

## Ocular and Systemic Pain, and Drug Diversion

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Disclosure Statement:  
• Nothing to disclose



### Course Description:

This course presents a review of pain, both ocular and systemic. It reviews ocular and local anesthesia and its relationship to pain management. The course then reviews in depth ocular pain and how systemic and topical pain management is used for ocular pain management. Finally the course reviews the use/need for opioids and drug diversion and its components.

### Course Learning Objectives :

- To understand the physiological pathways and components of ocular pain.
- To review how to management ocular and systemic pain with both topical and systemic medications.
- To understand drug diversion.

### PAIN



**An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.**

- Pain is always a subjective experience that is influenced to varying degrees by biological, psychological, and social factors.
- Pain and nociception are different phenomena: the experience of pain cannot be reduced to activity in sensory pathways.
- Through their life experiences, individuals learn the concept of pain and its applications.
- A person's report of an experience as pain should be accepted as such and respected.
- Although pain usually serves an adaptive role, it may have adverse effects on function and social and psychological well-being.
- Verbal description is only one of several behaviors to express pain; inability to communicate does not negate the possibility that a human or a non-human animal experiences pain.
- Etymology: Middle English, from Anglo-French *peine*, from Latin *poena* (penalty, punishment), in turn from Greek *poñē* (payment, penalty, recompense).

### Pain- Dictionary.com

Noun

- physical suffering or distress, as due to injury, illness, etc.
- a distressing sensation in a particular part of the body
- mental or emotional suffering or torment

Verb (used with object)

- to cause physical pain to hurt
- to cause (someone) mental or emotional pain distress

Verb (used without object)

- to have or give pain

• Definition of pain and classification of pain disorders K. Hanoch Kumar, P. Elavarasi- [http://icri.net/ejournals/ejournals/112\\_Review%20Article.pdf](http://icri.net/ejournals/ejournals/112_Review%20Article.pdf)



### PAIN and SUFFERING

• Pain is the physical sensations or signals (within your body) that tells you something is happening within your body in relation to an event or situation. Suffering is the interpretation or story that you tell yourself about the pain (i.e thoughts, judgements, beliefs etc).

• Pain and suffering is the legal term for the physical and emotional stress caused from an injury. Some damages that might come under this category would be: aches, temporary and permanent limitations on activity, potential shortening of life, depression or scarring.

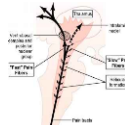
### 3 Types Nociceptor Pain Receptors

- **Nociceptor- Mechanical**
  - Respond to mechanical damage such as cutting, crushing or pinching
- **Nociceptor Thermal**
  - Temperature extremes (especially heat)
- **Poly-modal Nociceptors**
  - Respond to all kinds of damaging stimuli- including irritating chemicals

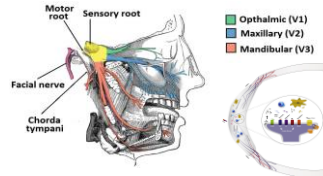


### Fast-Pain vs. Slow-Pain

- **Fast Pain**
  - A-Delta Fibers
  - Small Myelinated Fibers
  - 30 meters/sec
  - Nociceptors
  - Sharp pricking pain, easy to locate
- **Slow Pain**
  - C Fibers
  - Small Unmyelinated Fibers
  - 12 meters/sec
  - Poly-Modal
  - Dull, aching, burning sensation
  - Poorly localized
  - Persists for longer time period- more unpleasant

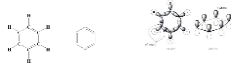


### Ocular Pain- Trigeminal Nerve





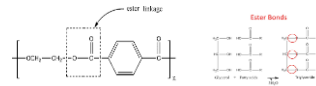
**Aromatic Ring**



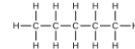
Aromatic rings (also known as aromatic compounds or arenes) are hydrocarbons which contain benzene, or some other related ring structure. Benzene, C<sub>6</sub>H<sub>6</sub>, is often drawn as a ring of six carbon atoms, with alternating double bonds and single bond

**Ester Linkage**

In an ester molecule, the bond connecting the atom doubly bonded to oxygen and the oxygen atom bearing the alkyl or aryl group is called the ester bond or, in biochemistry, ester linkage



**Hydrocarbon Chain**



A hydrocarbon chain is a molecule that consists of entirely hydrogen and carbon. They are the simplest of the organic compounds and may be a liquid, gas or solid. There are many types of hydrocarbon chains, including alkanes, alkenes, alynes, cycloalkanes and arenes. They can be branched, linear, or cyclic.

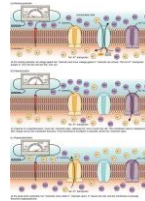
**Tertiary Amine Group**

Tertiary amine (3<sup>o</sup> amine): An amine in which the nitrogen atom is directly bonded to three carbons of any hybridization which cannot be carbonyl group carbons. In organic chemistry, amines are compounds and functional groups that contain a basic nitrogen atom with a lone pair.



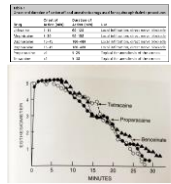
**Mechanism of Action**

- Prevent both GENERATION and CONDUCTION of nerve impulses.
- Work on Cell Membrane
  - Block the transient increase in membrane permeability to sodium ions which normally occurs during depolarization of the membrane.
  - Specific binding site located within voltage gated sodium channel
- Greater the Hydrophobicity, greater affinity for binding

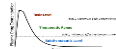


**Duration of Action**

- Proportional to the time in contact with the nerve tissue.
- As hydrophobicity increases so does potency and duration.
- As lipid solubility increased the potency also increased, however so does the toxicity.
- Ester compounds are topical and rapidly hydrolyzed
- Amine compounds are injected and absorbed by the drug



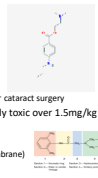
**Topical Anesthetics**



- Topical Ocular Anesthetic efficacy is determined by their ability to suppress corneal sensitivity.
- There is a point at which no further increase in activity of the drug occurs : maximum effective concentration.
  - Increasing dosage above maximum effective concentration only increases risk of toxicity.
- Optimum Effective Concentration can be less than maximum
  - Tetracaine 0.5% is less irritating vs. the maximum effective concentration of 1.0%.
- TOPICAL APPLICATION OF TWO OR MORE LOCAL ANESTHETICS DOES NOT PRODUCE AN ADDITIVE EFFECT.**

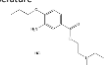
**Ocular Anesthetics**

- Tetracaine** 0.5% and 1.0%
- Ester of para-aminobenzoic acid (PABA)
- Onset time of 10-20 seconds
- Lasts for 10-20 minutes- 0.5%
  - Reported 1% can last up to 1 hour and be used for cataract surgery
- Should NOT be injected- potent and potentially toxic over 1.5mg/kg
- Adverse Reactions:
  - Stinging
  - Greater Corneal Compromise (microvilli, cell membrane)
  - Allergy



**Ocular Anesthetics**

- Proparacaine** 0.5%
- Ester of para-aminobenzoic acid (PABA)
- Onset time of 10-20 seconds
- Lasts for 10-20 minutes
- Does not penetrate into the cornea or conjunctiva as well as tetracaine
- Unopened bottles may be stored at room temperature
- Discard discolored solutions of Proparacaine
- Adverse Reactions:
  - Stinging- very mild
  - Hypersensitivity- rare
  - Corneal Thickness changes



Ocular Anesthetics

- **Benzoxinate** 0.4%
  - Ester of para-aminobenzoic acid (PABA)
  - Similar duration and effect as Tetracaine and Proparacaine 0.5%
    - 10-20 seconds for 10-20 minutes
  - Always combined with a vital dye (Sodium Fluorescein)
    - Sodium Fluorescein alone is good Pseudomonas aeruginosa medium
    - However in combination with Benzoxinate it is bactericidal
- Adverse Reactions:
  - Stinging
  - Allergy- very low profile
  - Can increase or decrease corneal thickness +/- 10um



Adverse Drug Reactions/Side Effects

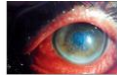
- Risk of those over 50 to get Superficial Punctate Keratitis
  - More risk for filamentary keratitis and corneal edema
- **Repeated administration of topical ocular anesthetics should be avoided. It significantly inhibits healing of the corneal epithelium.**
  - Systemic absorption of topical anesthetics or injection of them, can cause CNS depression, hypotension, low/absent pulse which can result in respiratory failure
- Allergic/Hypersensitivity reactions are uncommon, but mainly with ester compounds. Amine compounds occur at a much lower rate.
  - Occur 5-10 minutes after instillation

Adverse Drug Reactions/Side Effects

- No life threatening allergic responses to topically applied ocular anesthetic has ever been reported.
- Injected medications have a very rare chance at anaphylactoid responses
- Psychomotor-Fainting- can happen but mostly it is anxiety driven
- Contraindications
  - Hypersensitivity
  - Liver Disease (injectable)
  - Systemic Anti-cholinesterase agents (high dosages of topical anesthesia)
  - Dry Eye Testing
  - Penetrating Ocular Injury (BAK)
  - Cultures (lids/conjunctiva)

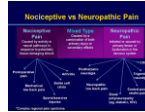
Self Administration of Topical Anesthetics

- DONT DO IT
- Leads to infiltrative keratitis and lose of eye
- Occurs from 6 days of usage to 6 weeks
- Loss of corneal epithelium
- Inhibits healing of epithelial defects, loss of microvilli
- Stromal Edema
- Descemets's Folds
- Yellow-White Ring around area of diseased area



Ocular Pain Treatment

- Peripherally Acting Agents
  - Act on peripheral pain receptors
  - Block Cyclooxygenase Pathway
- Anesthetic Agents
  - Nociceptive signal interrupted
  - Sodium Channel Block in nociceptor
- Centrally Acting Agents
  - Works on Central Nervous System blocking both pain and emotional response
  - Opioids



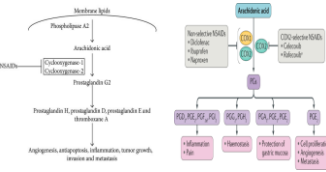
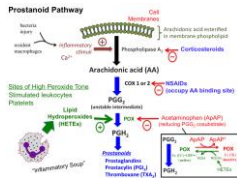
Non-Steroidal Anti-Inflammatory

- Salicylates
  - Oldest non-opioid analgesic
  - Inhibit prostaglandin E and inactivate cyclooxygenase
  - Analgesic mostly, not anti-inflammatory until 3-4 grams
  - GI disturbance is most common ADR
- Non-salicylate
  - Most used for anti-inflammatory but also effective analgesic
  - Propionic Acid and COX-2 Inhibitor classes
  - Primarily works by inhibiting cyclooxygenase in injured tissue and eliminating peripheral nociceptor sensitizers
- **Both have a Ceiling Effect- repeated/chronic use does not cause tolerance or addiction**



NSAID's

- NSAID's work by inhibiting the activity of cyclooxygenase enzymes COX-1 or COX-2. In brief, these enzymes are involved in the synthesis of key biological mediators, namely prostaglandins, which are involved in inflammation, and thromboxanes, which are involved in blood clotting.



Non-salicylates

- Ibuprofen
  - Motrin, Advil, etc.
- Naproxen
  - Naproxen
  - Specifically developed to reach peak plasma level rapidly
- Naproxen Sodium
  - Aleve
- Celecoxib
  - Celebrex
- ADR's: Decreased Attention, confusion, headache, GI risks
- Avoid in Renal Patients, Pregnancy and breast feeding





DEA Schedule

- Schedule III**  
Schedule III drugs, substances, or chemicals are defined as drugs with a moderate to low potential for physical and psychological dependence. Schedule III drugs share potential to less than Schedule I and Schedule II drugs but more than Schedule IV. Some examples of Schedule III drugs are:  
Products containing less than 90 milligrams of codeine per dosage unit (Tylenol with codeine), buprenorphine, anabolic steroids, testosterone
- Schedule IV**  
Schedule IV drugs, substances, or chemicals are defined as drugs with a low potential for abuse and low risk of dependence. Some examples of Schedule IV drugs are:  
Xanax, Sonata, Darvon, Darvocet, Valium, Ativan, Tizan, Ambien, Tramadol
- Schedule V**  
Schedule V drugs, substances, or chemicals are defined as drugs with lower potential for abuse than Schedule IV and consist of preparations containing limited quantities of certain narcotics. Schedule V drugs are generally used for antidiarrheal, antitussive, and analgesic purposes. Some examples of Schedule V drugs are:  
Cough preparations with less than 200 milligrams of codeine or per 100 milliliters (Robitussin AC), Lomotil, Motrin, Lyrica, Percocet

Optometry and Opioids (02/2020)

- Cannot RX: DC, Guam, HI, MD, MA, NY, PR, VI, CNMI
- Schedule I Limited: IN (Tramadol), MN, MS
- Schedule III Limited: AL, FL\*, ME, ND, NH, PA, TX\*, VT, WY
- TX can administer Schedule II, FL APAP with Codeine and Tramadol
- Schedule II ONLY HYDROCODONE: AK, AR, AZ, CO, DE, GA, IL, KY, MI, NM, NJ, OH, OK, OR, RI, SC, UT, VA, WA, WV, WI
- Schedule II Hydrocodone, Tramadol, Codeine: CA
- Schedule II Unrestricted: CT, ID, IA, LA, KS, MO, MT, NC, NE, NV, SD\*, TN
- SD Limited to 30 day supply
- October 6th, 2014- DEA reclassifies Hydrocodone

Drug Diversion

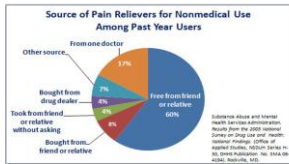
- <https://www.deadiversion.usdoj.gov/>
- The use of prescription drugs for recreational purposes
- The diverting of prescription drugs for other than it's intended purpose.
- From CMS:
  - Drug diversion is the illegal distribution or abuse of prescription drugs or their use for purposes not intended by the prescriber. (1) The diversion of prescription drugs may occur at any point as prescription drugs are distributed from the manufacturer to wholesale distributors, to pharmacies, and ultimately to the patient. (2) Members of the medical profession may also be involved in diverting prescription drugs for recreational purposes, relief of addictions, monetary gain, self-medication for pain or sleep, or the alleviation of withdrawal symptoms.

Drug Diversion- Common Types

- Selling prescription drugs
- Doctor shopping
- Illegal internet pharmacies
- Drug theft
- Prescription pad theft and forgery
- Illicit prescribing

Year	Maine pharmacy thefts (in drug units)	U.S. pharmacy thefts (in drug units)
2019	68 <sup>th</sup> 23 <sup>rd</sup> 9 <sup>th</sup>	26 <sup>th</sup> 46 <sup>th</sup> 28 <sup>th</sup>
2020	43 <sup>rd</sup> 37 <sup>th</sup> 20 <sup>th</sup>	11 <sup>th</sup> 44 <sup>th</sup> 45 <sup>th</sup>

Drug Diversion- Opioids



Drug Diversion

- **Clinical Practices That Can Minimize Drug Diversion**
  - Exercising caution with patients who use or request combination or "layered" drugs for enhanced effects (for example, anti-psychotics with opioids or benzodiazepines)
  - Documenting thoroughly when prescribing narcotics or choosing not to prescribe
  - Keeping a DEA or license number confidential unless disclosure is required
  - Moving to electronic prescribing so that paper prescriptions are not required
  - Adhering to strict refill policies and educating office staff
  - **Using State Prescription Drug Monitoring Programs (PDMPs), where available**
  - Referring patients with extensive pain management or prescription controlled medication needs to specialized practices
  - Collaborating with pharmacy benefit managers and managed care plans as they seek to determine the medical necessity of prescriptions for controlled substances.
  - Pill Counts at Random



Drug Diversion – REPORT IT!

- Local law enforcement and local fraud alert network
- DEA, for reporting theft or loss of controlled substances:
  - [https://www.deadiversion.usdoj.gov/webform\\_rpt.asp](https://www.deadiversion.usdoj.gov/webform_rpt.asp)
- U.S. Department of Health and Human Services, Office of Inspector General (HHS-OIG) by
  - e-mail at [HHS-Tips@oig.hhs.gov](mailto:HHS-Tips@oig.hhs.gov)
  - Telephone at 1-800-HHS-TIPS (1-800-447-8477)
  - TTY: 1-800-377-4950

Drug Diversions- Turn ins

• Drug Turn Ins

Case Study

- 48 yo Native American Male- Assaulted with Fist x 3 days ago
- Lost Glasses (i.e. never got them)
- All entrance testing normal
- Refraction:
  - OD: -6.00-2.50x177 20/25
  - OS: -6.50-1.75x10 20/25-



Acetaminophen and NSAID

- Alternating OTC medications consistently found to provide adequate acute pain relief
- Start with either at initial dosage
  - 500mg Extra Strength Tylenol to start (best)
  - 200mg Ibuprofen (Ibun)
  - 325mg or 500mg Tylenol (10pm)
  - 200mg Ibuprofen (Noon)
  - 325mg or 500mg Tylenol (8pm)
  - 200 mg Ibuprofen (4pm)
  - 325mg or 500mg Tylenol (6pm)
  - 200 mg Ibuprofen (2pm)
  - 325mg or 500mg Tylenol (10pm)
- 2500 mg Tylenol, 800 mg Ibuprofen or 2000mg Tylenol 1000mg Ibuprofen
- <https://www.fda.gov/oc/publications/fda-news/2020-archive/march/fda-approves-combination-ibuprofen-acetaminophen-drug-for-us>

Any NSAID

- Naproxen BID
- Ibuprofen 400mg, 600mg, 800mg TID
- Acetaminophen 500/325mg q4-6 hours
- Should be your "workhorse" medication for any acute short term pain relief

ICE PACKS

- Don't forget about ICE!
- Every 2 hours for 15-20 minutes for 72 hours.



A bit of everything...

- 76 year old Pueblo Male presents with Swollen Left Upper Eyelid (May 2015)
- Established patient, multiple co-morbidities
- Diabetes, Chronic Pain (opioid management), Hypertension, Neuralgia, Sleep Apnea, Obesity and Asthma



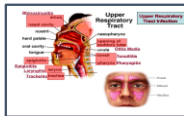
CASE HISTORY

- 76 year old Pueblo Male presents to the ER/Urgent Care
- Upper Respiratory Infection
- Augmentin
- Prednisone 40mg PO



URTI Background

- The upper respiratory tract includes:
  - Mouth
  - Nose
  - Sinus
  - Throat
  - Larynx (voice box)
  - Trachea (windpipe)
- Often referred to as "colds"
- Viral or bacterial



Complicated by amount of co-morbidities in this patient.

Follow-up

- Patient returns to the ER, stating no improvement in URTI
- Patient is given 2 grams of Intramuscular Steroid
- Stopped taking Augmentin



Back to optometry

- 76 year old Pueblo Male presents with Swollen Left Upper Eyelid
- History as presented—2 ER trips
- But now...



Treatment

- Started on Augmentin 875/125mg BID x 14 days
  - Can alter based on allergies
  - Prefer less total dosages (BID)
- Started on Acyclovir 800mg 5x/day x 7 days (formulary)



Medication	Initial Dosage
Zovirax (Acyclovir)	800mg 5x/day PO
Famvir (Famciclovir)	500mg tid PO
Valtrex (Valacyclovir)	1000mg tid PO

Follow-up

- Patient returns for 2 day follow up
- Pre-Septal is looking better
- Zoster looks the same, definitely not worse.
- Pain is WORSE
- Already taking Gabapentin, Percocet daily
- Capsaicin Cream: Pharmacy/Quick Order
- Amitriptyline 25mg PO TID



**Table 3. Medications to Treat Postherpetic Neuralgia**

Class	Indication	Dosage	Cost of generic (month)	AEI	Adverse effects
Anticonvulsants	Gabapentin (Parsiphen)	1,800 to 3,600 mg per day	\$30 to \$186	2.8 to 5.7	Somnolence, dizziness, vertigo, dry mouth
	Pregabalin (Lyrica)	300 to 600 mg per day	\$6.555 to \$1180	4.9	
Opioids	Codeine/acetaminophen (Tylenol)	Variable	\$4.52/30, 15 mg 15 (over-the-counter)	2.7	Constipation, nausea, vomiting, respiratory depression
	Long-acting morphine (Morphine)	Variable	\$60/300, 15 mg 15 (over-the-counter)	2.7	
	Tramadol (Ultram)	300 to 400 mg per day	\$46/300, 300 mg per day	4.8	Dependence
	Hydrocodone (Vicodin)	Applied twice or four times per day	\$4.52/30, 30 per day	3.3	Burning skin
Tricyclic antidepressants	Amitriptyline (Elavil)	Up to 150 mg per day	\$17/300	2.6	Headache, dry mouth, constipation, urinary retention
	Nortriptyline (Pamelor)	Up to 150 mg per day	\$180/300, 150 mg per day	4.9 to 5.3/300	

AEI = per 100 patients, AEI = a number related to cost.  
 \*Costs per month are based on information obtained from [www.drugs.com](http://www.drugs.com) accessed February 16, 2015. Consult your local formulary for the most current information.  
 †Only the generic or off-invented price (OIP) is listed. For the most up-to-date list of one or more national retail chains, please contact your local pharmacy.  
 ‡Adapted with permission from Gendrony, Chhabra S, Lewis J, Boudin DC. Clinical implications: what resources reduce postherpetic neuralgia? *Chin Med (Lond Engl)*.

Source: aetb.org

Over the next 6 Weeks

- Severe Post Herpetic Neuralgia
  - Cannot sleep at times
  - Cannot function daily
  - Taking all medications
- Pre-Septal Resolved in 7 days
- Eventually referred to pain management clinic
  - Lost to follow up/referral issues
- Steroids—can/did make it worse?
  - Small Studies- can be beneficial
  - Large Studies- can make it worse



Conclusion

- Work with your Pharmacist
  - \*\*\*if you don't have one, work to get one!\*\*\*
- Sometimes modern medicine is pushed for answers
- Get background information:
  - Case history
  - Recent medications



Thanks!

Feel free to email  
 Questions  
 Comments  
[Christopher.Cordes@ihs.gov](mailto:Christopher.Cordes@ihs.gov)  
 Find me on Facebook, etc.