Pain Management

**Learning Objectives**
- Identify most common barriers to effective treatment of pain.
- Describe principles of effective pain management
- Define: addiction, physical dependence, hypersomnolence, and oversedation

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**Case:** 60 year-old woman with breast cancer and h/o bony metastases presents with severe mid-lumbar back pain with radiation into bilateral buttocks. She has no new neurologic deficits but pain has made her bed-bound over the last few days. Her pain medication regimen is: MS contin 120mg bid, MS IR 30mg q4h prn. She has taken her prn medications 6 times in the last 24 hours. Her exam is normal, she is fully alert. She weighs 50kg.

**Overview**
- 1/3 of all cancer patients have either chronic or recurrent pain
- 60-90% of these patients have advanced cancer
- Eastern Cooperative Oncology Group (ECOG) conducted an “Outpatient Pain Needs Assessment Survey” to evaluate adequacy of pain relief:\textsuperscript{1}
  - 1308 ambulatory patients with metastatic disease were surveyed: 871 (67\%) had pain and took analgesics w/in one week and 475 (36\%) had severe enough pain to impair function. 250/597 patients (42\%) reported inadequate analgesic therapy
- Barriers to effective treatment of pain:
  - Patient factors leading to reluctance to report pain
    - Fear of disease progression
    - Cultural and religious preferences: suffering is good
    - If drugs are taken too soon, they might not work later when needed more
    - Pain medications are for the dying
    - Fear of addiction to pain medications
  - Physician factors leading to inadequate pain management
    - Inadequate pain assessment
    - Reluctance to prescribe narcotics
    - Inadequate knowledge regarding pain management
• Some of these barriers are easily addressed
  o In patients with no prior h/o addiction, cancer pain treatment with narcotic analgesics leads to <1% new addiction rate.
  o Addiction: psychological and behavioral syndrome characterized by loss of control over drug use and compulsive, continuous use despite harmful side effects.
  o Physical Dependence: pharmacologic property of drug that causes withdrawal when the drug is abruptly discontinued (e.g. rhinorrhea, lacrimation, diarrhea, anxiety, hyperventilation, hyperthermia, myalgias, vomiting, hostility, etc.)
• World Health Organization developed guidelines to improve cancer pain management in 1986.

*World Health Organization Guidelines for Cancer Pain Management- “Pain Relief Ladder”*

<table>
<thead>
<tr>
<th>Intensity of pain (subjective)</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1 (Mild, 1-4)</strong></td>
<td>Nonopiod agent (Around the clock coverage with Tylenol or NSAIDs ± adjuvant tx)</td>
</tr>
<tr>
<td><strong>Step 2 (Mild – Moderate, 5-6)</strong></td>
<td>Weak opioid (e.g. codeine, oxycodone) + nonopiod agent ± adjuvant tx</td>
</tr>
<tr>
<td><strong>Step 3 (Moderate – Severe, 7-10)</strong></td>
<td>Strong opioid (e.g. morphine, hydromorphone, fentanyl) ± nonopiod or adjuvant tx</td>
</tr>
</tbody>
</table>

• Several studies, including prospective studies, have confirmed that when the WHO guidelines are followed, up to 70-90% of patients have effective pain management with a low rate of complications.

*The "Analgesic Elevator” Model -*
• Challenges the clinical usefulness of "weak" opioids in mild to moderate pain
  o systematic reviews comparing the efficacy of NSAIDs vs. a weak opioid suggest that the transition from step I to step II drugs does not necessarily improve analgesia
  o delays optimal pain control, especially in patients with rapidly progressive pain
• Proposes immediate response with strong opioids as first-line treatment of mild-moderate pain.
  o “transport of analgesics inside a lift would be quicker than stepping up a ladder”
  o Phase III study in 100 terminal cancer patients with mild-moderate pain showed
    ▪ Patients had significantly better pain relief and greater satisfaction with treatment
    ▪ Patients required fewer changes in therapy and had greater reductions in pain when therapeutic changes were initiated
**Principles of Pain Management**-

- Adequate assessment of pain
  - Nature: elicit a good history
  - Cause: treat underlying pathophysiology if possible
  - Personal context: consider pain a serious and treatable symptom
    - Psychological
    - Social
    - Spiritual
    - Practical issues

- Use of appropriate interventions
  - Pharmacologic vs. Nonpharmacologic
  - Use opioids around the clock for frequent/continuous pain and add a breakthrough regimen as needed
  - Provide enough analgesia to permit normal functioning (e.g. sleep, social interactions)
  - Do not allow inappropriate concerns about addiction and dependence prevent the use of effective doses on a regular schedule

- Ongoing assessment of treatment outcomes and regular review of the plan of care
  - Obtain subjective measures of pain (0-10 scale, visual scale, etc)
  - Titrate analgesics to pain relief
  - Flexibility is essential—successful plans are tailored to the individual patient and family
  - Willingness to ask for help from colleagues with more expertise when the plan is not effective at controlling the patient’s pain

- Use of other members of an interdisciplinary team
- Education of the patient, family, and all caregivers about the plan

**Goals of Pain Management**-

- Either eliminate pain or reduce it by at least 50% by subjective ratings
- Keep side effects minimal
  - Sedation and respiratory depression: tachyphylaxis develops within a few days (far before tolerance develops)
    - Hypersomnolence: patient is not confused and awakens easily, just catching up after extended periods of sleep deprivation
    - Oversedation: altered mental status, delirium, hard to arouse, may need to use naloxone reversal if severe
    - Avoid full opioid reversal with naloxone in patients who are tolerant: use 1/10 of usual dose of naloxone (0.04mg) IV q 3-5 minutes and titrate to desired arousal
    - Most patients will improve with simply stopping opioids until more alert, then restarting at 75% of the previous opioid dose
  - Nausea: resolves usually within 24 hours of initiation
  - Physical dependence: develops after 2 weeks of treatment
    - Decrease dose by 50% every 2-3 days to taper.
    - If taper is smaller than unit dose, then taper frequency until can omit.
- Constipation: most common adverse effect. Should be managed prophylactically and aggressively with stool softeners and stimulants (docusate and senna).
- Itching: histamine release mediated (not a true allergy).
  - Can use antihistamines or switch agents if necessary.
- Urinary retention: may need to decrease dose or add adjuvant medications
- Choose the most appropriate pain regimen for your patient
  - Always consider age and hepatorenal function of patient
    - Opioids and their metabolites can accumulate in renal insufficiency as well as the elderly and can lead to excessive side effects
    - Avoid drugs with long t½ e.g. methadone (15-150 hrs).
    - **In these patients hydromorphone (dilaudid) is the best choice given short t½ (2-3 hrs):** has least adverse reactions but associated with increased psychological dependence.
  - Avoid Meperidine which has higher likelihood of neurotoxicity with repeated dosing
  - Nausea and CNS side effects: Oxycodone < Morphine.
  - Gastrointestinal side effects: Fentanyl Patch << oral pain medication
  - Rectal preparations bypass first pass hepatic metabolism and absorption is variable but similar bioavailability to oral preparations have been reported: can use similar doses to oral preparations but may need to lower doses as needed
### Equivalent Analgesic Doses of Selected Narcotics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (for equivalent analgesia)</th>
<th>Half-life (hr)</th>
<th>Peak (hr)</th>
<th>Duration (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>10 mg IM/IV 30-60 mg PO*</td>
<td>2-4</td>
<td>0.5-1</td>
<td>4-6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2-4</td>
<td>2</td>
<td>4-6</td>
</tr>
<tr>
<td>Morphine, slow release</td>
<td>30-60 mg PO*</td>
<td>3-4</td>
<td>4-6</td>
<td>8-12</td>
</tr>
<tr>
<td>(Kadian, MS Contin, Oramorph SR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydromorphone HCl (Dilaudid)</td>
<td>1.5 mg IM 7.5 mg PO</td>
<td>2-3</td>
<td>0.5-1</td>
<td>4-6</td>
</tr>
<tr>
<td></td>
<td>2-3</td>
<td>1-2</td>
<td></td>
<td>4-6</td>
</tr>
<tr>
<td>Levorphanol tartrate (Levo-Dromoran)</td>
<td>2.0 mg IM 4.0 mg PO</td>
<td>12-16</td>
<td>0.5-1</td>
<td>4-6</td>
</tr>
<tr>
<td></td>
<td>12-16</td>
<td>1</td>
<td></td>
<td>4-6</td>
</tr>
<tr>
<td>Methadone HCl (Dolophine HCl, Methadose)</td>
<td>Non-linear kinetics**</td>
<td>15-150+</td>
<td>0.5-1.5</td>
<td>4-6</td>
</tr>
<tr>
<td></td>
<td>15-150+</td>
<td>0.5-1.5</td>
<td></td>
<td>4-6</td>
</tr>
<tr>
<td>Codeine phosphate, codeine sulfate</td>
<td>130 mg IM 200 mg PO</td>
<td>2-4</td>
<td>1</td>
<td>4-6</td>
</tr>
<tr>
<td></td>
<td>2-4</td>
<td>1-2</td>
<td></td>
<td>4-6</td>
</tr>
<tr>
<td>Oxycodone HCl</td>
<td>20 mg PO</td>
<td>2-3</td>
<td>1</td>
<td>3-6</td>
</tr>
<tr>
<td>Meperidine HCl (Demerol)</td>
<td>75 mg IM 300 mg PO</td>
<td>3-4</td>
<td>0.5-1</td>
<td>3-5</td>
</tr>
<tr>
<td></td>
<td>3-4</td>
<td>1-2</td>
<td></td>
<td>4-6</td>
</tr>
<tr>
<td>Fentanyl (Sublimaze)</td>
<td>0.1 mg IV</td>
<td>3-4</td>
<td>0.25</td>
<td>0.5-2</td>
</tr>
<tr>
<td>Fentanyl (Duragesic)</td>
<td>Variable</td>
<td></td>
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</table>

*With long-term dosing, relative potency of IM:ORAL formulations changes from 1:6 to 1:3

** consult palliative care or pain service before prescribing methadone
Initiation of Oral/Outpatient Pain Management in opioid-naïve patient:

- Initial test dose (use short-acting agents):
  - 30-60mg codeine/5-10mg oxycodone/15-30mg morphine IR q4h
    (Morphine 5mg IV = Morphine 15-30mg PO = Oxycodone 10mg PO = Codeine 100mg)
- If pain not improved by ½ within 30-60 minutes of dose or pain control not lasting at least 3 hours, can double dose unless patient is excessively sedated
- Rescue dose of MS IR 15mg po q1h prn
- Assess pain relief and side effects over next 1-2 days.
  - Increase baseline dose to accommodate prn dose and continue q4h dosing until pain relief has been achieved (only 2-3 prn doses needed per day)
- Convert total daily dose to long-acting medication e.g. MS contin q12h or q8h
  - 10-20% of total 24h dose used for breakthrough dose q1-2h
- For mild to moderate pain, a dose escalation of 25-50% may be sufficient
- For severe pain, need to increase dose in at least 50% increments to double the drug effect:
  - e.g. MS Contin 100mg q12h → MS Contin 150mg q12h

Failure of Outpatient Pain Management/ Acute pain:

- Usually need to admit patient to the hospital for parenteral (PCA) administration of pain medications
- Consider loading dose of Morphine for immediate pain relief
  - Loading dose of Morphine 0.1mg/kg IV
    - Similar analgesic response pattern to lower dose Morphine 0.05mg/kg IV
    - Patients more likely to experience pain relief 10 minutes after the injection
    - Improved patient satisfaction with pain relief
    - Trend towards 2x incidence of adverse effects overall (4x level of emesis) but statistically not significant
- Need to monitor patients closely within the first 6-8 hours of initiation of IV narcotics to avoid overdoses
  - Danger of overestimating IV dose requirements if poor pain control was related to decreased absorption of oral medications.
### Institution of Patient-Controlled Analgesia (PCA) in Patients with Severe Cancer Pain

<table>
<thead>
<tr>
<th>Continuous IV dose</th>
<th>PCA dose</th>
<th>Oral dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Establish current 24 hour oral dose</strong></td>
<td></td>
<td>“total dose” used as oral morphine in 24 hours</td>
</tr>
<tr>
<td><strong>Initiate IV dosing</strong></td>
<td>1/3 of “total oral dose” over 24 hours</td>
<td>1/2 hourly dose is available every 1 hour</td>
</tr>
<tr>
<td><strong>Adjust IV dose</strong></td>
<td>Add prior 24 hours of PCA doses to provide new 24-hour rate</td>
<td>If doses are requested more than hourly, double the PCA dose</td>
</tr>
<tr>
<td><strong>Sufficient IV analgesia</strong></td>
<td></td>
<td>Only 2-3 supplemental doses required per day</td>
</tr>
<tr>
<td><strong>Convert to oral</strong></td>
<td>Reduce IV basal rate by 50%</td>
<td>Continue IV PCA at previously established dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If IV PCA requirements increase, increase oral dose</td>
</tr>
<tr>
<td></td>
<td>D/C IV basal rate</td>
<td>Continue IV breakthrough but encourage po meds</td>
</tr>
</tbody>
</table>
### Adjuvants to Opioids for Treating Cancer Pain

<table>
<thead>
<tr>
<th>Class</th>
<th>Drugs</th>
<th>Approximate daily adult dose (mg)</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anticonvulsants</strong></td>
<td>Carbamazepine</td>
<td>200-1,600</td>
<td>Decrease neuropathic pain</td>
</tr>
<tr>
<td></td>
<td>Phenytoin (Dilantin)</td>
<td>200-600</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gabapentin</td>
<td>300-900</td>
<td></td>
</tr>
<tr>
<td><strong>Antidepressants</strong></td>
<td>Amitriptyline HCl (Elavil)</td>
<td>10-100</td>
<td>Decrease neuropathic pain, improve sleep and appetite</td>
</tr>
<tr>
<td></td>
<td>Doxepin HCl (Sinequan)</td>
<td>10-100</td>
<td></td>
</tr>
<tr>
<td><strong>Antihistamines</strong></td>
<td>Hydroxyzine (Atarax, Vistaril)</td>
<td>15-400</td>
<td>Relieve itching; coanalgesic with opioids</td>
</tr>
<tr>
<td><strong>Anxiolytics</strong></td>
<td>Diazepam (Valium)</td>
<td>10-40</td>
<td>Relieve anxiety; sedative; relieve skeletal muscle spasms</td>
</tr>
<tr>
<td></td>
<td>Lorazepam (Ativan)</td>
<td>1-8</td>
<td></td>
</tr>
<tr>
<td><strong>Corticosteroids</strong></td>
<td>Dexamethasone sodium phosphate</td>
<td>8-96</td>
<td>Reduce swelling (e.g., spinal cord compression); improve appetite and sense of well-being</td>
</tr>
<tr>
<td></td>
<td>Prednisone</td>
<td>5-120</td>
<td></td>
</tr>
<tr>
<td><strong>Muscle relaxants</strong></td>
<td>Cyclobenzaprine HCl (Flexeril)</td>
<td>10-30</td>
<td>Relieve skeletal muscle spasms</td>
</tr>
<tr>
<td><strong>Neuroleptics</strong></td>
<td>Haloperidol (Haldol)</td>
<td>1-8</td>
<td>Relieve anxiety and restlessness; sedative; coanalgesic with opioids</td>
</tr>
<tr>
<td></td>
<td>Methotrimeprazine (Levoprome)</td>
<td>10-40</td>
<td></td>
</tr>
<tr>
<td><strong>Psychostimulants</strong></td>
<td>Dextroamphetamine sulfate (Dexedrine, Dextrostat)</td>
<td>5-10</td>
<td>Reduce opioid-induced sedation; coanalgesic with opioids</td>
</tr>
<tr>
<td></td>
<td>Methylphenidate HCl (Ritalin)</td>
<td>10-15</td>
<td></td>
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</table>
Bisphosphonates provide some pain relief resulting from bone metastases or osteoarthropathy.\textsuperscript{9}
References:


Pain Management Problem Set:

Case: 60 year-old woman with breast cancer and h/o bony metastases presents with severe mid-lumbar back pain with radiation into bilateral buttocks. She has no new neurologic deficits but pain has made her bed-bound over the last few days. Her pain medication regimen is: MS contin 120mg bid, MS IR 30mg q4h prn. She has taken her prn medications 6 times in the last 24 hours. Her exam is normal, she is fully alert. She weighs 50kg.

How do you address her pain?

Case continued: Patient continues to c/o 8/10 pain and pushes her morphine PCA every 10 minutes.

What do you do next?

Case continued: Patient uses her PCA only twice in the next hour and rates her pain as 2/10.

What do you do next?