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Treatment and Management of Ocular Pain: NSAIDs and Opioids



Blair Lonsberry, MS, OD, MEd., FAAO
Pacific University College of Optometry
blonsberry@pacificu.edu

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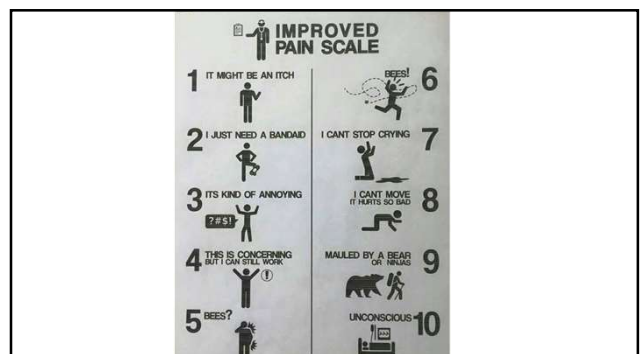
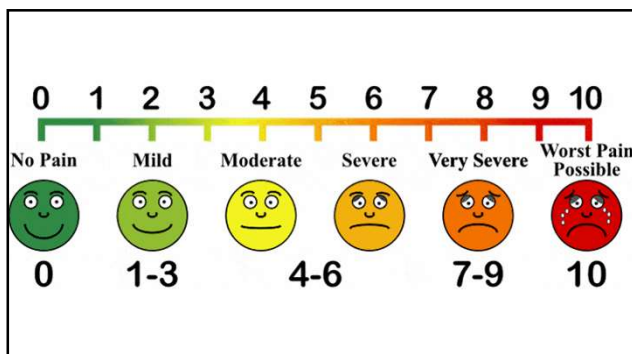
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Agenda

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



Addiction

- defined 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.

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Why Do People Take Drugs

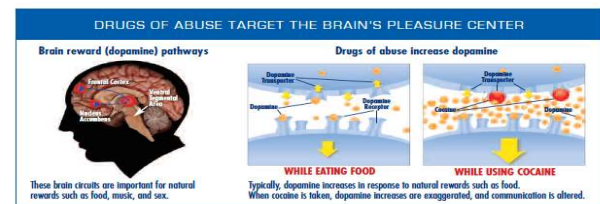
- To Feel Good:
 - Most abused drugs produce intense feelings of pleasure
- To Feel Better:
 - People who suffer from social anxiety, stress and depression begin the use of drugs to help lessen the feelings of distress
- To Do Better:
 - Some feel pressure to enhance their physical or mental edge
- Curiosity 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 typically 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

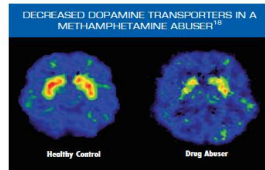
- Brain imaging studies have demonstrated that people with addiction have physical changes in areas of the brain that are critical to judgment, decision making, learning and memory, and behavior control
- It is believed that these changes alter the way the brain works and may help explain the compulsive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



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

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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/o-verdose.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/o-verdose.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/o-verdose.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/o-verdose.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/o-verdose.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.

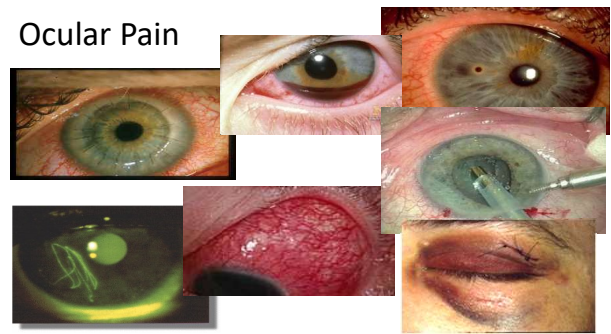
<https://www.cdc.gov/drugoverdose/data/o-verdose.html>

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>

Ocular Pain



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Academic Emergency Medicine ORIGINAL CONTRIBUTION

Topical Tetracaine Used for 24 Hours Is Safe and Rated Highly Effective by Patients for the Treatment of Pain Caused by Corneal Abrasions: A Double-blind, Randomized Clinical Trial

Neil Waldman, MD, FACEM, Ian K. Dennis, and Peter Herlihy, DSc

Abstract

Objectives: The objective of this study was to test the hypothesis that topical tetracaine would be safe to use for 24 hours and would not affect corneal healing. The primary end point was patient-rated pain relief, and the secondary end point was corneal healing.

Methods: The study was a 30-day, prospective, double-blind, randomized trial of tetracaine versus saline in the emergency department (ED) of a regional tertiary care teaching hospital. A total of 100 patients presented with documented corneal abrasions were enrolled in the study. The intervention was either topical tetracaine 0.5% or saline. Patients were followed up for 24 hours. Main safety outcomes measured were repeat ED visits, corneal healing, and patient-rated pain relief. Secondary outcomes measured were patient-rated pain relief, patient-rated corneal healing, and patient-rated corneal healing.

Results: At least one follow-up assessment was completed on each of the 100 patients. No significant differences in corneal healing or patient-rated pain relief were observed between the tetracaine and saline groups. The mean patient-rated corneal healing (CI) of the tetracaine group was 10.1% (95% CI, 0.1% to 19.1%), and the mean patient-rated corneal healing (CI) of the saline group was 10.1% (95% CI, 0.1% to 19.1%). There was no significant difference in VAS pain scores between the groups. Patients in the tetracaine group rated the study drug "more effective" significantly higher than the saline group (CI, 0.1% to 19.1% compared to patients in the saline group difference = 10.1% [95% CI = 0.1% to 19.1%, p = 0.0001]).

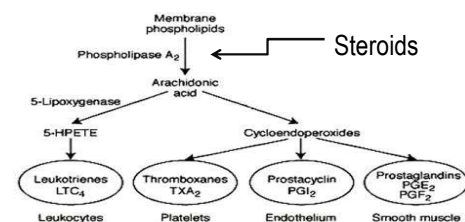
Conclusions: Topical tetracaine used for 24 hours is safe, and while there was no significant difference in patient VAS pain ratings over time, patient ratings on overall effectiveness showed that patients perceived tetracaine to be significantly more effective than saline.

ACADEMIC EMERGENCY MEDICINE 2016;23(10):1010-1015 by the Society for Academic Emergency Medicine

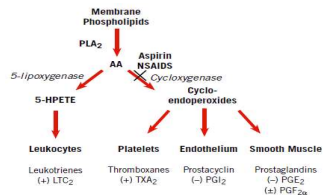
Inflammatory Cascade

- 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 A₂.

Steroids act at the beginning of the Arachidonic Acid Cascade.



NSAIDs

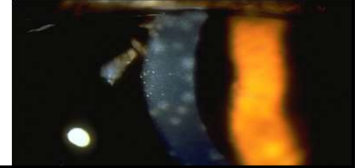


- Unlike steroids, NSAID's have only one mechanism for decreasing inflammation.
 - Inhibit the enzyme cyclooxygenase which produces prostaglandins, prostacyclins, and thromboxanes from Arachidonic Acid.

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 lipoxygenase pathway.

Leukotrienes
attract white blood
cells = Infiltrates.



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.

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



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 nociceptors
 - 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

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Flurbiprofen 0.03% (Ocufen)

- First FDA approved topical ophthalmic NSAID.
- FDA indication: Inhibition of intraoperative miosis due to 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 before 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 0.07% (Prolensa)

- FDA approved in April 2013.
- 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 Pharmaceuticals. Has Durasite to increase contact time.
- 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.



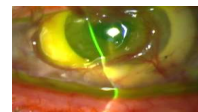
Nepafenac 0.3% (Ilevro)

- 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.

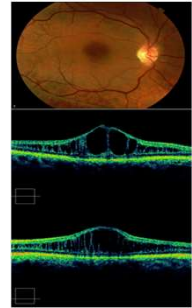


Side Effects of Topical NSAID's

- **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

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.



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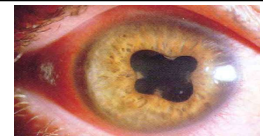
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Uveitis



Three Goals of Treatment:

- ☐ Relieves the pain of ciliary muscle spasm
- ☐ Prevents posterior synechiae – less iris in contact with the anterior lens capsule
- ☐ Decreases the permeability of inflamed vessels which reduces cells and protein in the AC

Cycloplegics

- Common cycloplegic agents include:
 - cyclopentolate 1-2% tid for mild-to-moderate,
 - homatropine 5% BID
 - scopolamine 0.25%
 - atropine 1% bid-tid for moderate-to-severe inflammation
- most common is the use of Homatropine 5% bid (though challenging to find due to manufacturing)
- be careful using atropine as there is potential for severe systemic side effects
 - also makes the iris essentially immobile

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Oral Pain Management

Pain Management: Oral Analgesics

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

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 alleviate 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.

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 tolerance.
 - Adult Dosage: 325 – 650 mg every 4 hours
 - Do not exceed 4 g/day.
 - Most Common use of ASA: Inhibit platelet aggregation in patients with history of heart attacks and heart surgery.
 - Most common dosing is 81 mg/day



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

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
 - Nausea
 - Vomiting
 - Abdominal Cramping
 - Ulcerations/Bleeding/Perforation



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.

Acetaminophen

- Mechanism of Action is not well understood.
 - Possibly some CNS component
 - Very weak inhibitor of prostaglandin synthesis
 - rapidly and completely absorbed from the gastrointestinal tract (duodenum)
 - Serum concentrations peak between one-half and two hours after an oral therapeutic dose
- 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 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

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



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 (US) 400 & 600 (Canada)
- 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.

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.



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.

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

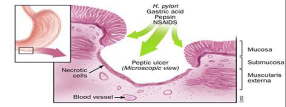
- Selective agents for only COX-2 designed to protect the GI system from the side effects seen with NSAID's.
- Major agent available on the market is Celecoxib (Celebrex).
 - Other agents Valdecoxib (Bextra) and Rofecoxib (Vioxx) were removed from the market due to increased risk of heart attacks and 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".

Stomach disease: peptic ulcer

- There are two major causes of peptic ulcer disease: NSAIDs and chronic H pylori infection.
- Evidence of H pylori infection or NSAID ingestion should be sought in all patients with peptic ulcer.
- Alcohol, dietary factors, and stress do not appear to cause ulcer disease.
- Less than 5–10% of ulcers are caused by other conditions



Stomach disease: peptic ulcer

- Traditional NSAIDs inhibit prostaglandins through reversible inhibition of both COX-1 and COX-2 enzymes.
- Aspirin causes irreversible inhibition of COX-1 and COX-2 as well as of platelet aggregation.
- Coxibs (or selective NSAIDs) preferentially inhibit COX-2—the principal enzyme involved in prostaglandin production at sites of inflammation—while providing relative sparing of COX-1, the principal enzyme involved with mucosal cytoprotection in the stomach and duodenum

Peptic Ulcers: Signs and Symptoms

- Epigastric pain (dyspepsia), the hallmark of peptic ulcer disease, is present in 80–90% of patients.
 - However, this complaint is not sensitive or specific enough to serve as a reliable diagnostic criterion for peptic ulcer disease.
- Pain is typically well localized to the epigastrium and not severe. It is described as gnawing, dull, aching, or “hunger-like.”
- Approximately 50% of patients report relief of pain with food or antacids (especially those with duodenal ulcers) and a recurrence of pain 2–4 hours later.

Peptic Ulcers: Signs and Symptoms

- Upper endoscopy is the procedure of choice for the diagnosis of duodenal and gastric ulcers



NSAID-related ulcers

- COX-2 inhibitors such as celecoxib (Celebrex) are less likely to cause ulcers than aspirin
- Proton pump inhibitors (e.g. Prevacid® or Prilosec®) help to offset the risk of NSAID-related stomach ulcers
 - patients should be treated with concomitant proton pump inhibitors once daily, which results in ulcer healing rates of approximately 80% at 8 weeks in patients continuing to take NSAIDs

Oral Analgesics: Guidelines

- Never exceed maximum recommended dosages:
 - ASA: 8 grams/day
 - Acetaminophen: 4 grams/day?? (3000 likely safer limit)
 - Naproxen sodium: 1375 mg/day
 - Ibuprofen: 1200 mg/day OTC and 2400 mg/day prescription
 - Codeine: 360 mg/day



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 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).

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 Acetaminophen in each capsule/tablet by January 2014.

Schedule II Opioids: Hydrocodone

- Approximately 6X more potent than codeine.
 - No ceiling effect occurs
- 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 Elixir: 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.
- No ceiling effect occurs
- 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

Newly Schedule IV: Tramadol (Ultram)

- Central acting narcotic
 - Synthetic 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