Virtual CE with Blair Lonsberry, OD – Jan. 26, 2021

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Pain Management in Optometric Practice

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Agenda

- Addiction
- Opioid epidemic
- Pain management:
  - Topical
  - Orals

Addiction

- defined as as a chronic, relapsing brain disease that is characterized by compulsive drug seeking and use, despite harmful consequences.
- considered a brain disease because drugs change the brain structure and how it works.
- these brain changes can be long-lasting and can lead to the harmful behaviors seen in people who abuse drugs.

Why Do People Take Drugs

- To Feel Good:
  - Most abused drugs produce intense feelings of pleasure
- To Feel Better:
  - People who suffer from social anxiety, stress and depression begin the use of drugs to help lessen the feelings of distress
- To Do Better:
  - Some feel pressure to enhance their physical or mental edge
- Curiosity or because others are doing it:
  - Adolescents particular prone to this type of peer pressure

Why Do People Take Drugs

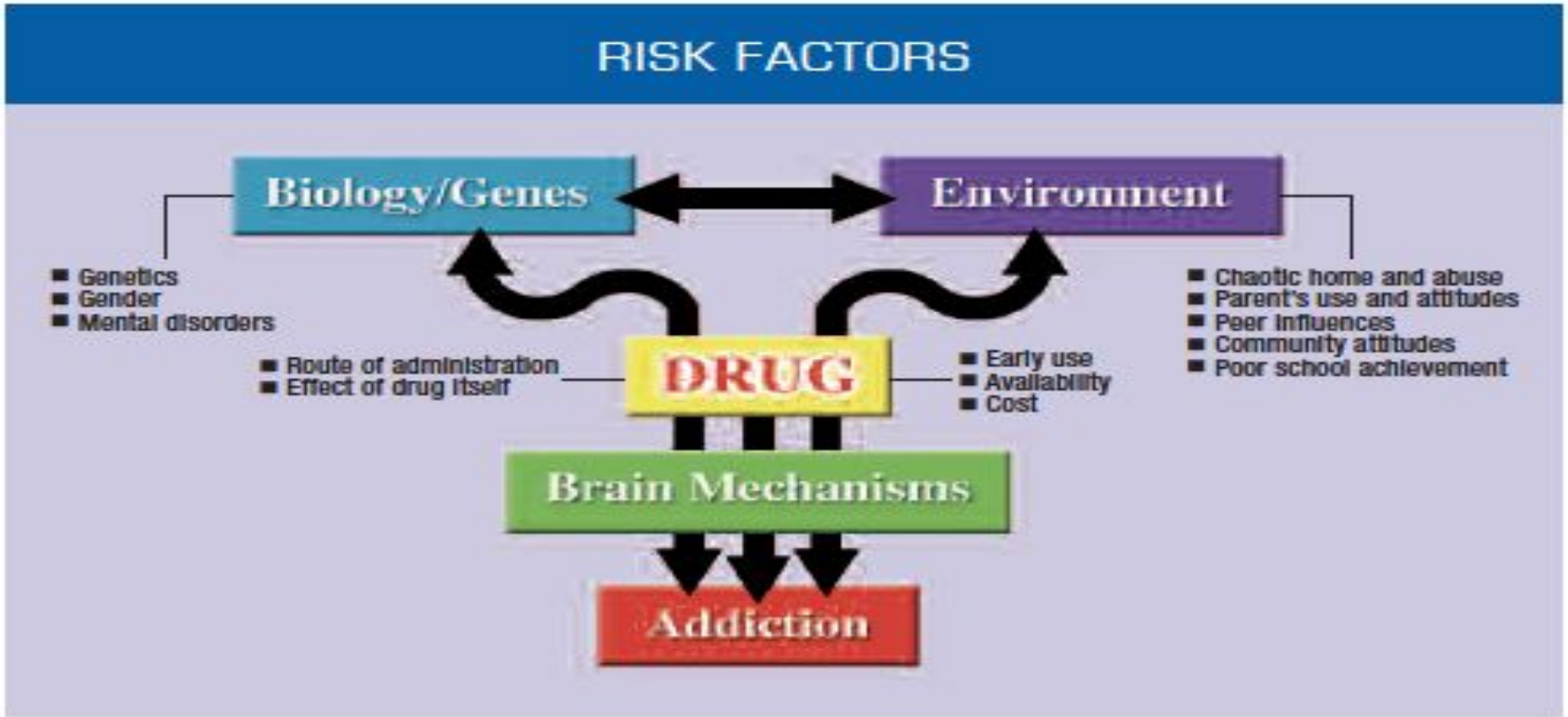
- Initial decision to take a drug is typical voluntary and they may perceive that first time as producing positive effects (and often believe they can control their use).
- With increased use of the drug, other pleasurable experiences lose their appeal and more drug is required to feel “normal” and the person quickly loses the ability for self-control (which is a hallmark of addiction).

Why Do People Take Drugs

- Brain imaging studies have demonstrated that people with addiction have physical changes in areas of the brain that are critical to judgment, decision making, learning and memory, and behavior control
- It is believed that these changes alter the way the brain works and may help explain the compulsive and destructive behaviors of addiction.

RISK AND PROTECTIVE FACTORS FOR DRUG ABUSE AND ADDICTION	
Risk Factors	Protective Factors
Aggressive behavior in childhood	*Good self-control*
Lack of parental supervision	*Parental monitoring and support*
Poor social skills	*Positive relationships*
Drug experimentation	*Academic competence*
Availability of drugs at school	*School anti-drug policies*
Community poverty	*Neighborhood pride*

National Institue of Drug Abuse: Drugs, Brains and Behaviour. The Science of Drug Addiction



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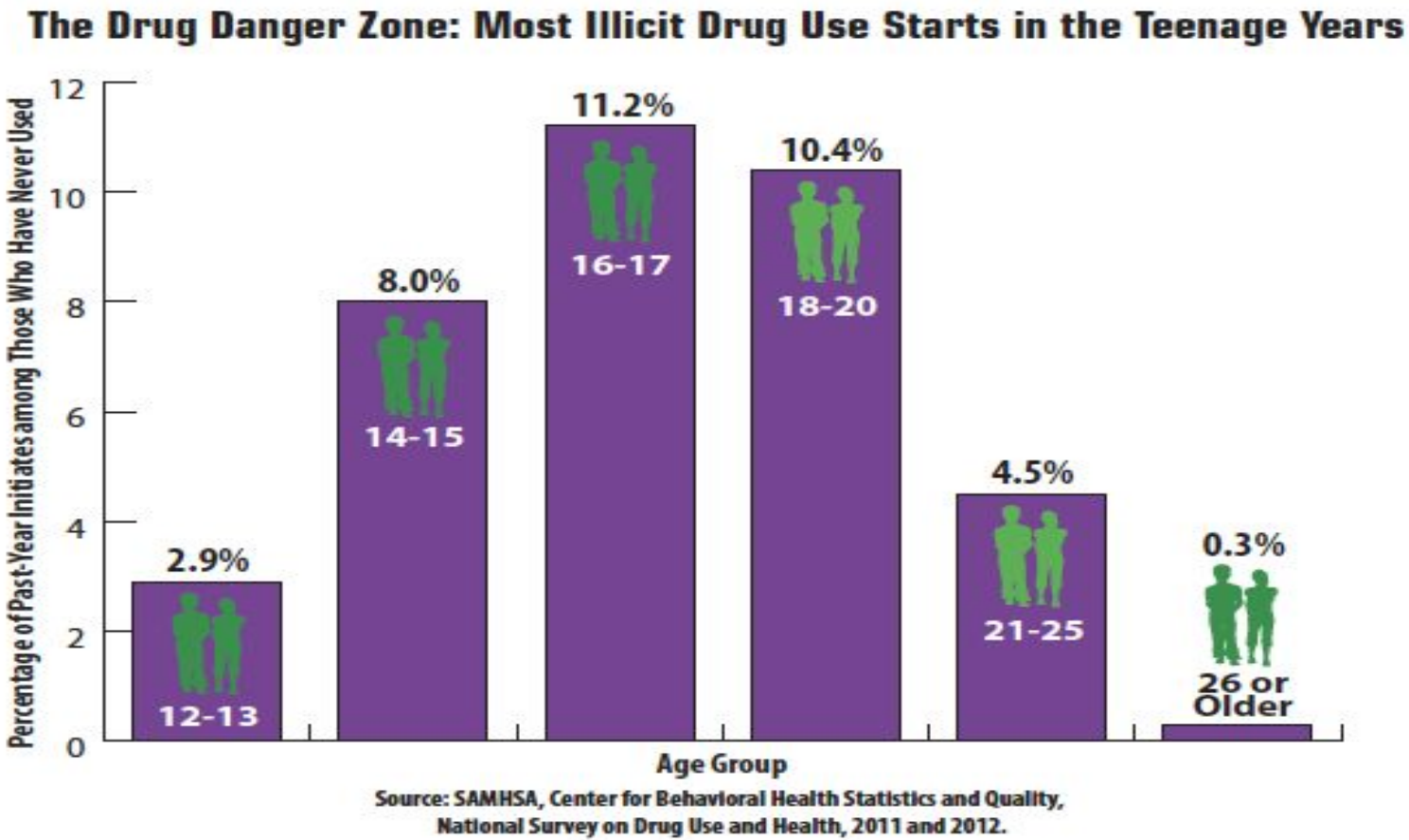
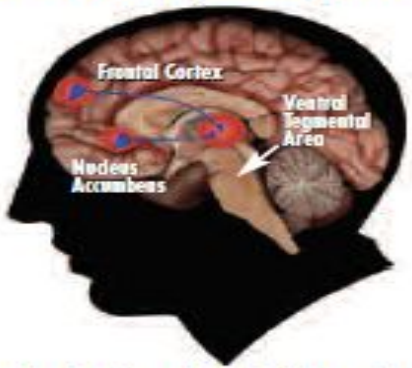


National Institute of Drug Abuse: Drugs, Brains and Behaviour. The Science of Drug Addiction

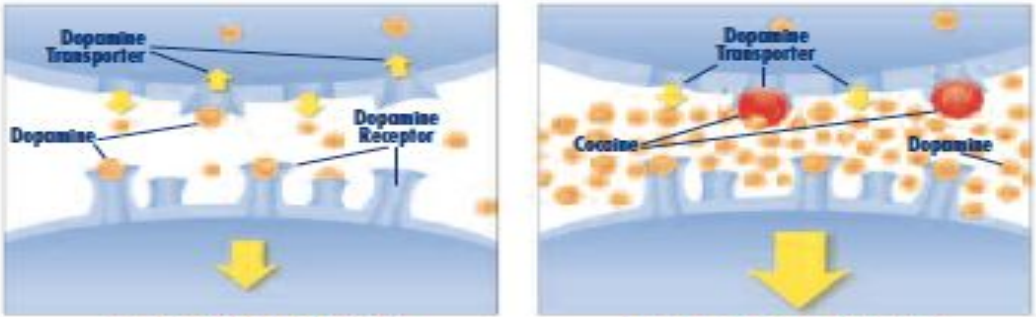
DRUGS OF ABUSE TARGET THE BRAIN'S PLEASURE CENTER

Brain reward (dopamine) pathways



These brain circuits are important for natural rewards such as food, music, and sex.

Drugs of abuse increase dopamine

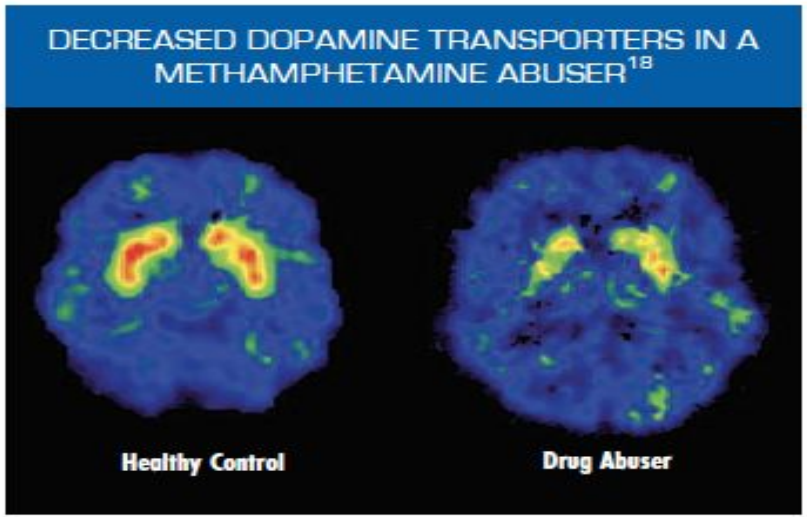


Typically, dopamine increases in response to natural rewards such as food.
When cocaine is taken, dopamine increases are exaggerated, and communication is altered.

National Institue of Drug Abuse: Drugs, Brains and Behaviour. The Science of Drug Addiction

Impaired Brain Function with Long Term Drug Abuse

- Long term drug use decreases the normal dopamine production or receptors making patients feel “flat”
- Patients’ require the drug in order to feel that high and in increased levels to obtain the previous “high”



National Institue of Drug Abuse: Drugs, Brains and Behaviour. The Science of Drug Addiction

Withdrawal

- The withdrawal syndrome may be very severe (except for codeine) and includes intense dysphoria (state of unease), nausea or vomiting, muscle aches, lacrimation, rhinorrhea (mucus discharge from the nose), mydriasis, piloerection, sweating, diarrhea, yawning, and fever.
- Beyond the withdrawal syndrome, which usually lasts no longer than a few days, individuals who have received opioids as analgesics only rarely develop addiction. In contrast, when taken for recreational purposes, opioids are highly addictive.
- The relative risk of addiction is 4 out of 5 on a scale of 1 = nonaddictive, 5 = highly addictive.

Prescription Drug Abuse

- Prescription medications, including opioid pain relievers (such as OxyContin® and Vicodin®), anti-anxiety sedatives (such as Valium® and Xanax®), and ADHD stimulants (such as Adderall® and Ritalin®), are commonly misused to self-treat for medical problems or abused for purposes of getting high or (especially with stimulants) improving performance

Opioid Abuse

- Opioid pain relievers are frequently abused by being crushed and injected or snorted, greatly raising the risk of addiction and overdose.
- there is a common misperception that because medications are prescribed by physicians, they are safe even when used illegally or by another person than they were prescribed for.

Opioid Abuse/Overdose

- The most common drugs involved in prescription opioid overdose deaths include:
  - Methadone (long acting opioid for heroin abuse)
  - Oxycodone (such as OxyContin®)
  - Hydrocodone (such as Vicodin®)
- Overdose rates were highest among people aged 25 to 54 years.
- Overdose rates were higher among non-Hispanic whites and American Indian or Alaskan Natives, compared to non-Hispanic blacks and Hispanics.
- Men were more likely to die from overdose, but the mortality gap between men and women is closing.

https://www.cdc.gov/drugoverdose/data/overdose.html

Opioid Abuse/Overdose

- Prescription opioids can be used to treat moderate-to-severe pain and are often prescribed following surgery or injury, or for health conditions such as cancer.
- there has been a dramatic increase in the acceptance and use of prescription opioids for the treatment of chronic, non-cancer pain, such as back pain or osteoarthritis, despite serious risks and the lack of evidence about their long-term effectiveness.

https://www.cdc.gov/drugoverdose/data/overdose.html

Opioid Abuse/Overdose

- Providers wrote nearly a quarter of a billion opioid prescriptions in 2013—with wide variation across states. This is enough for every American adult to have their own bottle of pills
- Studies suggest that regional variation in use of prescription opioids cannot be explained by the underlying health status of the population
- To reverse this epidemic, HCP need to improve the way we treat pain. HCP must prevent abuse, addiction, and overdose before they start.

https://www.cdc.gov/drugoverdose/data/overdose.html

Opioid Abuse/Overdose

- Research shows that some risk factors make people particularly vulnerable to prescription opioid abuse and overdose, including:
  - Obtaining overlapping prescriptions from multiple providers and pharmacies.
  - Taking high daily dosages of prescription pain relievers.
  - Having mental illness or a history of alcohol or other substance abuse.
  - Living in rural areas and having low income.

https://www.cdc.gov/drugoverdose/data/overdose.html

Opioid Abuse/Overdose

- Anyone who takes prescription opioids can become addicted to them
  - as many as one in four patients receiving long-term opioid therapy in a primary care setting struggles with opioid addiction.
  - In 2014, nearly two million Americans either abused or were dependent on prescription opioid pain relievers.
- Taking too many prescription opioids can stop a person's breathing—leading to death.

https://www.cdc.gov/drugoverdose/data/overdose.html

Opioid Abuse/Overdose

- Prescription opioid overdose deaths also often involve benzodiazepines.
- Benzodiazepines are central nervous system depressants used to sedate, induce sleep, prevent seizures, and relieve anxiety.
  - Examples include alprazolam (Xanax®), diazepam (Valium®), and lorazepam (Ativan®).
- Avoid taking benzodiazepines while taking prescription opioids whenever possible.

https://www.cdc.gov/drugoverdose/data/overdose.html

Preventing Opioid Abuse: PDMP

- A prescription drug monitoring program (PDMP) is an electronic database that tracks controlled substance prescriptions.
- PDMPs can help identify patients who may be misusing prescription opioids or other prescription drugs and who may be at risk for overdose.

https://www.cdc.gov/drugoverdose/data/overdose.html

Preventing Opioid Abuse: PDMP

- PDMPs improve patient safety by allowing clinicians to:
  - Identify patients who are obtaining opioids from multiple providers.
  - Calculate the total amount of opioids prescribed per day (in MME/day-morphine milligram equivalent).
  - Identify patients who are being prescribed other substances that may increase risk of opioids—such as benzodiazepines.

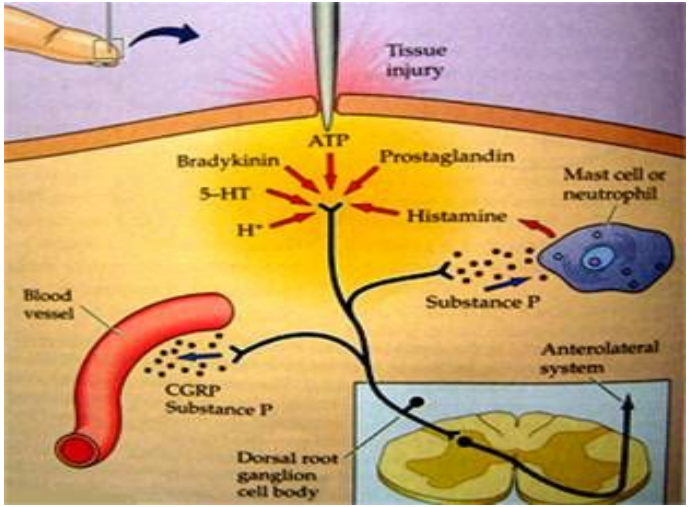
https://www.cdc.gov/drugoverdose/data/overdose.html

What if you find something suspicious in the PDMP?

- Patients should not be dismissed from care based on PDMP information. Use the opportunity to provide potentially life-saving information and interventions.
  - Confirm that the information in the PDMP is correct.
  - Assess for possible misuse or abuse.
  - Discuss any areas of concern with your patient and emphasize your interest in their safety.

https://www.cdc.gov/drugoverdose/data/overdose.html

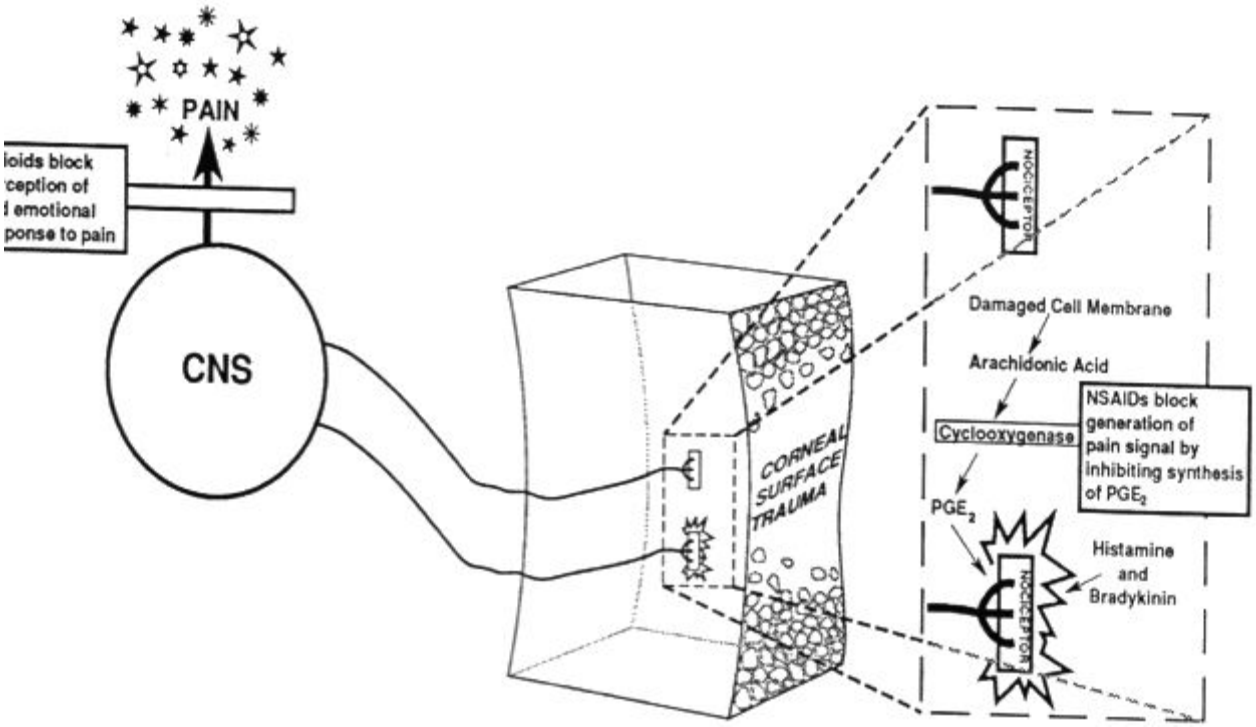
Pain Signal



- Pain occurs when specialized nerve endings in peripheral tissues (nociceptors) are stimulated.
  - Nociceptors exist in high levels in the eye and orbit.

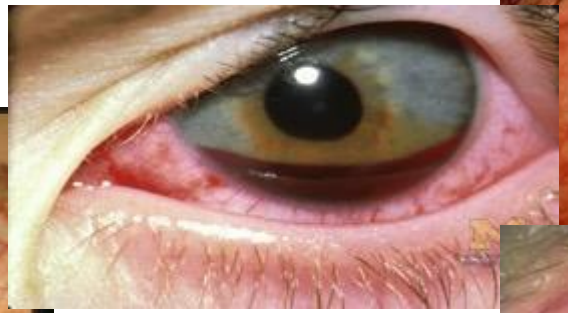
- Nociceptors are activated in response to mechanical stimulation (trauma) and chemical compounds such as serotonin, bradykinin, and histamine.
  - Prostaglandins and leukotrienes further sensitize the nerve endings to these mediators.

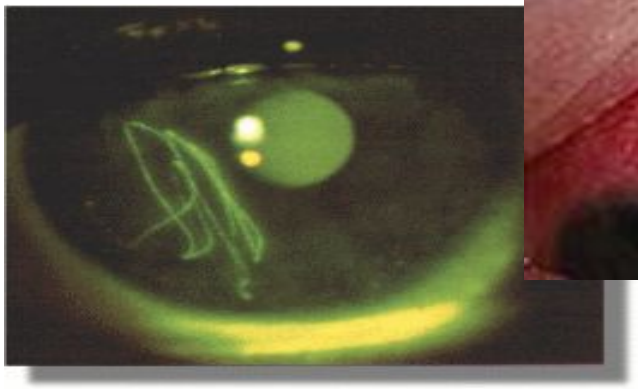
Pain



In the eye, the pain signal is then sent through the trigeminal nerve to the brainstem where they meet the nucleus and travel on to the somatosensory areas of the brain.

Ocular Pain

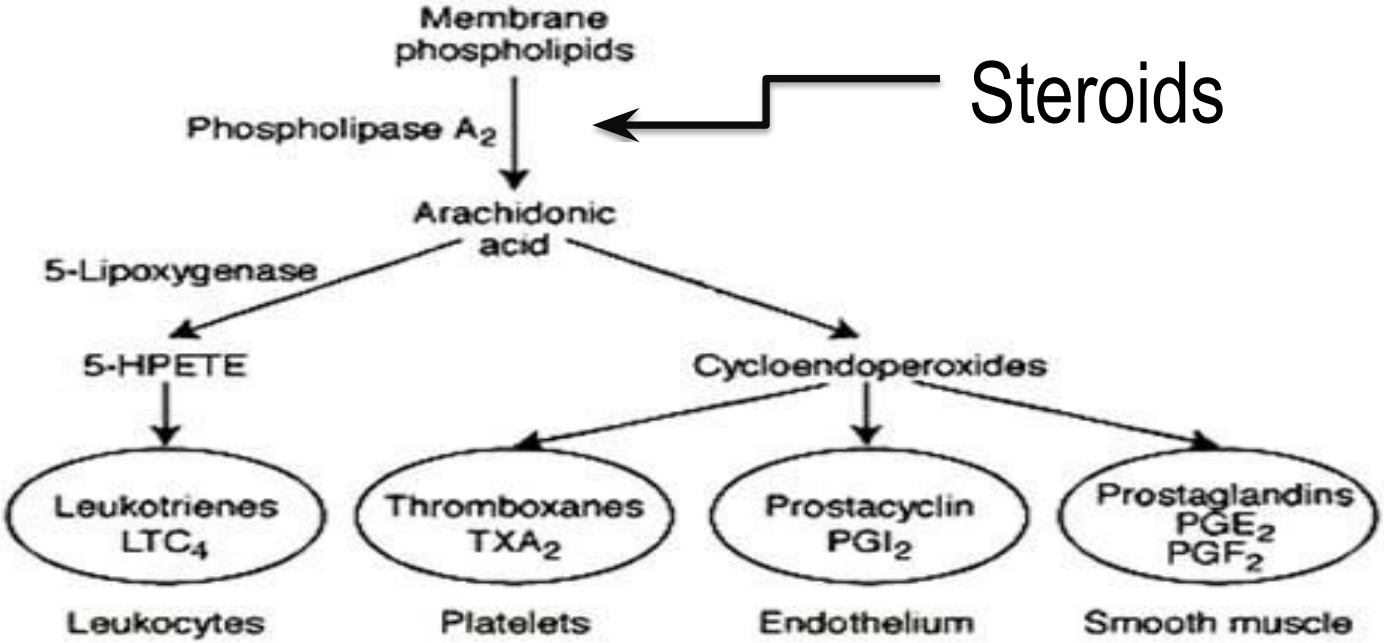




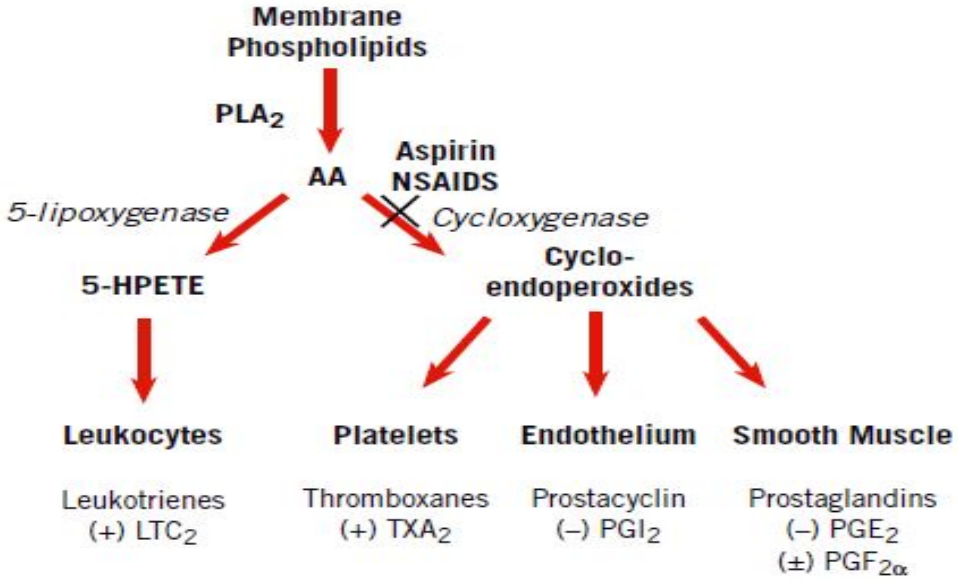
Inflammatory Cascade

- Steroids are the “Gold Standard” for stopping inflammation.
  - They are Non-selective in nature, unlike NSAID’s and act on multiple areas of inflammation such as:
    - Inhibit peripheral lymphocytes (T and B Cells) and macrophages.
    - Decrease amount of circulating eosinophils, basophils, and monocytes.
    - Inhibit activity of kinins.
    - Reduce the amount of histamine released from basophils.
    - Indirectly inhibit phospholipase A_2.

Steroids act at the beginning of the Arachidonic Acid Cascade.



NSAIDs

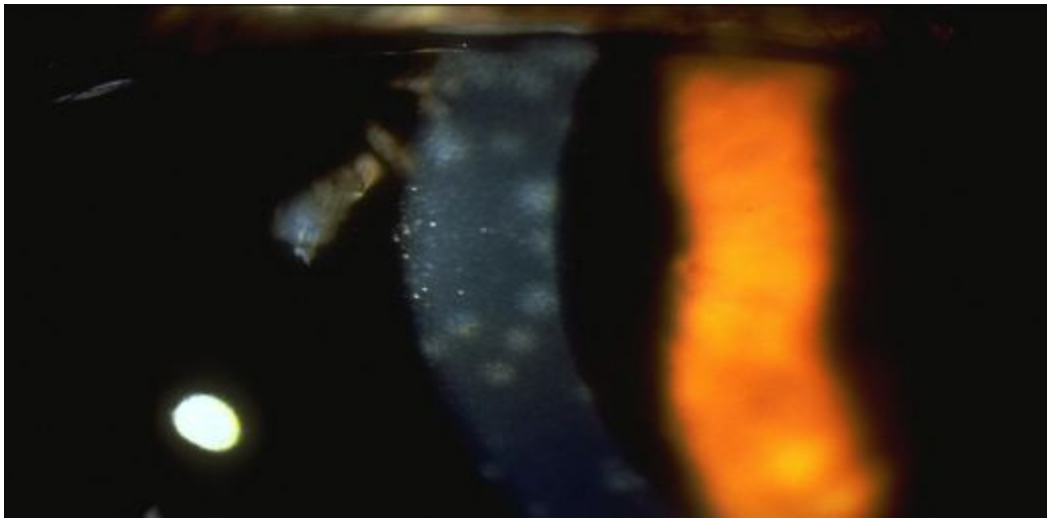


- Unlike steroids, NSAID's have <u>only</u> <u>one</u> mechanism for decreasing inflammation.
  - Inhibit the enzyme cyclooxygenase which produces prostaglandins, prostacyclins, and thromboxanes from Arachidonic Acid.

NSAID’s vs. Steroids

- NSAID’s are very successful at limiting inflammation systemically, but topically are less successful due to the lack of effect on the lypoxygenase pathway.

Leukotrienes
attract white blood
cells = Infiltrates.



Cyclooxygenase Pathway

- NSAIDs act only on inflammation through the COX pathway blocking the formation of:
  - Prostaglandins
    - Major inflammatory mediators found in virtually all tissues of the body – act locally as chemical mediators.
  - Thromboxanes
    - Promotes platelet aggregation and causes vasoconstriction
  - Prostacyclins
    - Inhibits platelet aggregation and causes vasodilation.
- There are two main enzymes involved: COX 1 and COX 2.

Cyclooxygenase Enzymes

COX 1

- Stimulated continuously by normal body physiology
  - Major player involved in secretion of mucous in the stomach and controlling blood flow to the kidneys.

COX 2

- Induced as the result of an immune response to cause higher levels of prostaglandins.

NSAIDs: Cyclooxygenase Pathway

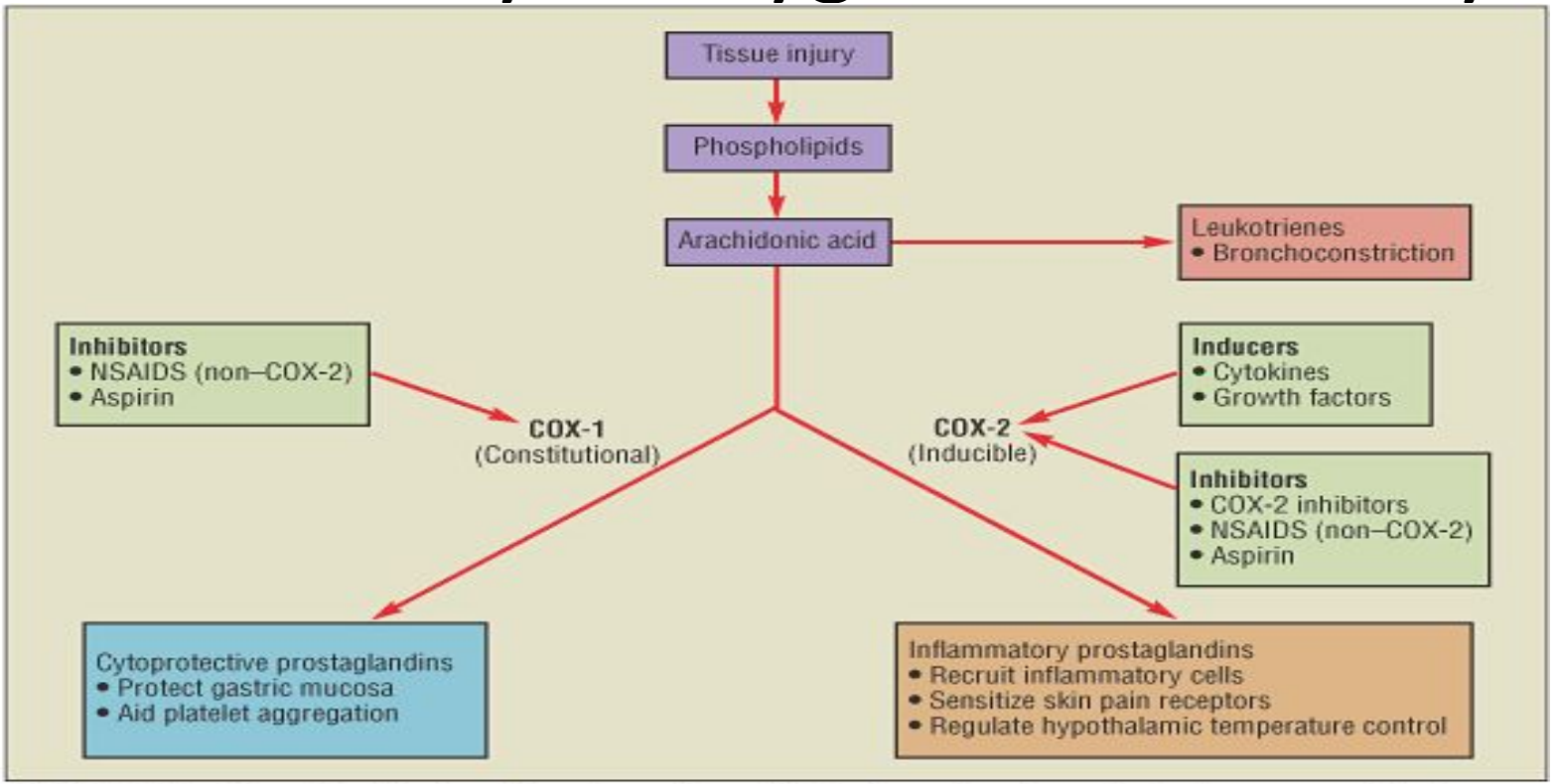


FIGURE 1. Algorithm of the biochemical pathway shows that the formation of prostaglandins occurs via both cyclooxygenase enzymes (COX-1 and COX-2).

Products of the COX 2 Pathway

- The COX 2 Pathway is responsible for the formation of inflammatory prostaglandins.
  - These prostaglandins play a role in many ocular conditions:
    - Postoperative inflammation
    - Uveitis
    - Allergic Conjunctivitis
    - Cystoid Macular Edema
  - They are also responsible for inducing miosis through sphincter contraction independent of cholinergic stimulation.

NSAID's also have other properties that make them useful in optometry.

ANALGESIC

NSAID's are primarily used for post-operative care of cataract surgery patients. However, additional uses include following FB removal or corneal abrasions as pain management.

NSAID's also act as antipyretics, but fevers are rarely a big concern in optometry.

Analgesic Medications

- Three principle categories of pain relief are seen:
  - Peripherally Acting agents
    - Act on the peripheral pain receptors and prevent sensitization and discharge of the nocireceptors
    - Ex) NSAIDS
  - Anesthetic Agents
    - Interrupt the pain signal between the peripheral source and the CNS target
    - Ex) Proparacaine
  - Centrally Acting Agents
    - Interact with specific receptors in the CNS to interrupt the pain message and its emotional responses.
    - Ex) Narcotics

Topical NSAID’s

Flurbiprofen 0.03% (Ocufen)

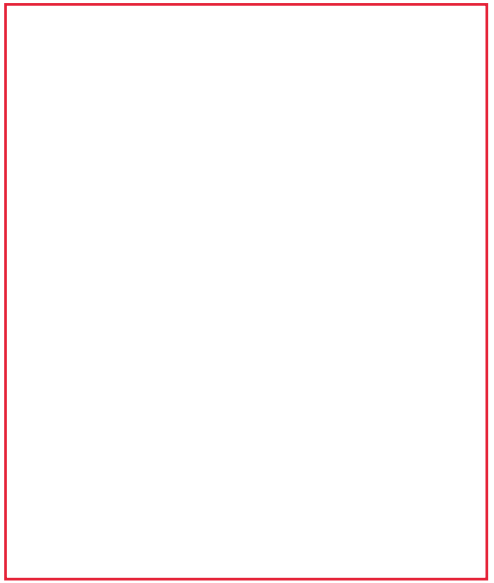
- First FDA approved topical ophthalmic NSAID.
- FDA indication: Inhibition of intraoperative miosis due t prostaglandins.
- The first topical to begin being used for inflammation leading to macular edema and dry eye – largely replaced now due to better options.
- FYI: Another early NSAID used for cataract surgery is Suprofen (Profenal).

Ketorolac tromethamine 0.5% (Acular)

- Solution available from Allergan or as a generic.
- FDA Labeling for:
  - Ocular itching due to seasonal allergic conjunctivitis
  - Post-op inflammation after cataract extraction
  - Dosage: 1 drop QID
- Major Pitfall:
  - High level of stinging upon instillation
- Corneal effects: May cause keratitis; continued use may cause severe corneal adverse effects, including corneal thinning, erosion, perforation, or ulceration; may result in loss of vision. Discontinue use in patients with evidence of corneal epithelial damage.

Ketorolac tromethamine 0.4% (Acular LS)

- Equal efficacy to Acular, without the sting.
- Most widely prescribed topical NSAID.
- FDA Labeling:
  - Reduction of ocular pain and discomfort following corneal refractive surgery.
    - Dosage: 1 drop QID for up to 4 days following surgery.
- Approved for patient 3 years +



Acuvail (Ketorolac 0.45%)

- FDA Approval in 2009
  - Very Expensive for Patient Use.
- Formulated in PF vials for use in post operative cataract surgery.
- Acuvail is formulated at pH 6.8, enabling de-ionized drug delivery on the corneal surface.
- Contains carboxymethylcellulose, a viscous molecule that enables the drug to adhere to the ocular surface.
  - **Dosage: BID X 2 weeks following surgery – start one day prior.**

Diclofenac sodium 0.1% (Voltaren)

- Voltaren is indicated for the treatment of postoperative inflammation:
  - Cataract Extraction: 1 drop QID beginning 24 hours after surgery and continuing for 2 weeks following
  - Corneal Refractive Surgery: 1-2 drops of prior to surgery and 1-2 drops within 15 minutes and continued QID for up to 3 days.

- Available brand name and generic.
  - Bottle Size: 2.5 and 5 mL

Major stinging as well!

Voltaren and Refractive Surgery

- Voltaren has been shown to inhibit the adherence of Staphylococcus epidermidis to soft contact lenses.
  - This is especially important during PRK when patients are put in bandage contact lenses to help control pain.
- The topical NSAIDs have been shown to have better pain management for these patients than oral analgesics.

Bromfenac 0.09%

- Originally FDA approved in 2005 as Xibrom for BID Dosing.
  - Approved for postoperative cataract surgery pain and inflammation.
- In 2010, ISTA received approval for once daily dosing and changed the name to Bromday.
  - ISTA was then sold to Bausch and Lomb.
- In 2012, a generic version of bromfenac 0.09% became available – this is the same medication, but is dosed BID as Xibrom previously was.

Bromfenac 0.07% (Prolensa)

- FDA approved in April 2013.
- 22% less medication than Bromday, but a lower pH of 7.8 making it more bioavailable.
- Solution - Available in 1.6 and 3 mL bottles from Bausch and Lomb.
- Pregnancy Category C.
- Dosage: One Drop Daily

Bromfenac 0.075% (Bromsite)

- FDA approved in November 26, 2016 by Sun Pharmceuticals.

- BromSite™ is nonsteroidal anti-inflammatory drug (NSAID) indicated for the treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery..
- approved to prevent ocular pain and treat inflammation in the eye following cataract surgery.

- Dosage: One Drop twice daily starting a day before surgery and 2 weeks after

Nepafenac 0.1% (Nevanac)

- FDA labeling is only for the treatment of pain and inflammation following cataract surgery.
- Manufactured by Alcon and sold in 3 mL bottles.
- Only NSAID that is a suspension.
- Dosage: TID beginning at one day prior to surgery and continuing for 2 weeks.

~$120 for 3 ml

Nepafenac 0.1% (Nevanac)

- First prodrug NSAID.
  - Hydrolyzed to amfenac in the AC.
  - This provides enhanced intraocular concentrations over the other topical NSAID's.

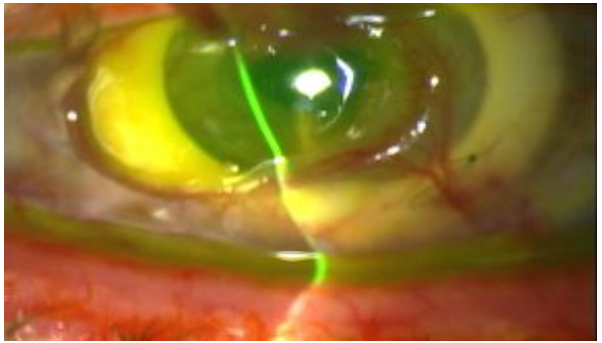
- Using Animal Models has been shown to inhibit prostaglandin synthesis in the retina and choroid.

Nepafenac 0.3% (Ilevro)

- FDA Approved in 2013.
  - Use for treatment of pain and inflammation associated with cataract surgery.
- Dosage: 1 Drop Daily
- Suspension that must be shaken.

Major Side Effect of Topical NSAID's

- Corneal Melt
  - Must use extreme caution in eyes with epithelial compromise.
    - NSAID's will delay wound healing (not quite to the extent as steroids, but still increase chance for infection).
    - "Melting" Ulcers will progressively take over the entire cornea.
  - Most commonly seen with generic diclofenac.
    - Has also been reported 3 times in Japan with Xibrom usage.



Side Effects of Topical NSAID's

- **Minor Side Effects:**
  - Burning and Stinging
  - Conjunctival hyperemia
  - Corneal SPK and Blurred Vision
  - Sub-epithelial Infiltrates

- **Avoiding Problems:**
  - Avoid chronic long-term use
  - Absolutely avoid in "sick" corneas…degens, Fuch's, etc

Ocular Conditions Treated with NSAID's

- Incidents Involving Corneal Induced Pain:
  - Corneal abrasions
  - Concurrently in office with Betadine for the treatment of EKC
  - Pre/Post foreign body removal
  - Post anterior stromal puncture

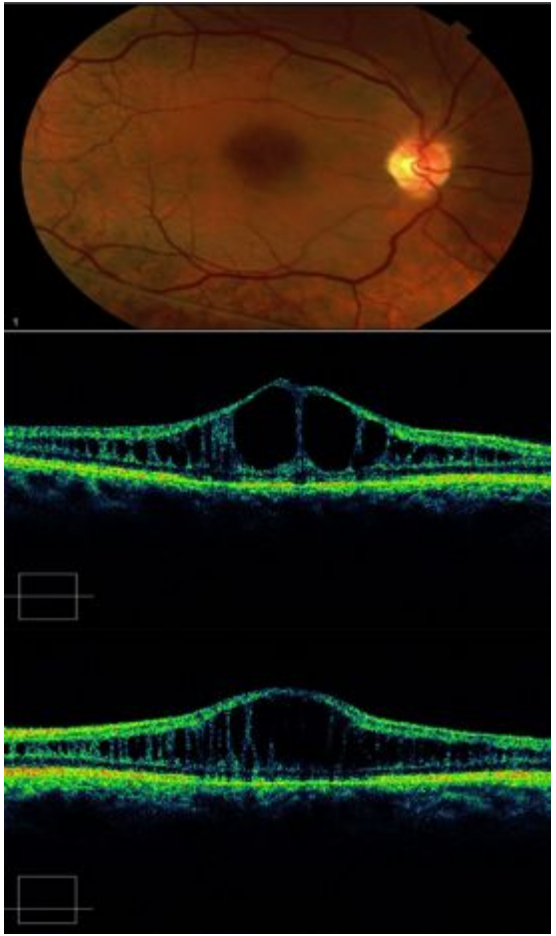
  - Pearls for Use:
    - Limit use to in office or less than 1 week to avoid corneal melt.
    - Stick to recommended FDA approved dosages.

Ocular Conditions Treated with NSAID's

- Active Ocular Inflammation:
  - Only prescribe if steroids are contraindicated and avoid using for more than 1 week.
  - Can be added to steroids to get a synergistic effect on inflammation.
    - Allergic conjunctivitis
    - Supplemental to steroids in treating recalcitrant uveitis
    - Supplemental to oral NSAIDs in treating scleritis
    - Treating and/or preventing inflamed pterygia and pingueculae

NSAID's and Macular Edema

- Cataract surgery results in the release of prostaglandins which breakdown the blood-aqueous barrier and move into the posterior pole.
- Once in the posterior pole they increase vascular permeability and breakdown the blood-retinal barrier resulting in macular edema.



NSAIDs and Ocular Therapy

- “Off-Label” use in preventing and treating macular edema.

- Dosage often depends on clinical picture and operating surgeon:
  - Recommended Pre-Treatment: 1-3 days in routine patients and up to 1 week in patients at risk.
  - Recommended Post-Treatment: 4 weeks for routine patients. May take 6-12 weeks in patients at risk.

Oral Pain Management

Pain Management: Oral Analgesics

- Conditions potentially requiring us of oral analgesics:
  - Corneal ulcers
  - Herpes simplex/zoster
  - Post-surgical
  - Trauma
  - Thermal burns

Managing Pain

- NSAID's and Aspirin are not the only mechanisms optometrists can use to help manage pain in our patients.
  - **Peripherally Acting Agents**: Act on the peripheral pain receptors and prevent sensitization and discharge of the nocireceptors.
    - Ex) NSAIDS, Salicylates (ASA), and Acetaminophen (APAP)
  - **Anesthetic Agents**: Interrupt the pain signal between the peripheral source and the CNS.
    - Ex) Proparacaine
  - **Centrally Acting Agents**: Interact with specific receptors in the CNS to interrupt the pain message and its emotional responses.
    - Ex) Narcotics (possibly Tylenol to a small extent)

Oral Analgesics: Guidelines

- Make the proper diagnosis first (ie. Don’t prescribe without knowing what you are prescribing for!)
- Treat the underlying cause for the pain
- Treat the pain at presentation..don’t wait!
- Treat pain continuously over a 24 hour schedule
- Non-prescription drugs should be first choice and tend to be low cost
- Treat patients with the simplest and safest means to alleve pain

Oral Analgesics: Guidelines

- Mild to moderate pain is often successfully treated with acetaminophen or NSAID
- Moderate to severe pain is best treated with opioid analgesics
- Adjunctive treatments are very valuable in pain management:
  - “RICE”: rest, ice, compression and elevation
  - Mydriatic/cycloplegic useful for ocular pain
  - Bandage CL or pressure patch

Systemic NSAID's

- NSAID's are the drug of choice for treating mild to moderate ocular pain.
  - Very beneficial for treating systemic inflammation as well.

- All NSAID's are rapidly absorbed from the GI tract, highly bound in the plasma, and capable of crossing the blood-brain barrier.

- Exhibit a "ceiling effect" – there is a dosage beyond which no further analgesia occurs.
  - Produce no tolerance or dependence, increasing their safety profile.

- Variability exists in patient responses to NSAID's
  - No definitive recommendation on treatment can be given.
    - If one NSAID does not work – TRY ANOTHER.

Major Classes of NSAID's

- Commonly Used:
  - Aspirin (ASA) and Other Salicylates
  - Propionic Acids
  - Indole acetic Acids
  - COX-2 Inhibitors

- Rarely Used NSAIDs in Optometry Include:
  - Oxicam Derivatives
    - Piroxicam (Feldane) and Meloxicam (Mobic)
  - Fenamates
    - Meclofenamate (Meclomen)
  - Acetic Acids
    - Ketorolac (Toradol) and Etodolac (Lodine)

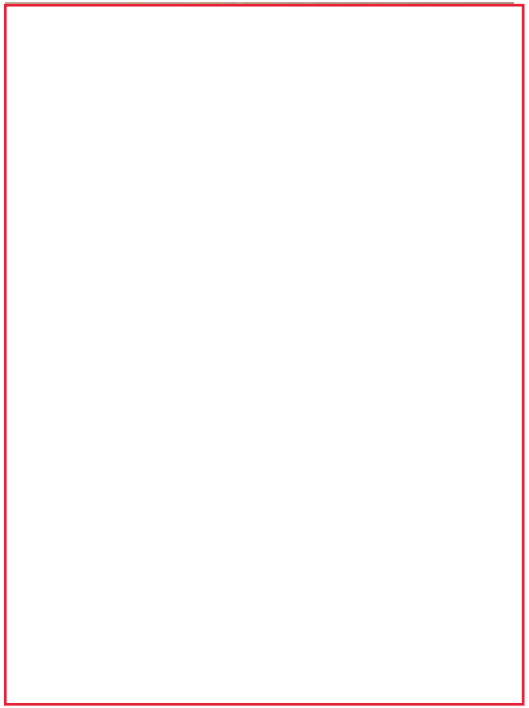
NSAID's

- NSAID selection depends on multiple factors:
  - Clinical experience
  - Patient convenience or preference
  - History of favorable analgesic effect
  - Side effects
  - Cost

- The medications with the most effective analgesia are generally those with rapid onset of action.

Aspirin (ASA)

- Weak organic acid.
- Oldest non-opioid analgesic available today.
  - Reduces pain by inhibiting synthesis of the prostaglandin E_2 by irreversible acetylation and inactivation.
  - Has some CNS effect on pain by acting on the hypothalamus.
- Very good anti-inflammatory and antipyretic properties.



Aspirin

- Commercially available in multiple formulations and dosages.
  - Formulations include controlled-release tablets, enteric coated, etc.
    - Add buffers to help increase GI tolera
  - Adult Dosage: 325 – 650 mg every
    - Do not exceed 4 g/day.

Aspirin

- Additional Analgesic Use: Beneficial for use with narcotics in the treatment of severe pain.

- Most Common use of ASA: Inhibit platelet aggregation in patients with history of heart attacks and heart surgery.
  - ASA inactivates COX irreversibly, causing prolonged bleeding time of 12 – 15 days or the entire life cycle of the platelet.

Aspirin

- Largely replaced as treatment for pain associated with inflammation by the other classes of NSAID's due to the frequent side effects.
  - GI Distress: Inhibit prostaglandin synthesis and the production of a mucous lining on the stomach leading to increased gastric acid secretion.

- Symptoms include:
  - Dyspepsia (indigestion)
  - Nausea
  - Vomiting
  - Abdominal Cramping
  - Ulcerations/Bleeding/Perforation

Additional Aspirin Side Effects

- Aspirin Hypersensitivity
  - Results in:
    - Respiratory problems
    - Type 1 hypersensitivity reactions such as itching and angioedema. (Occurs within 1 hour of ingestion).
  - ASA intolerance occurs most commonly in asthmatic patients (Up to 40% of steroid-dependent asthmatics).

- CNS effects including Headache, Tinnitus, dizziness, and deafness may occur.

ASA Contraindications

- **Children/Teenagers following a viral infection.**
  - Associated w/ Reye's syndrome (post-infectious encephalopathy).
- History of upper GI disease
- History of adult onset asthma
  - Can trigger attacks of severe bronchoconstriction and nasal congestion.
- Avoid in patients with bleeding disorders
- Avoid in patients who have had recent intraocular surgeries
- Avoid in patients who consume more than 3 alcoholic beverages in a day.
- Should not be used during pregnancy.
- Chronic renal or hepatic disease.

2019 Aspirin Recommendations

- American College of Cardiology:
  - *Aspirin should be used infrequently in the routine primary prevention of ASCVD because of lack of net benefit.*
  - low-dose aspirin should not be routinely given as a preventive measure to adults 70 years and older or to any adult who has an increased risk of bleeding

Acetaminophen

- Mechanism of Action is not well understood.
  - Possibly some CNS component
  - Very weak inhibitor of prostaglandin synthesis

- One of the most commonly used analgesics for mild to moderate pain.
  - Equal analgesic properties to ASA unless associated with inflammation, where it is less effective.

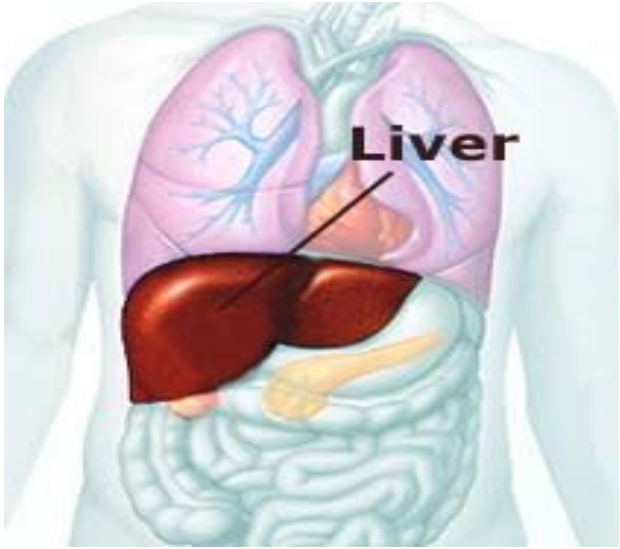
Take home: Good for pain; Good for fever;
No effect on inflammation

Acetaminophen

- Typical Adult Dosage (FDA Based):
  - 650 mg every 4 - 6 hours for Regular Strength (2 X 325)
    - Cannot take more than 10 caplets in 24 hours.
  - 1000 mg every 6 hours for Extra Strength (2 X 500)
    - Cannot take more than 6 caplets in 24 hours.
  - 1300 mg every 8 hours for Extended Release (2 X 650)
    - Cannot take more than 6 capsules in 24 hours.
- Daily dose of Extra Strength Tylenol should not exceed 3 grams!
  - This has been recently changed from 4000 mg which can be done with doctor approval.
- Should only be used for short term therapy
- Exhibits a ceiling effect, like NSAIDs and ASA.

Acetaminophen Side Effects

- Rare if used as recommended.
- 13 – 25 g is lethal, but > 7.5 grams leads to serious liver toxicity and possible death.
- Recommended dosages can cause liver damage in patients with pre-existing impairment.



Acetaminophen Contraindications

- Must be used in caution in all patients with chronic alcoholism or with preexisting liver impairment.
  - Should also avoid if using medications such as barbituates, phenytoin, or rifampin due to toxicity.

Dangers of Acetaminophen

- Acetaminophen overdose is the leading cause of liver failure in the U.S.
  - It sends 56,000 people to the emergency room annually and causes approximately 400 deaths yearly.

- Acetaminophen is used in so many products, people are often unaware that they are taking it, leading to more overdoses.
  - Combined with agents to get wide range of symptom coverage.
    - Antihistamines such as diphenhydramine – Tylenol PM
    - Diuretics such as Pyrilamine maleate – Midol Complete
    - Cough Suppressants such as Dextromethorphan - Nyquil

Acetaminophen in Combination

- Actifed
- Alka-Seltzer Plus
- Benadryl
- Butalbital
- CoGesic
- Contac
- Darvocet
- Excedrin
- Fioricet
- Lortab
- Midrin
- Norco

FDA Labeling

- FDA requires all acetaminophen products to carry a warning that individuals who consume more than three alcoholic beverages daily consult their doctors before taking the OTC medications.
  - Also seen with ASA and NSAIDs.

- As of April 2010 the FDA required labeling changes to further indicate the dangers of APAP, ASA, and NSAID use and that the medications be written clearly in **bold** print.

Combining Meds for More Severe Pain Relief

- Acetaminophen and Aspirin are often combined with each other and various agents to increase their analgesic effect.
  - Frequently seen in combination with narcotic analgesics.
  - Caffeine is also commonly used, especially in the treatment of migraines.
    - Excedrin Migraine
      - Acetaminophen 250 mg
      - Aspirin 250 mg
      - Caffeine 65 mg

Propionic Acids

- Most commonly used and largest class of NSAIDs.
- MOA is similar to ASA.
  - Metabolized in the liver and excreted in the urine.
- Superior analgesic efficacy over ASA with less incidence of side effects.
- Includes: Ibuprofen, Naproxen, Ketoprofen, Oxaprozin, and Fenoprofen.

Ibuprofen

- Adult analgesic dose: 200-400mg q4hours
  - Maximum Dosage: 2400 mg/day for pain (approved for 3200 mg/day in arthritis treatment)

- OTC: 200 mg tabs
- Rx: 300, 400, 600, 800mg tabs
  - Can prescribe 800 mg q8hrs

- Peak levels 1-2 hours

- Most renal toxic of all the NSAID's

- Brand Names: Motrin, Advil, and Nuprin

Consider Combining APAP with NSAID's for Mild to Moderate Pain Relief

1:00 pm: Two 325mg Tylenol

3:00 pm: Two 200mg Ibuprofen

5:00 pm: Two 325mg Tylenol

7:00 pm: Two 200mg Ibuprofen

Alternated every 2 hours while awake

- Each medication is q 4 hours.

Naproxen and Naproxen Sodium

- Sodium speeds up the absorption over Naproxen (Naprosyn) alone causing it to be used more frequently.

Naproxen Sodium

- Type of Medication Determines Dosage (This is for Naproxen Sodium):
  - OTC: 220mg tablets (Aleve)
  - Rx: 275 and 550 mg tablets (Anaprox and Anaprox DS)

- Adult Dose:
  - OTC: 220 or 440 initial dose followed by 220 mg q 8 – 12 hours.
  - Rx: 550 initial dose, followed by 275mg q6-8h or 550mg q12hours.
    - Maximum Dose: 1375mg/day.

Ketoprofen

- Adult dose:
  - 50 mg q 6-8 hours for pain
  - 50 – 100 mg TID for inflammation
- Maximum Dose: 300 mg/day
  - Limited to 7-14 days
- OTC: 12.5mg (No longer Available)
- Rx: 50, 75, 200ER mg capsules

Indole Acetic Acids: Indomethacin

- Rx Only
- Available as 25, 50, 75 ER, and IV
- Adult Dosage: 25 - 50 mg TID
- Mainly used as a short term anti-inflammatory especially for conditions that do not respond to less toxic NSAIDS.
  - Indomethacin has a very high level of intolerance compared to other NSAID's.
- Available in Canada as a topical Ophthalmic Suspension (Indocid).

Systemic NSAID Uses: Scleritis

- NSAID's are Treatment of Choice (?)
  - Ibuprofen 400-600 mg QID
  - Naproxen 250-500 mg BID
  - Indomethacin 25 mg TID

- Try three NSAIDs before considering treatment to be a failure and moving on to systemic steroids (?)

Side Effects of Oral NSAID's

- Very similar to the side effect profile of ASA.
  - GI Effects
    - Profile is dependent on COX selectivity.
    - Consider using PPI's while treating with NSAID or ASA.
  - CNS problems such as headache, confusion in the elderly, and loss of short-term memory.
  - Inhibit platelet function
    - Only while a high concentration exists in the body.
  - Risk of triggering asthma attacks is less with NSAID's than what is found with ASA.

Side Effects of Oral NSAID's

- NSAID's are excreted from the body via urine. Must monitor kidney function.

- NSAID's block prostaglandins to the kidney which causes renal blood flow to decrease and increases the retention of sodium and fluid.
  - Risk factors for kidney damage include:
    - Dehydration
    - Hypertension
    - Congestive Heart Failure
    - Use of ACE Inhibitors
    - Advanced Age
  - This will effect Cardiovascular homeostasis – can exacerbate heart failure.
    - NSAID's can cause hyperkalemia and have been linked to cardiac arrest in patients at risk.

NSAIDS Black Box Warning

- BLACK BOX WARNING:
  - May increase the risk of serious thrombotic events, MI, and stroke.
  - Increase risk of serious GI adverse effects such as bleeding, ulcer, and perforation.

NSAID Drug Interactions

- NSAID's are well known to displace medications from sites on plasma proteins and alter their metabolism/excretion.

- NSAID's inhibit platelet aggregation and can significantly increase the risk of bleeding if used along with anticoagulants such as warfarin.
  - Naproxen actually displaces the warfarin from plasma proteins causing increased serum levels and elevated prothrombin times.

- Antihypertensive agents such as ACE inhibitors, diuretics, and beta blockers may have decreased effectiveness.
  - Interaction is highly variable and difficult to predict.

Contraindications to NSAIDs

- Avoid in:
  - Pregnancy (especially the late trimesters)
  - Active Peptic Ulcer Disease
  - Cross Sensitivity to ASA
  - Previous Hypersensitivity to NSAIDs
  - Chronic Renal Insufficiency

- At Risk Patients Include:
  - Dehydration
  - HTN or CHF
  - Use of ACE Inhibitors
  - Advanced Age

Cox-2 Inhibitors

- Selective agents for only COX-2 designed to protect the GI system from the side effects seen with NSAID's.

- Major agent available on the market is Celecoxib (Celebrex).
  - Other agents Valdecoxib (Bextra) and Rofecoxib (Vioxx) were removed from the market due to increased risk of heart attacks and strokes.

- It is approved for the treatment of osteoarthritis and rheumatoid arthritis.
  - Dosage: 100 mg BID or 200 mg daily

COX-2 Selective Agents

- Must avoid use in patients with cardiovascular risk factors.
  - Studies have shown that the greater the Cox-2 selectivity the greater the risk for hypertension from NSAID's.

- Celebrex has still been shown to cause GI bleeding in patients at risk and should not be consider "safe".

Oral Analgesics: Guidelines

- Never exceed maximum recommended dosages:
  - ASA: 8 grams/day
  - Acetaminophen: 4 grams/day
  - Ibuprofen: 1200 mg/day OTC and 2400 mg/day prescription
  - Codeine: 360 mg/day

FIGURE 2. Case of herpes zoster ophthalmicus

Photo/MN Oxman, University of California, San Diego

Anesthetics

- Topical Ocular Anesthetics should not be used for pain relief outside of the clinical setting.

- However, topical skin creams do have one possible use in optometry – treatment of skin lesions caused by herpes zoster.
  - Cannot be used on open wounds – only once scabs have formed.

Anesthetic Agents for Pain Relief

- OTC Option: Zostrix Cream (Capsaicin)
- Prescription Option: EMLA Cream (lidocaine 2.5% and prilocaine 2.5%)

- Must use caution near the eye.

Narcotic Analgesics

- Also known as:
  - Opiates (Any agent derived from opium)
  - Opioids (Compounds that possess morphine-like analgesic properties)

- Morphine is the standard med used to compare the effects of all other opioids.

Opioids Mechanism of Action

- Mechanism of Action is binding to various brain, brainstem, and spinal cord receptors and mimicking the endogenous opioid peptides (Endorphins).
  - Alter the sensation of pain and the subjective distress/emotional component of pain.

- Act as agonists, partial agonists, or mixed agonist-antagonists.

Opioids Information

- Drug of first choice for the treatment of **severe** acute pain.
  - Block the body's natural protective mechanism for protecting areas in pain – thus never prescribe unless you know the direct cause of the pain.

- Often administered in combination with acetaminophen or aspirin to enhance the analgesic effect.
  - FDA recommended in 2011 that all prescription narcotics containing acetaminophen standardize and limit the dosage to 325 mg.
    - This is to be slowly phased in over three years (just required in January 2014).

Opioids Side Effects

- Side Effects are very hard to predict because opioids can cause CNS depression or stimulation.
- CNS Side Effects
  - Dizziness, lightheadedness, sedation, and drowsiness are the most common.
  - Mood elevation (euphoria) and disorientation can occur in some patients.
  - Exacerbated if used in combination with alcohol, depression medications such as tricyclic antidepressants, anticholinergics, antihistamines, anti-seizure medications, or muscle relaxants, etc.
  - Visual symptoms such as blurry vision, miosis, and diplopia can occur.

Opioid Side Effects

- GI Side Effects:
  - Nausea and Vomiting (more common in ambulatory pts.)
  - Constipation
    - Opioids inhibit intestinal trace motility.
    - Very commonly found side effect.
      - Can be relieved by OTC docusate sodium (Colace).

Opioid Side Effects

- Respiratory Side Effects:
  - Respiratory Depression
    - Most serious side effect of the opioids
    - Opioids suppress the brainstem respiratory centers
      - Alter tidal volume, respiratory rate, rhythmicity, and responsiveness to CO_2
    - Does not commonly occur at therapeutic doses in healthy patients, but must use caution in patients with pulmonary disease.

Opioids Side Effects

- Cardiovascular Side Effects:
  - Peripheral vasodilation can result in orthostatic hypotension, decreased BP, and changes in pulse rate.

- Others Include: Urinary retention, cough suppression, headaches, rashes, itching.

Tolerance to Opioids

- Patients experience shorter durations of analgesia from similar dosages, followed by increased levels of pain. Requires dosages to continually be adjusted to provide desired effects.

- Withdrawal can occur if long term use is discontinued abruptly resulting in increased heart rates and blood pressure, nausea, vomiting, dilated pupils, photophobia, shivering, etc. These symptoms peak approximately 2 to 3 days after the last dose and will subside over weeks.

Patient Education

- Avoid all depressants – especially using along with alcohol.
- Must educate all patients of risks of these symptoms and caution them for driving or operating dangerous machines.
- Stomach upset can be helped by consuming the medication with food.
- Watch for signs of breathing difficulty or changes in blood pressure.

Opioids Contraindications

- Avoid in patients with history of hypersensitivity to narcotics.
  - True allergic reactions are rare and often involve skin rashes or contact dermatitis.
- Avoid in patients with acute bronchial asthma or COPD.
- Avoid in patients with a history of depression or suicidal tendencies.
- Avoid in patients with history of addiction.
- Avoid in pregnancy (Most opioids are pregnancy category C).
  - Drug Effects seem to be insignificant in nursing infants, but should recommend waiting at least 4 – 6 hours to nurse.
- Use caution in kidney or liver dysfunction due to increased accumulation of the medication.
- Must be very cautious of drug interactions and always review medications with your patient prior to prescribing.

Scheduled Medications – Most Opioids

Schedule	Description	Optometric Medications
I	Not commercially available; no approved indication	
II	Very addictive medications that are accepted for medicinal use	Oxycodone = OxyContin, OxyFast Oxycodone + APAP = Percocet or Tylox Oxycodone + ASA = Percodan Oxycodone + NSAID = Combunox Hydromorphone (Dilaudid) Codeine Sulfate = Codeine Generic Meperidine (Demerol) **Hydrocodone + APAP = Lortab or Vicodin** **Hydrocodone + Ibuprofen = Vicoprofen**
III	Significant abuse risk, but less potent than I or II. May still contain narcotics.	Codeine + APAP = Tylenol 3 and Tylenol 4
IV	Relatively low abuse potential and limited risk	Propoxyphene (Darvon) Propoxyphene with APAP = Darvocet (Removed from Market in November 2010). Pentazocine + APAP (Talacen) Tramadol
V	Very limited abuse potential. May be OTC in some states.	Acetaminophen

Schedule III Opioids: Codeine

- Prodrug that relies on the cytochrome P-450 system to be metabolized to active drug morphine.
  - Schedule II medication if prescribed alone (Codeine Sulfate 15, 30, 60 mg generic.)

- Analgesic effect occurs within 20 minutes of ingestion and reaches a maximum at 1 – 2 hours.
  - Ceiling effect occurs.

Schedule III Opioids: Codeine

- Usually administered in combination with .
  - Tylenol 3 = Codeine 30 mg and Acetamenophin 300 mg
    - Dosage: 1-2 tablets every 4 hours.
  - Tylenol 4 = Codeine 60 mg and Acetamenophin 300 mg
    - Dosage: 1 tablet every 4 – 6 hours
  - Also available as generic with 15, 30, or 60 mg of Codeine with 300 mg of Acet. or elixer of 12 mg codeine + 120 mg Acet. per 5 mL.
    - Elixer can be used in children for pain management if >3 years.

The FDA has mandated that all prescription medications have no more than 325 mg of

Schedule II Opioids: Hydrocodone

- Approximately 6X more potent than codeine.
- Milder Side Effects than Codeine: Less constipation and sedation.
- Clinically believed to cause more euphoria than codeine, but this is not backed by clinical studies.

Schedule II Opioids: Hydrocodone

- Used in combination with APAP and Ibuprofen.
  - Lortab: Hydrocodone 5, 7.5, and 10 mg with APAP 325 mg
    - Dosage: 1-2 tablet every 4-6 hours
  - Lortab Elixer: Hydrocodone 10 mg with APAP 300 / 15 mL
    - Dosage: 3 tsp every 4-6 hours
  - Vicodin: Hydrocodone 5 mg with Acetaminophen 300 mg
  - Vicodin HP: Hydrocodone 10 mg with Acetaminophen 300 mg
    - Dosage: 1 tablet every 4-6 hours
  - Vicodin ES: Hydrocodone 7.5 mg with Acetaminophen 300 mg
    - Dosage: 1 tablet every 4 – 6 hours
  - Vicoprofen: Hydrocodone 7.5 mg with Ibuprofen 200 mg
    - Dosage: 1 tablet every 4-6 hours
  - Norco: Hydrocodone 5, 7.5, and 10 with 325 mg APAP

Schedule II Opioids: Oxycodone

- Approximately 10-12X more potent than codeine
  - As potent as parenteral morphine when given orally.

- Lower level of side effects in comparison to morphine, but high level of euphoria produced, thus higher level of abuse risk.

Schedule II Opioids: Oxycodone

- Available in combination with APAP, ASA, or Ibuprofen.
  - Percocet Tablets
    - 2.5, 5, 7.5 or 10 mg Oxycodone with 325 mg Acetaminophen
    - Dosage: 1 tablet every 6 hours
  - Tylox Capsules
    - 5 mg Oxycodone with 300 mg Acetaminophen
    - Dosage: 1 tablet every 6 hours
  - Percodan Tablets
    - 4.5 mg Oxycodone HCl
    - 0.38 mg Oxycodone terephthalate
    - 325 mg Aspirin
    - Dosage: 1 tablet every 6 hours
  - Combunox
    - 5 mg Oxycodone with 400 mg Ibuprofen
    - Dosage: 1 tablet daily to QID

Comparing Opioids

Drug	Analgesia	Sedation	N and V	Constipation	Euphoria
Codeine	+	++	++	++	+
Oxycodone	+++	++	+	+	+++
Hydrocodone	+	+	+	+	++
Propoxyphene	+/-	++	+	++	+

Newly Schedule IV: Tramadol (Ultram)

- Central acting narcotic
  - Synethetic analogue of codeine.
  - Binds to mu receptors and inhibits norepinephrine and serotonin reuptake.
  - Potential for abuse is very low, but has occurred.

- Available as 50 mg tablets.

- Dosage: 50 – 100 mg q4 – 6 hours.
  - Analgesia occurs after 1 hour.
  - Maximum dose: 400 mg/day

Tramadol Extended Release (Ultram ER)

- Available dosages of 100, 200, and 300 mg extended.
  - Begin taking 100 mg daily X 5 days
  - Increase by 100 mg if relief not met to 200 mg X 5 days.
  - 300 mg maximum daily.
- Does not work on all patients – some need heavy doses every 4-6 hours.

- More for chronic pain control.

Tramadol + APAP (Ultracet)

- Combination of:
  - 325 mg of APAP
  - 37.5 mg of Tramadol
- Dosage: 2 tablets every 4 – 6 hours
- Max: 8 tablets daily

Tramadol

- Must use with extreme caution in patients taking MAO inhibitors.
- Despite low risk for addiction should still use caution in patients with history of problems.
- Similar side effects to all opioids such as dizziness, nausea, dry mouth, and sedation.
- Avoid in patients with liver or renal impairment.
- Inferior pain relief with risk of side effects has limited Tramadol’s use clinically.

- First Step in Managing Acute Pain: Acetaminophen
  - If inadequate analgesia with 1000 mg TID

- Consider NSAID:
  - Ibuprofen 400 mg every 4-6 hours

- If NSAID inadequate or contraindicated:
  - Hydrocodone + APAP

- If inadequate consider in combination with Ibuprofen or may need to consider stronger options/comanagement.

Opioids

- The short-term effects may include:
  - drowsiness
  - constipation
  - light-headedness and dizziness
  - mild anxiety
  - dry mouth
  - headaches
  - nausea
  - reduced appetite
  - Confusion
- may experience the following:
  - vomiting
  - rash and itchiness
  - pinpoint pupils
  - difficult urination
  - burning sensation on the skin
  - cold clammy skin
  - trouble with breathing, such as slow or shallow breathing