Pain Management in Dermatology

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Disclosures

- I have no financial relationships to disclose
- I will not discuss off label and/or investigational use in my presentation

Objectives

- Discuss the importance of responsible opioid prescribing to help prevent abuse and misuse of opioids
- Determine when to initiate opioids for patients in pain
- Opioid selection, dosage, duration, follow-up, and discontinuation

Opioids and Adjuvants

What Is The Best Approach to Pain?

- Multidisciplinary approach with multimodal analgesia:
  - Minimizes dose requirements and potential toxicity
  - Effective pain relief by additive or synergistic use of two or more analgesics
  - Reducing the amount of each agent will reduce incidence and severity of serious side effects
  - Employs a variety of agents that interfere with pain transmission and perception in the central and peripheral nervous systems

World Health Organization…..“WHO”

- 1986 developed a three step analgesic ladder
- Provides a concrete tool for physicians worldwide to use in combating cancer pain with oral medications
- Used for non cancer pain conditions as well

WHO 3 Step Ladder

WHO 3 Step Ladder

- Begin with an non-opioid (Tylenol, Ibuprofen) and progress from weaker to stronger opioids (Step 1-3) for incremental pain severity
- Always consider adjuvant medications (TCAs, Anticonvulsants, NSAIDs, etc.) at any step of the ladder
- Estimated that 70-90% of cancer pain is relieved when clinicians apply the WHO ladder appropriately

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

- Used to treat mild to moderate acute and chronic pain, often due to musculoskeletal disorders
- Produce anti-inflammatory, analgesic, and antipyretic effects
- Use those with shorter half life over the shortest period of time to minimize renal and GI toxicity
- Can be associated with Renal, GI, and Hematologic toxicity
- Can worsen pre-existing renal disease

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

- Work by inhibiting cyclooxygenase (COX) and thereby limiting prostaglandin production
- Selective inhibition of COX2 produces less GI toxicity and can increase CV disease risk
- CI in CABG surgery
- Used for pain associated with inflammatory conditions (RA, gout)

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

- Examples:
  - Celecoxib (Celebrex)
    - 100mg p.o. Q 12 hours
    - 200mg p.o. Q day
  - Ibuprofen (Advil)
    - 600mg p.o. Q 8 hours
    - 800mg p.o. Q 8 hours
  - Diclofenac (Voltaren)
    - 50mg p.o. Q 12 hours
    - 75mg p.o. Q 12 hours
  - Meloxicam (Mobic)
    - 7.5mg po Q 12 hours
    - 15mg p.o. Q day
  - Naproxen (Naprosyn)
    - 500mg p.o. Q 12 hours

Acetaminophen

- Para-aminophenol derivative use to treat mild to moderate pain
- Analgesic and antipyretic activity similar to NSAIDs but weak anti-inflammatory effects
- No significant GI toxicity or platelet inhibition
- Be cautious of acetaminophen induced hepatoxicity
- Risk is increased in doses >3gm orally & >4gm IV
- Individual who drink 60g/d ETOH or history of binge drinking should take no more than 2g/d
- Tylenol 325mg p.o. Q 4-6 hours PRN PAIN

Anticonvulsants

- Most commonly used medication for neuropathic pain
- Thought to act as membrane stabilizers through different mechanisms of action
- Indications: treatment of neuralgias, peripheral neuropathy, painful diabetic neuropathy, post-herpetic neuralgia, cervical and lumbar radiculopathy

Anticonvulsants

- Gabapentin (Neurontin):
  - GABA analog that binds to subunit of Ca and decreases neurotransmitter release (exact MOA is unknown)
  - Good side effect profile, lacks drug interactions
  - Very little metabolism of drug, renal excretion
  - First choice anticonvulsant for treating chronic, neuropathic pain
  - Common adverse effects: dizziness, somnolence, fatigue, weight gain, nausea, withdrawal seizure if abruptly discontinued, and pedal edema

Anticonvulsants

- Gabapentin: 100-800mg p.o. Q 8 hours (max dose 3600mg/day)
  - Indications:
    - Post-herpetic neuralgia -> 300-600mg p.o. Q 8 hours
    - Painful DM neuropathy -> 300-1200mg p.o. Q 8 hours
    - Central pain
    - Phantom pain
    - Malignant pain
    - Trigeminal neuralgia
    - HIV neuropathy
- Horizant (Gabapentin Enacarbil)
- Gralise (Gabapentin ER)

Anticonvulsants

- Pregabalin (Lyrica): (max dose 600mg/day)
  - Acts at subunit of Ca channels (five times the receptor affinity of gabapentin), MOA unknown
  - Increases GABA concentration
  - Undergoes very little metabolism, renal excretion
  - Side effects: somnolence, dizziness, HA, nausea, weight gain
  - Indications:
    - FDA approved for:
      - Post-herpetic neuralgia -> 150-300mg p.o. Q 8-12 hours
      - Painful DM neuropathy -> 50-100mg p.o. Q 8 hours
      - Fibromyalgia -> 150-225mg p.o. Q 12 hours
      - Spinal cord injury pain -> 75-300mg p.o. Q 12 hours

Anticonvulsants

- Lyrica CR
  - Diabetic neuropathy -> 165-330mg p.o. Q day
  - Post herpetic neuralgia -> 165-330mg p.o. Q day
- Carbamazepine (Tegretol)
  - Trigeminal neuralgia ->200-400mg p.o. Q 12 hours
- Oxcarbazepine (Trileptal)
  - Trigeminal neuralgia ->450-1200 mg p.o. Q 12 hours

Opioids

- Among the most universally effective analgesic agents
- Derived from Poppy (papaver somniferum)
- Receptors in spinal cord and the brain modulate analgesic effect
- Specific receptors on the cell membranes are G-protein coupled

Side Effects and Adverse Reactions of Opioids

- Respiratory depression: dec RR, dec responsiveness of brain stem to inc CO_2 levels in arterial blood
- Constipation: reduction in GI motility
- N/V: activation of chemoreceptor trigger zone in the area postrema
- Pruritus: can be peripherally mediated due to histamine release or centrally mediated
- Bradycardia: stimulation of vagal efferent output
- Pupillary constriction: activation of nucleus Edinger-Westphal accessorius
- Opioid-Induced hyperalgesia: after prolonged administration and leads to inc pain
- Physical dependence, Tolerance (more to euphoric effects) and Addiction

Sleep-Disordered Breathing (Including Sleep Apnea)

- Risk factors for sleep-disordered breathing include congestive heart failure, and obesity.
- Experts noted that careful monitoring and cautious dose titration should be used if opioids are prescribed for patients with mild sleep-disordered breathing.
- Clinicians should avoid prescribing opioids to patients with moderate or severe sleep-disordered breathing whenever possible to minimize risks for opioid overdose.

Pregnant Women

- Opioids used in pregnancy might be associated with additional risks to both mother and fetus.
- Some studies have shown an association of opioid use in pregnancy with stillbirth, poor fetal growth, pre-term delivery, and birth defects.
- Importantly, in some cases, opioid use during pregnancy leads to neonatal opioid withdrawal syndrome.
- In addition, before initiating opioid therapy for reproductive-age women, clinicians should discuss family planning and how long-term opioid use might affect any future pregnancy.

Pregnant Women

- Neonatal toxicity and death have been reported in breast-feeding infants whose mothers are taking codeine.
- **Previous guidelines have recommended that codeine be avoided whenever possible among mothers who are breast feeding and, if used, should be limited to the lowest possible dose and to a 4-day supply**

Patients Aged ≥65 Years

- Pain management for older patients can be challenging given increased risks of both non-opioid pharmacologic therapies and opioid therapy in this population.
- Given reduced renal function and medication clearance even in the absence of renal disease, patients aged ≥65 years might have increased susceptibility to accumulation of opioids and a smaller therapeutic window between safe dosages and dosages associated with respiratory depression and overdose.

Patients Aged ≥65 Years

- Some older adults suffer from cognitive impairment, which can increase risk for medication errors and make opioid-related confusion more dangerous.
- In addition, older adults are more likely than younger adults to experience co-morbid medical conditions and more likely to receive multiple medications, some of which might interact with opioids (such as benzodiazepines).

Patients with Renal or Hepatic Insufficiency

- Clinicians should use additional caution and increased monitoring to minimize risks of opioids prescribed for patients with renal or hepatic insufficiency, given their decreased ability to process and excrete drugs, susceptibility to accumulation of opioids, and reduced therapeutic window between safe dosages and dosages associated with respiratory depression and overdose.

Clinical Usage of Opioids

- Immediate acting formulations are indicated for acute pain (post-surgical) – First 24-48 hours important to control pain relief

- Extended release formulations are used to treat chronic pain (malignant and non-malignant)

Determining When to Initiate or Continue Opioids for Chronic Pain

- Non-pharmacologic therapy and non-opioid pharmacologic therapy are preferred for pain.
- Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient.
- If opioids are used, they should be combined with non-pharmacologic therapy and non-opioid pharmacologic therapy, as this is deemed a "multi-modal" approach to pain management

Initiating Opioid Therapy

- Pain is moderate to severe?
- Pain has significant impact on function and quality of life?
- Opioids are indicated for specific pain condition?
- Non-opioid pharmacotherapy has been tried and failed?
- Start low, go slow → can titrate to optimal dose
- Always remember safety issues when selecting opioids, including altered pharmacokinetics (liver/kidney) &/or drug interactions

Initiating Opioid Therapy

- Assess pain score and level of function
- Appropriate trial of opioid therapy
  - +/- adjuvants
  - Limit the number of pills/patches that a patient may have at one time

Opioid Selection, Dosage, Duration, Follow-Up, and Discontinuation

- When opioids are started, clinicians should prescribe the lowest effective dosage.
- Clinicians should use caution when prescribing opioids at any dosage
- Clinicians should avoid increasing dosage to ≥90 Morphine Milligram Equivalent (MME)/day or carefully justify a decision to titrate dosage to ≥90 MME/day

Opioid Selection, Dosage, Duration, Follow-Up, and Discontinuation

- Long-term opioid use often begins with treatment of acute pain.
- **When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids.**
- **Three days or less will often be sufficient; more than seven days will rarely be needed**

Prescription Drug Monitoring Program (PDMP)

- State-ran electronic databases used to track the prescribing and dispensing of controlled prescription drugs to patients. They are designed to monitor this information for suspected abuse or diversion (i.e., channeling drugs into illegal use), and can give a prescriber or pharmacist critical information regarding a patient's controlled substance prescription history.
- PDMPs continue to be among the most promising state-level interventions to improve opioid prescribing, inform clinical practice, and protect patients at risk.

Prescription Drug Monitoring Program (PDMP)

- Clinicians should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at high risk for overdose.
- Clinicians should avoid prescribing opioids and benzodiazepines concurrently whenever possible.

Prescription Drug Monitoring Program (PDMP)

- If patients are found to have high opioid dosages, dangerous combinations of medications, or multiple controlled substance prescriptions written by different clinicians, several actions can be taken to augment clinicians' abilities to improve patient safety:
  - Clinicians should discuss information from the PDMP with their patient and confirm that the patient is aware of the additional prescriptions. Occasionally, PDMP information can be incorrect (e.g., if the wrong name or birthdate has been entered, the patient uses a nickname or maiden name, or another person has used the patient's identity to obtain prescriptions).
  - Clinicians should discuss safety concerns, including increased risk for respiratory depression and overdose, with patients found to be receiving opioids from more than one prescriber or receiving medications that increase risk when combined with opioids (e.g., benzodiazepines) and consider offering naloxone.

Prescription Drug Monitoring Program (PDMP)

- If clinicians suspect their patient might be sharing or selling opioids and not taking them, clinicians should consider urine drug testing to assist in determining whether opioids can be discontinued without causing withdrawal. A negative drug test for prescribed opioids might indicate the patient is not taking prescribed opioids, although clinicians should consider other possible reasons for this test result.

- Experts agreed that clinicians should not dismiss patients from their practice on the basis of PDMP information. Doing so can adversely affect patient safety, could represent patient abandonment, and could result in missed opportunities to provide potentially lifesaving information (e.g., about risks of opioids and overdose prevention) and interventions (e.g., safer prescriptions, non-opioid pain treatment, naloxone, and effective treatment for substance use disorder).

UDS Recommendations

- Urine drug tests can provide information about drug use that is not reported by the patient.
- Experts agreed that prior to starting opioids for pain and periodically during opioid therapy, clinicians should use urine drug testing to assess for prescribed opioids as well as other controlled substances and illicit drugs that increase risk for overdose when combined with opioids, including non-prescribed opioids, benzodiazepines, and heroin.
- While experts agreed that clinicians should use urine drug testing before initiating opioid therapy for chronic pain, they disagreed on how frequently urine drug testing should be conducted during long-term opioid therapy.

Commonly Used Opioids

- Codeine:
  - Mild to moderate pain
  - Available as a combination product with acetaminophen or ASA
  - Metabolized by liver: rate of conversion to morphine is highly variable
  - Avoid in patients with renal failure because its active metabolites can accumulate
  - Metabolized to morphine and hydrocodone
- Codeine Sulfate ->15-60mg p.o. Q 4-6 hours PRN PAIN (max dose 360mg/24 hours)

Commonly Used Opioids

- Tylenol with Codeine #3 -> Tylenol 300mg/30mg
  - Tylenol #3 p.o. Q 4-6 hours PRN PAIN
- Tylenol with Codeine #4 -> Tylenol 300mg/60mg
  - Tylenol #4 p.o. Q 4-6 hours PRN PAIN
- Codeine max dose is 360mg/24 hours
- Tylenol max dose is 1g/4hr and 3g/day
- Risk is increased in doses >3gm orally & >4gm IV
- Individuals who drink 60g/d ETOH or history of binge drinking should take no more than 2g/d

Commonly Used Opioids

- Tramadol (Ultram):
  - Mild to moderate pain in doses of up to 400mg/day
  - Synthetic codeine analog that shares properties of both opioids and TCAs
  - Weakly binds to Mu opioid receptor, inhibits reuptake of serotonin and NE
  - SE: similar to opioids in addition to potential for serotonin syndrome and elevated seizure risk with SSRIs, MOA-Is, or TCAs
  - Tramadol 50-100mg p.o. Q 4-6 hours PRN PAIN
  - Tramadol/Acetaminophen 37.5/325mg p.o. Q 4-6 hours PRN PAIN (up to 5 days)

Commonly Used Opioids

- Hydrocodone
  - Many different formulations
    - Norco, Lortab, Vicodin, Hycet – in combination with Acetaminophen
    - Vicoprofen, Reprexain, Ibudone – in combination with Ibuprofen
- A semisynthetic hydrogenated codeine derivative and opioid agonist with analgesic and antitussive effects
- Hydrocodone primarily binds to and activates the mu-opioid receptor in the central nervous system (CNS)
- Hydrocodone is converted to hydromorphone by the cytochrome P450 enzyme CYP2D6.

Commonly Used Opioids

- Commonly used Hydrocodone dosages:
  - Norco 5/325mg p.o. Q 4-6 hours PRN PAIN
  - Norco 7.5/325mg p.o. Q 4-6 hours PRN PAIN
  - Norco 10/325mg p.o. Q 4-6 hours PRN PAIN
- Continue to use caution with acetaminophen dosages

Commonly Used Opioids

- Oxycodone:
  - Used in combination with acetaminophen, ASA, and ibuprofen as a short acting analgesic for moderate to severe pain
  - Liver metabolizes oxycodone to small amounts of oxymorphone, the only active metabolite
  - Oxymorphone will accumulate in renal failure patients so beware
  - Combination with acetaminophen (Percocet) is prevalent and has increased street value

Commonly Used Opioids

- Oxycodone with acetaminophen (Percocet)
  - Percocet 5/325mg p.o. Q 4-6 hours PRN PAIN
  - Percocet 7.5/325mg p.o. Q 4-6 hours PRN PAIN
  - Percocet 10/325mg p.o. Q 4-6 hours PRN PAIN
- Oxycodone with ibuprofen (Combunox)
  - 5/400mg p.o. Q 4-6 hours PRN PAIN
- Caution with daily maximum dosages of acetaminophen and ibuprofen (3200mg)

Commonly Used Opioids

- Morphine:
  - Most commonly use opioid for treating severe pain
  - Metabolized in the liver producing M3G (morphine-3-glucuronide) an inactive metabolite and M6G (morphine-6-glucuronide) an active metabolite that is more potent than morphine
  - Both metabolites are excreted by the kidneys: be careful in renal failure patients
  - For decreased renal function, consider small doses of immediate release morphine or reducing the dosing frequency

Commonly Used Opioids

- Hydromorphone:
  - Used for severe pain
  - Semisynthetic derivative of morphine
  - Active, non-analgesic metabolites that may cause neuroexcitatory effects at high doses or in the setting of renal failure (ex. Myoclonus, allodynia, seizures, confusion)

Benzodiazepines

Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible

- Benzodiazepines and opioids both cause central nervous system depression and can decrease respiratory drive.
- Concurrent use is likely to put patients at greater risk for potentially fatal overdose.
- The contextual evidence review found evidence in epidemiologic series of concurrent benzodiazepine use in large proportions of opioid-related overdose deaths, and a case-cohort study found concurrent benzodiazepine prescription with opioid prescription to be associated with a near quadrupling of risk for overdose death compared with opioid prescription alone.
- Experts agreed that although there are circumstances when it might be appropriate to prescribe opioids to a patient receiving benzodiazepines (e.g., severe acute pain in a patient taking long-term, stable low-dose benzodiazepine therapy), clinicians should avoid prescribing opioids and benzodiazepines concurrently whenever possible.

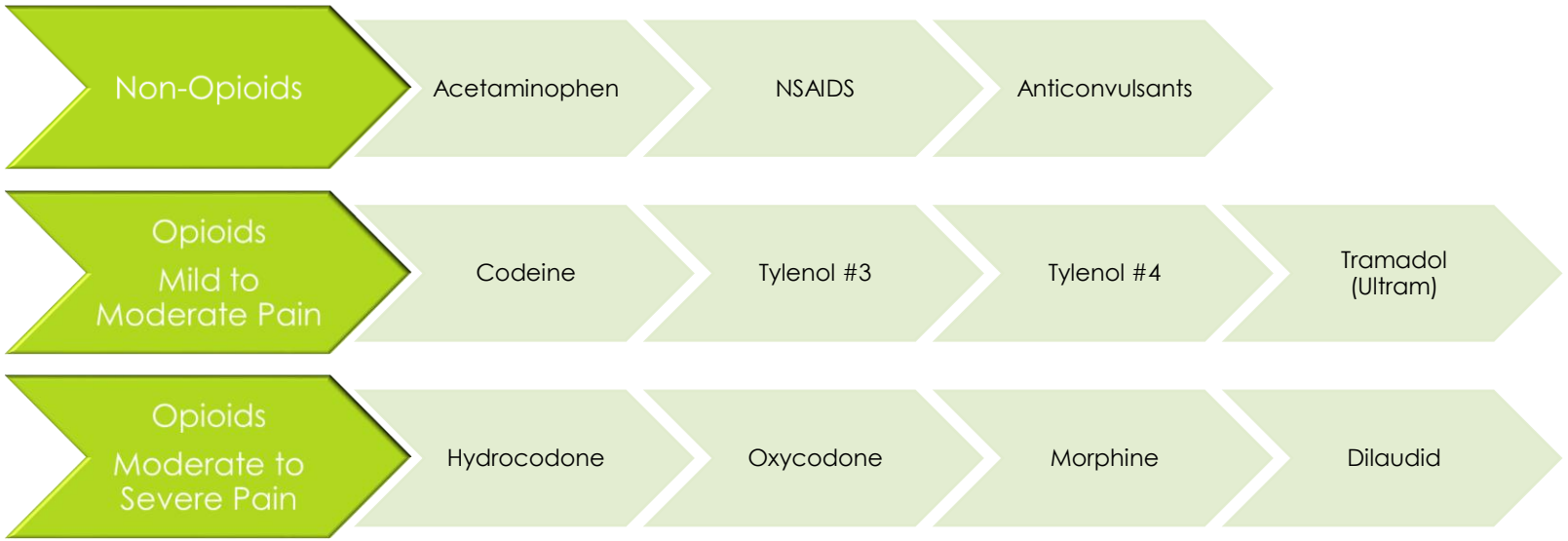
Benzodiazepines

- If patient expresses increased anxiety or concern before an in office procedure benzodiazepines can be considered
- Patient should always have a driver present with them if given a benzodiazepine to take pre-operatively
- SE's include but are not limited to drowsiness, fatigue, amnesia, confusion, dizziness, impaired concentration, respiratory depression, tachycardia, hypotension, angioedema

Benzodiazepines

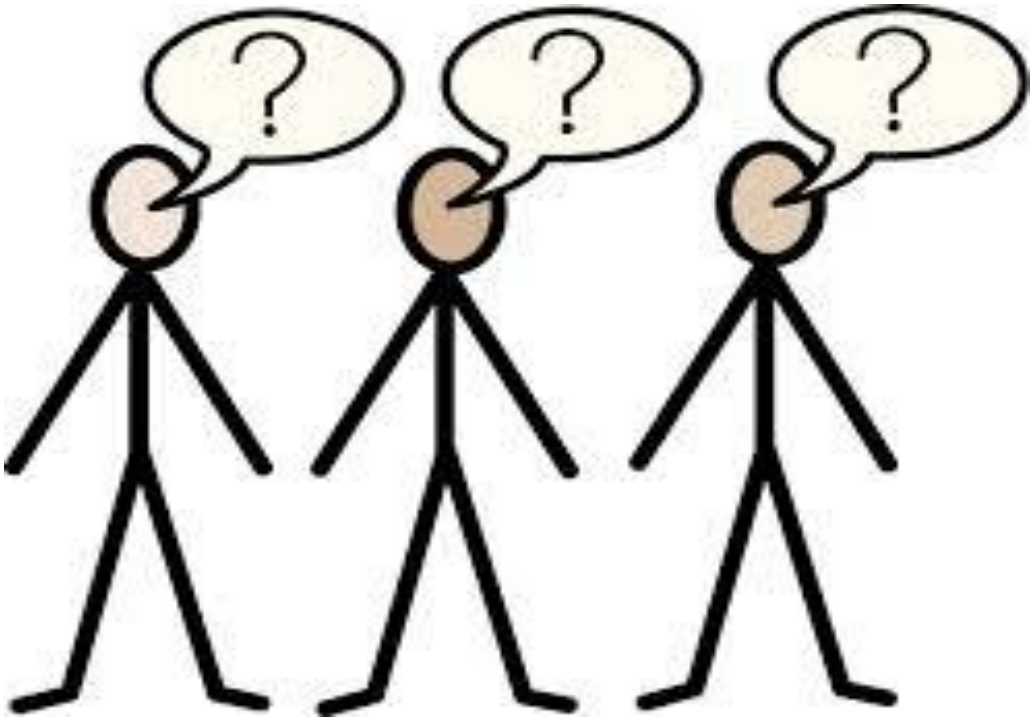
- If patient has a previous prescription for a benzodiazepine, encourage the patient to take their at home dosage before coming for their procedure
- Commonly used pre-operative formulations for in office procedures
- Diazepam (Valium) -> 2mg/5mg/10mg p.o. twenty minutes before in office procedure PRN ANXIETY
- Alprazolam (Xanax) ->0.25mg/0.5mg/1mg p.o. twenty minutes before in office procedure PRN ANXIETY

Non-Opioid and Opioid Review:



Benzodiazepine Review:

Questions??



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