Implementing and Monitoring Treatment in Chronic Pain: Improving Symptoms and Quality of Life

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Radisson Hotel at Los Angeles Airport
Los Angeles, California

Faculty
Perry Fine, MD
University of Utah
Salt Lake City, Utah

Gerald Sacks, MD
Pain Institute of Santa Monica
Santa Monica, California

Session 2: Implementing and Monitoring Treatment in Chronic Pain: Improving Symptoms and Quality of Life

Learning Objectives

- Identify advantages and disadvantages of current opioid analgesic therapies to optimize treatment for those patients most likely to benefit from opioid therapy.
- Examine how emerging technologies, including extended-release/long-acting agents, may lead to improved outcomes in patients with acute or chronic pain.

Faculty

Perry G. Fine, MD
Professor
Department of Anesthesiology
Pain Research and Management Centers
University of Utah, School of Medicine
Salt Lake City, Utah

Perry G. Fine, MD, is professor in the Department of Anesthesiology at the University of Utah School of Medicine. He also currently serves on the faculty in the Pain Research Center and is an attending physician in the Pain Management Center. Dr Fine received his medical degree from the Medical College of Virginia in Richmond, Virginia. He served an internship at the Community Hospital of Sonoma County in Santa Rosa, California and completed his residency at the University of Utah Health Sciences Center in Salt Lake City, Utah. In addition, Dr Fine completed a fellowship at the Smythe Pain Clinic of the University of Toronto in Ontario, Canada.

Dr Fine currently serves on the Board for Directors of the American Academy of Pain Medicine, the Society for Arts in Healthcare, and the American Pain Foundation. He has also served as the chair of the National Initiative on Pain Control from 2003 to 2008. Dr Fine is widely published in the fields of pain management and end-of-life care. He serves on the editorial boards of several peer-reviewed medical journals. Dr Fine is the recipient of the 2007 American Academy of Hospice and Palliative Medicine Distinguished Hospice Physician Award and the 2008 American Pain Society John and Emma Bonica Public Service Award.

Gerald M. Sacks, MD
Director of Pain Management
Saint John's Health Center
Pain Institute of Santa Monica
Santa Monica, California

Gerald M. Sacks, MD, is director of Pain Management at Saint John's Health Center and Director of Pain Management at the Pain Institute of Santa Monica, both located in Santa Monica, California. He received his medical degree from the University of Massachusetts Medical School in Worcester. Dr Sacks completed his residency training in orthopedic surgery at Grady Memorial Hospital in Atlanta, Georgia and in anesthesiology and critical care at the University of Chicago Hospitals and Clinics in Chicago, Illinois. After completing residency training, Dr Sacks received fellowship training in pain management at Brigham and Women's Hospital in Boston, Massachusetts. He is currently board certified in anesthesiology.

Faculty Financial Disclosure Statements

The presenting faculty reported the following
Dr Fine is an advisor for Abbott and Ortho-McNeil/PriCara and a consultant/advisor for Cephalon, Inc. He receives honoraria as a speakers bureau participant for Eli Lilly and Company, Ortho-McNeil, PriCara, and Wyeth.
Dr Sacks receives speaker honoraria from Abbott; Acorda; Alpharma; King Pharmaceuticals, Inc.; Eli Lilly and Company; Pfizer Inc.; and Wyeth Pharmaceuticals.

Education Partner Financial Disclosure Statements

The content collaborators at ACHL have reported the following
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

Generic	Trade
ibuprofen	*various*
aspirin	*various*
naproxen	*various*
ketoprofen	Ketoprofen, Actron, Orudis, Oruvail
celecoxib	Celebrex
rofecoxib	Vioxx
diclofenac	Voltaren
acetaminophen	*various*
gabapentin	Neurontin
pregabalin	Lyrica
tramadol	Ultram
propoxyphene	Darvon
codeine	*various*
morphine	*various*
oxycodone	OxyIR, OxyFast
atorvastatin	Lipitor
amoxicillin	Amoxil
fentanyl	Actiq, Duragesic
codeine/acetaminophen	Tylenol #3
hydrocodone/ acetaminophen	Vicodin/ES/HP, Anexsia, Co-Gesic, Lortab
hydrocodone/ibuprofen	Repraxain, Vicoprofen
oxycodone/ acetaminophen	Percocet
oxycodone/aspirin	Percodan
propoxyphene/ acetaminophen	Darvocet-N
tramadol/acetaminophen	Ultracet
omeprazole	*various*
oxycodone CR	OxyContin

Investigational

12 hour hydrocodone/APAP
QD tramadols
transmucosal fentanyl
sublingual fentanyl
oxycodone ER
oxycodone IR

Suggested Reading List

Audette JF, Nicholson BD, Stanos SP. Management of chronic pain syndromes; issues and interventions. *Pain Med.* 2005;6:S1-S21.

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.

Forbes JA, Bates JA, Edquist IA, et al. Evaluation of two opioid-acetaminophen combinations and placebo in postoperative oral surgery pain. *Pharmacotherapy.* 1994;14:139-146.

Furlan AD, Sandoval JA, Mailis-Gagnon A, et al. Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. *CMAJ.* 2006;174:1589-1594.

Gourlay DL, Heit HA, Almahrezi A. Universal precautions in pain medicine: a rational approach to the treatment of chronic pain. *Pain Med.* 2005;6:107-112.

Højsted J, Sjögren P. Addiction to opioids in chronic pain patients: A literature review. *Eur J Pain.* 2006.

Kehlet H, Dahl JB. The value of "multimodal" or "balanced analgesia" in postoperative pain treatment. *Anesth Analg.* 1993;77:1048-1056.

McCarberg B. Balancing patient needs and provider responsibilities in the use of opioids. *P & T Digest.* 2005;30:32-38.

McCarberg BH, Barkin RL. Long-acting opioids for chronic pain: pharmacotherapeutic opportunities to enhance compliance, quality of life, and analgesia. *Am J Ther.* 2001;8:181-186.

Nicholson B. Responsible prescribing of opioids for the management of chronic pain. *Drugs.* 2003;63:17-32.

Portenoy RK. Chronic opioid therapy in nonmalignant pain. *J Pain Symptom Manage.* 1990;5:S46-62.

Reuben SS, Connelly NR, Maciolek H. Postoperative analgesia with controlled-release oxycodone for outpatient anterior cruciate ligament surgery. *Anesth Analg.* 1999;88:1286-1291.

Stanos S, Houle TT. Multidisciplinary and interdisciplinary management of chronic pain. *Phys Med Rehabil Clin N Am.* 2006;17:435-450, vii.

Turturro MA, Paris PM, Larkin GL. Tramadol versus hydrocodone-acetaminophen in acute musculoskeletal pain: a randomized, double-blind clinical trial. *Ann Emerg Med.* 1998;32:139-143.

Zacny J, Bigelow G, Compton P, et al. College on Problems of Drug Dependence taskforce on prescription opioid non-medical use and abuse: position statement. *Drug Alcohol Depend.* 2003;69:215-232.

Notes

Advances in Combination Opioid Therapy: New Strategies for Acute Pain

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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 prescribing opioids? ?

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

Which of the following risk management tools do you use most in your practice? ?

1. Written consent/treatment agreements
2. Patient guidelines on proper disposal of unused pills
3. Patient risk assessment tools (eg, SOAPP, ORT, CAGE)
4. Physician guidelines on minimization of abuse and diversion of prescription opioids
5. Urine screening
6. None

Introduction to Pain Management in the Decade of Pain

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

Brookoff D. *Hosp Pract*. 2000;35:45-52.
National Pain Survey, Conducted for Ortho-McNeil Pharmaceutical;1999.
National Institutes of Health, The NIH guide: New directions in pain research I. Washington, DC: GPO;1998.

Primary Care Providers Are the Point of Care for Patients

- Primary care providers typically manage the relationship with their pain patients
  - Multiple, repeated exposures to patients
  - See patients in crisis
  - Aware of coping mechanisms
  - Know family members
- Primary care providers may be unable to refer pain patients due to shortage in pain specialists
  - Only 6 board certified pain specialists for 100 000 patients
  - Pain specialists are generally located in urban or university settings, with fewer of these physicians available in the rural populations
- Even after referral to a pain specialist, primary care providers are still responsible for the ongoing management of their patients' medical needs

McCarberg BH. *Pain Med News*. 2004;2:6.
Breuer B, et al. *J Pain*. 2007;8:244-250.

Defining Acute and Chronic Pain

PAIN
"An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."

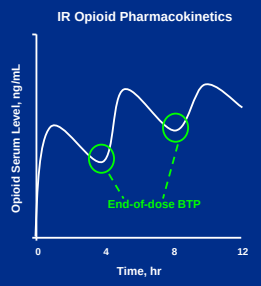
ACUTE: Symptom of Disease
- Brief in duration
- Typically follows body injury or operation
- Disappears when injury heals

CHRONIC: Disease Process
- Longer in duration (months to years)
- Persists beyond usual course of an acute condition or expected time for injury to heal
- May appear in the absence of identifiable organic pathology or be considered excessive for the degree of pathology identified

International Association for the Study of Pain website. Available at: http://www.iasp-pain.org/terms-p.html. Accessed August 9, 2006.
Gruener D. *Pain Control in the Primary Care Setting*. Glenview, IL: American Pain Society. 2006.

End-of-Dose Breakthrough Pain (BTP)

- End-of-dose pain must be differentiated from incident and idiopathic BTP episodes
  - More gradual onset of intensity
  - Longer duration
  - Linked to dissipating analgesic effect
- Adjusting analgesia to avoid troughs is critical to obviate end-of-dose BTP
  - Increasing dose or shortening dosing interval may overmedicate
  - Switching to extended-release formulation will reduce the frequency of end-of-dose BTP



Bennett D, et al. *Pharm Ther*. 2005;30:296-301.
McCarberg BH, Barkin RI. *Amer J Ther*. 2001;8:181-186.

Therapeutic Strategies in Pain Management

- Lifestyle changes
- Rehabilitative
- Psychological
- Complementary and integrative medicine
- Educational
- Pharmacotherapy
- Injection, surgical, neuromodulation

Fine PG, Portenoy RK. *A Clinical Guide to Opioid Analgesia*. Minneapolis, MN: McGraw-Hill; 2004.

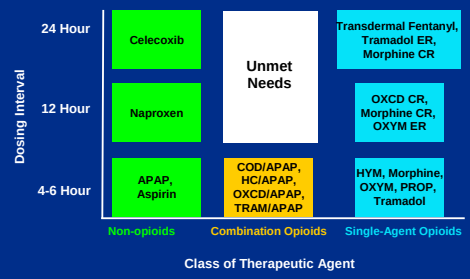
Nonpharmacological Approaches

- 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

van Tulder, et al. *Best Pract Res Clin Rheumatol*. 2002;16:761-775.
Cherkin DC, et al. *N Eng J Med*. 1998;339:1021-1029.
Schaeffer SD, et al. *Am J Nurs*. 2004;104:75-82.
Deyo, et al. *N Engl J Med*. 2001;344:363-370.

Pharmacological Management of Pain

Current Treatment Armamentarium



Treatment of Mild Pain: NSAIDs

- NSAIDs include aspirin, ibuprofen, naproxen, ketoprofen, non-acetylated salicylates, and COX-2 inhibitors
  - The only COX-2 inhibitor currently available 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
  - Ceiling effect: increase in dose does not increase analgesia but increases the risk of adverse effects
  - Drugs blocking transmission of pain (eg, local anesthetics and opioids) must often be added to achieve pain control
- Some NSAIDs may be associated with increased risk of cardiovascular disease

Mild Pain: 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**

Roberts LJ II, et al. In: Hardman JG, et al, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 2001:703-705.
Lucas R, et al. *FASEB J*. 2005;19:635-637.

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
- Counseling patients: APAP in OTC products
  - Regular-strength APAP products commonly contain 325 mg/tablet
  - Extra-strength APAP products commonly contain 500 mg/tablet
  - Sinus cold medications commonly contain 325 to 500 mg APAP/tablet
  - Sleep aid products commonly contain 500 mg APAP/tablet

Roberts LJ II, et al. In: Hardman JG, et al, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 2001:703-705.

Other Classes of Analgesic Agents

- Local anesthetics (Na^+ channel block)
- Steroids (prostaglandin and leukotriene inhibition)
- α-2 adrenoceptor agonists
- Anticonvulsants (carbamazepine, gabapentin, and pregabalin)
- Antidepressants (tricyclics, MAOIs, serotonin reuptake inhibition)
- Opioids

Tremont-Lukats IW, et al. *Anesth Analg*. 2005;101:1738-1749.
Bigat Z, et al. *Anesth Analg*. 2006;102:605-609.
Khan ZP, et al. *Anaesthesia*. 1999;54:146-165.
Gilron I. *Can J Anaesth*. 2006;53:562-571.
Mico JA, et al. *Trends Pharmacol Sci*. 2006;27:348-354.
Lynch ME. *J Psychiatry Neurosci*. 2001;26:30-36.
Furlan AD, et al. *CMAJ*. 2006;174:1589-1594.

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)

Furlan AD, et al. *CMAJ*. 2006;174:1589-1594.
Kalso E, et al. *Pain*. 2004;112:372-380.
Eisenberg E, et al. *JAMA*. 2005;293:3043-3052.

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

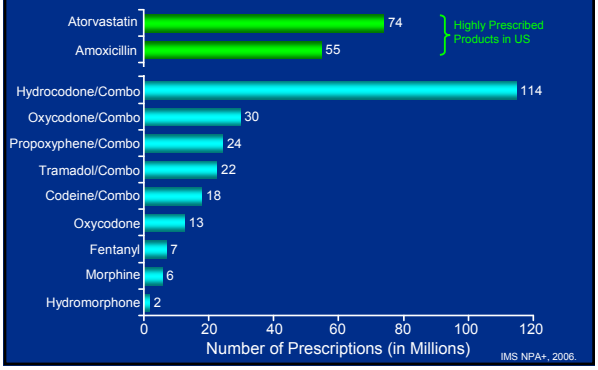
Gutstein HB, Akil H. Opioid analgesics. In: Hardman JG, et al. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 10th ed. New York: McGraw Hill; 2001:569-619.

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

Overview of Opioids: Current Landscape for Combination Opioid Therapy

Highly Prescribed Products Compared with Opioid Products Commonly Prescribed in the US



"Real World" Multimodal Analgesia: Combination Therapy

Opioids

\+

NSAIDs, COX-2 inhibitors, acetaminophen, nerve blocks

- Codeine/APAP
- Hydrocodone/APAP
- Hydrocodone/Ibuprofen
- Oxycodone/APAP
- Oxycodone/Aspirin
- Propoxyphene/APAP
- Tramadol/APAP

All combination opioid therapies currently available are immediate-release formulations

Profile of Currently Available Combination Opioids

Agent	Onset	Duration of Action	Equianalgesic Oral Dose*	DEA Sched
N/A‡	N/A	N/A	N/A	N/A
Oxycodone Combos	30 min	4-6 hrs	30 mg†	II
Hydrocodone Combos	30-60 min	4-6 hrs	30 mg	III
Codeine Combos	30-60 min	4-6 hrs	130 mg	III
Propoxyphene Combos	30-60 min	4-6 hrs	130 mg	IV
Tramadol Combos	60 min	6-7 hrs	100 mg	Not sched

*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
‡NA, not applicable

Gutstein HB, Akil H. Opioid analgesics. In: Hardman JG, et al. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 10th ed. New York: McGraw Hill; 2001:569-619.
www.musc.edu/pharmacyservices/medusepol/opiodanalgesicfinal.pdf.

APAP Content in Commonly Prescribed Combination Opioid Products

Opioid Combination	APAP/tablet (mg)	Dosing Schedule	Total APAP/day (mg/day)
Codeine/APAP	325	q4-6hr	1300-2000
Tramadol/APAP	325	q4-6hr	1300
Oxycodone/APAP	325-650	q4-6hr	1300-3900
Propoxyphene/APAP	325-650	q4-6hr	1300-3900
Hydrocodone/APAP	325-750	q4-6hr	1300-4500

Characteristics of Immediate- and Extended-Release Opioids

Immediate-release opioids

- Quick onset of action
- 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 (trough) breakthrough pain
  - 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 lower incidence of side effects (fewer peaks)
- May decrease pain-related sleep interference
- Potential improvement in compliance and quality of life

McCarberg BH, Barkin RI. *Amer J Ther*. 2001;8:181-186.

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 deterrence-sequestered naltrexone
  - Oxycodone + naltrexone

Cepeda MS et al. *Pain*. 2004;107:41-46.
Maxwell LG et al. *Anesth Analg*. 2005;100:953-958.
Gilderman L et al. Presented at: Annual Meeting of the American Pain Society; May 3-6, 2006; San Antonio, Tx.
Webster L et al. Presented at: Annual Meeting of the American Pain Society; May 3-6, 2006; San Antonio, Tx.

Emerging Strategies for the Treatment of Moderate to Moderately-Severe Acute Pain

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)
  - Pain relief is not adequate
  - Experiencing stomach discomfort

Case Study: Visit 2

- During visit 1, no signs of serious underlying pathology, conservative treatment indicated: 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 substance misuse, abuse, and addiction
- Physician prescribes hydrocodone/acetaminophen, 1 to 2 tablets prn

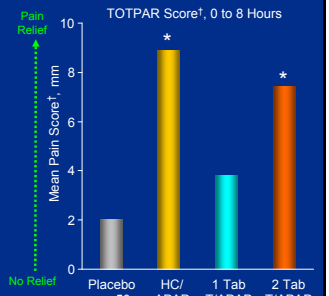
Goals of Therapy for Acute Pain

- Provide rapid and effective analgesia
- Maintain and restore quality of life
  - Functional abilities and physical and psychosocial well-being
- Treat the cause of the pain
- Minimize risk of adverse outcomes
- Reduce potential to progress to chronic pain

Fields HL, et al. In: *Harrison's Principles of Internal Medicine*. 1998:53-58.
American Society of Anesthesiologists Task Force. *Anesthesiology*. 2004;100:1573-1581.
Reuben SS, et al. *Reg Anesth Pain Med*. 2006;31:6-13.

Comparison Between Hydrocodone/APAP and Tramadol/APAP for Treatment of Postoperative Pain

- HC/APAP and 2 tablets of T/APAP provided effective analgesia compared with placebo for the treatment of postoperative dental pain

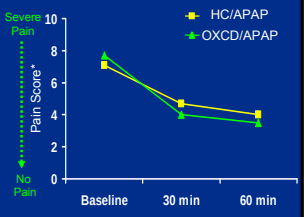


*P<.001 versus placebo
†TOTPAR = Time interval weighted sum of pain relief; Higher score indicates greater pain relief

Fricke JR, et al. *Clin Ther*. 2002;24:953-968.

Comparison of Hydrocodone/APAP and Oxycodone/APAP for Acute Pain

- HC/APAP and OXCD/APAP have similar analgesic effects in the first hour of treatment for severe acute pain
- Palangio et al (2000, 2002) demonstrated similar efficacy between HC/IBU and OXCD/APAP in reducing daily pain scores in patients with moderate to severe acute low back pain or postoperative pain

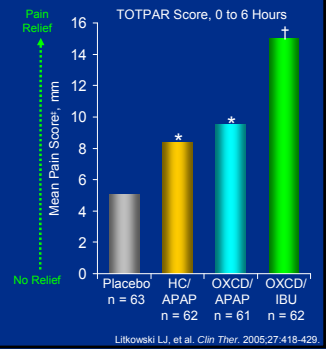


*0 = No pain; 10 = Worst pain imaginable

Marco CA, et al. *Acad Emerg Med*. 2005;12:282-288.
Palangio M, et al. *Clin Ther*. 2002;24:87-99.
Palangio M, et al. *Clin Ther*. 2000;22:600-612.

Comparison Among Combination Opioids for Treatment of Postoperative Pain

- All combination opioids provided greater analgesia compared with placebo
- OXCD/IBU provided greater pain relief compared with the other combination opioids



*P<.002 versus placebo
†P<.001 versus all other treatments
‡Higher score indicates greater pain relief

Litkowski LJ, et al. *Clin Ther*. 2005;27:418-429.

Comparison of Adverse Effects of Propoxyphene/APAP and Other Opioid Combinations

Opioid Combinations	Serious Adverse Effects
Propoxyphene/APAP	Severe CNS, cardiac, and respiratory depression, elevated seizure risk with moderate doses due to accumulation of metabolite
Oxycodone/APAP	Respiratory depression*
Hydrocodone/APAP	Respiratory depression*
Tramadol/APAP	Increased seizure risk

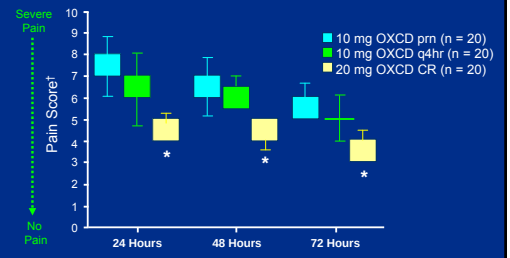
*With inappropriate dosing and/or drug interactions

- **"The side effects, adverse effects, and drug interactions precipitated by [propoxyphene/APAP] far outweigh any therapeutic benefits that may be perceived by administration of this agent."**
  - Robert Barkin, PharmD

Barkin RL, et al. *Am J Ther*. 2006;13:534-542.

Efficacy of Extended-Release Opioids for the Treatment of Acute Pain

- Among opioid formulations, extended-release opioids were associated with the lowest pain scores at each time interval postoperatively compared with immediate-release opioids

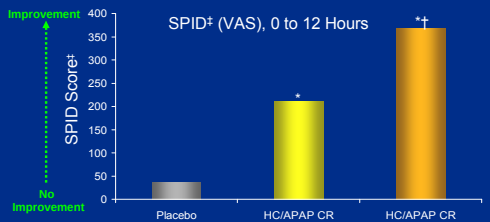


*P<.0001 for OXCD CR versus prn and q4hr
†0 = No pain; 10 = Worst pain imaginable

Reuben SS, et al. *Anesth Analg.* 1999;88:1286-1291.

Efficacy of Extended-Release Hydrocodone/APAP Combinations for Pain Relief After Bunionectomy

- 1 and 2 tablets HC/APAP CR§ provided significant pain relief compared with placebo, and 2 tablets of HC/APAP CR were more effective than 1 tablet of HC/APAP CR

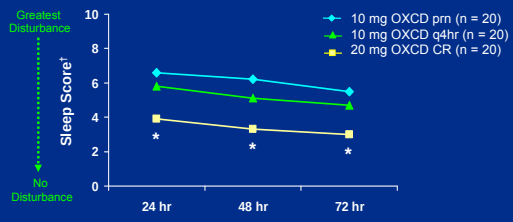


*P<.001 versus placebo
†P<.001 versus HC/APAP CR 1 tablet
‡Time weighted sum of pain intensity difference; higher score indicates greater improvement in pain
§HC/APAP CR is an unapproved product

Golf M, et al. *Am Acad Pain Med.* 2008;Abstract 164.

Efficacy of Extended-Release Opioids on Sleep in Patients With Acute Pain

- Among opioid formulations, extended-release opioids were associated with the least sleep disturbance at each time interval postoperatively compared with immediate-release opioids



*P<.0001 for OXCD CR versus prn and q4hr
†Patients rated sleep disturbance on a numerical scale
0 = No sleep disturbance; 10 = Greatest sleep disturbance

Reuben SS, et al. *Anesth Analg.* 1999;88:1286-91.

Summary

- 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)
- Opioid combination therapies are effective for the treatment of acute pain
  - All combination opioids are currently only available as immediate-release agents
- Extended-release opioids may offer important advantages over immediate-release opioids for the treatment of acute pain
  - Stable pain relief
  - Less sleep disturbance

Emerging Options for Chronic Pain Management

Gerald Sacks, MD
Director of Pain Management
Saint John's Health Center
Pain Institute of Santa Monica,
Santa Monica, California

Case Study: Visit 3

- During visit 2, physician prescribed 1 to 2 tablets hydrocodone/acetaminophen prn for this patient
- 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

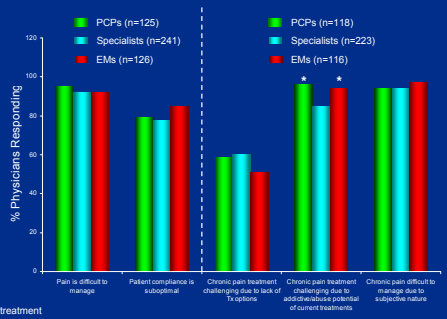
Goals of Therapy for Chronic Pain

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

Marcus DA. *Postgrad Med*. 2003;113:49-60.
American Society of Anesthesiologists Task Force. *Anesthesiology*. 1997;86:995-1004.

Impact of Pain on Physicians' Practice

- Pain is difficult to manage and patient compliance is suboptimal



Tx refers to treatment
*P<.05 versus specialists

McCarberg BH, et al. *Am J Ther*. 2008;15:312-320.

Four Steps in the Management of Chronic Pain

- Assess patient
- Determine course of treatment
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Patient Assessment

- Type of pain and pain intensity
- Mood and personality
- Psychopathology
- Coping
- Quality of life and daily functioning
- Opioid risk assessment

Patient Assessment: Type of Pain and Pain Intensity

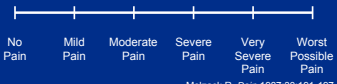
McGill Pain Questionnaire

Includes drawing of body to identify location of pain and intensity

Faces Pain Rating Scale

Visual Analog Scale

Verbal Rating Scale of Pain Intensity



Melzack R. *Pain*.1987;30:191-197.
Adapted from Chambers C, et al. *Pain*. 1999;83:25-35.
Seymour RA. *Eur J Clin Pharmacol*. 1982;23:441-444.
Sriwatanakul K, et al. *Clin Pharmacol Ther*. 1982;32:143-148.

Patient Assessment: Quality of Life and Daily Functioning

- Physical
  - Pain, discomfort, energy, fatigue, sexual activity, sleep
- Psychological
  - Positive and negative feelings, cognitive, self-esteem, appearance
- Level of independence
  - Mobility, daily activities, dependence on medication, work, communication

Skevington SM. *Pain.* 1998;76:395-406.

Patient Assessment: Opioid Risk Management

- SOAPP
  - Screener and Opioid Assessment for Patients in Pain
- ORT
  - Opioid Risk Tool
- DAST-20
  - Drug Abuse Screening Test
- CAGE Screening for Alcoholism
  - **C**ut down on drinking – have tried repeatedly without success
  - **A**nnoyed by criticism about drinking habits
  - **G**uilty feelings about drinking
  - **E**ye opener drink needed in the morning

Butler et al. *Pain.* 2004;112:65.
Webster, Webster. *Pain Med.* 2005;6:432.
Skinner HA, et al. *Addict Behav.* 1982;7:363-371.
Gavin DR, et al. *Br J Addict.* 1989;84:301-307.
Mayfield D, et al. *Am J Psychiatry.* 1974;131:1121-1123.
Ewing JA. *JAMA.* 1984;252:1905-1907.

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Individualized Treatment Plan and Education of Patients

- Involve the patient in building and implementing an individualized care plan
  - Assess the patient's understanding of the disease and the nature of the pain
  - Educate the patient, discuss pain options, review possible adverse effects
  - Work with the patient to establish realistic goals and manage his or her expectations
  - Empower the patient to choose a realistic overall treatment approach

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

American Society of Anesthesiologists Task Force. *Anesthesiology.* 1997;86:995-1004.
American Academy of Pain Medicine, American Pain Society. *Clin J Pain.* 1997;13:6-8.
Chou R, et al. *Ann Intern Med.* 2007;147:478-491.

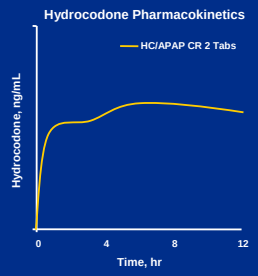
Practical Considerations for Chronic Opioid Therapy

- 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?

Jovey RD, et al. *Pain Res Manage.* 2003;8:3A-28A.
Gilron I, et al. *N Engl J Med.* 2005;352:1324-1334.

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

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

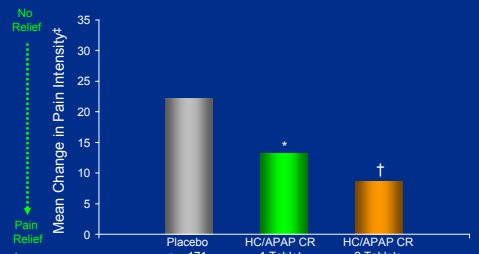


*Extended-release HC/APAP is an unapproved product

Klein CE, et al. *Am Acad Pain Med.* 2007;Abstract.

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

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

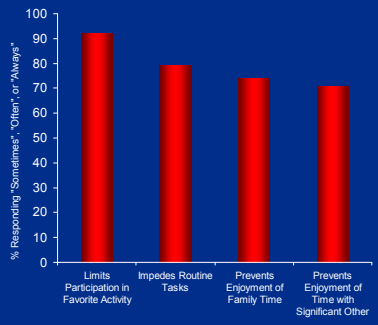


*P=.002 versus placebo
†P≤.001 versus placebo
‡Comparison is from double-blind baseline; measures increase in pain scores
[a]HC/APAP CR is an unapproved product

Codding C, et al. *Amer Pain Soc.* 2008;Abstract 248.

Impact of Chronic Pain on Daily Activities

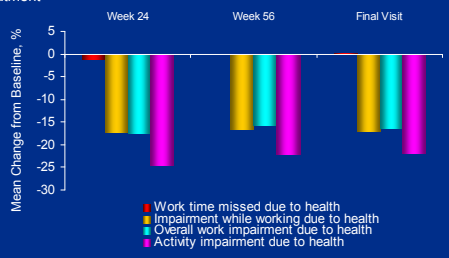
- Patients with chronic pain reported reduced ability to participate in or enjoy activities



McCarberg BH, et al. *Am J Ther.* 2008;15:312-320.

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

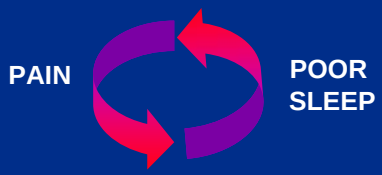


[a]HC/APAP CR is an unapproved product

Webster D, et al. *Am Acad Pain Med.* 2008;Abstract 167.

Relationship Between Insomnia and Pain

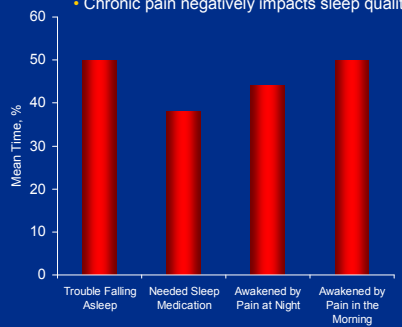
- Significant inter-relationship between insomnia and pain
- Sleep disturbances can predict later pain
- Pre-existing pain can predict subsequent insomnia
- Sleep disturbances can decrease ability to cope with pain



Morphy H, et al. *Sleep.* 2007;30:274-280.

Impact of Chronic Pain on Sleep

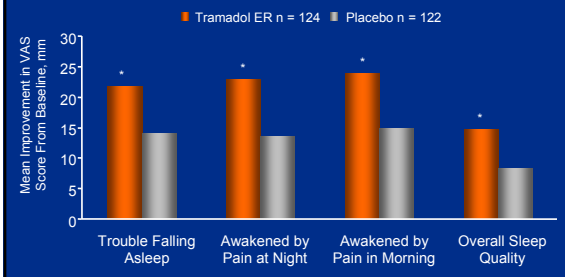
- Chronic pain negatively impacts sleep quality



McCarberg BH, et al. *Am J Ther.* 2008;15:312-320.

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

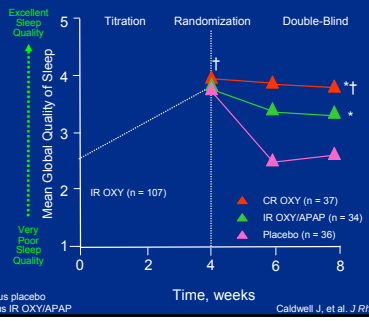


*P<.05 versus placebo

Babul N, et al. *J Pain Sympt Manage*. 2004;28:59-71.

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

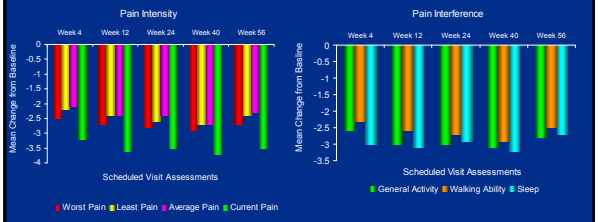


*P<.05 versus placebo
†P<.05 versus IR OXY/APAP

Caldwell J, et al. *J Rheumatol*. 1999;26:862-869.

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



[a]HC/APAP CR is an unapproved product

Webster D, et al. *Am Acad Pain Med*. 2008;Abstract 194.

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Monitor Clinical Outcomes: 4 As

- Analgesia (pain relief)
- Activities of daily living (physical/psychosocial function)
- Adverse side effects
- Aberrant drug-taking behaviors

Passik SD, et al. *Adv Ther*. 2000;17:70-80.

Managing Opioid Side Effects

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

TOLERANCE

and

≠ ADDICTION

PHYSICAL DEPENDENCE

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

Fine P, Portenoy RK. *Opioid Analgesia.* New York: McGraw Hill; 2004.
Portenoy RK, et al. Acute and chronic pain. In: Lowinson JH, et al, eds. *Comprehensive Textbook of Substance Abuse*. 4th ed. Baltimore: Williams and Wilkins; 2005:863-903.

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Reasons for Referral to Pain Specialist

- Uncontrolled, severe pain not responsive to therapy
- Significant ongoing disruption of physical and/or psychosocial functioning
- Need for diagnostic evaluation for unknown etiology or complex pain syndromes
- Need to validate a diagnosis and treatment plan or to interpret a diagnostic evaluation

Gruener D, et al. *Pain Control in the Primary Care Setting*. Glenview, IL: American Pain Society; 2006.

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

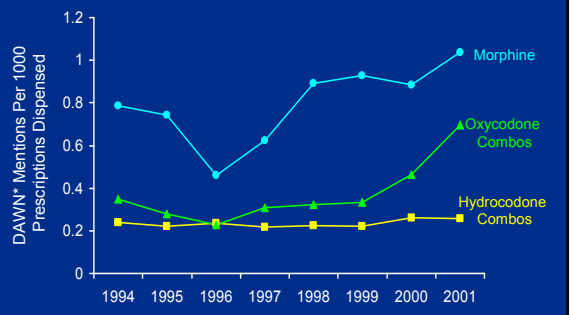
Dahl JL. *JAMA.* 2000;284:2785.
Filos KS, et al. *Eur Surg Res.* 1999;31:97-101.
Kaufman M. *Washington Post.* February 15, 2004:A03.
National Institutes of Health. *Prescription Drugs: Abuse and Addiction.* 2001.

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%

Martell BA, et al. *Ann Intern Med.* 2007;146:116-127.

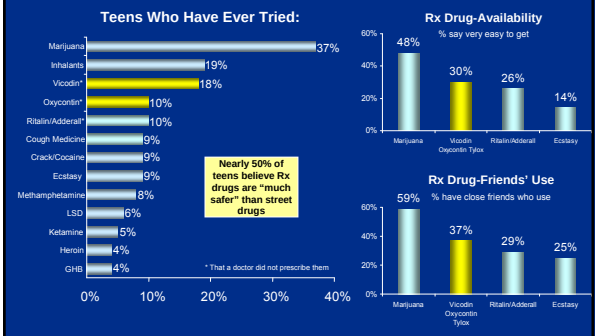
DAWN* Mentions Per 1000 Prescriptions Dispensed: Account for Opioid Availability



*DAWN, Drug Abuse Warning Network

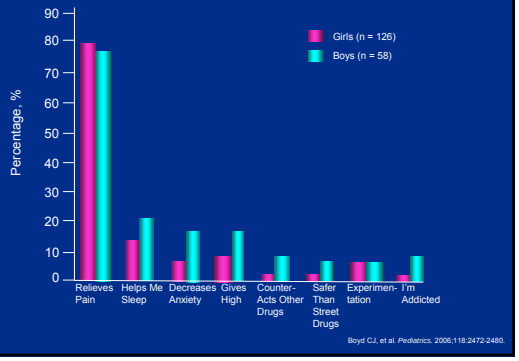
Zacny J, et al. *Drug Alcohol Depend.* 2003;69:215-232.

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



Source: Partnership Attitude Tracking Study (PATS) of 7,300 teenagers (margin of error: +/- 1.5 percent) . Released April 2005

Reasons for Nonmedical Use of Prescription Pain Medications According to Gender



Boyd CJ, et al. *Pediatrics.* 2006;118:2472-2480.

Response to Aberrant Drug-Related Behaviors

- Reassess to establish diagnosis
  - Addiction, pseudoaddiction, or both
  - Other psychiatric disorder
- Decide on appropriateness of continued treatment
- If treatment continued, consider strategies to address behavior, structuring therapy to match perceived risk
- Consider referral
- Document everything

Portenoy RK, et al. Acute and chronic pain. In: Lowinson JH, et al, eds. *Comprehensive Textbook of Substance Abuse.* 4th ed. Baltimore: Williams and Wilkins; 2005:863-903.

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 prescribing opioids?

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

After seeing today's presentation, which of the following risk management tools will you use most in your practice?

1. Written consent/treatment agreements
2. Patient guidelines on proper disposal of unused pills
3. Patient risk assessment tools (eg, SOAPP, ORT, CAGE)
4. Physician guidelines on minimization of abuse and diversion of prescription opioids
5. Urine screening