Practical Pain Management in Optometric Practice

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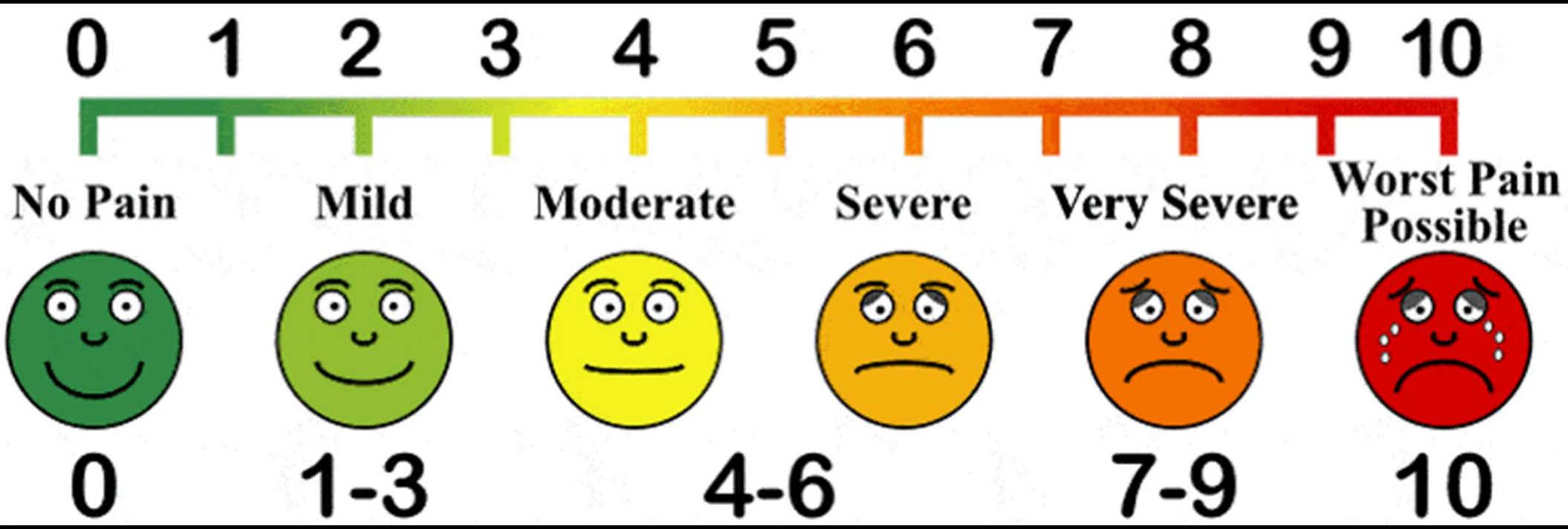
Disclosures:

- Sun Pharmaceuticals: speakers bureau,
- Dompe: advisory board, speakers bureau
- AbbVie: advisory board
- Thea: advisory board
- Apellis: speakers bureau

- All financial relationships have been mitigated.

Agenda

- Opioid epidemic
- Addiction/substance use disorder
- Pain management:
  - Topical
  - Orals
    - Responsible prescribing of opioids


0 1 2 3 4 5 6 7 8 9 10
No Pain
Mild
Moderate
Severe
Very Severe
Worst Pain Possible
0
1-3
4-6
7-9
10

IMPROVED PAIN SCALE

1 IT MIGHT BE AN ITCH

2 I JUST NEED A BANDAID

3 ITS KIND OF ANNOYING

4 THIS IS CONCERNING BUT I CAN STILL WORK

5 BEES?

6 BEES!

7 I CANT STOP CRYING

8 I CANT MOVE IT HURTS SO BAD

9 MAULED BY A BEAR OR NINJAS

10 UNCONSCIOUS

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

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

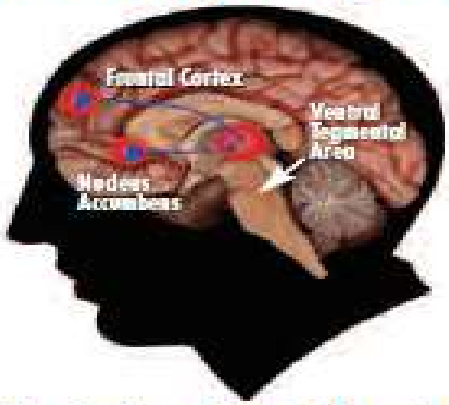
- To Feel Good:
  - Most abused drugs produce intense feelings of pleasure
    - Cocaine: the “high” is followed by feelings of power, self-confidence, and increased energy
- To Feel Better:
  - People who suffer from social anxiety, stress and depression begin the use of drugs to help lessen the feelings 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).

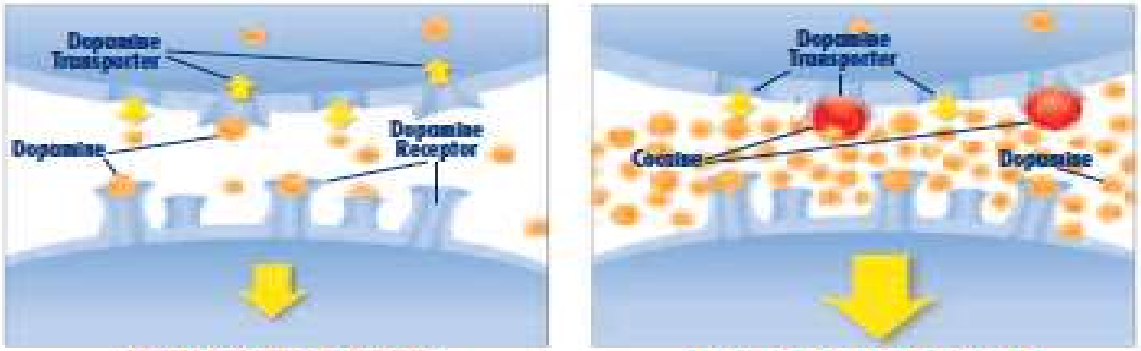
DRUGS OF ABUSE TARGET THE BRAIN'S PLEASURE CENTER

Brain reward (dopamine) pathways



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

Drugs of abuse increase dopamine



WHILE EATING FOOD

WHILE USING COCAINE

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

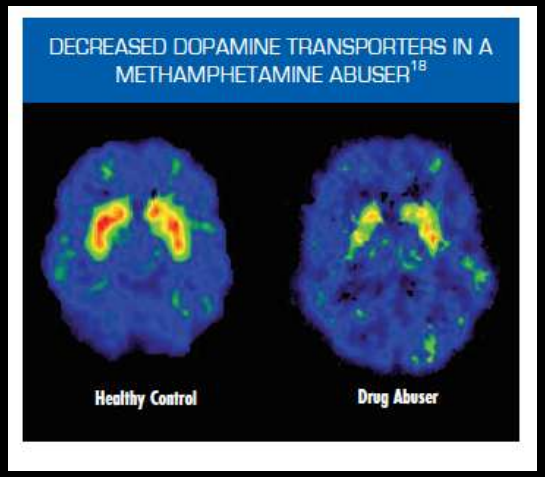
National Institue of Drug Abuse: Drugs, Brains and Behaviour. The Science of Drug Addiction

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.

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

- 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

SIGNS OF AN OPIOID OVERDOSE. B.L.U.E.

BREATHING — Breathing during an overdose is shallow, gurgling, erratic, or completely absent.

LIPS — Lips and fingertips are blue, due to decreased oxygen throughout the body.

UNRESPONSIVE — The victim will not respond to verbal or physical stimulation.

EYES — Pupils are pinpoint, as the opioids constrict the pupils to an unusally small size.

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})

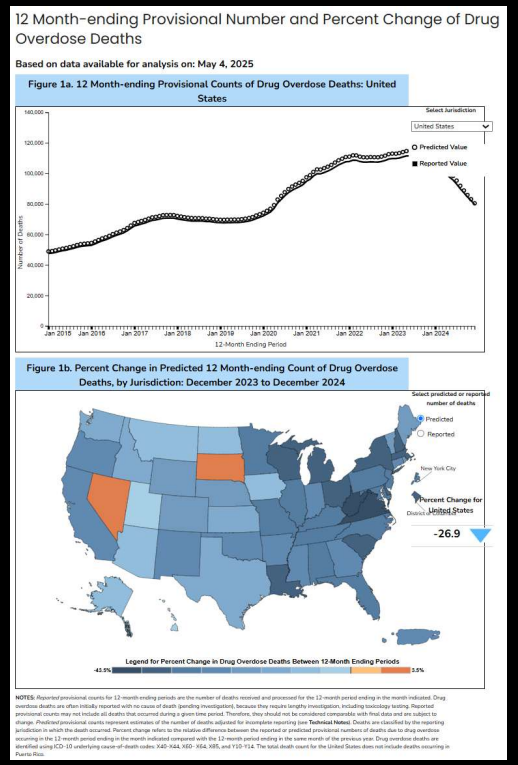
- 4 mg (contents of 1 nasal spray) as a single dose in one nostril; may repeat every 2 to 3 minutes in alternating nostrils until medical assistance becomes available

Approved Treatments

- March 29, 2023:
  - the FDA approved Narcan, 4 milligram (mg) naloxone hydrochloride nasal spray for over-the-counter (OTC), nonprescription, use – the first naloxone product approved for use without a prescription.
- May 22, 2023:
  - the FDA approved Opvee, the first nalmefene hydrochloride nasal spray for the emergency treatment of known or suspected opioid overdose in adults and pediatric patients 12 years of age and older. This is the first FDA approval of nalmefene hydrochloride nasal spray for health care and community use.

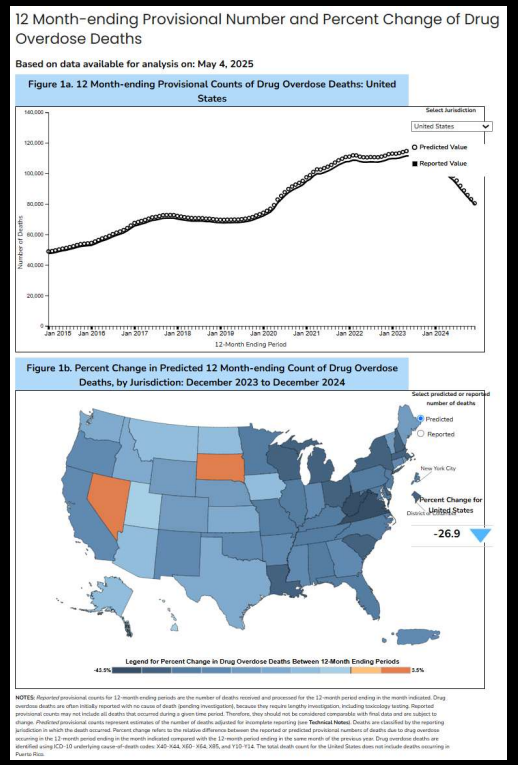
Decrease in Opioid Overdose Deaths in 2024

- Provisional data from the CDC's National Center for Health Statistics indicate there were an estimated 80,391 drug overdose deaths in the United States during 2024—a decrease of 26.9% from the 110,037 deaths estimated in 2023.
- Annual drug overdose deaths are projected to reach their lowest level since 2019.
- Almost all states across the nation saw decreases; Louisiana, Michigan, New Hampshire, Ohio, Virginia, West Virginia, and Wisconsin and Washington, D.C., experienced declines of 35% or more.



Decrease in Opioid Overdose Deaths in 2024

- In contrast, South Dakota and Nevada had slight increases compared to the same period in 2023.
- The new data show overdose deaths involving opioids decreased from an estimated 83,140 in 2023 to 54,743 in 2024.
- Overdose deaths involving cocaine and psychostimulants (like methamphetamine) decreased as well.



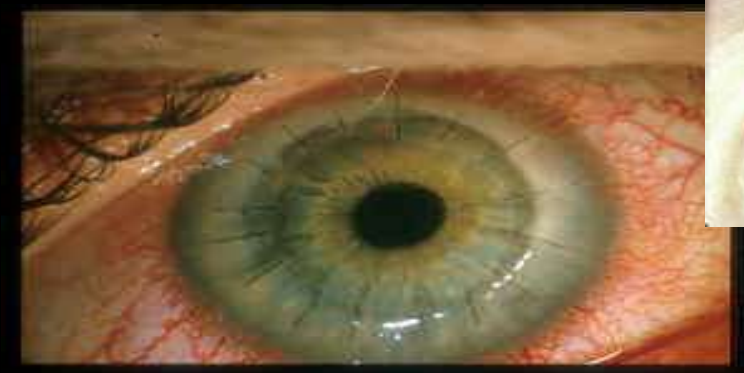
Fentanyl deaths in the U.S. have dropped faster than expected, CDC says. October 27, 2024

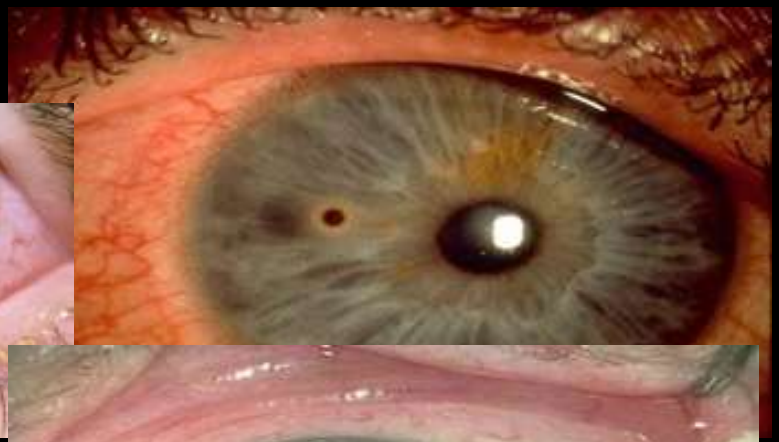
- Experts say the drop in street drug mortality marks a dramatic reversal from just a few years ago when fatal overdoses were spiraling upward at devastating speed, fueled largely by the spread of street fentanyl.
- public health experts said some communities, especially Blacks and Native Americans, are not yet seeing significant declines in overdose deaths.

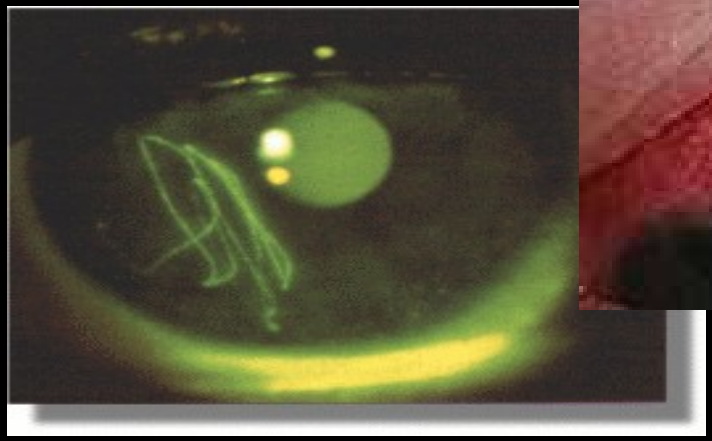
Fentanyl deaths in the U.S. have dropped faster than expected, CDC says. October 27, 2024

- While many people offered theories about why the drop in deaths is happening at unprecedented speed, most experts agreed that the data doesn't yet provide clear answers.
- Some pointed to rapid improvements in the availability and affordability of medical treatments for fentanyl addiction. "Expansion of naloxone and medications for opioid use disorder”
  - one survey in the Seattle area found 85% of high-risk drug users now carry the overdose-reversal medication.

Ocular Pain



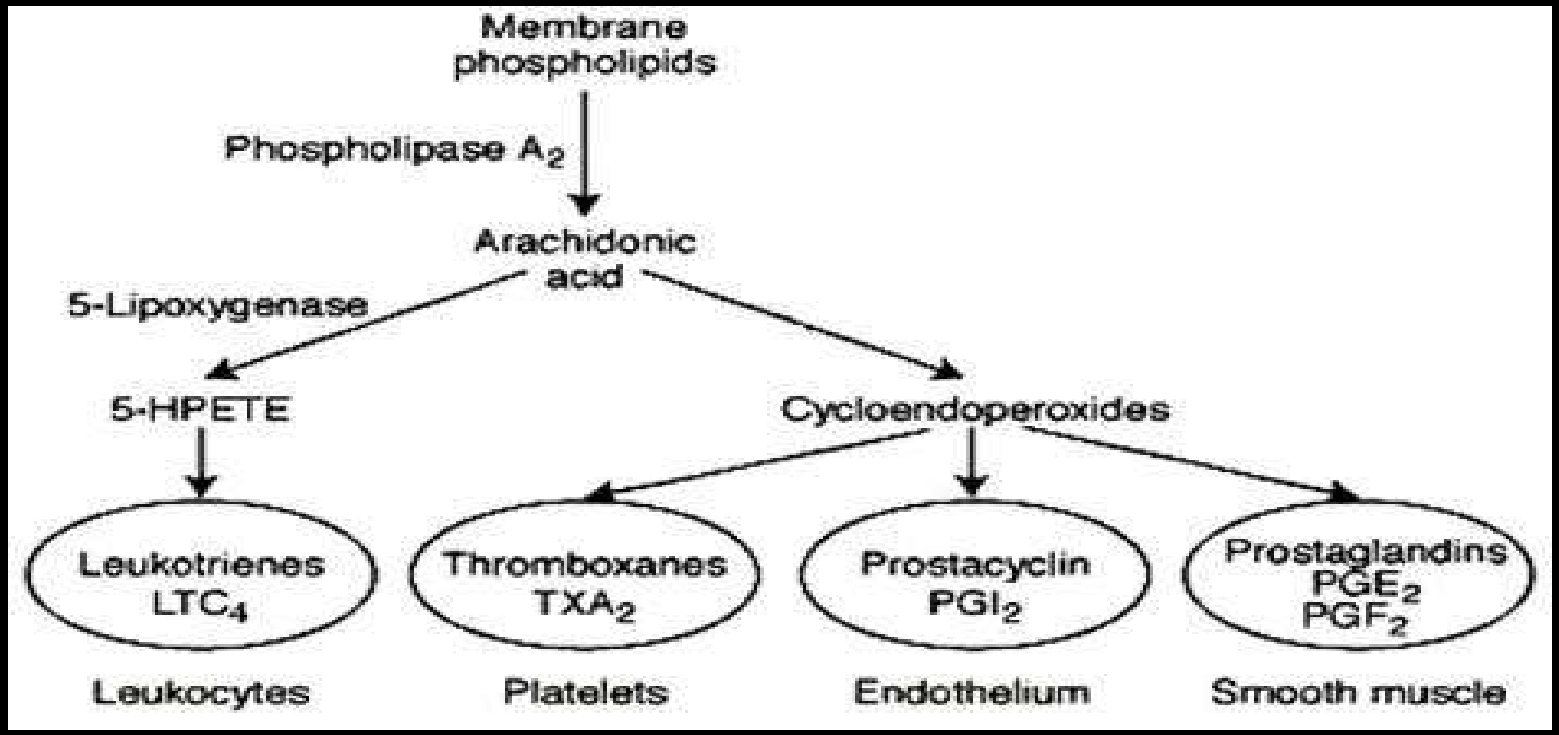




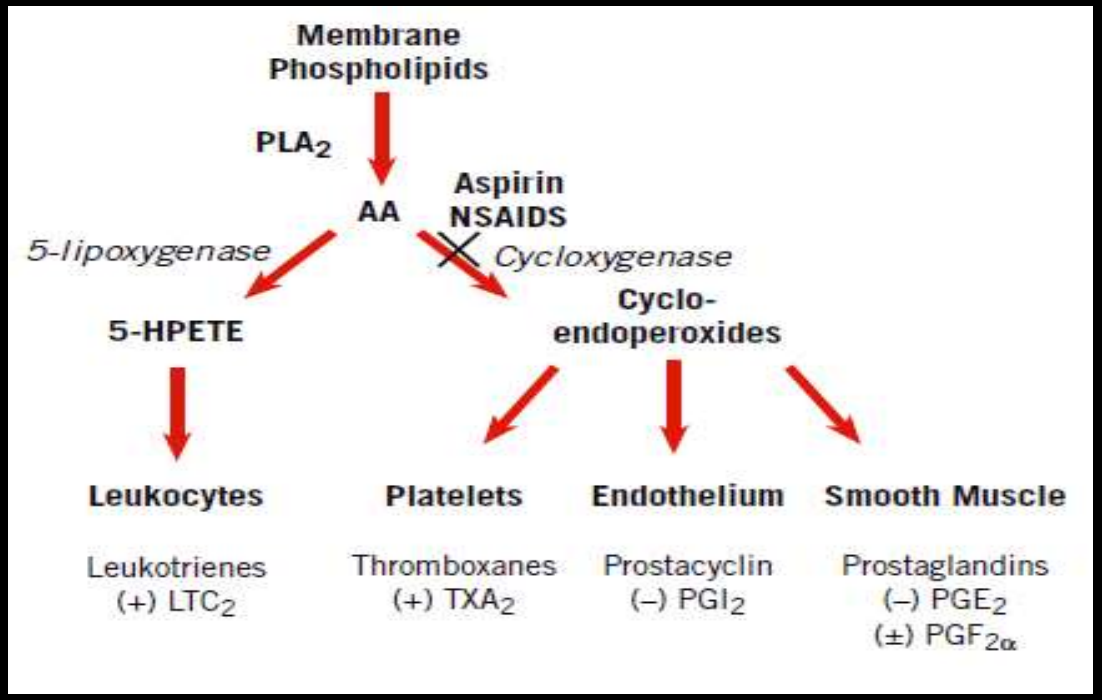
Inflammatory Cascade

- 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 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 lypoxygenase pathway.
- NSAIDs are not as effective as steroids in reducing inflammation, but are still quite potent and lack the side effects seen in steroid usage

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 principal categories of pain relief are seen:
  - Peripherally Acting agents
    - Act on the peripheral pain receptors and prevent sensitization and discharge of the nocioreceptors
    - 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

Role of NSAIDs in Eyecare

- commonly used in the treatment of post-operative inflammation following cataract extraction and various surgical refractive procedures
  - NSAIDs used in isolation are comparable to prednisolone in preventing inflammation and pain after uneventful phacoemulsification
- NSAIDs often used pre/postoperatively to minimize the development of CME (especially in patients with diabetes)
- NSAIDs combined with topical steroids often used in the treatment of CME

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!

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

Bromfenac 0.07% (Prolensa)

- FDA approved in April 2013.
- treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract surgery
- Solution - Available in 1.6 and 3 mL bottles from Bausch and Lomb.

- Dosage: One Drop Daily

Nepafenac 0.1% (Nevanac)

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

Nepafenac 0.3% (Ilevro)

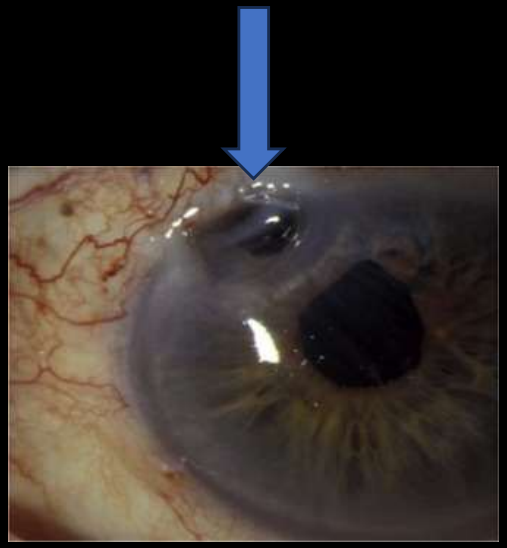
- FDA Approved in 2013.
  - Use for treatment of pain and inflammation associated with cataract surgery.

- Dosage: 1 Drop Daily
- 1 day prior to cataract surgery, continued on the day of surgery and through the first 2 weeks of the postoperative period.

- Suspension that must be shaken.

Major Side Effect of Topical NSAID's

- Corneal Melt
  - Must use extreme caution in eyes with epithelial compromise.
    - in patients whose cornea is compromised by ocular surgery, diabetes, or autoimmune diseases
    - NSAID's will delay wound healing
    - true incidence, most likely low, remains unknown.
    - NSAID dose and duration of treatment
  - Most commonly seen with generic diclofenac



Rigas B, Huang W, Honkanen R. NSAID-induced corneal melt: Clinical importance, pathogenesis, and risk mitigation. Surv Ophthalmol. 2020 Jan-Feb;65(1):1-11.

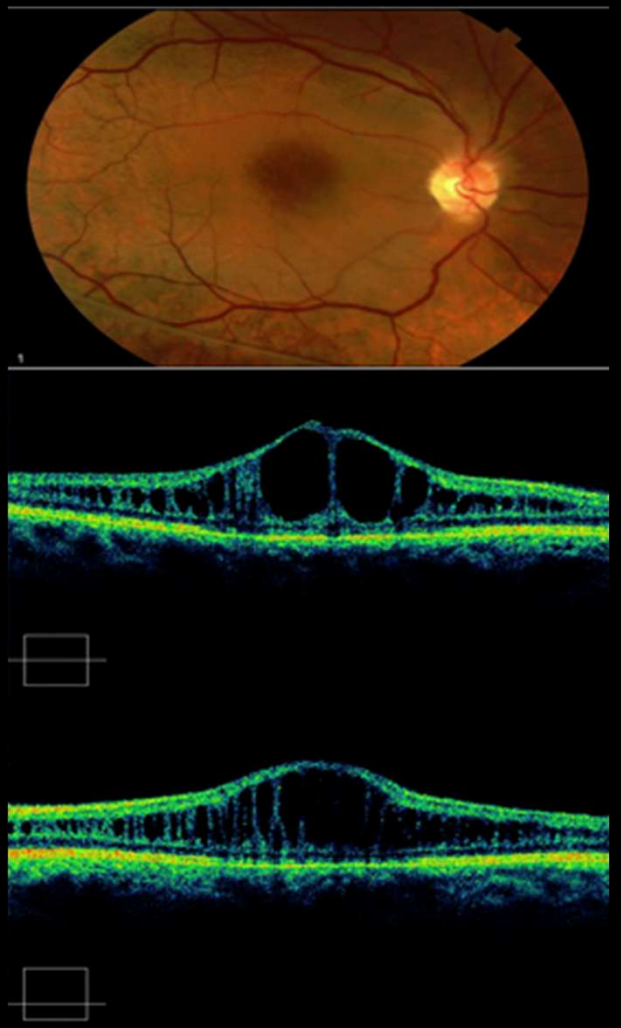
Side Effects of Topical NSAID's

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

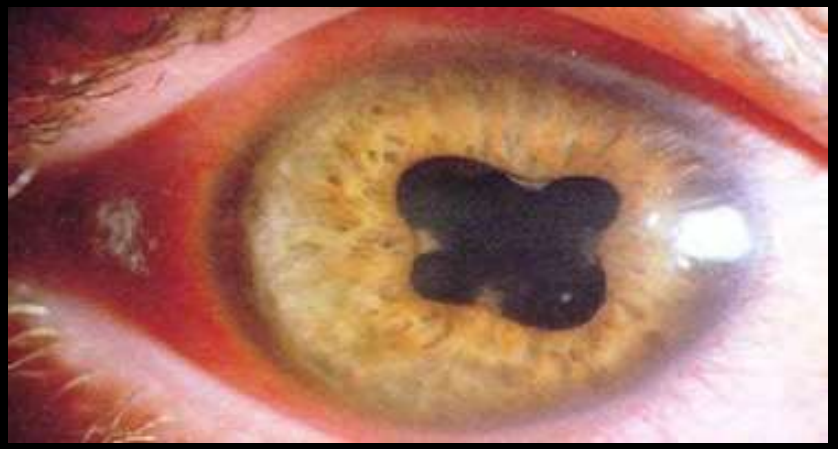
- **Avoiding Problems:**
  - Avoid chronic long-term use
  - Absolutely avoid in "sick" corneas…degenerations, Fuch's, etc

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.
- NSAIDs combined with topical steroids used in management



Uveitis: cycloplegics



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 (not commercially available)
  - scopolamine 0.25% (not commercially available)
  - atropine 1% bid-tid for moderate-to-severe inflammation
- most common was the use of Homatropine 5% bid (though challenging to find due to manufacturing)
- Most commonly used now is cyclopentolate
- be careful using atropine as there is potential for severe systemic side effects
  - also makes the iris essentially immobile

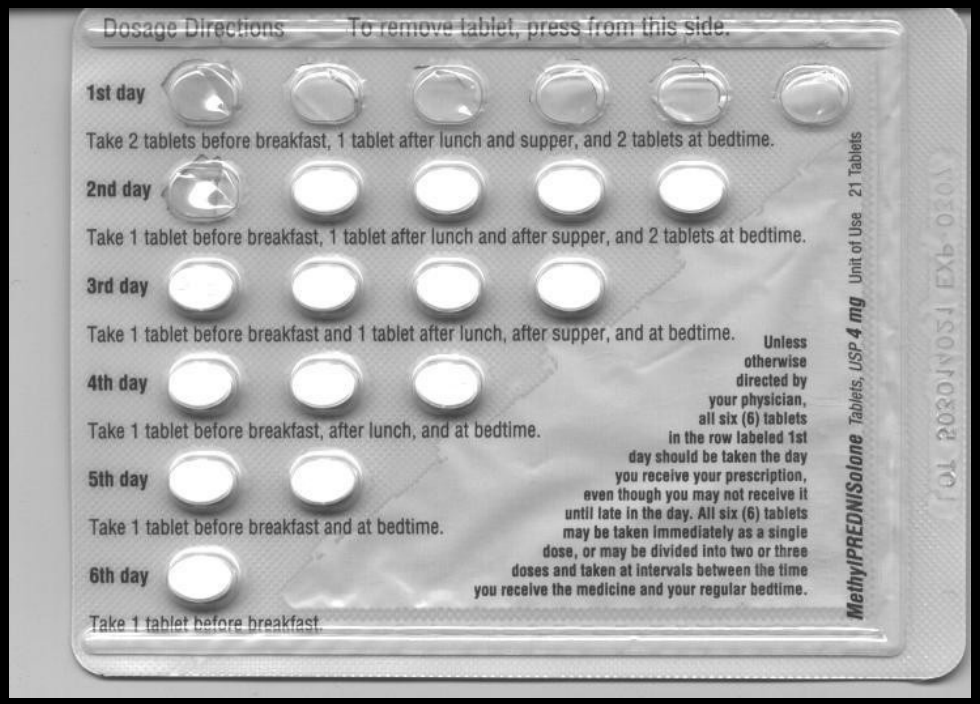
Systemic Corticosteroids

- Prednisone
  - Available as Oral: 1, 2.5, 5, 10, 20, 50 mg tablets and 1 and 5 mg/mL solution and syrup

- Ocular Treatment Guidelines:
  - Mild to Moderate: Initial dose of 20-40 mg
  - Moderate to Severe: 40 – 60 mg
  - Severe: Begin with 60 mg and increase if necessary
  - Specific Conditions: Giant Cell Arteritis
    - 80-100 mg Prednisone
    - Consider IV Methylprednisolone 250 mg IV q6hours for 12 doses

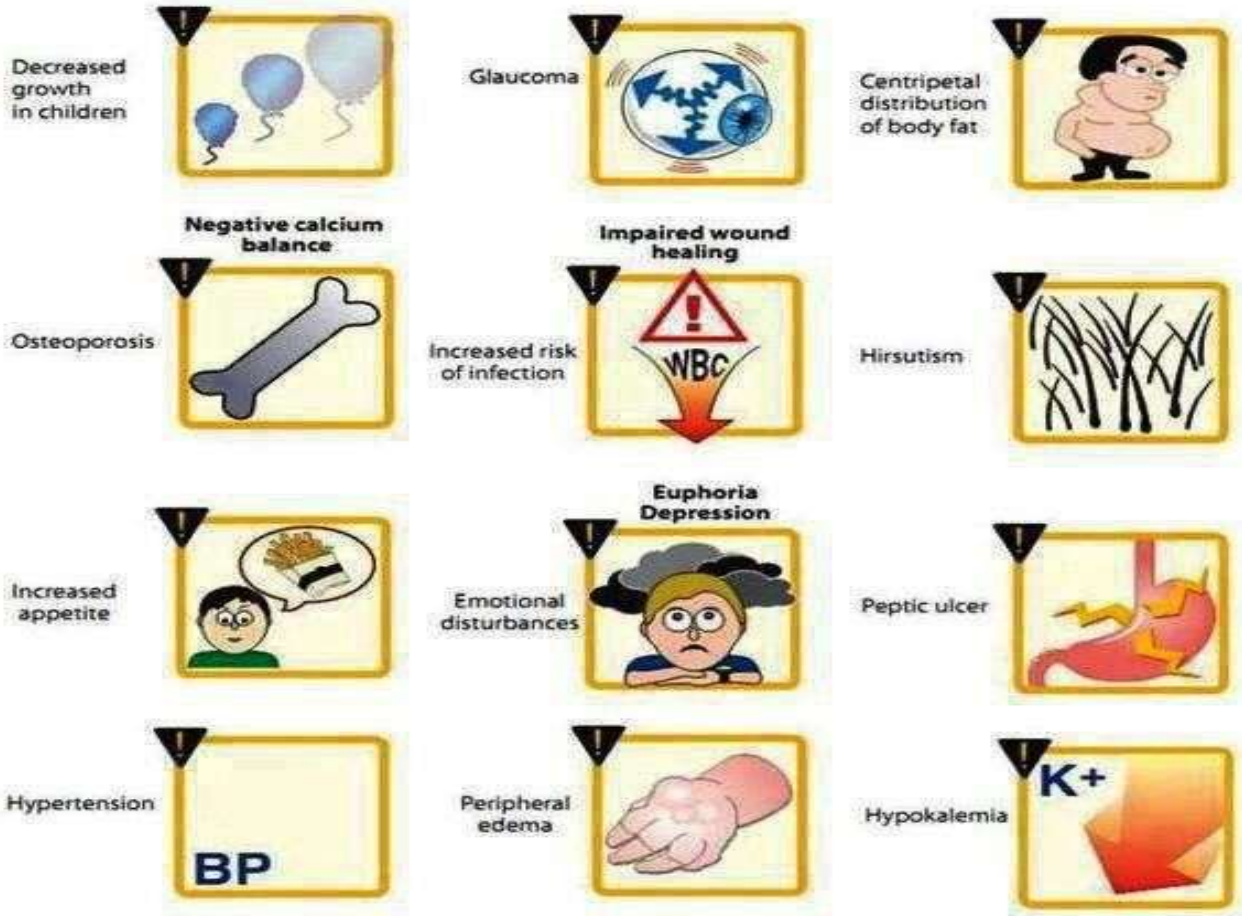
Tapering Systemic Medications

- Medrol Dose Pack (Methylprednisolone) – 4 mg pills
  - Provided with dosage for 6 days of treatment.



In Optometry, generally if we do an oral to a level that requires a taper we want dosages of higher than 24 mg to start and treatment for longer than 6 days.

CORTICOSTEROIDS
Side Effects



Academic Emergency Medicine
Official Journal of the Society for 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. 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 = –14% to 20%, p = 0.761) or persistent symptoms at 48 hours (21.7% vs. 21.3%, difference = 0.4%, 95% CI = –16% to 17%, p = 0.957). 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. 3.9) compared to patients in the saline group (difference = 3.9, 95% CI = 2.4 to 5.3, p < 0.0005).

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.

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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
  - Periorbital infections (e.g. dacryocystitis/preseptal)

Analgesic Ladder for Pain Management

- . The “original” analgesic ladder included:
- **First Step -** Mild pain: non-opioid analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen with or without adjuvants
- **Second Step -** Moderate pain: weak opioids (hydrocodone, codeine, tramadol) with or without non-opioid analgesics and with or without adjuvants
- **Third Step -** Severe and persistent pain: potent opioids (morphine, methadone, fentanyl, oxycodone, buprenorphine, tapentadol, hydromorphone, oxymorphone) with or without non-opioid analgesics, and with or without adjuvants.[35]

35. Ventafridda V, Saita L, Ripamonti C, De Conno F. WHO guidelines for the use of analgesics in cancer pain. Int J Tissue React. 1985;7(1):93-6

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 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.

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: 1200 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.

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

Ketoprofen

- Indicated for management of mild/moderate pain, menstrual cramps and swelling/pain associated with arthritis
- Oral:
  - Capsule: Generic: 25 mg, 50 mg
  - Capsule Extended Release 24 Hour: Generic: 200 mg
- Adults—25 to 50 milligrams (mg) every 6 to 8 hours as needed.
  - Some people may need to take as much as 75 mg every 6 to 8 hours.
  - Doses larger than 75 mg are not likely to give better relief
- For osteoarthritis and rheumatoid arthritis: Adults—At first, 75 milligrams (mg) 3 times a day or 50 mg 4 times a day.
- Has been used for scleritis patients to avoid the side effects seen with indomethacin

Ketorolac: (Toradol dsc in US)

- Used to treat moderate to severe pain
- Often used in managing post-operative pain and in ER in lieu of opioids
- Often IM or IV for pain management
- Oral: 10 mg
  - Adults (patients 16 years of age and older)—One 10 mg tablet four times a day, 4-6 hours apart. Some people may be directed to take two tablets for the first dose only.
  - Should not be used for more than 5 days.
- To lessen stomach upset, ketorolac tablets should be taken with food (a meal or a snack) or with an antacid.
- Take this medicine with a full glass of water. Also, do not lie down for about 15 to 30 minutes after taking it. This helps to prevent irritation that may lead to trouble in swallowing.

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

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.
  - Probably working on central nervous system
    - thought to inhibit the synthesis of prostaglandins in the central nervous system, leading to its analgesic and antipyretic effects
  - 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 and Neurodegenerative Disease??

- Acetaminophen has been considered the safest over-the-counter option in pregnancy among all analgesics and antipyretics.
- Conflicting reports in the literature
- Many studies use “parent reported” autism/ADHD
- Most studies do not include sibling data
- Many studies have low cohort numbers that were included in the data analysis
- Studies that do show a “link” do not demonstrate cause and effect

Acetaminophen

- Oral: available as a tablet, capsule, syrup, oral solution, or suspension.
- Rectal: available as a rectal suppository for both adult and pediatric patient populations.
- Intravenous: IV infusion for administration.
- Adverse effects:
  - Skin rash, hypersensitivity reactions
  - Nephrotoxicity (elevations in BUN, creatinine)
  - Hematological: anemia, leukopenia, neutropenia, pancytopenia
  - Metabolic and electrolyte

Acetaminophen

- Typical Adult Dosage (FDA Based):
  - 650 mg every 4 - 6 hours for Regular Strength (2 X 325)
  - 1000 mg every 6 hours for Extra Strength (2 X 500)
  - 1300 mg every 8 hours for Extended Release (2 X 650)
- 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 500 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 Acetaminophen with NSAID's for Mild to Moderate Pain Relief

1:00 pm: Two 325mg acetaminophen (Tylenol)

3:00 pm: Two 200mg Ibuprofen

5:00 pm: Two 325mg acetaminophen (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: 1200 mg/day OTC and up to 3200 mg/day prescription (for RA)
  - Naproxen: 1250/day
  - Naproxen sodium: 1375/day
  - Codeine: 360 mg/day

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.

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
  - The transition of gabapentinoids into a first-line pain medication is in part due to an intentional marketing strategy by the pharmaceutical industry without adequate studies.
- 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 2 300 mg BID (600 mg total dose)
  - Day 3 300 mg TID (900 mg total dose)
  - Can be titered up all the way to 1800 mg/day

Gabapentin (Neurontin^{R})

- Gabapentinoids have significant risks despite their reputation as safe drugs.
  - Central nervous system effects such as sedation, dizziness, gait instability, and feeling intoxicated are quite common; as many as one in three patients taking therapeutic doses will experience dizziness or somnolence

Opioids vs Ibuprofen + Acetaminophen:

1000mg acetaminophen and 400 mg ibuprofen = 5 mg hydrocodone

- **Ibuprofen Plus Acetaminophen Equals Opioid Plus Acetaminophen for Acute Severe Extremity Pain.** **Am Fam Physician. 2018;97(5):348**
- Effect of a Single Dose of Oral Opioid and Nonopioid Analgesics on Acute Extremity Pain in the Emergency Department: A Randomized Clinical Trial.
  JAMA. 2017;318(17):1661-1667.
  - no statistically significant or clinically important differences in pain reduction at 2 hours among single-dose treatment with ibuprofen and acetaminophen or with 3 different opioid and acetaminophen combination analgesics

Opioid 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).

Opioid 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

- Nausea and Vomiting (more common in ambulatory pts.)
- Constipation
  - Can be relieved by OTC docusate sodium (Colace).
- Respiratory Side Effects:
  - Respiratory Depression
    - Most serious side effect of the opioids

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 Oxycodone + APAP = Percocet Hydromorphone (Dilaudid) Codeine Sulfate = Codeine Generic Meperidine (Demerol) **Hydrocodone + APAP = Lortab** **Hydrocodone + Ibuprofen = Generic**
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	Tramadol
V	Very limited abuse potential. May be OTC in some states.	Cough medicine with codeine

Opioids: Codeine

Note: Tylenol 3 and 4 no longer available as Brand name

- 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

Codeine

- 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.
- Serious side effects:
  - Respiratory depression: caution in patients with asthma, COPD
  - Caution in patients taking sedative medications (Xanax/Valium), muscle relaxants or other pain medications
  - No alcohol consumption

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.

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
  - Generic:
    - Hydrocodone bitartrate 5, 7.5, 10 mg and acetaminophen 300 mg
    - Hydrocodone bitartrate 5, 7.5, 10 mg and acetaminophen 325 mg
  - Generic Elixer:
    - Hydrocodone bitartrate 7.5, 10 mg and acetaminophen 325 mg per 15 mL
  - Generic:
    - Hydrocodone bitartrate 5, 7.5, 10 mg and ibuprofen 200 mg

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.

Opioids: Oxycodone

- Available in combination with APAP (combinations with ASA or Ibuprofen discontinued in US).
- Dosage: 1 tablet every 4-6 hours
  - Endocet tablets:
    - 2.5, 5, 7.5 or 10 mg Oxycodone with 325 mg Acetaminophen
  - Nalocet:
    - Oxycodone hydrochloride 2.5 mg and acetaminophen 300 mg
  - Percocet Tablets
    - 2.5, 5, 7.5 or 10 mg Oxycodone with 325 mg Acetaminophen
  - Prolate:

    5, 7.5 or 10 mg Oxycodone with 300 mg Acetaminophen
  - Generic:
    - 2.5, 5, 7.5 or 10 mg Oxycodone with 325 mg Acetaminophen

Schedule IV: Tramadol

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

Tramadol Extended Release

- ConZip:
  - 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.
- Generic: 100 mg, 200 mg, 300 mg
- Does not work on all patients – some need heavy doses every 4-6 hours.

- More for chronic pain control.

Tramadol + APAP

- Generic: 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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