

Emerging Techniques in Acute Pain Management

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Faculty Disclosure

This presentation may include the discussion of unapproved uses of pharmaceuticals and devices.

Research Grants:

SkyePharma/Endo, OrthoMcNeil, Progenics, Adolor, Bristol-Myers Squibb, Pfizer

Consultant:

Adolor, Endo, Ortho McNeil

Speaker's Bureau:

Endo

Statistics in Post-Surgical Pain

- >80% of patients reported pain after surgery
 - 4 out of 5 of whom reported moderate to severe pain¹
- Approximately 50% of surgical patients felt their pain relief was inadequate²

1. Shang AB, et al. *Drugs*. 2003;63(9):855-867.

2. National Center for Health Statistics. Available at: www.ohsuhealth.com. Accessed April 2, 2004.

Rational for Development

Unmet needs

or

What we have leaves a
lot to be desired!

Analgesic Gaps

- Specific time period during pain therapy when pain is unrelieved
 - PRN
 - Transitions
 - Technology failures

Epidural Analgesia with Catheters

- Success rate of 70%¹
- Equipment may impede mobility
- Compatibility with anticoagulation²

1. Ready LB. Reg Anesth Pain Med. 1999;24:499-505

2. www.asra.com Consensus Statement

IV-PCA Problems

- IV site problems
- Pump issues
 - Failure
 - Medication and programming errors
- Catheter issues
 - Kinks and obstructions
 - Interference with patient mobility

IV PCA Safety Issues

- IV PCA-related issues are well-known^{1,2}
 - Programming errors
 - Patient tampering
 - Device malfunctions
- Approximately 2% of medication errors result in patient harm
 - When PCA pumps are involved, the chance for patient harm increases >3.5-fold³

1. Vicente KJ, et al. *Can J Anesth* 2003;50:328-332.

2. Ashburn MA, et al. *Clin J Pain*. 1994;10:52-56.

3. USP Center for the Advancement of Patient Safety. *Patient-Controlled Analgesia Pumps*. Rockville, Md: The United States Pharmacopeial Convention Inc; September 2004. USP Quality Review, No. 81.

External Pump and Catheter Technology

- Increased patient risk
- Interference with physical therapy, activities of daily living (ADLs)
- Burden of care on staff
- Total cost is difficult to estimate but is likely high
- Inherent failure rate

Iontophoresis

A system of drug delivery by which a charged molecule penetrates the skin in the presence of an electric field

The Barrier: Skin

- Lipophilic
- “Brick and mortar” structure

Iontophoresis

- Active delivery
- Small molecules
- Charged (positive) molecules
- Lipophilic
- Local or systemic delivery
 - Adjunctive agents

Iontophoresis

- Opioids (fentanyl HCl)
 - Patient activated transdermal analgesia (Fentanyl PATS)
 - Small, self contained system with patient control button placed on upper arm or chest
 - Needle-free
 - “Credit card” size

Fentanyl PATS vs. Morphine IV-PCA Study Design

- Randomized, open-label study
- Treatment
 - Fentanyl PATS 40 µg/10 min; up to 6 doses/hour
 - IV morphine PCA 1 mg bolus, 5-minute lockout, maximum 10 mg/hour
- Randomization
 - 1:1 (PATS:PCA)
 - Major abdominal, orthopaedic or thoracic surgery
- Patients treated and assessed for up to 72 hours

Endpoints

- Primary

- Patient global assessment

- Pain control rated as excellent, good, fair, or poor by patient (at 24 hours or at early withdrawal)

- Secondary

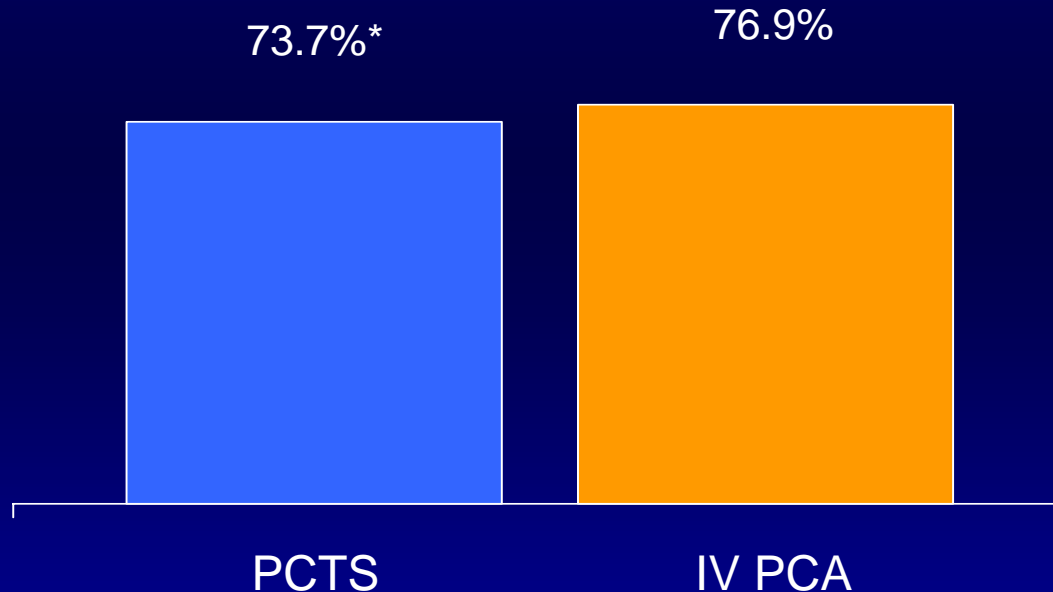
- Last pain intensity score (using VAS)

- VAS score obtained (every 24 hours or at early withdrawal)

- Discontinuation after ≥ 3 hours due to inadequate analgesia

Fentanyl PATS is equivalent to IV morphine PCA

Patient global assessment
of treatment success[†]



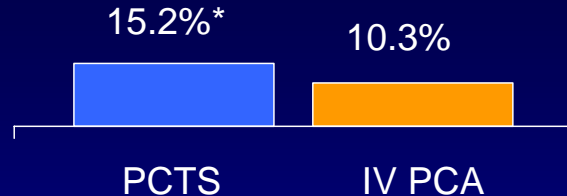
* $p=0.36$ vs IV PCA
(95% CI: -9.9 to -3.5)

[†]Defined as 'excellent' or 'good' pain control

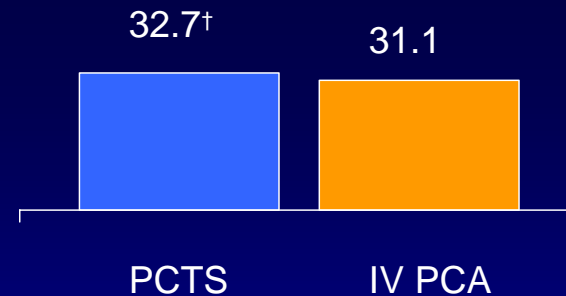
Viscusi ER, et al. JAMA 2004;291:1333–41.

Secondary endpoints support the equivalence of fentanyl PATS and IV morphine PCA

Withdrawal due to inadequate pain control



Last pain intensity score (100-point VAS scale)



*p=0.07 vs IV PCA

†p=0.45 vs IV PCA

Fentanyl PATS - Safety Results

| Adverse Events | Transdermal Fentanyl HCl (n=316) | IV PCA Morphine (n=320) |
|-----------------------|---|--|
| Nausea, % | 40.8 | 45.9 |
| Pruritus, % | 8.2 | 12.5 |
| Headache, % | 11.4 | 7.5 |
| Vomiting, % | 9.8 | 8.4 |
| Fever, % | 3.5 | 4.1 |
| Constipation, % | 3.8 | 2.2 |
| Hypoxia, % | 3.8 | 2.2 |
| Dizziness, % | 1.9 | 3.8 |

Liposomes

- Naturally occurring lipids slowly release content of vesicles
- Can deliver diverse agents
- Release profile can be varied by lipid composition

Lian T, et al: J Pharm Sci 2001;90:667-680.

Allen TM, et al: Science 2004;303(5665):1818-1822.

Viscusi ER, et al: Reg Anesth 2005;30: 292-294.

Liposome Structure

- Unilammellar vesicles
 - Single outer bilayer
- Multilammellar vesicles
 - Concentric lipid bilayers
- Multivesicular
 - DepoFoam™
 - Nonconcentric multiple lipid layers

Mantripragada S: Prog Lipid Res 2002;41:392-406 .

Kim S, et al: Biochim Biophys Acta 1983;728:339-348.

Multivesicular Liposome

- Spherical particles
 - Nonconcentric chambers
 - Aqueous phase (drug)
 - Lipid bi-layer
- Application
 - Intrathecal, chemotherapy
 - Epidural, morphine
 - Bupivacaine

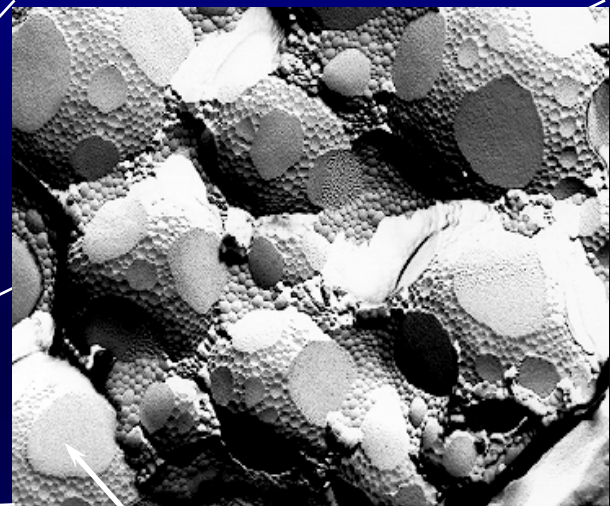
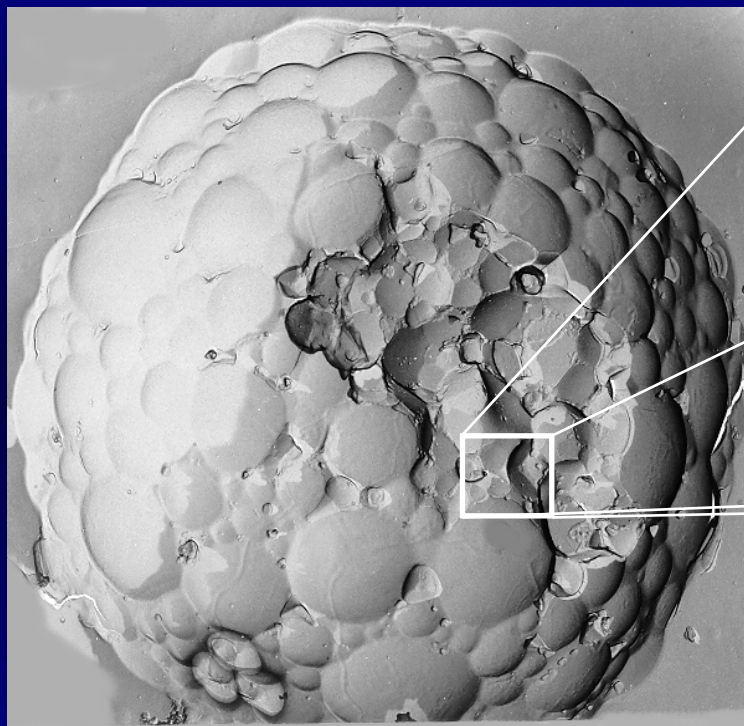
Howell SB: Cancer J 2001;7:219-227.

Mantripragada S: Prog Lipid Res 2002;41:392-406.

Yaksh, et al: Drug Deliv 2000;7:27-36.

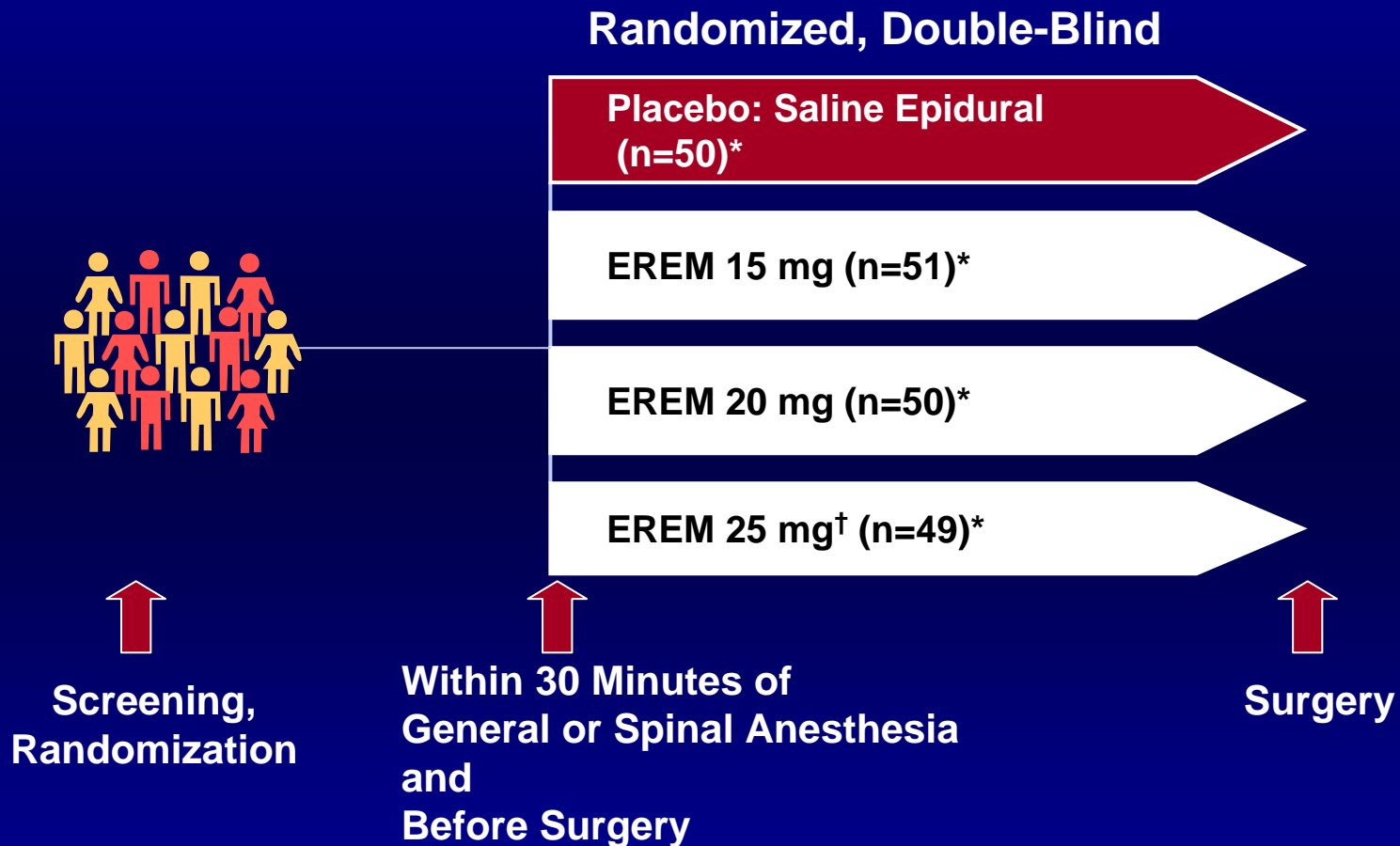
Viscusi ER, et al: Reg Anesth 2005;30: 292-294.

Multivesicular Lyposome



**Chambers filled
with drug**

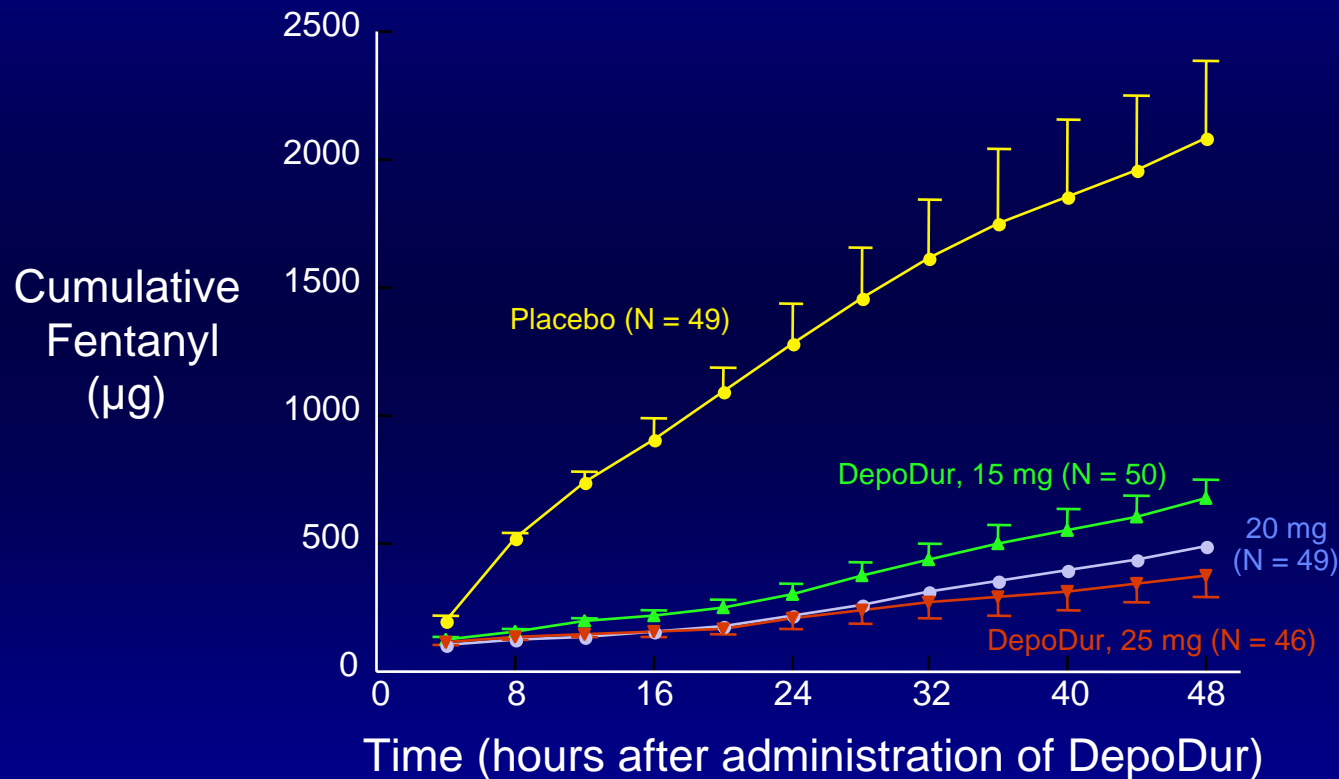
Hip Arthroplasty: Study Design



*Randomized patients;

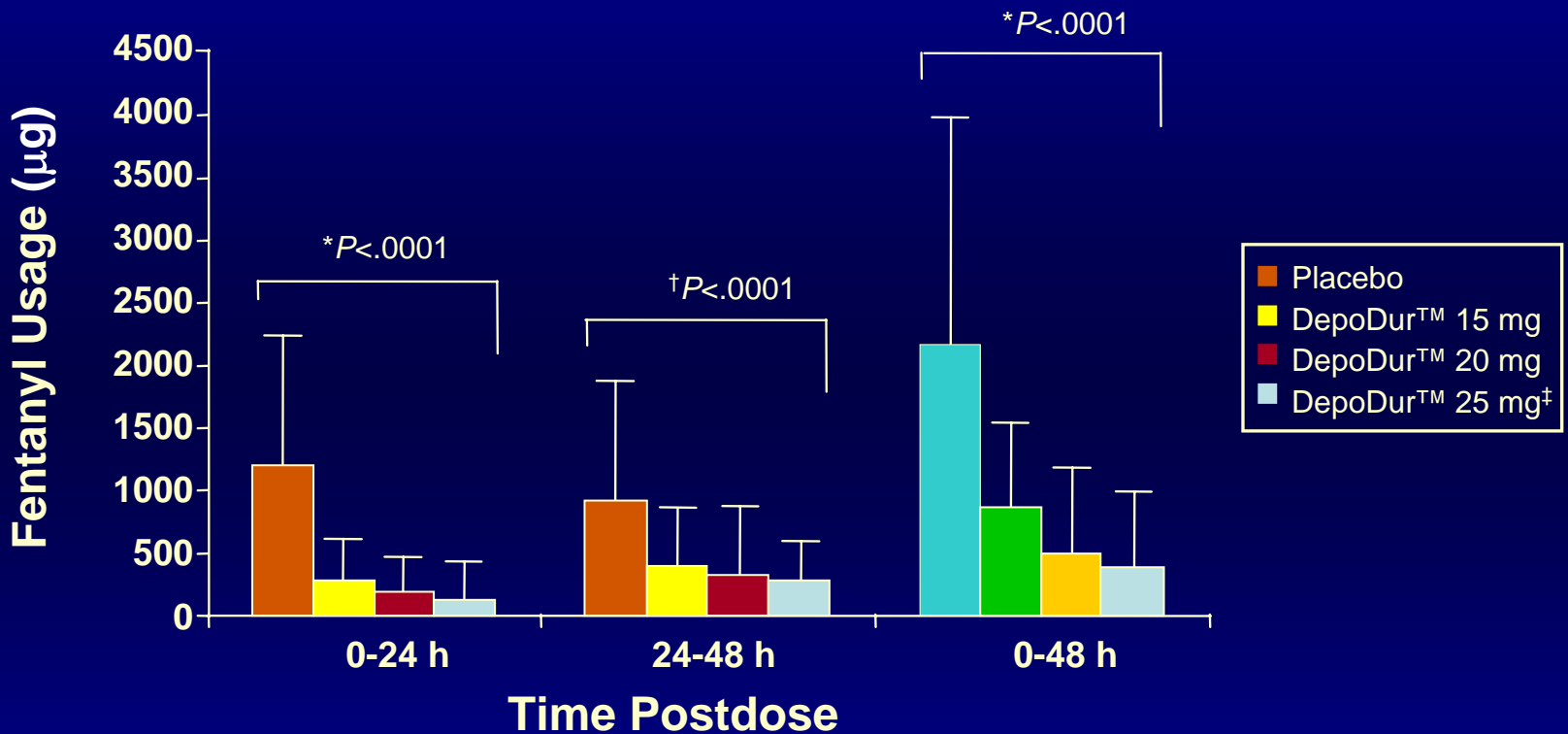
[†]EREM is not approved at the 25 mg dose.

Hip Arthroplasty: Cumulative Supplemental IV-PCA Fentanyl over 48 Hours Post-op



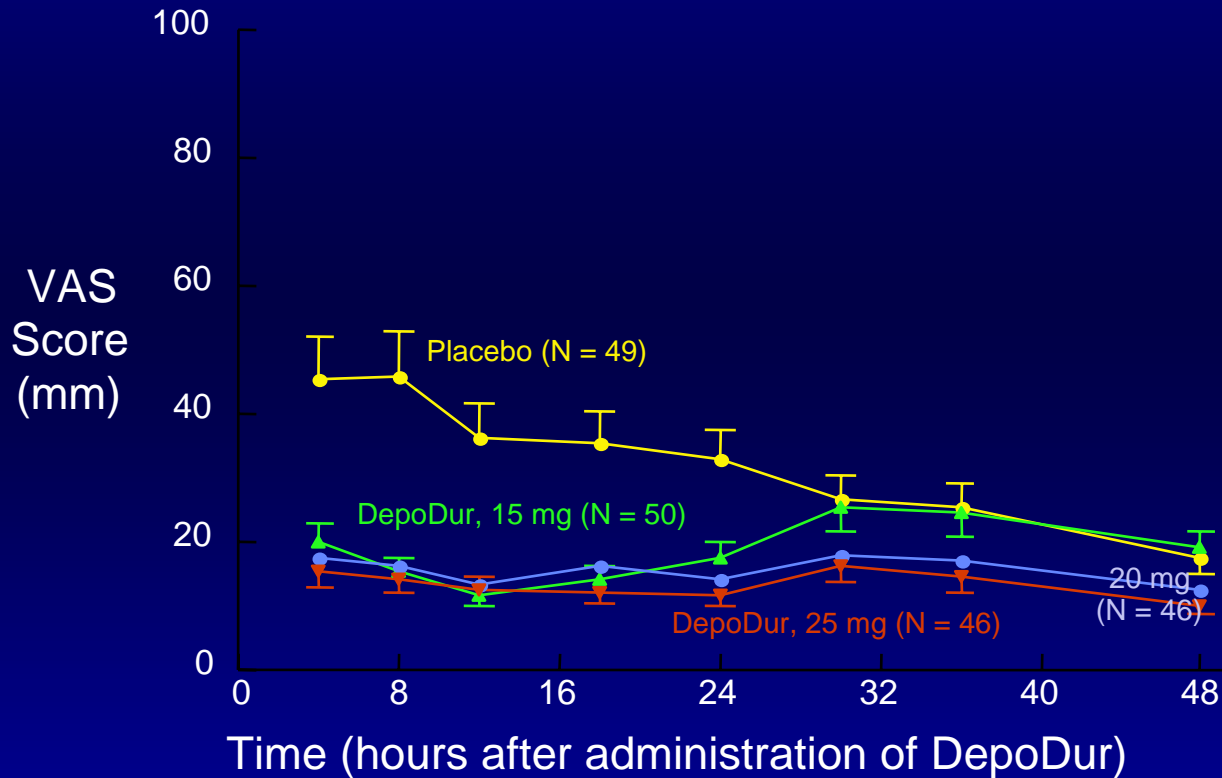
Mean, SE
 $P < 0.0001$ (overall ANOVA between groups)

Hip Arthroplasty: Total Postoperative Fentanyl Usage



**P* value is for overall treatment and all pairwise comparisons with placebo. †*P* value is for overall treatment; all pairwise comparisons with placebo were *P* < .0025.

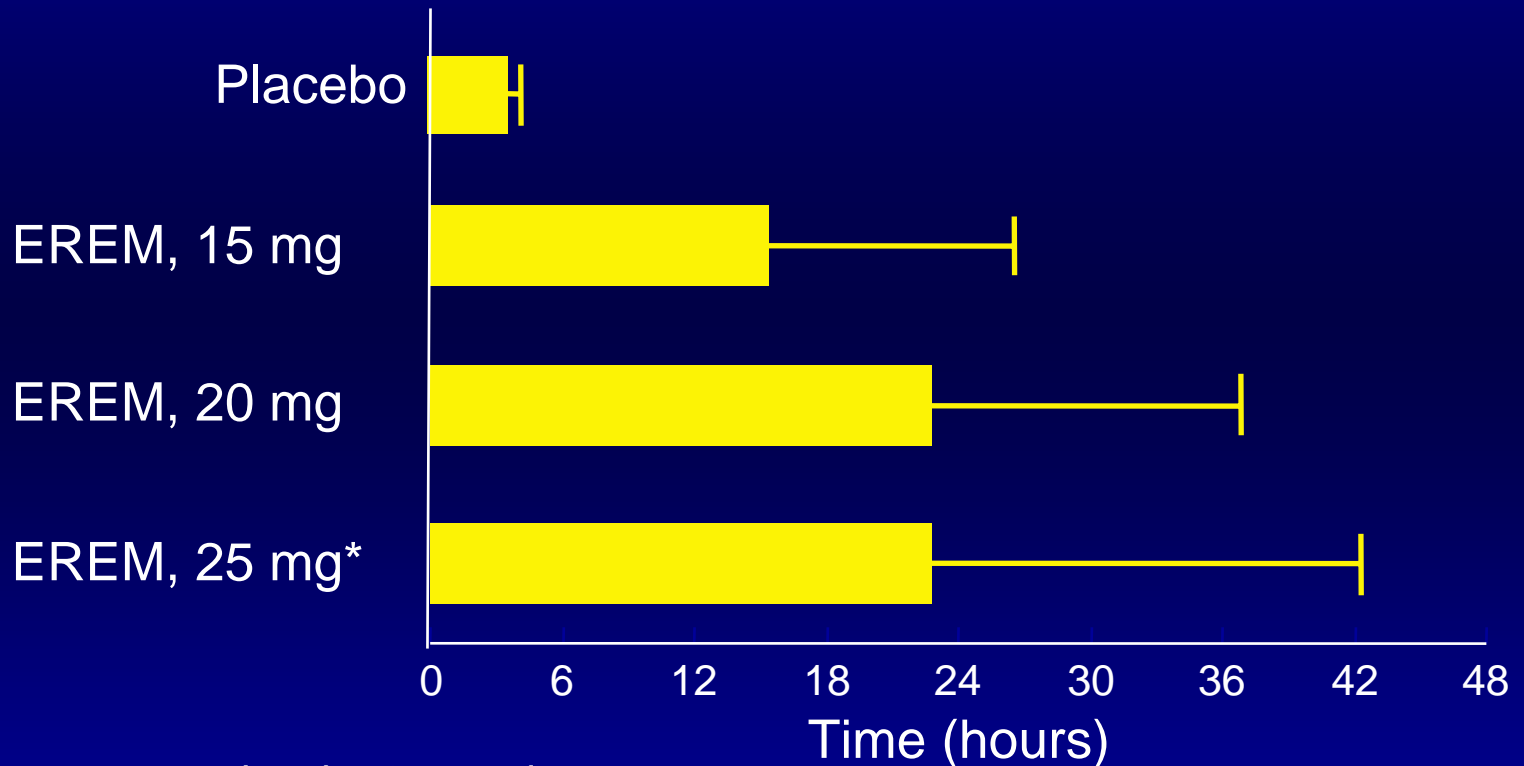
Hip Arthroplasty: Pain Scores Through 48 Hours Post-op



DepoDur™ full Prescribing Information.

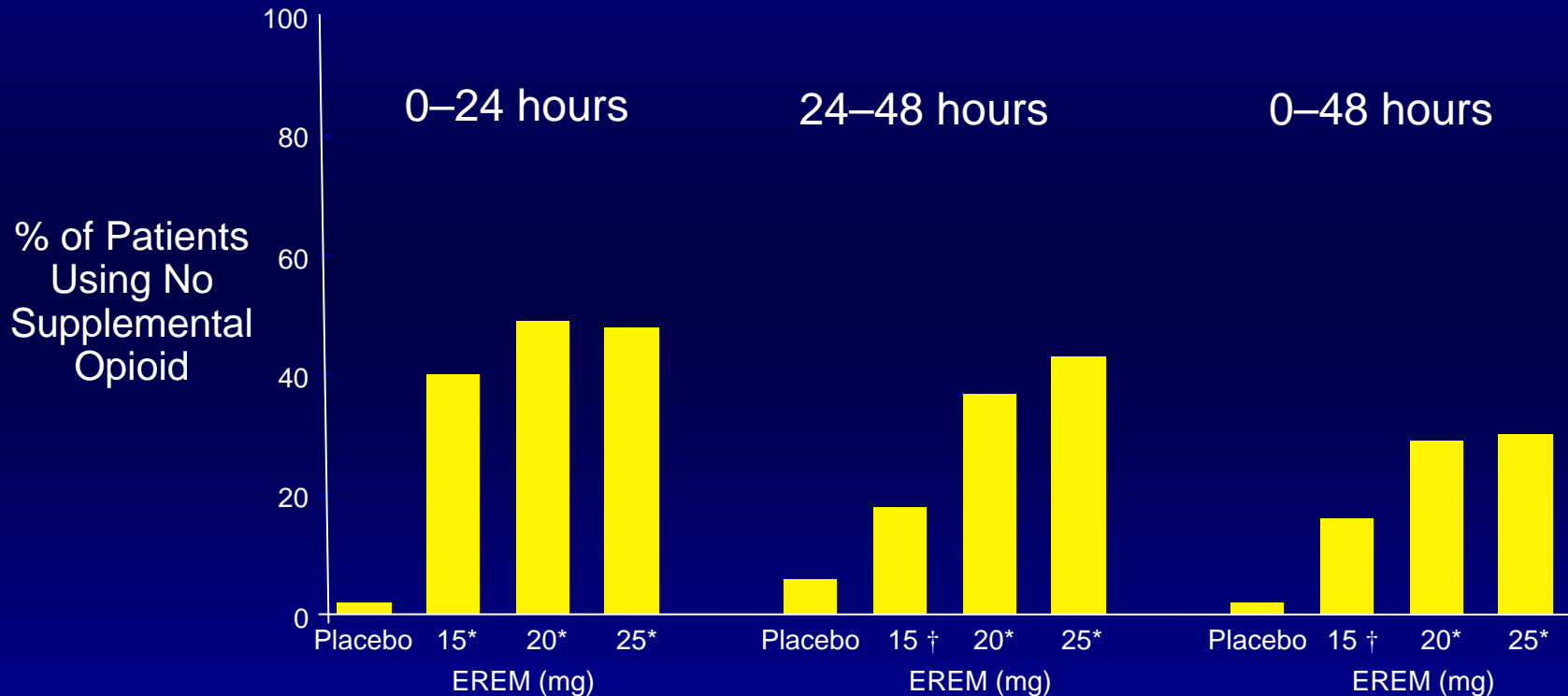
Chadds Ford, PA: Endo Pharmaceuticals Inc; 2004.

Hip Arthroplasty: Time to First Postoperative Fentanyl Request



*EREM is not approved at the 25 mg dose.

Hip Arthroplasty: Patients Using No Supplemental Opioid



*EREM is not approved at the 25 mg dose.

* $P < .01$ compared with placebo.

† $P < .05$ compared with placebo.

Extended Release Epidural Morphine: Respiratory Depression

- 4% of patients (all trials) received an antagonist
- At approved doses, RD occurred by 16 hours
- RD is dose dependent and increases in the elderly
- Consider risk factors (sleep apnea, morbid obesity, history of respiratory issues)
- Doses from clinical trials were likely higher than clinical practice since they were monotherapy.

Morphine Sulfate

Extended-release Liposome Injection

- Summary
 - Single epidural injection
 - 48 hours of continuous pain relief
 - Catheter-free delivery
 - No external pump technology
 - Side effects similar to standard opioids
 - Nausea, vomiting, pruritus, respiratory depression

Morphine Sulfate Extended-release Liposome Injection

- Indications and usage
 - Single-dose lumbar epidural administration
 - For pain following major surgery
 - Given prior to surgery or after umbilical cord clamping during cesarean delivery
 - 48 hours of monitoring in medically supervised setting

Morphine Sulfate

Extended-release Liposome Injection

- Drug Interaction
 - Epidural local anesthetic
 - Administer at least 15 minutes following test dose (lidocaine with epinephrine)

Introducing EREM: Clinician's Perspective

- Start at a low dose and plan some supplement
- Use familiar surgical models
- Avoid patients with opioid tolerance and respiratory risk factors
- Multimodal therapy works!
- Plan oral or a few IV rescue doses before initiating PCA

Selective Opioid Antagonists

- Selective postoperative inhibition of gastrointestinal opioid receptors
- Preserve analgesia
- Enhance gastrointestinal (GI) function

Selective Opioid Antagonists in Development

- Alvimopan
 - Oral delivery
 - Administered pre- and post-op
 - Submitted for approval
- Methylnaltrexone
 - IV delivery
 - Administered postop
 - Phase II trial completed

Selective Antagonism

- Earlier return of bowel function
- Can use a standard opioid but enhance side effect profile
- May reduce time to discharge
- Quality of life
- Excellent safety profile

Intravenous Acetaminophen (Paracetamol)

- Nonopioid, non NSAID
- Marketed in Europe
- Component of multimodal analgesia
- Effective analgesia with low incidence of adverse events following major orthopedic surgery¹

Parecoxib

- A parenteral COX-2 specific inhibitor
- Compared with nonspecific NSAIDs, COX-2 specific inhibitors may reduce risk of postoperative bleeding
- Effective analgesia following gynecologic and orthopedic procedures^{1,2,3}

1. Barton SF, et al: Anesthesiology 2002;97:306-14

2. Bikhazi GB, et al: Am J Obstet Gynecol 2004;191:1183-91

3. Rasmussen GL: Am J Orthop 2002;31:336-46

Future of Pain Management

- Ease of use
- Patient vs equipment focus
- Easy to administer
- Improved side effect profile
- High success rate
- Compatible with clinical practice

What will Pain Management Look Like in the Near Future?

- Multimodal
- Continuous delivery to avoid analgesic gaps
- Less invasive
- Decreased side effects
- Less cumbersome for patient and caregivers
- Enhanced satisfaction