Sharpen your analgesic decision-making skills with challenging, interactive case studies on the different options for controlling pain. In this in-depth session, you’ll learn the pharmacokinetics and pharmacodynamics of the opioids and co-analgesics most commonly prescribed in cancer care. Using difficult oncologic cases to highlight pharmacologic principles, speakers will discuss drug absorption, distribution, metabolism, and elimination. You’ll digest information on tailored opioid and co-analgesic selection based on individual patient characteristics, including pain type, hepatic and renal function, pharmacologic profile, and medical history. You’ll also cover dose titration using different administration routes (oral, transdermal, rectal, subcutaneous/IV, and intraspinal), opioid rotation and equianalgesic conversion, and route rotation.

**Content Area:** Clinical Practice

**Content Level:** Advanced

**Coordinator/Speaker:**
Jeannine Brant, PhD, APRN, AOCN®
Oncology Clinical Nurse Specialist and Nurse Scientist
Billings Clinic
Billings, MT
jbrant@billingsclinic.org

**Full Disclosure:**
Intends to discuss unapproved/investigational use of a commercial product/device during this educational activity

**Objectives:**
At the end of this session, participants will be able to:
1. Review the pathophysiology of pain and related pharmacologic modalities along the pain pathway.
2. Analyze challenging case studies and apply advanced pharmacologic concepts to manage pain.

**Content Outline:**
I. Overview
   A. Problem of uncontrolled cancer pain
   B. Nurses taking a leadership role in pain management

II. Pharmacodynamics—how the host processes the drug
   A. Absorption
   B. Distribution
   C. Metabolism
   D. Elimination

III. Pharmacodynamics—what the drug performs within the host
   A. Biochemical effects
   B. Mechanism of action
   C. Side effects

IV. Pathophysiology and related pharmacology of pain
   A. Transduction
      1. NSAIDS
      2. Capsaicin
      3. Antihistamines
   B. Transduction
      1. Anticonvulsants
      2. Local anesthetics
      3. Alpha-2 adrenergics
      4. NMDA antagonists
      5. Opioids
   C. Modulation
      1. Antidepressants
      2. Combination opioid/norepinephrine agents
   D. Perception

V. Tough cases and management principles
   A. Post-surgical pain
      1. Epidural analgesia
      2. Obesity
      3. Sleep apnea
   B. Bone pain
      1. Use of adjuvants
      2. Uncontrolled breakthrough pain
   C. Neuropathic pain/mixed
      1. Hyperalgesia
      2. Use of out-of-the-box adjuvants
      3. Alternative routes of administration
      4. Opioid rotation
      5. Use of methadone

**Bibliography:**
Colson, J., Koyyalagunta, D., Falco, F.J., & Manchikanti, L.


ADVANCED CONCEPTS IN PAIN MANAGEMENT: PHARMACOLOGY AND TOUGH CASES

Jeannine M. Brant, PhD, APRN, AOCN
Oncology CNS and Nurse Scientist
Billings Clinic in Billings, MT

Transduction of Pain

- Noxious Stimuli
  - Mechanical
  - Thermal
  - Chemical
- Peripheral Soup
  - Histamine
  - Substance P
  - Prostaglandins
  - Bradykinin
  - Serotonin

Acute Pain
Breaking the Cycle

- Surgical tissue injury produces neuroplastic changes
  - can lead to enhanced sensitivity to subsequent noxious stimuli (hyperalgesia)
  - can sensitize the pathway of previously nonpainful stimuli (allodynia)
  - enhance the response of the spinal neurons
- Overall result is sensitization of the central nervous system with potential for chronic pain, CRPS

Chronic Pain

Audience Response Question 1

- Which group of pharmacologic agents prevents transduction of pain by inhibiting prostaglandin synthesis?
  A. Anticonvulsants
  B. Opioids
  C. Nonsteroidal anti-inflammatory agents
  D. NMDA antagonists

NSAID Uses

- Mild pain
- Bone pain
  - Osteoporosis
  - Arthritis
- Metastatic cancer to the bone – adjuvant
- Fever


NSAIDs: Mechanisms and Toxicities

Phospholipids

\[ \text{Arachidonic acid} \]

Cyclooxygenase 1

COX-1 inhibitors

Activation of COX-1 leads to production of:
- Prostacyclin
- PGE\(_2\)
- PGF\(_2\)
- Thromboxane A\(_2\)

Cyclooxygenase 2

COX-2 inhibitors

COX-2 is induced in:
- Macrophages
- Fibroblasts
- Endothelial cells
- Chondrocytes
- Osteoblasts
- Synoviocytes

NSAIDs: Risk/Benefit Ratio

- NSAIDs are protein bound
  - Malnourished patients may have higher NSAID blood levels
- Adverse events
  - GI toxicity
  - Renal toxicity—fluid retention, hyperkalemia
  - Inhibition of platelet aggregation
  - CNS effects—confusion and dizziness
  - Exacerbation of hypertension
- Monitoring
  - Monitor renal status
  - GI prophylaxis with a proton pump inhibitor or H₂ antagonist

Role of Acetaminophen and NSAIDS – Post-op Pain

- Systematic Review
  - Studies that examined use of acetaminophen with an NSAID
  - 21 studies enrolling 1909 patients
- Results
  - Combination of Acetaminophen and NSAID more effective (85%) compared to either agent used alone (64%)
  - Analgesic supplementation less for combination group
    - Average 30-50% opioid sparing

Transmission of Pain

- Action Potential
  - A change in charge along the neuronal membrane
  - Occurs when Na⁺ moves into the cell or with other sensitizing substances
  - Abnormal central processing with neuropathic pain

Anticonvulsant: Gabapentin

- First line treatment for neuropathic pain of all types
- Dosing
  - Starting at 100-300 mg daily to effective dose 900-3,600 daily in 2-3 divided doses
  - Renal insufficiency
    - GFR 30-59 mL/min 600 mg twice daily
    - GFR 15-29 mL/min 300 mg twice daily
    - GFR < 15 mL/min 300 mg daily
- Titration
  - Multiple steps of 50-100% every 3 days
  - Slower with elderly and renal insufficiency
- Side Effects
  - Somnolence dose limiting toxicity
  - Dizziness, ataxia, edema, wt. gain, dyspepsia, leukopenia

Anticonvulsant: Pregabalin

- Advantages
  - More efficiently absorbed through the GI tract
  - More rapid onset of analgesia
  - Simpler titration
- Dosing
  - Starting 150 mg daily
  - Usual effective dose 150-300 mg bid
- Titration simple with 2-3 steps
- Side Effects
  - Somnolence, dizziness, edema, ataxia, HA, confusion, diarrhea

Miscellaneous Adjuvants

- NMDA Antagonists
- Local Anesthetics
- Alpha-2 Adrenergics
- Muscle Relaxants
- Antispasmodics
- Ziconotide
Transmission of Pain

- Three phases
  - Impulse travels up the primary afferent neuron where nociceptors terminate at the dorsal horn
  - Impulse continues up the spinothalamic tract to the brain stem and thalamus
    - Substance P and other neurotransmitters carry the impulse across the synapse
  - Thalamus relays message to the cerebral cortex

Opioid Receptors

- \( \mu \) opioids
  - Morphine, hydromorphone, fentanyl, codeine, oxycodone, oxymorphone, meperidine
  - High efficacy
  - Abuse potential, respiratory depression, constipation
- \( \Delta \) opioids: none in clinical use
- \( K \) opioids
  - Pentazocine, butorphanol, nalbuphine
  - No abuse potential
  - Dysphoric, low efficacy (gender differences?)

Opioid Analgesics

Mu (\( \mu \)) Agonists
- Codeine
- Fentanyl
- Hydrocodone
- Hydromorphone
- Meperidine
- Methadone
- Morphine
- Oxycodone
- Oxymorphone
- Tapentadol

Partial agonist
- Buprenorphine

Mixed agonist-antagonists
- Kappa (\( K \)) opioids
  - Butorphanol
  - Nalbuphine
  - Pentazocine

Morphine

- Standard for comparison
  - Oral controlled release and immediate release available
  - SC, IV, PR, epidural, intrathecal
- Metabolites
  - Morphine-3-glucuronide (M3G)
    - antagonizes analgesic effect of morphine and M6G
  - Morphine-6-glucuronide (M6G)
    - more potent analgesic activity than morphine
    - contributes to overall analgesic effect
  - Paradoxical neuroexcitatory effects

Oxycodone

- Availability: CR, IR, combination with acetaminophen
  - Solution: oxyfast
- Caution with acetaminophen
  - Should not exceed 4 gms/day
- Active metabolite: oxymorphone
  - No cumulative effects known
  - Mediated by CYP450 but implications not clear
- Recommendations
  - Lower the dose in the elderly
  - Safe drug to use in hepatic and renal insufficiency

Oxymorphone

- Synthetic lipophilic opioid
  - 10x stronger than intravenous morphine
  - 3x stronger than oral morphine
- Administration
  - 5 mg, 10 mg, 20 mg, 40 mg
  - Dosed every 12 hours for CR, IR also available
  - Administer on an empty stomach 1.2 hours after a meal
    - Food increases \( C_{\text{max}} \) and \( AUC \) by about 38%
  - Do not give with alcohol
  - 7%-101% increase in \( C_{\text{max}} \), \( AUC \) not significantly changed
- Recommendations
  - Oxymorphone contraindicated in moderate and severe hepatic impairment
  - Start dose low (5 mg): creatinine clearance < 50 mL/min, mild hepatic impairment, elderly patients
  - Consider for elderly/patients with polypharmacy due to no CYP459 drug-drug interactions
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Fentanyl

- Lipophilic — global tissue distribution
- Metabolized by CYP450 3A4 isoenzyme but implications controversial
- Recommendations
  - Lower the dose in the elderly — clearance is decreased
  - Those on CYP450 inhibitors should be monitored carefully
  - Consider delayed onset and delayed elimination (accumulation)

Hydromorphone

- Availability: CR, IR, SC, IV, epidural, intrathecal
  - High solubility eases use in SC/IV administration
  - New extended release available
    - Available in 8 mg, 12 mg, 16 mg tablets
    - Dosage is every 24 hours
- Active metabolites
  - Hydromorphone-3-glucuronide (H3G), hydromorphone-6-glucuronide (H6G)
  - Little data on the impact of these metabolites
- Recommendations
  - Safe drug to use in hepatic and renal compromise although NCCN guidelines state to use with caution in renal compromise

Methadone

- Long half-life may lead to drug accumulation
  - 15-60 hours average, up to 120 hours
- Recommendations for administration
  - Should only be used by experienced clinicians
  - Should be used with caution in all patients
  - Start low and go slow
  - Consider delayed onset and delayed elimination (accumulation)
    - 4-5 half-lives to reach steady state
  - May want to avoid with polypharmacy issues
- New guidelines recommend that everyone get a pretreatment EKG before starting methadone due to potential QT prolongation and cardiac arrhythmias; follow EKG up one at 30 days and then annually. And if the dose exceeds 100 mg/day.

Converting to Methadone

- If morphine equivalents:
  - <90 mg – 1 mg methadone: 4 mg morphine
  - 90-300 mg – 1:8
  - >300 mg – 1:12
CYP450 Considerations

• Inhibitors
  – Antibiotics
  – Antidepressants
  – Diazepam
  – Antivirals
• Leads to decreased clearance
• May prolong elimination and increase plasma concentration of opioids

• Inducers
  – Anticonvulsants
  – Rifampin
  – Corticosteroids
• Leads to increased clearance
• May have a surge in opioid levels followed by a decrease in plasma levels

Concern with methadone and fentanyl

Opioid Dosing and Titration

• Perform titration after reaching steady state
  – Average 4-5 half-lives for IR opioids
  – Average 2-3 days for CR opioids (or >)
• Titrate 24 hour dose by 25-33%
• Keep breakthrough dose at approximately 10-20% higher with severe incident pain
• Consider dose reduction for incomplete cross tolerance
  – 50-75% with good pain control
  – 0-25% with poor pain control

Opioid Rotation

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Parenteral</th>
<th>Oral</th>
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</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>NA</td>
<td>20</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1.5</td>
<td>7.5</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>25 ug TD fentanyl</td>
<td>75 mg oral morphine</td>
</tr>
</tbody>
</table>

Nonpharmacologic

• Interventions that affect perception
  – Distraction
  – Relaxation
  – Hypnosis
  – Anything that diverts the mind from the pain
• Psychological intervention
• Spiritual intervention

Modulation of Pain

• Descending mechanisms
  – Inhibition of nociceptive impulses
  – Release of endogenous opioids
    • Enkephalin
    – Release of neurotransmitters
    • Serotonin, Dopamine, Norepinephrine
  – Inhibition of transmission


Antidepressants: Tricyclics

- Options: amitriptyline, nortriptyline
- Start at 10 mg hs and titrate upward
- Side effects:
  - Anticholinergic—increased sensitivity in elderly
  - Orthostatic hypotension
  - AV heart block
  - CNS effects
- Amitriptyline not recommended in the elderly
- Side effects of all TCAs may outweigh benefits

Antidepressants: Serotonin Norepinephrine Reuptake Inhibitors

- Duloxetine—first antidepressant approved for neuropathic pain
- Dosing: 60 mg/day usual effective dose
- Side effects
  - Anticholinergic
  - Decrease seizure threshold
  - Somnolence
  - Glaucoma
  - Hepatotoxicity – lower dose or avoid with liver compromise
- Venlafaxine another SNRI (150-225 mg/day)