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**Practical Management of Ocular Pain**

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## Financial Disclosures

- None.

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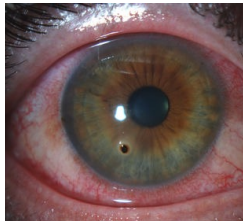
## Objectives

- 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/>

**Tylenol Extra Strength**  
acetaminophen

**Pregnancy/Lactation**

**Pregnancy**  
**Clinical Summary**  
Drug of choice for analgesic and antipyretic use during pregnancy; no known risk of fetal harm w/ short-term use based on human data.

**Lactation**  
**Clinical Summary**  
Drug of choice for analgesic and antipyretic use while breastfeeding; no known risk of infant harm based on human data; no human data available to assess effects on milk production.

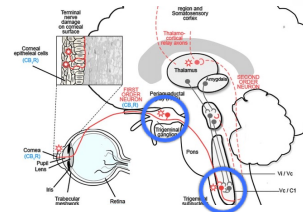
**Drug Monograph**

- Side Effects
- Uses
- Dosage
- Formulations
- Contraindications/Warnings
- Drug Interactions
- Adverse Reactions
- Pharmacokinetics
- Pharmacology
- Pharmacokinetics
- Alternatives
- Add to Medication Check
- Drug Calculator

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## Ocular Sensory Pathway

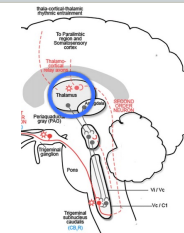
- *The simple approach*
- First order neuron
  - Nerve ending in the cornea → cell body in the trigeminal ganglion
  - Synapse in the subnucleus caudalis/upper cervical transition zone



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## Ocular Sensory Pathway

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

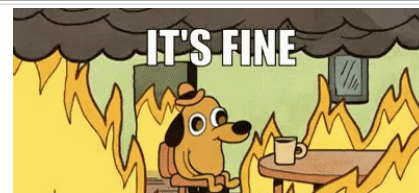


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## Ocular Sensory Pathway

- 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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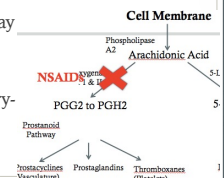
## NSAIDs

- 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- or history of stroke



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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; about \$100 without a coupon; approx. \$30-50 with
- **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 \$400

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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
    - \$290 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
- Bromsite (bromfenac sodium 0.075%)-2016
  - BID
  - Durasite vehicle
  - First NSAID to be approved for 'preventing ocular pain in patients undergoing cataract surgery'
  - \$195 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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**Acular (ketorolac 0.5% solution)**  
**Generic only; approved for tx of ocular allergy and treatment of inflammation following cataract surgery QID (\$50→\$20)**

*Or diclofenac 0.1%; BID*

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## Acetaminophen

- Antipyretic and analgesic effect-weak anti-inflammatory effect
  - Little to now effect on platelets or inflammation
    - But does increase 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
  - $\leq 30$ CrCL mL/min
- According to the Dietary Guidelines for Americans & NIAAA:
  - 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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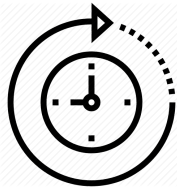
## Acetaminophen Toxicity

- 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 benzodiazepine, 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

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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 serotonin
- 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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## 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

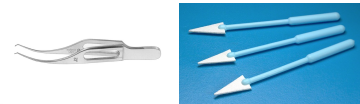
Neil Waldman, MD<sup>1</sup>; Ben Winrow, MBChB; Ian Densie, BSR; Andrew Gray, BA, BCom; Scott McMaster, DO; George Giddings, MBCh; John Meanley, MBChB

- 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

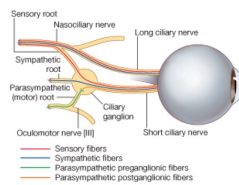
- Bandage contact lens
  - Protection from mechanical contact
  - Acuvue Oasys with hydraclear plus
  - Air Optix Night and Day Aqua
  - PureVision



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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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