End of Life Care: 
Blending Compassion with Pharmacology

Gregory L. Holmquist, PharmD, CPE
Certified Pain Educator
Board Certified Oncology Pharmacist
Pain Management / Palliative Care Pharmacist Specialist
Hospice Consultant
Chronic non-cancer Pain Team
LTC Elderly Pain Consultant
Private pain management consultant
Disclosure

- Salix Pharmaceuticals - honorarium
Wrong method of dealing with pain...
“Nothing would have a greater impact on the quality of life of (cancer) patients than the dissemination and implementation of knowledge already available in relation to pain and symptom management.”

World Health Organization, 1990
Symptoms, suffering . . .

- Fears, fantasy, worry
  - driven by experiences
  - media dramatization

- Multiple physical symptoms
  - inpatients with cancer averaged 13.5 symptoms, outpatients 9.7
  - pain, nausea / vomiting, constipation, breathlessness
  - weight loss, weakness / fatigue, loss of function

- Psychological distress
  - anxiety, depression, worry, fear, sadness, hopelessness, etc
  - 40% worry about “being a burden”
Steady decline, short terminal phase
Slow decline, periodic crises, sudden death
General strategies for managing end-of-life pain and symptoms...

- Prevent / palliate pain and symptoms as quickly as possible
  - Given what we know today about the efficacy of opioids for cancer pain, it is UNACCEPTABLE to deny the use of strong opioids or wait until death is imminent prior to using such therapy.

- Use bolus dosing to obtain rapid control of pain
  - Parenteral – IV or SQ
  - Oral / SL – short acting
    - Concentrated morphine 20mg/ml (Roxanol®)
    - Concentrated oxycodone 20mg/ml (Oxyfast®)
    - Fentanyl transmucosal (Actiq®, Fentora®)
  - Rectal – can use certain long-acting oral opioids rectally
General strategies for managing end-of-life pain and symptoms

- Once pain under control, if able to take oral, use long-acting opioid delivery systems
  - If unable to take oral, or if at imminent risk of losing the oral route, consider transdermal, continuous SQ / IV or rectal route
  - Around-the-clock dosing

- Consider role of selected adjuvants to assist in managing pain and other symptoms – examples:
  - Benzodiazepines: e.g. lorazepam (Ativan®) – for anxiety, SOB, restlessness
  - Antipsychotics: e.g. risperidone (Risperdal®), olanzapine (Zyprexa®), quetiapine (Seroquel®) – for delirium, hallucinations
  - Anticonvulsants: e.g. valproic acid (Depakote®), gabapentin (Neurontin®) – for agitation, neuropathic pain
Pain and Symptom Management: Compassion Principles

- Keep it simple – be willing to “weed out” that which is not now essential to palliative care
- Use a consistent approach, staying with the fundamental principles and scientifically proven approaches
- High tech ≠ high quality of life when managing pain and symptoms
- Treat the symptom, not the fear of the symptom
- Be willing to stop therapies that are ineffective or are not palliative
Compassion Avoids Confusion: “Keeping it simple when managing pain”

- Avoid the use of multiple different opioid agents.
  - √ Use **ONE** long-acting opioid for regularly scheduled pain medication.
  - √ Try to use the same “molecule” in a short-acting formulation for “break-through” / “rescue” dosing.

- Utilize adjuvants / co-analgesics when indicated - target adjuvant(s) to the specific symptom(s).

- Use analgesics with the lowest potential for side effects.
  - Avoid the “Band-Aid effect”
## Differentiating Types of Pain

<table>
<thead>
<tr>
<th></th>
<th>Nociceptive Pain</th>
<th>Neuropathic Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Somatic Pain</td>
<td>Visceral Pain</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td>Localized</td>
<td>Generalized</td>
</tr>
<tr>
<td></td>
<td>Radiating or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>specific</td>
<td></td>
</tr>
<tr>
<td><strong>Patient Description</strong></td>
<td>Pinprick, stabbing, or sharp</td>
<td>Ache, pressure, or sharp</td>
</tr>
<tr>
<td></td>
<td>Burning, prickling, tingling, electric shock-like, or lancinating</td>
<td></td>
</tr>
<tr>
<td><strong>Mechanism of Pain</strong></td>
<td>A-delta fiber activity</td>
<td>C Fiber activity</td>
</tr>
<tr>
<td></td>
<td>Located in the periphery</td>
<td>Involved deeper innervation</td>
</tr>
<tr>
<td></td>
<td>Dermatomal (periphery), or non-dermatomol (central)</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical Examples</strong></td>
<td>Periosteum, joints, muscles</td>
<td>Colic pain</td>
</tr>
<tr>
<td></td>
<td>Sickle cell</td>
<td>Appendicitis</td>
</tr>
<tr>
<td></td>
<td>Superficial laceration</td>
<td>Kidney stone</td>
</tr>
<tr>
<td></td>
<td>Superficial burns</td>
<td>Chronic pancreatitis</td>
</tr>
<tr>
<td></td>
<td>Intramuscular injections, venous access</td>
<td>IBS</td>
</tr>
<tr>
<td></td>
<td>Otitis media</td>
<td>Angina</td>
</tr>
<tr>
<td></td>
<td>Stomatitis</td>
<td>Menstrual cramps</td>
</tr>
<tr>
<td></td>
<td>Extensive abrasion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Colic pain</td>
<td>Trigeminal neuralgia</td>
</tr>
<tr>
<td></td>
<td>Appendicitis</td>
<td>Avulsion neuralgia</td>
</tr>
<tr>
<td></td>
<td>Kidney stone</td>
<td>Posttraumatic neuralgia</td>
</tr>
<tr>
<td></td>
<td>Chronic pancreatitis</td>
<td>Peripheral neuropathy (diabetes, HIV)</td>
</tr>
<tr>
<td></td>
<td>IBS</td>
<td>Limb amputation</td>
</tr>
<tr>
<td></td>
<td>Angina</td>
<td>Herpetic neuralgia</td>
</tr>
<tr>
<td></td>
<td>Menstrual cramps</td>
<td></td>
</tr>
</tbody>
</table>

Somatic pain

- Medication therapy overview:

  APAP/ NSAID  +  opioid
  based on symptoms
Visceral pain

- Medication therapy overview:

Anticholinergic ± opioid / NSAID ± corticosteroid
Neuropathic pain

- Medication therapy overview:

  adjuvant  +  opioid

  based on symptoms

  “Let the adjuvant be the engine and the opioid the caboose”
Proposed Neuropathic Pain Mechanisms

Primary afferent fibers:
- Ectopic discharge
- Sensitization
- Fiber loss/neuroma formation

Dorsal root ganglion:
- Loss of neuronal cell bodies and scarring
- Ectopic discharge

Dorsal horn:
- Central sensitization
- Loss of central inhibition
- Deafferentation-induced rewiring
Chemical Mediators of Neuropathic Pain

- ↑ sodium channels in nociceptor neurons
- ↑ numbers of substance P receptors in the dorsal horn (up-regulation)
- ↑ numbers of receptors for glutamate
- ↑ spinal cord levels of pain-producing cytokines (interleukins-1, -6 and tumor necrosis factor alpha)
- ↑ spinal cord and brain levels of cholecystokinin
- ↓ CNS levels of gamma-aminobutyric acid and/or opioid peptides or their receptors
Assessment of Pain

Key understandings:

- Wide interpatient variation in the amount of pain experienced in response to insult.
- Wide variations in responses to therapeutic strategies.
  - Genetic differences
  - Prior experiences with pain / management
  - Levels of anxiety, fear, meaning of pain, ethnocultural background, sense / lack of control
Tolerance

- “Needing increased doses to maintain level of pain control”
- Has not proven to be a limitation to short- or long-term opioid use.
- Rapid escalation of drug doses in cancer pain usually due to disease progression.
- Studies suggest that use of long-acting oral opioids as maintenance therapy for primarily nociceptive pain does not lead to uncontrolled dose escalation.
Hyperalgesia

 Thought to involved NMDA receptor activation → sensitization of pronociceptive pathways

 Characterized by patients who once responded to an opioid and in spite of being on a stable doses for a period of time now have increased pain sensitivity


Opioid-induced Hyperalgesia (OIH)

- Three forms of OIH can be distinguished
  - All can result in either: Increased sensitivity to pain; aggravation of pre-existing pain; or, expression of novel pain symptoms.
  - OIH$_1$: Opioid maintenance therapy
    - Involves up-regulation of pain facilitating neuronal pathways at multiple levels of the central and peripheral nervous system
    - Stimulation of excitatory amino acid neurotransmitter system.
  - OIH$_2$: Very high and escalating doses of opioids
    - Usually implicated with high doses of morphine or hydromorphone
    - Severe allodynia, myoclonus noted
    - Thought to be due to metabolites inhibiting glycineric inhibition at spinal cord level inducing a strychnine-like excitatory intoxication.
  - OIH$_3$: Observed in animals on ultra-low doses

Angst MS and Clark JD. Opioid-induced hyperalgesia. A qualitative systematic review. Anesthesiology 2006;104:570-587.

Should we be fearful of managing pain with opioids?
Decision points for using opioids

- Patient / pain syndrome factors
  - Type, intensity, quality, expected duration of pain
  - Reliability issues, history, preferences

- Molecule factors
  - Severity of pain, side effect profile

- Delivery (blood level) / scheduling factors
  - Blood levels, crescendo pain, risk of adverse effects

- Assessment factors
  - Communicative vs. non-communicative
  - Level of cognition
Managing pain with opioids: Using pharmacokinetics to your advantage

- Why does it make a difference which opioid delivery system we use in patients?
  - Outcomes desired:
    - Analgesia (comfort)
    - Minimization of side effects (sedation, N/V, hallucinations)
    - Improved functioning (ambulation, social/recreational activities, visiting with loved ones, self-care)

“A picture is worth a thousand words”
Immediate-Release, Short-acting Opioids: Characterized by a rapid onset, short duration

- **Oral formulations:**
  - Hydrocodone-acetaminophen combination products
    - Vicodin®, Lortab®, Lorcet®, Zydone®
  - Oxycodone-acetaminophen combination products
    - Percocet®, Tylox®, Roxicet®
  - Miscellaneous
    - Propoxyphene (Darvon®, Darvocet®)

- **Parenteral formulations:** (IM / IV prn injections)
  - Meperidine (Demerol®)
  - Morphine
The “Roller Coaster Ride” that can Occur with Immediate-Release Opioids

Theoretical depiction of blood levels and some side effects that can occur with administration of immediate-release opioids

- Sedation, dysphoria, euphoria
- Pain relief without side effects
- Pain returns

Time (hrs)
Comfort only is not enough!
Comfort only is not enough!
Obtaining Optimal Blood Levels: “Learning from the Cancer Pain Model”

Theoretical depiction of ideal blood levels / side effects that may occur with administration of well-designed delivery systems of extended-release oral opioids.

- Sedation, dysphoria and euphoria are minimized
- Pain relief with less side effects
- Return of pain occurs less frequently
Breakthrough Pain

- Breakthrough pain (BTP) occurs as frequently as 70-90% of advanced cancer patients vs. 74% in chronic non-cancer pain
- Fluctuation in intensity that interrupts tolerable background level of pain
- Numerous approaches to classification
  - Incident (due to a predictable or unpredictable trigger)
  - Spontaneous/Idiopathic (no predictable trigger)
  - End of dose failure (increase in pain as long-acting opioid wears off)

- Increase CR opioids vs. increase IR opioids
  - Patient specific variables
  - Drug specific variables
  - Environmental specific variables

### Commercially Available Oral Opioids in US

<table>
<thead>
<tr>
<th>Combination</th>
<th>Immediate Release</th>
<th>“Long acting”</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hydrocodone / APAP:</strong></td>
<td><strong>Morphine</strong> 10; 15; 30</td>
<td><strong>Morphine-LA</strong> 15; 30; 60; 100; 200;</td>
</tr>
<tr>
<td></td>
<td>Solutions: 2mg, 4mg &amp; 20mg/ml</td>
<td>Kadian specific: 10; 20; 50; 80</td>
</tr>
<tr>
<td></td>
<td><strong>Tramadol:</strong> 50</td>
<td>Avinza specific: 90; 120</td>
</tr>
<tr>
<td></td>
<td><strong>Tapentadol:</strong> 50, 75, 100</td>
<td>Embeda specific: 20;30;50;60;80; 100</td>
</tr>
<tr>
<td>2.5/500; 5/325; 5/500; 7.5/325; 7.5/500; 7.5/650; 7.5/750; 10/325; 10/500; 10/650; 10/660; 10/750</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hydrocodone / Ibuprofen:</strong></td>
<td><strong>Oxycodone</strong> 5; 10, 15; 30 IR</td>
<td><strong>Oxycodone-LA</strong> 10, 15, 20, 30, 40, 60, 80</td>
</tr>
<tr>
<td>5/200; 7.5/200</td>
<td>Solutions: 1mg &amp; 20mg/ml</td>
<td></td>
</tr>
<tr>
<td><strong>Oxycodone / APAP:</strong></td>
<td><strong>Hydromorphone</strong> 2; 4; 8 IR</td>
<td><strong>Oxymorphone-LA</strong> 5; 7.5; 10; 15; 20; 30; 40</td>
</tr>
<tr>
<td>2.5/325; 5/325; 7.5/325; 10/325; 5/500; 7.5/500; 10/650</td>
<td>Solution: 1mg/ml</td>
<td></td>
</tr>
<tr>
<td><strong>Oxycodone / Ibuprofen:</strong></td>
<td><strong>Oxymorphone</strong> 5; 10</td>
<td><strong>Fentanyl-TTS</strong> 12.5; 25; 50; 75; 100 (mcg/hour)</td>
</tr>
<tr>
<td>5/400</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Codeine / APAP:</strong></td>
<td><strong>Codeine</strong> 15; 30; 60</td>
<td><strong>Methadone</strong> 5; 10 (40mg restricted use in US)</td>
</tr>
<tr>
<td>15/300; 30/300; 60/300</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fentanyl (buccal / OTFC):</strong></td>
<td><strong>Fentanyl-TTS</strong> 0.1; 0.2; 0.4; 0.6; 0.8; 1.2; 1.6</td>
<td><strong>Levorphanol</strong> 2</td>
</tr>
<tr>
<td>0.1; 0.2; 0.4; 0.6; 0.8; 1.2; 1.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tapentadol</strong> 50, 100, 150, 200, 250</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hydromorphone</strong> 8, 12, 16</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Non-optimal oral opioid options…

“The No...oos”

- Propoxyphene products (Darvon®, Darvocet®)
  - Lack of proven activity (beyond placebo effect)
  - NO LONGER AVAILABLE IN THE U.S.

- Mixed agonist-antagonists
  - E.g. pentazocine (Talwin®), butorphanol (Stadol®)
  - Compete with agonists ➔ withdrawal
  - Analgesic ceiling effect, adverse effects

- Meperidine (Demerol®)
  - Metabolite (normeperidine) leading to seizures
  - Oral dosage form minimally effective

- Codeine (Tylenol #3®)
  - Side effects: constipation, nausea, vomiting
  - Needs activation via CYT P450 2D6
Morphine…
“Is it the best strong opioid?”

- Thought of by many practitioners and patients as the “strongest of pain medications”.
- Available in a variety of routes:
  - Oral: short-acting and long-acting
  - Parenteral: SQ, IM, IV, PCA, epidural, intrathecal
  - Miscellaneous: SL, rectal
- Utilized in some form for most pain conditions:
  - Acute incidental, post-operative, chronic non-cancer and cancer pain.
Why was using morphine in the 1980’s considered “the compassionate thing to do”, but over the past decade its use has declined?
The Potential "UGLY side" of Morphine

- Societal stigmatization
  - Patient and health care professional fears
  - "Addiction", "Pain medicine for cancer or dying"

- Adverse effects
  - Common to all opioids: constipation
  - Increased nausea and vomiting
  - Distinct to morphine: METABOLITE EFFECTS
    - Glucuronide byproducts (M3G) (M6G)
    - When do metabolite side effects become an issue?
Alternative Opioid Options for Managing Severe Pain

Hydromorphone
Fentanyl
Methadone
Oxycodone
Oxymorphone
Hydromorphone

- Semi-synthetic derivative of morphine, mainly mu agonist
- More lipophilic than morphine
- Major metabolite hydromorphone-3-glucuronide
  - Can accumulate in renal impairment, high doses
  - Neurotoxicity, seizures, myoclonus, alldynia
- More potent than morphine:
  - Parenteral: 6-8 times more potent than parenteral MS
  - Oral: 4-5 times more potent than oral MS
- Available in both oral and injectable formulations.
  - Oral: Short-acting: 2 mg, 4 mg, 8 mg
  - LA: Exalgo® 24 hour: 8mg, 12mg 16mg
  - Injectable: up to 10 mg/ml

Wright AW, Mather LE, Smith MT. Life Sci 2001;69:409-420
Barkin RL Lusco AM, Barkin SJ In: Boswell MV and Cole BE, eds. Weiner’s Pain Management: A practical
Fentanyl...

- **Activity:** mainly Mu agonist, minimal Kappa effects
- **Onset / peak:**
  - IV analgesia: peak effect 3 – 5 minutes
  - Transmucosal: onset 5 – 15 minutes; peak 20 – 30 minutes
  - Transdermal: onset 8 – 12 hours; peak may be as long as 34–38 hrs
- **Metabolism:**
  - Dependent on CYP3A4 (may be affected by drugs that induce or inhibit this isoenzyme – e.g. macrolide antibiotics, azole antifungal agents and protease inhibitors)

Fentanyl...

- **Availability:**
  - **Parenteral:**
    - Estimated to be 50-100X more potent than morphine
  - Spinal (epidural / intrathecal)
  - Transmucosal (Oralet®, Actiq®, Fentora®)
  - Passive transdermal (Duragesic®, generic versions)
    - Reservoir versus matrix systems—what are the differences?
    - Body fat, body temperature, edema, placement of transdermal system can affect bioavailability
    - Absorption of fentanyl does not vary to a clinically significant extent between the chest, abdomen and thigh.
  - Active transdermal (IONSYS ®)

Fentanyl

- Potential issues with transdermal delivery
  - May be variability in total absorption and variability in the overall rate of absorption
    - Subcutaneous body fat
    - Body temperature (absorption estimated to increase by about one-third with a rise in body temperature to 40°C)
    - Edema
    - Sweating
    - Placement site of transdermal system

- Very lipophilic – rapid onset for transmucosal and IV

- May induce analgesia without incurring same degree of constipation as morphine.

Fainsinger RLJ Palliative Care 1996;124;48-53.
Checklist for Appropriate Use of Transdermal Fentanyl

- Patient should not be cachectic or edematous or sweaty.
  
  **(remember fentanyl is lipophilic, doesn’t pass easily through aqueous media)**
  **AND**

- Patient should not be running fevers or putting a heat source (pads, water beds, etc) directly on or near the transdermal patch
  
  **(remember heat dramatically speeds up transdermal delivery of drug)**
  **AND**

- Patient’s pain should be relatively stable.
  
  **(remember fentanyl has a lag time of 16-24 hrs to absorb)**
  **AND**

- Patient has pain described as “moderate” or “severe” and is not opioid naive.
  
  **(remember even the lowest size patch is “worth” ≥ 30 mg oral morphine per day)**
  **AND**

- Patient cannot tolerate oral therapies
  
  **(remember sustained-release oral morphine provides greater consistency in serum opioid levels)**
Methadone...

- Synthetic mu-agonist opioid
  - Not necessarily any “stronger” or “weaker” than other opioids in the “strong” class.
  - Methadone (as it available in USA and most other countries) is a racemic mix (50:50 mix) of (R)- and (S)-methadone
    - (R) – methadone accounts for most, if not all of its analgesic effects
    - (R) – methadone aka *levo*- or *l*-methadone
    - (S) – methadone aka *dextro*- or *d*-methadone
Why all the excitement about methadone?

😊 “Cheap” to buy compared to pharmaceutically designed long-acting opioids
😊 Not perceived to be associated with abuse / misuse / diversion stigma of OxyContin®
😊 Non-competitive blockade of the N-methyl-D-aspartate (NMDA) receptor
What makes the use of methadone more complex than other opioids?

Methadone has unique pharmacokinetics leading to variations in serum levels, the amount of free drug available at receptor and drug accumulation.

- Long, and variable half-life: mean 40 hours (range: 5 - 130 hours)
- Good, and variable bioavailability: mean 75% (range: 36 – 100%)
- Highly bound to plasma proteins: mean free fraction 13% (4-fold interindividual variation)

Methadone has numerous drug interactions.

Unique and potentially dangerous side effects

Titration and conversion to- and from- other opioids does not follow “textbook” standards

Eap CB, Buclin T and Baumann P. *Clin Pharmacokinet* 2002;41:1153-1193.
Drug interactions with methadone...

- Methadone is metabolized mainly through the CYT P450 3A4 and 2D6 isoenzymes

- Common inhibitors of 3A4 and 2D6
  (↑ METH serum levels → ↑ opioid effects, ↑ sedation, ↑ risk resp. depression)
  - 3A4: amitriptyline, ciprofloxacin, fluconazole, sertraline
  - 2D6: fluoxetine, paroxetine, sertraline

- Common inducers of 3A4
  (↓ METH serum levels → ↓ opioid effects, ↑ risk withdrawal reaction)
  - Amprenavir, efavirenz, nelfinavir, nevirapine, phenobarbital, phenytoin, rifampin, ritonavir, spironolactone

Eap CB, Buclin T and Baumann P. *Clin Pharmacokinet* 2002;41:1153-1193.
Methadone and Torsades

- Methadone, by itself, in low to moderate doses (< 100 mg/day), most likely has little risk to cause torsades.
- By itself, at higher doses (> 100 mg/day) or at low- to moderate doses in conjunction with other drugs associated with QT prolongation, methadone can cause Torsades.
- Drugs that prolong QT and/or induce Torsades
  - Azithromycin, chlorpromazine, cisapride, clarithromycin, dolasetron, erythromycin, haloperidol, levofloxacin, lithium, methadone, ondansetron, quetiapine, risperidone, tizanidine, venlafaxine

“Textbook” methadone conversions...WARNINGS!!

- Most textbook equianalgesic tables underestimate the potency of methadone.
- Conversion ratios in many textbooks do not apply to repeated doses of opioids.
- As the dose of morphine (and other opioids) rises, the relative potency of methadone increases.
- Conversion ratios are NOT bi-directional
- LARGE interpatient variability
- Patients who have been on large AND INEFFECTIVE doses of morphine or other opioids prior to converting to methadone, may need a much GREATER ratio of methadone compared to patients on large and EFFECTIVE doses of other opioids.
Day 1 – reduce morphine total daily dose (MTDD) by 30% and start oral methadone as follows:
  - MTDD 30-90mg, use 4:1 (MS:methadone)
  - MTDD 90-300mg, use 6:1 (MS:methadone)
  - MTDD > 300 mg, use 8:1 (MS:methadone)

Day 2 – reduce MTDD by 30%. Increase methadone only if patient is in severe pain.

Day 3 – DC morphine and continue methadone Q8H around the clock with 10% dose for breakthrough pain.
Mercadente et al, 2001

- DC morphine
- Convert immediately to methadone:
  - MTDD < 90 mg, use 4:1 (MS : methadone)
  - MTDD 90 – 130 mg, use 8:1 (MS : methadone)
  - MTDD > 300 mg, use 12:1 (MS : methadone)
- Give TDD methadone as Q8H with 1/6th TDD as breakthrough
- Titration based on breakthrough dose
### More conversion recommendations

<table>
<thead>
<tr>
<th>TDD Oral Morphine</th>
<th>EPERC Conversion (morphine : methadone)*</th>
<th>% of morphine dose (FDA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 100 mg</td>
<td>3 : 1</td>
<td>20 - 30%</td>
</tr>
<tr>
<td>101 – 300 mg</td>
<td>5 : 1</td>
<td>10 - 20%</td>
</tr>
<tr>
<td>301 – 600 mg</td>
<td>10 : 1</td>
<td>8 – 12%</td>
</tr>
<tr>
<td>601 – 800 mg</td>
<td>12 : 1</td>
<td>5 – 10%</td>
</tr>
<tr>
<td>801 – 1000 mg</td>
<td>15 : 1</td>
<td>5 – 10%</td>
</tr>
<tr>
<td>&gt; 1000 mg</td>
<td>20 : 1</td>
<td>&lt; 5%</td>
</tr>
</tbody>
</table>

*Gazelle G and Fine P  End-of-life Physician Education Resource Center, July 2006*
Friedman method

< 1000mg per day AND < 65 yo

< 1000mg per day BUT > 65 yo

> 1000mg per day BUT < 2000mg per day

> 2000mg per day

10 : 1

20 : 1

20 : 1

Call pharmacist

Friedman LL, Rodgers PE Clinics in Family Practice 2004;6:371-393
Methadone notes....

- After determining total daily dose, divide into every 8 or 12 hour dosing.
- Adjust dose NO SOONER than every 4 – 7 days
- What to use for breakthrough dosing
- How to account for drug interactions when converting
- Torsades risk...is it clinically significant or relevant?
- When should methadone be trialed?
Where does methadone fit in??

- Is it a better opioid for pain?
  - ☺ Possible NMDA receptor blockade – 1st choice for neuropathic pain?
  - ☻ Potentially less metabolite side effects than morphine?
  - ☺ Less euphoria
  - ☹ Drug interactions
  - ☹ Accumulation risk
  - ☹ Torsades risk – is it clinically significant?
  - ☹ Difficulty in titration and dose conversion
Oxycodone

- Semi-synthetic opioid analgesic
  - Mechanism of action:
    - Not the same as morphine (mu receptor)
    - Active metabolite oxymorphone only plays minor role via mu receptor
      - Metabolites of oxycodone:
        - Noroxycodone and glucuronides
          - Major metabolite of oxycodone.
          - 1/100th the antinociceptive effect of oxycodone.
        - Oxymorphone and glucuronides
          - Represents less than 10% of the metabolic output for oxycodone.
          - 10 times the antinociceptive effect of oxycodone.
          - Main activity at mu receptors.
    - Kappa opioid receptor agonist

Fraser FB, Smith MT. Pain 1997;73:151-157
Oxymorphone

- Receptor activity: Agonist: Mu₁ and Delta
- Metabolism: 6-OH-oxymorphone, analgesic potency similar to oxymorphone
  - No clinically significant CYP drug-drug interactions
- Onset:
  - Oral immediate release: 30 minutes, duration 4-6 hours
  - Oral extended release: steady state levels achieved in 3 days
- Oral bioavailability: approximately 10%
  - Elderly patients may experience 40% increase in plasma concentrations
  - Food can increase rate of absorption by as much as 50% (most of the effect occurs in the first four hours)
    - AUC unchanged to increased by 18% when taken with food

Oxymorphone

- **Formulations: (Opana®)**
  - IR: 5mg and 10mg
  - ER: 5mg, 7.5mg, 10mg, 15mg, 20mg, 30mg, 40mg
    - Appears to have a 12 hour duration of action

- **Drug / alcohol interactions:**
  - Effect of alcohol on ER delivery system (Cmax)
    - Concomitant administration had a highly variable effect on Cmax
    - *In vivo* the bioavailability of a single 40 mg dose ER ↑ Cmax on average by 70% and up to 270% in individual subjects with co-administration of 240ml of 40% alcohol.
      - AUC 13% higher
    - Following the concomitant administration of 240 mL of 4 % ethanol, the Cmax increased 7% on average and by as much as 110% for individual subjects.
      - AUC unaffected

Levorphanol

- Mu and Kappa$_3$ agonist, NMDA receptor antagonist
- Long plasma half-life (12 – 16 hours)
  - Can accumulate within 2-3 days of continuous administration.
  - Longer duration of analgesic effect (6-8 hours)
- Potent opioid (about 5 times more potent than parenteral morphine)
- Oral : parenteral ratio 2:1

Prommer E. Support Care Cancer. 2007:15:259-264
# Opioid Equivalent Doses

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Approximate Equianalgesic Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine (reference)</td>
<td>30 mg oral</td>
</tr>
<tr>
<td></td>
<td>10 mg intravenous / SQ</td>
</tr>
<tr>
<td>Codeine</td>
<td>200 mg oral</td>
</tr>
<tr>
<td>Fentanyl transdermal</td>
<td>12.5 mcg/hr transdermal</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>30 mg oral</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>7.5 mg oral</td>
</tr>
<tr>
<td></td>
<td>1.5 mg intravenous / SQ</td>
</tr>
<tr>
<td>Methadone</td>
<td>Chronic 4 mg – 7.5 mg*</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>20 mg oral</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>10 mg oral</td>
</tr>
<tr>
<td>Tapentadol</td>
<td>100 mg oral</td>
</tr>
<tr>
<td>Tramadol</td>
<td>N/A</td>
</tr>
</tbody>
</table>

* Conversion highly variable based on dose, drug interactions, unique patient variables
Dose titration – EOL pain

- Using the typical “0” to “10” pain scale:
  - Pain level $\leq 2$: Stay the course
  - Pain level 3 - 4: ↑ Dose by up to 25 %*
  - Pain level 5 - 6: ↑ Dose by up to 50 %*
  - Pain level $\geq 7$: ↑ Dose by up to 100 %*

*Assumption is that patient is not experiencing adverse effects, that appropriate adjuvants are being trialed and that ongoing monitoring is occurring.
Side Effects from Opioids

- CNS toxicities
  - Dysphoria, euphoria, agitation, disorientation
  - Sedation
- Gastro-intestinal
  - Nausea / vomiting
  - Constipation
- Respiratory depression
- Hypersensitivity, itching
- Urinary retention
- Myoclonus
Constipation from opioids . . .

- Occurs with all opioids
- Pharmacologic tolerance developed slowly, or not at all
- Dietary interventions alone usually not sufficient
- Avoid bulk-forming agents in debilitated patients
Constipation....
Constipation from opioids . . .

- Occurs with all opioids
- Pharmacologic tolerance developed slowly, or not at all
- Dietary interventions alone usually not sufficient
- Avoid bulking agents
Opioid-Induced Constipation (OIC) – Pathophysiology

- Opioids primarily exert analgesic effects via central mu-opioid receptors.
- In contrast, OIC is largely mediated by opioid actions on mu-opioid receptors in the GI tract.
- Opioid effects on intestines:
  - ↓ GI motility
  - ↑ Absorption of fluid from gut
  - ↓ Intestinal secretion
  - ↑ Sphincter tone
  - ↓ Defecation reflex

GI = gastrointestinal; OIC = opioid-induced constipation.

Oral Laxatives Used for Prevention and Treatment of OIC\textsuperscript{1-3}

<table>
<thead>
<tr>
<th>Laxative class</th>
<th>Agent</th>
<th>Time to efficacy/Limitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulking agents</td>
<td>Dietary fiber</td>
<td>• 1-3 days</td>
</tr>
<tr>
<td></td>
<td>Bran</td>
<td>• Fiber may not be appropriate in palliative care\textsuperscript{1,2}</td>
</tr>
<tr>
<td></td>
<td>Psyllium</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Methylcellulose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Calcium polycarbophil</td>
<td></td>
</tr>
<tr>
<td>Surfactant laxatives/Stool softeners</td>
<td>Docusate</td>
<td>• 1-3 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Water required for ingestion of capsules</td>
</tr>
<tr>
<td>Stimulant laxatives</td>
<td>Senna</td>
<td>• 6-12 hours</td>
</tr>
<tr>
<td></td>
<td>Bisacodyl</td>
<td>• Water required for ingestion of capsules</td>
</tr>
<tr>
<td>Osmotic agents</td>
<td>Lactulose</td>
<td>• 1-2 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Sweet taste may be intolerable\textsuperscript{3}</td>
</tr>
<tr>
<td>Saline laxatives</td>
<td>Magnesium hydroxide</td>
<td>• 1-6 hours</td>
</tr>
<tr>
<td></td>
<td>Magnesium citrate</td>
<td>• Magnesium hydroxide should be used as last resort\textsuperscript{3}</td>
</tr>
<tr>
<td></td>
<td>Magnesium sulfate</td>
<td></td>
</tr>
<tr>
<td>Macrogols</td>
<td>Polyethylene glycol</td>
<td>• 1-4 days</td>
</tr>
</tbody>
</table>

Insufficient Response to Standard Laxative Therapy

**Signs That May Indicate Insufficient Response**

- Hard stools
- Infrequent stools (<3 per week)
- Excessive straining
- Sense of incomplete evacuation
- Excessive time spent on toilet
- Unsuccessful defecation

Methylnaltrexone for OIC

- ~50% of patients who responded within 4 hours reported laxation within 30 minutes of treatment
- Median time to laxation was 1 hour with methylnaltrexone 0.15 mg/kg versus >24 hours with placebo ($P<0.0001$)

Is the opioid always the answer?
Non-steroidal anti-inflammatory drugs (NSAIDS)

- Analgesic, anti-inflammatory, antipyretic

- Non-selective - egs
  - Ibuprofen (Motrin®)
  - Naproxen (Aleve®)
  - Sulindac (Clinoril®)
  - Nabumetone (Relafen®)
  - Choline magnesium trisalicylate (Trilisate®)

- Selective – egs.
  - Celecoxib (Celebrex®)
  - Rofecoxib (Vioxx®)

- Topical – egs.
  - Diclofenac epolamine 1.8% (Flector® topical patch)
  - Diclofenac sodium 1%(Voltaren® gel)
NSAIDS…generalities

- Overall…comparable in efficacy
- Ceiling for analgesic effect
  - Anti-inflammatory dose > analgesic dose
- Responses to different agents may be variable / highly individual
- Combining different agents may increase risks of serious adverse GI toxicities
- Major risks of non-selective agents:
  - GI bleeds, renal toxicity
- Role of COX-2 selective agents?
# Topical NSAIDs

<table>
<thead>
<tr>
<th></th>
<th>FDA indications</th>
<th>Serum levels</th>
</tr>
</thead>
</table>
| Diclofenac epolamine topical patch 1.8% (Flector® patch) | Acute pain due to sprains, strains, contusions | Single application: range 0.7 – 6 ng/ml  
Continuous therapy one patch BID: range 1.3 – 8.8 ng/ml |
| Diclofenac sodium 1% topical gel (Voltaren® gel)          | Chronic pain due to OA           | Continuous @ 4 gm gel QID  
$C_{\text{max}}$ 15 ± 7.3 ng/ml  
Continuous @12 gm gel QID  
$C_{\text{max}}$ 53.8 ± 32 ng/ml |
| Diclofenac oral    | Acute and chronic pain           | ORAL dosing @ 150 mg / day  
$C_{\text{max}}$ 2270 ± 778 ng/ml |
Neuropathic pain…

- Neuropathic pain usually refers to pain not caused by a specific discernable somatic tissue injury.
- Involves complex interactions between the peripheral sensory systems and the central nervous system.
- Often described by patients as feeling like “tingling”, “burning”, “tearing”, “crushing”, “electric shock”
- Common features:
  - Allodynia (aberrant perception)
  - Hyperalgesia (exaggerated response)
  - Areas of decreased sensitivity
  - Worse at night or when not distracted
- Can be continuous or paroxysmal
Common types of neuropathic pain…

- **Peripheral neuropathies**
  - Carpal tunnel syndrome
  - HIV sensory neuropathy
  - Diabetic neuropathy
  - Postherpetic neuralgia
  - Postthoracotomy pain
  - Trigeminal neuralgia
  - Radiculopathy

- **Complex regional pain syndromes**
  - Type I (RSD)
  - Type II (causalgia)

- **Central neuropathic pain**
  - Central post-stroke pain
  - Multiple sclerosis pain
  - Spinal cord injury pain
  - Phantom limb pain

- **Cancer-associated syndromes**
  - Chemotherapy-induced polyneuropathy
  - Tumor infiltration or nerve compression
  - Postmastectomy pain
  - Post-radiation plexopathy
Adjuvant Analgesics

- Medications that supplement primary analgesics
  - May provide a synergistic effect with opioids
  - May help with co-existing depression, anxiety, insomnia, PTSD

\[
\text{adjuvant} \pm \text{opioid} \pm \text{corticosteroid}
\]

*based on symptoms*
Neuropathic pain: Main adjunctive medication options

- **Antidepressants**
  - Tricyclics (e.g. desipramine, nortriptyline)
    - Up to 30-50% reduction in pain in about 1/3rd of patients.
    - Disadvantages: onset: 1-2 weeks, maximal effect: 3 to 6 weeks
      tolerability may be poor, especially in elderly
  - Atypicals: (e.g. venlafaxine (Effexor®), bupropion (Wellbutrin®)
    duloxetine (Cymbalta®)
    - Evidence supports a benefit in neuropathic pain, fibromyalgia
  - SSRIs: (e.g. fluoxetine (Prozac®), paroxetine (Paxil®), sertraline (Zoloft®)
    - No evidence to support direct effect on neuropathic pain
    - Chief benefit may be in headaches

- **Anticonvulsants** (e.g. gabapentin, lamotrigine, pregabalin)
  - Up to 30-50% reduction in pain in about 30-50% of patients
  - Main adverse effects: dizziness, sedation
  - Cost of therapy can be high

- **Topical lidocaine** (Lidoderm® patch)
  - FDA indicated for post-herpetic neuralgia, being studied in diabetic neuropathy, low back pain, osteoarthritis
  - Well tolerated, main side effects: local edema, erythema
N-methyl-D-aspartate (NMDA) receptor inhibitors

- Stimulation of the (NMDA) receptor has been implicated in the generation and maintenance of central (spinal) states of hypersensitivity.
- Combining NMDA-receptor antagonists with opioid analgesics may increase the potency and may even prevent opioid-induced tolerance and dependence.
N-methyl-D-aspartate (NMDA) receptor inhibitors

- Ketamine
- Dextromethorphan
- Amantidine
- Methadone
Antipsychotics / Neuroleptics

- **Older agents**
  - Haloperidol (Haldol®)
  - Chlorpromazine (Thorazine®)

- **Newer agents**
  - Risperidone (Risperdal®)
  - Olanzapine (Zyprexa®)
Antipsychotics / Neuroleptics

- Generalities (with respect to analgesia)
  - Limited evidence to support direct analgesic effect
  - Value is often related to managing other issues which may be affecting pain (indirect effect)
    - Opioid-induced delirium, hallucinations
    - Anxiety
    - Terminal restlessness, delirium
Muscle spasms / spasticity

- **Skeletal muscle relaxants**
  - Efficacy greater in acute pain, not much value for severe spasms associated with end stage cancer pain syndromes
  - E.g. methocarbamol (Robaxin®), carisoprodol (Soma®)

- **Baclofen (Lioresal®)**
  - Spasticity / severe spasms

- **Benzodiazepines**
  - Diazepam (Valium®)
  - Lorazepam (Ativan®), Oxazepam (Serax®)
Visceral pain

- Aching, bloating, crampy abdominal pain
- Only use drugs when pain from bowel obstruction / constipation has been ruled out.
- Dicyclomine (Bentyl®)
- Bladder spasms - oxybutynin (Ditropan®)
- Atropine 1% ophthalmic
- Avoid scopolamine in the geriatric patient
Miscellaneous adjuvants

- **Antihistamines**
  - Hydroxyzine (Vistaril®), diphenhydramine (Benadryl®), promethazine (Phenergan®)

- **Psychostimulants**
  - Methylphenidate (Ritalin®, Concerta®)

- **Cannabinoids**
  - Marinol, marijuana

- **Steroids** (dexamethasone, methylprednisolone)

- **Others:**
  - Dextromethorphan, antipsychotics, baclofen,
Breathlessness (dyspnea) . . .

- Can be one of the most frightening symptoms
- May be described as
  - Shortness of breath
  - A smothering feeling
  - Inability to get enough air
  - Suffocation
  - Sense of drowning
Management of breathlessness

- Treat the underlying cause
- Symptomatic management
  - oxygen
  - opioids
  - anxiolytics
  - nonpharmacologic interventions
Nonpharmacologic interventions . . .

- Reassure, work to manage anxiety
- Behavioral approaches, e.g., relaxation, distraction, hypnosis
- Limit the number of people in the room
- Open window
Nonpharmacologic interventions . . .

- Eliminate environmental irritants
- Keep line of sight clear to outside
- Reduce the room temperature
- Avoid chilling the patient
Nonpharmacologic interventions

- Introduce humidity
- Reposition
  - Elevate the head of the bed
  - Move patient to one side or other
- Educate, support the family
  - Anxiety of family $\Rightarrow$ ↑ anxiety of patient
Opioids

- Relief not related to respiratory rate
- No ethical or professional barriers
- Small doses
- Central and peripheral action
- May convert to long-acting if patient complains of excessive sedation from short-acting opioids
- Role of inhaled (nebulized) opioids?
Anxiolytics

- Safe in combination with opioids
  - Lorazepam
    - 0.5-2 mg po q 1 h prn until settled
    - Then dose routinely q 4–6 h to keep settled
    - Can administer via SL / IV routes
  - Other benzodiazepines:
    - Oxazepam 10 – 15 mg Q 4-6 H
    - Clonazepam 0.25 – 2 mg Q 12 H
“One of the main reasons the public is so enamored of physician-assisted suicide is that the current medical system is failing to adequately care for people at the end of their lives. What we really should be doing is eradicating the suffering rather than eradicating the patient”.

Dr. Nicholas Christakis, University of Chicago, Los Angeles Times, January 8, 1997