Multimodal Analgesia

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Objectives

- Examine pharmacological approaches to multimodal analgesia in targeting specific peripheral and central mechanisms and pathways for pain
- Apply critical thinking and utilize clinical decision making to manage and treat patients with mixed pain
- Evaluate scientific information and incorporate evidence-based practice guidelines in the treatment of mixed pain with multimodal therapies.
How Pain is Transmitted and Processed
Physiology of Pain: Pathways and Effects on Pain Perception

- Pain is a complex process mediated by multiple pathways and mechanisms in both the peripheral and central nervous systems (PNS and CNS [spinal cord and brain]).

- Fundamental characterization of pain:
  - Nociceptive/inflammatory
    - Activation of pain-sensitive afferent neural pathways in response to injury
  - Neuropathic
    - Abnormal pain processing due to lesions in the PNS, CNS or both

# Nociceptive Pain

## Somatic Pain
- **Complaints:** constant, achy
- **Location:** well-localized in skin and subcutaneous tissues; less well-localized in bone, muscle, blood vessels, connective tissues
- **Examples:** incision pain, bone fractures, bony metastases, degenerative joint/spinal disease, osteoarthritis, rheumatoid arthritis, peripheral vascular disease, chronic stasis ulcers

## Visceral Pain
- **Complaints:** cramping, splitting
- **Location:** originates in internal organs or body cavity linings; poorly localized, diffuse, deep
- **Examples:** chest or abdominal tubes, drains; bladder distention or spasms; intestinal distention; pericarditis; constipation; organ metastases; spastic bowel; inflammatory bowel disease; hiatal hernia; chronic hepatitis

## Neuropathic Pain
- **Complaints:** shooting, burning, electric-shock-like, sharp, numb, motor weakness
- **Location:** originates in injury to peripheral nerve, spinal cord, or brain; poorly localized
- **Examples:** radiculopathy, diabetic neuropathy, post-herpetic neuralgia, tumor-related nerve compression, phantom limb pain, trigeminal neuralgia, central post-stroke pain
Treatment Goals for Acute and Chronic Pain

- Early intervention, with prompt adjustments in the regimen for inadequately controlled pain\textsuperscript{1,2}
- Reduction of pain to acceptable levels\textsuperscript{1}
- Facilitation of recovery from underlying disease or injury\textsuperscript{1}
- Multidisciplinary pain management\textsuperscript{3}
- Reassess and adjust pain management plan as needed\textsuperscript{3}
- Monitor processes and outcomes of pain management\textsuperscript{3}
- Diminish suffering, including pain and associated emotional distress\textsuperscript{1}
- Increase/restore physical, social, vocational and recreational function\textsuperscript{1}
- Optimize health including psychological well being\textsuperscript{1}
- Improve Coping Ability and relationships with others\textsuperscript{1}

Physiology of Pain Perception

- Transduction
- Transmission
- Modulation
- Perception
- Interpretation
- Behavior

Adapted with permission from WebMD Scientific American® Medicine.
Physiology of Pain: Excitatory Mediators

- Glutamate
  - Excitatory amino acid that acts both in the periphery and on N-methyl-D-aspartic acid (NMDA) receptors in the dorsal horn

- Substance P
  - Released by peripheral nerves in response to injury
  - Also acts in spinal cord

- Prostaglandins
  - Mediate the inflammatory process
  - Sensitize nociceptors
Acute Tissue Injury May Lead to Chronic Pain

Stimulus (acute tissue injury)

Neurotransmitter Release
- Glutamate, aspartate
- Substance P, Calcitonin gene-related peptide

Electrophysiological Responses
- Excitatory postsynaptic potential
- Sensitization
- Wind-up

Intracellular Stress Responses
- Calcium
- Nitric oxide synthase
- Protein kinase C

Structural Responses
- C-fos
- C-jun
- Sprouting
- Remodeling
- ?Apoptosis/ cell death

Neuropsychological Responses
- Perception
- Aversion
- Avoidance
- Stimulation-produced analgesia
- Allodynia, impairment
- Chronic pain syndrome
- Disability
- Quality of life

Time in Seconds (logarithmic scale):
-3 -2 -1 0 1 2 3 4 5 6 7 8 (s) (min) (h) (days) (months) (years)

Central sensitization is an increased sensibility of pain in the dorsal horn. Central sensitization leads to complex mechanisms that sustain chronic pain states.

Adequate Pain Control Prevents Central Sensitization

Spinothalamic Tract

Dorsal Horn

Afferent Pain Fiber
Pathophysiology of Pain

- Prevent development of chronic pain syndromes
  - Poorly managed acute pain can lead to hypersensitization and persistent pain syndrome\(^1\)

  - Tissue Damage
  - Inflammatory response
    - Sensitizes active neurons
    - Activates dormant neurons
  - Amplification of noxious process
  - Peripheral Sensitization
  - Released of excitatory amino acids
  - Increased sensibility to pain
  - Central Sensitization
  - Sustained Neuronal Firing

Tailoring Analgesic Regimens: Adopting a Multimodal Strategy

• What is multimodal therapy?
  – Combines classes of drugs and techniques that target more than 1 pain mechanism (eg, opioids plus NSAIDs)
  – Provides a way to reduce doses—and adverse effects—of individual agents
  – Not a new concept, but one that is gaining increasing attention as a therapeutic framework
  – Evidence-based approach incorporated into guidelines
    • American Pain Society (APS)¹
    • American Society of Regional Anesthesia and Pain Medicine (ASRA)²
    • American Society of Anesthesiologists (ASA)³

Multimodal Therapy: Targeting Pain Throughout the Pathway

- Different classes of agents act on different parts of the pain pathway based on their receptor targets.
- Multimodal regimens use these differences to improve pain control.
- Result is a more rational approach to pain therapy.
Multimodal Strategy: Combining Classes of Agents

• Foundation of multimodal analgesia is the combination of 2 or more types of medications
  – Generally involves adding a second class of drug to an opioid
    • NSAID blocks production of inflammatory mediators
    • Anticonvulsant inhibits propagation of pain impulses

• Significant clinical evidence shows that an opioid plus another class of agent better controls pain than opioids alone
  – Addition of an NSAID reduced postoperative morphine use by as much as 50%, with an associated decrease in opioid-induced adverse effects and increase in patient satisfaction1-3
  – Opioid plus gabapentin or pregabalin reduced opioid requirements, pain, and opioid-induced adverse effects4,5

Multimodal Therapy: Clinical Advantages

- Multimodal therapy provides a way to achieve balanced, safer pain therapy\(^1\)
  - Improved quality of analgesia\(^2,3\)
  - Fewer side effects\(^2,3\)
  - Better functional status\(^4\)
- Distinct from polypharmacy

### Peripheral
- Local anesthetics
- Anticonvulsants
- TCAs
- Opioids
- Anti-inflammatory agents

### Central
- Anticonvulsants
- Opioids
- Tricyclic/SNRI antidepressants
- \(\alpha_2\)-agonist (clonidine)
- Local anesthetics

### Descending
- Anticonvulsants
- Opioids
- Tricyclic/SNRI antidepressants
- \(\alpha_2\)-agonist (clonidine)

---
Pharmacologic Agents Affect Pain Differently

**Descending Modulation**
- Anticonvulsants
- Opioids
- Tricyclic/SNRI Antidepressants

**Central Sensitization**
- Anticonvulsants
- Opioids
- NMDA-Receptor Antagonists
- Tricyclic/SNRI Antidepressants

**Peripheral Sensitization**
- Local Anesthetics
- Topical Analgesics
- Anticonvulsants
- Tricyclic Antidepressants
- Opioids

**CNS**

**PNS**

**BRAIN**

**Spinal Cord**

**Dorsal Horn**
Multimodal Analgesia for Pain Prevention

• Prevent development of chronic pain syndromes
  – Significant number of postoperative patients develop chronic pain\(^1,2\)
    • Inguinal hernia: 4%–40%
    • Mastectomy: 20%–49%
    • Thoracotomy: up to 67%
    • Phantom limb: up to 90%
  – Severity of acute pain predicts chronic pain, although causal relationship is not fully established\(^2\)

**Pharmacological Therapy for Acute and Chronic Pain**

<table>
<thead>
<tr>
<th>Medication Class</th>
<th>Action</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids</td>
<td>Agonistic effect ; acts at the mu receptor</td>
<td>Respiratory depression, GI irritation</td>
</tr>
<tr>
<td>Nonopioids (NSAIDs, acetaminophen)</td>
<td>Principle mechanism of action is prostaglandin synthesis</td>
<td>Impaired hemostasis, GI irritation/bleeding, cardiovascular risk, renal toxicity</td>
</tr>
<tr>
<td>Dual-mechanism</td>
<td>Target multiple pain mechanism</td>
<td>Similar to opioids with better GI tolerability</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Decrease excitability of neurons by modulating sodium channels</td>
<td>Sleepiness, dizziness, fatigue</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Inhibit both NE and serotonin reuptake</td>
<td>Vary by class, include, dry mouth, blurred vision, nausea, constipation</td>
</tr>
<tr>
<td>Local anesthetics</td>
<td>Modulate sodium channels; interrupts some nerve conduction</td>
<td>Local reactions at application site</td>
</tr>
<tr>
<td>Alpha-2 agonists</td>
<td>Inhibition of NE release</td>
<td>Sedation and hypotension</td>
</tr>
</tbody>
</table>

# Drug Classes for Analgesia

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drugs</th>
<th>Treatment Considerations</th>
</tr>
</thead>
</table>
| NSAIDs                   | Nonselective – ibuprofen, naproxen sodium, diclofenac, COX-2 selective - celecoxib | Associated with reduced risk of GI toxicity, increased in the elderly  
Bleeding with nonselective NSAIDs  
COX-2 selective NSAIDs have no known effect on thromboxane-induced platelet activity |
| Opioids, opioid-like drugs | Oxycodone, methadone, hydromorphone, hydrocodone, morphine, tramadol | Long-acting opioids provide more consistent pain relief  
Start low and go slow in the elderly |
| Tricyclic anti-depressants | Nortriptyline, desipramine, amitriptyline, maprotiline | Slow onset to therapeutic effects and requires dose titration to pain relief and dose adjustments to minimize side effects  
Co-treatment of neuropathic pain and depression |
| SNRIs                    | Venlafaxine, duloxetine                    | Co-treatment of neuropathic pain and depression                                                                   |
| Anticonvulsants          | Gabapentin and pregabalin                  | Requires dose titration to pain relief and dose adjustments to minimize side effects                              |
## Implementing Multimodal Therapy: Classes of Medication

<table>
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<tr>
<th>Class of Agent</th>
<th>Target</th>
<th>Clinical utility</th>
<th>Clinical concerns</th>
</tr>
</thead>
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<tr>
<td><strong>Opioids</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mu opioid receptors</td>
<td></td>
<td>Mainstay for moderate to severe pain</td>
<td>Sedation, Respiratory depression, Constipation, Nausea/vomiting, Potential for tolerance</td>
</tr>
</tbody>
</table>
Does Your Patient Respond to Opioids?

Examples: morphine, oxycodone, fentanyl

• Remain therapeutic mainstay for moderate to severe pain management\(^1\)
• Most common agents in the class act at the mu receptor\(^1\)
• Agonistic effects both in peripheral nociceptors and centrally (spinal cord and descending pathway)\(^1\)
• Some severe chronic neuropathic pain conditions can be successfully managed with opioid therapy\(^4\)
• Prescribed as part of multimodal and interdisciplinary treatment plan\(^2\)

• Considerations
  – Past hX of drug or alcohol abuse
  – Low starting dose
  – Dosing spread around the clock and not prn

Opioid Analgesics

- **Opioids**
  - Opioids regulate pain throughout the pathway in the
    - Periphery—to inhibit calcium influx and activation of nociceptors
    - Spinal cord—to prevent release of neurotransmitters
    - Ascending pathway—to block transmission
    - Brain—to turn on the descending pathways
  - Endogenous opioids include endorphins and enkephalins
    - Work via a lock-and-key mechanism at the opioid receptor
    - Of 3 types of receptors (kappa, delta, mu), mu is most relevant
Characteristics of Immediate- and Controlled-Release Opioids

Immediate-release opioids
- Quick onset of action (within minutes)
- May be more appropriate for some types of acute pain and some types of BTP
- Can be used for dose finding during initial treatment
- Inconvenient repetitive dosing
- Peak and trough phenomenon
  - Not ideal for chronic pain
  - Increased end-of-dose breakthrough pain
  - Increased potential for euphoria and adverse effects (peaks)

Controlled-release opioids
- More stable blood levels
- More appropriate for persistent acute pain and chronic pain because avoids peaks and troughs
- Reduced end-of-dose breakthrough pain
- Lower potential for euphoria (due to fewer peaks) when taken as prescribed
- Decreased risk for side effects (fewer peaks)
- Improved compliance and quality of life

When you Need Mechanism of Different Action: Methadone and Ketamine
Methadone, Just Another Opioid?

- Synthetic opioid
- Indicated for detoxification and treatment of opioid addiction
- Increasingly used for treatment of moderate to severe pain
- Mu-opioid receptor agonist (kappa and delta)
- NMDA-receptor antagonist
- Inhibits reuptake of norepinephrine and serotonin
- At high doses, blocks potassium channels
- Cost-effective
Pharmacokinetics

- Rapidly absorbed by the GI tract
- Quick onset of action → 30-60 minutes (PO), steady state in 3-5 days; 10-20 minutes (IV), peaks in 2.5-4 hr
- Lipophilic
  - Analgesic efficacy → 6-12 hours
  - Elimination half-life → 24-36 hours
    - Long and highly variable (range 5-130 hours)
    - Eliminated through feces and produces nontoxic metabolites with minor activity
      - Preferred in renal insufficiency**
  - Takes 4 days to reach steady state
Breakthrough Pain: Definition Problems

• Definition is by consensus and has arbitrary quality

• Basis for definition is an acute, transitory pain over controlled baseline pain

• But what definitions should apply?
  – Timing
  – Severity
  – Population
  – Treatment of baseline pain
Breakthrough Pain: Definition Problems

• Most stringent definition
  – In the cancer population, breakthrough pain is a transitory, severe, or excruciating pain, which lasts seconds to hours and is superimposed on a baseline pain controlled to a moderate or better intensity by an opioid regimen

• Very broad definition
  – Any severe, transient pain with intensity exceeding baseline

Breakthrough Pain: Definition Problems

- Definitional imprecision increased by use of alternative terms
  - Episodic pain
  - Incident pain
  - End-of-dose failure
- Incident pain also considered a subtype of breakthrough pain associated with a voluntary action
- End-of-dose failure not considered to be breakthrough pain by some
Breakthrough Pain: Characteristics

• Phenomenology usually similar to baseline pain, but large inter-individual differences
• Frequency: <1 episode/day to many per hour
• Most episodes brief, but may last hours
• Onset usually over minutes, but varies
• 50% associated with volitional action (some nonvolitional)
• May be predictable or appear without warning
• May appear or worsen at end-of-dosing interval (“end-of-dose failure”)

# Characteristics of Breakthrough Pain

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Average</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to peak severity</td>
<td>3-5 minutes</td>
<td>10 seconds to 180 minutes</td>
</tr>
<tr>
<td>Severity</td>
<td>Severe or excruciating</td>
<td>Mild to excruciating</td>
</tr>
<tr>
<td>Duration</td>
<td>15-30 minutes</td>
<td>1 second to more than 24 hours</td>
</tr>
<tr>
<td>Number of episodes per day</td>
<td>1-5</td>
<td>Less than 1 to 3600</td>
</tr>
<tr>
<td>Precipitated by event</td>
<td>55%-60%</td>
<td>52%-77%</td>
</tr>
<tr>
<td>Predictable</td>
<td>50%-60%</td>
<td>41%-81%</td>
</tr>
</tbody>
</table>

Components of Chronic Pain

- Around-the-clock medication
- Breakthrough pain
- Persistent pain

Comparison of Oral Transmucosal Fentanyl Citrate to Fentanyl Buccal Tablet

<table>
<thead>
<tr>
<th></th>
<th>OTFC</th>
<th>FBT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route of use</td>
<td>Oral, mucosal</td>
<td>Oral, buccal</td>
</tr>
<tr>
<td>Dose range, mcg</td>
<td>200-1600</td>
<td>100-800</td>
</tr>
<tr>
<td>Time to peak plasma level, median, min</td>
<td>90.8*</td>
<td>46.8*</td>
</tr>
<tr>
<td>Half-life, hr</td>
<td>6.4†</td>
<td>11.09*</td>
</tr>
<tr>
<td>Bioavailability, absolute, %</td>
<td>47 ± 10.5*</td>
<td>65 ± 20†</td>
</tr>
<tr>
<td>Time to significant decrease in pain intensity, min</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Adverse events (≥5%), long-term treatment</td>
<td>Asthenia, headache, accidental injury, nausea, vomiting, constipation, dizziness, anxiety, somnolence, confusion, depression, insomnia, dyspnea, rash</td>
<td>Anemia, neutropenia, nausea, vomiting, constipation, diarrhea, abdominal pain, peripheral edema, asthenia, fatigue, pneumonia, decreased weight, dehydration, anorexia, hypokalemia, back pain, arthralgia, cancer pain, dizziness, headache, somnolence, confusion, depression, insomnia, cough, dyspnea</td>
</tr>
</tbody>
</table>

*400-mcg adjusted dose; †400-mcg dose; ‡across dose range.

OTFC, oral transmucosal fentanyl citrate; FBT indicates fentanyl buccal tablet.
Oral Transmucosal Opioids

- Sublingual preparations:
- Fentanyl sublingual (Abstral™)

**ABSTRAL TITRATION PROCESS**

Starting dose 100 µg

Adequate pain relief achieved within 15-30 minutes?

- Yes
  - Use this dose for subsequent breakthrough pain episodes

- No
  - Take a second tablet (See table to determine strength of second tablet)
  - Increase first tablet to next higher strength for next breakthrough pain episode
Intranasal Opioids

- Intranasal fentanyl spray (Instanyl™)

- Fentanyl nasal spray (PecFent™)
Fentanyl Buccal Soluble Film (Onsolis®)

- Inactive layer
- Mucoadhesive (drug) layer
- Mucosal surface
- Delivery through the buccal mucosa

- 200 mcg
- 400 mcg
- 600 mcg
- 800 mcg
- 1200 mcg
Is this Patient Developing Tolerance or Is Pain Worsening?

- Opioid tolerance is a “shift to the right” in the dose-response curve
  - Higher dose required over time to maintain the same level of analgesia
- Tolerance can be pharmacokinetic…
  - Drug or concomitant medications upregulate metabolic pathways that remove opioids from the body
- …or pharmacodynamic
  - Desensitization
    - Physiological changes to the opioid receptors
  - Downregulation
    - Internalization of opioid receptors by endocytosis, reducing their numbers

Could Your Patient have Opioid-induced Hyperalgesia (OIH)?

• Increased sensitivity to pain resulting from opiate administration

• Opioids, in addition to providing analgesia, set in motion anti-analgesic or hyperalgesic processes

• Pain-free animals made tolerant to morphine have significantly decreased tolerance to pain\(^1\)

• Opioid “tolerance” may not be a downregulation of analgesic systems, but an upregulation of hyperalgesic systems\(^2\)

Differentiating OLH from Other Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Nature of Pain</th>
<th>Presentation or Onset of Pain</th>
<th>Response to Opioid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioid Induced Hyperalgesia</td>
<td>Increased sensitivity to pain; diffuse pain, extending beyond the distribution of pre-existing pain; alldynia may be present</td>
<td>Abrupt onset with rapid opioid escalation or high-dose opioid administration</td>
<td>Pain worsens</td>
</tr>
<tr>
<td>Worsening Pain Pathology</td>
<td>Localized to site of pre-existing pain or new site of pathology</td>
<td>Variable, depending on source of pain</td>
<td>Pain improves</td>
</tr>
<tr>
<td>Opioid Tolerance</td>
<td>Localized to site of pre-existing pain</td>
<td>Gradual onset</td>
<td>Pain improves</td>
</tr>
<tr>
<td>Opioid Withdrawal</td>
<td>Increased sensitivity to pain; diffuse, extending beyond the distribution of pre-existing pain</td>
<td>Abrupt with short-acting opioids or antagonist administration; gradual with long-acting opioids</td>
<td>Pain improves</td>
</tr>
<tr>
<td>Opioid Addictive Disease</td>
<td>Increased sensitivity to pain; diffuse, may extend beyond the distribution of pre-existing pain.</td>
<td>Gradual onset</td>
<td>Pain may improve but functionality may worsen</td>
</tr>
<tr>
<td>Pseudoaddiction</td>
<td>Localized to site or pre-existing pain.</td>
<td>Variable, depending on source of pain</td>
<td>Pain improves</td>
</tr>
</tbody>
</table>

Table adapted from Mitra 2008.

Moving to a Multimodal Strategy: Dual-mechanism Analgesics

• A single medication with dual mechanisms of action
  – First in class: tramadol

• Newest dual-mechanism agent is tapentadol
  – Acts on mu opioid receptors and inhibits reuptake of NE
  – Clinical trial experience
    • Comparable to oxycodone in acute pain (bunionectomy)\(^2\)
      and in more chronic pain (up to 90 days in joint or back pain)\(^3\)
    • Comparable or better pain relief than morphine in dental surgery\(^4\)
    • Main side effects similar to conventional opioids (GI, CNS), but significantly better GI profile, including lower rate of constipation\(^3,5\)
  – May be associated with less tolerance\(^1\)
  – May be useful in patients with opioid sensitivity

Tapentadol IR: Efficacy and Safety Profile

- Nausea, vomiting and constipation were significantly less likely with tapentadol IR
- Pain intensity showed similar efficacy for tapentadol IR and oxycodone

![Percentage of Gastrointestinal Events](chart)

Tapentadol ER: Improved Tolerability

- Incidences of Treatment Emergent Events for Tapentadol ER and Oxycodone CR

## Implementing Multimodal Therapy: Classes of Medication

<table>
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<tr>
<th>Class of Agent</th>
<th>Opioids</th>
<th>NSAIDs</th>
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<td>Target</td>
<td>Mu opioid receptors</td>
<td>Prostaglandins</td>
</tr>
<tr>
<td>Clinical utility</td>
<td>Mainstay for moderate to severe pain</td>
<td>First-line adjunct to opioids</td>
</tr>
<tr>
<td>Clinical concerns</td>
<td>Sedation</td>
<td>Renal impairment</td>
</tr>
<tr>
<td></td>
<td>Respiratory depression</td>
<td>Liver impairment</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>G1 bleeding/ulcers</td>
</tr>
<tr>
<td></td>
<td>Nausea/vomiting</td>
<td>Hemostasis</td>
</tr>
<tr>
<td></td>
<td>Potential for tolerance</td>
<td>CV risk</td>
</tr>
</tbody>
</table>
Classes of Pain Medications: Nonopioids

• Nonsteroidal anti-inflammatory drugs (NSAIDS)
  – Examples: celecoxib, ketorolac
  – Anti-inflammatory and analgesic effects
  – Principal mechanism of action: inhibition of prostaglandin synthesis
  – Activity at peripheral nociceptors and in spinal cord
  – Side effects due in part to selectivity for cyclooxygenase-2
    • Impaired hemostasis (nonselective)
    • GI irritation/bleeding (nonselective)
    • Cardiovascular risk
    • Renal toxicity

• Acetaminophen
  – Analgesic but not anti-inflammatory
  – Less potent than NSAIDs
  – Lacks adverse effects of NSAIDs
  – Hepatotoxic in overdose
Comparative Acetaminophen Pharmacokinetics (1000 mg)

- **Oral Acetaminophen**¹,²:
  - Median $T_{\text{max}}$ of regular release formulation is ~45 to 60 minutes
  - Mean $C_{\text{max}}$ of ~10 mcg/mL (with up to 1/3\textsuperscript{rd} below the therapeutic level)
  - Bioavailability (AUC) – 87% (tablets) to 93% (elixir)
  - First pass hepatic exposure

- **Rectal Acetaminophen**³:
  - Median $T_{\text{max}}$ – 200 minutes
  - Mean $C_{\text{max}}$ of 4 to 9 mcg/mL with most failing to achieve the therapeutic level of 10 mcg/mL
  - Bioavailability – 50 to 80% with erratic and unpredictable absorption

- **IV Acetaminophen**¹:
  - Median $T_{\text{max}}$ by end of 15-minute infusion
  - Mean $C_{\text{max}}$ of ~27 mcg/mL with all patients above the therapeutic level
  - 100% bioavailability

## Implementing Multimodal Therapy: Classes of Medication

### Classes of Agent

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<td>Mu opioid receptors</td>
<td>Prostaglandins</td>
<td>Sodium channels</td>
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<tr>
<td>Mainstay for moderate to severe pain</td>
<td>First-line adjunct to opioids</td>
<td>Differential (sensory) blockade</td>
</tr>
<tr>
<td>Sedation Respiratory depression Constipation Nausea/vomiting Potential for tolerance</td>
<td>Renal impairment Liver impairment GI bleeding/ulcers Hemostasis CV risk</td>
<td>Allergic reactions</td>
</tr>
</tbody>
</table>
Classes of Pain Medications: Local Anesthetics

**Examples: lidocaine, bupivacaine**

- Modulate sodium channels
- When administered peripherally, may produce differential—also known as sensory—block
  - Interrupts some nerve conduction, but leaves motor function unaffected
  - Some nerves are more readily blocked than others, depending on size and myelination
- Interrupts pain input at the nerve roots
- Associated with few adverse effects

Tropical vs Transdermal Medication Delivery Systems

Topical (lidocaine patch 5%)\(^1,2,3\)
- Peripheral tissue activity
  - Applied directly over painful site
  - Minimal systemic absorption
  - Systemic AEs rare

Transdermal (fentanyl patch)\(^4\)
- Systemic activity
  - Applied away from painful site
  - Serum levels necessary
  - Systemic AEs common

---

Lidocaine Patch 5%

- Lidocaine 5% in pliable patch
- Up to 3 patches applied once daily directly over painful site
  - 12 h on, 12 h off (FDA-approved label)
  - Recently published data indicate 4 patches (18–24 h) safe
- Efficacy demonstrated in 3 randomized controlled trials on PHN
- Drug interactions and systemic side effects unlikely
  - Most common side effect: application-site sensitivity
- Clinically insignificant serum lidocaine levels
- Mechanical barrier decreases allodynia

1. Lidoderm (lidocaine patch 5%) [package insert].
## Implementing Multimodal Therapy: Classes of Medication

<table>
<thead>
<tr>
<th>Class of Agent</th>
<th>Opioids</th>
<th>NSAIDs</th>
<th>Local anesthetics</th>
<th>Anticonvulsants</th>
</tr>
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<tbody>
<tr>
<td><strong>Target</strong></td>
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<td>Sodium channels</td>
<td>Sodium and calcium channels</td>
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<tr>
<td><strong>Clinical utility</strong></td>
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<td>Hemostasis</td>
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<tr>
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<td>Potential for tolerance</td>
<td>CV risk</td>
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</table>
Classes of Pain Medications: Anticonvulsants

- **Examples:** gabapentin, pregabalin, lamotrigine

- Decrease excitability of neurons by modulating sodium channels; do not act on GABA

- Emerging as top-line adjunct in acute pain and first-line therapy in chronic pain

- Adverse effects/limitations
  - Most common adverse effects are CNS related, including sleepiness, dizziness, and fatigue

Anticonvulsant Drugs for Neuropathic Pain Disorders

- Postherpetic neuralgia
  - gabapentin*
  - pregabalin *

- Diabetic neuropathy
  - carbamazepine
  - phenytoin
  - gabapentin
  - lamotrigine
  - pregabalin *

- HIV-associated neuropathy
  - lamotrigine

- Trigeminal neuralgia
  - carbamazepine*
  - lamotrigine
  - oxcarbazepine

- Central poststroke pain
  - lamotrigine

*Approved by FDA for this use.
HIV = human immunodeficiency virus.
## Implementing Multimodal Therapy: Classes of Medication

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<td>CNS-related adverse effects, including dizziness, sedation, and fatigue</td>
<td>Limited analgesic effect of serotonin-specific agents</td>
</tr>
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</table>
Classes of Pain Medications: Antidepressants

- **Tricyclics** Examples: amitriptyline, nortriptyline, desipramine
  - Inhibit both norepinephrine (NE) and serotonin reuptake to varying degrees
  - Possess other properties (e.g., local anesthetic-like activity)

- **SNRIs (serotonin norepinephrine reuptake inhibitors)** Examples: venlafaxine, duloxetine, bupropion
  - Selective serotonin reuptake inhibitors (SSRIs) have not been shown to be particularly effective as pain therapy

Adverse effects vary by class of agent, and include dry mouth, blurred vision, nausea, constipation, agitation, dizziness, and drowsiness

Tricyclic Antidepressants: Adverse Effects

• Commonly reported AEs (generally anticholinergic):
  – Blurred vision
  – Cognitive changes
  – Constipation
  – Dry mouth
  – Orthostatic hypotension
  – Sedation
  – Sexual dysfunction
  – Tachycardia
  – Urinary retention

Multimodal Strategy: Implications for Nursing Practice

• Effective and safe practices with multimodal strategies require that nurses:
  – Understand the rationale for combining analgesics\textsuperscript{1,2,4}
  – Be knowledgeable about classes of analgesics\textsuperscript{1,2,4}
    • Mechanisms of action and pharmacodynamics
    • Synergistic and AEs
  – Ensure timely administration of all analgesics, avoiding gaps in analgesia\textsuperscript{2-4}
  – Institute proper assessment and monitoring practices\textsuperscript{2,3}
  – Aggressively manage AEs of analgesics\textsuperscript{1,2,4}
  – Remain informed about novel dual-mechanism analgesics and drug delivery systems\textsuperscript{1,2,4}

Drug Therapy of Chronic Pain: Implications for Future Practice

• Multimodal therapy will continue to evolve through use of novel agents and technologies
  – Dual-mechanism agents

• Increased knowledge of the physiology of pain and pharmacotherapy helps nurses safely and effectively understand and administer multimodal analgesia
  – Focused assessments and reassessments
  – More consistent and reliable dosing to reduce analgesic gaps
  – More options to advocate for individual patient’s treatment needs

Pain protocols

- Consider what constitutes best clinical care
  - Protocols are useful tools to direct care, but nurses must also apply their clinical judgment
- Treat the patient, not the number
  - Evidence shows that the incidence of opioid-induced adverse effects increases significantly after implementing a policy to titrate opioids to a specific numeric rating scale (NRS) number

Multimodal Analgesia For Acute Pain

- Acute postoperative pain remains significantly undertreated and is associated with substantial short- and long-term consequences
- Despite multiple guidance documents, barriers to the successful management of acute and chronic pain still remain
- Multimodal analgesia and the avoidance of “analgesic gaps” are central to effective management of postoperative pain
- Emerging treatment options may assist in removing barriers to optimal postoperative pain management
Multimodal Analgesia For Chronic Pain

- Chronic neuropathic pain is a disease, not a symptom
- “Rational” polypharmacy is often necessary
  - combining peripheral and central nervous system agents enhances pain relief
- Treatment goals include:
  - balancing efficacy, safety, and tolerability
  - reducing baseline pain and pain exacerbations
  - improving function and QOL
- New agents and new uses for existing agents offer additional treatment options
“Mr. Osborne, may I be excused? My brain is full.”