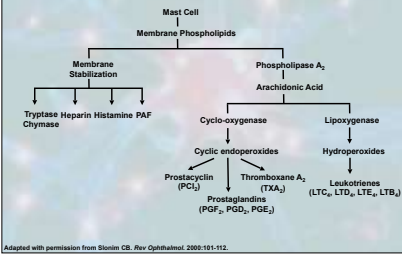


The Inflammatory Cascade



Pain - One in a Million

- Pain receptors are specific to location and stimuli
 - Sharp immediate pain A-delta fibers
 - Prolonged unpleasant burning pain mediated by smaller unmyelinated C fibers
- These lay dormant until stimulated and are often sensitized by inflammation



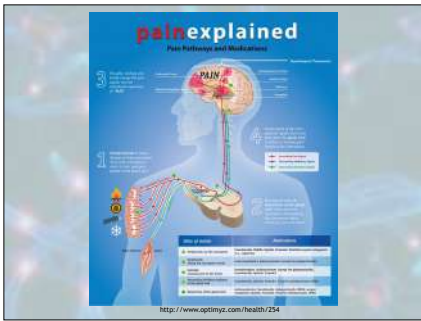
Nociceptors

- In all peripheral tissue
- Distribution will vary
- Stimulated by
 - Heat
 - Energy
 - Trauma
 - Emotion?
 - Chemicals
 - Bradykinins
 - Serotonins
 - Histamines
 - GABA
 - Capsaicin
 - Prostaglandins



Modern Pain Perspective

- When a nerve cell communicates with another it uses just a millionth of the energy that a digital computer expends to perform an equivalent operation.
- Reliability - a signal traveling from one cortical cell to another typically has only a 20 percent possibility of arriving at its ultimate destination



Pain - Remember ME


- Various stimuli may signal a specific pattern of neuronal response based on a learned response
 - Think “suspicious coincidences” (Horace Barlow) as seen in the visual cortex

Common Painful Ocular Conditions

- Allergic conjunctivitis
- Angle closure glaucoma
- Conjunctivochalasis
- CL Related Pain
- Dacryoadenitis
- Dacryocystitis
- Dry eye disease
- EKC
- Episcleritis
- Foreign bodies
- Headache
- Hordeolum
- Optic neuritis
- Orbital cellulitis
- Preseptal cellulitis
- Pterygium
- Refractive Surgery
- Scleritis
- Trauma
- Uveitis

Importance of History

- History
 - Medical
 - Family
 - Social
 - Any drug allergies
- DOFDAR
 - Reproducible factors
 - Associated features
- Tell me about your pain
 - Quality
 - Duration
 - Frequency



http://mysurgeon.health.ca/55/e120.library/Ortho/images/upat.gif

Eyelids and Pain

- Typically inflammation induced
- Many capsaicin receptors



Vaccines for HZO - Zostivax

- Zostivax is live attenuated herpes zoster (HZ) virus
 - 50% reduction in the incidence of HZ
 - 60% reduction in symptom severity in patients who developed HZ
 - 66.5% reduction in postherpetic neuralgia.
- Must have chicken pox as a child
- May help patients who've had HZO already

1. Oxman MN, Levin MJ, Johnson GR, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Engl J Med*. 2005 Jun 2;353(12):2271-84.

Eyelids

- Pain is often inflammation and swelling based
- Decrease swelling = decrease pain
 - Cold compress
 - Medrol Dosepak
 - Lotemax ung

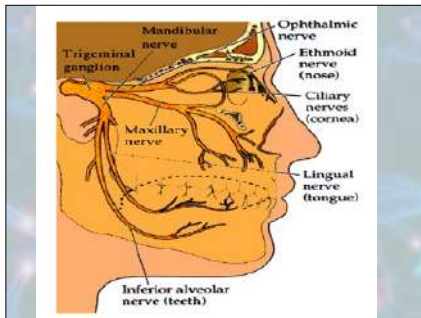


Corneal Pain Anatomy

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

Autonomic Nerve Fibers in Cornea

- Sympathetic fibers from the superior cervical ganglion
- Parasympathetic fibers from the ciliary ganglion
- Corneal sensation is essential for maintaining the integrity of the ocular surface



What Does it Look Like?

- 70-90 nerve bundles enter the cornea at the level of the mid stroma (in all clock hours)
- Run anteriorly toward the central cornea
- Form plexiform arrangements
- Form a dense subepithelial plexus and penetrate Bowman's membrane
 - Largest concentration of perforation sites in the mid periphery
 - Form a whirl like pattern in the central cornea (clockwise)

Corneal Sensitivity Changes

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



Insensitive Old People

- Corneal sensitivity decreases with age
 - Explain decreased tear production
 - When elderly complain of significant pain it should be taken seriously



Contacts

- Decrease corneal sensitivity
 - Decrease tear production
 - Sensory adaptation to mechanical abrasion



Dry Eye

- The king of chronic eye pain



The mean corneal sensitivity in dry eye patients is significantly lower than normals (EYE 2005; 19; 1276-1279)

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

- Mean corneal sensitivity was significantly lower in the NSDD group as compared with the control group ($P = 0.014$).
- NSDD patients have both structural and functional alterations of subbasal corneal nerves and these changes are related to the severity of dry eye.
- [Antoine Labbé¹](#) 2013 ARVO

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

- Corneal sensitivity was significantly decreased in dry-eye and glaucoma patients compared with controls. The density and number of subbasal corneal nerves were also significantly decreased in dry eye and glaucoma patients compared with controls.
- Labbe 2012 IOVS

Neuropathy is end stage organ damage

- Diabetics know this first hand
- All diabetics get dry eye, few complain about it.



What's Happening in Dry Eye

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

The Other Edge of the Sword

- Long term exposure to low levels of prostaglandins from dry eye sensitize the receptors for pain

How do we attack this?

- Indirectly go after the immune modulation in the lacrimal gland
- What if we could directly address the nerve issue in the cornea?
 - How can we do this?



Refractive Surgery Considerations

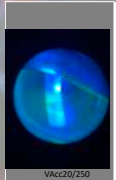
- Do more nerves enter the cornea nasally?
- Initially several studies showed that nasal or superior LASIK flaps had no effect on corneal sensation
- Transient light sensitivity syndrome

Unilateral Herpes Zoster Ophthalmicus Results in Bilateral Corneal Nerve Alteration : An In Vivo Confocal Microscopy Study

- Patients with unilateral HZO demonstrated a profound and significant bilateral loss of the corneal nerve plexus as compared with controls, demonstrating bilateral changes in a clinically unilateral disease. Loss of corneal sensation strongly correlated with subbasal nerve plexus alterations as shown by IVCN.
- Hamrah - Ophthalmology 2012

Patient Information	• 82 yr, male, Caucasian, OU
History of Presenting Illness	• Cataract Extraction OU 2013 • Biepharoplasty OU 2013 • Chronic DES • MIA PDAG OU 2000 – being treated with a topical prostaglandin analogue
Relevant Medical History	• Diabetes (poorly controlled)
Corneal Sensitivity	• Complete anesthesia • Sensitivity testing performed with cotton swab
Diagnosis	
Previous Treatments	• Cyclosporine 0.05% bid OU • Preservative free artificial tears
Management Plan	

Patient Information	<ul style="list-style-type: none"> 82 yr, male, Caucasian, OU
History of Presenting Illness	<ul style="list-style-type: none"> Cataract Extraction OU 2013 Blepharoplasty OU 2013 Chronic DES Mild POAG OU 2000 – being treated with a topical prostaglandin analogue
Relevant Medical History	<ul style="list-style-type: none"> Diabetes (poorly controlled)
Corneal Sensitivity	<ul style="list-style-type: none"> Complete anesthesia Sensitivity testing performed with cotton swab
Diagnosis	<ul style="list-style-type: none"> Stage 1 NK – Central superficial punctate keratitis
Previous Treatments	<ul style="list-style-type: none"> Cyclosporine 0.05% bid OU Preservative free artificial tears
Management Plan	<ul style="list-style-type: none"> Overvate 20mg/ml, 1 drop 6 times daily, for 8 weeks Concomitant Medications: <ul style="list-style-type: none"> Preservative free artificial tears



Vacc20/250

- Factors for this patient case include:
 - Patient has a history of multiple etiologies that can lead to NK: Chronic dry eye syndrome, poorly controlled diabetes, and a history of eye lid surgery. These all may lead to damage to the corneal innervation, increasing the patients risk of epithelial breakdown/progression.
 - Long term use of preserved glaucoma medication. 20 plus years on a prostaglandin analogue. The patient has not improved on cyclosporine 0.05% bid for many years and has not improved with the use of preservative artificial tears, as well as multiple thermal pulsed treatments.
- Other considerations may include:
 - Age
 - Comorbid Conditions – uncontrolled diabetes
 - Visual Potential
 - OSD refractory to long term use of topical cyclosporine 0.05% drops
 - Combination of previous blepharoplasty, chronic ocular surface disease, and meibomian gland dysfunction

Neurotrophic Keratitis: Etiology

- Infectious: HSV, VZV, leprosy
- CN V palsy
 - Surgery for trigeminal neuralgia, neoplasia (acoustic neuroma), aneurysm, facial trauma, congenital, familial (Guerrero-Willy Day syndrome), Goldfarb-Gazit syndrome, Möbius syndrome, familial corneal hypoaesthesia
- Topical medications: anesthetic abuse
- Iatrogenic: LASIK/PRK, corneal incisions (RK, AK), contact lens wear, scleral bands, vitrectomy and photocoagulation to treat DM retinopathy^{1,2}
- Chemical and physical burns
- Systemic: DM, multiple sclerosis, Vit A deficiency
- Increasing age, chronic DED³

1. Blanespa PJ. JAMA ophthalmology 2014;132:750-2.
2. Tellez CO. Eye 2006;20:1819-23
3. Ocul Surf 2007 Apr;5(2):75-92.

Neurotrophic Keratitis: Classification

Mackie classification

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

Mackie IA. Neuroparalytic keratitis. Current Ocular Therapy. Philadelphia, PA: WB Saunders; 1995:462-4.

Classification of Uveitis

- Anatomical / structural location
- Etiology
- Acute vs. Chronic
- Non-granulomatous vs. Granulomatous
- Unilateral vs. Bilateral

Clinical Signs

- VA
- Conjunctiva
- Cornea
- Anterior chamber
- Iris
- Pupil
- IOP
- Lens
- Vitreous
- Disc edema
- Macular edema
- Periphlebitis

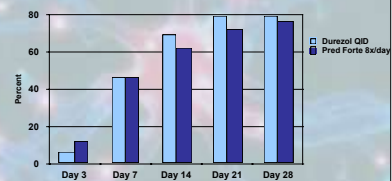


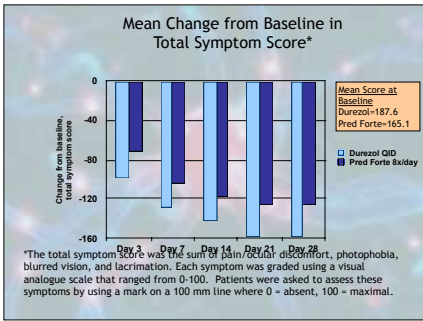
Photo accessed from http://www.medicinenet.com/image-collection/uveitis_picture/picture.htm

Uveitis



Percent of Subjects with Clearing of Anterior Chamber Cells (Grade 0 defined as ≤ 1 cell)





Ciliary Spasm

- What about orals?
- Indirect control of pain
- Central nervous control works better than sight specific in the oral class
 - Opioids



Controlling Ciliary Spasm

- Limit light
- Decrease inflammation
- Steroids and NSAIDS
- Mydriasis (blocks acetylcholine)
 - Cycloplegia does not equate to mydriasis
 - How often do we use Atropine/homatropine?

Don't Forget the Cycloplegics

- Comfort
- Break synechia
- Stabilize blood-aqueous barrier



Cycloplegic Agents

Drug	Max Effect (min)	Duration of Action
Tropicamide 0.5, 1%	20-30	3-4 hours
Cyclopentolate 1, 2%	20-45	1 day
Homatropine 2, 5%	20-90	2-3 days
Scopolamine 0.25%	20-45	4-7 days
Atropine 0.5, 1, 2%	30-40	1-2 weeks

Non-Therapeutic Treatments

- Hot compress
- Sunglasses / Hats
- Stay indoors
- Low lighting
- Plus for near
- Patching



Photo accessed from <http://deverespub.com/kentuckyderby-day-hat-contest/5738/>
Photo accessed from <http://www.sandfamily.com/programs/988-a-new-outlook.htm>

Ciliary Spasm Tip

- Have patient look down and touch upper eyelid to assess pain

Best Drug



Topical Route

- Direct drug delivery
 - Higher concentrations
- Minimize or eliminate systemic side effects

Topical Pain Control Anesthetics (not long term analgesics)

- Tetracaine
 - 10-20 min
- Benoxinate
 - Only in combos
 - 10-20 min
- Proparacaine
 - Diet Tetracaine
 - Poor penetration
 - VERY LITTLE CROSS SENSITIVITY TO TETRACAIN AND BENOXINATE

Corticosteroids

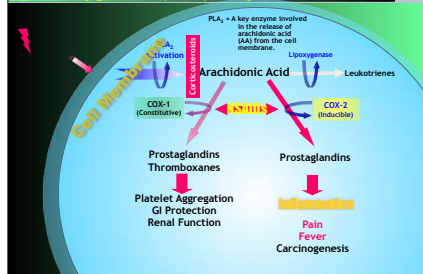
- Longer onset of action due to full system shut down
- Inflammation resolution tends to mirror analgesic effect
- Some tissues are not that prone to swelling



NSAIDS

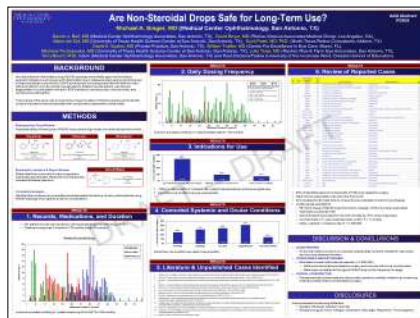
- Act peripherally - avoid CNS
- Very good pain control
- Low dose - analgesic
- High dose - anti-inflammatory

Inflammatory - Arachidonic Acid Pathway: Cyclo-oxygenase (COX) Enzymes



NSAIDS

- Very Safe
- Most of ophthalmology is still caught up in the hysteria of the generic voltaren saga.
- Diclofenac Paranoia



NSAIDs

- Inhibit prostaglandin synthesis
 - 1. irreversible inactivation of COX
 - 2. reversible competitive inhibition
 - Reversible non-competitive inhibition (“free radical trapping”)

NSAIDs

- The most underutilized drug class in optometry

Relative IC₅₀s: Rank - Order Greatest to Least Activity

Cyclo-oxygenase 2 (COX-2)	IC ₅₀ (µm)	Relative Potency
Bromfenac	0.0075	4.10 X
Amfenac	0.0204	1.50 X
Ketorolac	0.0279	1.10 X
Diclofenac	0.0307	1.00 X

Opava, Seshu. Accepted ASCRS 2007

Indications for Topical NSAIDs

	Diclofenac 0.1%	Ketorolac 0.5%	Ketorolac 0.4%	Nepafenac 0.3%	Bromfenac 0.36%
Post-Operative Inflammation	✓	✓	✓	✓	✓
Ocular Pain	✓	✓	✓	✓	✓
Post-traumatic Ocular Pain	✓	✓	✓	✓	✓
Photophobia	✓	✓	✓	✓	✓
Ocular Itching (Superficial Abrasion)	✓	✓	✓	✓	✓
Uveit	✓	✓	✓	✓	✓

All else fails

- Pressure patch
 - Corneal pain





Orals

Acetaminophen

- #1 stunner (mild to moderate pain)
- We have no idea how it works (probably CNS effects)
- No real GI effects
- Additive with other pain meds
- No cross reactions
- Not associated with Reye's syndrome (kids dying from NSAIDS)
- Max 4 grams a day?

Aspirin

- The Original NSAID
- Anticoagulant
- No mood altering effect
- Irreversibly acetylating COX
 - Most others are reversible competitive inhibitors
 - Watch asthma patients



NSAIDS

- All NSAIDS can cause GI problems and gastric bleeding all high/long term dosages



NSAIDS

- Studies have shown NSAIDS to have same analgesic effect as narcotics
 - Some studies show better pain control than morphine (what?.....)
- Almost all have a ceiling effect

Not all COX are the same

- COX-1
 - Constitutive variant
 - Mucus production and renal blood flow
- COX-2
 - Inducible
 - Sensitizes nociceptors

NSAIDS

- Have cross sensitivities with aspirin, ibuprofen, and other NSAIDS
- Can delay wound healing

Opioids

- Best drug for severe acute pain
- Not used nearly enough by ODs
- Most are addictive and patients can develop tolerance
 - **Addiction very unlikely with short term use**
- Start all at q 4-6h
- All are compared to morphine for efficacy and potency

Opioids

- No ceiling effect
- Sympathomimetic - miosis, blurred vision, diplopia

Codeine

- Available with acetaminophen
- Most commonly used
- Works in 20 min, peaks at 2 hours
- The Greece of opioids
 - Less toxicity
 - Less addiction potential
 - Less sedation and constipation

Hydrocodone

- With acetaminophen (Vicodin, Loretab)
- 6X more potent than codeine with less sedation and constipation



Oxycodone

- Available with acetaminophen (Percocet)
- 10X effective than codeine
- Less side effects than codeine
- Higher addiction potential



Ultram (tramadol hydrochloride)

- Moderate to severe pain
- Non-narcotic opioid receptor agonist
- Pregnancy Category C
- 50-100mg q4-6 hours
- Side effects
 - Hallucinations
 - Fever
 - Nausea and vomiting
 - Seizure
 - Skin rash
 - Shallow breathing, weak pulse

Neurontin

- Recently failed study for ocular pain control after PRK (JCRS)
- Used for suppressing exaggerated pain and seizures



Non-Narcotics

- Skin patches
 - Lidocaine
 - Capsaicin
- Anticonvulsants
 - Lyrica
 - Neurontin
 - Tegretol
- Antidepressants
 - Cymbalta



3rd Nerve Palsy

- Can be extremely painful
- Start with NSAIDS



Bandage Contact Lens

- Not used nearly enough
- Filamentary or severe punctate keratitis
- Allows a bridge for re-epithelialization and establishment of a normal glycocalyx



Tips for using amniotic membranes and pain

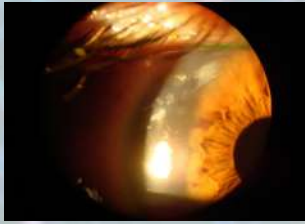
- they are not uniquely pain controlling
- always have an anti-inflammatory on board and always consider an antibiotic for infection prophylaxis

Diagnostic Approach

- Complete history, including contact lens use
- Presenting symptoms
- Physical examination
 - Slit Lamp exam
 - Signs
 - Rule out viral/fungal infections
 - Pay attention to the details



Corneal Infection



Corneal Infection

- Be careful of adding cycloplegic
 - Pain will indicate success of therapy
- Eyelid edema great indicator of infectious etiology

Chronic Pain

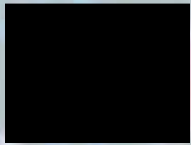
- Many types
- Often a chemical or physiological imbalance (not just Mucho Dolor Syndrome)
- We all see it on a daily basis

Posterior Segment Pain

- Neovascular glaucoma
- Ocular ischemic syndrome
- Optic neuritis
- Posterior uveitis
- Pars planitis



What About IOP?



- Angle closure
- Postoperative
- High IOP in non-seeing eyes

High IOP in Non-seeing Eyes

- Cyclo-cryo ablation
- Retrobulbar alcohol injection



Thank you

derek.n.cunningham@gmail.com