Postoperative Pain Management:
Overview of Clinical and Economic Considerations

Presented as a Live Webinar
Tuesday, September 20, 2011
Wednesday, October 5, 2011

Planned and conducted by ASHP Advantage.
Supported by an educational grant from Cadence Pharmaceuticals.

Postoperative Pain Management:
Overview of Clinical and Economic Considerations

Webinar Information

How do I register?
Go to http://www.ashpadvantage.com/pain and click on the date that best fits your schedule. You will be e-mailed computer and audio information.

What is a live webinar?
A live webinar brings the presentation to you – at your desk, in your home, through a staff inservice program. You listen to the presentation in "real time" as you watch the slides on the screen. You will have the opportunity to ask the speaker questions at the end of the program. Please join the conference at least 5 minutes before the scheduled start time for important program announcements.

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1. Computer with internet access and basic system requirements. When you register, the webinar system will assess your system to ensure compatibility.
2. Telephone to dial the toll-free number and listen to the presentation (if you choose not to use Voice Over IP [VoIP] via your computer).

Webinar System Requirements
PC-based attendees
Required: Windows® 7, Vista, XP, 2003 Server or 2000

Macintosh®-based attendees
Required: Mac OS® X 10.4.11 (Tiger®) or newer

What if I would like to arrange for my colleagues to participate in this webinar as a group?
One person serving as the group coordinator should register for the webinar. That group coordinator will receive an e-mail confirmation with instructions for joining the webinar. A few minutes before the webinar begins, the group coordinator should launch the webinar link. Once the webinar has been activated, the coordinator will have the option to open the audio via VoIP (Voice Over IP) on the webinar toolbar or use a touch tone phone with the provided dial-in information. At the conclusion of the activity, the group coordinator will complete a brief online evaluation and report the number of participants at that site. Each participant will process his or her individual continuing education statement online at the ASHP CE Center.

How do I ask a question of the presenter?
Follow the instructions provided at the beginning of the activity for submitting text questions using the webinar tool. The speaker will answer as many questions as possible at the conclusion of the activity.

Agenda

Economic Consequences of Postoperative Pain Management
Joseph F. Dasta, M.S., FCCM, FCCP (25 minutes)

Evolving Role of Non-opioid Medications for Postoperative Pain Management
Leslie N. Schechter, Pharm.D. (25 minutes)

Questions and Answers (10 minutes)

Faculty

Joseph F. Dasta, M.S., FCCM, FCCP, Activity Chair
Professor Emeritus
The Ohio State University College of Pharmacy
Columbus, Ohio
Adjunct Professor
The University of Texas College of Pharmacy
Austin, Texas

Leslie N. Schechter, Pharm.D.
Advanced Practice Pharmacist, Pain Management and Nutritional Support
Thomas Jefferson University Hospital
Clinical Assistant Professor
University of the Sciences in Philadelphia College of Pharmacy
Philadelphia, Pennsylvania

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The faculty and planners report the following relationships:

Joseph F. Dasta, M.S., FCCM, FCCP, Activity Chair

Mr. Dasta declares that he has served as a consultant for Cadence Pharmaceuticals, Hospira, and Pacira Pharmaceuticals, Inc. and on the speakers bureau for Cadence Pharmaceuticals.

Leslie N. Schechter, Pharm.D.

Dr. Schechter declares that she has served as a consultant for Cadence Pharmaceuticals and Pacira Pharmaceuticals, Inc. and on the speakers bureau for Cadence Pharmaceuticals and PriCara, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc.

Carla J. Brink, M.S., B.S.Pharm.

Ms. Brink declares that she has no relationships pertinent to this activity.

Susan R. Dombrowski, M.S., B.S.Pharm.

Ms. Dombrowski declares that she has no relationships pertinent to this activity.

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The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. The activity provides 1 hour (0.1 CEU) of continuing pharmacy education credit (ACPE activity # 204-000-11-436-L01P).

Attendees must complete a Continuing Pharmacy Education Request online and may immediately print their official statements of continuing pharmacy education (CPE) credit at the ASHP CE Center at http://ce.ashp.org following the activity.

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Methods and Format

This is a live online activity consisting of audio, online presentation slides, and an activity evaluation tool. Participants must participate in the entire presentation and complete the course evaluation to receive continuing pharmacy education credit. Participants may print their official statements of continuing pharmacy education credit immediately. This activity is provided free of charge.

Target Audience

This continuing pharmacy education activity was planned to meet the needs of pharmacists practicing in hospitals, components of health systems, and surgery centers. This activity would be especially beneficial for pharmacists, clinical specialists, managers, leaders, and educators who are interested in pain management, improving postoperative care, new drug therapies, and pharmacoeconomics.

Available soon
www.ashpmedia.org/symposia/pain

A web-based version of this educational activity is being developed, and it is approved for 1 hour of CPE. Encourage your pharmacist colleagues who were unable to attend today's webinar to look for this free online educational activity in November 2011.

Please note that individuals who claim CPE credit for the live webinar are ineligible to claim credit for the web-based activity.

Activity Overview

This educational activity will provide an overview of the economic consequences of postoperative analgesia, as well as a review of injectable non-opioid medications for the management of postoperative pain. Factors contributing to the economic burden of inadequate pain relief, such as inability to mobilize patients in the intensive care unit, readmissions associated with pain, and development of delirium, will be discussed. In addition, the potential costs of adverse drug events associated with opioid use for postoperative analgesia will be reviewed. Several non-opioid injectable analgesic medications are available, and the faculty will provide an overview of their clinical use for postoperative pain management. These injectable medications provide non-opioid options to combine with other therapies in a multimodal approach for the management of postoperative pain.

Activity Learning Objectives

At the conclusion of this knowledge-based educational activity, participants should be able to

- Identify at least three economic consequences of inadequate control of postoperative pain.
- Describe the economic impact of adverse drug events associated with opioids used to treat postoperative pain.
- Explain the rationale for using multimodal therapy for postoperative analgesia.
- Describe the clinical implications of injectable non-opioid medications for management of postoperative pain.

Faculty

Joseph F. Dasta, M.S., FCCM, FCCP, Activity Chair
Professor Emeritus
The Ohio State University College of Pharmacy
Columbus, Ohio
Adjunct Professor
The University of Texas College of Pharmacy
Austin, Texas

Joseph F. Dasta, M.S., FCCM, FCCP, is Professor Emeritus at The Ohio State University College of Pharmacy in Columbus and Adjunct Professor at The University of Texas College of Pharmacy in Austin. He retired from The Ohio State University (OSU) in 2007 after 31 years, and he currently lives in Austin. He serves as a health care consultant to pharmaceutical and device companies, and he provides pharmacy consulting services for the intensive care unit (ICU) at a local hospital.

Mr. Dasta earned his Bachelor of Science degree in pharmacy from West Virginia University School of Pharmacy. He began his academic career at OSU following completion of his Master of Science degree and residency in hospital pharmacy there in 1976. He developed one of the first practice sites and post-doctoral training programs in critical care pharmacy at OSU, through which he trained 11 residents and 9 fellows who are prominent practitioners, researchers, and leaders in the profession and pharmaceutical industry. He received OSU's Jack L. Beal Post-baccalaureate Alumni Award in 2008.

Mr. Dasta was one of the first pharmacist members of the Society of Critical Care Medicine (SCCM), and he helped establish the role of pharmacists in this multidisciplinary society. He was a member of SCCM Council, the governing body of SCCM, from 2007-2010. SCCM honored him by creating the Joseph F. Dasta Critical Care Pharmacy Outcomes Research Grant in 2000. Ten years later, he was the first pharmacist to receive the SCCM Distinguished Investigator Award. Mr. Dasta's contributions have also been recognized by other organizations. He received the Education Award from the American College of Clinical Pharmacy (ACCP) in 2002 and the Sustained Contributions to the Literature Award from the American Society of Health-System Pharmacists in 2010. He serves on the editorial board of *Critical Care Medicine* and *Annals of Pharmacotherapy*.

Mr. Dasta is a fellow of ACCP and the American College of Critical Care Medicine. He has authored more than 200 peer-reviewed publications, abstracts, brief communications, and book chapters, and he has given over 250 lectures on topics related to critical care and health outcomes. Mr. Dasta's research has focused on health economics and patient safety of acute care pharmaceuticals. Specific areas of interest include acute pain, sedation, sepsis, acute renal failure, acute heart failure, and hypertensive emergencies.

Faculty

Leslie N. Schechter, Pharm.D.
Advanced Practice Pharmacist, Pain Management and Nutritional Support
Thomas Jefferson University Hospital
Clinical Assistant Professor
University of the Sciences in Philadelphia College of Pharmacy
Philadelphia, Pennsylvania

Leslie N. Schechter, Pharm.D., is Advanced Practice Pharmacist specializing in Pain Management and Nutritional Support at Thomas Jefferson University Hospital in Philadelphia, Pennsylvania. She is also Clinical Assistant Professor at Philadelphia College of Pharmacy at the University of the Sciences in Philadelphia, Adjunct Assistant Professor at Temple University School of Pharmacy, and Preceptor at Jefferson School of Pharmacy.

At Thomas Jefferson University Hospital (TJUH), Dr. Schechter serves as Pharmacy Liaison for the Acute Pain Management Service (APMS) and is involved in APMS clinical trials. She also provides pharmacotherapy recommendations relating to pain management, conducts medication use reviews related to pharmaceutical pain management therapy, and is involved in the drug review process for formulary addition considerations for anesthesia and pain medications. Dr. Schechter is a member of the TJUH Pain Initiative, an interdisciplinary group that developed a booklet of pain management guidelines, which is updated periodically and distributed to all medical, surgical, nursing, and pharmacy staff.

Dr. Schechter earned her Bachelor of Science degree in pharmacy from the Virginia Commonwealth University's Medical College of Virginia in Richmond and her Doctor of Pharmacy degree from Purdue University College of Pharmacy and Pharmaceutical Sciences in West Lafayette, Indiana. She completed a residency accredited by the American Society of Health-System Pharmacists (ASHP) at the Medical College of Virginia Hospitals.

Dr. Schechter is a member of ASHP and the American Society for Parenteral and Enteral Nutrition. She has contributed chapters to several textbooks on pain management, including *The Essence of Analgesia and Analgesics* (Cambridge University Press), *Handbook of Drug-Nutrient Interactions* (Humana Press), *Acute Pain Management*, 1st ed. (Cambridge University Press), and *Textbook of Regional Anesthesia and Acute Pain Management* (McGraw-Hill). She has also authored several articles related to pain management. She is frequently invited to speak on topics related to pain management for interdisciplinary health care audiences.

Economic Consequences of Postoperative Pain Management

Joseph F. Dasta, M.S., FCCM, FCCP
Professor Emeritus
The Ohio State University
Adjunct Professor
The University of Texas

Challenges of Conducting Economic Analyses of Acute Pain Management

- Pain occurs in a wide variety of conditions, including medical patients
- Hard to separate costs associated with pain from the primary disease costs
- Only a few studies have documented the economics of acute pain management
- Currently no data on comparative cost-effectiveness of injectable analgesics

Pharmacy Costs in Joint Replacement Therapy

- One of the first studies to document post-operative drug costs in orthopedic surgery
- Stanford University database of patients following hip and knee surgery in first half of 1999
- Hospital costs estimated using micro-costing methods
- Patients: 145 hip replacement, 121 knee, and 32 bilateral knee replacement

Marcario A et al. *J Pain.* 2003; 4:22-8.

Results: Hospital Cost/Patient Undergoing Joint Replacement Surgery

	Total Hospital Cost ($)	Total Pharmacy Cost ($)	Approximate Cost of Analgesics ($)
Hip replacement	18,024	560	180
Knee replacement	16,484	595	164
Bilateral knee replacement	28,559	922	286

- Pharmacy and operating room (OR) costs were 3.3% and 60% of total costs, respectively
- 2010 costs are approximately 30% higher than 1999

Marcario A et al. *J Pain.* 2003; 4:22-8.

Clinical Consequences and Economics of Pain Management

- Continued pain can result in increased readmissions
- Pain and opioid use are associated with the development of delirium in ICU patients
- Difficult to implement early mobilization efforts when ICU patients experience pain
- Continued pain has negative effect on quality of life
- Effects of poor pain management are associated with increased costs

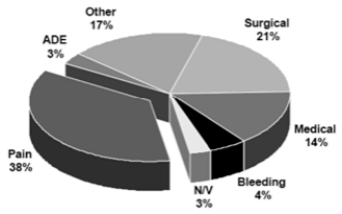
ICU = intensive care unit

Cost of Readmissions after Same-Day Surgery

- Retrospective analysis of same-day surgery in patients at University of Pittsburgh Medical Center during 1999
- Evaluated patients returning to the ER or hospital on a non-elective basis within 7-30 days
- Data obtained from chart review
- Financial data consisted of hospital charges
  - 2010 charges approximately 30% higher than 1999

Coley KC et al. *J Clin Anesth.* 2002; 14:349-53.

Readmissions from Same-day Surgeries: Pain Is Most Common Reason



38% of those reporting pain underwent orthopedic surgeries

ADE = adverse drug event
N/V = nausea/vomiting

Coley KC et al. *J Clin Anesth.* 2002; 14:349-53.

Consequences of Inadequate Pain Control after Ambulatory Surgery

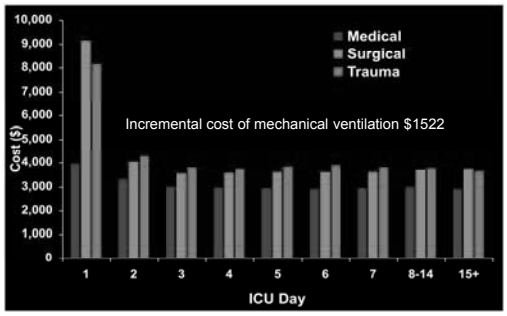
Mean Cost for Follow-up Care for Pain after Ambulatory Surgery		
	N	**Mean Cost/Patient ($)***
All pain admissions/readmissions**	117	1,869
Emergency department (ED) visits	109	986
Inpatient admissions/readmissions	8	13,902

*Based on cost of care in 1999
**Includes ED visits and inpatient admissions/readmissions

Cumulative charges of 303 patients is $2.4 million (in 1999 dollars).

Coley KC et al. *J Clin Anesth.* 2002; 14:349-53.

Estimated ICU Daily Cost



Dasta J et al. *Crit Care Med.* 2005; 33:1266-71.

Clinical Consequences and Economics of Delirium

During the ICU/Hospital Stay

- Increased mortality
- Longer time on ventilator
- 3 times greater re-intubation rate
- Average 10 additional days in hospital
- Higher costs of care
  - ICU $9,000
  - Hospital $14,800

After Hospital Discharge

- Increased mortality
- Development of dementia
- Long-term cognitive impairment
- Requirement for care in chronic care facility
- Decreased functional status at 6 months

Pun B et al. *Chest.* 2007; 132:624-36.

Effects of Early Mobilization in Mechanically-Ventilated ICU Patients

- Shift in care from deep to light sedation
- Early mobilization of patients may improve functional outcomes and delirium
- 104 ICU patients ventilated < 72 hours
- Randomized trial
  - Daily sedation interruption with early exercise and mobilization (PT and OT)
  - Daily sedation interruption and standard care

PT = physical therapy
OT = occupational therapy

Schweickert WD et al. *Lancet.* 2009; 373:1874-82.

Results: Effects of Early Mobilization in Mechanically Ventilated ICU Patients

Variable	Control*	Intervention*	*P*-value
Days ICU delirium	4 (2-7)	2 (0-6)	0.03
Time with delirium (%)	57 (33-69)	33 (0-58)	0.02
Days of ventilation	6.1 (4-9)	3.4 (2-7)	0.02
Days of ICU stay	7.9 (6-13)	5.9 (4-13)	0.08

*Reported as median (interquartile range).

Schweickert WD et al. *Lancet.* 2009; 373:1874-82.

Example of Patient in ICU during Exercise

Needham DM et al. *Arch Phys Med Rehabil*. 2010; 91:536-41.

Consider the Following Issues Surrounding that Patient

- If experiencing pain, ability to perform this task would be hampered
- If over sedated from opioids or sedatives or both, ability to perform this task would be hampered
- Conclusion
  - Inadequate analgesia and excessive opioid analgesic dosing are a problem

Cost Issues of Opioid-associated ADEs

- Clinical findings of opioid ADEs have been well described for many years
- Few studies have estimated costs from adverse effects associated with their use
- Minimizing dosage or eliminating opioids is one approach to reduce these costs

Pain and Opioid Use Is Associated with Delirium

- Total of 541 hip surgery patients from one NY hospital prospectively assessed for delirium
- Confusion Assessment Method (CAM) performed daily until discharge
- Numerous potential risk factors, including pain-related variables, collected
- Multiple logistic regression performed

Morrison RS et al. *J Gerontol.* 2003; 58:76-81.

Results: Pain and Opioid Use

- 16% developed delirium after admission
- Independent risk factors for delirium in cognitively intact patients
  - Severe pain before delirium (RR 9.0 [1.8-45.2])
  - < 10 mg i.v. morphine equivalent per day (RR 25.2 [1.3-493.3])
  - Administering meperidine (RR 2.6 [0.4-15.8])

RR = relative risk

Morrison RS et al. *J Gerontol.* 2003; 58:76-81.

Cost of Opioid-associated ADE

- Retrospective matched cohort study in one hospital, 1998-2003
- 40,368 surgical patients receiving opioids
- Computer-based trigger of possible ADE
- 741 (1.8%) opioid-related ADE
- Most common ADEs
  - Nausea/vomiting (50%)
  - Itching/rash (34%)
  - Mental status changes (17%)
  - Bradypnea (16.7%)

Oderda GM et al. *Ann Pharmacother.* 2007; 41:400-7.

Cost of Opioid-associated ADE (2003 dollars)

- Median increase in total hospital cost $568
  - Would result in additional $421,000 for 741 patients
- Type of surgery and increased costs
  - OB-GYN $541
  - Orthopedic $862
- 10% increase in length of stay (LOS) (0.6 days)
- Odds ratio (OR) of factors associated with ADE
  - > 10 mg parenteral morphine-equivalent dose OR 1.3
  - Orthopedic surgery OR 1.7
  - OB-GYN surgery OR 2.7

Oderda GM et al. *Ann Pharmacother.* 2007; 41:400-7.

Costs of Managing Nausea, Vomiting, and Constipation (NVC) from Analgesics

- Retrospective analysis Premier database
- January 2005 – December 2007
- 434,000 patients received an order for opioid or non-opioid analgesic (NSAID or COX-2 inhibitor)
- Use of drugs for nausea, vomiting, or constipation within 14 days of first analgesic order

NSAID = nonsteroidal anti-inflammatory drug
COX-2 = cyclooxygenase-2

Suh D-C et al. *Clin J Pain.* 2011; 27:508-17.

Results: Managing NVC from Analgesia

- 55% received drugs for NVC
  - 50% for nausea or vomiting
  - 12% for constipation
  - 4% for NVC
- Treatment costs statistically higher in patients with NVC
  - $756 higher overall
  - $232 higher with injectable opioids
  - $868 higher with injectable non-opioids
  - $1464 higher with oral non-opioids
  - $2223 higher with oral opioids

Suh D-C et al. *Clin J Pain.* 2011; 27:508-17.

Costs of Postoperative Ileus

- Retrospective review of 186 colectomy patients from one hospital, July 2007 – June 2008
- Primary ileus defined as > 3 episodes of emesis in 24 hours, and return to NPO status and/or insertion of NG tube
- Secondary ileus defined as an intraabdominal complication
- 24% had ileus (84% primary)

Asgeursson T et al. *J Am Coll Surg.* 2010; 210:228-31.

Clinical and Economic Results

Variable*	Primary Ileus	No Ileus
LOS (days)	8.9	4.0
Duration of opioids (hours)	142	43
Hospital cost ($)	15,914	8316
Pharmacy cost ($)	2639	454

*Data reported as mean values

Asgeursson T et al. *J Am Coll Surg.* 2010; 210:228-31.

Conclusion

- Higher total hospital costs generated from
  - Inadequately managed pain
  - ADEs from opioids
- Use of non-opioid analgesics has potential to reduce these excessive costs
- Cost-effectiveness studies needed

Evolving Role of Non-opioid Medications for Postoperative Pain Management

Leslie N. Schechter, Pharm.D.
Advanced Practice Pharmacist
Thomas Jefferson University Hospital

Impact of Surgical Pain

- Negative clinical outcomes of ineffective postoperative pain management
  - Deep vein thrombosis
  - Pulmonary embolism
  - Coronary ischemia and myocardial infarction
  - Pneumonia
  - Poor wound healing and recovery
  - Insomnia
  - Reduced quality of life
  - Chronic pain
  - Cognitive dysfunction

Apfelbaum JL et al. *Anesth Analg.* 2003; 97:534-40.
Carr DB et al. *Lancet.* 1999; 353:2051-8.
Kehlet H. *Br J Anaesth.* 2001; 87:62-72.

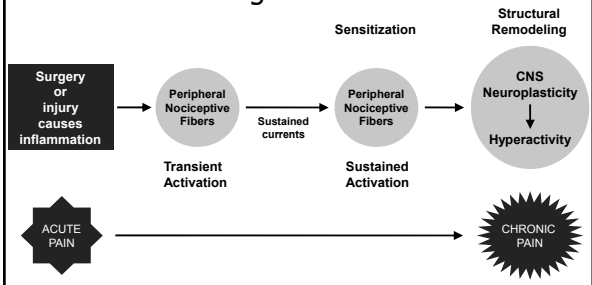
Severity of Acute Postoperative Pain: Link to Chronic Pain

- In first postoperative week, patients undergoing thoracotomy who developed chronic pain (n=78)* vs. those who did not (n=71) reported
  - Greater incidence of acute pain (*P*=0.002)
  - More severe acute pain (*P*=0.0001)
  - Greater total amount of time spent having pain (*P*=0.02)
- Incidence of progression to chronic pain increased with intensity of acute postoperative pain

*Chronic pain assessed 6 months to 3.5 years after surgery

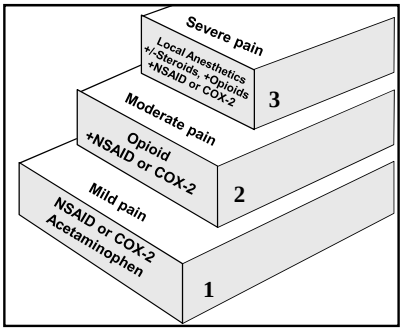
Pluijms WA et al. *Acta Anaesthesiol Scand*. 2006; 50:804-8.

Long-Term Consequences of Acute Pain: Potential for Progression to Chronic Pain



Woolf CJ et al. *Ann Intern Med*. 2004; 140:441-51;
Petersen-Felix S et al. *Swiss Med Weekly*. 2002; 132:273-8;
Woolf CJ. *Nature.*1983; 306:686-8; Woolf CJ et al. *Nature.* 1992; 355:75-8.

WHO Pain Ladder



World Health Organization. (URL in ref list).

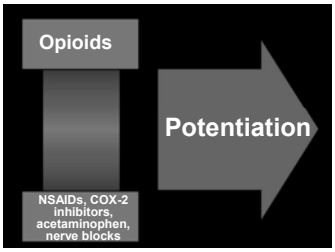
Benefits of Multimodal Analgesia

- Reduced doses of each analgesic
- Improved pain relief secondary to synergistic or additive effects of particular agents
- Adverse effects of individual medications may be reduced
- Fewer analgesic gaps
- Outcomes of acute pain are improved

Pain is complex and multifactorial, thus appropriate management requires a "balanced" therapeutic approach

Kehlet H et al. *Anesth Analg.* 1993; 77:1048-56.

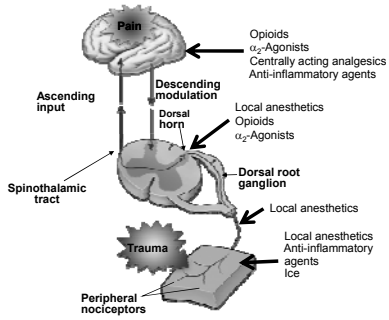
Multimodal Analgesia



- Reduced doses of each analgesic
- Improved pain relief due to synergistic and/or additive effects
- May reduce severity of adverse effects of each drug

Kehlet H et al. *Anesth Analg.* 1993; 77:1048-56.

Multimodal Approach



Adapted from Gottschalk A et al. *Am Fam Physician.* 2001; 63:1979-84.

Injectable NSAIDs

- Currently available products in the U.S. include ketorolac and ibuprofen
- Diclofenac injection received a complete response letter from FDA in October 2010
  - Issues related to manufacturing quality processes and particulates found in European products
  - Timing of resolution is uncertain
- Tenoxicam and parecoxib are available in Europe

Bookstaver PB et al. *J Pain Res.* 2010; 3:67-79.
Hospira Inc. Form 10-K (URL in reference list).

Injectable NSAIDs

- Mechanism of action for non-selective NSAIDs
  - Inhibition of prostaglandin biosynthesis via non-selective inhibition of cyclo-oxygenase enzymes to decrease the conversion of arachidonic acid into prostaglandin endoperoxides, including thromboxane and prostacyclin
- Adverse effects for all products are similar
  - Gastrointestinal ulceration by inhibiting prostaglandins involved in protection of GI mucosa
  - Potential to prolong bleeding by inhibiting platelet thromboxane A_2 synthesis resulting in inhibition of platelet aggregation
  - Renal impairment by inhibiting renal prostaglandins

GI = gastrointestinal

Bookstaver PB et al. *J Pain Res.* 2010; 3:67-79.

Injectable NSAIDs

- Studies have demonstrated that administration of intravenous NSAIDs will decrease opioid requirements and incidence of adverse events compared to opioids alone
- To date, there are no clinical trials on comparative efficacy between intravenous ketorolac and ibuprofen
- Currently, ibuprofen is not restricted by duration of therapy
  - Only studied for up to 5 days
  - Use with caution for therapy > 5 days

Pavy TJ et al. *Anesth Analg.* 2001; 92:1010-4.
Southworth S et al. *Clin Ther.* 2009; 31:1922-35.

Intravenous Acetaminophen (Paracetamol)

- Known outside the U.S. as paracetamol, acetaminophen is a non-opioid, non-NSAID analgesic and antipyretic
- 20-40% opioid reduction across studies
- Component of multimodal analgesia
- Effective analgesia with low incidence of adverse events following major orthopedic surgery
- Approved by FDA in November 2010

Sinatra RS et al. *Anesthesiology.* 2005;102:822-31..

Intravenous Acetaminophen (Paracetamol)

- Exact mechanism is unclear, but current evidence points to variety of central and peripheral mechanisms
  - Inhibition of cyclooxygenase activity and prostaglandin formation
  - Interactions with various neurotransmitters and modulators controlling pain processing and perception (serotonergic system)
- Contraindicated in patients with severe hepatic impairment

Smith HS. *Pain Physician.* 2009; 12:269-80.

Intravenous Acetaminophen

- Available in 1000 mg/100 mL glass vials
- Recommended dosage for adults and adolescents weighing ≥ 50 kg
  - 650 mg IVPB over 15 minutes every 4 hr
  - 1000 mg IVPB over 15 minutes every 6 hr
  - Maximum daily dose 4000 mg
- Recommended dosage for children ≥ 2 years and for adolescents and adults weighing < 50 kg
  - 12.5 mg/kg every 4 hr
  - 15 mg/kg every 6 hr
  - Maximum single dose 750 mg
  - Maximum daily dose 3750 mg

IVPB = i.v. piggyback

Ofirmev injection prescribing information. 2010 Nov (URL in ref list).

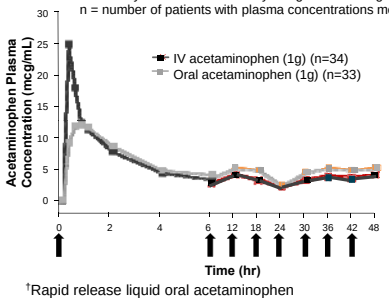
Intravenous Acetaminophen

- Doses < 1000 mg
  - Withdraw dose from vial and place in syringe, plastic i.v. container, or glass bottle
  - Once original vial is punctured or contents transferred to another container, dose should be administered within 6 hours

Golembiewski J. *J Perianesth Nurs.* 2011; 26:116-9.
Ofirmev injection prescribing information. 2010 Nov (URL in ref list).

Pharmacokinetics of Intravenous vs. Oral Acetaminophen

38 healthy adult males randomly assigned to each group
n = number of patients with plasma concentrations measured



- Mean acetaminophen concentration over time: 6-hour dosing regimen (arrows)[1]
- Mean maximum concentration up to 70% higher in intravenous than in oral acetaminophen[1,2]

†Rapid release liquid oral acetaminophen

[1]Schutz RA et al. Presented at ASRA 32nd Annual Regional Meeting, Vancouver, Canada; 2007 Apr 19-22; [2]Ofirmev injection prescribing information. 2010 Nov (URL in ref list).

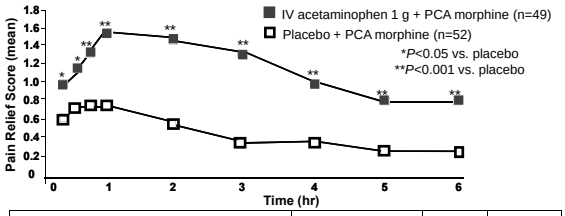
Clinical Study in Orthopedic Surgery

- Randomized, double-blind, placebo-controlled multidose study in total hip or knee arthroplasty
- 7 U.S. centers, N=151 (n=101 excluding propacetamol* group)
- Patients with moderate to severe pain, 3 treatment groups
  - Acetaminophen injection 1 g
  - Propacetamol i.v. 2 g
  - Placebo
- Rescue medication: PCA morphine plus PRN bolus doses available
- Treatment initiated morning following surgery
- Endpoints measured at selected intervals
  - Pain intensity, pain relief, patient satisfaction, and morphine use

*Prodrug for paracetamol, not available in the U.S.
PRN = as needed

Sinatra RS et al. *Anesthesiology.* 2005; 102:822-31.

Clinical Study in Orthopedic Surgery: Results



Outcome	IV Acetaminophen	Placebo	P value
Patient satisfaction: good to excellent at 24 hr	40.8%	23.1%	0.004†
Median time to first use of rescue	3.0 hr	0.8 hr	0.0001
Morphine consumption over 24 hr‡	38.3 mg	57.4 mg	<0.01

‡ Clinical benefit of reduced opioid consumption was not demonstrated
PCA = patient controlled analgesia

Sinatra RS et al. *Anesthesiology.* 2005; 102:822-31.

Intravenous Acetaminophen

- Alternative to intravenous NSAIDs for management of post-operative pain
  - Avoid NSAID adverse effects, including risk of postoperative bleeding from inhibition of platelet function, and minimize risks for nephrotoxicity
- Alternative for oral and rectal acetaminophen
  - Oral administration may not be feasible immediately after surgery
  - Rectal administration produces slow and unpredictable absorption

Ketamine

- Renewed interest in enhancing post-operative analgesia
- Antagonist at the NMDA receptor
  - At low sub-anesthetic doses, exerts a specific NMDA blockade, modulating central sensitization induced by the incision and tissue damage
- Opioid-sparing effect with advantages in patients in whom high post-operative opioid consumption (opioid-tolerant patient) is anticipated

NMDA = N-methyl-D-aspartate

Weinbroum AA. *Anesth Analg.* 2003; 96:789-95.
Yamauchi M et al. *Anesth Analg.* 2008; 107:1041-4.

NMDA Receptor Antagonism: Ketamine as a Multimodal Agent

- In RCT, perioperative ketamine use[1]
  - Reduces opioid dose by 30%
  - Reduces chronic post surgical pain syndromes
- Dose[2]
  - 0.1 - 0.5 mg/kg bolus ± 0.1- 0.5 mg/kg/hr infusion
  - Adverse effects: < 10% of patients had complaints of psycho-cognitive effects (These were opioid naive; rarely if ever seen in opioid tolerant)
- With chronic opioid use (TJUH experience)
  - Pre-incision bolus 0.5 mg/kg
  - Intraoperative 0.1-0.15 mg/kg/hr
  - Postoperative 0.1 mg/kg/hr (+/- 0.05)

TJUH = Thomas Jefferson University Hospital

[1]Lavand'homme P et al. *Anesthesiology*. 2005; 103:813-20.
[2]Visser E et al. *Biomed Pharmacother.* 2006; 60:341-8.

Local Anesthetics

- Membrane stabilizers
  - Reversibly decrease the rate of depolarization and repolarization of excitable membranes, including nociceptors
  - Act primarily by inhibiting sodium influx through sodium-specific ion channels in the neuronal cell membrane
  - When the influx of sodium is interrupted, an action potential cannot arise, and signal conduction is inhibited

Local Anesthetic Techniques

- Wound and joint[1]
  - Single injection
  - Catheters
- Peripheral nerve blocks[2]
  - Single injection
  - Catheters
- Epidural
- These techniques rarely provide complete analgesia but work best with multimodal analgesia and opioid rescue

[1]Badner NH et al. *J Bone Joint Surg Am*. 1996; 78:734-8.
[2]Richman JM et al. *Anesth Analg.* 2006; 102:248-57.

Benefits of Continuous Peripheral Nerve Block (CPNB): What We Know

- Superior pain control over parenteral opioids[1]
- Fewer opioid-related adverse effects[1]
- CPNB does not completely eliminate need for analgesic supplement (opioid)[1]
- Improved sleep[2]
- Improved rehabilitation[3]
- Enhanced patient satisfaction[2]

[1]Richman JM et al. *Anesth Analg.* 2006; 102:248-57.
[2]Ilfeld BM et al. *Anesthesiology.* 2002; 97:959-65.
[3]Singelyn FJ et al. *Anesth Analg.* 1998; 87:88-92.

CPNB: What We Don't Know

- Failure rate of catheters
- Comprehensive cost analysis
- How does CPNB compare with single injection PNB
  - Less pain, earlier ambulation, greater patient satisfaction, earlier discharge, PACU bypass
  - Is it worth the additional effort (cost)?

Hadzic A et al. *Anesthesiology.* 2005; 102:1001-7.

Ambulatory Continuous Brachial Blockade

- Study comparing efficacy of single injection interscalene brachial plexus blockade with continuous peripheral nerve block
- Continuous infusion ropivacaine 0.2% at 10 mL/hr resulted in
  - Dramatic reduction in pain scores
  - 47% reduction in supplemental analgesics

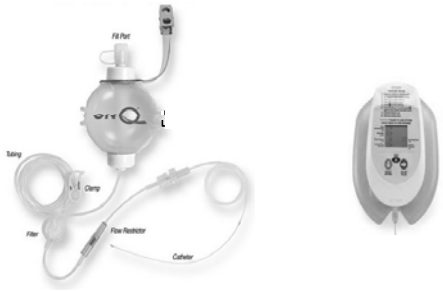
Clinical pearl
- Consider the logistics of managing outpatient infusions

Klein SM et al. *Anesth Analg.* 2000; 91:1473-8.

Wound Infiltration: Elastomeric Balloon Infusion Devices

- Device used for continuous wound infiltration with local anesthetic
- Approved by new products or value analysis committee within hospital organizations
- Local anesthetic is placed in device either in operating room (OR) or filled by pharmacy department in accordance with USP 797
- Requires mechanism to dispense and record administration of local anesthetic
- Physician, nurse, and pharmacy education

Elastomeric Balloon Infusion Devices



Concerns with Elastomeric Balloon Infusion Devices

- Preparation considerations
  - Filling devices in OR versus pharmacy
  - Labeling of the device
- ISMP recommends safety improvements
  - Ensure proper education of hospital staff and the patient
  - Ensure pharmacy involvement
  - Pharmacy and nursing profiling of order
  - Identify medications that may added to the device
  - Verify infusion rate and concentration
- Evaluate concomitant analgesic administration

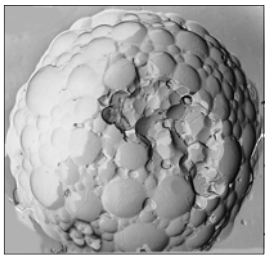
Institute for Safe Medication Practices. ISMP medication safety alert. Jul 16, 2009 (URL in ref list).

Epidural Administration of Local Anesthetics

- Continuous infusion
  - Used for acute and chronic pain
  - Advantages
    - Permits concomitant use of local anesthetics and shorter-acting opioids
    - Eliminates need for catheter re-injection, lowering risk for catheter contamination
    - Greater potency than systemic administration
  - Disadvantages
    - Potential for catheter migration and adverse effects
- Single injections

Pyati S et al. *CNS Drugs.* 2007; 21:185-211.

Multivesicular Liposome: DepoFoam®



FF-SEM image

- Particle suspension in isotonic aqueous solution
- 10 – 30 mm diameter
- Injected with fine-gauge needles
- Well tolerated
  - Phospholipids, triglycerides, cholesterol
- Release: 1 to 30 days
- Delivery: mcg to mg/day
- Water-soluble and solution-stable drugs

Viscusi ER et al. *Reg Anesth Pain Med*. 2005; 30:292-4.

Liposomal Bupivacaine for Intradermal Administration

- Extended-release bupivacaine*
  - Bupivacaine is a short-acting local anesthetic with duration of action averaging 6 to 8 hours
- Bupivacaine extended-release liposome injection releases bupivacaine over several days
  - DepoFoam uses membrane components that are neutral and cleared by normal metabolic pathways
  - FDA PDUFA goal date for review of New Drug Application is October 28, 2011

*Pacira Pharmaceuticals, Inc.
PDUFA = Prescription Drug User Fee Act

Viscusi ER et al. Presented at International Anesthesia Research Society, Vancouver, Canada; 2011 May 23.

Liposomal Bupivacaine for Intradermal Administration

- Clinical phase III trials demonstrated a sustained-release profile of bupivacaine compared with placebo or bupivacaine single injection
  - Included hemorrhoidectomy, herniorrhaphy, breast augmentation, bunionectomy, total knee arthroplasty, and cardiac surgery
- Clinical trials demonstrated
  - Reduction in pain scores
  - Reduction in opioid consumption
- Patients avoided opioids until later in their hospital stay
- No clinical trials compared extended-release bupivacaine with CPNB

Viscusi ER et al. Presented at International Anesthesia Research Society, Vancouver, Canada; 2011 May 23.

Conclusion

- Advances in understanding the mechanisms of pain have led to improvements in the management of acute pain
- Multimodal therapy offers improvement in acute pain management and better clinical outcomes
- Improperly managed acute pain can trigger long-term plastic neuronal changes leading to chronic pain
- The optimal combination of adjuvant agents and understanding of dose-response relationships requires further investigation

Thank you!

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- CPE instructions in handout and on webinar web page

  www.ashpadvantage.com/pain
- Please be sure to note the IMPORTANT codes required to process CPE (Activity code and Session code)

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Self-assessment Questions

1. As shown by Coley et al., the mean hospital charge (in 1999 dollars) for patients having same-day surgery who were admitted or readmitted as inpatients because of pain was

   a. $982.
   b. $1,390.
   c. $13,902
   d. $19,982.

2. Hospital costs in patients developing primary postoperative ileus compared with patients who do not develop this disorder are higher by a factor of

   a. 1.
   b. 2.
   c. 4.
   d. 8.

3. Which of the following statements can be used to describe the multimodal analgesia approach to the management of acute postoperative pain?

   a. Uses the same medication either by the oral or intravenous route depending on the patient's diet.
   b. Reduces the dose of each analgesic prescribed and improves pain relief due to synergistic or additive effects.
   c. Incorporates use of a second analgesic after optimizing a single drug dosing regimen.
   d. Involves complex drug regimens and is difficult to implement outside of the intensive care unit.

4. Which of the following statements best describes the role of injectable local anesthetic options in the management of postoperative pain?

   a. Injectable local anesthetics usually eliminate need for analgesic supplement.
   b. Single injection peripheral nerve blocks result in less pain, earlier ambulation, and greater patient satisfaction compared with continuous peripheral nerve blocks.
   c. The use of elastomeric balloon infusion devices for local anesthetic administration requires physician, nurse, and pharmacist education and policy development for preparation and profile documentation.
   d. Liposomal bupivacaine for intradermal administration has been shown to have equal efficacy to continuous peripheral nerve blocks.

Answers

1. c
2. b
3. b
4. c

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