

Ask the Experts: Issues Related to the Management of Postoperative Pain

Presented as a Live Webinar
Thursday, February 13, 2014
1:00 p.m. – 2:00 p.m. ET

Planned and conducted by ASHP Advantage and supported by an educational grant from Pacira Pharmaceuticals, Inc.



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Webinar Information

How do I register?

Go to <http://www.ashpadvantagemedia.com/postoppain/webinar.php> and click on the **Register** button. After you submit your information, you will be e-mailed computer and audio information.

What is a live webinar?

A live webinar brings the presentation to you – at your work place, in your home, through a staff in-service program. You listen to the speaker 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 announcements.

How do I process my Continuing Education (CE) credit?

Continuing pharmacy education for this activity will be processed on ASHP’s new eLearning system and reported directly to CPE Monitor. After completion of the live webinar, you will process your CPE and print your statement of credit online at <http://elearning.ashp.org/my-activities>. To process your CPE, you will need the enrollment code that will be announced at the end of the webinar.

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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.

What do I need in order to participate in the webinar?

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

Be sure to view the webinar [system requirements](#) for Windows, Mac, iOS, and Android prior to the activity.

Ask the Experts: Issues Related to the Management of Postoperative Pain

Activity Faculty

Julie Golembiewski, Pharm.D., FASHP, Activity Chair

Clinical Pharmacist, Anesthesia and Pain
University of Illinois Hospital and Health Sciences System
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Julie Golembiewski, Pharm.D., FASHP, is Clinical Pharmacist in Anesthesia and Pain at the University of Illinois Hospital and Health Sciences System (UI Health) in Chicago. She also has a shared appointment in the Departments of Pharmacy Practice and Anesthesiology and a faculty appointment of Clinical Associate Professor at the University of Illinois at Chicago (UIC) Colleges of Pharmacy and Medicine. She serves as co-coordinator for the UIC Department of Anesthesiology Midwest Anesthesia Residents Conference. Dr. Golembiewski teaches pharmacy students and anesthesiology resident physicians, as well as participates in research and committees at UI Health.

Dr. Golembiewski earned her Bachelor of Science in Pharmacy and Doctor of Pharmacy with honors degrees from the UIC College of Pharmacy. She has over 20 years of active pharmacy experience with the majority concentrated in the areas of operating room pharmacy, anesthesiology, and pain management.

Dr. Golembiewski is on the editorial advisory board of *Pharmacy Practice News*, writes a regular column for the *Journal of PeriAnesthesia Nursing*, and is a senior editor for LexiComp's *Anesthesiology & Critical Care Drug Handbook*. She also co-authored the chapter on perioperative care in the text, *Applied Therapeutics: The Clinical Use of Drugs*. In addition to these contributions to the literature, Dr. Golembiewski has presented extensively on the topics of operating room pharmacy practice, anesthesia, and pain management.

Dr. Golembiewski is an active member of numerous professional organizations, including the American Society of Health-System Pharmacists (ASHP), American Society for Pain Management Nursing, International Anesthesia Research Society, and Illinois Council of Health-System Pharmacists. She is a fellow of ASHP and received the University of Illinois Class Act Award.

Ask the Experts: Issues Related to the Management of Postoperative Pain

Virginia L. Ghafoor, Pharm.D.

Pharmacy Specialist, Pain Management
University of Minnesota Medical Center
Minneapolis, Minnesota

Virginia L. Ghafoor, Pharm.D., is Pharmacy Specialist in Pain Management at University of Minnesota Medical Center in Minneapolis. For more than 10 years, she has been instrumental in developing pharmacy services for acute and chronic pain management at the University of Minnesota Medical Center and throughout the Fairview health system. She advocates for pain medication safety, promotes pharmacy pain medication stewardship, and leads the health system's Pain Medication Committee to advance evidence-based practice standards.

Dr. Ghafoor earned her Doctor of Pharmacy degree from the University of Nebraska Medical Center in Omaha. Early in her career she received a two-year fellowship award from the American Society of Health-System Pharmacists (ASHP) Research and Education Foundation for oncology research at University of Wisconsin-Madison, and the fellowship involved working with nationally recognized leaders in cancer and pain management research. Before assuming her current position, Dr. Ghafoor was on the faculty at the University of Rhode Island (URI) College of Pharmacy and conducted research and pharmacy education programs in pain management at Rhode Island Hospital in Providence. During this time she also developed an ASHP-accredited pharmacy practice residency program for the URI College of Pharmacy.

Dr. Ghafoor has authored several articles on pain topics, including intrathecal pumps, palliative sedation, and patient-controlled analgesia. She has also contributed chapters on pain management to the texts, *Koda-Kimble and Young's Applied Therapeutics: The Clinical Use of Drugs*, *Smart Infusion Pumps* published by ASHP, and *Core Curriculum for Pain Management Nursing* published by American Society of Pain Management Nurses. Dr. Ghafoor is a member of ASHP and Minnesota Society of Health-System Pharmacists. She currently serves on the ASHP Advisory Group for Pain Management and Palliative Care.

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The faculty planners listed below reports relationships pertinent to this activity:

- Dr. Golembiewski declares that she has served on the pharmacist advisory board for Durect Corporation and Pacira Pharmaceuticals, Inc.
- Dr. Ghafoor declares that she has served on the pharmacist advisory board for Pacira Pharmaceuticals, Inc.

The following planners report no relationships pertinent to this activity:

- Carla J. Brink, M.S., B.S.Pharm.
- Susan R. Dombrowski, M.S., B.S.Pharm.

ASHP staff has no relevant financial relationships to disclose.

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Activity Overview

This activity will provide health-system pharmacists with pearls that can be incorporated into the management of postoperative pain, focusing on multimodal therapy and the use of local anesthetics. The content for this activity is based on questions raised by participants in a recent educational symposium on this topic.

Time for questions and answers from the webinar audience will be provided at the end of the presentation.

Learning Objectives

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

- Address current issues related to multimodal therapy for postoperative pain management.
- Outline factors to consider when evaluating local anesthetics for postoperative pain management.

Continuing Education Accreditation



The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This activity provides 1.0 hour (0.1 CEU) of continuing pharmacy education credit (ACPE activity #0204-0000-14-467-L01-P).

Participants will process CE credit online at <http://elearning.ashp.org/my-activities>, with the option of printing a CE certificate. CPE credit will be reported directly to CPE Monitor.

Complete instructions for processing CE can be found on the last page of this handout.

Additional Educational Opportunities on this Topic

- **On-demand activity**, “Optimizing Postoperative Pain Management: Role of Local Anesthetics” (2 hours CPE, available March 2014)
- **On-demand activity** based on today’s webinar (1 hour CPE, available April 2014)
 - Note: individuals who claim CPE credit for a live activity are ineligible to claim credit for the web-based activity
- Informational **podcasts** featuring the faculty in a roundtable discussion
- **e-Newsletters** featuring updates on emerging information, as well as pearls for managing postoperative pain

www.ashpadvantage.com/postoppain

Ask the Experts: Issues Related to the Management of Postoperative Pain

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Learning Objectives

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- Outline factors to consider when evaluating local anesthetics for postoperative pain management

Mission Impossible or Not?

Your Mission:

Determine the best perioperative multimodal pain regimen for a new order set for total knee arthroplasty



Audience Poll



You have to make your decision on one of the multimodal mission choices below.

A	B	C
<ul style="list-style-type: none"> • Opioid • NSAID or acetaminophen • Pregabalin • Local anesthetic nerve block 	<ul style="list-style-type: none"> • Opioid • NSAID or acetaminophen • Local anesthetic nerve block 	<ul style="list-style-type: none"> • Opioid • NSAID or acetaminophen

NSAID = nonsteroidal anti-inflammatory drug, LA = local anesthetic

Our Quest Begins:

What is the best multimodal regimen?

- Ovid Medline search from 1996-2013
- Search terms
 - Multimodal and pain management (420)
Limit to randomized, controlled trials (68)
 - Multimodal and analgesia (695)
Limit to randomized, controlled trials (203)
 - Randomized, controlled trials for arthroplasty total knee with multimodal pain management or multimodal analgesia (40)

When should long-acting opioids be used?

- Food and Drug Administration (FDA): updated label to state long-acting and extended release opioids are indicated in selected pain management situations¹
 - Pain severe enough to require daily around-the-clock administration
 - Alternative treatment options are inadequate
- American Academy of Orthopaedic Surgeons²
 - Preop: Long-acting oxycodone 10 mg orally for patients ≥ 75 years and 20 mg orally for patients < 75 years
 - Postop: Long-acting oxycodone 10 mg or 20 mg orally (depending on preop dose) every 12 hours for 24 hours postop

¹U.S. Food and Drug Administration. News release. Sept 10, 2013. URL in ref list.
²Dalury DF et al. *J Bone Joint Surg Am.* 2011; 93:1938-43.

Long-Acting Morphine Study

- Randomized, double-blind study of 200 patients with standard postop pain management and one of the following
 - Treatment group: Long-acting morphine 30 mg orally twice daily for 3 days
 - Control group: Placebo orally twice daily for 3 days
- Results
 - Change in pain scores did not reach clinical significance for either group
 - No statistical difference between groups for general activity and walking 72 hours after surgery
 - Opioid group
 - Increase opioid use ($P < 0.0001$)
 - Vomiting ($P = 0.0148$)
 - Oversedation ($P = 0.08$)

Musclow SL et al. *Pain Res Manag.* 2012; 17:83-8.

IV Opioid PCA vs. Long-acting Oxycodone

- TKA or THA cohorts matched for demographic characteristics, surgical procedure, surgeon, and anesthesia
 - 62 patients: IV opioid patient-controlled analgesia (PCA)
 - 62 patients: long-acting oxycodone 20 mg orally twice daily for 3 days with oxycodone 5-20 mg po q 3 hours as needed
- Results
 - Both groups: similar pain ratings all 3 days
 - Oxycodone group: less opioid compared with IV PCA in first 24 hr postop ($37.8 \text{ mg} \pm 23.45$ vs. $59.4 \text{ mg} \pm 37.0$, $P < 0.001$)
 - Oxycodone group: interference with walking on day 1 ($P = 0.24$), deep breathing on day 2 ($P = 0.11$)
 - Statistical difference in patient satisfaction with pain management only on day 3 with oxycodone

TKA = total knee arthroplasty

THA = total hip arthroplasty

Illgen RL et al. *J Arthroplasty.* 2006; 21:814-20.

Chronic Opioid User

- TKA opioid and nonopioid cohorts matched for surgical center, procedure, age, sex, body mass index, preop diagnosis and insurance
 - 49 patients in chronic opioid group
 - 49 patients in nonopioid group
- Results

Outcome	Chronic Opioid User	Non-opioid User	P Value
# days to discharge	4.3	3.4	0.013
Surgical revision for pain or stiffness	8	0	<0.001
Referral to pain specialist	10	1	<0.001

Zywiel MG et al. *J Bone Joint Surg Am.* 2011; 93:1988-93.

Order Set Tips for Postoperative Opioids in Adult Patients



- Create selection buttons to force prescriber to acknowledge the patient's age
 - Age < 65 years
 - Age \geq 65 years
- Create separate headers for long-acting and short-acting opioids to improve prescribing safety
- Clarify opioid naive vs. tolerant for doses
- Identify drugs and doses that are appropriate for patients with renal impairment
- Provide instructions for starting long-acting oral opioids when patient on IV PCA

Example: Postoperative Long-Acting Opioids University of Minnesota Medical Center

- Long-acting oxycodone dose in elderly 10 mg orally twice daily
- Long-acting oxycodone for opioid-tolerant patients only

☑ Moderate to severe pain - Oral opioids (Long Acting - ONLY for OPIOID TOLERANT patient) select one
 Long acting oxycodone for > 65 years old with low urine output or low GFR
 Long acting oxycodone (NOT for elderly patients with poor renal function)

EPIC Order Set Instruction: patient must be opioid-tolerant taking an equivalent of 30 mg oral morphine per day

Example: Postoperative Pain Orders for Elderly University of Minnesota Medical Center

☑ Moderate to severe pain - Oral opioids (short acting - immediate release) select one

☑ Pain Meds for > 65 years old with low urine output or low GFR

oxycodone (ROXICODONE) immediate release tablet

5 mg, Oral, EVERY 3 HOURS PRN, moderate to severe pain, Hold while on PCA or with regular IV opioid dosing, Post-procedure

oxycodone-acetaminophen (PERCOCET) 5-325 MG per tablet

1 tablet, Oral, EVERY 4 HOURS PRN, moderate to severe pain, Hold while on PCA or with regular IV opioid dosing, Post-procedure

HYDROcodone-acetaminophen (NORCO) 5-325 MG per tablet

1 tablet, Oral, EVERY 4 HOURS PRN, moderate to severe pain, Hold while on PCA or with regular IV opioid dosing, Post-procedure

HYDROcodone-acetaminophen (LORTAB) solution 7.5-325 mg/15 mL

10 mL, Oral, EVERY 4 HOURS PRN, moderate to severe pain, Hold while on PCA or with regular IV opioid dosing, Post-procedure

HYDROmorphine (DILAUDID) tablet

1-2 mg, Oral, EVERY 3 HOURS PRN, moderate to severe pain, Hold while on PCA or with regular IV opioid dosing, Post-procedure

See page 16 for enlarged view

See page 16 for enlarged view

Acetaminophen

- Central mechanisms
 - Inhibits cyclooxygenase in locations where ambient peroxidase is low (i.e., brain)
 - Reinforces descending serotonergic inhibitory pain pathway
 - Cannabinoid receptor agonist
- Absorption after 1000 mg dose
 - Oral Tmax 45 minutes, Cmax 15.1 mcg/mL
 - Intravenous Tmax 25 minutes, Cmax 28.4 mcg/mL
- Maximum analgesic and antipyretic activity occurs 1-2 hours after peak plasma levels

Lachiewicz PF. *Orthopedics*. 2013; 36(suppl 2):15-9.

Acetaminophen Paradox

- Intravenous vs. oral preoperatively
 - Evidence does not support one route over another
 - Cost is the driver toward oral
- Maximum dose limit
 - Literature recommends ≤ 3000 mg per day for chronic use¹
 - FDA still allows 4000 mg per day maximum
- Combined with opioids
 - Low acetaminophen dose (325 mg per dosage unit) inadequate for pain relief
 - Commonly used for postoperative pain management

¹Watkins PB et al. *Reg Anesth Pain Med*. 2011; 36:417-9.

Example: Acetaminophen Route Interchange University of Minnesota Medical Center

- For conversion from intravenous to oral, patient must be receiving other medications orally or through a gastric tube that are intended for systemic therapeutic purpose.
- Pharmacist can substitute oral acetaminophen without discussion with the medical team as long as patient able to take oral medications.

IV Acetaminophen Use: Examine Your Evidence

- Medication-use evaluation
 - Indication
 - Patient oral status
 - Prescriber trends
- Cost assessment
 - Comparison based on use outside of justified indications

Which of the following is a valid concern with postoperative use of NSAIDs for total knee arthroplasty?



Select all that apply.

- a. Impaired tissue healing
- b. Non-union of joint
- c. Cardiovascular event in patient 6 months post myocardial infarction
- d. Use in a patient 60 years of age

Tissue and Bone Healing

- Non-union studies are cohort and case-controlled due to the low number of patients reported
 - Meta-analysis of spine studies found no statistically significant difference with NSAIDs vs. no NSAIDs¹
 - Non-union of bone not a complication with total joint arthroplasty
- Soft tissue healing relies on platelet-derived growth factors so NSAID use is not detrimental to healing
- Studies needed in humans on NSAID inhibition of soft tissue to bone healing
- Retrospective studies show delayed healing of bone fractures with NSAIDs²

¹Dodwell ER et al. *Calcif Tissue Int*. 2010; 87:193-202.

²Chen MR et al. *Knee Surg Sports Traumatol Arthrosc*. 2013; 21:540-9.

Cardiovascular Risks

- No well-tolerated window for NSAID use after MI
- Large Danish cohort study of 99,187 patients post MI

Risk of Death Associated with NSAIDs after MI		
Year	# of Events	Hazard Ratio
1	1086	1.59 [1.49-1.69]
2	712	1.84 [1.70 – 1.69]
3	546	1.81 [1.66 – 1.99]
4	468	1.83 [.66 – 2.01]
5	377	1.73 [1.56 – 1.93]
>5	963	1.63 [1.52 – 1.74]

MI = myocardial infarction
 Olsen AM et al. *Curr Opin Cardiol.* 2013; 28:683-8.
 Olsen AM et al. *Circulation.* 2012; 126:1955-63.

Is naproxen safe post MI?

- FDA Advisory Committee review of post marketing cardiovascular safety from 2006-2013 (1/10/2014)
- Majority of data from observational studies or meta-analysis
- Results
 - No evidence of statistically significant increased risk of MI or stroke during OTC or prescription use of naproxen
 - Selected data suggest some interaction between naproxen and the antiplatelet activity of aspirin, if dosed prior to or concomitantly with aspirin
- Review of thromboembolic risk with non-aspirin NSAIDs will occur in February 2014
- Recommendations for changes in naproxen labeling will be reviewed by a cardiology advisory panel

U.S. Food and Drug Administration. FDA briefing document. January 28, 2014. URL in ref list.

Gabapentin

- Design flaws common with studies
- Randomized, double-blind study in total knee arthroplasty
 - Preop for both groups: 1000 mg acetaminophen oral and 15 mg ketorolac oral
 - Treatment group: 52 subjects gabapentin 600 mg oral preop and 200 mg oral every 8 hr x 2 days postop along with morphine intravenous patient controlled analgesia
 - Control group: 49 subjects placebo along with morphine intravenous patient controlled analgesia
- Results
 - Morphine consumption primary outcome
 - 66.3 mg gabapentin group vs. 72.5 mg placebo (P=0.59)
 - No difference in pain score
- Limitations: Postop gabapentin dose low and primary-end point not a definitive outcome

Paul JE et al. *Can J Anaesth.* 2013; 60:423-31.

Pregabalin

- Randomized, double-blind study in total knee arthroplasty
 - Both groups: celecoxib 400 mg preop and epidural with fentanyl and bupivacaine postop
 - Treatment group: 113 patients received oral pregabalin 300 mg preop, 150 mg twice daily days 1-10, 75 mg twice daily days 11-12, 50 mg twice daily days 13-14
 - Control group: 115 patients received placebo
- Results
 - Pregabalin group used less epidural opioid infusion than placebo (5.77±1.31 mL/hr vs. 6.40±1.26 mL/hr, P=0.003)
 - Greater flexion over 30 days with pregabalin group
 - Less neuropathic pain, allodynia, and hyperalgesia at 3 and 6 months postop with pregabalin group

Buvanendran A et al. *Anesth Analg.* 2010; 110:199-207.

Example of Preoperative Analgesia Protocol for TKA

MEDICATION	DOSE	CAUTION
Acetaminophen	1000 mg oral or IV	Avoid in patients with liver disease
Celecoxib	200 mg – 400 mg oral	Avoid in patients with renal disease or sulfur allergy
Naproxen	500 mg oral	Use if patient has sulfur allergy; avoid in patients with renal disease
Pregabalin	75 mg oral	Avoid in patients at risk for postoperative delirium

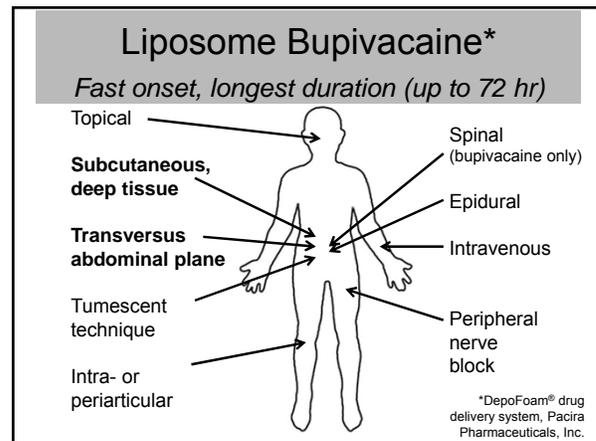
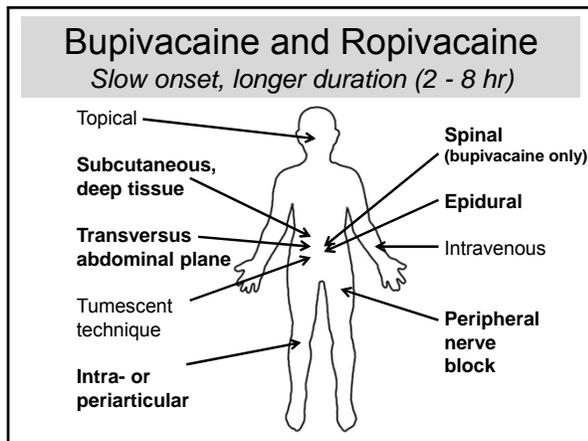
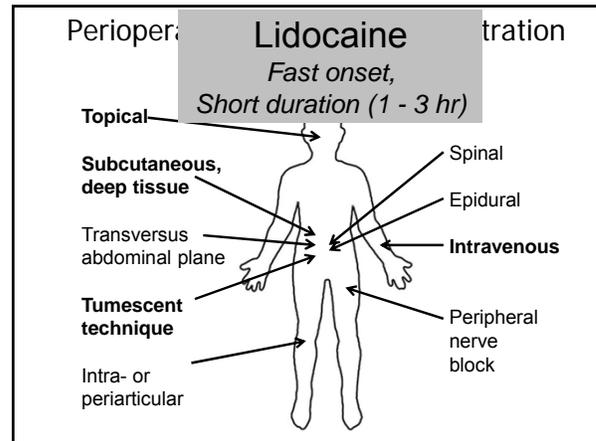
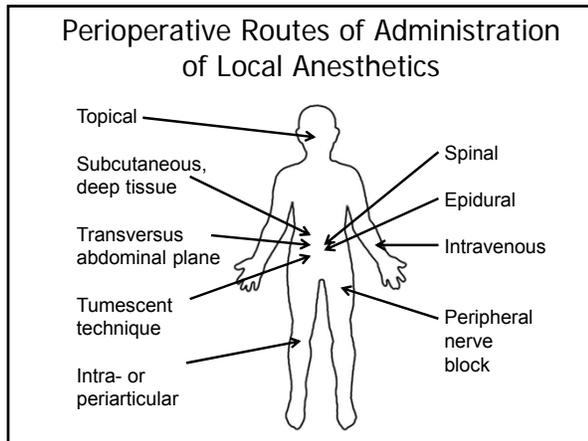
Protocol: Give medications 1 hour before surgery with sips of water.

Parvizi J et al. *Orthopedics.* 2013; 36(suppl 2):7-14.

Your Mission Continues...

The surgeon requests liposome bupivacaine for total knee arthroplasty





Continuous Wound Catheters

- 32 randomized controlled trials (RCTs)
 - Obstetrical and gynecologic surgery
 - Major abdominal surgery
 - Inguinal herniorrhaphy
 - Cardiothoracic surgery
 - No orthopedic surgery
- Patients with continuous wound catheters
 - No significant reduction in pain at rest or with activity, except OB-gyne surgery
 - No significant reduction in opioid consumption except for first 24 hr in OB-gyne surgery
 - Magnitude of these effects was small

Gupta A et al. Acta Anaesthesiol Scand. 2011; 55:785-96.

Local Infiltration Analgesia (LIA): Orthopedic Surgery

- 10 reports (N = 893)
 - 8 RCTs, two case series
 - Hip resurfacing arthroplasty, total hip replacement, total knee replacement
- Results
 - 8 reports → LIA was an effective analgesic
 - 2 reports → no benefit when LIA was added to a multimodal analgesic regimen
 - LIA efficacy questioned in total hip replacement

McCarthy D et al. Anesthesiol Res Pract. 2012; 2012:709531.

Additives

- **Epinephrine¹**
 - Slows systemic absorption, lowering peak plasma concentration of local anesthetic
 - Prolongs duration of lidocaine and mepivacaine
 - High epinephrine concentration (e.g., > 5 mcg/mL) reduces bleeding
- **Ketorolac²**
 - Analgesic effects when given locally or systemically
- **Clonidine³**
 - Prolongs duration of peripheral nerve block by about 2 hr, but adverse effects can be problematic

¹Rosenberg PH et al. *Reg Anesth Pain Med.* 2004; 29:564-75.

²Romsing J et al. *Acta Anaesthesiol Scand.* 2000; 44:672-83.

³Popping DM et al. *Anesthesiology.* 2009; 111:406-15.

Periarticular Injection Additives

- Assess pain severity, range of motion, inpatient walking distance, and Knee Society Score (KSS) in 160 adults undergoing total knee arthroplasty
- Randomized to
 - Ropivacaine + epinephrine + ketorolac + clonidine (group A)
 - Ropivacaine + epinephrine + ketorolac (group B)
 - Ropivacaine + epinephrine + clonidine (group C)
 - Ropivacaine + epinephrine (group D, control group)
- Results
 - Significantly lower pain scores in groups A and B vs. group D
 - No significant differences between groups for range of motion, inpatient walking distance, functional KSS, or mean postop opioid consumption

Kelley TC et al. *J Arthroplasty.* 2013; 28:1274-7.

Additives: Morphine

- Systematic review, intra-articular morphine, arthroscopic knee surgery
- 45 studies identified but only 19 studies suitable for meta-analysis
 - Reduction in pain intensity (12 - 17 mm) in morphine group vs. placebo in early (0 - 2 hr), intermediate (2 - 6 hr) and late (6 - 24 hr) phases
 - Six studies found decreased postop opioid consumption; six studies found no difference
 - No clear dose-response effect
 - Systemic effect could not be ruled out
- Conclusion: “definite but mild analgesic effect”

Gupta A et al. *Anesth Analg.* 2001; 93:761-70.

Liposome Bupivacaine (LB): Pooled Results, Phase 2 & 3 Trials (N = 10)

- Cumulative pain scores
 - 16/17 treatment arms favored LB through 24 hr
 - 5/17 treatment arms favored LB through 72 hr
- Time to first use of rescue opioid
 - Longer with LB (9.3 hr) vs. bupivacaine hydrochloride (bupivacaine) (6.4 hr, P = 0.013) and placebo (3.6 hr, P < 0.0001)
- Proportion of patients avoiding opioid rescue
 - 1 study favored LB; no difference in 8 studies
- Total postop opioid consumption
 - 4 studies favored LB at 24 hr; 2 studies favored LB at 72 hr
- Patient satisfaction
 - 1/6 studies favored LB at 24 hr and 72 hr

Bergese SD et al. *J Pain Res.* 2012; 5:107-16.

Liposome Bupivacaine: Phase 4 Trials

Study design: Multicenter, open-label, sequential groups
Study groups: IV PCA vs. multimodal analgesia (liposome bupivacaine, scheduled NSAID and APAP for 72 hr, opioid rescue)
Primary outcomes: total postop opioid consumption, length of stay, and hospital costs

	Ileostomy Reversal (Marcet et al. <i>J Pain Res.</i> 2013; 6:549-55)	Laparoscopic Colectomy (Candiotti et al. <i>Curr Ther Res.</i> 2014; 76:1-6)
N (PCA, multimodal)	27 (11, 16)	82 (56, 26)
Total postop opioid consumption (mean)	112 mg PCA vs. 20 mg multimodal (P<0.01)	96 mg PCA vs. 32 mg multimodal (P<0.0001)
Length of stay (median)	5.1 days PCA vs. 3.0 days multimodal (P<0.001)	4.0 days PCA vs. 3.0 days multimodal (P=0.0019)
Hospital costs (geometric mean)	\$9,282 PCA vs. \$6,484 multimodal (P=0.01)	\$13,018 PCA vs. \$11,234 multimodal (P=NS)

Liposome Bupivacaine vs. Continuous Wound Catheter

- Retrospective, single surgeon, robotic-assisted and laparoscopic urologic surgery
 - 54 consecutive patients received ropivacaine infusion; next 54 patients received liposome bupivacaine
- Primary endpoint: postop opioid consumption
- Liposome bupivacaine group had
 - Lower postop opioid consumption (23.8 vs. 65.9 mg; P<0.0001)
 - Longer time to first opioid use (186 vs. 64 min, P=0.043)
 - No difference in length of stay (1.6 vs. 1.8 days; P=0.64)

Walker PW et al. *J Endourol.* 2013; 27(Suppl):A41-2. Abstract MP2B-24.

Compatibility of Liposome Bupivacaine with

- Bupivacaine HCl
 - LB:bupi HCl ratio $\leq 1:12 \rightarrow$ excessive release of free bupivacaine
 - LB:bupi HCl ratio $\geq 2:1 \rightarrow \leq 5\%$ release of free bupivacaine
 - “Co-administration of both drug forms will increase overall exposure to bupivacaine.”
- Lidocaine, ropivacaine, mepivacaine
 - If given 1, 5, or 10 min before LB, rapid release of free bupivacaine
 - If given 20 or 40 min before LB, free bupivacaine does not increase
- Epinephrine
 - Minor physicochemical interaction
- Morphine 10 mg and ketorolac 30 mg
 - Minimal increase in free bupivacaine levels

Kharitonov V. *Postgrad Med.* 2014; 126:129-38.

Exparel (bupivacaine liposome injectable suspension) prescribing information. Pacira Pharmaceuticals, Inc.; 2011 Oct.

- “Non-bupivacaine based local anesthetics, including lidocaine, may cause an immediate release of bupivacaine from EXPAREL if administered together locally. The administration of EXPAREL may follow the administration of lidocaine after a delay of 20 minutes or more.
- Bupivacaine HCl, when injected immediately before EXPAREL, may impact the pharmacokinetic and/or physiochemical properties of the drugs when the milligram dose of bupivacaine HCl solution exceeds 50% of the EXPAREL dose. EXPAREL contains bupivacaine; therefore, coadministration of both drugs will increase the overall exposure to bupivacaine.
- EXPAREL should not be admixed with other drugs prior to administration.

Kharitonov V. *Postgrad Med.* 2014; 126:129-38.

Transversus Abdominis Plane (TAP) Block

- Technique
 - Ultrasound-guided
 - Laparoscopic assisted
 - Direct visualization
- Provides analgesia for surgery involving lower abdominal wall
 - Bowel surgery, appendectomy, cesarean delivery, hysterectomy, prostatectomy, laparoscopic cholecystectomy
- Optimal surgical procedures, dosing, technique and timing are not clear

Young MJ et al. *Anesthesiol Res Pract.* 2012; 2012:731645.
Abdallah FW et al. *Br J Anaesth.* 2012; 109:679-87.
Siddiqui MR et al. *J Clin Anesth.* 2011; 23:7-14.

TAP Block after Laparoscopic Surgery

- Systematic review
 - 10 RCTs, 633 subjects
 - TAP block (ultrasound-guided) vs. placebo (or no treatment)
- Primary outcomes
 - Early (0-4 hr) and late (24 hr) postop pain at rest and on movement
 - Postop opioid consumption (up to 24 hr)
- Results
 - TAP block reduced early and late pain at rest and postop opioid consumption; no improvement in early and late pain with movement or postop nausea/vomiting
 - Preop administration more effective than postop
 - Association between total dose and opioid consumption

De Oliveira GS Jr et al. *Anesth Analg.* 2014; 118:454-63.

Peripheral Nerve Blocks and IV Lidocaine

- Systematic review evaluated preventive analgesia* by local anesthetics
 - 89 peripheral nerve block studies
 - TKA, THA, anterior cruciate ligament (ACL) reconstruction, arthroscopic knee and shoulder surgery, foot and ankle surgery, open shoulder surgery, hand/upper limb surgery, TAP block for various abdominal and bowel surgeries
 - 16 IV lidocaine studies
- Primary outcome
 - Postoperative pain and/or opioid consumption

* Defined as a reduction of postoperative pain that persists for more than 5.5 half-lives (8 hr for lidocaine and 12-16 hr for bupivacaine and ropivacaine)

Barrevelde A et al. *Anesth Analg.* 2013; 116:1141-61.

Results

- Peripheral nerve blocks
 - Provide better analgesia than placebo, PCA, and intra-articular infusions
 - Some effects attributed to systemic distribution
 - Total dose appears to be more important than volume and concentration
 - Timing of block (before or after incision) does not appear to affect efficacy
- IV lidocaine
 - Provided better analgesia than placebo (0.9% sodium chloride) in 13/16 studies

Barrevelde A et al. *Anesth Analg.* 2013; 116:1141-61.

Liposome Bupivacaine and Total Knee Arthroplasty: Wound Infiltration

- Phase 2, dose-ranging study¹
 - LB 133, 266, 399, and 532 mg vs. bupivacaine 150 mg + epinephrine
 - LB 532 mg provided better analgesia than bupivacaine + epinephrine
- Emerging reports of experiences in individual surgeon practices²

¹Bramlett K et al. *Knee*. 2012; 19:530-6.

²Barrington JW et al. *Am J Orthop*. 2013; 42(suppl):S1-S15.

Maximum Recommended Dose and Plasma Concentration

- Although not necessarily evidence-based, maximum dose highlights “dose” as a risk factor for systemic toxicity
- “...because drug concentrations in various regions of heart and brain tissue differ quite markedly, the deterministic notion of a “toxic” or “lethal” blood or tissue concentration of local anesthetic appears invalid even with standardized conditions. Others have noted that blood concentrations of local anesthetics in dogs that survived a particular dose were not significantly different from pre-mortem blood concentrations in those that died.”^{1,2}

¹Feldman HS et al. *Anesth Analg*. 1989; 69:794-801.

²Copeland SE et al. *Anesth Analg*. 2008; 106:1440-9.

Local Anesthetic Systemic Toxicity (LAST)

- More than one third of reports involved patients with underlying cardiac, neurologic, renal, hepatic, pulmonary, or metabolic disease
- Treatment is different from other cardiac arrest scenarios
 - Airway management, seizure suppression (avoid propofol)
 - Avoid vasopressin, calcium channel blockers, beta-blockers, local anesthetics
 - Reduce epinephrine doses to < 1 mcg/kg
 - Lipid emulsion (20%)
 - 1.5 mL/kg (lean body mass) over 1 min, then 0.25 mL/kg/min infusion
 - Repeat bolus once or twice for persistent cardiovascular collapse
 - Double infusion rate if blood pressure remains low
 - Continue infusion for at least 10 min after circulation stabilizes
 - Upper limit: 10 mL/kg over first 30 min

Neal JM et al. *Reg Anesth Pain Med* 2010; 35:152-61.

Rosenberg PH et al. *Reg Anesth Pain Med*. 2004; 29:564-75.

Weinberg G. LipidRescue Resuscitation for drug toxicity. URL in ref list.

Example: Colorectal Surgery

- Open
- Minimally-invasive
 - Laparoscopic
 - Robotic-assisted



Laparoscopic Colorectal Surgery

- Assessed efficacy of SC bupivacaine +/- IP lidocaine in reducing postoperative pain
- Case-controlled, sequential cohorts*
 1. No local anesthetic (control group) (N = 61)
 2. SC bupivacaine in all ports and wound (N = 67)
 3. SC bupivacaine + IP lidocaine under diaphragm and within peritoneal cavity (N = 44)
- Enhanced recovery pathway
 - PCA, avoid drains and tubes, early feeding and mobilization
- Results
 - No difference between groups in VAS
 - No difference between groups in amount of postoperative opioid

*After surgeon performed > 600 laparoscopic colorectal procedures

SC = subcutaneous, IP = intraperitoneal, PCA = patient-controlled analgesia, VAS = visual analog score

Stuhldreher JM et al. *Surg Endosc*. 2012 ;26:1617-23.

Enhances Recovery After Surgery (ERAS®)

- Comprehensive for entire surgical process, particularly key factors that prevent hospital discharge
 - Need for parenteral analgesics
 - Need for IV fluids secondary to gut dysfunction
 - Lack of mobility
- ERAS for colorectal surgery¹
 - Pre-, intra- and post-operative protocol with about 20 care elements
 - Examples of care elements: preoperative patient education, fluid management, no drains, early oral nutrition, epidural + acetaminophen + NSAID analgesia
 - 137 patients in ERAS program compared with historical cohort (N=99)
 - Significantly reduced²
 - Length of stay (6 vs. 8.4 days, P<0.001)
 - Readmissions (8.8% vs. 20.2%, P=0.012)
 - Hospital costs (by 15%)

¹Enhances Recovery After Surgery (ERAS) Society. ERAS protocol (EP). URL in ref list.

²Miller T et al. Presented at ASA Annual Meeting; October 15, 2013. Abstract A4293.

Back to Request from Surgeon for Liposome Bupivacaine . . .

- Evaluate current state
 - Use of multimodal analgesia
 - Protocol and order sets
 - Enhanced recovery pathway
- Expected outcome(s)
 - Pain intensity, HCAHPS patient satisfaction scores, opioid use, adverse effects, length of stay, etc.
- Limited trial, attention to safety
- Medication-use evaluation

HCAHPS = Hospital Consumer Assessment of Healthcare Providers and Systems

Another Long-acting Bupivacaine in Development . . .

- Saber® delivery system
 - 15 clinical trials, various surgical procedures
 - Up to 72 hr
- Prescription Drug User Fee Act (PDUFA) date of February 12, 2014

Durect Corporation. http://www.durect.com/wt/durect/page_name/postop (accessed 2014 Jan 27).

Mission Impossible or Not?

Your Mission:

Determine the best perioperative multimodal pain regimen for a new order set for total knee arthroplasty



Audience Poll



You have to make your decision on one of the multimodal mission choices below.

A	B	C
<ul style="list-style-type: none">• Opioid• NSAID or acetaminophen• Pregabalin• Local anesthetic nerve block	<ul style="list-style-type: none">• Opioid• NSAID or acetaminophen• Local anesthetic nerve block	<ul style="list-style-type: none">• Opioid• NSAID or acetaminophen

NSAID = nonsteroidal anti-inflammatory drug, LA = local anesthetic

Conclusion

- Know your institution
 - Organizational structure, resources, type of services and specialties
- Work as a interprofessional team
- Formulate a plan, implement, and evaluate
 - Data driven
 - Safety

Example: Postoperative Long-Acting Opioids University of Minnesota Medical Center

- Long-acting oxycodone dose in elderly 10 mg orally twice daily
- Long-acting oxydodone for opioid-tolerant patients only

▼ Moderate to severe pain - Oral opioids (Long Acting - ONLY for OPIOID TOLERANT patient) select one

- Long acting oxyCODONE for > 65 years old with low urine output or low GFR
- Long acting oxyCODONE (NOT for elderly patients with poor renal function)

EPIC Order Set Instruction: patient must be opioid-tolerant taking an equivalent of 30 mg oral morphine per day

Example: Postoperative Pain Orders for Elderly University of Minnesota Medical Center

▼ Moderate to severe pain - Oral opioids (short acting - immediate release) select one

Pain Meds for > 65 years old with low urine output or low GFR

oxyCODONE (ROXICODONE) immediate release tablet

5 mg, Oral, EVERY 3 HOURS PRN, moderate to severe pain, Hold while on PCA or with regular IV opioid dosing., Post-procedure

oxyCODONE-acetaminophen (PERCOCET) 5-325 MG per tablet

1 tablet, Oral, EVERY 4 HOURS PRN, moderate to severe pain, Hold while on PCA or with regular IV opioid dosing., Post-procedure

HYDROcodone-acetaminophen (NORCO) 5-325 MG per tablet

1 tablet, Oral, EVERY 4 HOURS PRN, moderate to severe pain, Hold while on PCA or with regular IV opioid dosing., Post-procedure

HYDROcodone-acetaminophen (LORTAB) solution 7.5-325 mg/15 mL

10 mL, Oral, EVERY 4 HOURS PRN, moderate to severe pain, Hold while on PCA or with regular IV opioid dosing., Post-procedure

HYDROmorphine (DILAUDID) tablet

1-2 mg, Oral, EVERY 3 HOURS PRN, moderate to severe pain, Hold while on PCA or with regular IV opioid dosing., Post-procedure

Ask the Experts: Issues Related to the Management of Postoperative Pain

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