# Pain Management in Optometric Practice in an Era of Opioid Abuse

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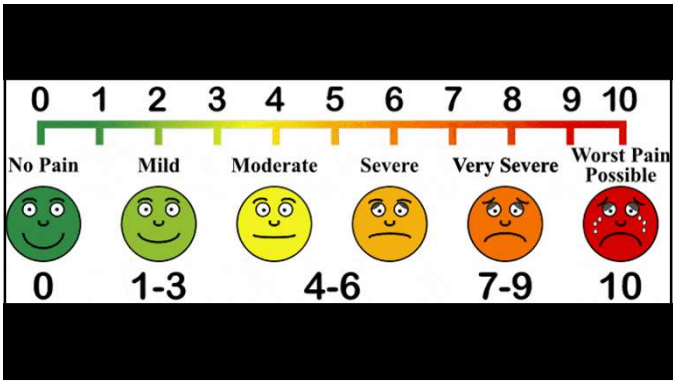
## Disclosures:

- Maculogix: advisory board
- Sun Pharmaceuticals: speakers bureau,
- Avellino: advisory board,
- Dompe: advisory board,
- RVL Pharmaceuticals: advisory board

## Agenda

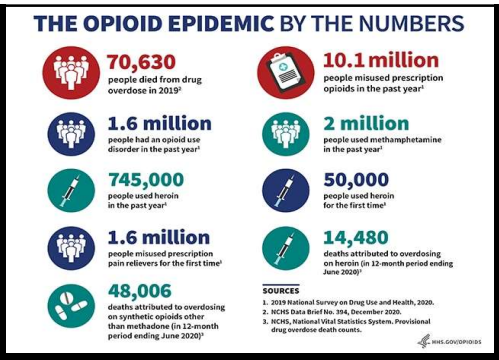
- Opioid epidemic
- Substance Use Disorder (SUB)/Addiction
- Pain management:
  - Topical
  - Orals




## The Opioid Epidemic

- In the late 1990s, pharmaceutical companies reassured the medical community that patients would not become addicted to opioid pain relievers and healthcare providers began to prescribe them at greater rates.
- Increased prescription of opioid medications led to widespread misuse of both prescription and non-prescription opioids before it became clear that these medications could indeed be highly addictive.
- In 2017 HHS declared a public health emergency

https://www.hhs.gov/opioids/about-the-epidemic/index.html




https://www.hhs.gov/opioids/about-the-epidemic/index.html

## What do we know about the opioid crisis?

- Roughly 21-29% of patients prescribed opioids for chronic pain misuse them.
- Between 8-12% of people using an opioid for chronic pain develop an opioid use disorder.
- An estimated 4- 6% who misuse prescription opioids transition to heroin
- About 80% of people who use heroin first misused prescription opioids.
- Likelihood of developing an opioid use disorder depends on many factors, including length of time a person is prescribed to take opioids for acute pain, and length of time that people continue taking opioids (whether as prescribed, or misused).

https://www.drugabuse.gov/drug-topics/opioids/opioid-overdose-crisis

## Dependence versus Addiction

- the term "dependence," usually refers to a physical dependence on a substance.
  - Dependence is characterized by the symptoms of tolerance and withdrawal.
  - While it is possible to have a physical dependence without being addicted, addiction is usually right around the corner
- Addiction is marked by a change in behavior caused by the biochemical changes in the brain after continued substance abuse.

## Withdrawal

- Drug withdrawal, drug withdrawal syndrome, or substance withdrawal syndrome, is the group of symptoms that occur upon the abrupt discontinuation or decrease in the intake of medicational or recreational drugs.
- In order for the symptoms of withdrawal to occur, one must have first developed a form of drug dependence. This may occur as physical dependence, psychological dependence or both.
- Withdrawal symptoms from opiates include anxiety, sweating, vomiting, and diarrhea.
  - Alcohol withdrawal symptoms include irritability, fatigue, shaking, sweating, and nausea.
  - Withdrawal from nicotine can cause irritability, fatigue, insomnia, headache, and difficulty concentrating.

## Withdrawal

- The withdrawal syndrome may be very severe (except for codeine)
- Onset of withdrawal depends on which opioid was used last.
  - With heroin this typically occurs five hours after use, while with methadone it might not occur until two days later.
  - The length of time that major symptoms occur also depends on the opioid used.
    - For heroin withdrawal, symptoms are typically greatest at two to four days, and can last for up to two weeks.
    - Less significant symptoms may remain for an even longer period, in which case the withdrawal is known as post-acute-withdrawal syndrome.

## Tolerance

- Tolerance happens when a person no longer responds to a drug in the way they did at first.
- It takes a higher dose of the drug to achieve the same effect as when the person first used it.
- This is why people with substance use disorders use more and more of a drug to get the "high" they seek.

## Substance Use Disorder/Addiction

- Substance use disorder (SUD) is a preferred term in the scientific community.
- Complex condition in which there is uncontrolled use of a substance despite harmful consequence.
- People with SUD have an intense focus on using a certain substance(s) such as alcohol, tobacco, or illicit drugs, to the point where the person's ability to function in day to day life becomes impaired.
- People keep using the substance even when they know it is causing or will cause problems.

## Substance Use Disorder/Addiction

- The most severe SUDs are sometimes called addictions.
- defined as a chronic, relapsing brain disease
  - 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
- individuals who have received opioids as analgesics only rarely develop addiction.
  - In contrast, when taken for recreational purposes, opioids are highly addictive.

## Why Do People Take Drugs

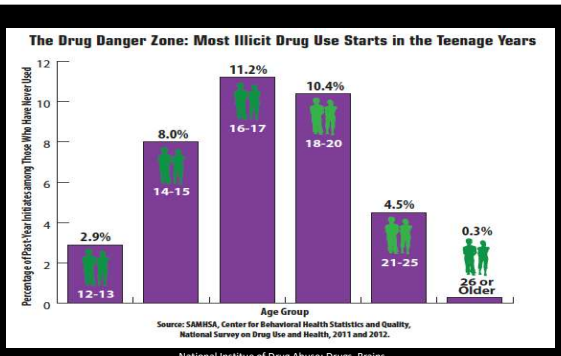
- To Feel Good:
  - Most abused drugs produce intense feelings of pleasure
    - Cocaine: the "high" is followed by feelings of power, self-confidence, and increased energy
- To Feel Better:
  - People who suffer from social anxiety, stress and depression begin the use of drugs to help lessen the feelings of distress
    - Stress can play a major role in beginning drug use, continuing drug abuse, or relapse in patients recovering from addiction
- To Do Better:
  - Some feel pressure to enhance their physical or mental edge
    - prescription stimulants or anabolic/androgenic steroids
- Curiosity or because others are doing it:
  - Adolescents particular prone to this type of peer pressure
    - Teens are more likely than adults to engage in risky or daring behaviors to impress their friends

## Why Do People Take Drugs

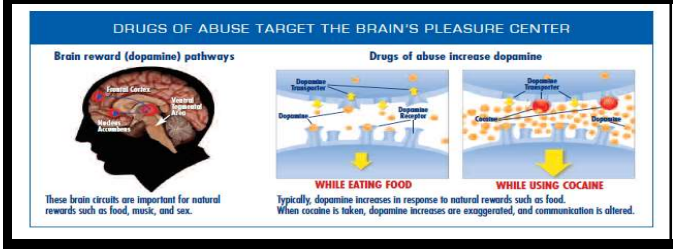
- Initial decision to take a drug is typically voluntary and they may perceive that first time as producing positive effects (and often believe they can control their use).
- With increased use of the drug, other pleasurable experiences lose their appeal and more drug is required to feel "normal" and 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.



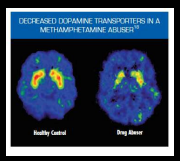

National Institue of Drug Abuse: Drugs, Brains and Behaviour. The Science of Drug Addiction




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

## Most Commonly Abused Drugs

- Marijuana (cannabis) refers to the dried leaves, flowers, stems, and seeds from the *Cannabis sativa* or *Cannabis indica* plant and is the most commonly used illicit substance.
- Prescription:
  - opioid pain relievers (such as OxyContin® and Vicodin®),
  - anti-anxiety sedatives (such as Valium® and Xanax®),
  - stimulants (such as Adderall® and Ritalin®)
- OTC:
  - commonly misused include:
    - dextromethorphan (DXM), a cough suppressant,
    - loperamide, an antidiarrheal
  - Both DXM and loperamide are opioids

## 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

- 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

- 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

## Opioid Overdose: Management Naloxone (Narcan$^{R}$)

- Opioid antagonist
- Available routes of administration include IV (preferred), IM, SubQ, and intranasal
- For the initial treatment of an opioid-associated life-threatening emergency, the American Heart Association recommends, after initiation of CPR, the use of intranasal or IM naloxone with a repeat dose as needed.
- If there is an initial patient response (ie, purposeful movement, regular breathing, moan or other response) but the patient then stops responding, begin CPR and repeat naloxone dose.
- If no initial response, continue CPR and use AED as appropriate

## Opioid Overdose: Management Naloxone (Narcan$^{R}$)

- 4 mg (contents of 1 nasal spray) as a single dose in one nostril; may repeat every 2 to 3 minutes in alternating nostrils until medical assistance becomes available

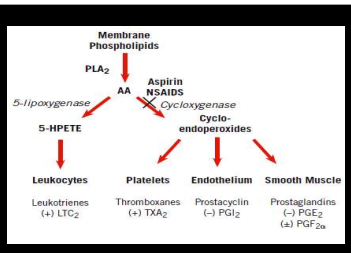
## Preventing Opioid Abuse: PDMP

- 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

# Pain Management

## NSAIDs

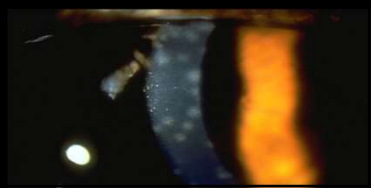



- Unlike steroids, NSAID's have only one mechanism for decreasing inflammation/pain
  - Inhibit the enzyme cyclooxygenase which produces prostaglandins, prostacyclins, and thromboxanes from Arachidonic Acid.

## 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

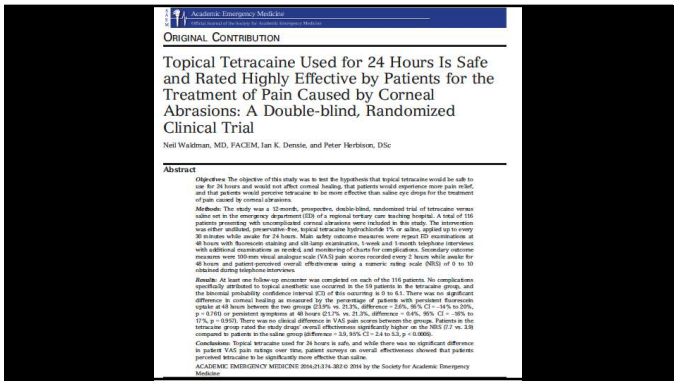
- Induced as the result of an immune response to cause higher levels of prostaglandins.

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


**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.



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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. Densie, and Peter Herbison, 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, that patients would experience more pain relief, and that patients would perceive tetracaine to be more effective than saline eye drops for the treatment of pain caused by corneal abrasions.

**Methods:** The study was a 12-month, prospective, double-blind, randomized trial of tetracaine versus saline set in the emergency department (ED) of a regional tertiary care teaching hospital. A total of 116 patients presenting with uncomplicated corneal abrasions were included in this study. The intervention was either undiluted, preservative-free, topical tetracaine hydrochloride 1% or saline, applied up to every 30 minutes while awake for 24 hours. Main safety outcome measures were repeat ED examinations at 48 hours with fluorescein staining and slit-lamp examination, 1-week and 1-month telephone interviews with additional examinations as needed, and monitoring of charts for complications. Secondary outcome measures were 100-mm visual analogue scale (VAS) pain scores recorded every 2 hours while awake for 48 hours and patient-perceived overall effectiveness using a numeric rating scale (NRS) of 0 to 10 obtained during telephone interviews.

**Results:** At least one follow-up encounter was completed on each of the 116 patients. No complications specifically attributed to topical anesthetic use occurred in the 59 patients in the tetracaine group, and the binomial probability confidence interval (CI) of this occurring is 0 to 6.1. There was no significant difference in corneal healing as measured by the percentage of patients with persistent fluorescein uptake at 48 hours between the two groups (23.9% vs. 21.3%, difference = 2.6%, 95% CI = −9% to 20%, p = 0.761) or persistent symptoms at 48 hours (21.7% vs. 21.3%, difference = 0.4%, 95% CI = −9% to 17%, p = 0.910). There was no clinical difference in VAS pain scores between the groups. Patients in the tetracaine group rated the study drugs' overall effectiveness significantly higher on the NRS (7.7 vs. 3.0) compared to patients in the saline group (difference = 3.0, 95% CI = 2.4 to 3.5, 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 surveys on overall effectiveness showed that patients perceived tetracaine to be significantly more effective than saline.

ACADEMIC EMERGENCY MEDICINE 2014;21:374–382 © 2014 by the Society for Academic Emergency Medicine

# Topical NSAID's

## 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 +

## 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!

## Bromfenac 0.07% (Prolensa)

- FDA approved in April 2013.
- Indicated for treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract extraction
- 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)

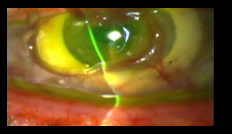
- FDA labeling is only for the treatment of pain and inflammation following cataract surgery.
- Manufactured by Alcon and sold in 3 mL bottles.
- Only NSAID that is a suspension.
- Dosage: TID beginning at one day prior to surgery and continuing for 2 weeks.

## 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.



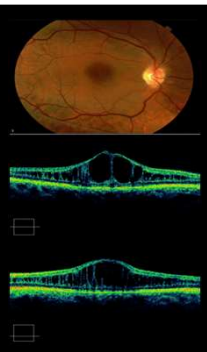
## Side Effects of Topical NSAID's

- **Minor Side Effects:**
  - Burning and Stinging
  - Conjunctival hyperemia
  - Corneal SPK and Blurred Vision
  - Sub-epithelial Infiltrates
  - Increased Bleeding Time of Ocular Tissue
- **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.

## 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 use of oral analgesics:
  - Corneal ulcers
  - Herpes simplex/zoster
  - Post-surgical
  - Trauma
  - Thermal burns
  - Periorbital infections (e.g. dacryocystitis/preseptal)

## 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 NSAIDs
- Moderate to severe pain is best treated with opioid analgesics
- Adjunctive treatments are very valuable in pain management:
  - Mydriatic/cycloplegic useful for ocular pain
  - Bandage CL or pressure patch
  - Topical skin: Zostrix Cream (Capsaicin), EMLA Cream (lidocaine 2.5% and prilocaine 2.5%)

## 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.
- Very good anti-inflammatory and antipyretic properties.
  - Adult Dosage: 325 – 650 mg every 4 hours
    - Do not exceed 4 grams/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
- 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.

## 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.

## 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
    - Just updated (2021): no longer recommended for patients 60 and older, and for patients aged 40-59 it should be on a case to case basis.

## Ibuprofen

- Mild to moderate pain, fever
- Adult analgesic dose: 200-400mg q4-6 hours
  - Maximum Dosage: 2400 mg/day for pain (approved for 3200 mg/day in arthritis treatment)
- OTC: 200 mg tabs (US) 400 mg and 600 mg (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

## Naproxen Sodium

- OTC: 220 mg (Aleve$^{R}$)
- Rx: 550 mg tablets (Anaprox$^{R}$ and Crysanal$^{R}$)
- For mild to moderate pain
- Adult Dose:
  - OTC: 2 tablets first dose, then 1 tablet 8-12 hours (max dose 1250 mg)
  - Rx: 550 initial dose, followed by 275 (half tablet) every 6-8 hours.
    - Maximum Dose: 1375mg/day.

- Fenoprofen (Nalfon): For mild to moderate pain
- ▪ 200mg q 4-6 hours
- Meloxicam (Mobic): For OA, RA and JRA
- ▪ 7.5mg qd

## Indomethacin (Indocin)

- used to treat moderate to severe osteoarthritis, rheumatoid arthritis, gouty arthritis, or ankylosing spondylitis.
- Usual Adult Dosage for Pain: 25-50 mg two to three times/day
- Rx Only: 25, 50 and 75mg capsules
- 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.
- Oral NSAID most widely used in Tx of ocular inflammation
  - E.g. Scleritis treatment 75 mg BID

## Cox-2 Inhibitors

- Selective agents for only COX-2 designed to protect the GI system from the side effects seen with NSAID's.
- It is approved for the management of the signs and symptoms of osteoarthritis, rheumatoid arthritis, JRA (in patients >2), ankylosing spondylitis and acute pain
- 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.
- Available: 50, 100, 200 and 400 mg capsules
- Osteoarthritis Dosage: 100 mg BID or 200 mg single dose daily
- RA: 100 to 200 mg BID daily

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

## 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, diuretics and B-blockers
    - Higher doses of NSAIDs and chronic therapy extending beyond a week will be more likely to increase BP
  - Advanced Age

## 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-related ulcers

- COX-2 inhibitors such as celecoxib (Celebrex) are less likely to cause ulcers than aspirin
- Proton pump inhibitors (e.g. Losec$^{R}$ 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

## 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 acetaminophen 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.

## 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

## 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.

## Oral Analgesics: Guidelines

- Never exceed maximum recommended dosages:
  - ASA: 4 grams/day
  - Acetaminophen: 4 grams/day???? (newer data suggest should be closer to 3-3.2 grams/day)
  - Ibuprofen: 2400 mg/day OTC and up to 3200 mg/day prescription (for RA)
  - Naproxen: 1250/day
  - Naproxen sodium: 1375/day
  - 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.



## Gabapentin (Neurontin$^{R}$ )

- Classified as an anticonvulsant drug
- Additionally, used in the treatment of patients with chronic pain
- **Gabapentin**, is not currently classified as a **controlled substance** in most states, however, its abuse potential is still being investigated.
  - Kentucky, Michigan, Tennessee, West Virginia ??, Virginia ??, and Ohio ?? have reclassified **gabapentin** as a Schedule V **controlled substance**.

## Gabapentin (Neurontin$^{R}$ )

- Gabapentin has primarily been studied and found effective for the treatment of postherpetic neuralgia and painful diabetic neuropathy; evidence for efficacy in other types of neuropathic pain is limited
- Treatment with gabapentin should be initiated at a low dose with gradual increases until pain relief or dose-limiting adverse effects are achieved.
- Dosage:
  - Day 1 single 300 mg dose
  - Day 2 600 mg dose
  - Day 3 900 mg dose
  - Can be titered up all the way to 1800 mg/day

## Gabapentin (Neurontin$^{R}$ )

- The typical effective daily dose range for immediate-release (IR) gabapentin is 1200 to 2400 mg/day on a three times a day schedule, with a maximum daily dose of 3600 mg.
- As gabapentin can be sedating, dose it asymmetrically with a larger dose at night to facilitate sleep.
- For the extended release formulation, one regimen starts with 300 mg orally once daily, gradually increasing to a maximum of 1800 mg orally once daily if needed.
- Adjustment for renal impairment is required for both immediate and extended release, and use of extended-release (ER) is not recommended in patients with severe renal impairment.

## Gabapentin (Neurontin$^{R}$ )

- Adverse events:
  - can produce dose-dependent dizziness and sedation that can be reduced by starting with lower doses and titrating slowly.
  - Importantly, respiratory depression has been reported in older patients and in those who receive gabapentin along with other analgesics and sedatives
  - may be associated with increased risks of mental health disturbances (eg, depression, suicide), unintentional overdose, and motor vehicle accidents

## 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.

## 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.

## 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<br>Oxycodone + APAP = Percocet or Tylox<br>Oxycodone + ASA = Percodan<br>Oxycodone + NSAID = Combunox<br>Hydromorphone (Dilaudid)<br>Codeine Sulfate = Codeine Generic<br>Meperidine (Demerol)<br>**Hydrocodone + APAP = Lortab or Vicodin**<br>**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)<br>Propoxyphene with APAP = Darvocet<br>(Removed from Market in November 2010).<br>Pentazocine + APAP (Talacen)<br>Tramadol (Ultram and Utltracet) |
| V | Very limited abuse potential. May be OTC in some states. | Cough medicine with codeine |

## 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.

## Opioids: Codeine

- Analgesic effect occurs within 20 minutes of ingestion and reaches a maximum at 1 – 2 hours.
  - Ceiling effect occurs.
- Usually administered in combination with acetaminophen .
  - Tylenol 1 (222): codeine 8 mg, 300 mg acetaminophen and 15 mg caffeine (Canada)
  - Tylenol 3 = Codeine 30 mg and Acetaminophen 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.

## 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

## Thank You!

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