Palliative Care: Treatment at the End of Life

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PharmCon is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This program will assist pharmacists and nurses in understanding the facets of the palliative pain felt by patients who are dying and the benefits of alleviating the pain during this process. It will also enhance their knowledge of the available options for those patients in the situation. The program includes information on pharmacological treatments, patient counseling, and a question/answer period.

Objectives:

1. Inform patients and their families of detrimental effects that end of life pain may have on terminally ill patients, incorporating information on the pharmacologic options to minimize this unnecessary pain.
2. State currently available treatment options, including mechanism of action and adverse effects for palliating pain at end of life.
3. Describe regulations and guidelines for dispensing opioids for terminally ill patients, and how this differs from managing chronic non-cancer pain and acute pain.

Speaker: Dr. Mary Lynn McPherson is a Professor in the Department of Pharmacy Practice and Science at the University of Maryland School of Pharmacy. She serves as a consultant pharmacist for both local and national hospice and palliative care programs, and has designed a critical thinking process for appropriate drug use in end of life patients. She serves on the Board of the Hospice Network of Maryland, chairing the Education and Outreach Committee. She also serves on the Board of the Maryland Pain Initiative and the Advisory Board of the American Society of Pain Educators.

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**Definition of Pain**

- Pain is an unpleasant *sensory* and *emotional* experience associated with actual or potential tissue damage, or described in terms of such damage. (IASP)
- Pain is always subjective.
- Pain is what the patient says hurts. (McCaffery)
- “Passion of the soul.” (Aristotle)

- Goal of pain management is to relieve and **PREVENT** the pain from recurring.
- May involve use of non-pharmacologic interventions.
- Pharmacologic interventions are a significant part of pain management.
- Medications should be used judiciously in appropriate combinations.

**Symptom Analysis**

- **P** (palliative/precipitating/previous therapy)
- **Q** (quality)
- **R** (region/radiating)
- **S** (site/severity)
- **T** (temporal)
- **U** (YOU - associated symptoms)

**Classifying Pain**

- **Temporal**
  - Acute vs. chronic (what do we mean by chronic pain?)
    - Pain that lasts greater than 3 months
    - Pain that persists beyond the expected healing period
  - Persistent vs. episodic
  - Persistent plus breakthrough pain
- **Malignant vs. nonmalignant**
  - Chronic malignant (cancer)
  - Nonmalignant (non-cancer)
- **Pathophysiological**
  - Nociceptive (visceral, somatic), vs. neuropathic
Admitting diagnoses into Hospice

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<tr>
<td>ALS</td>
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Prevalence of Pain at End of Life

- Advanced cancer – 40-90% patients have pain
- Cardiovascular disease (CHF) – 75% patients
- HIV/AIDS – 50-93%
  - Due to virus or treatment
- Neurologic diseases
  - Multiple sclerosis, Parkinson’s disease, cerebral vascular disease or spinal cord injury patients
  - Dementia patients – difficult to assess
    - Skin breakdown, contractures

Pharmacotherapeutic Options

- **Nociceptive Pain**
  - Antineoplastic treatment
  - Conventional analgesics
    - Opioids, non-opioids, co-analgesics
    - Metastatic bone pain – NSAIDs
- **Neuropathic pain**
  - Opioids
  - Co-analgesics (anticonvulsants, antidepressants)

**Nociceptive Pain**
- Somatic
  - Dull, aching, well-localized.
  - Skin, bone, joint, soft tissues.
  - Mets to bone, fractures.
- Visceral
  - Diffuse, deep, aching, gnawing.
  - Poorly localized.
  - Bladder distension/cramping, intestinal distension, constipation, angina

**Neuropathic Pain**
- Peripheral Or Central
  - Burning, shooting, pricking, paresthesias, dysesthesias.
  - Phantom limb pain, SCI pain, stroke, diabetic neuropathy, post-herpetic neuralgia

**Nondrug Interventions**
Setting Comfort-Function Goals

- “What would you like to do that you can’t do now because of your pain?
  - “I’d like to be able to to my needlework.”
  - “I’d like to walk to the bathroom – alone.”
  - “I want to get a good night’s sleep so I’m not tired all day long”
  - “I want to go back to work”
  - “I want to be able to play with my children”

Treatment Modalities

- Non-pharmacologic
  - Heat, cold, massage, TENS units, physical and occupational therapy, guided imagery, aromatherapy, comfort food

- Pharmacologic
  - Non-opioid
  - Opioid
  - Adjuvant analgesics

- Rationale polypharmacy!

Acetaminophen

- Mechanism of action – centrally mediated
  - Analgesic and anti-pyretic
  - Lacks anti-inflammatory activity

- Ceiling effect

- Acute and chronic toxicity
  - Acute liver failure increased from 28% in 1998 to 51% in 2003

- May cause liver or renal toxicity

- Common in multi-ingredient products
  - consider OTC products

- Maximum daily dosage is 4 grams per day
  - Or is it?

Aminotransferase Elevation in Healthy Adults Receiving 4 Grams of APAP Daily

- Objective
  - To characterize the incidence and magnitude of ALT elevations in health participants receiving 4 g acetaminophen per day

- Methods – participants received either:
  - Placebo; acetaminophen/opioid combo; acetaminophen

- Results – maximum ALT more than 3 x ULN incidence 31-44% in 4 treatment groups

- Acetaminophen levels never exceeded therapeutic limits; were often undetectable before ALT levels resolved

JAMA 2006;296:87-93
"In the beginning there was salicylate, and that begat acetylsalicylic acid (ASA; aspirin), and that begat non-salicylate NSAIDs, and more NSAIDs and more until there 100, and that begat selective cyclo-oxygenase (COX)-2 NSAIDs: and then here was celebrating in the land."

Roth SH. Drugs 2005;65(14):1915-1917

**NSAIDs**

- Effective in the treatment of bone metastasis, soft tissue infiltration, arthritis, serositis.
- Mechanism - inhibits prostaglandin-mediated irritation of nociceptive receptors.
- Toxicities – dyspepsia, gastritis, gastric bleeding, fluid retention, hypertension, CHF, renal failure, platelet dysfunction, salicylism, confusion.
- Pick your poison- gastrointestinal or cardiotoxicity??

**Cyclooxygenase Pathways**

**Arachidonic Acid**

**Inflamed Tissues**

**Prostaglandins**

- stomach, kidney, endothelium, brain

**Prostaglandins**

- found in synovial fluid, vascular SM, endothelium, macrophages, monocytes, tumor cells, brain

**COX-1**

- Prostaglandins,
  - COX-1 Specific Inhibitors
  - Normal Physiologic Stimulus

**COX-2**

- Prostaglandins
  - NSAI Ds
  - Inflammatory Stimulus

**Step 2 - 3 Agents - Opioids**

- Codeine
- Propoxyphene
- Hydrocodone
- Dihydrocodeine
- Oxymorphone
- Meperidine
- Heroin
- Morphine
- Hydromorphone
- Oxycodone
- Levorphanol
- Methadone
- Fentanyl
- Agonist/Antagonist or partial agonists
Variables Effecting Therapy

- Agent Variables
  - Things about the drugs that effect response
- Patient Variables
  - Things about the patient that alter therapeutic response
- How do these variables affect your selection of an opioid?

Agent Related Variables

- Mechanism of action and efficacy
  - Opioids have similar MOA
    - Mu opioid agonist
    - Methadone – NMDA receptor antagonist
  - Generally speaking - “weak” vs. “strong” terminology not applicable, with some exceptions
    - Propoxyphene
    - Codeine
    - Tramadol ??

Agent Related Variables

- Available dosage formulations
  - Long-acting oral pharmaceutical preparations (morphine, oxycodone, oxymorphone, hydromorphone, tramadol)
  - Inherently longer-acting (methadone)
  - Long-acting transdermal (fentanyl, buprenorphine)
  - Immediate-acting (morphine and oxycodone elixir, transmucosal fentanyl [Actiq, Fentora], Onsolis)
  - Only available in combination (hydrocodone)

Dosing Breakthrough Analgesics

- Oral long acting opioid is “basal” therapy
- Rapid/quick onset, short acting analgesic used for episodic pain, incident pain and breakthrough pain.
  - End of dose deterioration – increase dose/change dosing interval
- Dosed as 10-15% total daily dose
  - MS Contin 90 mg po q12h
  - TDD 180 mg morphine
  - MSIR 20 mg po q2h prn
Dosing Opioids

- Evaluate average pain intensity rating
  - < 5/10 – increase by 25-50%
  - ≥ 6/10 – increase by 50-100%
- Evaluate use of breakthrough analgesic.

Agent Related Variables

- Pharmacokinetics
  - Onset and duration of action
    - Most opioids are short-acting
    - Can alter with oral long-acting dosage formulations
    - Methadone – longer half-life in body than half-life of analgesic effect
  - Metabolic fate
    - Propoxyphene, meperidine, morphine have active metabolites
    - Oxycodone, hydromorphone – less active metabolites
    - Fentanyl, methadone – inactive metabolites

Agent Related Variables

- Side effects and toxicities
  - many opioid adverse effects are class-wide
    - constipation, nausea, sedation
  - codeine causes dose-limiting adverse effects
  - opioids with active metabolites contribute to toxicity
- Cost

Opioid Adverse Effects

- Common Adverse Effects
  - constipation
  - nausea/vomiting
  - sedation
- Uncommon Adverse Effects
  - respiratory depression
  - pruritus
Specific Pain Syndromes

- Bone pain due to malignancy
  - NSAIDs, corticosteroids, osteoclast inhibitors
  - CCS – pain, nausea, anorexia
- Refractory pain
  - Parenteral lidocaine
  - Ketamine (NMDA inhibitor)
- Interventional strategies (neural blockade)

Treatment of Neuropathic Pain

General Considerations

- Reduction of 30% on a severity rating scale
  - Clinical important
  - Considered to be “moderate relief” or “much improved”
- Statistical vs. clinically significant improvement
- Drug-induced adverse effects are common in treating neuropathic pain
  - Nature of the medications used
  - Patients older, taking other medications, more comorbid illnesses

Agents Approved for Neuropathic Pain

<table>
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<tr>
<th>Co-analgesic</th>
<th>Trigeminal Neuralgia</th>
<th>Diabetic Neuropathy</th>
<th>Post-herpetic Neuralgia</th>
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<td>Gabapentin</td>
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<tr>
<td>Pregabalin*</td>
<td>X</td>
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First-Line Medications

- Tricyclic antidepressants (TCAs)
  - Nortriptyline, desipramine, amitriptyline, etc.
- Selective serotonin and norepinephrine reuptake inhibitors (SNRIs)
  - Duloxetine, Venlafaxine
- Calcium channel α2-δ ligands
  - Gabapentin, pregabalin
- Topical lidocaine

Second- and Third-Line Medications

- Second line
  - Opioid analgesics
  - Tramadol
- Third line
  - Antiepileptic medications
  - Antidepressant medications
  - Mexiletine
  - NMDA receptor antagonists
  - Topical capsaicin

Tricyclic Antidepressants (TCA)

- First medication category proven effective in neuropathic pain
- MOA – inhibit reuptake of norepinephrine and serotonin
- Main problem with TCAs is adverse effect profile
  - Sedation, dry mouth, blurred vision, weight gain, urinary retention, constipation, delirium
  - Amitriptyline > nortriptyline, desipramine

Tricyclic Antidepressants (TCA)

- Use with caution in:
  - Cardiovascular disease (screening EKG?)
  - Glaucoma, urinary retention
  - Autonomic neuropathy
  - Risk of suicide or accidental death from OD
  - Concurrent use of tramadol (or methadone?)
- Analgesic effect independent of antidepressant effect
- Start TCA dose low – 10-25 mg qhs; 50-75 qhs
- Adequate trial is 6-8 weeks with 1-2 weeks at maximally tolerated dosage
SNRIs: Duloxetine and Venlafaxine

- **MOA** – inhibit the reuptake of biogenic amines, primarily norepinephrine
- **Duloxetine (Cymbalta)**
  - **AE** – insomnia, somnolence, headache, nausea, xerostomia, constipation, anorexia, liver issues
  - Starting dose 30 mg once daily; increase to 60 mg once daily after one week
  - Maximum dose 60 mg twice daily

- **Venlafaxine (Effexor)**
  - Efficacy shown in PDN, painful polyneuropathy
  - **AE** – headache, somnolence, dizziness, insomnia, nervousness, nausea, xerostomia, constipation, anorexia, weakness
  - Starting dose 37.5 mg once or twice daily; increase by 75 mg each week
  - Maximum daily dose 225 mg

Gabapentin

- **MOA** – bind to the α2-δ subunit of voltage-gated calcium channels, decreasing release of glutamate, norepinephrine, and substance P
- **Approved for the treatment of post-herpetic neuralgia**
- **Also used to treat:**
  - peripheral diabetic neuropathy
  - mixed neuropathic pain syndromes
  - phantom limb pain
  - Guillain-Barre syndrome
  - acute and chronic pain from spinal cord injuries
- **Adverse effects:**
  - Somnolence, dizziness
  - Cause or exacerbate gait or balance problems OR cognitive impairment in elderly
  - Gastrointestinal symptoms
  - Peripheral edema
- **In general, fairly tolerable, safe, and relatively free of drug interactions**
- **Titrate dosage against adverse effects**
  - 100 or 300 mg qhs; 100 or 300 mg tid
### Gabapentin and Renal Impairment

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<tr>
<th>CLcr (ml/min)</th>
<th>TDD (mg/d)</th>
<th>Dosage Regimens Based on Renal Function (mg)</th>
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<td>300 tid 400 tid 600 tid 800 tid 1200 tid</td>
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<tr>
<td>15-29</td>
<td>200-700</td>
<td>200 qd 300 QD 400 QD 500 QD 700 QD</td>
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<tr>
<td>&lt;15</td>
<td>100-300</td>
<td>100 QD 125 QD 150 QD 200 QD 300 QD</td>
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### Pregabalin

- Administer in 3 divided doses per day
- Begin dosing at 150 mg/day
- Increase to 300 mg/day within 1 week
- Maximum daily dose 450-600 mg/day
- Dose adjust with renal impairment
- Common AE: dizziness, somnolence, dry mouth, edema, blurred vision, weight gain, difficulty concentration/attention

### 5% Lidocaine Patch

- Indicated for treatment of post-herpetic neuralgia
- Topical preparation (apply to intact skin)
- In patients with normal hepatic function, blood levels of the drug are minimal
  - On 12 hours, off 12 hours (max 3 patches)
  - Adequate trial is 2 weeks
- Only adverse effect is mild skin reactions (erythema or rash)

### Opioid Analgesics

- Several clinical trials have demonstrated the effectiveness of opioids (e.g., oxycodone) in the management of PHN and PDM.
- Considered second line due to:
  - Head-to-head trials with TCAs or gabapentin, opioids caused more adverse effects
  - Long-term safety of opioids not systematically studied
    - Immunologic changes, hypogonadism, hyperalgesia, addiction risk
Opioid Analgesic Selection

• Short-acting vs. long-acting
• Role of methadone?
  – NMDA receptor antagonist
• Rational polypharmacy is an attractive option

Tramadol

• A norepinephrine and serotonin reuptake inhibitor with a major metabolite that is a mu opioid agonist.
• Evaluated in PHN and polyneuropathy from various causes (including PDM)
  – Effective when titrated to 400 mg/day; improves allodynia
• Adverse effects include:
  – Dizziness, nausea, constipation, somnolence, orthostatic hypotension. Worsened with rapid dosage escalation.
  – Increased risk of seizures in patients with history, or drugs that lower seizure threshold
  – Caution with serotonin syndrome

When would an Opioid or Tramadol as First Line Agent

• During titration of a first-line medication to an efficacious dosage for prompt pain relief
• Episodic exacerbations of severe pain
• Acute neuropathic pain
• Neuropathic cancer pain


Other Therapeutic Options

• Lamotrigine
• Carbamazepine
• Levetiracetam
• Oxcarbazepine
• Tiagabine
• Topiramate
• Zonisamide
• Valproic Acid
• Phenytoin
• Citalopram
• Paroxetine
• Bupropion
• Mexiletine
• Dextromethorphan
• Memantine
• Topical capsicain
• Topical NSAIDs
• Corticosteroids
Dispensing Opioids at EOL

- Prescription needed prior to dispensing (“emergency” supply not usual)
- Limit quantities
- Altering dosage formulations
- Issues with delivering opioids
- Physical dependence vs. addiction vs. tolerance
- Need to taper opioids / signs of withdrawal