



Treatment of Pain
Opioid Choices and Issues for
Patient and Practitioner

Greg Caldwell, OD, FAAO
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Disclosures- Greg Caldwell, OD, FAAO

- Will mention many products, instruments and companies during our discussion
 - I don't have any financial interest in any of these products, instruments or companies
- Pennsylvania Optometric Association - President 2010
 - POA Board of Directors 2006-2011
- American Optometric Association, Trustee 2013-2016
- I never used or will use my volunteer positions to further my lecturing career
- Lectured for: Alcon, Allergan, Aerie, BioTissue, Maculogix, Optovue
- Advisory Board: Allergan, Maculogix, Sun, Kala
- Involve: PA Medical Director, Credential Committee
- HealthCare Registries: Consultant
- Optometric Education Consultants - Scottsdale, WDW, St. Paul, Quebec City, and Nashville, Owner



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Agenda

- The opioid crisis
- Pain definition
- Pathways of pain and the receptors
- Types of pain
- Grading pain - pain scales
- The opioids - opioids, semisynthetic, and synthetic
- Formulation changes to help prevent ease of abuse
- Allergies to opioids and the alternatives
- Opioid adverse drug reactions
- Opioid antagonists
- Tolerance
- True Addiction
- Alternatives or additions to opioids
- Ocular cases where opioids were used
- Questions and answers

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NIH: National Institute on Drug Abuse
As of March 2018

- Every day, more than 115 people in the United States die after overdosing on opioids
- The misuse of and addiction to opioids
 - Prescription pain relievers, heroin, and synthetic opioids such as fentanyl
- Serious national crisis that affects public health as well as social and economic welfare
- The Centers for Disease Control and Prevention estimates that the total "economic burden" of prescription opioid misuse alone in the United States is \$78.5 billion a year
 - Including the costs of healthcare, lost productivity, addiction treatment, and criminal justice involvement

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What do we know about the opioid crisis?
NIH: National Institute on Drug Abuse (March 2018)

- Roughly 21 to 29 percent of patients prescribed opioids for chronic pain misuse them
- Between 8 and 12 percent develop an opioid use disorder
- An estimated 4 to 6 percent who misuse prescription opioids transition to heroin
- About 80 percent of people who use heroin first misused prescription opioids
- Opioid overdoses increased 30 percent from July 2016 through September 2017 in 52 areas in 45 states
- The Midwestern region saw opioid overdoses increase 70 percent from July 2016 through September 2017
- Opioid overdoses in large cities increase by 54 percent in 16 states

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What are HHS and NIH doing about it?

- In the summer of 2017, NIH met with pharmaceutical companies and academic research centers to discuss:
 - Safe, effective, non-addictive strategies to manage chronic pain
 - New, innovative medications and technologies to treat opioid use disorders
 - Improved overdose prevention and reversal interventions to save lives and support recovery

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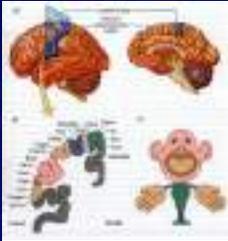
Pain

- ~ Pain is very important to our survival
- ~ Pain is defined as the perception of a noxious (harmful) stimulus
- ~ Pain can also occur in the absence of injury or long after an injury has healed
- ~ Pain provides humans with information about:
 - * Tissue-damaging stimuli
 - * Thus enables them to protect themselves from greater damage
- ~ Pain is protective in two ways:
 - * It removes a person from stimuli that cause tissue damage through withdrawal reflexes
 - * Learning associated with pain causes the person to avoid stimuli that previously caused pain
- ~ Pain often initiates the search for medical assistance and helps us to pinpoint the underlying cause of disease

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Somatosensory System

- ~ Diverse sensory system composed of the receptors and processing centers to produce the sensory modalities:
 - * Touch
 - * Temperature
 - * Proprioception (body position)
 - * Nociception (pain)
- ~ The system reacts to diverse stimuli using different receptors
 - * Thermoreceptors
 - * Nociceptors
 - * Mechanoreceptors
 - * Chemoreceptors



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Pain

- ~ Pain is an unpleasant sensory experience associated with actual or potential damage to the body, or perception of such damage. It is a subjective experience
- ~ Subjective experience
- ~ Memories of events associated with extreme pain persist for a long time
- ~ Mental state is known to have a powerful influence over pain
 - * An athlete may not notice a twisted ankle until after the competition is over.
 - * Soldiers in battle often continue to fight even after sustaining serious injury, and they may report afterwards that they experienced no pain until after battle
- ~ The scientific explanation for this phenomenon is that the brain not only receives pain messages, but also has a descending system of neurons that suppresses pain messages

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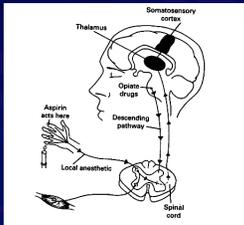
Pharmacology of Pain Management

- ~ **Peripheral acting agents**
 - * Prevent sensitization of receptors to substance P
 - * Example: NSAIDs, ibuprofen
- ~ **Signal inhibiting agents**
 - * Prevent pain signal from travelling to cortex
 - * Example: Anesthetics, proparacaine
- ~ **Central acting agents**
 - * Act on pain perception centers in the cortex (CNS)
 - * Example: opioids/narcotics

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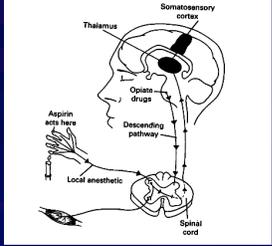
Descending Pathway

- ~ This system inhibits cells in the spinal cord that transmit pain signals
- ~ A pathway for natural pain modulation
- ~ Opioids that occur naturally such as the endorphins are important neurotransmitters in some of these descending pathways



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Peripheral versus Central Acting



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Four Major Types of Pain

- ☞ Nociceptive Pain
 - * Typically the result of tissue injury
- ☞ Inflammatory Pain
 - * An abnormal inflammation caused by an inappropriate response by the body's immune system
- ☞ Neuropathic Pain
 - * Pain caused by nerve irritation
- ☞ Functional Pain
 - * Pain without obvious origin but can cause pain

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Drug Treatment Options... Neuropathic Pain

- ☞ Not the focus of today's discussion...
- ☞ Why is this relevant?
- ☞ Adjuvants – means “add on” medications
 - * Some of them have addiction potential
 - ☐ Anti-seizure medications that address nerve damage/inflammation
 - MOA: work on the GABA system – similar to benzodiazepines (ex. Xanax)
 - Gabapentin (Neurontin) – controlled substance in multiple states
 - Pregabalin (Lyrica) – controlled substance in all 50 states
 - ☐ Anti-anxiety and sleep medications
 - Zolpidem (Ambien)
 - Alprazolam (Xanax), Lorazepam (Ativan), Diazepam (Valium)

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Neuropathic Pain Chronic Pain

- ☞ Trigeminal neuralgia
- ☞ Post-herpetic neuralgia
- ☞ Diabetic neuropathy
- ☞ Phantom limb pain following an amputation
- ☞ Multiple sclerosis
- ☞ Pain following chemotherapy
- ☞ HIV infection
- ☞ Alcoholism
- ☞ Tension headache
- ☞ Migraine
- ☞ Fibromyalgia
- ☞ Low back pain

- ☞ Tricyclic antidepressants for pain
 - * The most effective type of antidepressant used for pain
 - * Imipramine Tofranil
 - * Clomipramine Anafranil
 - * Nortriptyline Pamelor
 - * Desipramine Norpramin
- ☞ Anticonvulsants for pain
 - * Gabapentin Neurontin
 - * Topiramate Topamax
 - * Pregabalin Lyrica
 - * Carbamazepine Tegretol
 - * Oxcarbazepine Trileptal

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Acute versus Chronic Pain

- ☞ Acute
 - * Where we are most of the time as optometrists
 - * Acetaminophen
 - * NSAIDS
 - * Opioid
- ☞ Chronic
 - * Acetaminophen
 - * NSAIDS
 - * Opioid
 - * Tricyclic antidepressants
 - * Gabapentin (Neurontin)

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Goals of Pain DO Differ...

The goal for managing **acute pain** is to keep the patient as comfortable as possible while minimizing the **adverse drug reactions (ADRs)** from the pain meds.

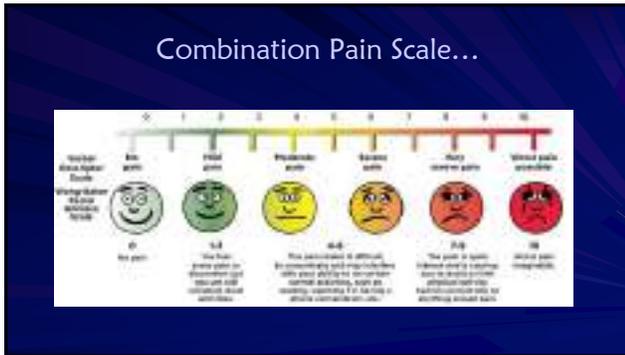
The goals for managing **chronic pain** are to keep the patient as comfortable as possible (this may not mean the patient is pain free) and integrating the patient back into a “normal life” and activities of daily living, while minimizing the ADRs from the pain meds.

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Pain Assessments and Scales

- ☞ Adds objective data to a patient's feeling of pain
 - * It is a subjective problem to assess!
 - * Remember...no patient should needlessly suffer!
- ☞ “Does the injury or wound or diagnosis fit the patient's presentation?”
 - * It is important to be able to assess the degree of pain in a patient.

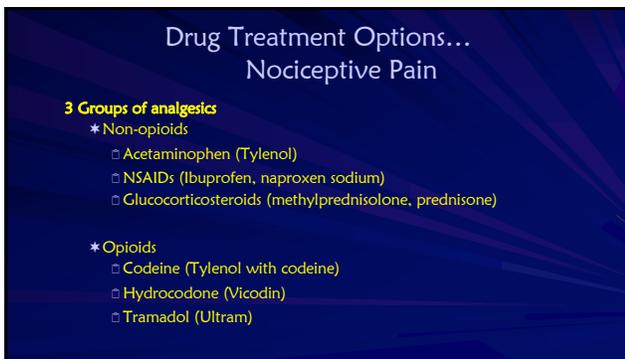
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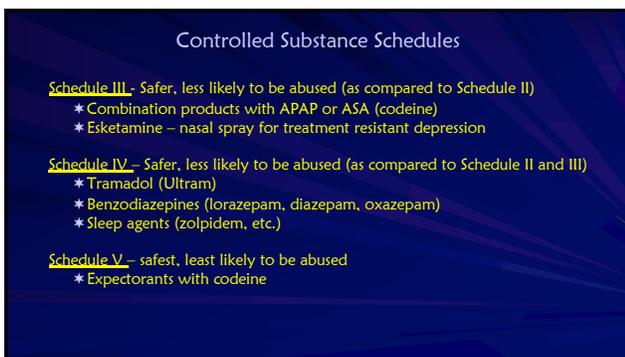
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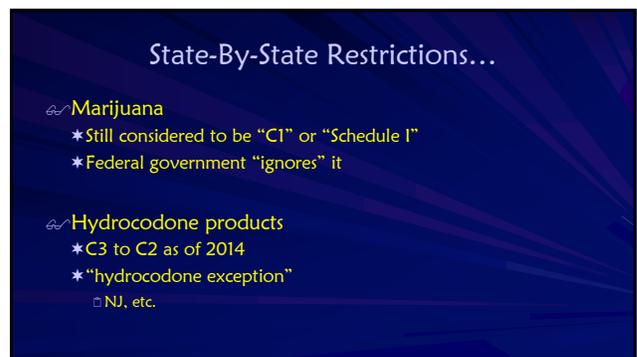
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Formulations

- ~ **Immediate release**
 - * AKA short-acting
 - * Uses: acute pain
 - Percocet, Tylenol w/ codeine, tramadol, Vicodin
- ~ **Controlled release:**
 - * AKA long-acting; sustained release; extended release
 - * Uses: basal control of chronic pain
 - * Typically NOT for acute pain nor in opioid naive patients!
 - OxyContin, MS Contin, Duragesic patch

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Morphine Products

- ~ Standard for comparison of other agents
- ~ Used for severe pain
- ~ Multiple Brand/Trade names for long-acting morphine products, with very diverse delivery and release systems
 - * **MSIR** (IR caps) (q 3-4 hours prn)
 - * **MS Contin** (CR tabs) (q 8-12 hours)
 - * **Kadian** (CR caps) (q 12 - 24 hours)
 - * **Avinza** (CR caps) (q 24 hours)

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Hydromorphone Products

- ~ **Hydromorphone (Dilaudid)** tablets – immediate release
 - * Take 1 – 2 tablets every 4 to 6 hours as needed for pain
- ~ **Hydromorphone ER (Exalgo)** tablets – extended release
- ~ Used for severe pain
- ~ Very potent
 - * Compare to morphine
 - 30mg PO morphine = 8mg PO hydromorphone



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Codeine-Based

- ~ **Codeine – C3; Schedule III**
 - * Naturally occurring opioid
- ~ **Hydrocodone – C2; Schedule II**
 - * Semi-synthetic derived from codeine
 - * More potent than codeine
 - * Retains cough suppression
- ~ **Oxycodone – C2; Schedule II**
 - * Semi-synthetic derived from codeine
 - * Pain only, **no cough** suppression



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Codeine tablets

- ~ **WEAK analgesic: 30mg PO morphine = 200mg PO codeine**
 - * Weakest of morphine, hydrocodone, and oxycodone
- ~ **Add acetaminophen/ aspirin – Schedule III**
 - * Tylenol #2 = 300 mg acetaminophen & 15 mg codeine
 - * **Tylenol #3** = 300 mg acetaminophen & 30 mg codeine
 - * Tylenol #4 = 300 mg acetaminophen & 60 mg codeine
- * 1 – 2 tablets every 4 – 6 hours as needed for pain
 - Not to exceed **3 grams** of APAP per day
- ~ Add expectorant – Schedule V

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Oxycodone Products

- ~ **Long-Acting, Extended-Release**
 - * OxyContin
- ~ **Immediate Release; short-acting tablets**
 - * OxyIR (IR cap)
 - * Roxicodone solution
- ~ **Combination with acetaminophen**
 - * Percocet and Endocet (oxycodone/APAP dose)
- ~ Take 1 – 2 tablets by mouth every 4 to 6 hours as needed for pain
 - * Not to exceed 3 grams of APAP per day

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Oxycodone Products

- ⚡ **Percodan** (oxy + asa) – no one uses this product
- ⚡ **Percocet**
 - * Oxycodone is combination with acetaminophen
 - * Various strengths
- ⚡ 30mg PO morphine = 20mg PO oxycodone

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Hydrocodone Products

- ⚡ As of August 2014, hydrocodone products are ALL CII
 - * Moved from schedule III to schedule II
- ⚡ Immediate-Release Products
 - * **Hydrocodone 7.5 mg + IBU 200 mg**
 - **Vicoprofen**
 - * **Hydrocodone + acetaminophen:**
 - **Vicodin** = 5/300; 7.5/300; 10/300
 - **Lortab** = 2.5/300, 5/300, 7.5/300, 10/300
 - **Norco** = 5/325, 7.5/325, 10/325
- ⚡ Take 1 – 2 tabs/caps every 4 – 6 hours as needed for pain
 - * Not to exceed 3 grams of APAP per day
- ⚡ 30mg PO morphine = 20mg PO hydrocodone

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Tramadol – another great choice

Tramadol (Ultram) tabs
Tramadol with 325 mg APAP (Ultracet), Tramadol ER tabs

- ⚡ tramadol (50 – 100 mg q 4 – 6 hours; do not exceed 400 mg/day)
- * Dual action: **mu** receptors & inhibits neuronal uptake of **serotonin** & **norepinephrine**
- * Lowers seizure threshold; increases serotonin levels
 - watch drug interactions with other meds that ↑ serotonin
 - Selective serotonin reuptake inhibitors (SSRI): fluoxetine/Prozac
 - Migraine meds (“triptans”): sumatriptan/Imitrex
- * **Not controlled**
 - AS OF AUGUST 2014, NOW A C4 (Schedule IV)
 - “tramies” = abuse potential; helps decrease withdrawal symptoms

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Miscellaneous

- ⚡ **Fentanyl Patch (Duragesic)**
 - * **MOST potent opioid**
 - * **Black Box Warning** against use in acute pain and in opioid naïve patients
- ⚡ **Meperidine (Demerol)**
 - * **ACTIVE metabolites = undesirable**
- ⚡ **Methadone**
 - * Typically reserved for morphine/codeine allergic patients

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Methadone tidbits...

- ⚡ Chronic pain or opioid abuse deterrent
- ⚡ 2-phase elimination
 - * Alpha phase = 8 hrs
 - Offers pain control
 - * Beta phase = 16+ hrs
 - Mitigates withdrawal symptoms
- ⚡ Patient 1: On a short-acting pain med = likely being used to treat chronic pain
 - * Twice per day dosing
- ⚡ Patient 2: On methadone ONLY; lower doses
 - * Once daily dosing

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Analgesic Medications in Pregnancy

- ⚡ Acetaminophen (Tylenol)
 - * Analgesic of choice in pregnancy
- ⚡ NSAIDs should generally be avoided in pregnancy
 - * Despite Category B
 - * Miscarriage risk in first trimester
 - Ibuprofen
 - * Second trimester use is likely safe
 - Ibuprofen
 - * Third trimester avoid ALL NSAIDs
 - Premature Ductus Arteriosus closure in third trimester
- ⚡ Opioids should be avoided in pregnancy unless there is no viable alternative
 - * First trimester use is associated with heart defects and spina bifida

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Opioid Allergies

- ~ If a patient states "codeine allergic" ask appropriate questions
 - * "You have indicated that you have an allergy to codeine, can you describe what happens when you take codeine?"
- ~ If a patient is truly allergic to codeine
 - * Most likely allergic to morphine, hydromorphone, oxycodone, hydrocodone, and tramadol
- ~ And...if they had an opioid IV after surgery, then their "reaction" may have been due to histamine release
 - * NOT always an allergic reaction



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Opioid Allergies

- ~ Do you know what a patient can take if true codeine allergy?
 - Fentanyl
 - Methadone
 - Meperidine
- ~ Assessing "allergies" appropriately helps practitioner sort through Actual allergy potential and "placebo allergies"
 - Fear versus drug seeking

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Specific Medications Using Numeric Pain Scale

Mild pain = 1 – 3

- ~ Acetaminophen (APAP; Tylenol)
- ~ Ibuprofen (Advil, Motrin)
- ~ Naproxen sodium (Aleve)
- ~ Tramadol (Ultram) - low dose



Moderate pain = 4 – 6

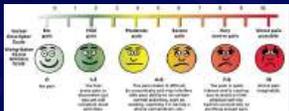
- ~ Tramadol (Ultram) – mid to high dosing
- ~ Tylenol with codeine (Tylenol #3)
- ~ Acetaminophen with oxycodone (Percocet)
- ~ Acetaminophen with hydrocodone (Vicodin) – lower dosing

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Specific Medications Using Numeric Pain Scale

Severe pain = 7 – 10

- ~ Tylenol with hydrocodone
 - * Vicodin, etc. – higher doses
- ~ Tylenol with oxycodone
 - * Percocet, etc. – higher doses
- ~ Morphine (MSIR)
- ~ Hydromorphone (Dilaudid)
- ~ Fentanyl (Duragesic patch; Actiq lozenge on a stick)



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"Ceiling Effect"

- ~ Commonly used when discussing *analgesics*
- ~ Phenomenon in which a drug reaches a maximum effect
 - * Increasing the drug dosage does not increase its effectiveness
- ~ Central Nervous System Agents
 - * No ceiling effect
 - * Part of the problem
- ~ Peripheral Nervous System Agents
 - * Has a ceiling effect

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Tolerance

- ⚡ Escalation of dose to maintain effect
 - * Analgesia or euphoria
 - * Happens to everyone
- ⚡ Regarding euphoria = may be life threatening because respiratory depression does not show much tolerance

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Opioid Effects/ADRs

- ⚡ CONSTIPATION-anticipate it!
 - * **ALL** patients should receive a stool softener + stimulant
 - * Combo: docusate + senna/Senna+S
- ⚡ Sedation
- ⚡ Euphoria – mu receptors
- ⚡ Dysphoria/Hallucinations
- ⚡ Pruritis – allergy versus normal release of histamine
- ⚡ Nausea/vomiting
 - * Triggers CTZ
 - * Codeine "allergy"

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Opioid Effects/ADRs

- ⚡ Confusion
- ⚡ Miosis
- ⚡ Respiratory depression
 - * This is what kills a patient
 - * **Mixing opioids with other CNS depressants**
 - ☐ Alcohol
 - ☐ Benzodiazepines
 - ☐ Muscle relaxers
 - ☐ Sleep agents
 - ☐ Antihistamines
 - ☐ Anti-seizure medications



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Opioid Effects/ADRs

- ⚡ Withdrawal symptoms:
 - * Short half-life agents are more likely to cause abrupt withdrawal symptoms
 - * Sweating
 - * High sympathetic tone: increase in heart rate and blood pressure, mydriasis
 - * Agitation
 - * Irritation
 - * Irrational behavior
 - * Symptoms disappear with (immediate) use of an opioid

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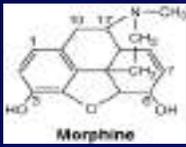
Respiratory Affects

- ⚡ Inhibition of cough reflex
- ⚡ Respiratory depression
 - * This is what kills a patient
 - * **Important to make sure that the patient doesn't**
 - ☐ Increase dose on their own
 - ☐ Add another CNS depressant with it!

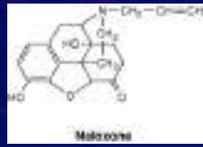
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Overdosing

- ⚡ Opioid antagonists
- ⚡ **Naloxone (Narcan) & Naltrexone (ReVia)**
 - * Used to treat opioid overdose



Morphine



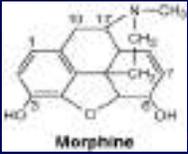
Naloxone

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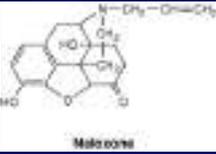
Opioid Antagonist

Naloxone (Narcan) & Naltrexone (ReVia)

- * Used to treat opioid overdose



Morphine



Naloxone

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Mixed Opioid Agonist-Antagonist For the Treatment of Abuse/Addiction

- Exhibit partial agonist or antagonist activity at the opioid receptors
- Agonist/Antagonist combinations for the treatment of opioid abuse/addiction**
 - * **Buprenorphine (Buprenex)**
 - * Buprenorphine/Naloxone (Suboxone)
- Schedule III**
- Adverse effects
 - * Less respiratory depression & less abuse potential?
 - * Precipitate withdrawal in an opioid-dependent patient

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Mixed Opioid Agonist-Antagonist for the Treatment of Chronic Pain

- Exhibit partial agonist or antagonist activity at the opioid receptors
- Agonist/Antagonist combinations for the treatment of chronic pain**
 - * **Not appropriate for the treatment of acute pain**
 - * Morphine/Naltrexone (Embeda)
 - * Oxycodone/Naltrexone (Troxyc ER)
- Schedule II controlled substance**

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Substance Abuse History

- Avoid all opioids in a patient with a history of heroin use
 - * This includes tramadol
 - * May trigger dopamine reward and the drug "need"
 - * Stick with higher doses of a NSAID +/- acetaminophen
- Patients with abuse history for other substances
 - * Ex. Benzodiazepines, alcohol, amphetamines?
 - * It is a judgement call
 - * Some evidence to suggest that all addictive meds should be avoided!

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"True Addiction" formerly "Psychological Dependence"

- Compulsive use despite harm
- Quality of life is not improved by the medication and eventually it becomes compulsive
 - * "Wanting without liking"
- Relapse is very common even after "successful" withdrawal
 - * It is a relapsing disease that is incredibly hard to treat

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Identifying Behaviors of Abuse/Addiction

- "Fast talkers"
- Strange allergies
- Excuses for "loss" of meds
- Excuses why they need "a strong pain medication"

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Ways to respond

- ~ Avoid getting "bullied"
- ~ Avoid acting like you are judging the patient
- ~ Use the tools that are available
 - * Call your local pharmacy/pharmacist
 - * State databases
 - o PDMP = Prescription Drug Monitoring Program
- ~ Legal/ethical issues
 - * If you didn't write it down, then it didn't happen!

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Prescription Monitoring Program (PMP)



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Ways to Combat Abuse

Drug Company Approaches

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OxyCONTin (Controlled release tablets (q 12 hours...once in a while q 8 hours): new formulation is out to help control abuse

Manual Crushing Followed by Dissolution



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Tampering for IV Abuse

- * New formulation results in gelatinous material which cannot be drawn into a syringe for injection (the syringe is empty)

New formulation



Original formulation



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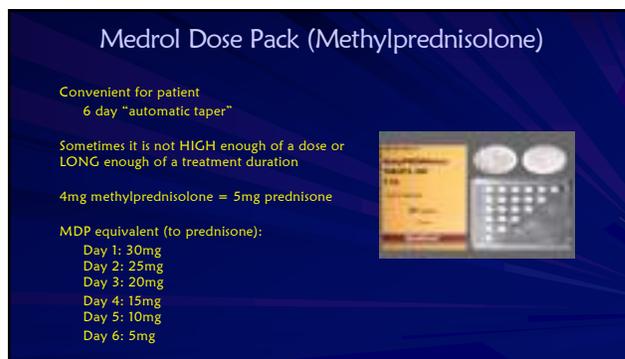
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Acetaminophen (Tylenol)

- o Mechanism: largely unknown
- o Mild to moderate pain
- o No anti-inflammatory potential
- o Available in 325mg, 500mg, and 650mg tablets/capsules
- o Dosing: 1,000mg every 6 to 8 hours OR 650mg every 6 hours
 - o Max daily dose: DO NOT EXCEED 3,000 to 4,000mg in 24 hours
 - o OK to use ALONG with or ALTERNATING with ibuprofen or naproxen
- o ADRs: avoid in patients who consume > 3 alcoholic beverages per day

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NSAIDs – Ibuprofen (Advil/Motrin)

- Mechanism: prostaglandin inhibitors = decrease in inflammatory mediators
- Good for pain and inflammation
- Mild to moderate pain
- Available in 200mg (OTC) and 400mg, 600mg, and 800mg tablets (RX only)
- Dosing: 200mg to 800mg every 6 to 8 hours
 - Max daily dose: do not exceed 3,200mg in 24-hour period
 - MUST reach 1,200mg daily to achieve anti-inflammatory potential

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NSAIDs – Naproxen Sodium (Aleve)

- o Mechanism: prostaglandin inhibitors = decrease in inflammatory mediators
- o Good for pain and inflammation
- o Mild to moderate pain
- o Available in 220mg, 275mg, 375mg, and 550mg tablets
- o Dosing: 220 to 440mg every 8 to 12 hours OR 660mg every 24 hours OR 550mg every 12 hours
 - o Acute pain: more often is BETTER
 - o Maximum daily dose is 1,000 to 1,100mg in 24 hours period
 - o OK to dose 1,375mg to 1,500mg on DAY 1 ONLY!
- o Anti-inflammatory potential: dose at HIGHER END of range

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NSAIDs – Adverse Effects

- o Take with food – tough on the stomach
- o May cause vasoconstriction in the kidneys
- o Inhibits platelet aggregation, so ibuprofen interacts with warfarin (Coumadin) = ↑ INR
- o May increase risk of heart attack and stroke in patients at "high risk" and with "regular use"
- o May increase blood pressure and IOP

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SYNERGY...

It is acceptable to use an ALTERNATING dosing regimen OR an ADDITIVE dosing schedule

Good in moderate to severe pain



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Pain Reliever Help

Know your maximum daily allowances:

- APAP 3000 mg (4000 mg*)
- ASA 6000 mg
- Ibuprofen 3200 mg
- Naproxen Sodium 1650 mg (Aleve/Anaprox)
- Naproxen 1500 mg (Naprosyn)
- Codeine 240 mg
- Hydrocodone 60 mg
- Tramadol 300-400mg

2 ibuprofen and 2 Tylenol
4 ibuprofen and 2 Tylenol

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Alternative?



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Practical Application- Side Effects

- Elevated LFTs (liver function tests)
 - * AST and ALT – why *THESE???*
 - * High doses of CBD
- Drowsiness/Dizziness
- Diarrhea
- Dry mouth
- Hypotension
- Increase in IOP
- Change in appetite

Generally, side effects are most often seen in people taking HIGH doses of CBD

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Our Associations Fought Hard

We took this course for a reason

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Cases Where I Recently Used My DEA

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Conditions Which May Require Pain Management

- Large cornea abrasions
 - * Cornea burn
 - * PRK/PTK
- Orbital trauma
- Orbital blowout fractures
- Scleritis

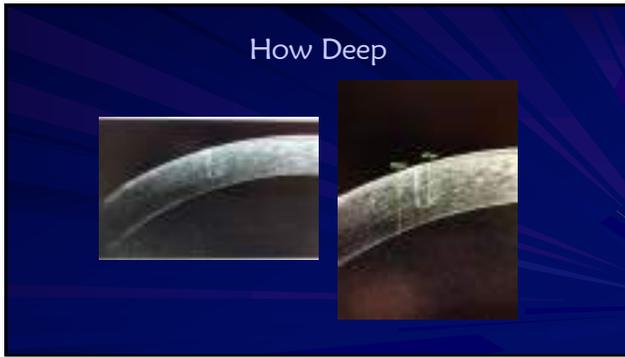


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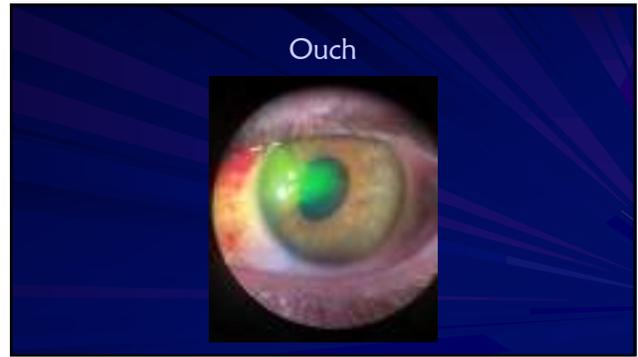
A “bit” Too Close



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Optometric
Education
Consultants

Thank you!

Treatment of Pain Opioid
Choices and Issues for
Patient and Practitioner



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