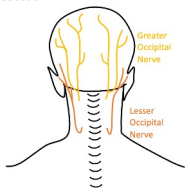


Image Courtesy of Jacqueline Theis

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How's Your Sleep?

- How many hours do you sleep?
- What position do you sleep in?
  - Why do you sleep in this position?
- Do you have to avoid certain positions when you sleep?
- Do you wake up with headaches or from headaches?
  - Occipital Neuralgia, Cervicogenic pain, Increased intracranial pressure, Sleep Apnea, Bruxism

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Temporomandibular Joint Dysfunction

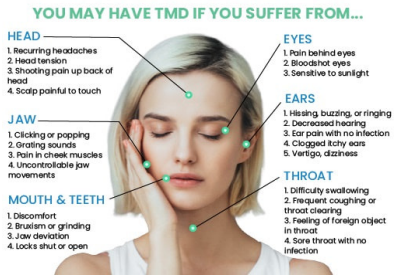

Image courtesy of Jana Powell with Attune Massage Therapy

59

Case: 54yo Caucasian male

- Chief Complaint: Right eye – dry, sandy, watering right eye only.
  - Started immediately after concussion 12/2020 – he was on an elevator and fell ~9ft to the floor. Fell on top of a ladder and hit the left side of his head. Has persistent neck/brain injury complaints
  - Proparacaine challenge: Negative
  - Tearing Symptoms alleviated with oral Indomethacin
  - But dry sandy feeling persists…

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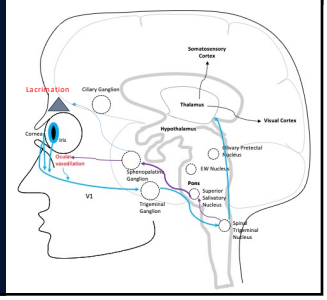
Neural Regulation of Tear Production

Lacrimal Gland

- Autonomically regulated
  - Corneal cold thermoreceptors sense change in dryness of ocular surface→ reflex for basal aqueous tear formation
- Secretomotor parasympathetic innervation through lacrimal nerve (branch of the ophthalmic division of trigeminal nerve) → increased secretion
  - Vasomotor sympathetic innervation →vasoconstriction in lacrimal gland (indirectly decreases secretion)
  - Vasomotor parasympathetic innervation → vasodilation of choroidal blood vessels



Belmonte C, Nichols JJ, Cox SM, Brock JA, Begley CG, Bereiter DA, Dartt DA, Galor A, Hamrah P, Ivanusic JJ, Jacobs DS, McNamara NA, Rosenthal MI, Stapleton F, Wolffsohn JS. TFOS DEWS II pain and sensation report. Ocul Surf. 2017 Jul;15(3):404-437. doi: 10.1016/j.jtos.2017.05.002. Epub 2017 Jul 20. PMID: 28736335; PMCID: PMC5706540.

61

Neural Regulation of Blinking

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Neural Regulation of Blinking

Pathophysiology

- Primary muscle of eyelid closure is the orbicularis oculi (CN7)
- Mechanism
  - Levator stops firing while palpebral (but not orbital) portion of orbicularis oculi contracts → active eyelid closure
  - Once closure is complete, OO stops firing and basal level of levator resumes (eyelid opens)

Esteban A, Salinero E. Reciprocal reflex activity in ocular muscles: implications in spontaneous blinking and Bell's phenomenon. Eur Neurol (1979) 18:157–65. doi:10.1159/000115072
Schmidtke N, Buttner-Ennever JA. Nervous control of eyelid function: a review of clinical, experimental, and pathological data. Brain (1992) 115:227–47. doi:10.1093/brain/115.1.227
Gnadt JW, Lu SM, Brezner B, Basso MA, Henriquez VM, Evinger C. Influence of the superior colliculus on the primate blink reflex. Exp Brain Res (1997) 116:389–98. doi:10.1007/PL00005767
Basso MA, Powers AS, Evinger C. An explanation for reflex blink hyperexcitability in Parkinson's disease. I. Superior colliculus. J Neurosci (1996) 16(22):7308–17

63

Pathophysiology of Blinking

- Pathoanatomy
  - Reflexive Blinking
    - Corneal afferents→ Vi/Vc neurons → facial motor nucleus
  - Superior colliculis → facial motor nucleus and supraoculomotor area over the central caudal nucleus (CCN)
    - SC also gets afferent input from trigeminal sensory nucleus (tactile eyelid/corneal reflex) and dorsal midbrain (light reflex)
    - SC is inhibited by the pars reticulata of substantia nigra through dopaminergic projections in the nigra-collicular pathway

Esteban A, Salinero E. Reciprocal reflex activity in ocular muscles: implications in spontaneous blinking and Bell's phenomenon. Eur Neurol (1979) 18:157–65. doi:10.1159/000115072
Schmidtke N, Buttner-Ennever JA. Nervous control of eyelid function: a review of clinical, experimental, and pathological data. Brain (1992) 115:227–47. doi:10.1093/brain/115.1.227
Gnadt JW, Lu SM, Brezner B, Basso MA, Henriquez VM, Evinger C. Influence of the superior colliculus on the primate blink reflex. Exp Brain Res (1997) 116:389–98. doi:10.1007/PL00005767
Basso MA, Powers AS, Evinger C. An explanation for reflex blink hyperexcitability in Parkinson's disease. I. Superior colliculus. J Neurosci (1996) 16(22):7308–17

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Spontaneous Blinking

- Mean blink rate 19.74 +/-9.12 per min… 15-20, higher in women than men
- Mean blink rate with reading a book 11.35 +/-10.20 per min
- Mean blink rate with reading a tablet 14.93 +/-10.90 per min
- PD - reduces by 30% ~ 4.5-6 blinks/min
- PSP – significantly reduces to 3 blinks/min
- Dry eye and contact lenses presumably increase blinking (enhanced innervation of cornea)
- Spontaneous eye blink rate (EBR) is correlated to dopamine levels in the brain, may be useful for predicting motor status in patients with PD
  - non-invasive indirect marker of central dopamine function
  - Levodopa and DBS increase EBR

Abusharha, Ali A. "Changes in blink rate and ocular symptoms during different reading tasks." *Clinical optometry* vol. 9 133-138. 20 Nov. 2017, doi:10.2147/OPTO.S142718
Bologna M, Fasano A, Modugno N, Fabbrini G, Berardelli A. Effects of subthalamic nucleus deep brain stimulation and L-DOPA on blinking in Parkinson's disease. Exp Neurol. 2012 May;235(1):265-72. doi: 10.1016/j.expneurol.2012.02.004. Epub 2012 Feb 14. PMID: 22366535.
Korosec M, Zidar J, Repis D, Evinger C, Vanderwerf F. Eyelid movements during blinking in patients with Parkinson's disease. Mov Disord (2006) 21(8):1248–51. doi:10.1002/mds.20930
Sforza C, Rango M, Galante D, Bresolin N, Ferrario VF. Spontaneous blinking in healthy persons: an optoelectric study of eyelid motion. Ophthalmic Physiol Opt (2008) 28(4):345–53. doi:10.1111/j.1475-1313.2008.00577.x
Bousse V, Skibell BC, Watts RL, Loupe DN, Drews-Botsch C, Newman NJ. Ophthalmologic features of Parkinson's disease. Neurology (2004) 62(2):177–80. doi:10.1212/01.WNL.0000103444.45882.D8
Golbe LI, Davis PH, Lepore FE. Eyelid movement abnormalities in progressive supranuclear palsy. Mov Disord (1989) 4(4):297–302. doi:10.1002/ mds.870040402

65

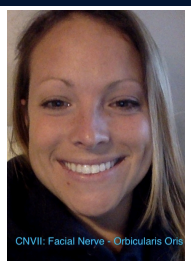
Reflexive Blinking

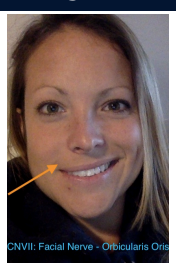
- Inverse relationship between dopamine and reflex blinking so reduced dopamine would lead to increased reflexive blinking
- Myerson's sign – trigeminally mediated blink in response to tapping the forehead
  - Normally habituated
  - Can occur in PD and other structural, metabolic and degenerative disorders
- Increased blinking to light (PSP>PD)
- Blepharospasm – overactivity of reflexive blinking

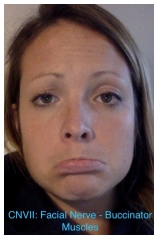
Brodsky H, Dat Vuong K, Thomas M, Jankovic J. Glabellar and palmomental reflexes in parkinsonian disorders. Neurology (2004) 63(6):1096–8. doi:10.1212/01.WNL.0000140249.97312.76 57. Kuniyoshi S, Riley DE, Zee DS, Reich SG, Whitney C, Leigh RJ. Distinguishing progressive supranuclear palsy from other forms of Parkinson's disease: evaluation of new signs. Ann N Y Acad Sci (2002) 956:484–6. doi:10.111 1/j.1749-6632.2002.tb02862.x

66

Facial Nerve Testing







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Facial Nerve Testing

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Dry Eye Disease in PD

Prevalence 53-60% in patients with Parkinson's Disease
- Vs. 5-35% of general population (50yo+)

Pathophysiology
- Decreased blink rate → reduced lipid distribution→ increased aqueous evaporation
- Decreased tear production due to autonomic (parasympathetic) innervation to lacrimal gland

You need to ask!

You need to test!
- Corneal desensitivity
- Schirmer's
- TBUT
- Blink Rate
  - Normally blink rate decreases with saccades, in PD and PSP it increases

You need to treat!

E.S.o.t.I.D.E. WorkShop, The epidemiology of dry eye disease: report of the epidemiology subcommittee of the international dry eye WorkShop (2007), Ocul. Surf. 5 (2007) 93e107.

C. Tamer, I.M. Melek, T. Duman, H. Oksuz, Tear film tests in Parkinson's disease patients, Ophthalmology 112 (2005) 1795.

69

Ocular Pain Response to Treatment in Dry Eye Patients

- Importance of treating underlying dry eye component in patients with ocular pain
- Dry-eye assoc ocular pain – improvement with artificial tears
  - 14-19% no improvement
  - 62-55% partial improvement
  - 19-31% "a lot" of improvement
- Autologous serum tears – one of the most effective topical agents
- Anti-inflammatory agents
  - Topical steroids
  - Cyclosporine

Siedlecki A, Smith S, Siedleck AR, Hayel SM, Sayegh R. Ocular pain response to treatment in dry eye patients. *Ocular Surface*. 2020: 305-311.

70

Siedlecki A, Smith S, Siedleck AR, Hayel SM, Sayegh R. Ocular pain response to treatment in dry eye patients. *Ocular Surface*. 2020: 305-311.

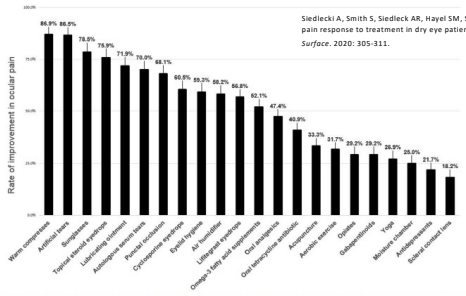


Fig. 2. Treatment response for the entire patient cohort. The percentage of subjects reporting complete or partial improvement in ocular pain is shown with each treatment modality surveyed.

71

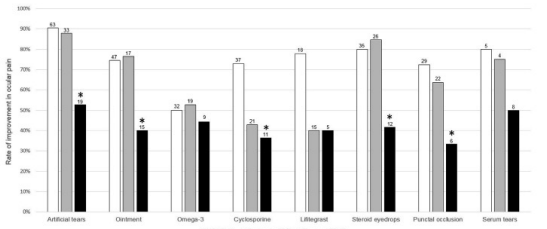


Fig. 3. Treatment response to topical therapies by pain group. The percentage of subjects reporting complete or partial improvement in ocular pain with each treatment is displayed, subdivided by pain severity group. Patients who reported not trying these treatments were excluded. Groups designated with an asterisk represent statistically significant differences at $p \leq 0.05$.

Siedlecki A, Smith S, Siedleck AR, Hayel SM, Sayegh R. Ocular pain response to treatment in dry eye patients. *Ocular Surface*. 2020: 305-311.

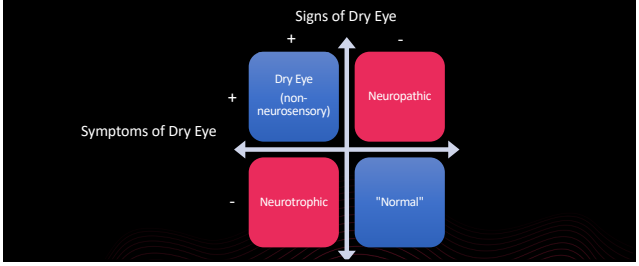
72

Case: 54yo Caucasian male

- Chief Complaint: Right eye – dry, sandy, watering right eye only.
  - Started immediately after concussion 12/2020 – he was on an elevator and fell ~9ft to the floor. Fell on top of a ladder and hit the left side of his head. Has persistent neck/brain injury complaints
  - Proparacaine challenge: Negative
  - Tearing Symptoms alleviated with oral Indomethacin
  - But dry sandy feeling persists…

73

"Signs and symptoms don't make sense" if you don't understand the neurosensory innervation of the eye



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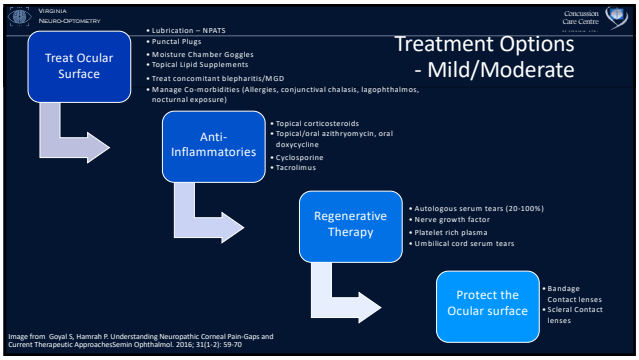
Treatment options for neuropathic pain

Treat the symptom generator – not the symptom!

75

Treatment Options - Mild/Moderate



76

Autologous Serum Tears

Aggarwal S, Colon C, Kheirkhah A, Hamrah P. Efficacy of autologous serum tears for treatment of neuropathic corneal pain. Ocul Surf. 2019 Jul;17(3):532-539. doi: 10.1016/j.jtos.2019.01.009. Epub 2019 Jan 24. PMID: 30685437; PMCID: PMC6956846.

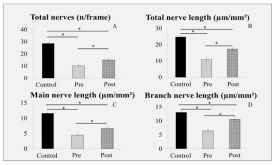


Figure 2: Severity of Neuropathic Corneal Pain Pre- and Post-Treatment
Bar graphs showing severity of corneal pain A. pre-treatment and B. post-treatment.

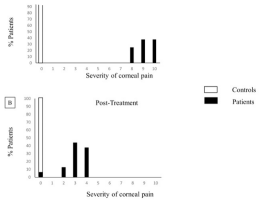


Figure 3: In Vivo Confocal Microscopy (IVCM) Images Pre- and Post-Treatment

77

Future Treatment Options

> Front Med (Lausanne). 2022 Aug 24;9:946828. doi: 10.3389/fmed.2022.946828. eCollection 2022.

Initial experiences using plasma rich in growth factors to treat keratoneuralgia

Margaret Wang [1], Sowmya Yennam [1], Stephen Pflugfelder [1]

Affiliations + expand

PMID: 36091697 PMCID: PMC9448984 DOI: 10.3389/fmed.2022.946828

Free PMC article

> Ocul Surf. 2018 Jan;16(1):132-138. doi: 10.1016/j.jtos.2017.10.003. Epub 2017 Oct 13.

Efficacy of self-retained cryopreserved amniotic membrane for treatment of neuropathic corneal pain

Melina I Morkin [1], Pedram Hamrah [2]

Affiliations + expand

PMID: 29032001 PMCID: PMC5798468 DOI: 10.1016/j.jtos.2017.10.003

Free PMC article

78

Case: 54yo Caucasian male

- Chief Complaint: Right eye – dry, sandy, watering right eye only.
  - Started immediately after concussion 12/2020 – he was on an elevator and fell ~9ft to the floor. Fell on top of a ladder and hit the left side of his head. Has persistent neck/brain injury complaints
  - Proparacaine challenge: Negative
  - Tearing Symptoms alleviated with oral Indomethacin
  - But dry sandy feeling persists…
  - Referred back to corneal specialist – punctal plugs!

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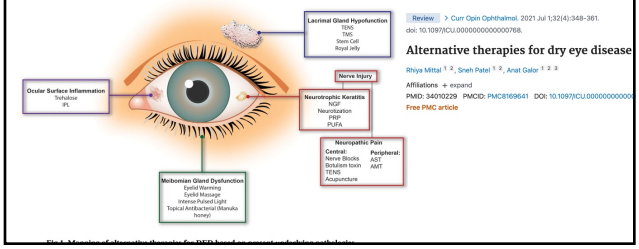
Alternative Treatment Options

Alternative Therapies for Dry Eye Disease



Review > Curr Opin Ophthalmol. 2021 Jul 1;32(4):348-361.
doi: 10.1097/ICU.0000000000000768.

Alternative therapies for dry eye disease

Rhiya Mittal [1 2], Sneh Patel [1 2], Anat Galor [1 2 3]

Affiliations + expand

PMID: 34010229 PMCID: PMC8169641 DOI: 10.1097/ICU.0000000000000

Free PMC article

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Treatment Options – Differences with NK vs NP occurs at Severe Stages

Neuropathic Pain	Neurotrophic Keratitis
Tacrolimus	Cenegermin Amniotic Membrane
Systemic pharmacotherapy • TCAs • Carbamazepine • GABAergic drugs (gabapentin) • SNRI • Opioids • Class 1B Na+ channel blockers Botox/Injectable nerve blocks – anesthethic/steroid TMS/Neurostimulators Acupuncture Diet Yoga/Exercise	Tissue adhesives Nonsurgical eyelid closure Surgical interventions • Tarsorrhaphy • Conjunctival flap • Corneal transplant • Corneal Neurotization • Sutured amniotic membrane transplant

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Treatment Options

Systemic Pharmacotherapy for Pain

- Tricyclic Antidepressants (Nortriptyline, Amitryptiline)
- Carbamazepine
- GABAergic drugs (Gabapentin)
- SNRI (Duloxetine, Venlafaxine)
- Opioids (Tramadol)
- Class 1B Na+ channel blockers (Mexiletine)

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Hot Compresses vs. Cold Compresses?

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Referrals

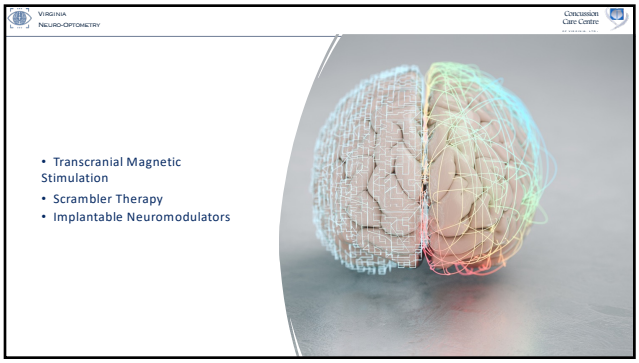
Physical Therapy	• Orthopedic – Ergonomics, Dry Needling • Neuromodulation • Medical Massage
Lifestyle	• Acupuncture • Nutrition • Exercise • Meditation/Mindfulness • Sleep Studies/Sleep medicine/coaching
Orals	• NSAIDs • Acetaminophen/Ibuprofen • GABAergic (gapapentin) • Antidepressants – TCAs (nortriptyline, amitryptiline), SNRI (duloxetine, venlafaxine)
Injectables	• Botox • Steroid • Anesthetic
Implantables	• Transcranial magnetic stimulation • Scrambler therapy • Implantable Neuromodulators
Surgery	• Rhizotomy • Gamma Knife Surgery

PCP
PT/OT
Acupuncture
PMR/Physiatry
Pain Management
Certified Docs
Functional Medicine
Psychology
Neurosurgery

84

Injectables

85



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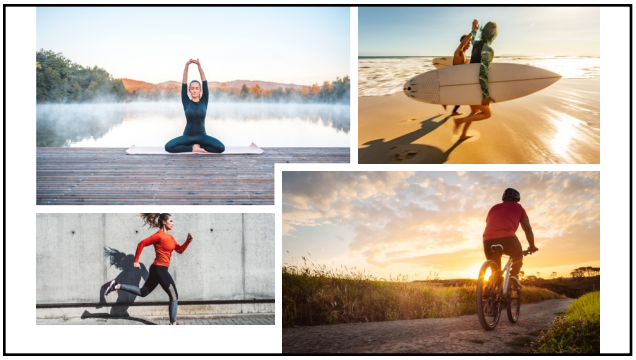

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