Title: Pain, Photophobia, and Ocular Pathology: What you should know to help your patients
Author: Scott G. Hauswirth, O.D.

Abstract: This course reviews the connections between ocular surface disease and symptomatology of neuropathic pain, including pathophysiology and treatments for patients.

Objectives:
1) To review the understanding of pain as it relates to alterations to normal physiology
2) To illustrate the connections of the pathology of ocular surface disease and the induction of ocular pain processes
3) To illustrate the differential between centralized and nociceptor pain, and methods of treatment

Outline:

I. The Anatomy of Pain
   A) Symptom of pathology or injury
   B) Review of neuroanatomy
      1) Components of the sensory neuron
      2) Sensory nerve endings
         a) mechanoreceptors
         b) thermoreceptors
         c) polymodal receptors
         d) nociceptors
   C) Process of signaling
      1) Detection of noxious stimuli
      2) Activation of ion channels
      3) Conduction to somatosensory cortex/paralimbic structures
      4) Role of the thalamus
      5) Cerebral cortex
   D) Peripheral sensitization
      1) Occurs via injury/inflammation
         a) cytokines
         b) prostaglandins
         c) substance P
      2) Changes trigger from noxious stimuli to non-noxious
      3) Lowered threshold potentials
         a) Spreads to adjacent nociceptors
         b) Activation of silent receptors -> increased number of receptors
      4) Leads to increased corneal sensitization (hyperalgesia)

II. The Overlap of Pain and Dry Eye
A) The normal cornea
  1) Most densely innervated tissue in the body (7000/mm²)
  2) 200-300 times greater than skin
  3) Primarily sensory function – high density of nociceptors

B) Alterations to normal physiology in the OSD patient
  1) Inflammatory cascade
     a) NK cells
     b) IL-1B
     c) Dendritic cells – increases in central and peripheral cornea in dry eye patients
  2) Decrease in barrier function

C) Alterations to the corneal nerve plexus
  1) Decreased axons in central cornea
  2) Tortuosity
  3) Beading
  4) Nerve sprouting – sensory nerve regeneration
     a) capsaicin induced overexpression of NGF
     b) may represent hypertrophy of peripheral NS
  5) Neuroma – localized nerve sprouting

III. Differentiation and Diagnosis
A) Symptoms
  1) May be itch, irritation - nonspecific
  2) Photophobia
  3) Chronic pain
B) Surveys
  1) UNC
  2) Mass Eye and Ear Ocular Pain Assessment Survey
C) Nociceptive vs. Centralized pain
  1) 0.5% proparicaine 1gtt OU
  2) If patient notes reduced pain, then nociceptive
D) Confocal microscopy
  1) Corneal nerve plexus changes
  2) Presence of dendritic cells

IV. Treatment
A) Anti-inflammatory agents
  1) Best for acute phase – 2-6 weeks
  2) Decrease cytokines and other transcriptional pro-infl. Signals
  3) Decrease NK/T-cell infiltration
  4) Do not promote healing of corneal nerve tissue
  5) May inhibit pain to small degree
  6) Steroids
     a) Dose to suit level of inflammation
     b) Lotemax QID 2-4 weeks with taper
c) May use Alrex-FML or Pred Forte-Durezol
d) Promote T-cell apoptosis via MPTP pathway

7) Cyclosporine-A
   a) Calcineurin inhibitor affecting key component of NF-kB pathway
   b) Downregulates cytokine production upstream from nucleus
   c) Helps prevent epithelial cell apoptosis
   d) Safe for long-term maintenance therapy

8) ICAM-LFA antagonists
   a) prevent binding of subunit to activate T-cell
   b) promote vascular endothelial integrity
   c) long-term safety/efficacy data

B) Autologous serum
   1) Thought to contain EGF/NGF
   2) Evidence to support nutritional/healing role in nerve plexus
   3) 20% AS/80% BSS QID 3-6 months or longer

C) Amniotic membrane
   1) Cryopreserved being examined for regenerative role
   2) HC-HA/PTX-3 and fetal healing of epithelium and surface structure

D) Oral medications
   1) GABA
      a) Gabapentin
      b) Pregabalin
      c) Upregulate gamma-aminobutyric acid
         1) Bind to a-2-delta subunit of voltage-dependent Ca+ channels
         2) Decreases Ca+ influx into neurons, stabilizing them
   2) Carbamazepine 800-1600mg/day (2-4 doses)
      a) mechanism
      b) once pain is decreased may taper to minimally effective dose