On behalf of Vision Expo, we sincerely thank you for being with us this year.

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We have eliminated all paper session evaluation forms. Please be sure to complete your electronic session evaluations online when you login to request your CE Letter for each course you attended! Your feedback is important to us as our Education Planning Committee considers content and speakers for future meetings to provide you with the best education possible.

VISION EXPO

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House of Pain

Jessica Steen OD, FAAO, Dipl. ABO

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Financial Disclosures

- Speaker-Carl Zeiss Meditec, Bausch and Lomb, Oyster Point Pharma, Thea Pharma, Alcon, Allergan
- Advisory Board-Bausch and Lomb, Carl Zeiss Meditec, Santen, Peripherex, Ocuphire, Ocuterra, Oyster Point Pharma, Allergan, Iveric Bio
- Shareholder-Clearside Biomedical (<0.01% ownership)
- *All relevant relationships have been mitigated*

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Objectives

- 1. Discuss specific ocular conditions for which pain management may be necessary
- 2. Discuss pharmacologic options for management of ocular pain
- 3. Understand the decision making process in the choice of analgesics

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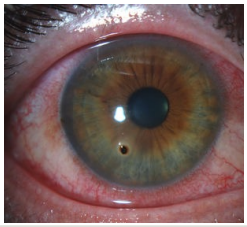
Case

- 38 year old Hispanic male presents with 3 day history of tearing, redness, and irritation in the right eye
  - He thinks something got in his eye at work…
    - He had to leave work because of the severe discomfort that day
- Remove the foreign body, dilate, then what?



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Prescription Choices

- In emergency situations resulting in pain:
  - NSAIDs or Tylenol
  - …or narcotics…
  - *Very few options in between*
- Topical options?
  - Cycloplegic agent
  - NSAID
  - Bandage contact lens
  - *Anesthetic?*

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Pain Management

- Anterior segment pain
  - Corneal abrasion, erosion
  - Corneal ulcers, severe ocular surface disease
  - Uveitis(?)
  - Scleritis
  - Acute angle closure
  - Herpes zoster ophthalmicus (& post-herpetic neuralgia)
    - Ocular neuropathic pain
- Posterior segment conditions causing pain
  - …
  - Posterior scleritis
  - Idiopathic orbital inflammation
  - Tolosa-Hunt syndrome
    - Cavernous sinus inflammation
  - Inflammatory optic neuropathy

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Treatment Goals in Ocular Pain Management

- Find and treat the underlying cause!
- Then, manage the associated pain
- **Reduce (not eliminate) pain to restore functionality**

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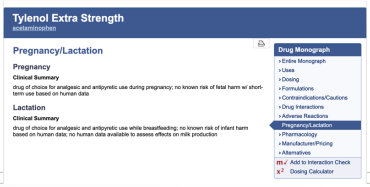
Resources

- Epocrates Online
- https://online.epocrates.com/



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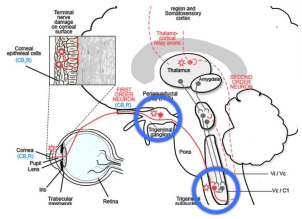
Ocular Sensory Pathway

- *The simple approach*
- First order neuron
  - Nerve ending in the cornea→cell body in the trigeminal ganglion
  - Synapse in the subnucleus caudalis/upper cervical transition zone



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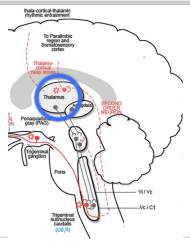
Ocular Sensory Pathway

- Second order neuron
  - Cross and join the (contralateral) spinothalamic pathways
  - Synapse in the thalamus



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Ocular Sensory Pathway

- Third order neuron
  - Relay information to the supraspinal centers
    - Somatosensory cortex
- Perception of pain is modified by descending pathways

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Complex Experience of Pain

- Multisystem illness that involves the neurologic, endocrine, and immune system
  - Thousands of genetic modifiers influence risk of experience of chronic pain
- Everyone with chronic pain experiences it differently

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Understanding Pain Mechanisms

- Multiple molecular pathways which lead to a single pain syndrome
  - i.e. migraine. Even in a small subgroup, there may be variation in response to treatment
- Common pathways in pain, addiction, and depression
  - May look beyond targeting the mu-receptor and type 3 dopamine receptor

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Challenges in Clinical Trials

- The placebo effect is real
  - Biological, genetic, neurocircuitry mechanisms underlie the response
- How do we measure pain?
  - Currently, most common used pain assessment measures are subjective i.e. numerical pain rating scales
- Plus emotional, experiential, cultural, and cognitive factors

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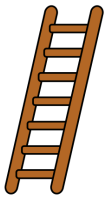
WHO Ladder Approach

- General approach to pain management:
  - Begin with non-opioid medications
  - Mild opioids (i.e. codeine) +/- adjuvants +/- non-opioids
    - Adjuvants enhance analgesics, may be prescribed to control side effects
      - Nausea, depression, insomnia, anxiety
        - i.e. pregabalin, gabapentin, amitriptyline



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NSAIDs

- Inhibit COX-1 and COX-2
- Ibuprofen
  - Advil or Motrin IB (200mg tablets)
  - Up to 1200mg daily (OTC)
  - Up to 2400mg daily (Rx) for pain (although maybe up to 3200mg/day for rheumatoid arthritis)
    - Available as 100mg, 200mg, 400mg, 600mg, 800mg tabs

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What is the maximum daily dosage?!

Adult Dosing ⓘ

Dosage forms: CAP: 200 mg; TAB: 100 mg, 200 mg, 400 mg, 600 mg, 800 mg; CHEWABLE: 50 mg, 100 mg; SUSP: 100 mg per 5 mL, 50 mg per 1.25 mL

osteoarthritis

[300-800 mg PO tid-qid]

Max: 3200 mg/day; Info: use lowest effective dose, shortest effective tx duration; give w/ food if GI upset occurs

rheumatoid arthritis

[300-800 mg PO tid-qid]

Max: 3200 mg/day; Info: use lowest effective dose, shortest effective tx duration; give w/ food if GI upset occurs

for anti-inflammatory uses (off-label)

[600 mg PO qid x7-14 days]

Max: 2400 mg/day; Info: 800 mg PO tid; Info: use lowest effective dose, shortest effective tx duration; give w/ food if GI upset occurs

pain, mild-moderate

[400 mg PO q4-6h prn]

Max: 2400 mg/day; Info: use lowest effective dose, shortest effective tx duration; give w/ food if GI upset occurs

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NSAIDs

- Naproxen sodium
  - Available as 220mg, 275mg, 550mg, 375mg ER, 500mg ER Up to 1375mg-acute; 1100mg-maintenance; 1500mg ER
- Aleve (naproxen sodium)
  - 220mg tabs, max 660mg/day (3 tabs)

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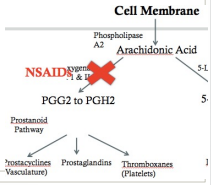
NSAID Cautions

- Increased risk of bleeding
  - Inhibits thromboxane production
- Decreases stomach mucous production-may result in gastric ulcers and intestinal perforation
- Caution in patients with CV disease history, history of stroke, heart failure, and hypertension
- Risk of nephrotoxicity in CKD-do not use in individuals with kidney disease



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Topical Ocular NSAIDs

- Block COX-1 and COX-2
  - Leaves the leukotriene pathway unaffected
- Reduces prostaglandin formation
  - Reduces pain at the level of the ocular surface
- Some indication that inhibition of COX-2 inhibits MMPs within the corneal epithelium
  - Pan 2002, Ottino 2001

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Ocular ADRs of Topical NSAIDs

- Generally very mild
  - **Stinging upon instillation**
  - Corneal infiltrates, corneal melting, delayed epithelial growth (most problematic with 'old' generic Voltaren)
    - Those at risk include RA, corneal denervation, DM, dry eye
  - Prolonged use can mask signs of infection
  - Infiltrates (WBC) due to over production of leukotrienes which cause leakage of WBC

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Topical NSAIDs-Older

- Acular LS (ketorolac 0.4% solution)
  - Dosed **QID** for up to 4 days after keratorefractive surgery
  - Generic
- **Acular (ketorolac 0.5% solution)**
  - Generic only; approved for tx of ocular allergy QID ($50→$20)
- Acuvail (ketorolac tromethamine 0.45% solution); PF
  - **BID** for pain and inflammation following cataract surgery x 2 weeks
    - Approx $360 for 30 vials

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Topical NSAIDs-Newish

- Bromday (bromfenac sodium 0.09% solution)-generic only
  - QD for post-operative inflammation and reduction of pain
  - Mainly used to decrease risk of CME post op
    - $65 for 1.7 mL bottle (2.5mL bottle discontinued)
- ***Bromfenac should not be used in patients with sulfite allergy***
- Nevanac (nepafenac 0.1% **suspension**)
  - TID x 2 weeks for post-op pain and inflammation associated with cataract surgery; increased posterior segment action
    - $350 for 3mL bottle

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Topical NSAIDs-Newer

- Prolensa (bromfenac sodium 0.07%)-2013
  - QD for treatment of postoperative inflammation and reduction of ocular pain
  - Lower concentration vs Bromday; also more physiologically neutral pH = improved penetration
  - $340 for 3mL bottle—with a coupon as low as $90
- Bromsite (bromfenac sodium 0.075%)-2016—and generic (February 2024)
  - BID
  - Durasite vehicle
  - First NSAID to be approved for 'preventing ocular pain in patients undergoing cataract surgery'
  - $285 for 5mL bottle
  - ***Bromfenac should not be used in patients with sulfite allergy***
- Ilevro (nepafenac sodium 0.3% suspension)-2012
  - QD for treatment of postoperative inflammation and reduction of ocular pain (2 weeks)
  - $340+ for 3mL bottle

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ketorolac 0.5% solution QID

Or diclofenac 0.1% solution BID

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Acetaminophen

- Antipyretic and analgesic effect-weak anti-inflammatory effect
  - Little to now effect on platelets or inflammation
    - But does increases the blood thinning effect of warfarin
- Typically weaker effect than NSAIDs, but overall, better tolerance
- Well absorbed orally, peak blood levels reached in 30-60 minutes

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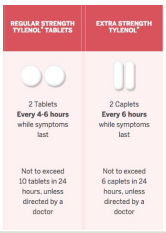
Acetaminophen Dosing

- Regular strength (325mg): 325-650mg q4-6hours
  - Max 3250mg/day
- Extra strength (500mg): 1000mg q6-8 hours
  - Max 3000mg/day



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Acetaminophen

- Caution in patients with liver disease
  - Cirrhosis, Hepatitis C
- Caution in heavy alcohol drinkers
  - *5 oz. glass of wine*
  - *1.5 oz 80-proof spirit*
- Caution in patients with severe renal disease
  - <= 30CrCL mL/min (Stage 4…of 6)
- *According to the Dietary Guidelines for Americans & NIAAA (National Institute on alcohol abuse and alcoholism):*
  - *Moderate = 1 drink per day for women, 2/day for men*
  - *Heavy = 3 drinks/day for women, 4 drinks per day for men*
    - *8 drinks per week for women, 15 drinks/week for men (CDC)*

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Acetaminophen Toxicity

- Partially metabolized by hepatic enzymes and converted to inactive metabolites
- Small amount is metabolized into a highly active metabolite-toxic to liver and kidney
  - This is quickly broken down into no-toxic compounds in the normal state

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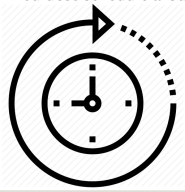
Pain Management Pearl

- Aim to treat on a fixed-dose schedule around the clock
  - Vs. "PRN"



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Common Opioids

- **Tramadol**
- **Codeine**
  - **Tylenol #3**
- Hydrocodone
  - Hydrocodone/acetaminophen
- Oxycodone
  - Percocet, Percodan
- Morphine

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General Pharmacokinetics

- Well-absorbed orally
- Cross placental barrier
- Metabolized by hepatic enzymes, eliminated by the kidneys
- Codeine, hydrocodone, tramadol target the mu opioid receptor
  - G protein coupled receptors in the brain and spinal cord (and gut)

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Opioid Effects

- **Limbic system:** create feelings of pleasure, euphoria, and relaxation
- **Brainstem:** slow breathing, stop coughing, reduce pain
- **Spinal Cord:** reduce pain
- ***Cause analgesia, sedation, euphoria, respiratory depression, suppression of the cough reflex***

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Opioid Side Effects and Contraindications

- Significant side effects-especially with chronic use
  - GI effects-constipation
  - Pupillary miosis
  - Fatigue, cognitive impairment, dry mouth, sweating, weight gain
  - Tolerance→dependence
- Contraindications-asthma, respiratory depression, history (or family history) of addiction
  - MAOi use within 14 days
  - Hypersensitivity
  - Concomitant benzodiazipine, alcohol use

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Polypharmacy

- Increasing trend of concurrent use of benzodiazepines
  - Alprazolam (Xanax), lorazepam (Ativan), clonazepam (Klonopin)
- Combination is correlated with higher levels of pain, physical and mental health disability
  - Increased risk of opioid related fatality

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Polypharmacy

- Black box warning added in 2016

WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS

Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death *[see Warnings, Drug Interactions]*.

- Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

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Opioid Side Effects and Contraindications

- Caution in treatment of pain in children younger than 12
  - Codeine and tramadol contraindicated in under 12 years of age
- Warning in breastfeeding mothers and pregnant individuals

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Opioids and Sleep Apnea

- Sleep apnea
  - Obstructive-periodic closure of the upper airway during sleep
    - Pauses in breathing for at least 10 seconds
- Opioids depress respiratory rate
  - May relax the tongue and upper airway muscles
- May increase sensitivity to opioids

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Prior to Prescribing

- Perform a **complete** history
- Determine a diagnosis and document your managing plan for the condition causing pain
- Establish treatment goals
  - Pain relief, improvement in activity, while minimizing adverse effects
- Opioid Agreement:
  - Informed consent and treatment consent
  - Include clear descriptions and expectations regarding use and abuse—and the consequences for violating the contract
- Discussion of risks:
  - **Even when taken as prescribed**, risk of physical or psychological dependence
  - Taking more opioids than prescribed, or mixing sedatives, benzodiazepines or alcohol with opioids, can result in fatal respiratory depression

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Prescribing Reminders

- Aim to treat for the shortest period of time possible
  - Maximum number of days varies by State
- Lowest effective dose of immediate-release opioid drug
  - **Low dose = 40 morphine milligram equivalent (MME)**
  - Moderate = 41-90 MME
  - High >91 MME
- *Patients who do not respond to low or medium dose will typically not respond to higher dosages*

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Acetaminophen 300mg with codeine 30mg

- Trade name: Tylenol #3
  - *Tylenol No. 1-4. Vary by strength of codeine (7.5mg-60mg)*
- Little to no effect on platelets—or inflammation
- 1-2 tabs q4-6h as needed for pain
  - Max. 3250mg acetaminophen daily *(max max is 4000mg daily)*
  - Max. 300mg codeine daily (0.15MME); 40MME/day = 266.67mg/day
    - 10 tablets daily = 3000mg/day acetaminophen
    - 10 tablets daily = 300mg/day codeine
  - ***Take two tablets by mouth every 6 hours*** ✓
  - ***Take one tablet by mouth every 3 hours*** ✓
    - 8 tablets daily—maximum 3 days; no refill

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Opioid Medications

- Hydrocodone
  - 1 MME; maximum 40 MME/day
  - Moved to Schedule II in 2014
    - Changed the ability to prescribe for some of our colleagues
- Hydrocodone + acetaminophen (2.5mg, 5mg, 7.5mg, 10mg + 300mg or 325mg)
  - Vicodin: 5mg/300mg (max 8 tablets per day)
  - Most common generic is 5mg/325mg (max 8 tablets per day)
  - 1-2 tablets every 4-6 hours as needed for pain

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Tramadol

- Trade Name: Ultram
- Weak mu-receptor agonist; inhibits reuptake of seratonin
- Synthetic analogue of codeine (less effective)
- **Opioid** analgesic
  - Avoid in history of anaphylaxis secondary to codeine or other opioids
  - Analgesia 1 hour after administration

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Tramadol

- Tramadol (MME 0.1)
  - 40 MME/day = 400mg of tramadol per day
  - 50mg tabs (immediate release); maximum 8 tablets per day
  - i.e. 50mg q4h (6 tablets per day) = 300mg per day = 30 MME/day
  - i.e. 2 x 50mg q6h (8 tablets per day) = 400mg per day = 40 MME/day
  - *Take one tablet by mouth every 4 hours*
  - *Take two tablets by mouth every 6 hours*
- Contraindications and cautions are similar to codeine

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What Else Have We Got?

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Evidence-based clinical practice guideline for the pharmacologic management of acute dental pain in adolescents, adults, and older adults

A report from the American Dental Association Science and Research Institute, the University of Pittsburgh, and the University of Pennsylvania

JADA 2024:155(2):102-117
https://doi.org/10.1016/j.adaj.2023.10.009

Recommendations

1. For the management of acute postoperative dental pain in adolescents, adults, and older adults* undergoing surgical tooth extraction(s), the panel recommends the postprocedural use of nonopioid analgesics† as first-line therapy instead of opioid analgesics (conditional, low certainty).
   - 1.1. For surgical tooth extraction(s), the panel suggests initiating the postoperative pain management using a nonsteroidal anti-inflammatory drug (NSAID) alone (eg, 400 mg of ibuprofen or 440 mg of naproxen sodium) or in combination with acetaminophen (eg, 500 mg) (conditional, low certainty).
   - 1.2. In the rare instances when postprocedural (ie, surgical tooth extraction) pain control using NSAIDs alone is inadequate, the panel suggests the addition to the previous first-line therapy prescription (ie, NSAID) of 325 mg of acetaminophen plus a combination of 325 mg of acetaminophen with an opioid‡,§,¶ (eg, 5-7.5 mg of hydrocodone or 5 mg of oxycodone) at the lowest effective dose, fewest tablets, and the shortest duration, which rarely exceeds 3 days (conditional, low certainty).

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An Observational Study to Determine Whether Routinely Sending Patients Home With a 24-Hour Supply of Topical Tetracaine From the Emergency Department for Simple Corneal Abrasion Pain Is Potentially Safe

Neil Waldman, MD*; Ben Winrow, MBCHB; Ian Densie, BSR; Andrew Gray, BA, BCom; Scott McMaster, DO; George Giddings, MBCH; John Meanley, MBCHB

- 1.5mL preservative free tetracaine 1% dispensed for 24 hours was 'a safe and effective means of controlling ocular pain'

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Bandage Soft Contact Lens

- Bandage contact lens
  - Protection from mechanical contact

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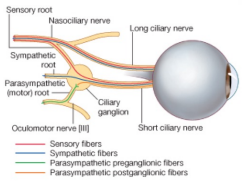
Cycloplegic Agents

- Cycloplegic agent
  - Prevents ciliary body spasm



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Case

- 38 year old Hispanic male presents with 3 day history of tearing, redness, and irritation in the right eye
  - He thinks something got in his eye at work…
- Remove the foreign body, dilate, then what?

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Case

- Remove the foreign body
  - 30G needle
- 1 drop of 5% homatropine instilled in office
- Prescribed topical antibiotic (Polytrim QID)
- ***Recommended (FL)*** to take over the counter ibuprofen (2x200mg every 4 hours)
  - Max 1200mg or 2400mg/day?
- Emergency contact information provided; scheduled for follow up next day
- *Lost to follow up…telephone number disconnected*

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Bottom Line

- Pain is the complex manifestation that involves the neurologic, endocrine, and immune system
- Oral and topical ocular agents are effective in the treatment of short term pain
- Prescribe opioids when necessary, as allowed by your State—but must ensure to do your due diligence as an Optometric Physician

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Thank You!

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- 480.289.0613

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