Opioids for Pain

David E. Weissman, MD
Professor Emeritus,
Medical College of Wisconsin
Palliative Care Education, LLC
2015
Acknowledgement

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

Mild Pain 1-3/10
- ASA, APAP, NSAIDS

Moderate Pain 4-6/10
- Weak opioids +/- non-opioids (e.g. Tylenol #3)

Severe Pain 7-10/10
- Potent opioids (e.g. morphine) +/- non-opioids
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 \textit{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 effect** 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.
Calculate: 2 oxycodone tabs (5mg) being taken every 4 hours is equal to what daily dose of Morphine ER?
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
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.

- **Mild pain**
  - 1-3/10
  - 25% increase

- **Moderate pain**
  - 4-6/10
  - 25-50% increase

- **Severe pain**
  - 7-10/10
  - 50-100% increase
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.
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, urticaria, bronchospasm
- Urinary retention
- Endocrine effects
- Opioid hyperexcitability syndrome
  - Hyperesthesia, myoclonus, seizure
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 4\textsuperscript{th} 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
List 3 new things you learned from this presentation.

1.
2.
3.


