Pharmacology of Pain – Opioids and Beyond

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Learning Objectives

- Review the safest and most effective pain treatment options
- Identify opioid risks
- Discuss considerations for opioid therapy initiation and continuation
- Identify patients appropriate for naloxone
- Evaluate when to taper off opioid therapy and how to go about it

Pain Management Goals

- Education of patient that total relief of pain is rare, medications MAY reduce by up to 30%
- Number 1 goal is to focus on improving function and quality of life
  - Restore physical, emotional and social function so the patient can reconnect with what is important to them
- Improve the patient's ability to manage their own pain and return to healthy lifestyle
- Address any underlying body tissue injuries or other medical issues

Non-pharmacologic pain management

- Self-management is the foundation of high quality pain care
- Pain self-management is helping patients develop healthy skills and behaviors to improve their ability to cope with chronic pain
- Helps reset the expectation that there is a pill for everything

Self-Management > Medication Management

Physical • **Gentle exercise** • **Manual Therapies** • **Physical Therapy** • **TENS** • **Acupuncture** • **Other modalities (heat, cold, stretch, weight loss)**	**Psycho-behavioral** • **CBT for Pain** • **Treatment of mood/trauma** • **Substance abuse treatment** • **Sleep hygiene and/or CBT for Insomnia** • **Meditation/Relaxation**
Medication • NSAIDS • Anticonvulsants • Antidepressants • Topical agents • Opioids • Other	Procedural • Nerve blocks/ablation • Steroid injections • Trigger point injections • Stimulators

Non-opioid Pharmacotherapy – 1st Line Treatment

- Acetaminophen
- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Antidepressants
- Anticonvulsants
- Muscle relaxants
- Topical therapy

Acetaminophen

- Relatively safe and inexpensive
- Antipyretic and analgesic effects but no anti-inflammatory activity
- Able to provide additive analgesia when combined with other analgesics for moderate to severe pain
- Not to exceed 4000mg per day or 2000mg in patients with liver disease or those drinking alcohol even with normal liver function (caution w/OTC preparations)

NSAIDs

- Analgesic, antipyretic and anti-inflammatory properties
- No particular NSAID appears more efficacious than others
  - Salsalate may be better in older patients, lower risk of GI toxicity, nephrotoxicity and atherothrombotic risk
- Consider risk factors for GI effects and may consider PPI or H2 antagonist
  - History of ulcer
  - Age >65
  - High dose NSAIDs
  - Concurrent aspirin or anticoagulant

NSAIDs

- Avoid in patients with known coronary artery disease, renal dysfunction and CHF
- Risks include CVA, MI, HTN, GI ulceration, HF exacerbation, bleeding
- If you prescribe an NSAID, educate patient not to use additional OTC NSAIDs
- Topical NSAIDs
  - Lower risk of systemic side effects
  - Good for patients with localized painful conditions
  - Avoid concomitant use of oral NSAIDs

Topical NSAIDs: Diclofenac Gel, Solution, Patch

- For osteoarthritis, patch for acute pain d/t minor strains/sprains/contusions
- Lower extremities apply 4g of 1% gel to affected area 4x/day
- Upper extremities apply 2g of 1% gel to affected area 4x/day
- Maximum total body dose of 32g per day

Analgesic Adjuvants

- May help reduce over-reliance on opioids
- Reduce poor pain outcomes
- Examples include:
  - Tricyclic antidepressants (TCAs)
  - Serotonin norepinephrine reuptake inhibitors (SNRIs)
  - Anticonvulsants
  - Muscle relaxants
  - Topicals

Tricyclic Antidepressants (off-label)

- **Amitriptyline, Nortriptyline, Imipramine, Desipramine**
  - Start with low dose at bedtime and increase every 1-2 weeks as tolerated until pain relief
  - Adequate trial 6-8 weeks
  - Adverse effects: drowsiness, confusion, orthostatic hypotension, dry mouth, constipation, urinary retention, weight gain, arrhythmia
  - Useful for neuropathic pain, migraine prevention
  - Monitoring: blood pressure, ECG in older adults or preexisting cardiac disease, electrolytes

SNRIs – Duloxetine

- Initiate with 30mg daily for 7 days, may then increase to 60mg daily as one dose
  - Dose adjust: do not use in those with hepatic impairment or CrCl <30mL/min
- Adverse effects: sedation, nausea, constipation
- Adequate trial 8-12 weeks, may reduce pain in 1 week
- FDA approved for diabetic neuropathy, fibromyalgia, chronic musculoskeletal pain in addition to anxiety and depression
- Monitoring: blood pressure, changes in mood such as worsening depression or increase in anxiety

SNRIs – Venlafaxine (off-label)

- Initiate with 75mg daily and may increase weekly as tolerated until pain relief
  - At doses <150mg/day primarily a serotonin effect
  - Max dose of 225mg/day
  - Dose adjust for both hepatic and renal impairment
- Adverse effects: nausea, dizziness, drowsiness, hypertension, constipation
- Adequate trial 6-8 weeks
- Monitoring: blood pressure, changes in mood such as worsening depression or anxiety

Anticonvulsants – Gabapentin (off-label)

- Initiate with 100-300mg at bedtime and increase by 100-300mg every 1-7 days as tolerated until pain relief
  - Max dose 3600mg/day in divided doses
  - Dose adjustment for renal impairment
- Adverse effects: CNS depression, dizziness, drowsiness, peripheral edema
- Adequate trial 3-8 weeks of titration + 2 weeks at maximum tolerated dose
- Monitoring: periodic renal function, changes in mood, substance abuse
- May be useful for patients with insomnia

Anticonvulsants – Pregabalin

- Initiate 50-75mg/day 2-3 times per day depending upon indication, increasing every 3-7 days as tolerated until pain relief
  - Max dose 450mg/day
  - Dose adjust for renal impairment
- Adverse effects: drowsiness, dizziness, peripheral edema
- Adequate trial 4 weeks
- Monitoring: periodic renal function, weight gain/edema, degree of sedation, changes in mood

Anticonvulsants – Additional Precautions

- Avoid abrupt cessation d/t increase risk of seizures
- When combined with opioid therapy, increased risk of respiratory depression
- Gabapentin is considered a controlled substance in some states
  - Taking higher dosage than prescribed resulting in a high
- Start low and go slow, **particularly** in the **elderly** to reduce risk of falls

Muscle Relaxants

- Baclofen, Carisoprodol, Chlorzoxasone, Cyclobenzaprine, Metaxalone, Methocarbamol, Orphenadrine, Tizanidine
  - Varying degrees of sedation, anticholinergic properties, dizziness, dry mouth
  - Typically meant for short-term use
  - Use lowest effective dose

  - **Diazepam – should be avoided as muscle relaxant, particularly if prescribing opioid d/t increased risk of respiratory depression and unintentional overdose

Topical Analgesics

- Do not apply to broken or irritated skin
- Occlusion of the skin over the topical with any type of material or heat over application site increases risk of serious side effects
- Large amounts of topical preparations increases the risk of systemic toxicity

Topical Analgesics: Lidocaine

- For neuropathic pain
- Lidocaine 4% can be used up to 4x/day
- Lidocaine patch 5% may apply up to 3 patches 12 hours on/12 hours off

- OTC patch also available

Topical Analgesics: Capsaicin

- For musculoskeletal or neuropathic pain
- Takes a few weeks for full effect
- Apply to affected area 3-4 times/day **scheduled**
- Wear gloves and/or wash hands after applying, avoid contact w/mucus membranes
- May cause burning/tingling sensation for first few days
- d/c if severe burning or itching occurs

Classes of Opioids

Natural (from opium)	Semisynthetic (derived from opium)	Synthetic (man-made)
Codeine Morphine	Hydrocodone Hydromorphone Oxycodone Oxymorphone Buprenorphine	Fentanyl Methadone Meperidine Tapentadol Tramadol

Natural Opioids - Codeine

- Low potency analgesic with antitussive properties
- Duration of action 4-6 hours
- Must be converted to morphine via CYP2D6
  - No analgesic activity by itself
- May accumulate in renal dysfunction, toxic metabolite morphine-3-glucuronide
- Caution in elderly

Natural Opioids - Morphine

- Gold standard
- Opioids dosed (compared) using “oral morphine equivalents”
- Short and long acting with duration of 3-6 hours IR, 8-12 hours ER
  - 2-4 hours IV, 3-4 hours IM,SC
- ADEs: nausea/vomiting, respiratory depression, constipation, pruritis
- Two major toxic metabolites: morphine-3-glucuronide and morphine-6-glucuronide may accumulate in renal dysfunction as they are renally cleared
- Caution in elderly

Semisynthetic - Hydrocodone

- Parent compound and metabolite active
- Hydrocodone converts to hydromorphone by CYP2D6
- Available in tablet and liquid, immediate release and extended release
- Duration of 4-8 hours IR or 24 hours ER
- Generally comes in a formulation with APAP
  - In recent years 2 single ingredient long-acting were approved by FDA
- Approximately equal to morphine, mg to mg

Semisynthetic - Hydromorphone

- Parent drug active, metabolized to inactive compounds via glucuronidation
- Oral, IV, SC, IM formulations available
- Duration 3-6 hours IR, 12-24 hours ER
  - 3-4 hours IV, SC, IM
- Abuse deterrent long-acting formulation also available, 24 hour
- Approximately **5 times** more potent than morphine
- Caution in renal impairment

Semisynthetic - Oxycodone

- Active parent compound
- Metabolized to oxymorphone via CYP2D6
- Available with many abuse deterrent strategies
- Oral formulations only, both short and long-acting
  - Short acting both with or without APAP
- Duration 3-6 hours IR, 8-12 hours ER
- Approximately 1.5 times as potent as morphine

Semisynthetic - Oxymorphone

- Active metabolite of oxycodone
- Metabolized to inactive metabolites
- Available as oral or IV
- 3-4 times more potent than morphine
- 10% orally bioavailable
- Half-life 7-9 hours

Synthetic - Tramadol

- Central acting analgesic, both immediate release and extended release available
- Weak mu-opioid agonist and SNRI, increased risk of serotonin syndrome
- Duration of 4-9 hours IR, 24 hours ER
- Metabolized by CYP2D6 to active metabolite (O-desmethyltramadol)
- Naloxone not as effective in reversing tramadol but seizure more likely adverse outcome
- Caution in seizure disorder

Synthetic - Tapentadol

- Central acting analgesic, both immediate release and extended release available
- Mu opioid agonist and SNRI activity
- Duration: 4-6 hours IR, 12 hours ER
- Metabolized primarily by CYP2C9

Synthetic - Fentanyl

- Metabolized via CYP3A4 to inactive metabolites
- Onset of analgesia 12-24 hours with transdermal formulation (cross titration if rotating opioids)
- Duration 2 hours buccal, 0.5-1 hour IV, SC, 12 hours after patch removal
- Caution with heat sources around patch
- Drug interactions can be fatal, recommend naloxone
- Fast acting formulations (lozenges, buccal film or tab, intranasal, sublingual spray or tab) are NOT equivalent, REMS available

Synthetic - Fentanyl

Oral 24-hr Morphine (mg/day)	Fentanyl dose (mcg/hr)
60 to 134	25
135 to 224	50
225 to 314	75
315 to 404	100
405 to 494	125
495 to 584	150
585 to 674	175
675 to 764	200

Synthetic - Methadone

- Opioid receptor activity as well as NMDA antagonist
- Half-life highly variable (7 to 59 hours; 12-150 hours)
- Slow release from liver and other tissues prolong action
- May cause QTc prolongation
- Pain relief wears off (4-8 hours) before respiratory depressant activity early on
- Dose adjustments every 5-7 days, may titrate faster with cancer pain
- High interpatient variability when converting to methadone, deaths have occurred

Synthetic - Methadone

- Recommend ECG prior to initiation and repeat every 2-4 weeks after initiating therapy and after significant dose increases
- Monitor respiratory status
- Issue naloxone!!!

Takeaway Points

- Oral IR time to peak analgesia of 1-2 hours, with duration of 4-6 hours
- Oral ER time to peak analgesia 4-6 hours, duration 8-12
- Several opioids are prodrugs, some with toxic metabolites, and have interindividual variability
- All are metabolized by liver
- Opioid metabolites are excreted renally and accumulate with renal dysfunction

Renal Impairment

- Opioid metabolites are excreted in the urine
- Active and toxic metabolites can accumulate with renal dysfunction
- Opioids with active or potentially toxic metabolites include:
  - Codeine/Morphine
  - Hydromorphone
  - Oxycodone
  - Meperidine
- Opioids with no active or toxic metabolites include: Fentanyl and Methadone

Hepatic Impairment

- All opioids are hepatically metabolized
- Hepatic dysfunction results in
  - Decreased first pass metabolism
  - Decreased protein binding
  - Decreased hepatic clearance
- Patients will require lower doses and extended dosing intervals
- Fentanyl, hydromorphone and methadone are preferred

Opioid therapy, what does the evidence show?

- Limited research on effectiveness of long-term therapy for non-end-of-life pain
- While evidence supports short-term efficacy of opioids, there is no high-quality evidence that long-term opioid therapy improves pain, function or quality of life
- Risk of significant harms from opioid therapy: Overdose/death, OUD, many adverse effects
- Risk of OUD starts at any dose of opiate and increases in dose-dependent manner
- Strategy of escalating dose to achieve benefit increases risk and has NOT been show to improve function

Potential Opioid Benefits

- Modest short-term improvement in pain
- Possible short-term improvement in function

Potential Opioid Risks

- Increase all-cause mortality
- Increase risk of unintentional overdose death
- Increase risk of developing opioid use disorder
- Risk of developing or worsening:
  - Sleep disordered breathing, dizziness, sedation, cognitive dysfunction
  - Depression, falls fractures, motor vehicle crashes
  - Nausea, constipation, dry mouth

When might opioid therapy be appropriate?

- Opioid therapy has a role primarily in the treatment of severe acute pain, post-operative pain, and end-of-life pain
- Acute pain treatment:
  - Consider multimodal pain care including non-opioid medications
  - Only use opioids for SEVERE acute pain
  - Use immediate release formulation at lowest effective dose with small days supply
  - Reassess within 3-5 days to determine if adjustments or continuing opioid therapy is indicated

When might opioid therapy be appropriate?

- Chronic pain treatment:
  - Pain lasting 3 months or more
- Optimize non-opioid treatments including self-management before considering opioids
- Educate on treatment options, realistic expectations and limitations of medical treatment, opioid risks, need for risk mitigation
- Evaluate individual opioid risk factors
- Establish realistic, clear and measurable treatment goals with focus on function

Before starting an opioid for chronic pain

- Consider how opioid therapy will be discontinued if benefits do not outweigh risks
- Discuss and complete an opioid informed consent together with patient
  - Include goals of therapy
  - When/why the therapy may be stopped
  - Safe storage and disposal of the opioid
- Check state prescription drug monitor prior to initiating and periodically during therapy

Other Considerations in Opioid Prescribing

- Consider age as well as comorbid conditions that may place patient at increased risk of adverse outcomes such as respiratory disorders, untreated sleep apnea, CHF, substance use disorders, dehydration, compromised renal or hepatic function ***THESE ARE THE PATIENTS THAT NEED NALOXONE***
- Always initiate a bowel regimen
- Avoid combinations that increase risk of respiratory depression such as benzodiazepines or z-drugs
- Initiation or dose changes are when patient is most vulnerable for unintentional overdose

Initiation of Opioids

- Start with immediate-release agent in opioid naïve
- Use short duration of treatment. Carefully weigh risks vs benefits if considering continuation beyond 90 days
  - Discuss evidence with patient upon initiation and continuously thereafter (eg: little evidence for sustained analgesic efficacy but substantial increase in OUD risk with long-term treatment)
- Abuse deterrent formulations provide no additional safety mechanism to prevent opioid use disorder. There is NO SAFE OPIOID

Continuing Opioid Therapy

- Follow up frequently to assess for meaningful improvement in pain and **function** compared to baseline and to assess risk factors and adverse effects
  - Per CDC, follow up 1-4 weeks from initiation or dose change; frequency can be extended up to 3 months if no dose change and clinically stable
  - Reassess opioid risks vs benefits and re-examine rationale for continuation at least every 3 months and document

Components of an Opioid Regimen

- Scheduled dosing for persistent pain
  - Pain is easier to prevent than treat
  - Both CDC and SAMSHA recommend short acting
- As needed dosing for breakthrough pain
  - Use short acting opioids
  - Use the same opioid for PRN and continuous dosing
  - Scheduled long acting: use 10-15% of the total daily opioid dose
  - Scheduled short acting: use 50-100% of the scheduled short acting dose

Dosing Interval

- Scheduled doses should be base on DURATION of action
  - Sustained release: 8-12 hours
  - Oral short acting: 4 hours
  - IV/SC: 4 hours
- Breakthrough doses should be based on ONSET of action
  - Oral short acting: 1-2 hours
  - IV/SC: 0.5 – 1 hour

Titrating Doses

- Goal is to manage pain with scheduled doses and require few or no breakthrough doses
- Evaluate relationship of pain to scheduled doses
- Titrate regimen after steady state is reached
  - Short acting: 24 hours
  - Long acting: 48 hours
  - Methadone: 5-7 days
  - Fentanyl Patch: 72 hours

Titrating Doses (cont.)

- Titrate regimen if:
  - Pain is unmanaged with current regimen
  - More than 3-4 breakthrough doses are required per day
- If pain is stable, distribute breakthrough doses to scheduled doses
- If pain is unstable, adjust dose based on pain score
  - Mild to moderate pain: Increase total daily dose 25%
  - Moderate to severe pain: Increase total daily dose 50%

Naloxone

- Opioid receptor antagonist
- Reverses opioid-induced respiratory depression
- Offer to anyone prescribed an opioid with an increased risk
  - (or just anyone prescribed an opioid, Surgeon General's recent advisory)
- Educate the patient, family, friends, caregivers, etc. how to recognize symptoms
  - Breathing is slow, irregular or has stopped, unable to arouse, pinpoint pupils, blue/grey skin, lips, nails
- This medication will put patient in withdrawal as it removes opioid from receptor

Narcan Nasal Spray

- Remove from packaging
- Do NOT prime, single dose
- Gently insert the tip of nozzle into nostril and press plunger firmly
- Call 911, place in recovery position
- If no response in 2-3 minutes, repeat dose in opposite nostril

Evzio Autoinjector

- Pull from case
- Voice walks you through steps

Naloxone Pearls

- Duration of action approximately 30-120 minutes depending on route
- This is SHORTER than duration of most opioids
- Stress importance of obtaining emergency help even if patient revives
- Fentanyl – make sure they understand to remove the patch!!
- Methadone – d/t long and varied half-life, need hospital monitoring

Opioid Rotation

- Development of tolerance to analgesic effect
- Development of treatment limiting toxicities
- Change in health status

- ****Requires knowledge of equianalgesic doses of different opioids****

Calculating Morphine Equivalent Daily Dose (MEDD) for ORAL dosage forms

Medication	Conversion Factor
Codeine	0.15
Fentanyl Patch	2.4 x 3 days
Hydrocodone	1
Hydromorphone	4
Methadone	3
Oxycodone	1.5
Oxymorphone	3
Tapentadol	0.4
Tramadol	0.1

Incomplete Cross Tolerance

- When rotating, reduce dose of new opioid 25-50%
- Increased sensitivity to the new opioid regiment
- Accounts for inter-patient variability in equianalgesic dosing
- Consider patient's current pain score when adjusting
- Every patient is different!!

Indications for Tapering an Opioid

- No clinically meaningful improvement in function
- Concomitant meds that increase overdose risk
- Concerns about OUD or other substance use disorder, diversion of meds
- Non-compliance with opioid safety measures and risk mitigation strategies
- Non-participation in comprehensive pain care plan
- Dose over 90mg MEDD
- Unmanageable side effects

Tapering process

- When safety allows, a gradual taper (5-20% reduction every 4 weeks) allows time for neurobiological, psychological and behavior adaptations
- Faster taper (5-20% every week) may be used when risks are too high for gradual taper
- When a faster taper is required, there are medications that may help with withdrawal symptoms

Medications to assist with withdrawal symptoms

- Clonidine, baclofen or gabapentin for autonomic symptoms such as sweating, tachycardia, myoclonus. Average required use of up to 15 days
- Hydroxyzine or diphenhydramine for anxiety, dysphoria, lacrimation, rhinorrhea
- NSAIDs, acetaminophen or topicals for myalgias
- Trazodone for sleep disturbance
- Procloperazine, promethazine or ondansetron for nausea
- Dicyclomine for abdominal cramping
- Loperamide or bismuth subsalicylate for diarrhea

This was A LOT of information!