



Pain Management

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Pain remains unrecognized and undertreated in US

- 850 bed hospital--NYC
- General Medicine population
- Cancer related issues in 20%
- 2/3 with prior exposure to opioids
- 22% in severe pain
- 67% with multiple days in severe pain
- 18% without pain relief within 2 hours.

Pain and cancer

- How often—80-90% of individuals with cancer will have pain during the course of the illness
- WHO estimates that 50% of individuals with cancer worldwide will die with pain not controlled
- Pain is the most feared symptom of cancer
- Pain in individuals with cancer can also be for unrelated reasons such as arthritis that was present before the cancer appeared



What patients want

Patients with life-limiting chronic illness (n=126)
say their primary goals are:

- receiving adequate pain management
- avoiding prolongation of dying
- achieving sense of control
- relieving burdens
- strengthening relationships

Singer PA et al. JAMA 1999; 281:163-168

How non-cancer pain differs from pain from cancer

- Often present over years, not months or weeks
- Level of pain remains stable
- Often controlled with modest amounts of pain medicine or non-drug related therapy such as physical therapy

Pain pathways in the nervous system

- Pain is first felt at the periphery—skin, outer area of organ, where the receptors are
- The impulse (message) is sent to the spinal cord and ascends up the spinal cord to reach the thalamus in the cortex, an area where pain is perceived
- The message may be modified at the level of the hindbrain so that what gets further up the brain first is altered—rub a slap.

How does cancer cause pain

- Pressure of the mass of cancer cells on nerves. The nerves can be in bone or any place in the body
- Injury to the nerve from treatment from cancer—scar related to surgery, direct damage from chemotherapy or radiation
- Release of substances that affect nerves, for example pain from a mass in the pancreas may be in part related to a substance that stimulates nerve growth.

Pressure from tumor on nerve, bone, and other structures



Measuring pain and other contributors

- Pain has a subjective component—each individual differs in how they perceive minor or major pain
- Anxiety and depression may have strong influence on how pain is perceived

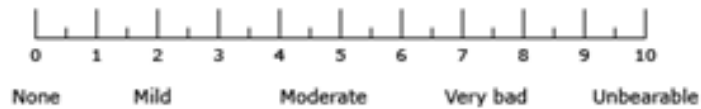
Assessment of pain

- Time/duration component—short, long
- Character—dull, aching, poorly localized, sharp, burning, stinging
- Radiating?
- Change from low level to worsening
- **With individuals with cancer, change is most often equated with progression**

MEASURING PAIN

Pain scale

What does your pain feel like?



Date: _____

UpToDate®

Managing pain from cancer

- Balance activities that cause the pain with need to carry out the activity
- Distraction—relaxation techniques such as biofeedback, or imagery may help
- Anesthesia—injection of a nerve with anesthetic, other specialized techniques that place anesthetic over the spinal cord, or coverings of the cord.
- Medicines

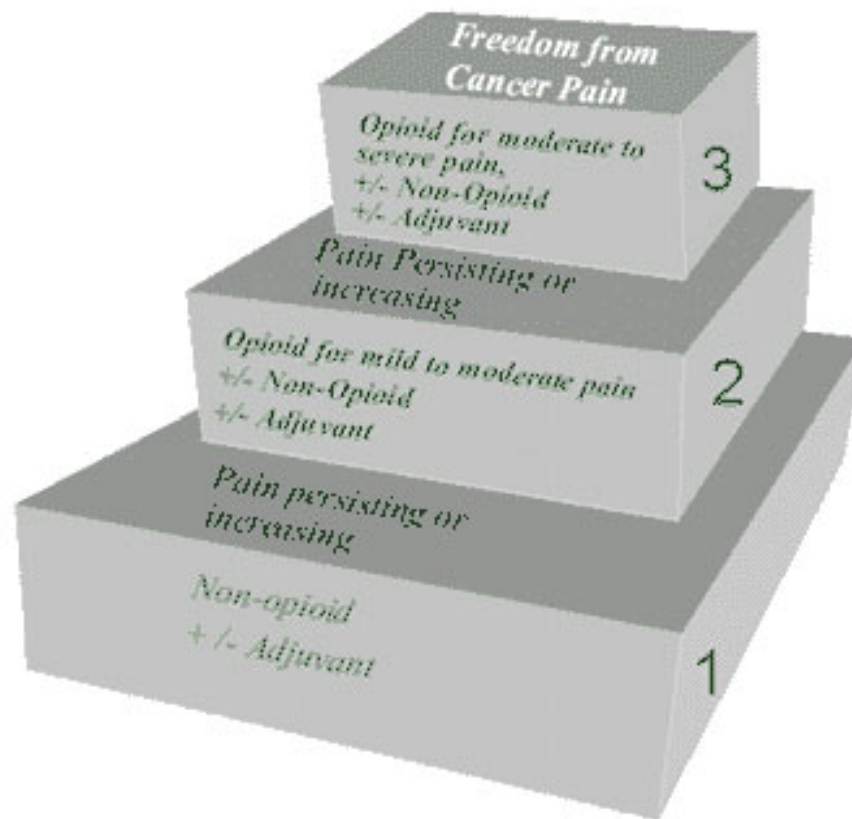
Surgery and Radiation

- Radiation plays a major role in palliating selected instances of pain, especially bone involvement by cancer. It can shrink a mass that is producing pressure on the nerve
- Surgery may play a role in pain management in selected individuals with cancer, e.g.
 - Setting or pinning a bone involved with cancer so movement cant send a pain message

Medicines

- Opioids (Narcotics)
- Non-steroidal anti-inflammatory medications
- Anti-depressants
- Acetaminophen (CAUTION)

WHO's Pain Relief Ladder



Types of pain

- Nociceptive
 - Specific receptors on surface of skin, bone, or organs such as bowel or appendix
 - Not spontaneously active
 - Rare cases of newborns without these receptors—these individuals don't generally survive.
 - Can recruit other nerves so pain worsens and becomes more diffuse, e.g. the headache that spreads from the front to the whole head
 - Described as aching, dull, constant
- Neuropathic
 - Usually with a specific nerve or group of nerves
 - Described as shooting or burning

Types of pain

- Movement or incidental pain—occurs when the movement of a limb worsens pain—usually because the bone is weakened from cancer or there is an overt fracture in the bone and the two parts of bone move—requires different strategy to manage—need rapid relief and oral medicines take 30-45 minutes

Patients with cancer—the cause of pain

- Often combination of sharp (nociceptive) and shooting (neuropathic) pain
- A movement component may also be present
- Management may involve treating for both types of pain or using a delivery system that gets adequate pain medicine on board quickly

Opioids

- Derived from the poppy plant
- Heroin(di-acetyl morphine) is the original compound
- Modified by the liver to form morphine
- Other opioids, are partly derived from morphine but have a synthetic part of the molecule added—hydromorphone
- Some opioids are entirely synthetic-fentanyl

Opioids (Narcotics)

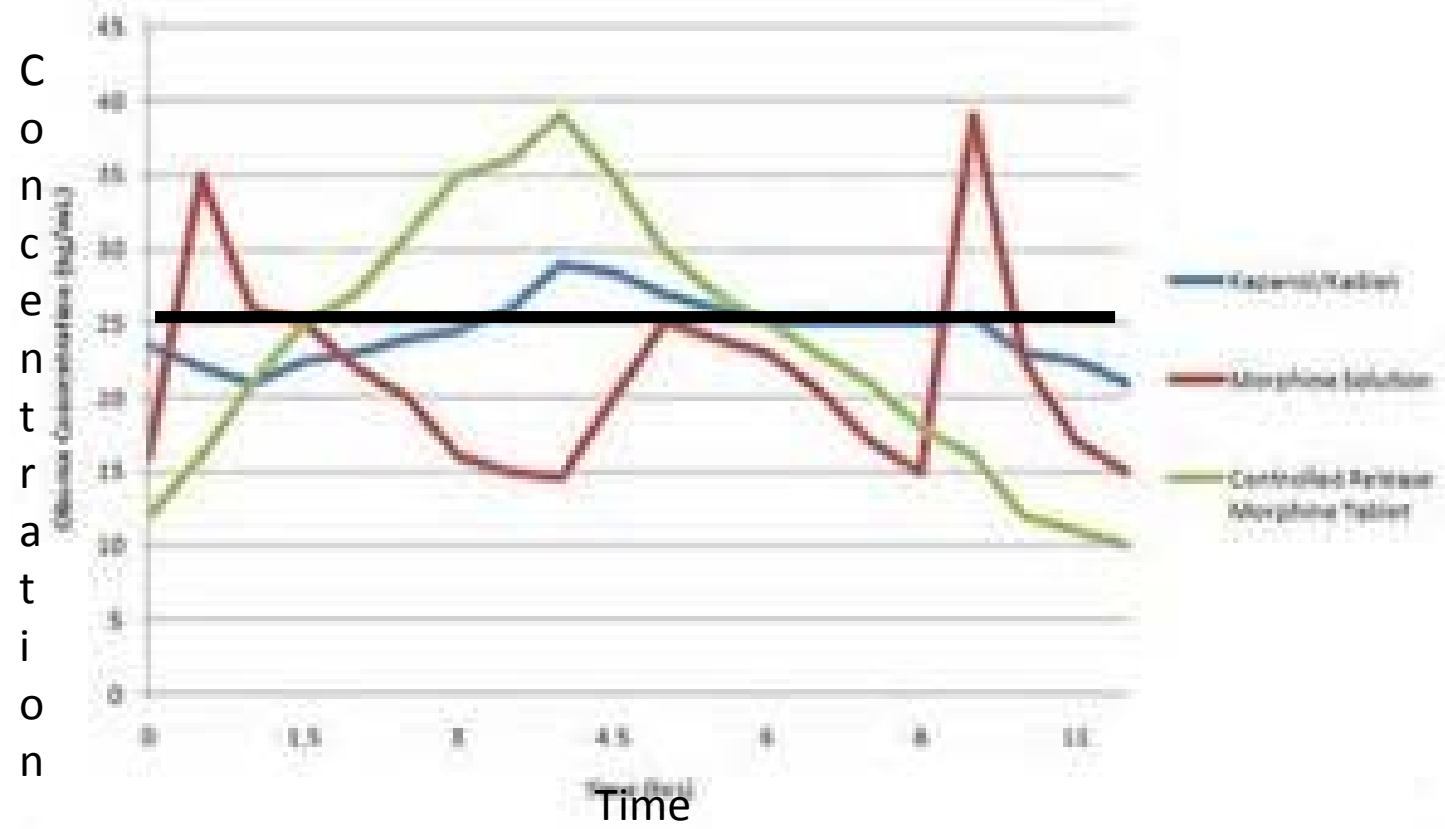
- Act on receptors (mu, kappa, or delta) in the nervous system to stabilize membranes and not let the nerve discharge, either peripherally, or centrally in the spinal cord. This action decreases messages reaching the centers in the brain where pain is perceived.

Patterns of pain and their management

- Pain may be continuous with flares(breakthrough)
 - The mechanism of breakthrough pain is not fully understand but it is a real phenomenon.
- Flares don't always imply failure of control unless they are frequent
- May need to use opioids that last longer as well as those that are short acting

Typical regimen

- Use long acting medication that is taken all the time at set intervals regardless of whether the individual is in pain to suppress pain continuously—Prevention strategy
- Use short acting medication periodically as needed to decrease pain more acutely when breakthrough episodes occur—Treatment strategy
- If there are many episodes of breakthrough, may need to increase the amount of long acting medication to decrease the frequency



Side effects of opioids

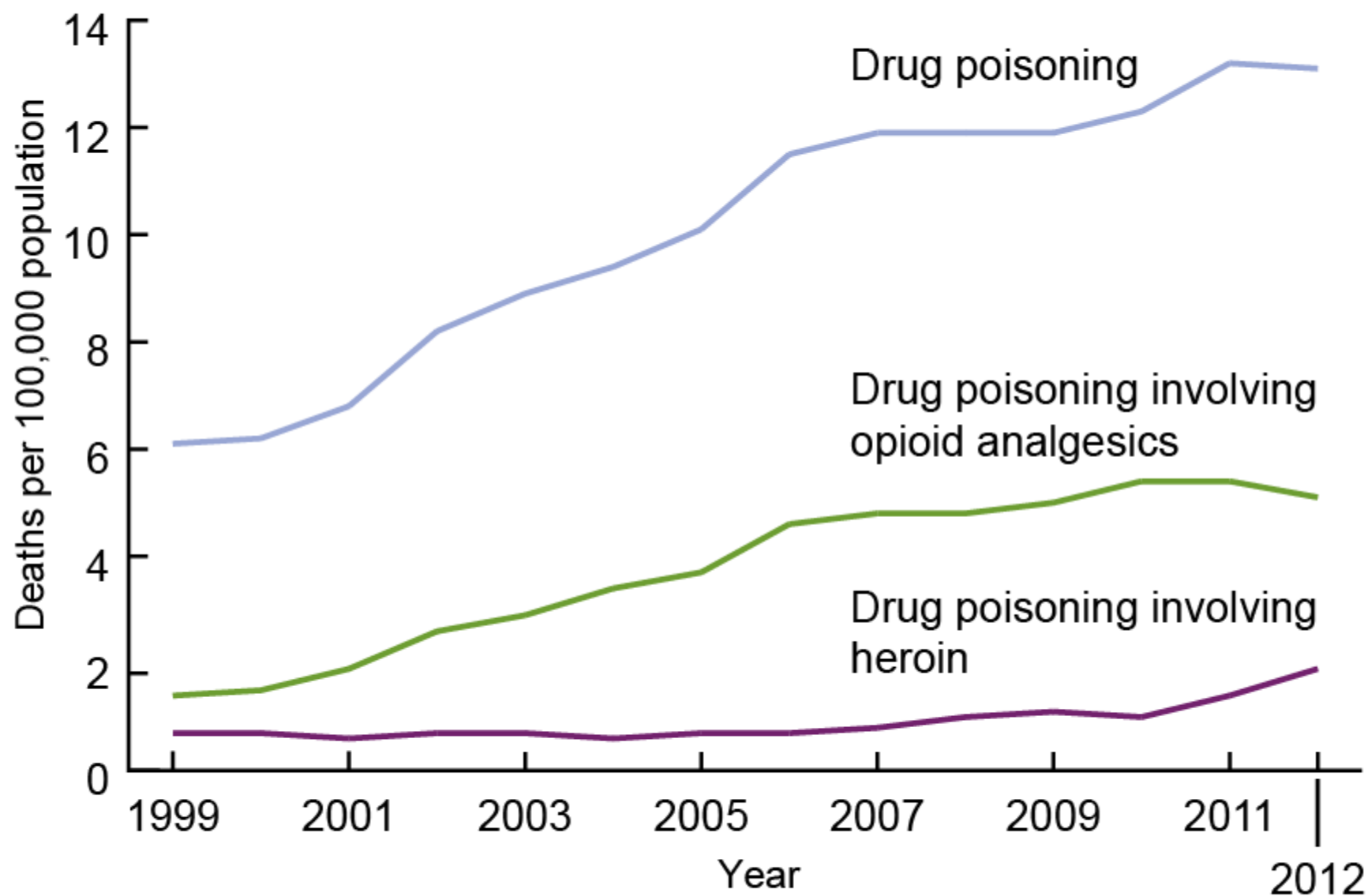
- Constipation--? More likely with long acting medications such as “contins”, requires aggressive laxative regimens that are taken daily, not as needed
- Sedation—may be temporary and improve while person remains on the medication
- Allergies—not common, more common is itching which is not an allergy but release of histamine in the skin; can be managed with anti-histamines such as Benadryl



Opioid Induced Neurotoxicity

- AH, VH, or Tactile Halluc.
- Myoclonia
- Seizures
- Seen more frequently due to increased doses of analgesia being used.

**Figure 1. Age-adjusted drug-poisoning death rates:
United States, 1999–2012**



NOTE: Drug-poisoning deaths may involve both opioid analgesics and heroin.

SOURCE: CDC/NCHS, National Vital Statistics System, Mortality File.

Side effects of opioids

- Most concerning is respiratory depression and potentially breathing stops
- The opioids have been responsible for an epidemic of drug related deaths due to this side effect
- The opioid that is most often responsible is methadone.
- Methadone, used correctly is a valuable drug for certain types of pain

Clearance of opioids, the role of the liver and kidney

- These drugs are first broken down by a several pathways in the liver, but the breakdown products can be irritating to the nervous system
- The breakdown products are cleared by the kidney and in individuals with kidney problems, there are preferred opioids—methadone, hydromorphone, fentanyl, that are less likely to have this problem



Implications of alteration in hepatic clearance

- In case of codeine, may not yield 30% conversion to morphine
- O,N demethylation, glucorindation vary in amount and susceptibility to reduction
- CYP isoenzymes vary in proportion in liver and relative significance if reduced
- Net result may be reduction in clearance and persistence of parent compound, with prolongation of individual dose effect

Renal disease and opioids

- Morphine 6-glucuronide potent active metabolite
 - Renal excretion; slow to cross BBB
 - Half-life may exceed 24 hours in renal failure
- AVOID NSAIDs, tramadol, morphine, codeine
- Reduced GFR –hydromorphone, oxycodone*, methadone, fentanyl
- DIALYSIS – hydromorphone, methadone, fentanyl

Genetic variability and opioids

- Some opioids, for example codeine, require breakdown into the liver to morphine for their ability to work.
- If the individual has a genetic (inherited) enzyme that works more slowly, no benefit from codeine may be seen; if the enzyme works very fast higher levels can be seen
- Not common—1-10% of different populations of people



Equianalgesic Dosing

- Decrease side effects when present-OIN
- Overcomes tolerance
- Intolerant of current drug-vomiting, sedation, constipation
- Not more effective, but equi-potency
- Tables are approximation
- **CAUTION RE: INCOMPLETE CROSS TOLERANCE**

Case #1

- RB is a 58 yo M with newly diagnosed prostate cancer with diffuse osseous metastases. He is being referred to the palliative care service for pain management related to pelvic mets.
- Current pain medications: oxycodone/APAP 5/325mg 1-2 tabs q4h prn, ibuprofen 200mg po TID

Case #1

- Pain scores:
 - Worst: 10/10
 - Best: 4/10
 - Average: 7/10
- Opioid use over last 7 days:
 - “I’ve been taking more than I should...” – 2 tabs/dose of oxycodone/APAP 5/325mg. Takes q3h around-the-clock.

Case #1

- What medication change(s) should be made for RB?
 - Issues with current regimen?
 - Add long-acting agent?
 - Change short-acting agent?

Opiate Equianalgesic Dosing Chart

| Dosing Table for Opioids | | | | | | |
|--|--|---|---|----------------------|--|--|
| Drug | Oral to Parenteral (IM, SQ, IV) Ratio | Approximate equianalgesic dose | ADULTS | | PEDIATRICS | |
| | | | Recommended starting dose (adults more than 50 kg body weight) | | Recommended starting dose (children and adults less than 50 kg body weight) ¹ NOTE: when assessing doses in larger children, note usual initial adult dose | |
| | | | oral | parenteral | oral | parenteral |
| Opioid Agonist | | | | | | |
| Morphine | 3 mg oral to 1 mg parenteral | 10 mg PARENTERAL | 10-20 mg every 4 hours | 3-5 mg every 4 hours | 0.3-0.5 mg/kg/dose every 6 hours | 0.05-0.2 mg/kg/dose every 4 hours (MAX 2-4 mg) |
| Codeine ^{2,3} (as Tylenol #3: 30 mg codeine/300 mg APAP) | 1.7 mg oral to 1 mg parenteral | Use of parenteral codeine is not recommended. | 30-60 mg Every 4 hours | N/A | 0.5-1.5 mg/kg/dose every 6 hours | N/A |
| Fentanyl | N/A | Fentanyl 100 mcg (0.1 mg) PARENTERAL = Morphine 10 mg PARENTERAL (see next Table for conversion from fentanyl patches to parenteral morphine) | Actiq TM , Fentora TM are not available at UNC. | 50 mcg every 2 hours | N/A | 1 – 2 mcg/kg/dose every 4 hours |
| Hydrocodone ³ (as Norco: 5 mg hydrocodone/325 mg APAP) | N/A | Hydrocodone 1 mg ORAL is equal to Morphine 1 mg ORAL | 5-10 mg every 4 hours | N/A | 0.05-0.2 mg/kg/dose every 4 hours | N/A |
| Hydromorphone (Dilaudid) | 5 mg oral to 1 mg parenteral | Hydromorphone 2 mg PARENTERAL is equal to Morphine 10 mg PARENTERAL | 2 mg every 4 hours | 1 mg every 4 hours | 0.03-0.08 mg/kg/dose every 4 hours | 0.015 mg/kg/dose every 4 hours |
| Meperidine | 4 mg oral to 1 mg parenteral | Meperidine 75 mg PARENTERAL is equal to Morphine 10 mg PARENTERAL | NOT RECOMMENDED AS AN ANALGESIC (FOR TREATMENT OF RIGORS ONLY) | | | |
| Methadone ⁴ | Caution is advised when converting to methadone due to variability in patient response and delayed peak effects. Reliable equianalgesic conversion for repeated dosing is not available. Parenteral methadone is not available at UNC. | | 5 mg every 8 hours | N/A | 0.1 mg/kg/dose every 8 hours | N/A |
| Oxycodone ³ (as Percocet: 5 mg oxycodone/325 mg APAP) | N/A | Oxycodone 1 mg ORAL is equal to Morphine 1.5 mg ORAL | 5 -10 mg every 4 hours | N/A | 0.05-0.2 mg/kg/dose every 6 hrs | N/A |
| Opioid Agonist-Antagonist and Partial Agonist | | | | | | |
| Butorphanol | N/A | Butorphanol 2 mg PARENTERAL is equal to Morphine 10 mg PARENTERAL | N/A | 2 mg every 4 hours | N/A | 10-20 mcg/kg/dose every 4 hours |
| Nalbuphine | N/A | Nalbuphine 10 mg PARENTERAL is equal to Morphine 10 mg PARENTERAL | N/A | 10 mg every 4 hours | N/A | 0.1 mg/kg/dose every 4 hours |

Converting from oxycodone to morphine

| | | |
|---|--------------------------|--|
| | is not available at UNC. | |
| Oxycodone³ (as Percocet: 5 mg oxycodone/325 mg APAP) | N/A | Oxycodone 1 mg ORAL is equal to Morphine 1.5 mg ORAL |

Case #2

- GP is a 40 yo M with SCC of the supraglottis who is currently undergoing concomitant chemotherapy and radiation. He is being evaluated for oropharyngeal pain.
- Current medications: Oxycontin 20mg po TID, hydromorphone 4mg – 1-2 tabs q3h prn

Case #2

- Pain scores:
 - Worse: 8/10
 - Best: 3/10
 - Average: 6/10
- Opioid use over last 7 days:
 - Oxycontin 20mg TID
 - Hydromorphone 4mg – 3 tablets ~0700, 3 tablets ~1030, 2 tabs ~1400, 2 tabs ~1800, 2 tabs ~2100, 2 tabs ~0100

Case #2

- What medication change(s) should be made for GP?

| Dos | | |
|--|--|---|
| Drug | Oral to Parenteral (IM, SQ, IV) Ratio | Approximate equianalgesic dose |
| Opioid Agonist | | |
| Morphine | 3 mg oral to 1 mg parenteral | 10 mg PARENTERAL |
| Codeine ^{2,3} (as Tylenol #3: 30 mg codeine/300 mg APAP) | 1.7 mg oral to 1 mg parenteral | Use of parenteral codeine is not recommended. |
| Fentanyl | N/A | Fentanyl 100 mcg (0.1 mg) PARENTERAL = Morphine 10 mg PARENTERAL (see next Table for conversion from fentanyl patches to parenteral morphine) |
| Hydrocodone ³ (as Norco: 5 mg hydrocodone/325 mg APAP) | N/A | Hydrocodone 1 mg ORAL is equal to Morphine 1 mg ORAL |
| Hydromorphone (Dilaudid) | 5 mg oral to 1 mg parenteral | Hydromorphone 2 mg PARENTERAL is equal to Morphine 10 mg PARENTERAL |
| Meperidine | 4 mg oral to 1 mg parenteral | Meperidine 75 mg PARENTERAL is equal to Morphine 10 mg PARENTERAL |
| Methadone ⁴ | Caution is advised when converting to methadone due to variability in patient response and delayed peak effects. Reliable equianalgesic conversion for repeated dosing is not available. Parenteral methadone is not available at UNC. | |
| Oxycodone ³ (as Percocet: 5 mg oxycodone/325 mg APAP) | N/A | Oxycodone 1 mg ORAL is equal to Morphine 1.5 mg ORAL |