

## Understanding the Pharmacology of Analgesics

Friday, September 5, 2008  
 6:00 PM – 6:30 PM  
 Registration and Dinner  
 6:30 PM – 8:00 PM Presentation  
 JW Marriott Starr Pass Resort & Spa  
 Arizona Ballroom Salons 7-12

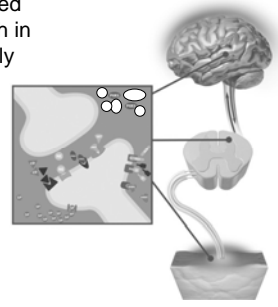
## Educational Objectives

- 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
- Analyze best practices in patient assessment and monitoring

## Physiology of Pain: Pathways and Effects on Pain Perception

Complex process mediated by multiple pathways both in the periphery and centrally

- Transduction
- Transmission
- Perception
- Modulation



## 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

Excitatory (promote or intensify the pain process)	Inhibitory (block or dampen the pain process)
Key excitatory mediators: <ul style="list-style-type: none"> <li>• Glutamate</li> <li>• Substance P</li> <li>• Prostaglandins</li> </ul>	Key inhibitory mediators: <ul style="list-style-type: none"> <li>• Opioids</li> <li>• Norepinephrine</li> <li>• Serotonin</li> <li>• Gamma aminobutyric acid (GABA)</li> </ul>

## 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 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 one pain mechanism; not two drugs that target the same one
  - 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<sup>1-3</sup>

1. Gordon DB, et al. Arch Intern Med. 2005;165:1574-1580.  
 2. Rathmel, JP Reg Anesth Pain Med. 2006;31 (Suppl 1): 1-42.  
 3. American Society of Anesthesiologists Task Force on Acute Pain Management. Anesthesiology. 2004;100:1573-1581.

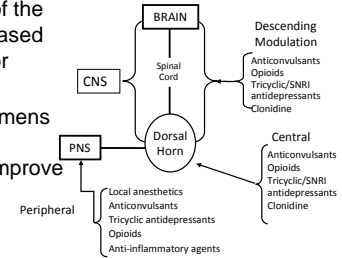
## Drug Therapy of Acute Pain: An Evolving Understanding

- Advantages of a multimodal drug strategy
  - Improved quality of analgesia
  - Fewer side effects
  - Better functional status
  - Earlier GI recovery following surgery

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## Drug Therapy of Acute Pain: Moving to a Multimodal Strategy

- Analgesics affect different parts of the pain pathway based on their receptor targets
- Multimodal regimens exploit these differences to improve pain control



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## 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 (e.g., extended release epidural agents)
  - New delivery systems (e.g., controllable transdermal systems)
- Result will be more balanced, more tolerable and safer analgesic therapy
  - More consistent and reliable pain relief
  - Reduced doses of opioids with comparable pain relief
  - Reduce side effects
  - More options to meet each patient's treatment needs

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## Case Presentation

- 65 year-old female; works from home as a telemarketer; ~180 pounds
- 15-year history of uterine fibroids that have recently increased significantly in size
- Mild to moderate dysfunctional uterine bleeding and occasional transient mild pain
- Admitted for total abdominal hysterectomy via midline incision

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## Patient Characteristics to Consider in Planning Care for this Patient

- Obesity with sedentary lifestyle habits, obstructive sleep apnea (OSA), and a highly invasive (large incision) surgical technique = increased risk of numerous postoperative adverse effects and complications
- Opioid naïve and has never received opioid analgesics before = unable to provide any historical information in terms of her tolerance of opioid analgesics

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## Populations of Special Concern

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

1. Miskowski C, et al. Guideline for the Management of Cancer Pain in Adults and Children. APS, 2005.  
 2. Weinger MB. Danger of postoperative opioids. APSF Newsletter. 2007; 21:61.  
 3. Taylor S. Amer J Surg. 2005; 190:752.  
 4. Taylor S. Amer J Surg. 2003; 186:472-475.

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## Populations of Special Concern

- Obesity
  - At increased risk for respiratory depression<sup>1</sup>
    - May result from mechanical causes
    - May result from erroneous practice of dosing opioids based on weight, leading to overdosing<sup>2</sup>
  - Therapy
    - Implement a multimodal analgesic approach, start pre-op
    - Give lowest effective opioid dose, titrate gradually
    - In general, avoid basal rate PCA opioid<sup>3</sup>
    - Monitor closely for side effects

1. Horlocker T. Practice Guidelines for the Prevention, Detection and Management of Respiratory Depression Associated With Neuraxial Opioid Administration: Preliminary Report by ASA Task Force on Neuraxial Anesthesia. *ASA Newsletter*, June 2007.  
2. Shibutani K, et al. *B. J Anaesth* 2005; 95(3):377-383.  
3. Krenzschek DA, et al. *J PeriAnesth Nursing* 2008; 23:528.

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## Populations of Special Concern

- Obstructive Sleep Apnea
  - At increased risk for respiratory depression<sup>1</sup>
  - Often overlooked in association with opioid administration
  - Assessment should include
    - More frequent monitoring of sedation and respiratory depression
    - Sedation precedes opioid-induced sedation
    - Respiratory Therapist consultation; CPAP; consider capnography
  - Therapy
    - Lowest effective opioid dose
    - More aggressive use of other classes of analgesics

1. Horlocker T. Practice Guidelines for the Prevention, Detection and Management of Respiratory Depression Associated With Neuraxial Opioid Administration: Preliminary Report by ASA Task Force on Neuraxial Anesthesia. *ASA Newsletter*, June 2007.

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## Principles of Analgesic Use in High Risk Patients

- 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

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## Case Presentation

- 45 year-old woman with a history of depression who was diagnosed 2 years ago with fibromyalgia
- School teacher and mother of 3 children
- Visits her PCP's office at least once a month with ongoing complaints of pain, fatigue and inability to sleep

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## Goals of Therapy

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

Nampiaparampil DE, Shmerling RH. *Am J Manag Care* 2004;10(1 Pt 1):794-800.

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## Fibromyalgia Fast Facts

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

1. Wolfe F, et al. *Arthritis Rheum* 1990;33:160-172  
2. Robinson RL, et al. *J Rheumatol* 2003;30:1318-1325.  
3. Goldenberg DL. *Arthritis Rheum* 1993;36:1499-1492.  
4. Hudson JL, et al. *Am J Med* 1992;92:363-367.  
5. Goldenberg DL, et al. *Arthritis Rheum* 1990;33:381-387.

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## Treatment Strategies for Fibromyalgia

### Specific Treatment Recommendations

- Analgesics
  - Opioids
  - Anticonvulsants
  - Antidepressants (low dose)
    - Tricyclics, SSRIs, SNRIs
- Sleep medications
- Exercise, physical medicine
- Patient education
- Counseling, mental health professional

### Advanced Fibromyalgia Management

- Multidisciplinary care
- Rheumatologist
- Psychiatrist, physical therapist, etc.
- Psychiatrist, psychologist, etc.
- Pain management expertise
- Offer structured, supervised exercise, rehabilitation programs
- Offer cognitive-behavioral therapy, stress reduction programs

Goldenberg DL. *Best Pract Res Clin Rheumatol* 2007;21(3):499-511.  
Goldenberg DL. *Rheum Dis Clin North Am* 2002;28(2):437-446. xi.

Wiffen PJ, et al. *Cochrane Database Syst Rev* 2005 Jul 20;(3):CD005452.

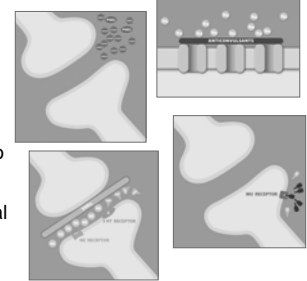
Arnold LM, 1 et al. *Arthritis Rheum* 2007;56(4):1336-1344.  
Hammond A, Freeman K. *Clin Rehabil* 2006;20(10):835-846.

Arnold LM, et al. *Pain* 2005;119(1-3):5-15.

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## 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



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## Ongoing Treatment Plan

- Refer to a physical therapist
- Attend support group meetings
- Access to on-line resources
  - The American Chronic Pain Association
    - [www.theacpa.org](http://www.theacpa.org)
  - The Fibro Center
    - [www.fibrocenter.com](http://www.fibrocenter.com)
  - The Fibromyalgia Network
    - <http://www.fmnetnews.com>
  - And more

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## Summary

- Pain is a complex process involving a range of inputs in the periphery, spinal cord and brain
- Consider patient's complete medical and psychological status to identify key barriers to effective therapy
- Enhance analgesic effectiveness and avoid side effects through multimodal strategies

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