Opioids for Pain

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Acknowledgement

This course was developed in 2004 with many revisions since then; Drs. Drew Rosielle and Kathryn Neuendorf were important contributors to past editions.

Objectives/Acknowledgement

- Describe four pharmacological principles when using opioids.
- Describe the concept of equianalgesia and practice dose calculations.
- List three principles of using opioid infusions.

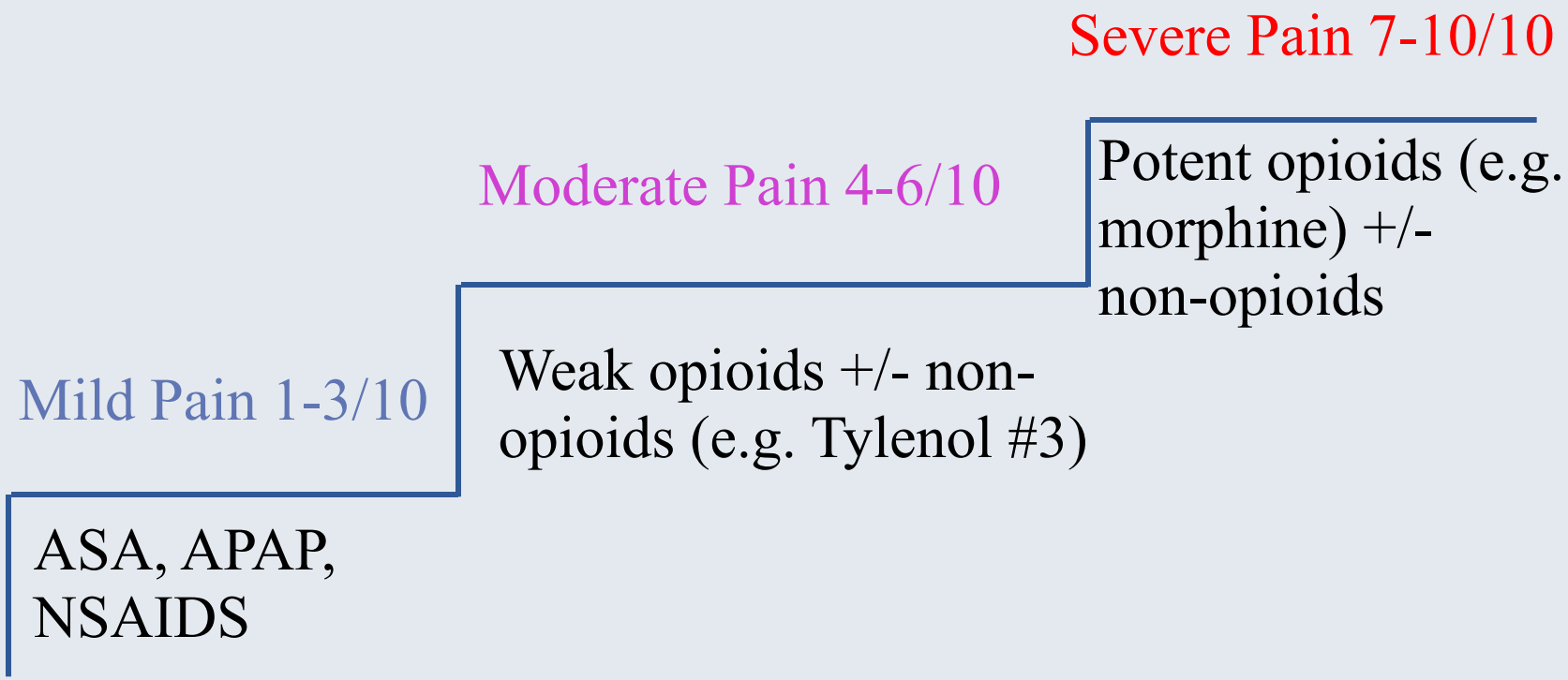
Comprehensive pain management

- Drug therapy is only one important aspect of pain treatment.
  - Non-drug therapies should always be used at the same time drug therapy is started.
- This module will only focus on opioid therapy; learners are encouraged to seek other sources for reviews discussing other aspects of pain treatment.

Classes of Analgesics

- Non-Opioid Analgesics (NSAIDS, acetaminophen, aspirin)
- Opioids (morphine is the prototype)
- Adjuvant Analgesics (antidepressants, anticonvulsants, steroids, others)

World Health Organization
(WHO) Step Ladder



World Health Organization
(WHO) Step Ladder

- Patients should be treated as individuals
  - If pain is severe at presentation, starting at step 1 is not appropriate
  - It may take longer to achieve acceptable pain control while using this method
  - Adjuvants and pain interventions can and should be considered at all steps of the ladder

Analgesics for moderate to severe pain

- OPIOIDS
  - All opioid analgesics produce pain relief via interaction with opioid receptors in the brain/spinal cord and perhaps via peripheral opioid receptors.
  - The *mu* receptor is the dominant analgesic receptor, but other receptors play a role in analgesia for certain opioids.
  - There is no pharmacologic dose ceiling for opioids, only for acetaminophen in combination products.

Analgesics for moderate to severe pain

- Opioids are classified by their interaction with the opioid receptors.
  - **pure agonist**: morphine, hydromorphone (Dilaudid ®) oxycodone, codeine, meperidine, fentanyl, methadone
  - **mixed agonist-antagonist**: butorphanol (Stadol ®), pentazocine (Talwin ®), nalbuphine (Nubain ®)
  - **partial agonist**: buprenorphine
  - **pure antagonist**: naloxone, naltrexone

Analgesics for moderate to severe pain

- Mixed Agonist-Antagonists
  - Claim to have less respiratory depressant effects—not substantiated
  - Claim to be less addicting—not substantiated
  - Will potentiate withdrawal in patients being treated with pure agonists
  - Have an analgesic ceiling
  - Are psychotomimetic—can cause psychosis

There is little if any indication in palliative care for the use of mixed agonist-antagonists; the remainder of this module will focus on pure agonists.

Oral Opioids—Duration of Action

A. Ultra short
B. Short
C. Long

A. Ultra short acting opioid

- Fentanyl
  - Very potent (given IV, it has 50-100 times the potency of morphine)
  - Transmucosal (buccal) delivery systems are available for breakthrough pain:
    - Actiq ® (Lozenge), Fentora ™ (Buccal tablet)
    - Onset of analgesia within ~10 minutes; peak effect ~20-40 mins; duration of analgesia 2-3 h
    - ***NOTE:*** *Should only be used in opioid tolerant patients by clinicians familiar with the pharmacology of transmucosal systems.*

B. Oral Short Acting Opioids

- Parenteral or Oral
  - morphine
  - hydromorphone (Dilaudid ®)
  - oxymorphone
  - meperidine (Demerol ®)
  - codeine
- Oral only
  - oxycodone (Percocet ® , Tylox ®)
  - hydrocodone (Vicodin ® Lortab ®, Lorcet ®)
  - propoxyphene (Darvon ®, Wygesic ®)
  - Note: hydrocodone is only available as a combination product or as a long-acting agent.

B. Oral Short Acting Opioids

- Duration of Action
  - With the exception of meperidine and oxymorphone, all the oral short acting opioids should be prescribed at a dosing interval not to exceed 4 hours, since the typical duration of effect from an oral dose is 3-4 hours.
  - Oxymorphone should be dosed every 6 hours due to its longer half life

Meperidine

- Shortest acting PO opioid (only 2-3 hr duration)
- Weak potency; 300 mg PO = 10 mg IV morphine
- Converted to a long acting toxic metabolite--a CNS stimulant
  - Tremor, myoclonus and seizure
  - Risk highest with prolonged use and renal insufficiency

Meperidine Recommendations

- *Indicated for short term, procedural pain* –
  - NO more than 48 hour course
  - NO more than 600 mg (parenteral) within 24 hours
- No evidence to support the use of meperidine as the drug of choice for
  - biliary or pancreatic pain
  - sickle cell pain

Tramadol (Ultram ®)

- A synthetic analog of codeine
- Analgesic effect roughly equivalent to Tylenol #3 ®
  - Efficacy variable; has an analgesic ceiling and maximum 24 hour dose of 400 mg
- No anti-inflammatory effects
- Side effects similar to opioids at high dose--nausea, confusion, dizziness, constipation
- Does have abuse potential
- Appropriate for *mild to moderate* pain

Opioid combination products

- The following opioids are available as combination products with acetaminophen, aspirin, or ibuprofen
  - Codeine; hydrocodone; oxycodone; propoxyphene; tramadol
- Typically used for
  - Moderate, episodic (PRN) pain
  - Breakthrough pain in addition to a long-acting opioid (for moderate, and for some patients severe, pain).
- Never prescribe more than one combination drug at any one time.

Oral Short Acting Opioids

- Oral dosing:
  - onset in 20-30 min
  - peak effect in 60-90 minutes
  - duration of effect 2-4 hours (6-8 hours for oxymorphone)
  - Can be dose escalated or re-administered every 2-4 hours for poorly controlled pain (as long as the daily acetaminophen dose stays < 4 grams for combination products).

Which combination product?

- Analgesic potency:
  - hydrocodone and oxycodone are more potent than codeine, which is more potent than propoxyphene, which some studies suggest is equipotent to aspirin.
  - there is little difference between hydrocodone products and oxycodone products in terms of potency.

Note: *Propoxyphene products are not recommended for pain in most national pain guidelines, due to worse side effects (increased cardiovascular toxicity, delirium) without improved efficacy compared to other opioids.*

Which combination product?

- Toxicity:
  - All the combination products can cause opioid toxicities: nausea, sedation, constipation, etc.
  - There is little published data that supports the use of one product over another in terms of routine toxicity;
  - however …
    - Codeine is probably the most emetogenic opioid.
    - Propoxyphene should be avoided due to delirium and cardiovascular toxicity

Which combination product?

- Cost:
  - Generic products (e.g. oxycodone with acetaminophen) are cheaper than trade name products (e.g. Percocet®).

Single Agents

- morphine
- oxycodone
- hydromorphone (Dilaudid ®)
- oxymorphone (Opana ®)

Single Agents.

- Oral dosing:
  - **Onset** in 20-30 min;
  - **Peak effec**t in 60-90 minutes
  - **Duration** of effect 2-4 hours
  - Can be **dose escalated** or re-administered every 2 hours for poorly controlled pain.

C. Long Acting Opioids

- Oral
  - Extended-release morphine:
    - MS Contin®
    - Kadian®
    - Oramorph SR
  - ER oxycodone
    - Oxycontin®
    - Oxycodone SR
  - ER oxymorphone
    - Opana SR
  - ER Oxycodone
    - Hysingla ER
  - methadone
- Transdermal
  - Fentanyl Patch (Duragesic®)

Morphine ER vs. Oxycodone ER

- No clear benefit of one product over another
  - *No difference in toxicity, pain relief, or addiction potential*
- Both are equipotent with their short-acting formulations (30 mg morphine IR per day = 15 mg morphine ER bid)
- Both provide 8-12 hours of analgesia – dose q12h (rarely q8h)
- Onset of analgesia ~1-2 hours.

Morphine ER and Oxycodone ER

- Both can be dose escalated every 24 hours.
- Both must be taken intact—they cannot be crushed; they do not fit down G-tubes, except:
  - Kadian and Avinza (Morphine ER formulations which are ‘sprinkles’ which can be flushed down G-tubes)

Transdermal Fentanyl

- Slow onset of action: 13-24 hours
  - Duration of action: 48-72 hours
- Should only dose escalate q 3 days
  - Fentanyl stays in circulation for up to 24 hours after patch removal
- Place on hairless, non-irradiated skin
- No ceiling dose, but practically limited by available skin

Equianalgesia

- Since all potent opioids produce analgesia by the same mechanism, they will produce the same degree of analgesia if provided in ‘equianalgesic’ doses.
- Thus, there is little basis to say, “morphine did not work, but hydromorphone did work”. *Such a statement generally means that non-equianalgesic doses were used.*

Equianalgesia

- 10 mg IV MS = 30 mg po MS
- 10 mg IV MS = 1.5 mg IV Hydromorphone
- 30 mg po MS = 7.5 mg po Hydromorphone
- 30 mg po MS = 20-30 mg po Oxycodone

Note: Conversion factors are only a rough guide to approximate the correct dose.

PAUSE & *Calculate*

- Calculate: 2 oxycodone tabs (5mg) being taken every 4 hours is equal to what daily dose of Morphine ER?

Answer

- Each oxycodone tab contains 5 mg oxycodone;
  - 2 tabs every four hours = 12 tabs/day
  - 12 tablets @ 5 mg/tab = 60 mg/24 hours
- 60 mg oxycodone = 60-90 mg po morphine
- 60 mg morphine divided into two dosing intervals = 30 mg q12 of ER Morphine

Transdermal Fentanyl Conversions

- Conversion formula
  - 24 hour total dose of oral morphine, divided by 2 = dose in micrograms/hour of transdermal fentanyl
  - Example:
    - Morphine ER 30 mg q12h = 60 mg MS/24 hours
    - 60 divided by 2 = 30; rounded to one 25 mcg/hr Fentanyl Patch

Breakthrough pain

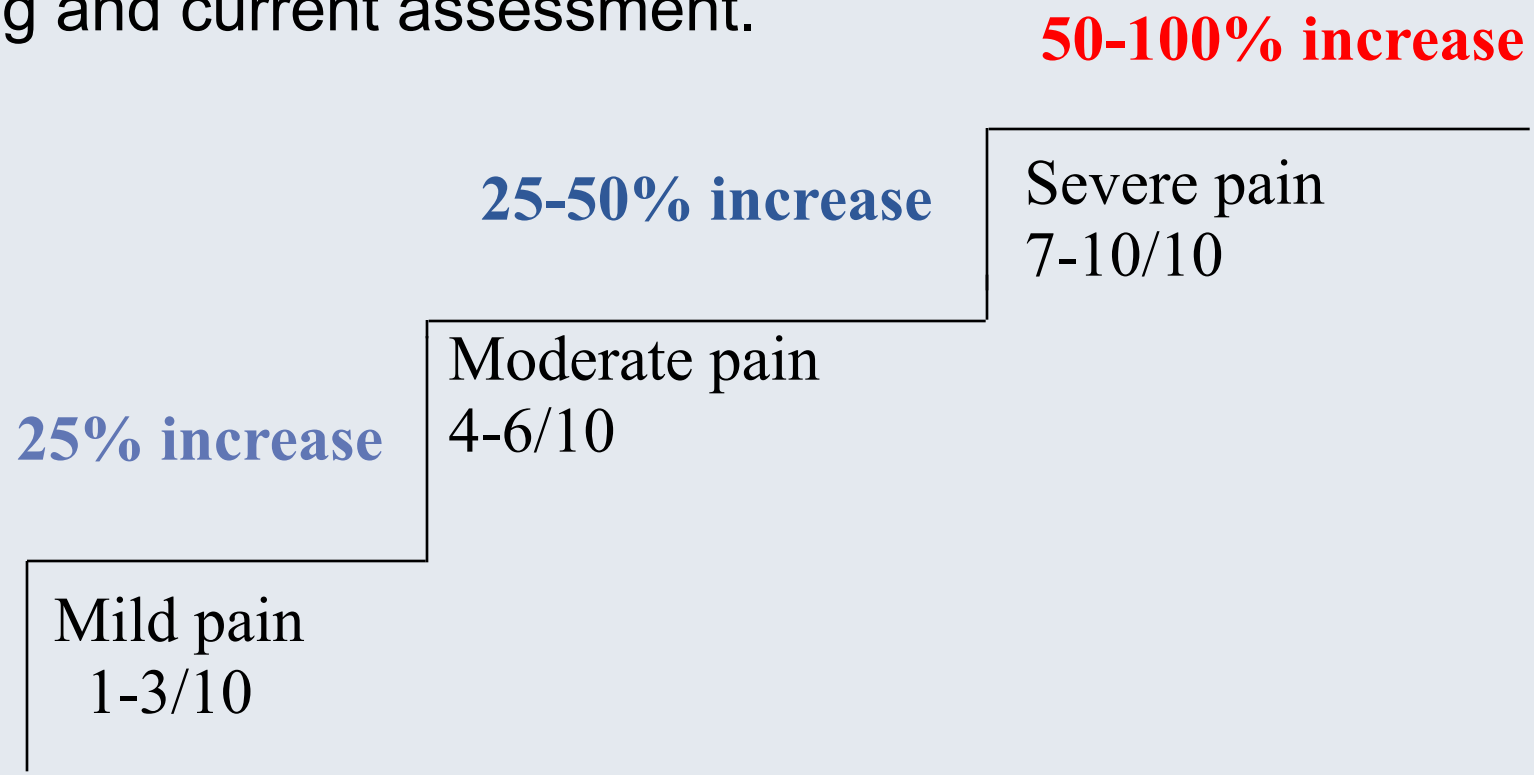
- Patients on any long-acting med always need a short-acting med available for breakthrough pain; something they can take at least every 4 hours, preferably less.
- Generally, the dose of breakthrough opioid should be:
  - 10% of 24 hour dose of analgesics and made available q2 hours.
  - Example: breakthrough dose for Morphine ER 60mg q12hrs should be in range of 10-15mg q2hrs of oxycodone or immediate release morphine (since 10% of 120 mg is 12)

Methadone – for experts only

- Inexpensive, potent oral opioid
- Complex pharmacology
- Consult a pharmacist or palliative care specialist for dosing and dose escalation information

Opioid Dose Escalation

Always increase by a percentage of the present dose based upon patient's pain rating and current assessment.

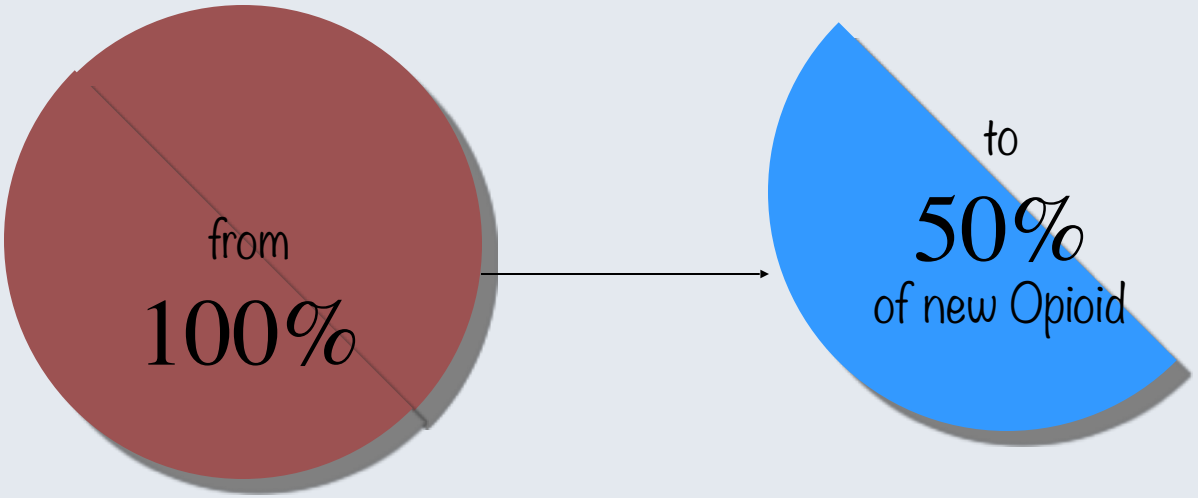


Frequency of dose escalation

- The frequency of dose escalation (oral opioids) depends on the particular opioid …
  - short acting oral: q 2-4 hours
  - long acting oral, except methadone: q 24 hours
  - methadone: q 72 hours
  - transdermal fentanyl: q 72 hours.

Incomplete cross-tolerance

- If a switch is being made from one opioid to another it is recommended to **start the new opioid at ~50%** of the equianalgesic dose.
- This is because the ***tolerance*** a patient has towards one opioid, may not completely transfer ("incomplete cross-tolerance") to the new opioid.



Parenteral Opioids

- IV is the route of choice if access is available.
  - There is NO indication for IM opioids (painful, no benefit over SQ route)
  - All standard opioids can be given SQ, by either bolus dose or by continuous infusion.
- PCA (basal rate plus a patient initiated dose) is an effective and well accepted modality; either IV or SQ.

Parenteral Opioids

- IV or SQ bolus doses have a shorter duration of action than oral doses; typically 1-3 hours.
- The peak effect from an IV bolus dose is 5-15 minutes.
- Dose escalation of parenteral opioids is the same as with oral—always by a percentage of the starting dose.

Opioids Side Effects

- Sedation, confusion, respiratory depression
- Dizziness, dysphoria
- Nausea
- Constipation
- Itching, uticaria, bronchospasm
- Urinary retention
- Endocrine effects
- Opioid hyperexcitability syndrome
  - Hyperesthesia, myoclonus, seizure

Sedation / Respiratory Depression

- With increasing dose, all opioids lead to a predictable sequence of CNS events:

Sedation with or without delirium then …

Further decrease in consciousness then …

Coma and respiratory depression

Respiratory Depression

- Risk Factors
  - Renal insufficiency
  - Liver failure
  - Parenteral opioids; especially rapid dose escalation in opioid naïve patients
  - Severe pulmonary disease (CO_2 retainers)
  - Sleep apnea
  - Rapid dose escalation of transdermal fentanyl or methadone

Naloxone (Narcan®)

- In palliative care, naloxone is indicated when:
  - The goals of care are such that reversing CNS depression is appropriate to patient's goals
  - Patients have decreased respirations and decreased level of consciousness (arousal)
- Administer naloxone—1 amp (0.4 mg) diluted in 9 cc saline—push 1cc per minute until level of consciousness improves.
  - Administering more can precipitate severe, painful, and traumatic opioid withdrawal, and can be dangerous
  - Naloxone's effects last only ~20mins, so continued monitoring will be necessary after initially reviving the patient

Nausea and Vomiting

- Caused by stimulation of the CTZ (chemoreceptor trigger zone) at base of 4th ventricle.
  - Nausea is not an allergy!!
- Tolerance develops within 3-7 days for most patients
- Standard anti-emetics can reduce symptoms
  - No “best” anti-emetic

Constipation

- Multifactorial cause
- Tolerance does not develop
- Start a bowel *stimulant* at the time opioids are started
  - Stool softeners alone are not adequate
  - Senna (with or without docusate) is good first choice
- Add saline or osmotic laxatives as needed (e.g. MOM, sorbitol, Lactulose)
- Goal is at least one BM every other day

Itching and Urticaria

- Tolerance may or may not develop.
- Not life threatening
  - not anaphylaxis
  - does not mean that opioids can never be used
- Treatment of symptoms is not very effective (anti-histamines, steroids)
  - Trial of different opioid is indicated as some patients will itch with one product but not another.

Tolerance and Dependence

- Tolerance is *not* an inevitable consequence of chronic opioid therapy
- Physical dependence is expected with chronic therapy
- Do not confuse physical dependence with ADDICTION, defined as
  - **compulsive use of drugs**
  - **loss of control**
  - **use despite harm**

Learning Points

List 3 new things you learned from this presentation.

1.
2.
3.

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