Clinical Considerations for Recommending, Assessing, and Modifying Chronic Pain Treatment

Saturday, September 20, 2008
10:45 AM – 12:00 PM
South San Francisco Conference Center
San Francisco, California

Faculty
Jeffrey Fudin, PharmD
Stratton Veterans Administration Medical Center
Albany, New York

Bill McCarberg, MD
University of California
San Diego, California
Session 3: Clinical Considerations for Recommending, Assessing, and Modifying Chronic Pain Treatment

Learning Objectives

- Discuss unmet needs in pain management and the emerging pharmacological technologies that can lead to improved outcomes in patients with chronic pain.
- Identify the advantages and disadvantages of the current opioid analgesic therapies.

Faculty

**Jeffrey Fudin, PharmD**  
Adjunct Associate Professor  
Albany College of Pharmacy  
Clinical Pharmacy Specialist  
Stratton Veterans Administration Medical Center  
Albany, New York

Dr Fudin is a clinical pharmacy specialist at the Stratton Veterans Administration Medical Center in Albany, New York. He is an adjunct associate professor of pharmacy practice at the Albany College of Pharmacy, and has been an instructor of pharmacology and psychopharmacology at SAGE Graduate School of Nursing for several years. He is CEO and founder of NovaPain Consultants, a private Internet-based pain resource. Dr Fudin is also a clinical pharmacy consultant to Homedical Associates. Dr Fudin received his doctorate of pharmacy from the Albany College of Pharmacy. He is a board-certified diplomate to the American Academy of Pain Management, and a member of several other professional organizations, including the American College of Clinical Pharmacy, the American Society of Health-System Pharmacists, the American Pain Society, and the Phi Delta Chi Pharmaceutical Fraternity. He was a peer reviewer for the recently established American Pain Society Clinical Practice Guidelines for Arthritis, for Fibromyalgia, and for Cancer Pain and Palliative Care. He is a panel member for establishing guidelines for the “Use of Chronic Opioids for Chronic Non-Cancer Pain.” Dr Fudin is a reviewer for publications and poster submissions for both the American College of Clinical Pharmacy (ACCP) and the American Society of Health-System Pharmacists (ASHP). He is a 2-time past chair and founder of the ACCP Pain Pharmacy Practice Network group. Dr Fudin is a medical advisory board consultant member for the Dammiller Memorial Education Foundation (an on-line public service for pain practitioners and patients). He is an active lecturer, writer, and researcher on pain management issues. Dr Fudin has advocated for the adequate and balanced approach of pain management in patients with the disease of addiction.

**Bill H. McCarberg, MD**  
Assistant Clinical Professor (Voluntary)  
University of California at San Diego  
Founder  
Chronic Pain Management Program  
Kaiser Permanente  
San Diego, California

Dr McCarberg is the founder of the Chronic Pain Management Program for Kaiser Permanente in San Diego, California; he specializes in cognitive behavioral management of chronic pain. He obtained his medical degree from Northwestern University, Chicago, Illinois, and completed his residency in family practice at Highland Hospital in Rochester, New York. Dr McCarberg was on the board of directors and the Fibromyalgia Guidelines Committee of the American Pain Society. He is currently president of the Western Pain Society and an assistant clinical professor at the University of California at San Diego School of Medicine. He is a member of the American Academy of Family Physicians, the American Academy of Pain Medicine, the American Pain Society, and the International Association for the Study of Pain. In addition, Dr McCarberg teaches classes on pain management and fibromyalgia syndrome at Kaiser Permanente.

Faculty Financial Disclosure Statements

The presenting faculty reported the following:

Dr Fudin receives honoraria for serving as an advisory board participant for Abbott; he is an advisory board and speakers bureau participant for PriCara and a speakers bureau participant for Alpharma Pharmaceuticals LLC.
Dr McCarberg receives honoraria as a speakers bureau participant for Alpharma Pharmaceuticals LLC; Cephalon, Inc.; Endo Pharmaceuticals; King Pharmaceuticals, Inc.; Eli Lilly and Company; Merck & Co., Inc.; Pfizer Inc.; Pricara; and Purdue Pharma L.P.

Education Partner Financial Disclosure Statements

The ACHL staff members and others involved with the planning, development, and review of the content for this activity have no relevant affiliations or financial relationships to disclose.

**Drug List**

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade</th>
<th>Generic</th>
<th>Trade</th>
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<tbody>
<tr>
<td>ibuprofen</td>
<td>various</td>
<td>morphine</td>
<td>various</td>
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<tr>
<td>aspirin</td>
<td>various</td>
<td>oxycodone</td>
<td>OxyIR, OxyFast</td>
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<td>various</td>
<td>atorvastatin</td>
<td>Lipitor</td>
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<td>ketoprofen</td>
<td>Actron, Orudis, Oruvail</td>
<td>amoxicillin</td>
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<td>fentanyl</td>
<td>Actiq, Duragesic</td>
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<td>oxycodone/acetaminophen</td>
<td>Percocet</td>
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<td>gabapentin</td>
<td>Neurontin</td>
<td>oxycodone/aspirin</td>
<td>Percodan</td>
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<tr>
<td>pregabalin</td>
<td>Lyrica</td>
<td>propoxyphene/acetaminophen</td>
<td>Darvocet-N</td>
</tr>
<tr>
<td>tramadol</td>
<td>Ultram</td>
<td>tramadol(acetaminophen)</td>
<td>Ultracet</td>
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<tr>
<td>propoxyphene</td>
<td>Darvon</td>
<td>omeprazole</td>
<td>Prilosec</td>
</tr>
<tr>
<td>codeine</td>
<td>various</td>
<td>oxycodone ext-rel</td>
<td>OxyContin</td>
</tr>
</tbody>
</table>

**Investigational**

- 12 hour hydrocodone/APAP
- QD tramadols
- Transmucosal fentanyl

**Suggested Reading List**


Fishman SM. Risk of the view through the keyhole: there is much more to physician reactions to the DEA than the number of formal actions. *Pain Med*. 2006;7:360-362; discussion 365-366.


Session 3
Emerging Technologies in the Pharmacological Management of Pain

Jeffrey Fudin, PharmD
Adjunct Associate Professor, Albany College of Pharmacy
Clinical Pharmacy Specialist
Stratton Veterans Administration Medical Center
Albany, New York

Case Study: Visit 1
- 68-year-old man
- Experiencing back pain after lifting something heavy at home
  - Pain for ~2 weeks
- Patient rates pain 7/10
  - Pain interferes with his ability to function
  - Pain disrupts his sleep
- Patient is taking OTC ibuprofen (~1200 mg/day)
  - Pain relief is not adequate
  - Experiencing stomach discomfort

Which benefit of opioid treatment do you perceive to be most important for patients with moderate to moderately-severe pain?

1. Potential decrease in frequency of end-of-dose pain episodes
2. Improved quality of life
3. Stable blood levels with controlled-release formulations
4. Increased patient compliance

What is your greatest concern when dispensing opioids?

1. DEA scrutiny
2. Extensive documentation
3. Potential patient abuse/addiction
4. No concerns

Burden of Pain in the United States
- Unrelieved pain negatively affects quality of life
  - Functional impairment and disability
  - Psychological distress (anxiety, depression)
  - Sleep interruption
- Pain is the most common cause of long-term disability
- Lost work days due to pain are estimated at >50 million days per year
- The annual cost of pain, including medical expenses, lost income, and lost productivity, is an estimated $100 billion

Therapeutic Strategies in Pain Management
- Lifestyle changes
- Rehabilitative
- Psychological
- Complementary and integrative medicine
- Educational
- Pharmacotherapy
- Injection, surgical, neuromodulation
Nonpharmacological Approaches

- Exercise therapy
- Cognitive and behavioral therapy
- Patient education
- Physical and occupational therapy
- Relaxation techniques
- Chiropractic therapy
- Complementary medicine (eg, manipulative techniques, acupuncture, nutraceuticals, yoga, massage)
- Multidisciplinary treatment programs

Recall Case Study: Visit 1

- 68-year-old man
  - Experiencing back pain after lifting something heavy at home
    - Pain for ~2 weeks
  - Patient rates pain 7/10
    - Pain interferes with his ability to function
    - Pain disrupts his sleep
  - Patient is taking OTC ibuprofen (~1200 mg/day)
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Pharmacological Management of Pain

Current Treatment Armamentarium

<table>
<thead>
<tr>
<th>Dosing Interval</th>
<th>Class of Therapeutic Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-6 Hour</td>
<td>Non-opioids</td>
</tr>
<tr>
<td>24 Hour</td>
<td>Combination Opioids</td>
</tr>
<tr>
<td>12 Hour</td>
<td>Single-Agent Opioids</td>
</tr>
<tr>
<td></td>
<td>Antidepressants/Anticonvulsants</td>
</tr>
</tbody>
</table>

Treatment of Mild Pain: NSAIDs

- NSAIDs include aspirin, ibuprofen, naproxen, ketoprofen, non-acetylated salicylates, and COX-2 inhibitors
  - The only COX-2 specific inhibitor currently marketed as such in the US is celecoxib
  - Inhibit pain sensitivity caused by COX-2 at
    - Peripheral site of injury: "peripheral sensitization"
    - Spinal cord: "central sensitization"
  - Do not block transmission of pain

Risks Associated With NSAIDs

- GI toxicity
  - Affects 15% to 30% of NSAID users
- Renal toxicity
  - Can cause renal insufficiency in patients with renal impairment (eg, volume depleted states, severe congestive heart failure, hepatic cirrhosis, dehydration, or intrinsic renal disease)
  - Use with caution in patients with diabetes and patients taking ACE inhibitors
- Association with hypertension
  - ~8% increased risk of hypertension in women taking NSAIDs ≥22 days per month

References:

Cardiovascular Risks Associated With NSAIDs

- 2006 review of 17 case-control and 6 cohort studies
  - 86,193 cases with CV events and 527,236 controls
  - 75,520 COX-2 Inhibitor users; 375,619 nonselective NSAID users; 594,720 controls
- At least 4 studies demonstrating increased risk of MI (RR: 1.52-1.73) with celecoxib were published after this meta-analysis was completed

<table>
<thead>
<tr>
<th>Drug</th>
<th>Relative CV Risk</th>
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<tbody>
<tr>
<td>Celecoxib</td>
<td>1.06 (0.91-1.23)</td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>1.35 (1.15-1.59)</td>
</tr>
<tr>
<td>Rofecoxib (&gt;25 mg/d)</td>
<td>2.19 (1.64-2.91)</td>
</tr>
<tr>
<td>Naproxen</td>
<td>0.97 (0.87-1.07)</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>1.40 (1.16-1.70)</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>1.07 (0.97-1.18)</td>
</tr>
</tbody>
</table>


Acetaminophen (APAP)

- A centrally acting analgesic that increases the pain threshold
- Mechanism of action is not fully known
  - May selectively inhibit a distinct form of COX (COX-3)
  - Most likely has no affinity for the active site of COX, but blocks activity by reducing the active oxidized form of COX to an inactive form
- Indicated to reduce fever and for the temporary relief of minor aches and pains
  - Fewer GI side effects than NSAIDs/COX-2 inhibitors
  - Adverse effects associated with chronic use

Relative CV Risk

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Acetaminophen (Cont’d)

- Relative bioavailability 85% to 98%
- Liver metabolized
  - Conjugation with glucuronide (phase II)
  - Conjugation with sulfate
  - Oxidation via cytochrome P-450 (phase I)
- Low molecular weight and protein binding: passes blood brain barrier

Acetaminophen Dosing Considerations

**Dosing for mild pain:** 325 to 1000 mg PO/PR q4 to 6 hr
- Maximum recommended dose: 1 gram, 4 g24 hr
- 10 g24 hr is dose that can induce toxicity
- Single maximum dose is 5.56 g
- **Renal Impairment:** patients should not exceed 3 g/day for any prolonged period of time, based on evidence by Watkins et al.

**Considerations for the Use of Acetaminophen**

- APAP is one of the most well-tolerated medications available to treat mild pain, when administered appropriately
- Dosing should be adjusted when metabolism of APAP is adversely affected
  - Increased activity of P450 system (nicotine, ethanol, barbiturates, rifampin, carbamazepine, phenytoin, isoniazid, phenobarbital)
  - Decreased glutathione stores
- Chronic alcohol ingestion depletes glutathione stores and also induces P450 system, increasing risk for APAP toxicity

**Other Classes of Analgesic Agents**

- Local anesthetics (Na++ channel block)
- Steroids (prostaglandin and leukotriene inhibition)
- α-2 adrenoceptor agonists
- Anticonvulsants (carbamazepine, gabapentin, and pregabalin, topiramate)
- Antidepressants (tricyclics, MAOIs, SNRIs)
- Opioids
Moderate to Severe Pain: Opioids

Recent meta-analyses have revealed that opioids are effective in the management of moderate to severe pain.

- Chronic noncancer nociceptive and neuropathic pain
  - Meta-analysis of 41 randomized trials (N = 6019)
  - Meta-analysis of 15 randomized trials (N = 1145)
- Noncancer neuropathic pain
  - Meta-analysis of 22 randomized trials (N = 670)

Opioids

- Synthetic phenylpiperidines
  - Meperidine, fentanyl
- Synthetic diphenylheptanes
  - Methadone, propoxyphene
- Phenanthrenes
  - Natural
  - Semi-synthetic
  - Synthetic

Opioid Receptors

- Mu (Endorphin)
- Delta (Enkephalin)
- Kappa (Dynorphin)
  - Mu agonist: morphine, hydromorphone, fentanyl, oxycodone, hydrocodone, codeine, methadone, and meperidine
  - Mixed agonist-antagonist: butorphanol, nalbuphine, pentazocine
  - Partial agonist: buprenorphine

Opioid Receptor Structure

Recent FDA Approved Extended-Release Opioids

- Tramadol ER oral tablet
  - Q24h ER technology
- Oxymorphone ER oral tablet
  - Q12h ER technology
  - Hydrophilic gel matrix with slowly eroding core

Potential Risks of Opioid Use

- Adverse events
  - Constipation, nausea, vomiting, cognitive or functional impairment, pruritus, respiratory depression, sweating, apnea, skeletal muscle rigidity, bradycardia, sedation
- Hyperalgesia (with high doses and prolonged use)
- Dependence, tolerance, withdrawal problems, addiction
Highly Prescribed Products Compared With Opioid Products Commonly Prescribed in the US

Number of Prescriptions (in Millions)

<table>
<thead>
<tr>
<th>Product</th>
<th>Number</th>
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</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>74</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>55</td>
</tr>
<tr>
<td>Hydrocodone/Combo</td>
<td>30</td>
</tr>
<tr>
<td>Oxycodone/Combo</td>
<td>24</td>
</tr>
<tr>
<td>Propoxyphene/Combo</td>
<td>22</td>
</tr>
<tr>
<td>Codeine/Combo</td>
<td>18</td>
</tr>
<tr>
<td>Oxycodone/Fentanyl</td>
<td>13</td>
</tr>
<tr>
<td>Morphine</td>
<td>6</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>2</td>
</tr>
</tbody>
</table>

IMS NPA+, 2006.

“Real World” Multimodal Analgesia: Combination Therapy

Opioids

• Codeine/APAP
• Hydrocodone/APAP
• Hydrocodone/ibuprofen
• Oxycodone/APAP
• Oxycodone/Aspirin
• Propoxyphene/APAP
• Tramadol/APAP

All combination opioid therapies currently available are immediate-release formulations

Analgesic Combinations: Potential Benefits

• Combination analgesics may provide better pain control
• May be possible to use lower doses of individual agents
• May reduce severity of adverse events with each drug

Profile of Currently Available Combination Opioids

<table>
<thead>
<tr>
<th>Agent</th>
<th>Onset Duration of Action Equianalgesic Oral Dose* DEA Sched</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Oxycodone Combs</td>
<td>10-15 mins 4-6 hrs 30 mg† II</td>
</tr>
<tr>
<td>Hydrocodone Combs</td>
<td>30-60 min 4-6 hrs 30 mg† III</td>
</tr>
<tr>
<td>Codeine/Combs</td>
<td>30 min 4-6 hrs 130 mg† III</td>
</tr>
<tr>
<td>Propoxyphene/Combs</td>
<td>15-60 min 4-6 hrs 130 mg† IV</td>
</tr>
<tr>
<td>Tramadol Combs</td>
<td>60 min 6-7 hrs 130 mg† Not sched</td>
</tr>
</tbody>
</table>

*Doses reflect opioid component only and are equianalgesic to 30 mg morphine
†Doses for moderate to severe pain not necessarily equivalent to 30 mg morphine
N/A, not applicable

NSAID Content in Commonly Prescribed Combination Opioid Products

<table>
<thead>
<tr>
<th>Opioid Combination</th>
<th>NSAID/tablet (mg)</th>
<th>Dosing Schedule</th>
<th>Total NSAID/day (mg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxycodone/ASA</td>
<td>325</td>
<td>q4-6hr</td>
<td>1300-1950</td>
</tr>
<tr>
<td>Oxycodone/IBU</td>
<td>400</td>
<td>q4-6hr</td>
<td>1600-2400</td>
</tr>
<tr>
<td>Hydrocodone/ASA</td>
<td>500</td>
<td>q4-6hr</td>
<td>2000-3000</td>
</tr>
<tr>
<td>Hydrocodone/IBU</td>
<td>200</td>
<td>q4-6hr</td>
<td>800-1200</td>
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APAP Content in Commonly Prescribed Combination Opioid Products

<table>
<thead>
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<th>Opioid Combination</th>
<th>APAP/tablet (mg)</th>
<th>Dosing Schedule</th>
<th>Total APAP/day (mg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine/APAP</td>
<td>325</td>
<td>q4-6hr</td>
<td>1200-1800</td>
</tr>
<tr>
<td>Tramadol/APAP</td>
<td>325</td>
<td>q4-6hr</td>
<td>1300</td>
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<tr>
<td>Oxycodone/APAP</td>
<td>325-650</td>
<td>q4-6hr</td>
<td>1300-3900</td>
</tr>
<tr>
<td>Propoxyphene/APAP</td>
<td>325-650</td>
<td>q4-6hr</td>
<td>1300-3900</td>
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<tr>
<td>Hydrocodone/APAP</td>
<td>325-750</td>
<td>q4-6hr</td>
<td>2000-4000</td>
</tr>
</tbody>
</table>


Combination Opioid/APAP Therapy Does Not Increase APAP-Induced ALT Elevations

- 145 healthy adults (18-45 years old), randomized, single-blind, placebo-controlled, inpatient, longitudinal study
- Subjects received either placebo or 4 g/day APAP either alone or in combination with an opioid for 2 weeks
  - 7.5 mg oxycodone
  - 2 mg hydromorphone
  - 15 mg morphine

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Ratio of 2 Median Maximum ALT (95% CI)</th>
<th>P-Value</th>
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</thead>
<tbody>
<tr>
<td>Versus Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APAP</td>
<td>2.78 (1.47-4.09)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Morphine/APAP</td>
<td>2.67 (1.40-3.94)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Oxycodone/APAP</td>
<td>2.57 (1.37-3.77)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Versus APAP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine/APAP</td>
<td>0.96 (0.45-1.47)</td>
<td>NS*</td>
</tr>
<tr>
<td>Oxycodone/APAP</td>
<td>0.93 (0.45-1.41)</td>
<td>NS*</td>
</tr>
</tbody>
</table>

Characteristics of Immediate- and Extended-Release Opioids

**Immediate-release opioids**
- Quick onset of action (within minutes)
- Potential use 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
  - May increase frequency of end-of-dose BTP
- Increased potential for euphoria and adverse effects (peaks)

**Extended-release opioids**
- More stable blood levels
- Potential benefit for persistent acute pain and chronic pain because avoids peaks and troughs
- May reduce frequency of end-of-dose BTP
- Potential for fewer side effects (lower peaks)
- May decrease pain-related sleep interference
- Potential improvement in compliance and quality of life

Opioid Formulations in Development

- Extended-release combination opioids
  - 12-hour hydrocodone/APAP
- Tamper-resistant opioid formulations
  - Extended-release oxycodone
- Improved effectiveness/side effects profile formulations
  - Morphine + naloxone
- Abuse deterrent-sequestered naltrexone
  - Oxycodone + naltrexone
- Centrally acting analgesic with dual mode of action
  - Tapentadol

Summary

- Pain is prevalent in the US, and unrelieved pain is associated with significant adverse physical, psychosocial, and financial consequences
- Acetaminophen and NSAIDs, including COX-2 inhibitors, are useful for treating mild pain; however, careful monitoring of adverse events is required, particularly when these agents are used in high doses and/or to treat chronic pain
- Opioids are efficacious agents used as therapy for moderate to severe acute and chronic pain; however, careful patient selection and ongoing risk assessment are important, as well as monitoring adverse events (eg, constipation and sedation) associated with opioid administration
- Opioid combination therapy can provide effective pain control and may allow for lower doses of each agent to be used (less risk for adverse events)

Advances in Combination Opioid Therapy: New Strategies for Chronic Pain Management

Bill McCarberg, MD
Assistant Clinical Professor (Voluntary)
University of California School of Medicine
Founder, Chronic Pain Management Program
Kaiser Permanente
San Diego, California
Recall Case Study: Visit 1

- 68-year-old man
- Experiencing back pain after lifting something heavy at home
  - Pain for ~2 weeks
- Patient rates pain 7/10
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  - Pain disrupts his sleep
- Patient is taking OTC ibuprofen (~1200 mg/day)
  - Pain relief is not adequate
  - Experiencing stomach discomfort

Case Study: Visit 2

- During visit 1, physician recommended physical therapy for the patient and prescribed naproxen (500 mg) with omeprazole
- 4 weeks later
  - Physical therapy was not successful in reducing pain
  - No adequate pain relief with naproxen
  - Patient experiencing abdominal pain
- Physician assesses risk of addiction
- Physician prescribes hydrocodone/acetaminophen, 1 to 2 tablets prn

Case Study: Visit 2 Cont’d

- 4 weeks later, patient is better, functional due to pain relief
  - End-of-dose breakthrough pain
  - Sleep disrupted
  - No adverse effects
- Physician documents
  - Pain level
  - Function level
  - Addiction risk for this patient
- Physician prescribes extended-release opioid formulation
  - Bowel regimen

Goals of Therapy for Chronic Pain

- Enhance function
- Reduce pain
- Enhance psychosocial well-being
- Minimize adverse outcomes and costs

Impact of Pain on Physicians’ Practice

- Pain is difficult to manage and patient compliance is suboptimal

Opioids for the Treatment of Chronic Pain

- Opioid use for chronic pain is supported by multiple societies
  - American Society of Anesthesiologists
  - American Academy of Pain Medicine
  - American College of Physicians
  - American Pain Society
- Benefits of opioids
  - Effective in wide and long-term clinical usage
  - Wide variety of formulations, dosage strengths
Extended-Release Opioids May Be Better Suited for Treatment of Chronic Pain

- Extended-release opioids may have greater utility than immediate-release opioids in treating chronic pain patients
  - Fewer peaks = less risk for overmedication, side effects, euphoria
  - Fewer troughs = less end-of-dose breakthrough pain

Immediate-release

Extended-release

Serum Level

Dose

Time

No Relief

Pain Relief

Toxic

Controlled-Release Opioids Are Effective Therapy for Chronic Osteoarthritis Pain

- OXCD CR (20 mg) was significantly more effective than placebo in reducing mean pain intensity (at 1 and 2 weeks and overall)

12-Hour Extended-Release Hydrocodone/APAP*: Single-Dose Pharmacokinetics

- AUC with single dose of HC/APAP CR (15 mg/500 mg; 2 tabs)

Efficacy of HC/APAP CR* as a Treatment for Chronic Low Back Pain (CLBP)

- 1 and 2 tablets of HC/APAP CR* provided significantly greater CLBP pain relief versus placebo

Impact of Chronic Pain on Daily Activities

- Patients with chronic pain reported reduced ability to participate in or enjoy activities
Extended-Release Pain Medications: Effects on Pain-Related Work Productivity and Activity Impairment

- HC/APAP CR\(^a\) improved work productivity after 24 and 56 weeks of treatment

![Graph showing mean change from baseline in work productivity over weeks](image)

\(^a\)HC/APAP CR is an unapproved product


Relationship Between Insomnia and Pain

- Significant inter-relationship between insomnia and pain
- Sleep disturbances can predict later pain
- Pre-existing pain can predict subsequent insomnia
- Sleep disturbances can decrease ability to cope with pain

![Diagram showing relationship between pain and sleep](image)


Impact of Chronic Pain on Sleep

- Chronic pain negatively impacts sleep quality

![Graph showing mean time spent in sleep parameters](image)


Extended-Release Pain Medications: Pain Relief Associated With Improved Sleep in Patients With Chronic OA Pain

- Least squares mean change in sleep parameters averaged over 12 weeks

![Graph showing mean improvement in sleep parameters](image)


Extended-Release Pain Medications: Improved Sleep Quality Compared With Placebo in Patients With Chronic OA Pain

- Controlled-release oxycodone was superior to placebo for improving quality of sleep

![Graph showing mean global quality of sleep](image)


Extended-Release Pain Medications: Effects On Pain Intensity, Pain-Related Physical Function, and Sleep

- HC/APAP CR\(^a\) was effective in providing pain relief and decreased pain-related interference in general activity, walking ability, and sleep

![Graph showing mean improvement in pain and sleep parameters](image)


\(^a\)HC/APAP CR is an unapproved product
Practical Considerations for Chronic Opioid Therapy

- Opioids may be considered for patients with moderate to severe chronic pain, but
  - Is there a medical necessity?
  - Have reasonable alternatives been considered?
  - What is the risk/benefit analysis?
  - Responsible and compliant with the treatment plan?

Opioid Rotation

- Switching a chronic pain patient from one opioid to another
  - Reported to provide more effective analgesia
    - Interpatient variability of response
    - Incomplete cross-tolerance
  - Indications for opioid rotation
    - Poorly controlled pain with inability to increase dose due to side effects
    - Adverse event or toxicity with current opioid
    - Rapid development of tolerance
    - Development of opioid hyperalgesia

Managing Opioid Side Effects

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>Increase fluid intake; use of cathartics, stool softeners, enemas, and nonopioid analgesics</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>Switch opioid; use antiemetics</td>
</tr>
<tr>
<td>Sedation</td>
<td>Lower dose; add stimulants</td>
</tr>
<tr>
<td>Itching</td>
<td>Switch opioid; antihistamines</td>
</tr>
<tr>
<td>Edema and sweating</td>
<td>Switch opioids</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Antivertiginous agents</td>
</tr>
<tr>
<td>Confusion</td>
<td>Titrate dose; switch opioid; add neuroleptic</td>
</tr>
<tr>
<td>Endocrine dysfunction</td>
<td>Endocrine monitoring, testosterone replacement</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>Switch opioids</td>
</tr>
<tr>
<td>Risk of falling for the elderly</td>
<td>Lower dose; use nonopioid analgesics</td>
</tr>
</tbody>
</table>

Compliance Monitoring

- Written documentation
- Frequent visits and small quantities (month’s supply)
- One pharmacy; pill counts; no replacements or early scripts
- Urine drug screen
- Complete medical records
- Required contact with other treating clinicians
- Required consultation with other specialists

Medico-Legal Considerations in the Treatment of Pain
Case Study: Continued

- During visit 3, physician prescribed controlled-release opioid formulation
- Physician’s disgruntled business partner reports the physician to the state medical board
- Doctor writes letter with support documents showing
  - History and physical evaluation
  - Treatment plan
  - Informed consent and agreement for treatment
  - Periodic review
  - Consultations and referrals
- No action taken against physician by board

Physician Concerns When Prescribing Opioids

- Worry about potential adverse effects like nausea, vomiting, constipation, sedation, and respiratory depression
- Lack of comfort about appropriate opioid dosing and administration regimens
- Fear of regulatory scrutiny
- Concern about physical dependence, tolerance, and addiction
- Increasing reports of prescription drug abuse

Variability of Substance Abuse and Aberrant Behaviors in Patients Receiving Prescription Opioids

- Recent meta-analysis examined prevalence of substance use disorders and aberrant drug-taking behaviors in patients receiving opioid medications for chronic back pain
  - Prevalence of current substance use disorders: 3%-43%
  - Prevalence of aberrant drug-taking behaviors: 5%-24%

DAWN* Mentions Per 1000 Prescriptions Dispensed: Account for Opioid Availability

Adolescent Use of Opioids Without a Prescription (*Generation Rx*)

- Teens Who Have Ever Tried:
  - Morphine: 19%
  - Oxycodone: 50%
  - Hydrocodone Combos: 18%
  - Hydromorphone: 37%
  - Methadone: 36%
  - Ketamine: 15%
  - Baclofen: 5%
  - Add: 2%
  - Others: 1%

- Rx Drug-Availability: 68%
  - 18% very easy to get

- Rx Drug-Friends’ Use: 59%
  - 37% have close friends who use

- Reasons for Nonmedical Use of Prescription Pain Medications According to Gender
  - 59% for pain
  - 37% for sleep
  - 29% for anxiety
  - 20% for depression
  - 18% for relaxation
  - 12% for cough
  - 7% for headaches

*DAWN, Drug Abuse Warning Network

Source: Partnership for Drug-Free Kids (PDF) at 1-800-729-SAFE or www.pdkids.org, 2004; Partnership Attitude Tracking Study (PATS) of 7,300 teenagers (margin of error: +/- 1.5 percent) , Released April 2005.

Nearly 50% of teens believe Rx drugs are “much safer” than street drugs.

Reasons for Nonmedical Use of Prescription Pain Medications According to Gender

- Over 60% of teens believe Rx drugs are much safer than street drugs.

Girls (n = 126)
Boys (n = 58)

Relieves Pain
Helps Me Sleep
Decreases Anxiety
Gives High
Counter-Acts Other Drugs
Safer Than Street Drugs
Experimen-tation
I’m Addicted

Percentage, %

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What Steps Can Be Taken to Minimize Abuse and Diversion?

• Counsel the public on how to properly safeguard and discard unused pills
  – Track pills
  – Safeguard pills
  – Properly discard pills
    - Unused prescription pills should be disposed of in the trash, not in the toilet

Importance of Medical Record Documentation

• Poor medical record documentation is a common cause of problems before licensing boards, and this can be corrected
  - Medical record documentation must cover 5 areas
    - History and physical evaluation of the patient
    - Treatment plan
    - Informed consent and agreement for treatment
    - Periodic review
    - Consultations and referrals

Summary

• The goal of any therapy for the management of chronic pain is to optimize positive outcomes and reduce potential risks
• Opioid combination therapies and extended-release opioid formulations offer important advantages for the treatment of chronic pain
• There is a difference among physical dependence, tolerance, and addiction
• Compliance with controlled substance laws and regulations and accurate medical documentation are critical strategies for physicians to appropriately manage chronic pain and avoid unwarranted DEA scrutiny
• Safe and effective management of chronic pain with opioid therapy requires comprehensive assessment and continuous monitoring of both the pain state and the patient

Which benefit of opioid treatment do you perceive to be most important for patients with moderate to moderately-severe pain?

1. Potential decrease in frequency of end-of-dose pain episodes
2. Improved quality of life
3. Stable blood levels with controlled-release formulations
4. Increased patient compliance

After seeing today's presentation, what is your greatest concern when dispensing opioids?

1. DEA scrutiny
2. Extensive documentation
3. Potential patient abuse/addiction
4. No concerns