To Use or Not to Use Liposomal Bupivacaine: Managing Pharmacotherapy Costs in Orthopedic Procedure Pain Management

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Heather Weese, PharmD, BCPS
Director, Pharmacy Operations & Informatics
Community Health Systems
Franklin, TN

Yin Wong, PharmD, BCPS
Fellow, Health Information & Clinical Outcomes
Wolters Kluwer Health & Community Health Systems
Franklin, TN

Disclosure

- Dr. Heather Weese - Nothing to disclose
- Dr. Yin Wong – Employee of Wolters Kluwer Health: a medical content company

Today's Presentation Format

1. Literature Review of liposomal bupivacaine (LB) use in orthopedic procedures: total knee arthroplasty and total hip arthroplasty
2. Health economic outcomes study of liposomal bupivacaine use at Community Health Systems
3. Formulary management approach for liposomal bupivacaine

Learning Objectives

- Discuss the current literature on the efficacy and safety of liposomal bupivacaine in orthopedic procedures
- Describe the findings of an enterprise-wide liposomal bupivacaine health economic study
- Propose new strategies on managing liposomal bupivacaine use for possible cost savings

Liposomal Bupivacaine Literature Review

Use of Liposomal Bupivacaine in Orthopedic Procedures (TKA/THA)

Background

Liposomal Bupivacaine Injectable Suspension (Exparel®)

- Liposomal bupivacaine (Exparel®) approved by FDA in Nov. 2011 indicated for administration into the surgical site to produce postsurgical analgesia
  - Bone model – Bunionectomy
  - Soft tissue model – Hemorrhoidectomy
- Comparing Exparel® to bupivacaine hydrochloride:
  - Differ in duration of action: 24 – 96 hours vs. 2 – 9 hours, respectively
  - Half life: 24 – 34 hours vs. 2.1 hours, respecti
- Efficacy demonstrated in trials: decrease in score and reduction in opioid consumption

Picture credit: Which Drug is Better for Post-op Pain Control?
https://www.outpatientsurgery.net/surgical-services/pain-management/which-drug-is-better-for-post-op-pain-control--ambulatory-anesthesia-15

HEALTHTRUST

Background

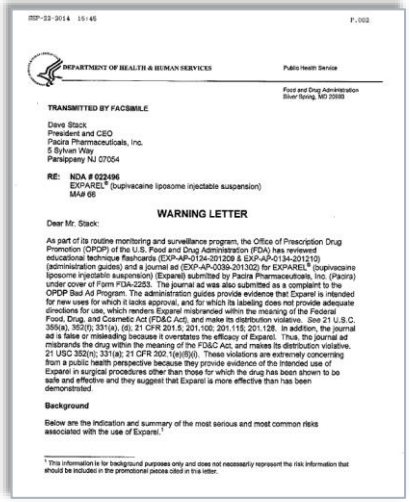
Food and Drug Administration Warning

- September 2014 – FDA issued a warning letter to Pacira Pharmaceuticals, Inc. for Exparel®(liposomal bupivacaine):
  - Administration: Inadequate directions for use
  - Indications: Claims suggest Exparel® can be used for other procedures but evidence for Exparel® efficacy and safety came from bunionectomy and hemorrhoidectomy
  - Overstatement of efficacy: claims suggest Exparel® effectiveness last up to 72 hours but evidence suggest that Exparel® effectiveness beyond
  - 24 hours has not been demonstration type or site

Background, *continued*

Food and Drug Administration Warning

- March 2016 – Resolution of FDA Legal Action:
  - Administration: Exparel® can be mixed with bupivacaine HCl
  - Indications: use of Exparel® for administration at surgical site is NOT limited to any specific surgery type or site
  - Efficacy: significant treatment effect for Exparel® compared to placebo for the first 72 hours in the pivotal hemorrhoidectomy study



DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Dave Stack
President and CEO
Pacira Pharmaceuticals, Inc.
5 Sylvan Way
Parsippany NJ 07054

RE: NDA # 022496
EXPAREL® (bupivacaine liposome injectable suspension)
MA# 66

WARNING LETTER

Dear Mr. Stack:

As part of its routine monitoring and surveillance program, the Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed educational technique flashcards (EXP-AP-0134-201209 & EXP-AP-0134-201210) (administration guides) and a journal ad (EXP-AP-0039-201302) for EXPAREL® (bupivacaine liposome injectable suspension) (Exparel) submitted by Pacira Pharmaceuticals, Inc. (Pacira) under cover of Form FDA-2253. The journal ad was also submitted as a complaint to the OPDP Bad Ad Program. The administration guides provide evidence that Exparel is intended for new uses for which it lacks approval, and for which its labeling does not provide adequate directions for use, which renders Exparel misbranded within the meaning of the Federal Food, Drug, and Cosmetic Act (FD&C Act), and make its distribution violative. See 21 U.S.C. 369(a), 352(f); 331(a), (d); 21 CFR 201.5, 201.100; 201.115, 201.128. In addition, the journal ad is false or misleading because it overstates the efficacy of Exparel. Thus, the journal ad misbrands the drug within the meaning of the FD&C Act, and makes its distribution violative. 21 USC 352(n); 331(a); 21 CFR 202.1(e)(6)(i). These violations are extremely concerning from a public health perspective because they provide evidence of the intended use of Exparel in surgical procedures other than those for which the drug has been shown to be safe and effective and they suggest that Exparel is more effective than has been demonstrated.

Background

Below are the indication and summary of the most serious and most common risks associated with the use of Exparel.[1]

[1] This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional pieces cited in this letter.

Literature Review

Methods

Electronic databases searched: **CENTRAL** (Cochrane Library), **MEDLINE** (Ovid), **EMBASE** (Ovid), **International Pharmaceutical Abstracts** (Ovid), **SCOPUS**

Medical subject headings (MeSH) or equivalent and key terms used: liposomal bupivacaine, Exparel, postoperative pain, postoperative complications, orthopedic, knee arthroplasty or replacement, hip arthroplasty or replacement

Criteria for Literature Review

Types of studies

- Randomized controlled trials
- Pro/retrospective evaluative studies

Types of participants

- Age ≥ 18 undergoing total knee or hip arthroplasty receiving liposomal bupivacaine

Types of outcome measures

- Pain scores
- Opioid consumption
- Adverse events
- Range of motion/ ambulation distance
- *Length of stay/ satisfaction*

Results

- Total of 115 articles from 5 databases identified
- Investigator screened the results and removed abstracts/articles based on prespecified criteria
  - **5 randomized controlled trials**
  - **10 cohort/case-control studies**

RANDOMIZED CONTROLLED TRIALS ANALYSIS

Literature Review

Summary Table of Analyzed Randomized Controlled Trials

Parameter	Bramlett et al. (2012)	Schroer, et al. (2015)	Surdam, et al. (2015)	Snyder, et al. (2016)	Collis, et al. (2016)
No. of Patients	138	111	80	70	105
Patient Population	Adults, TKA	Adults, TKA	Adults, TKA	Adults, TKA	Adults, TKA
Study Location	Multicenter; US and Czech Republic	Single center; US	Single center; US	Single center; US	Single center; US
Study Design	Phase 2, RCT, DB, PG, dose-ranging	PRO, Blinded, RCT	Randomized, PRO, blinded, RCT	PRO, DB, RCT	PRO, RCT
Follow-up	36 Days	4 days	4 days	10 days	42 days
Intervention	PAI LB vs. Bupivacaine + Epi	PAI LB + bupivacaine mix vs. bupivacaine	PAI LB vs. Femoral nerve block	PAI LB vs. combo cocktail¥	PAI LB vs. Modified Ranawat suspension*
Primary endpoints	AUC for NRS-A through Day 4	Pain scores (VAS)	Pain score (NRS)	Pain scores (NRS)	Pain scores (VAS)
		post-op opioid consumption		post-op opioid consumption	post-op opioid consumption
				Pain control satisfaction	ambulation distance
				Adverse events	Range of motion (ROM)
Secondary endpoints	NRS-A and NRS-R		Range of motion (ROM)		
	AUC of NRS-R through Day 4		Adverse events		
	post-op opioid consumption		post-op opioid consumption		
	care provider's satisfaction with postoperative analgesia		ambulation distance		
	Time to resumption of normal activities		Length of stay		
	Adverse events				

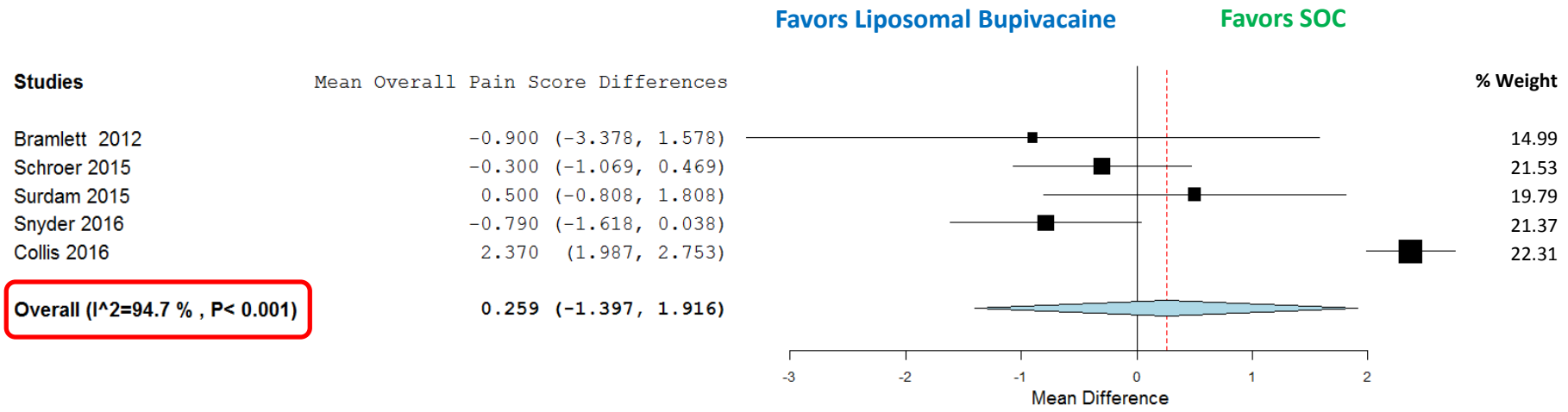
TKA = total knee arthroplasty; RCT = randomized, controlled trial; DB = double blinded; PG = parallel-group; PRO = prospective; PAI = periarticular injection; LB = liposomal bupivacaine; AUC = area under the curve; NRS = numeric rating scale; NRS-A = numeric rating scale on activity; NRS-R = numeric rating scale at rest; VAS = visual analog scale.

¥ combo cocktail consists of: ketorolac 30mg, morphine PF 5mg, epinephrine 0.6mg, Ropivacaine 400mg, QS to 100mL with 0.9% Normal Saline

*Ranawat cocktail consists of: 49.25mL of Ropivacaine (5mg/mL), 0.5mL of epinephrine (1mg/mL), 1mL of ketorolac (30mg/mL), 0.8mL of clonidine (0.1mg/mL), diluted with 48.45mL of 0.9% Normal Saline

Comparison of Overall Pain Scores

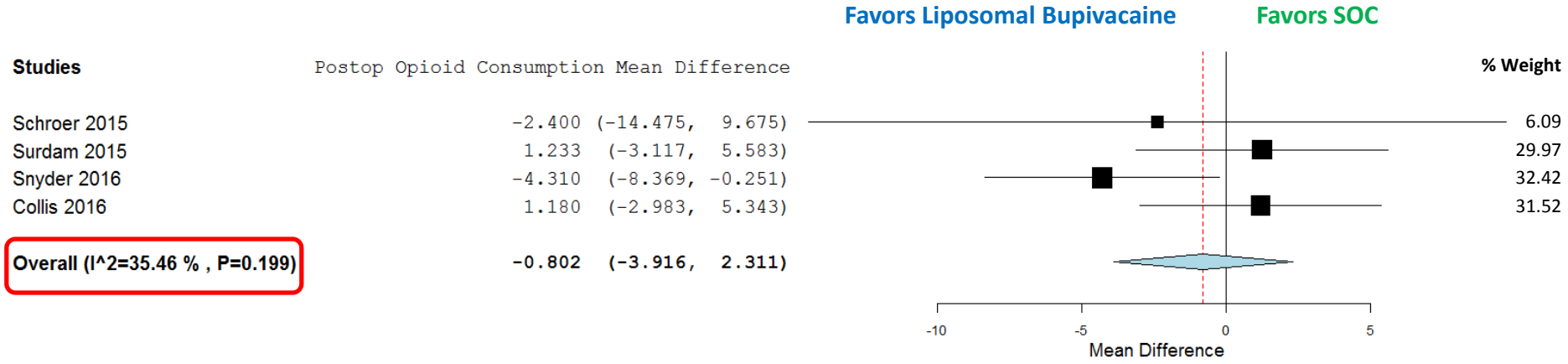
Forrest Plot



*SOC = Standard of Care: PAI bupivacaine ± epinephrine, femoral nerve block, concentrated cocktail, Ranawat suspension

Comparison of Postoperative Opioid Consumption

Forrest Plot



*SOC = Standard of Care: PAI bupivacaine ± epinephrine, femoral nerve block, concentrated cocktail, Ranawat suspension

Other Outcomes & Considerations

Other Outcomes

- **Range of motion (ROM)**
  - Surdam et al. 2015: greater ROM for FNB grp but only the first 24 hrs
  - Collis et al. 2016: no difference
- **Ambulation distance**
  - Surdam et al. 2015: no difference but more LB patients can ambulate on POD#0
  - Collis et al. 2016: LB grp had increase ambulation distance trend but no statistical significance
- **Adverse events**
  - Bramlett et al. 2012: no difference
  - Surdam et al. 2015: no difference
  - Snyder et al. 2016: 67.9% in control grp reported nausea vs. 32.1% in LB grp ($p<0.05$)
- **Length of stay (LOS)**
  - Surdam et al. 2015: avg. LOS is lowered in the LB grp (2.36 ± 0.71) vs. FNB grp (2.65 ± 0.48), ($p=0.03$) → mean difference = 6.9 hours

Considerations

- Post-op opioid consumption
  - Bramlett et al. 2012: no statistical significance to that endpoint, time to resumption of normal activities
- Interventions
  - PAI LB vs. (1) Bupivacaine +/- Epi
    (2) Femoral Nerve Block
    (3) Combo cocktail
  - Surdam et al. 2015: while FNB improves pain control and flexion on POD#0, FNB contributes to quadriceps weakness, delaying ambulation.
    - LB group had a 6x increase in the number of patients who can ambulate the day of surgery
- Variation between study site specific pain management protocol

Study Site Based Multimodal Pain Control Protocol

Parameter	Bramlett et al. (2012)	Schroer, et al. (2015)	Surdam, et al. (2015)	Snyder, et al. (2016)	Collis, et al. (2016)
Study Site	Multicenter	Single center, single surgeon	Single center, single surgeon	Single center	Singled center, single surgeon
Pre-op education		1 hour total knee education	education class		education class
Before surgery	APAP 1000mg TID x 24 hrs	APAP per instruction x 72 hrs			
Pre-op meds	IV Fentanyl or analogs allowed	Celecoxib 400mg x 1 OxyCONTIN 20mg x 1 Scopolamine patch 6mg x 1	Oxycodone SR Ondansetron Scopolamine patch (if <65)		
Intra-op meds		Spinal fentanyl 25mcg + bupivacaine 15mg Dexamethasone 8 mg Ondansetron 8mg Tranexamic acid 10mg/kg (max 1000mg)	Spinal bupivacaine 0.75% FNB group: single shot block, 40mL ropivacaine 0.5%, 1:200,000 epi, 30mg Tetracaine 1%	Spinal regional anesthesia ropivacaine 0.75% general anesthesia propofol 1%	single shot femoral & sciatic block with ropivacaine
Post-op meds	Ketorolac 30mg IV, Ketoprofen 100mg or diclofenac 75mg x 1 Rescue morphine via PCA on PRN; no basal rate	Morphine PCA PRN Ondansetron 8mg q6hrs x 24hrs then PRN	Ondansetron IV PRN or metoclopramide PO PRN		PCA
If PO is allowed	APAP 1000mg for 96 hrs Oxycodone IR 5-10mg PO q4-6hrs PRN	Celecoxib 400mg daily OxyCONTIN 10mg q12hrs x 2 doses Hydrocodone or Oxycodone PRN	Celecoxib BID Oxycodone SR q12 hrs x 2 doses Hydrocodone q4hrs scheduled Oxycodone PRN		APAP 1000mg q8hrs x 24 hrs Tramadol 50mg q8hrs x 24hrs Oxycodone 5-10mg PO q4hrs PRN

Questions remain…

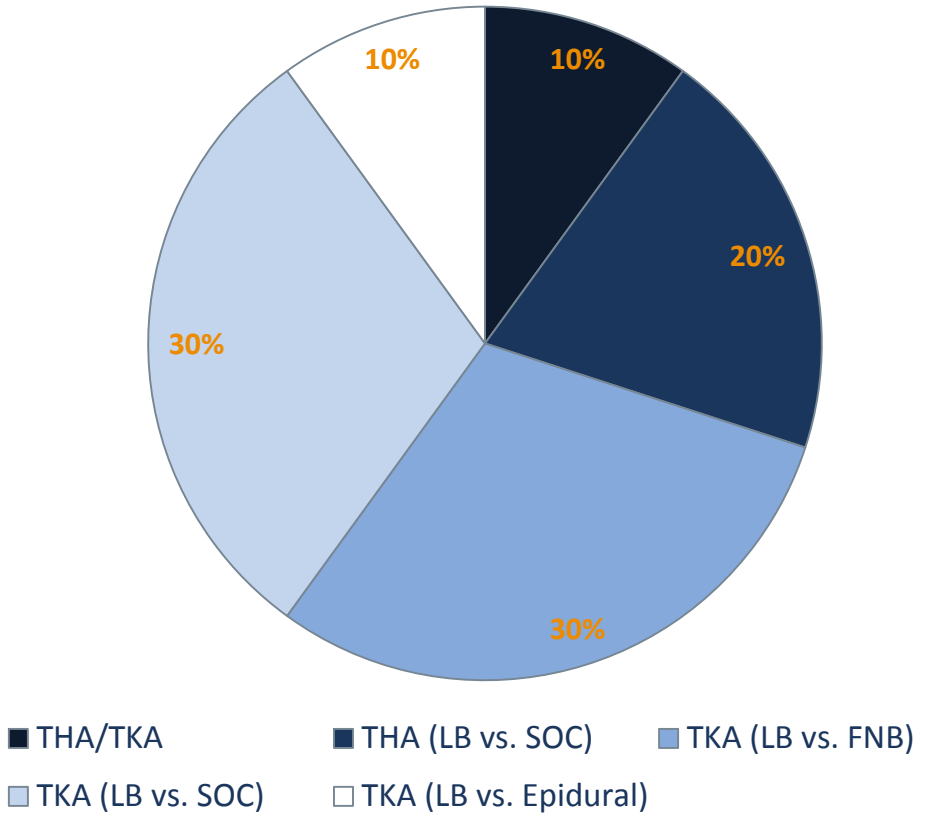
As a summary of all the RCTs on Exparel® use in TKA

1. Can the use of Exparel® lead to better postoperative pain control in orthopedic surgery?
2. Does the use of Exparel® as part of multimodal pain management protocol leads to reduction of opioid consumption? Reduction in opioid related adverse events?
3. Does the use of Exparel® associate with early ambulation and lead to **shorter length of stay**?

OBSERVATIONAL STUDIES ANALYSIS

Observation Studies For Exparel® (Liposomal Bupivacaine) in Total Hip/Knee Arthroplasty (THA/TKA)

Total # of Observation Studies



Total of 10 observational studies from literature search

Periarticular injection of liposomal bupivacaine vs.

- Standard of Care
- Femoral Nerve Block
- Epidural

Assessed in:

- Total Hip Arthroplasty
- Total Knee Arthroplasty

Exparel® Use in Total Hip Arthroplasty

Periarticular Injection of Liposomal Bupivacaine vs. Standard of Care

Trial	Study Design	Intervention	Results
Barrington, et al. (2015)	Quasi-experimental study for TKA/THA (n=2248)	Pre-group: PAI bupi + morphine ± ketorolac vs. Post-group: PAI LB	▪ **Avg. VAS score:** 2.30 vs. 1.67 (p<0.0001) ▪ **% of VAS pain score as 0:** 43.4% vs. 57.3% (p<0.0001) ▪ **Total direct hospital costs**: avg. reduction of $1246/pt ▪ **LOS:** reduced from 2.69 to 2.40 days (p<0.001) *Funded by Pacira Pharmaceuticals, did not report opioids consumption, some patients received FNB (did not specify), did not report multimodal analgesia protocol*
Domb et al. (2014)	Retrospective cohort study for THA (n=58)	PAI LB + bupi + epi vs. PAI bupi + epi	▪ **Post-op opioid consumption:** 24mg vs. 53.35mg (p<0.0001) only in the first 24hrs; no diff after ▪ **VAS pain score:** no diff ▪ **LOS:** 1.93 days vs. 2.47 days (p≤0.05) *No difference in pain score, reduction of opioid consumption only for first 24 hours*
Yu et al. (2016)	Quasi-experimental study for THA (n=1272)	Pre-group: SOC (no PAI LB) vs. Post-group: PAI LB	▪ **Pain scores**: LB grp less pain in the first 8 hrs (p=0.031) ▪ **Post-op opioid consumption:** LB grp used less narcotics for POD 0 and POD 1 (p<0.001), no diff after ▪ **LOS**: 2.93 vs. 2.62 days (p<0.001) mean diff = 0.31 days ▪ **Discharge location:** LB grp 5.19% more pts discharged home rather than rehab *Similar pain scores except for the first 8 hours*

TKA = total knee arthroplasty; THA = total hip arthroplasty; PAI = periarticular injection; LB = liposomal bupivacaine; Bupi = bupivacaine HCl; Avg. = average; VAS = visual analog scale; LOS = length of stay; FNB = femoral nerve block; epi = epinephrine; diff = difference; SOC = standard of care; grp = group

Exparel® Use in Total Knee Arthroplasty

Periarticular Injection of Liposomal Bupivacaine vs. Femoral Nerve Block

Liposomal Bupivacaine

Broome et al. (2014): *stats significance not provided*

- Pain scores: POD#1 4.0 vs. 4.9; POD#2 4.7 vs. 5.3
- LOS: 53 vs. 60 hours
- Cost savings: $600 per patient for PAI LB

Horn et al. (2015):

- Physical therapy sessions: 2.3 vs. 3.5 sessions (p=0.002)
- LOS: 1.5 vs. 1.9 days (p=0.032) → avg. reduction of 0.375 days
- Cost savings: PT $480, LOS $795

Cien et al. (2015):

- LOS: 1.58 vs. 2.05 days (p<0.001)
- Avg. hospitalization costs: $26,472 vs. $28,546 (p<0.001)

Femoral Nerve Block

Broome et al. (2014):

- IV rescue opioid use: reduced by 19% in LB grp (not stats significant)

Cien et al. (2015):

- Opioid consumption: 121 vs. 199mg (p=0.075)

Patients who received FNB also got PCA Hydromorphone post-op as part of protocol

Favors LB **Favors FNB**

Exparel® Use in Total Knee Arthroplasty

Periarticular Injection of Liposomal Bupivacaine vs. Standard of Care

Liposomal Bupivacaine

Webb et al. (2015) *No PAI*

- Opioids consumption at 48 – 72 hours: 60.97 mg vs. 89.74mg (p=0.009)
- LOS: 2.64 days vs. 3.06 days (p=0.004) in subset of patients with BMI <40, CCI 0 – 3

Heim et al. (2015) *Epidural and PAI ropivacaine + ketorolac + epi*

- Pain scores sum after POD#1: 2.0 ± 3.6 vs. 32.7 ± 23.4 (p<0.001)
- Overall opioid consumption: 18.7 ± 23.6mg vs. 42.4 ± 25.2mg (p=0.001)
- Ambulation distance POD#1: 133.8 ± 47.2 feet vs. 75.0 ± 46.7 feet (p<0.001)
- LOS: 1.04 vs. 2.0 days (p<0.001)

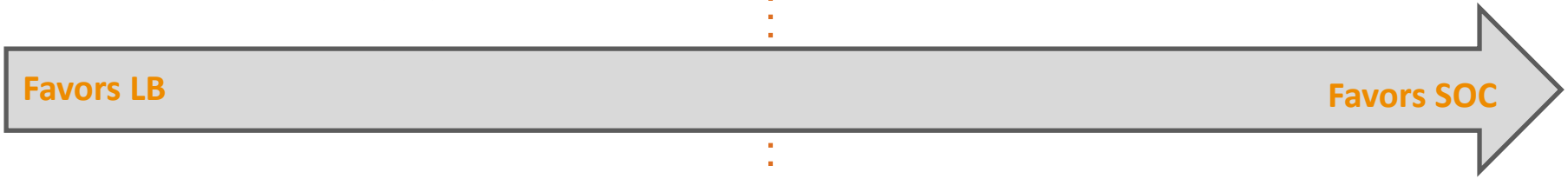
Standard of Care

Bagsby et al. (2014) *PAI ropivacaine + morphine + epi*

- Pain scores: after the first 24 hours 4.89 ± 1.35 vs. 4.38 ± 1.60 (p=0.04)
- % of patients reporting mild pain: 16.9% vs. 47.6% (no stats significance provided)
- Opioid consumption: no difference

White et al. (2015) *No PAI*

- AUC of NRS pain score: 199.6 ± 67.1mg vs. 192.9 ± 70.4mg (p=0.658)
- Opioid consumption: LB grp consumed more opioids in the first 48 hrs by 10mg (no stats significance)



Where does Exparel® stand in terms of its use in total knee/hip arthroplasty?

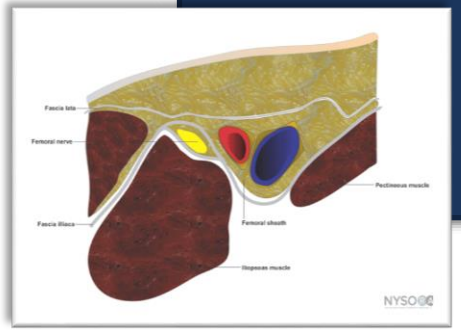
Standard of Care

?

Liposomal Bupivacaine (Exparel®)

>

Femoral Nerve Block



Do we now have answers for the questions?

As a summary of all the observational studies + RCTs on Exparel® use in TKA/THA

1. Can the use of Exparel® lead to better postoperative pain control in orthopedic surgery?
2. Does the use of Exparel® as part of multimodal pain management protocol lead to reduction of opioid consumption? Reduction in opioid related adverse events?
3. Does the use of Exparel® associate with early ambulation and lead to **shorter length of stay**?

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Health Economic Outcomes Evaluation of Liposomal Bupivacaine (Exparel®) for Orthopedic Procedures Diagnosis Related Group 469 & 470

A Community Health Systems Enterprise-wide Study

Acknowledgement

This health system study has been a collaborative effort; we would like to acknowledge the following individuals:

Primary Investigators:

- Heather Weese, PharmD, BCPS (CHS Pharmacy Operations & Informatics Director)
- Yin Wong, PharmD, BCPS (Health Information & Clinical Outcomes Fellow)

Research Supervising Investigators:

- Trent Beach, PharmD, MBA, MHA, BCPS, FASHP, FACHE (CHS Clinical Pharmacy & Education Director)
- Robert Fink, PharmD, MBA, FACHE, FASHP, BCNSP, BCPS (Quorum Health Corporation VP of Pharmacy & Ancillary Services)
- Beverly Bowman, RN, MNSc (CHS Surgical Services Senior Director)
- Kimberly Wellborn, PT, MBA (CHS Physical Therapy Services Senior Director)

We have also received assistance from the following individuals:

- Andrew Moseley Jr, CPA (CHS Clinical Analysis Director)
- Philip Odom (CHS Data Analytics & Reporting Analyst II)
- Bobby Parker, RPh (InPharmics® Founder)
- Paul Talley, MBA (CHS Quality, Risk & Management Director)
- Facility Joint Care Coordinators who participated in data collection

Study Design

Study Design	Multicenter retrospective-prospective observational case-control study
Primary Endpoint	• Drug-cost per case (by DRGs) • Length of stay (LOS)
Secondary Endpoints	• Total analgesic consumption: opioid, NSAID, Ofirmev®, acetaminophen PO/PR • Pain intensity score • Ambulation distance
Inclusion	• ≥18 years of age • Undergoing a major joint replacement or reattachment of lower extremity surgical procedure (DRG 469/470)
Exclusion	• Pregnant or nursing • Concurrent surgery required analgesic treatment • Hypersensitivity or contraindication to bupivacaine
Study Period	• Primary endpoints: July 1st to October 31st, 2014 • Secondary endpoints: October 1st to 31st, 2014

Methods: Study Timeline & Data Collection

Retrospective

Prospective

Facility-based Joint Care Coordinators

- Pain Intensity Score
- Ambulation Distance

InPharmics Tool

Query patients who meet study criteria: cases identified by DRG 469 or 470 with Exparel® use, controls identified by DRG 469 or 470.

- Drug Acquisition Costs
- Patients' Length of Stay

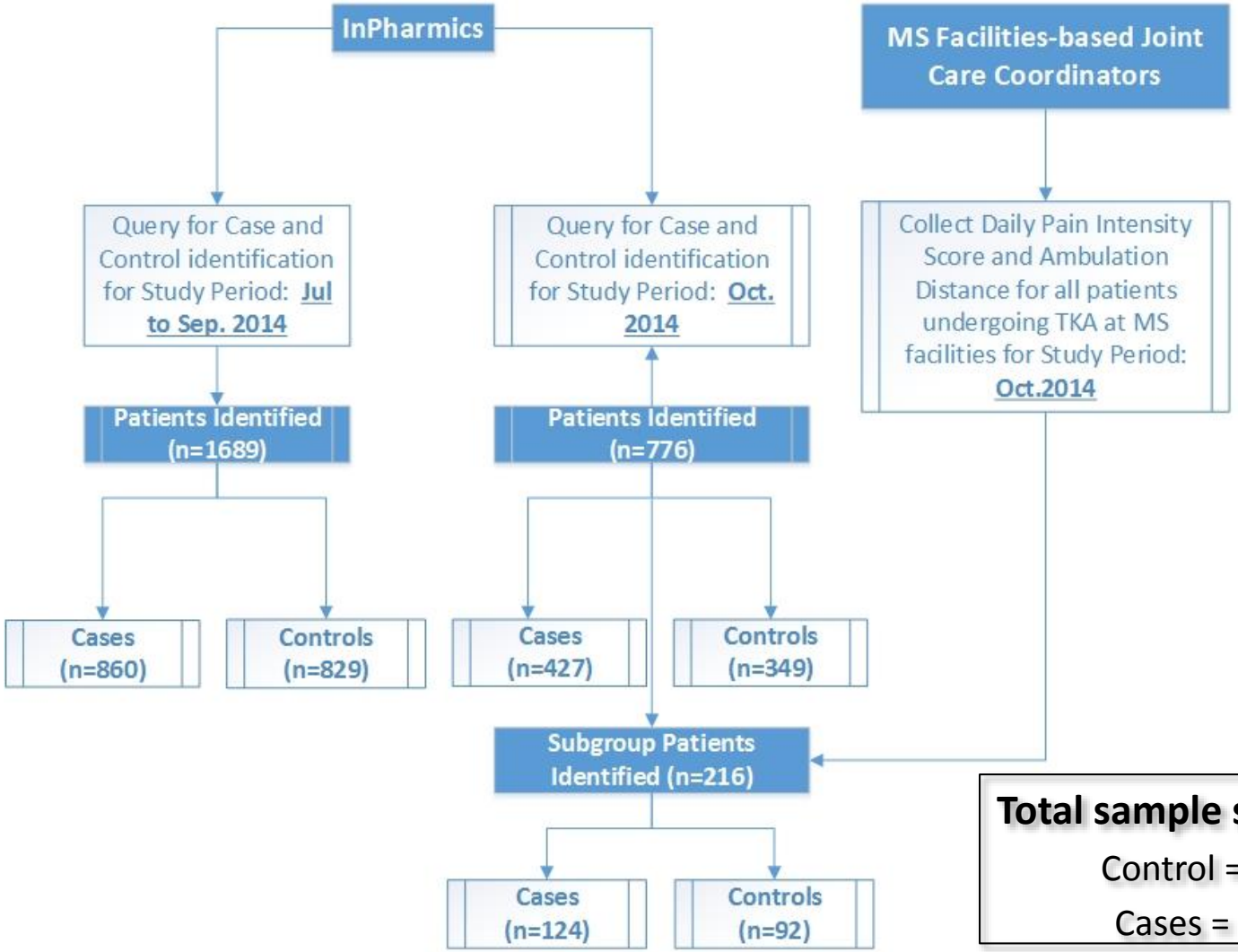
- Drug Acquisition Costs
- Patients' Length of Stay
- Total Analgesic Consumption During Hospitalization

Study Period

July – September 2014

October 2014

Methods: Flow Chart of Enrollment



Total sample size = 2,465

Control = 1,178

Cases = 1,287

Results: DRG-based Drug Cost Per Case Composite Endpoint (DRG 469 + 470)

Pooled Data

	Study	Control	p value	95% CI
DRG 470[£] + 469[¥]	$499.41 (n=1287)	$205.26 (n=1178)	p<0.0001	$285.38 – $331.67

£DRG 470 = Major Joint Replacement or Reattachment of Lower Extremity without Major Complications and/or Comorbidities

¥DRG 469 = Major Joint Replacement or Reattachment of Lower Extremity with Major Complications and/or Comorbidities

The 95% CI for composite primary endpoint is very similar to the DRG 470-based drug costs per case

Results: DRG-based Drug Cost Per Case

	Study	Control	p value	95% CI
DRG 470[£]	$497.15 (n=1264)	$198.54 (n=1163)	<0.0001	$285.83 – $325.71
DRG 469[¥]	$1041 (n=23)	$979.07 (n=15)	Insufficient sample size for statistical analysis	

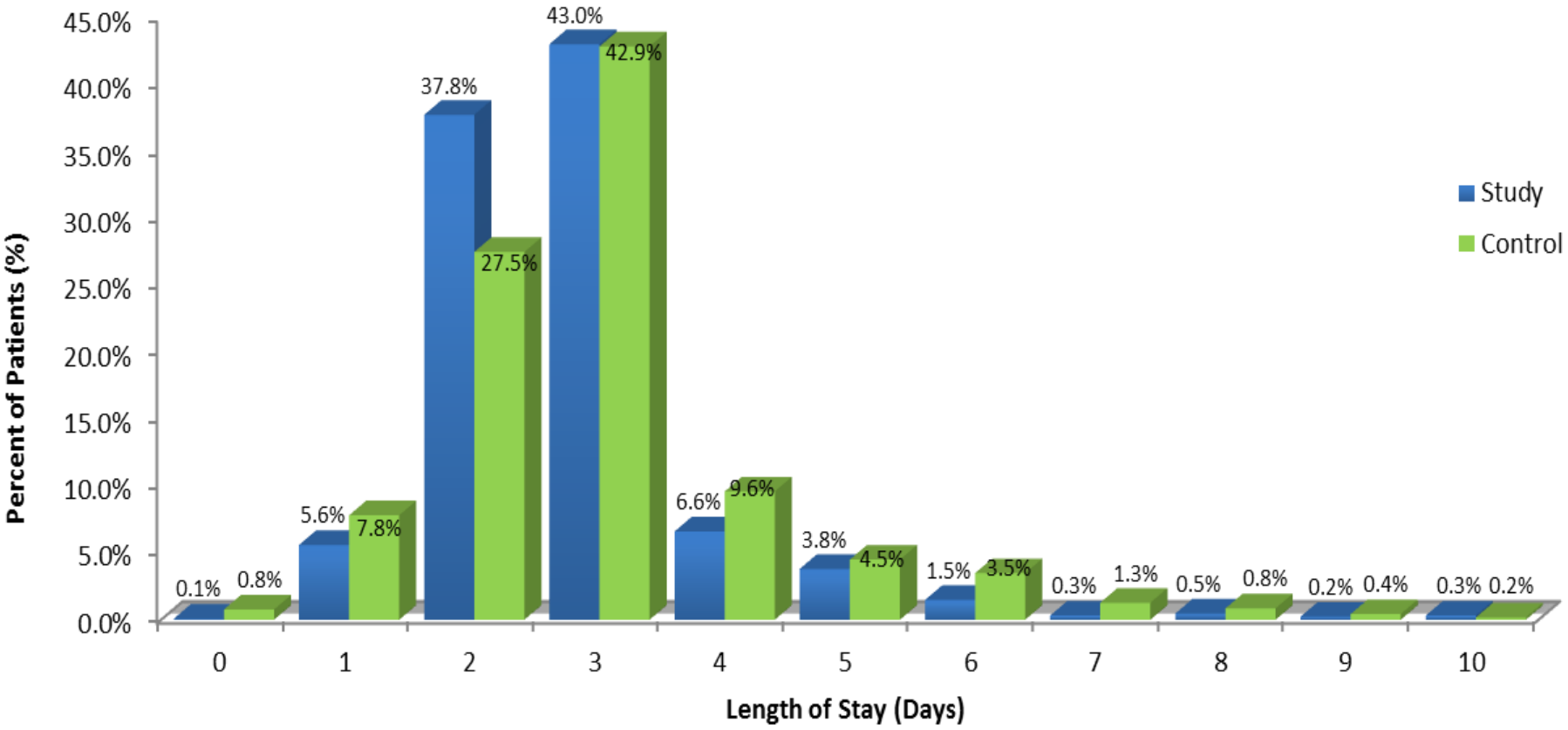
[£]DRG 470 = Major Joint Replacement or Reattachment of Lower Extremity Without Major Complication and/or Comorbidity

[¥]DRG 469 = Major Joint Replacement or Reattachment of Lower Extremity With Major Complication and/or Comorbidity

Results: Length of Stay (LOS)

Study 2.81 (± 1.28) vs. Control 3.04 days (± 1.60), (p<0.0001)

Mean LOS difference = 0.23 days (5.5 hours)



HEALTHTRUST℠

Results: Length of Stay – *Calculation 1*

Financial Implications: What is the LOS cost savings associated with Exparel® use?

Cost savings per day reduction in LOS = $500 per day*

Step 1: 1287 patients in study group; mean LOS for study group 2.81 days

$$1287\ patients\ x\ 2.81\ days = 3616.47\ patient\ days$$

Step 2: 1178 pts in control group; mean LOS for control group 3.04 days

$$1178\ patients\ x\ 3.04\ days = 3581.12\ days$$

Step 3: To determine cost savings per day

$$3616.47\ - 3581.12\ patient\ days\ x\ \$500\ \frac{cost\ savings}{day} = 35.35\ patient\ days\ x\ \$500\ \frac{cost\ savings}{day}$$

= $17,675 savings achieved by LOS reduction within our 4 month study data

Step 4: Annualized cost savings

$$\$17{,}675\ cost\ savings\ within\ our\ 4\ months\ study\ data\ x\ 3$$

$$= \$53,025\ annual\ cost\ savings\ achieved\ by\ LOS\ reduction$$

Results: Length of Stay – *Calculation 1*

Financial Implications: What are the overall healthcare costs associated with these Exparel® cases?

Step 1: # of patients received Exparel® in FY2014

$$12{,}498\frac{patients}{FY2014}\ x\ 52\%\ Exparel\ Usage\ patten\ = \mathbf{6{,}499\ patients\ who\ received\ Exparel}$$

Step 2: Cost of Exparel® in comparison to SOC* for FY 2014

$$6{,}499\ patients\ x\ \$294.15\ DRG\ based\ drug\ costs\ per\ case\ diff\ = \mathbf{\$1\,,911,680.85}$$ ***($1.9 million)***

Step 3: Overall healthcare costs associated with Exparel® use

$$\$1{,}911{,}680\ Cost\ of\ Exparel\ in\ FY2014\ -\ \$53{,}025\ Annual\ LOS\ reduction\ cost\ saving$$

$$= \mathbf{\$1,858,655\ (\$1.86\ million)}$$

* SOC = Standard of care : patients in control group NOT receiving Exparel®

Results: Length of Stay – *Calculation 2*

Clinical Significance: How many patients can get discharged earlier by one day?

Estimated 65 patients in 1264 patient sample size (5.1%) could be discharged one day sooner

One in every 19 patients

19 patients receiving Exparel® for DRG 469/470

Results: Length of Stay – *Calculation 2*

Financial Implications: What are the overall healthcare costs associated with these Exparel® cases?

Cost for Exparel in 19 pts

– ***Cost savings for reducing LOS by 1 day***

– ***Cost for SOC* in 19 patients***

Cost difference = $2506.85

Annualized cost difference: $500,314.48£

¥Based on CHS FY2013 acute care hospitalization data: Operation expenses include salaries & wages, benefits, contract labor, supplies, medical spec fees, purchased services, physician recruiting, repairs & maintenance, marketing, utilities, prop taxes & ins., HITECH incentives, rent, equity & earn – uncon subs and other operating expenses

£Patient utilization calculated based on 4 months study period: n=1287 for 4 months; n=3861 for 12 months

* SOC = Standard of care : patients in control group NOT receiving Exparel®

Results: Length of Stay

What are the overall healthcare costs associated with these Exparel® cases?

Summary:

- FY2014, as an enterprise, CHS spent $1.9 million for Exparel® in DRG 469/470 alone
- There is $53,025 – $500,314 annualized cost savings due to LOS reduction associated with Exparel® use

The overall health care costs associated with Exparel® use for FY2014 was **$1.41 to 1.86 million** with considerations of LOS reduction cost savings based on the two calculation models.

Results: Total Analgesic Consumption

Oct. 2014 data (n=776)

Average Total Analgesic Consumption per Patient Day (mg/day)

	Ofirmev	Acetaminophen	Ibuprofen	Ketorolac	Opioid
Study	530	1330	8	18	92
Control	155	1533	16	10	90
95% CI	298 to 510	-365.6 to -41.2	-29.4 to 13.7	3.7 to 11.3	-7.1 to 11.4

- ANOVA statistical analysis indicates the p-value = 0.3173
- Zoom-in student's t-test was performed to test the difference for opioid consumption, p-value = 0.6525

SUBGROUP ANALYSIS: ORTHOPEDIC CONSULTING SERVICES

Results: Secondary Endpoints Subgroup Analysis

Average Daily Highest Pain Intensity Score

	POD 0	POD 1	POD 2	POD 3
Study	5.9 ± 2.9 (n=121)	6.6 ± 2.2 (n=123)	5.7 ± 2.5 (n=107)	5.4 ± 2.6 (n=43)
Control	5.4 ± 2.9 (n=92)	6.8 ± 2.1 (n=91)	6.4 ± 2.5 (n=77)	5.7 ± 2.7 (n=35)

Average Daily Distance Ambulated (feet)

	POD 0	POD 1	POD 2	POD 3
Study	95.8 ± 139.5 (n=109)	362.7 ± 354.1 (n=119)	515 ± 540.7 (n=94)	315.8 ± 491.5 (n=39)
Control	63.2 ± 110 (n=78)	295.8 ± 322.6 (n=90)	446.2 ± 525 (n=78)	337.3 ± 495.5 (n=35)

*** Insufficient power to detect difference**

£ Protocolized goal for ambulation distance: walk ≥ 300 feet

Study Summary

What we have learned thus far…

Quality patient care was provided to all patients

- No difference was detected in pain control and patient's ability to recover
- The effects of Exparel® on pain score and ambulation distance could not be adequately assessed due to limited subset sample size
- No difference was observed in total analgesic consumption throughout hospitalization

Higher DRG-based drug cost per case was associated with the use of Exparel® for DRG 469/470

The effects of Exparel® use on LOS for DRG 469/470 was lower; however, the economic impact did not approach breakeven

Study Limitations & Discussions

Here are the limitations we have observed from the study:

Study Limitations
Patient demographic data: severity of illness, comorbidities were not considered
Case-control matching was not performed (100% real world patient sample)
Total analgesic consumption was performed vs. focus only on post-operative analgesic consumption
Adverse event monitoring data were not collected
Use of femoral nerve block or adductor canal block was not assessed → variability of surgical protocol
DRG-based drug costs per case limitation

Study results do not detect clinical advantages to support the use Exparel® for patients with DRG 469/470

Formulary Approach for the Management of Liposomal Bupivacaine Pharmacotherapy Costs

Community Health Systems

Formulary Management Strategy

How formulary management works at Community Health Systems

Enterprise-wide formulary and formulary process

- Single, centralized Formulary Management Committee (FMC)
  - Establishes formulary category status of medications
    - Category A – Eligible for local Pharmacy and Therapeutics Committee (P&T) decision
      - May be associated with restriction
    - Category B – May be approved on a case-by-case basis; not eligible for local P&T decision
      - May be associated with usage criteria
    - Category C – Appeals process needed for ordering medication; not eligible for local P&T decision
  - Local hospital formularies may be maintained an integrated formulary through their local P&T and Medical Executive Committees
    - May be more restrictive
  - Physicians may appeal FMC decisions through written process including primary literature documentation

Liposomal Bupivacaine– Formulary Management Strategy

Originally reviewed in April 2014

- Assigned a Category Status of Category B (May be approved on a case-by-case basis; not eligible for local P&T decision)
  - Usage Criteria: Marshall Steele Orthopedic Program **AND** setting of Total Knee Arthroplasty **ONLY**
- Enterprise-wide appeals process
  - Two appeals thus far

Orthopedic Consulting Services

How did this enter the picture?

Focus on:

- Best practice protocols
- Quality outcomes
- Care team coordination
- Outcome measurement
- Improved standardization

Challenges

What is impacting our strategy?

- Resolution of FDA Legal Action:
  - Administration at surgical site is NOT limited to any specific surgery type or site
    - Total hip arthroplasty?
    - Spinal surgery?
    - Shoulder surgery?
    - Bariatric surgery?
    - Other gastrointestinal surgeries?
    - Reconstructive breast surgery?
- Orthopedic consulting services
- Impact on other medications
- Impact of administration technique on results
- Marketing

Opportunities

What else could we do?

- Implement further restrictions of liposomal bupivacaine
- Improvement in standardization of standard of care
- Orthopedic consulting services
- Explore alternatives
  - Cocktails

Joint Cocktails

Investigator	Cocktail	Surgical Procedure	Sample Size	Results
Snyder et al. (2016)	Ketorolac 30 mg Morphine PF 5 mg Ropivacaine 400 mg	Total knee arthroplasty	N = 70	Liposomal bupivacaine was associated with lower pain scores in both the PACU (M = 2.11 vs 3.49; p <M 0.05) and postoperatively (p < 0.05 for POD #1 and p < 0.01 for POD#2), less narcotics administration in the PACU and post-operatively (p , 0.01 for PACU and p < 0.01 for POD#2), and higher patient satisfaction with in-hospital pain control and pain control overall was high in the liposomal bupivacaine group (p < 0.01 and p < 0.0001)
Collis et al. (2016)	Ropivacaine 246.25 mg Epinephrine 0.5 mg Ketorolac 30 mg Clonidine 0.08 mg	Total knee arthroplasty	N = 105	Similar with respect to pain levels, narcotic usage, and range of motion
Yu et al. (2016)	Bupivacaine 10 mg Morphine 5 mg Ketorolac 30 mg	Total hip arthroplasty	N = 1272	Liposomal bupivacaine was associated with lower total narcotic use (p < 0.001), higher achievement of physical therapy goals (p < 0.001), and a reduction in length of stay by 0.31 days (p < 0.001)
Heim et al. (2015)	Ropivacaine Epinephrine Ketorolac (no doses provided)	Total knee arthroplasty	N = 50	Liposomal bupivacaine was associated with lower pain scores (p < 0.001), shorter hospital stay (p < 0.0001), and greater walking distance on post-operative day 1 (p < 0.001)

Conclusions

- Would like to implement further restriction
  - Further research required?
  - Potential changes with accountable care?
- Develop true standard of care
- Continue to evaluate use of cocktails

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Questions?

CONTACT US

Heather Weese, PharmD, BCPS

Director, Pharmacy Operations & Informatics

Email: heather_weese@chs.net

Office phone: 615-628-6616

Yin Wong, PharmD, BCPS

Fellow, Health Information & Clinical Outcomes

Email: yin.wong@wolterskluwer.com

Office cell: 617-610-9255