Ocular Pain Management

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Pain Management 101

#1 Identify the cause

#2 Treat the pain

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Anatomy & Physiology of Pain

- COX enzymes play a key role in inflammation and pain
  - COX-1 is involved in maintenance of GI mucosa
  - COX-2enzyme signals pain and inflammation
- Prostaglandins role

References
1. Ahuja M. The AAPS Journal. 2008;10(2):229-241.
2. Radi ZA, Ostroski R. Mediators Inflamm. 2007;2007:85091.

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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

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Nociceptors

- In all peripheral tissue
- Distribution will vary
- Stimulated by
  - Heat
  - Energy
  - Trauma
  - Emotion
  - Chemicals

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Common Painful Ocular Conditions

- Allergic conjuctivitis
- 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

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Importance of History

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

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What Can Be Used During Pregnancy?

- Antibiotics
  - Amoxicillin
  - Amoxicillin/clavulanate
  - Azithromycin
  - Erythromycin
- Antivirals
  - Acyclovir
  - Valacyclovir
- Anti-inflammatory
  - Prednisone
- Analgesics
  - Acetaminophen
  - Ibuprofen
  - Tylenol #3
  - Vicodin
- Allergy
  - Diphenhydramine
  - Loratadine

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Prescribing for Children

- Children >12 years old and >88 lbs can be dosed as adults unless otherwise noted
- Look up dosage for child (mg/kg/day)
- Determine how many kg child weighs
  - 1 kg=2.2 lbs
- NO ASPIRIN

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Internal Hordeolum

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Cellulitis

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Contact Dermatitis

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Eyelids

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

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Corneal 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
  - Possess both sensory and efferent functions
  - Mechanical, thermal and chemical stimulation usually is perceived as pain

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Corneal Sensitivity Changes

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

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TFOS DEWS II Definition

*"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."*

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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 Labbé[1] 2013 ARVO

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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

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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

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Refractive Surgery Considerations

- Several studies showed that nasal or superior LASIK flaps had no effect on corneal sensation
- Transient light sensitivity syndrome

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Neuropathic Pain

- Treatment to either:
  - Regenerate nerves
  - Reduce inflammation that makes nerves more sensitive
- Treatment Options
  - Serum tears
  - Steroids
  - Amniotic membrane
  - Neurostimulation
  - Blue filter glasses
  - Systemic neuro-modulatory therapies
  - Biologics

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Uvea Pain Considerations

- Pain receptors diffusely distributed
  - Localization very difficult
  - Similar to sinus pain
- Light sensitivity

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Classification of Uveitis

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

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Clinical Signs

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

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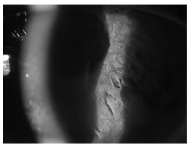
Posterior Segment Pain

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



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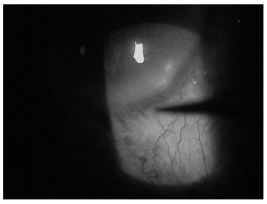
What About IOP?



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

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Addressing Ocular Pain

- Complete history
- What is underlying cause?
- Consider case appropriate anti-inflammatory therapy

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Analgesics for Pain

- Anesthetics
  - Blocks action potential signal from nociceptor to brain or spinal cord
  - Lidocaine, proparacaine, tetracaine, benoxinate
- Central-acting agents
  - Interrupts pain signals and emotional responses to pain at the brainstem to cerebral cortex level
  - Opioid (narcotic) analgesics
- Peripheral-acting agents
  - Blocks peripheral nociceptor stimulation, and the inflammatory pathway that contributes to nociceptor stimulation.
  - Non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, aspirin

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Artificial Tear Supplements

- Improve comfort
- Reduce irritation and friction
- Improve ocular surface
- Store in the fridge

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Topical Anesthetics

- Benoxinate
  - Only available with fluorescein
  - Onset 10-20 seconds
  - Duration 10-20 minutes
- Proparacaine 0.5%
  - Poor penetration
  - Very little cross sensitivity to tetracaine and benoxinate
- Tetracaine
  - Onset 10-20 seconds
  - Duration 10-20 minutes

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Corticosteroids

- Longer onset of action due to full system shut down
- Inflammation resolution tends to mirror analgesic effect

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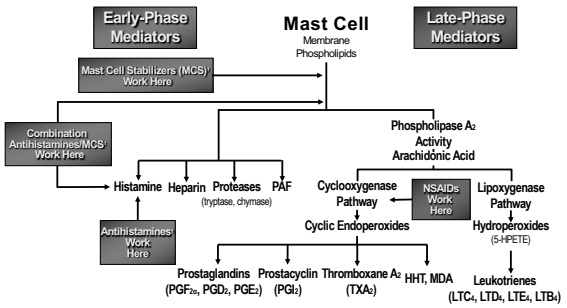
Most Prescription Treatment Options Have a Limited Effect on the Inflammatory Cascade



1. Adapted with permission from Donnenfeld ED. *Refract Eyecare*. 2005;9(suppl):12-16.
2. Slonim CB. *Rev Ophthalmol*. 2000:101-112.

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Corticosteroids

- Will control prostaglandins and leukotrienes
- STOPS THE INFLAMMATION CASCADE
- Suppresses inflammation
- Allows for reestablishment of the neural feed back loop

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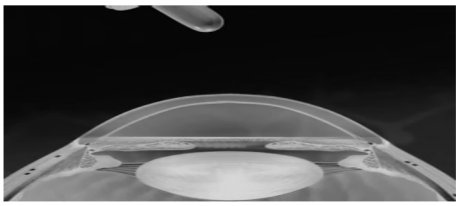
Steroid Efficacy

- Difluprednate ≥ Prednisolone ≥ Loteprednol ≥ Dexamethasone > Fluorometholone



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Steroid Pulse Therapy

- QID to Q 1 Hour for 7 to 10 Days
- Zero Tolerance for AC Cells
- Avoids Surface Toxicity
- Quick & Dirty
- Hit It Hard and Fast: Aggressive
- **Treat and Follow**

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Topical NSAIDS

- Act peripherally – avoid CNS
- Very good pain control
- Very safe
- The most underutilized drug class in optometry

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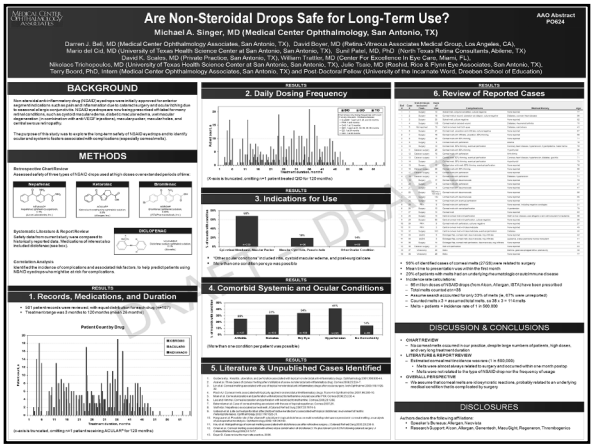

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Other Pain Management Options

- Cycloplegics
- Pressure patch
- Bandage Contact Lens
- Amniotic Membranes
- Anxiolytics

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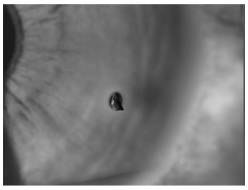
Don't Forget the Cycloplegics

- Comfort
- Break synechiae
- Stabilize blood-aqueous barrier



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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

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Non-Therapeutic Treatments

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

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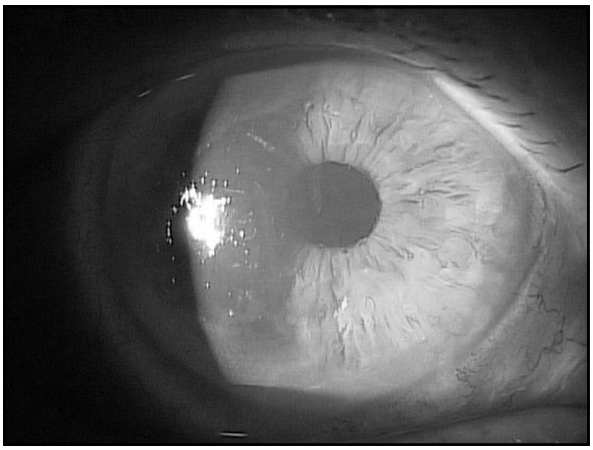

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Bandage Contact Lens

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

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Amniotic Membranes

- Used to manage ocular surface healing for a variety of indications including:
  - Corneal epithelial defects
  - High-risk corneal transplants
  - Recurrent Corneal Erosion
  - Infectious Diseases (Herpes/Keratitis)
  - Stevens-Johnson Syndrome & Chemical Burns

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Hindawi
Journal of Ophthalmology
Volume 2017, Article ID 6404918, 10 pages
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Hindawi

Clinical Study

Corneal Nerve Regeneration after Self-Retained Cryopreserved Amniotic Membrane in Dry Eye Disease

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[8]Wang Vision Institute, Nashville, TN, USA

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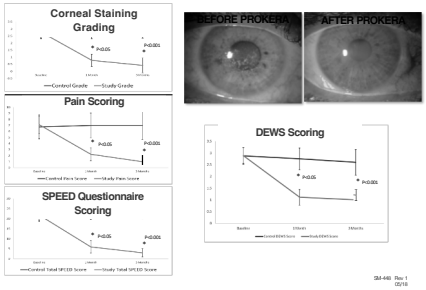
Improvements in Clinical Signs and Symptoms



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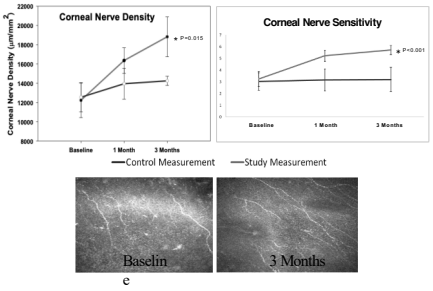
Improvements in Corneal Nerve Density & Sensitivity



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Neurontin

- Used for suppressing exaggerated pain and seizures
- Glutamate is also involved in transmitting pain signals in the brain and nervous system
- Gabapentin reduces the release of glutamate
- Recently failed study for ocular pain control after PRK (JCRS)

Dosage 300 mg BID to QID

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Efficacy and tolerability of Nortriptyline in the management of neuropathic corneal pain

- **Purpose**:
  - Off-label use of Nortryptyline has been used successfully in the management of non-ocular neuropathic pain – helpful in the management of neuropathic corneal pain (NCP)?
- **Methods**:
  - Retrospective cohort study at the New England Eye Center, Tufts Medical Center, Boston, Massachussetts from July 2015-March 2019
    - 54 patients with NCP with centralized component who were treated with Nortryptyline
    - Centralized NCP:
      - Discordance in clinical signs and symptoms
      - Persistent ocular discomfort/pain after 90s of instillation of 0.5% proparacaine hydrochloride
    - Nortryptilline dosed at 10mg initially and tapered upward to 100mg based on response and tolerability
  - Response to treatment measured using Ocular Pain Assessment Survey (OPAS)

Ozmen et al. 2020

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- **Results**:
  - 30 patients included in final efficacy analysis:
    - 40% (n = 12) reported 50% or greater reduction in overall pain score (table 5)
    - Statistically significant reduction in all pain level dimensions (table 6)
    - Statistically significant reduction in many quality of life dimensions (table 7)
  - 19 of 54 discontinued due to side effects:
    - 8 of 19 were included in final analysis and discontinued despite reduction in pain score by 22.4%
    - Lethargy, dry mouth, constipation, nausea, headache, tachycardia, unspecified
- **Conclusion**:
  - Noteworthy pain decrease in patients with centralized component of NCP

Table 6
Results from the questions in pain level dimension of the Ocular Pain Assessment Survey.

OPAS #	Eye Pain Question	First Visit Score	Last Visit Score	Percent Change in Pain Score	p
4	Most in 24 h	7.3 ± 2.2	5.5 ± 2.7	−9.3 ± 83.3	**0.028**
5	Least in 24 h	3.8 ± 2.6	2.4 ± 2.0	−16.7 ± 76.5	**0.013**
6	Average in 24 h	5.7 ± 2.1	3.6 ± 2.1	−37.4 ± 32.6	**<0.0001**
7	Most in 2 w	7.7 ± 1.7	5.9 ± 2.9	−25.0 ± 35.0	**0.003**
8	Least in 2 w	4.8 ± 2.8	2.8 ± 2.2	−34.1 ± 46.6	**0.002**
9	Average in 2 w	6.3 ± 2.0	4.2 ± 2.1	−30.5 ± 39.9	**0.001**

Table 7
Results from the questions in quality of life dimension of the Ocular Pain Assessment Survey.

OPAS #	QoL dimension: pain effecting,	First Visit Score	Last Visit Score	Percent Change in QoL Score	p
13	Reading/computer use	6.8 ± 3.3	4.3 ± 2.4	−29.2 ± 55.5	**0.007**
14	Driving/watching tv	5.3 ± 3.5	3.9 ± 3.5	−11.5 ± 107.7	0.247
15	General activity	5.3 ± 2.8	3.9 ± 3.1	−26.8 ± 62.9	0.053
16	Mood	6.7 ± 2.9	4.4 ± 3.1	−16.0 ± 89.8	**0.029**
17	Sleep	3.8 ± 4.0	1.5 ± 2.7	−41.1 ± 52.7	**0.011**
18	Enjoying life	6.5 ± 3.2	4.6 ± 3.5	−20.4 ± 63.5	0.068
19	Time spent thinking about pain	7.6 ± 3.3	5.2 ± 3.5	−23.9 ± 57.6	**0.041**

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Oral Analgesics

- Hydrocodone/acetaminophen is the most frequently prescribed oral medication in the U.S.
- Indicated for:
  - Corneal abrasions
  - Recurrent corneal erosions
  - Severe keratitis
  - Severe uveitis
  - Refractive surgery

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

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Advil (Ibuprofen)

- Analgesic, antipyretic, anti-inflammatory properties
- Suppresses inflammatory cascade by inhibiting COX pathway
- Pregnancy Category
  - C – Prior to 30 weeks gestation
  - D – After 30 weeks gestation
- OTC 200 mg tablets/capsules
- Analgesic dosage - 1,200 mg / day
- Anti-inflammatory dosage – 3,200 mg / day
- Generics available

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Oral Corticosteroid Considerations

- Accurate diagnosis is essential
- Indicated for acute inflammatory eye, orbital and eyelid conditions
- Pregnancy category C
- Dosepaks available
  - 24 mg, 30 mg, 60 mg with taper
- Best taken with meals
- Short term rarely has ocular side effects
- Consider H2 antagonist to protect stomach

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Prednisone

- Suppresses inflammatory cascade and immune response
- Optic neuritis
  - Methylprednisolone 1g/day i.v. for 3 days
  - 60-100mg qd p.o. for 11 days
  - Only after initial IV steroid treatment per ONTT to decrease risk of recurrence
- AION: 60-100mg qd
- Scleritis/Uveitis
  - Not responding to topical treatment
  - 40-80 mg as an initial dose with taper

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Prednisone

- Side Effects/Contraindications:
  - Increased IOP
  - Cataract formation
  - Fluid retention (moon face, buffalo hump)
  - Increase blood sugar levels in diabetics
  - Gastric ulcers
  - Not to be used if pregnant
  - Mood changes
- Advantages:
  - Widely available
  - Inexpensive

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Extra Strength Tylenol (Acetaminophen)

- Analgesics and antipyretic
- Indications:
  - Pain relief associated with corneal abrasions, chemical burns, headaches associated with eye pain, scleritis
- Pregnancy Category B
- Side Effects/Contraindications:
  - Rash, Hives
  - Itching
  - Difficulty swallowing/breathing
  - Overdose may damage liver
  - Do not take with alcohol

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Oral Narcotic Analgesics

- Centrally acting opioid receptor blockers
- Safe and effective for acute, short-term pain
- Clinically used in combination with acetaminophen
- Generally prescribed as one tablet po q4-6hours prn
- Onset 20 minutes, peak 1 hour, duration 4-6 hours
- Addiction potential

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Codeine

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

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Hydrocodone

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

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Vicodin (hydrocodone/acetaminophen)

- Dosage:
  - Vicodin contains 5mg hydrocodone with **300 mg** APAP
  - Vicodin ES contains 7.5mg hydrocodone with **300 mg** APAP
  - 7.5mg hydrocodone with 200 mg ibuprofen
  - Pregnancy Category C
- 1 tablet po q4-6 hours
- Indicate how many in writing
- Generics available

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Controlled Drug Act

- ***Schedule I - drugs with a high abuse risk.*** These drugs have NO safe, accepted medical use in the United States. Some examples are heroin, marijuana, LSD, PCP, and crack cocaine.
- ***Schedule II - drugs with a high abuse risk, but also have safe and accepted medical uses in the United States.*** These drugs can cause severe psychological or physical dependence. Schedule II drugs include certain narcotic, stimulant, and depressant drugs.
- ***Schedule III, IV, V - drugs with an abuse risk less than Schedule II. These drugs also have safe and accepted medical uses in the United States.*** Schedule III, IV, or V drugs include those containing smaller amounts of certain narcotic and non-narcotic drugs, anti-anxiety drugs, tranquilizers, sedatives, stimulants, and non-narcotic analgesics.

Accessed from http://www.deadiversion.usdoj.gov/schedules/index.html on 8/20/11

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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

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Medical Marijuana

- Used for chronic pain in patients
  - Nerve damage
  - Terminal cancer
  - Nausea
  - Glaucoma
  - Movement disorders

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Neuropathic Dry Eye Pain

- Role of cannabis
- EyeSol – a novel semi-fluorinated alkane drug delivery technology
  - Low surface tension
  - No water
  - Metabolically inert
  - Refractive index similar to H20

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Conclusions

- Treat the underlying cause
- Consider all treatment options
- Follow up is key

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