Understanding the Pharmacology of Analgesics

Part of the INROADS into Pain Management Series

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Welcome & Introduction

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Learning Objectives

• Review the pharmacology and therapeutic rationale for major classes of pain medications

• Discuss multimodal therapy as a means to enhance analgesia and reduce side effects

• Identify key factors for tailoring pain regimens based on a patient’s individual health profile

• Explore appropriate uses of multimodal therapy through case-based learning
Agenda

• Pursuing a More Mechanistic Approach to Analgesia: Multimodal Therapy
  – Debra B. Gordon, RN-BC, MS, ACNS-BC, FAAN

• Multimodal Management of Postoperative Pain in a High-risk Patient
  – Chris Pasero, MS, RN-BC, FAAN

• A Multimodal Approach to the Care of a Patient With Fibromyalgia
  – Colleen J. Dunwoody, MS, RN-BC

• Questions & Answers
  – Moderated by Rosemary C. Polomano RN, PhD, FAAN
Audience Response

What is your primary area of focus within pain management?

1. Acute
2. Chronic
3. Acute and chronic
• What is your office setting?
  1. Education/university/research
  2. Family/general practice
  3. Hospital–PACU
  4. Hospital–other
  5. Long-term care facility or hospice
  6. Outpatient surgery center
  7. Pain clinic
Pursuing a More Mechanistic Approach to Analgesia: Multimodal Therapy

Debra B. Gordon RN-BC, MS, ACNS-BC, FAAN
Senior Clinical Nurse Specialist
University of Wisconsin Hospital and Clinics
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Optimizing analgesic therapy requires an individualized approach to each patient.

Treatment should be based on a comprehensive assessment of the patient’s needs.

Issues involved in this process can be divided into 2 areas:

<table>
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<tr>
<th>Patient Factors</th>
<th>Practice Factors</th>
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<tr>
<td>General health status and predisposing risk factors</td>
<td>Systematic assessment and monitoring</td>
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<tr>
<td>Pre-existing pain syndromes</td>
<td>Implementation of protocols</td>
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<td>Injury/surgery type</td>
<td>Formulating initial pain plan</td>
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<tr>
<td>Medication history</td>
<td>Reassessment and adjustment of pain plan</td>
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When determining goals of pharmacologic therapy, it is important to:

1. Advocate for PRN range orders that ensure pain is <4/10
2. Individualize goals based on surgical protocols
3. Ensure that therapy includes a drug that both inhibits and excites pain processes
4. Balance analgesia and side effects
Individualizing Pain Therapy

• Formulating a pain plan
  – Recognize each patient represents an individual therapeutic “experiment” that requires careful selection and titration of therapy¹
    • Lack of predictable relationship between opioid dose and pain relief makes it inadvisable to prescribe predetermined dose based on pain intensity
    • Determine regimens based on drug pharmacokinetics, patient characteristics, and clinical situation
  – PRN orders should be specific but not absolute
    • Avoid explicit dosing recommendations that leave little room for clinical judgment based on patient response
    • Avoid vague or open-ended orders, such as “titrate to comfort”¹

Pharmacologic Management of Pain: Goals

• Produce clinically meaningful acute pain relief
  – Data from clinical trials suggest that a 33% to 50% decrease in pain intensity is meaningful\(^1\)
  – Severity of acute pain predicts chronic pain, although causal relationship is not fully established\(^2\)

• Achieve balanced analgesia that maximizes pain relief while minimizing side effects
  – Enhance consistency/reduce analgesic gaps
  – Avoid unnecessary sedation
  – Mitigate serious risks
  – Reduce effects that impair patient comfort/compliance

• Individualize treatment based on each patient’s current response and past medical history\(^3\)
  – Avoid dosing to a specific pain rating number

Physiology of Pain: Neurochemical Mediators

• A large number of neurotransmitters and other chemical mediators play a role in pain processing and modulation
• Mediators act in a complex and interrelated process

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<tr>
<th>Excitatory (promote or intensify the pain process)</th>
<th>Inhibitory (block or dampen the pain process)</th>
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<tbody>
<tr>
<td>Key mediators</td>
<td>Key mediators</td>
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<tr>
<td>• Glutamate</td>
<td>• Opioids</td>
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<tr>
<td>• Substance P</td>
<td>• Norepinephrine</td>
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<tr>
<td>• Prostaglandins</td>
<td>• Serotonin</td>
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<td></td>
<td>• Gamma-aminobutyric acid (GABA)</td>
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Mechanisms of Action of Analgesics

- Decrease excitability of nociceptors
- Decrease transmission in peripheral nervous system
- Block transmission of pain signals centrally
- Upregulate descending pain modulatory pathways
Drug Therapy for Acute Pain

• Classes of medications
  – Opioids
  – Nonopioids (NSAIDs, acetaminophen)
  – Anticonvulsants
  – Antidepressants
  – Local anesthetics
  – Alpha-2 agonists

NSAID=nonsteroidal anti-inflammatory drug.
Classes of Pain Medications: Opioids

Examples: morphine, oxycodone, fentanyl

- Remain therapeutic mainstay for moderate to severe pain management
- May also play a role in mild to moderate pain when NSAIDs are contraindicated
- Most common agents in the class act at the mu receptor
- Agonistic effects both in peripheral nociceptors and centrally (spinal cord and descending pathway)
- Side effects/limitations
  - Risk of respiratory depression
  - Risk of other side effects (eg, nausea, constipation)
  - Potential for tolerance over time
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Classes of Pain Medications: Nonopioids

• **NSAIDs**  **Examples: celecoxib, ketorolac**
  – Possess both anti-inflammatory and analgesic effects
  – Principle mechanism of action is inhibition of prostaglandin synthesis
  – Act at peripheral nociceptors and in the spinal cord
  – Side effects depend partly on whether drugs are selective (COX-2) or nonselective
    • Impaired hemostasis (nonselective)
    • GI irritation/bleeding (nonselective)
    • Cardiovascular risk
    • Renal toxicity

• **Acetaminophen**
  – Analgesic but not anti-inflammatory
  – 20%-30% weaker than NSAIDs
  – Lacks the adverse effects of NSAIDs
  – Hepatoxic in overdose

GI=gastrointestinal.
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
• Side effects/limitations
  – Most common side effects are CNS related, including sleepiness, dizziness, and fatigue

CNS=central nervous system.
Classes of Pain Medications: Antidepressants

- **Tricyclics** Examples: amitriptyline, nortriptyline, desipramine
  - Inhibit both norepinephrine (NE) and serotonin reuptake to varying degrees
  - Possess other properties (eg, 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

- Side effects vary by class of agent, and include dry mouth, blurred vision, nausea, constipation, agitation, dizziness, and drowsiness
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
- Epidurally, interrupts pain input at the nerve roots
- Associated with few side effects
Classes of Pain Medications: Alpha-2 Agonists

Examples: clonidine, dexmedetomidine

- Exerts its antinociceptive through inhibition of norepinephrine release
- Clonidine may be used epidurally as primary analgesic postoperatively
- Limited by sedation and hypotension
Audience Response

• Which of the following statements best describes multimodal analgesia?

  1. Any combination of 2 or more analgesics
  2. Combining analgesics with pre-emptive side-effect treatment
  3. Combinations of drugs and techniques with differing mechanisms of action
  4. Using regional local anesthetic techniques with systemic analgesia
Drug Therapy of Acute Pain: an Evolving Understanding

- Recognizing the need for a multimodal approach to drug therapy
  - Combinations of drugs and techniques that target more than 1 pain mechanism, not 2 drugs that target the same
  - Not a new concept, but one that is gaining increasing attention as a therapeutic framework
  - Strong evidence to support the utility of this approach; incorporated into major pain management guidelines
    - American Pain Society (APS)^1
    - American Society of Regional Anesthesia and Pain (ASRA)^2
    - American Society of Anesthesiology (ASA)^3

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

Drug Therapy of Acute Pain: Moving to a Multimodal Strategy

- **Multimodal therapy: combining classes of agents**
  - Opioids plus NSAIDs reduced postoperative morphine use by approximately 50%, with associated decrease in opioid-induced side effects and increase in patient satisfaction\(^1\)-\(^3\)
  - Opioid plus gabapentin or pregabalin reduced opioid requirements, pain, and opioid-induced side effects\(^4\)\(^,\)\(^5\)
  - Combining 2 classes of agents with opioids extends the multimodal model

- **Use of pregabalin and COX-2 selective NSAID in conjunction with PCA morphine\(^6\)**
  - Reduced pain and opioid use compared with each agent alone
  - Also reduced incidence of nausea and vomiting

PCA=patient-controlled analgesia.

Moving to a Multimodal Strategy: Dual-action Analgesics

- A single drug with dual mechanisms of action
  - First in class: tramadol

- Newest dual-mechanism agent is tapentadol:
  - Acts on mu opioid receptors and inhibits reuptake of norepinephrine\(^1\)
  - 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

Drug Therapy of Acute Pain: Implications for Future Practice

• Multimodal therapy will continue to evolve through use of novel agents and technologies
  – Dual-mechanistic agents
  – New formulations (eg, extended-release epidural agents)
  – New delivery systems (eg, controllable transdermal systems)

• Nurses need to have increased knowledge of the physiology of pain and pharmacotherapy in order to better understand and safely 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
Multimodal Management of Postoperative Pain in a High-risk Patient

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Educator and Clinical Consultant
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Case Presentation

• NB is a 60-year-old female admitted for total abdominal hysterectomy

• She has a 15-year history of uterine fibroids that have recently increased significantly in size and are now accompanied by mild to moderate dysfunctional uterine bleeding and occasional transient mild pain

• Enlarged uterus necessitates an invasive midline incision
Case Presentation: Secondary Diagnoses

- **Obesity**
  - Weight=185 lb (84 kg)
  - Height=5’4”
  - BMI=32 kg/m² (>30 kg/m² = obese)

- **Obstructive sleep apnea (OSA)**
  - This is a recent diagnosis post sleep analysis
  - Room air CPAP during sleep has been prescribed

CPAP=continuous positive airway pressure.
Case Presentation:
Current Medications

- Estradiol 0.5 mg daily
- Progesterone 100 mg daily
- Calcium 500 mg twice daily
- Acetaminophen 325 mg every 6 hours PRN for uterine pain
- Ibuprofen 400 mg every 6 hours PRN for uterine pain (held for 5 days preoperatively)
Which of the following increases the risk of opioid-induced respiratory depression for this patient?

1. Occasional mild preoperative pain
2. BMI of 32 kg/m²
3. History of uterine fibroids
4. Preoperative use of NSAIDs and acetaminophen
Case Presentation: Other Considerations

- This is the patient’s first surgery; she has been hospitalized previously only for the births of her children
- She has a very sedentary lifestyle
- She admits poor compliance with use of prescribed room air CPAP during sleep
Case Presentation: Other Considerations

- This patient has never taken opioids before
- The only analgesics she has ever taken are nonopioids, such as ibuprofen
- Though intraspinal analgesia would be an excellent option considering her risk factors, she absolutely refuses intraspinal analgesia
Patient Characteristics to Consider in Planning Care for This Patient

• Obesity with sedentary lifestyle habits, OSA, and a highly invasive (large incision) surgical technique

  =

  increased risk of numerous postoperative adverse effects and complications

• Opioid naïve; never received opioid analgesics

  =

  unable to provide any historical information in terms of her tolerance of opioid analgesics
Audience Response

• Which of the following is most appropriate for this patient during the first 24 hours postoperatively?

1. PRN oral opioid-nonopioid analgesia
2. Around-the-clock IV opioid bolus doses and acetaminophen
3. IV opioid PCA, IV ketorolac, and oral pregabalin
4. IV opioid PCA with a low-dose basal rate
Populations of Special Concern

• Opioid naïve
  – Tolerance to respiratory depressant effects of opioids develops within several days\(^1\)
  – First 24 hours after surgery represents a high-risk period for a respiratory event\(^2,3\)
    • Of patients experiencing respiratory depression associated with a serious or fatal outcome, the event occurred in the first 24 hours in 50% of IV PCA cases and in 62% of spinal/epidural cases\(^2\)
  – Opioid-related sedation is greatest within the first 4 hours after discharge from the PACU\(^4\)

Populations of Special Concern

• Obesity
  – At increased risk for respiratory depression\(^1\)
    • May result from mechanical causes
    • May result from erroneous practice of dosing opioids based on weight, leading to overdosing\(^2\)
  – Therapy
    • Implement a multimodal analgesic approach, start preoperatively
    • Give lowest effective opioid dose, titrate gradually
    • In general, avoid basal rate with opioid PCA\(^3\)
    • Monitor closely for side effects

• Obstructive sleep apnea
  – At increased risk for respiratory depression\(^1\)
  – Often overlooked in association with opioid administration
  – Assessment should include
    • More frequent monitoring of sedation and respiratory status
    • Sedation precedes respiratory depression
    • RT consultation; CPAP; consider capnography
  – Therapy
    • Lowest effective opioid dose
    • More aggressive use of other classes of analgesics

RT=respiratory therapist.

Populations of Special Concern

- Extensive surgery and tissue injury
  - Physical components of pain
    - Type of surgery\(^1,2\)
    - Extent of injury/invasiveness of procedure\(^3\)
    - Location of incision\(^2\)
    - Incision size\(^1\)
    - Presence of tubes and drains\(^3\)
  - Emotional components of pain
    - Effects of particular diagnosis or reason for surgery

Multidisciplinary Postoperative Treatment Plan

• Foster a coordinated effort between nursing, medicine, and other disciplines that focuses on the patient’s risk factors
  – Aggressive ambulation is critical but could be hampered by invasive surgery and potential reluctance or difficulty ambulating because of obesity and sedentary habits
  – Preoperative education: patient must understand the necessity and expectation of frequent scheduled ambulation
  – Effective pain control will be imperative
Address All Patient Risk Factors

• Develop a pain treatment plan that focuses on reducing the potential for complications related to the patient’s primary risk factors
  – Obesity
  – Sleep apnea
• Involve other disciplines as needed to maximize patient outcomes
Establish Comfort-function Goal

- Establish a realistic comfort-function goal that allows the patient to ambulate and participate in recovery with relative ease\(^1\)
- Maximize the pain treatment to facilitate achievement of the comfort-function goal\(^1\)
- Keep patient focused on achievement
- Immobility is the obese postoperative patient’s worst enemy!

Selected Regimen

- “On call to the OR” acetaminophen 1000 mg, celecoxib 400 mg, pregabalin 150 mg
- Pre-incision local anesthetic infiltration
- Slow IV Dilaudid comfort in PACU
- Initiate IV Dilaudid PCA in PACU (0.2 mg/PCA dose; 6-minute lockout)
- Transition from IV Dilaudid to modified-release opioid after 24 hours
- Continue acetaminophen, celecoxib, and pregabalin throughout postoperative period
Principles of Analgesic Use in Patients at High Risk for Opioid-induced Adverse Effects

• Administer the lowest effective opioid dose
  – Minimize opioid-induced adverse effects

• Multimodal analgesia
  – Combinations that target different mechanisms
  – Lower doses = fewer and less severe side effects

• Preemptive (preventive) approach

• Vigilant monitoring
Summary

• Thorough preoperative assessment with a focus on identification of high-risk factors for postoperative complications

• Provision of lowest effective opioid dose through a multimodal analgesic approach

• Vigilant monitoring for pain, adverse effects

• Aggressive postoperative rehabilitation aimed at reducing pulmonary dysfunction and increasing mobility and function
Multimodal Approach to the Care of a Patient With Fibromyalgia

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Advanced Practice Nurse
University of Pittsburgh Medical Center Presbyterian
Pittsburgh, PA
Danielle is a 45-year-old woman with a history of depression who was diagnosed 2 years ago with fibromyalgia. She is a school teacher and a mother of 3 children, ages 8-14. She visits her PCP’s office at least once a month with ongoing complaints of pain (5-10/10), debilitating fatigue and inability to sleep, inability to maintain household responsibilities and keep up with her children.
Current Treatment

• Medications
  – Controlled-release oxycodone 20 mg PO BID
  – Oxycodone IR 5-10 mg Q4H PRN (typically takes 4 doses/day)

• Lifestyle features
  – Physically inactive
  – Comforts herself with food
  – Catnaps on the couch rather than sleeping through the night
  – Uses no stress management techniques
• Using a multimodal analgesic approach, what would you add to Danielle’s medication regimen?

1. Transdermal fentanyl with celecoxib (Celebrex™)
2. Amitriptyline (Elavil™) and gabapentin (Neurontin™)
3. Prednisone and fluoxetine (Prozac™)
4. Duloxetine (Cymbalta™) and pregabalin (Lyrica™)
Patient education has a positive therapeutic benefit in patients with fibromyalgia.

1. True

2. False
Goals of Therapy

- Effectively manage pain
- Restore normal sleep
- Improve physical stamina
- Provide emotional and social support

And for our patient, Danielle...

Taper opioids with goal of eventual discontinuation
Fast Facts

- Patients with fibromyalgia have approximately 10 outpatient clinic visits per year and 1 hospitalization per 3 years\(^1\)
- Estimated health care costs range from $2,000 to $6,000 per year\(^2\)
- Symptoms are often exacerbated by exertion, stress, lack of sleep, and weather changes, or after physical or emotional trauma\(^3\)
- Approximately 30% of patients with fibromyalgia are diagnosed as having concurrent depression or anxiety disorders\(^4\)
- 70% of patients with chronic fatigue syndrome meet criteria for fibromyalgia\(^5\)

Common Symptoms and Severity:
National Fibromyalgia Association Survey

N=2,569

Treatment Strategies for Fibromyalgia

Specific Treatment Recommendations\textsuperscript{1}

- Analgesics\textsuperscript{1,2}
  - Opioids
  - Anticonvulsants\textsuperscript{2-5}
  - Antidepressants (low dose)\textsuperscript{1,6}
    - Tricyclics, SSRIs, SNRIs
- Sleep medications\textsuperscript{1}
- Exercise, physical medicine\textsuperscript{1}
- Patient education\textsuperscript{1}
- Counseling, mental health professional\textsuperscript{1}

Advanced Fibromyalgia Management\textsuperscript{1}

- Multidisciplinary care\textsuperscript{1}
  - Rheumatologist
  - Physiatrist, physical therapist, etc.
  - Psychiatrist, psychologist, etc.
- Pain management expertise\textsuperscript{1}
- Structured, supervised exercise; rehabilitation programs\textsuperscript{1}
- Cognitive-behavioral therapy, stress reduction programs\textsuperscript{1,5}

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\textsuperscript{3} Hammond A, Freeman K. *Clin Rehabil.* 2006;20:835-846.
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 Analgesia in Fibromyalgia

• Anticonvulsants
  – Decrease excitability of neurons by modulating sodium and calcium channels
  – Emerging as first-line adjunct in acute pain and first-line therapy in chronic pain

• Antidepressants
  – Tricyclics, SNRIs
  – Inhibit both NE and serotonin (5HT) reuptake to varying degrees
  – Possess other properties, such as local anesthetic-like activity

• Both classes shown to have utility in fibromyalgia

Initial Treatment Plan

• SNRI: Duloxetine (Cymbalta™)
• Aerobic exercise
• Cognitive-behavioral therapy
• Patient education including sleep hygiene and diet
• Interdisciplinary approach
Top Reasons to Refer Patients to a Pain Specialist or Pain Center

- Uncontrolled, severe pain (eg, pain that is unresponsive to escalating doses of medication)
- Significant, ongoing disruption of physical and/or psychosocial functioning (eg, deteriorating coping skills, excessive disability)
- Comorbid psychiatric disorder (eg, substance abuse, severe depression, anxiety disorder)
• Diagnostic evaluation for unknown etiology or complex pain syndromes
• Validation of a diagnosis and treatment plan
• Consultation for treatment recommendations (eg, physical therapy, acupuncture, surgery, epidural injections) or modalities not available in the primary care setting
• Inability to establish mutually agreeable treatment goals (eg, poor patient adherence, persistent demands for new tests or treatments)
Continuing Treatment Plan

- Continue Lyrica and duloxetine
- Refer to a physical therapist
- Attend support group meetings
- Access to online resources
  - The American Chronic Pain Association
    - www.theacpa.org
  - The Fibro Center
    - www.fibrocenter.com
  - The Fibromyalgia Network
    - www.fmnetnews.com
Summary

- Fibromyalgia is a relatively common, complex syndrome characterized by widespread musculoskeletal and soft tissue pain and associated with medical and psychiatric comorbidities.
- The most effective treatment for fibromyalgia includes both pharmacologic and nonpharmacologic approaches.
- Medications may reduce symptoms but are more likely to be effective if taken in conjunction with exercise, cognitive behavioral therapy, and patient education.
Multimodal Strategy: Implications for Nursing Practice

Rosemary C. Polomano, RN, PhD, FAAN, Chair
Multimodal Strategy: Implications for Nursing Practice

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

Questions & Answers

Faculty Panelists
Moderated by Rosemary C. Polomano, RN, PhD, FAAN, Chair
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