

Bupivacaine Liposome Injectable Suspension (Exparel®) Update

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VHA Pharmacy Benefits Management Services, Medical Advisory Panel and VISN Pharmacist Executives

BACKGROUND: Bupivacaine liposomal injectable suspension (Exparel®) is an amide-type local anesthetic in an encapsulated liposomal formulation developed with the goal of providing a longer duration of anesthesia compared with its non-liposomal counterpart, bupivacaine hydrochloride or other local anesthetics. The product utilizes the DepoFoam® drug delivery system consisting of an aqueous suspension of multivesicular liposomes containing bupivacaine in a honeycomb-like structure that allows for a more gradual release. The FDA approved bupivacaine liposomal in October 2011 for single-dose infiltration into the surgical site for postoperative analgesia.¹

The VISN Pharmacist Executives (VPEs) and Medical Advisory Panel (MAP) voted in November and December of 2013 to include Liposomal Bupivacaine (LBup) on the non-promotable list because of 1) the lack of evidence supporting an advantage in terms of safety or efficacy versus traditional bupivacaine or other local anesthetics; 2) evidence was limited to bunionectomy and hemorrhoidectomy; 3) evidence was limited to single-dose local infiltration only; 4) concern for use outside of existing evidence and using routes of administration where safety and efficacy had not been established; and 5) extreme cost compared to other local anesthetics. The MAP had requested the VPEs consider methods to ensure utilization of LBup paralleled the existing evidence, if it was used at all, because of the issues listed above. The decision to make it non-promotable in late 2013 was the method selected. At that time, the VPEs indicated that there was increasing promotion of LBup for off-label uses, for which evidence was lacking and making it non-promotable was the best method for ensuring appropriate use. The groups recommended that the PBM review the updated evidence, labeling, utilization, cost, etc. and present the information to the MAP and VPEs in approximately one year. The non-promotable status would also be re-visited and changes made if applicable.

In December 2014, the MAP and VPEs determined that evidence from studies completed after initial FDA approval of LBup were insufficient to prove a consistent or substantive advantage of LBup over traditional local anesthetics in various types of surgery. There were two routes of administration that were used with LBup (local infiltration or peri-articular injection [PAI]) compared to PAI, femoral nerve block (FNB) or local infiltration of ropivacaine/epi or standard bupivacaine/epi in total knee arthroplasty (TKA) or total hip arthroplasty (THA). The published cost effectiveness studies were not included since they were of poor quality preventing a valid assessment of the added effect of LBup on improving pain scores, reducing opioid use and time to discharge because of differences in multimodal pain control regimens between groups. Additionally, because the updated evidence does not address prior concerns regarding safety and efficacy when LBup is used in other types of surgery (other than bunionectomy or hemorrhoidectomy) or when given by other routes of administration or methods of analgesia, and since there is not sufficient evidence supporting an advantage of LBup over other local anesthetics, LBup will remain on the non-promotable list and remain nonformulary. No safety concerns or signals were observed in the updated evidence.

In September 2014, the FDA sent a letter to the manufacturer of Exparel® warning the company for allegedly misbranding their product in a print advertisement since the ad appeared to be promoting the use of Exparel® in surgeries for which it had not been formally studied and for inflating efficacy claims. Reportedly, Pacira Pharmaceuticals and the FDA have been involved in ongoing settlement discussions with regard to the violations contained in warning letter. In December 2015, the FDA and Pacira reached a compromise which involved several labeling changes and removal of the warning letter from the FDA website.²As a result, Pacira Pharmaceuticals has requested that the PBM, MAP and VPEs reconsider the non-promotable status in VHA.

For the purposes of being comprehensive, the studies included in the December 2014 update were maintained in this review.

FDA APPROVED INDICATION

Liposomal bupivacaine is approved for single-dose infiltration into the surgical site to produce postsurgical analgesia. Other types of analgesia or routes of administration (e.g., epidural, intrathecal, regional nerve block or intravascular or intra-articular use) have not been adequately studied and therefore, are not recommended.¹

LABELING CHANGES¹⁻²

- Dosing for specific surgeries (e.g., bunionectomy and hemorrhoidectomy) was modified and is now provided as two dosing examples given as general guidance. There is also guidance for recommended dose based upon certain factors: 1) size of surgical site, 2) volume required to cover the area, 3) individual patient factors that may impact the safety of an amide local anesthetic, and 4) maximum dose of 266 mg (20 mL).
- Detailed guidance is provided in the compatibility considerations section regarding the ability for standard bupivacaine to be administered in the same syringe or injected immediately prior to LBup as long as the ratio of the milligram dose of standard bupivacaine to LBup does not exceed 1:2. *If this ratio is exceeded, the pharmacokinetic and/or physiochemical properties of LBup may be impacted.*
- Removal of the following sentence from the first sentence of the clinical trials section: *“EXPAREL has not been demonstrated to be safe and effective in other procedures.”* The first part of that paragraph remains, as follows: *“The efficacy of EXPAREL was compared to placebo in two multicenter, randomized double-blind clinical trials. One trial evaluated the treatments in patients undergoing bunionectomy; the other trial evaluated the treatments in patients undergoing hemorrhoidectomy.”*

UPDATED EVIDENCE

Literature Search Summary

A literature search was performed on PubMed/Medline (January 2012 to February 2016) using the search terms bupivacaine liposome, liposomal bupivacaine, and Exparel®. The search was limited to studies performed in humans and published in the English language. Many of the studies were either funded by Pacira or authors had a financial conflict of interest.

The literature search identified eight studies involving patients undergoing total knee arthroplasty³⁻¹⁰, three studies in hip arthroplasty^{6,11-12} and four in non-orthopedic surgical procedures.¹³⁻¹⁶ The maximum dose was 266 mg of liposomal bupivacaine. **(For Study details, refer to Table 1 or Appendix A).** There were several phase IV, unblinded health economic studies in which the comparison groups were not equal in the non-study drug treatments that were provided for post-operative analgesia. These trials were not included because the studies were of poor quality since they were not blinded and included too many variables; preventing a true comparison between groups.¹⁷⁻¹⁹

Total Knee Arthroplasty

Of the studies examining the efficacy and safety of LBup in patients have total knee arthroplasty (TKA), four of the eight studies were retrospective, case-control in design^{3,5-7} while three were prospective, randomized trials.^{4,8-10} In the studies, local wound infiltration or peri-articular injection (PAI) of LBup was compared to PAI of standard bupivacaine (SBup) or ropivacaine (as part of a multimodal analgesic cocktail), femoral nerve block or no active control. Use of LBup was not superior to the active comparator in six of the eight studies. Four of those studies were prospective randomized trials^{4,8-10} and two were retrospective.^{3,7} One of the prospective studies that did not find a significant difference in outcomes measured was conducted in patients with a history of chronic opioid use.¹⁰ The two studies reporting improvement in certain outcome measures with LBup vs. comparators were both retrospective, case-control trials.⁵⁻⁶ In the largest case-control study⁶, there were four surgeons performing knee or hip arthroplasty and differences in pain scores using visual analogue scale (VAS) were statistically better for 2/4 of the surgeons. The two surgeons, for whom statistical improvements in VAS were reported, performed 68% of the operations. The

differences in pain scores were more marked for THA vs. TKA but pain scores were low overall. Statistical differences in pain scores using VAS were <1 point and it is unclear if the differences are clinically meaningful. In most studies, length of stay and patient satisfaction did not differ.

Limitations of the various studies include retrospective study design, use of a different mode of analgesia in several trials (PAI vs. femoral nerve block [FNB]) or lack of an active comparator. In the case of comparing PAI to FNB or to no comparator, evidence supports the benefit of PAI in improving pain scores, opioid requirements, knee range of motion, etc. in patients undergoing TKA and total hip arthroplasty (THA) despite the wide variation of local anesthetics used and other agents included in these multimodal analgesic cocktails.²⁰⁻²¹ One author indicated that the use of PAI in TKA has increased significantly over the past few years and that unfortunately, the initial experience of many of these orthopedic surgeons is with the use of LBup PAI because of the aggressive marketing campaign and that although this has indirectly increased the use of PAI in TKA, “The use of any PAI is better than none.”⁸ Additionally, although FNB is effective in controlling postoperative pain, there can be impairment of the quadriceps muscle, which may delay walking and increase the risk of falls.²²⁻²⁴ The available evidence does not support a substantive or consistent advantage of LBup over standard bupivacaine (SBup), ropivacaine or other modes of postoperative analgesia in patients following TKA.

Total Hip Arthroplasty

There are three retrospective, case-control studies comparing local infiltration or PAI of LBup to PAI SBup or to no PAI. In the study by Barrington, et al.⁶, which included patients having TKA or THA, pain scores were approximately 0.6 points less on VAS and a higher percentage of patients reported no pain but length of stay and patient satisfaction did not differ. Postoperative VAS pain scores were <3 in all groups. In a small study by Domb, et al.¹¹, pain scores did not differ during any time point but opioid use was less in the LBup vs. SBup group in the first 24 hours, but not thereafter. Length of stay was 1.93 days in the LBup vs. 2.47 days in the SBup group. The third study was a large case-control trial by Yu, et al. comparing LBup PAI vs. no PAI.¹² Pain scores were not different between LBup PAI vs. no PAI except within the first 8 hours. Through the duration of hospitalization, the LBup group received 15.49 mg less morphine than control and length of stay was 2.62 days vs. 2.93 days in favor of LBup. In the trials comparing local infiltration/PAI of LBup to PAI with SBup or to no PAI, pain scores generally did not differ, use of opioids was less in the first 24 hours and although statistically significant, length of stay was shorter by approximately 0.31-0.54 days in two studies in favor of LBup.

Limitations of the three studies are similar to those in the TKA studies including retrospective study design and lack of an active PAI control in one large study.¹² Although there were some minor differences in outcomes measured favoring LBup, the clinical significance of these differences is uncertain and the findings were not consistent across trials.

Non-Orthopedic Surgery

There are four studies that have examined the use of LBup in other types of surgeries. One is retrospective while the other three are prospective, randomized trials. In a small retrospective study of 108 patients undergoing major thoracic surgery (pulmonary resection), an intraoperative posterior intercostal nerve block plus local wound infiltration with LBup was compared to thoracic epidural analgesia (TEA) with SBup.¹³ In this study, there were no differences in pain scores or opioid use but length of stay was reduced from 4.5 days with TEA vs. 3.5 days with LBup with no difference in postoperative complications. Authors commented that nerve block with LBup produces similar postoperative pain control to TEA but may require less nursing time and costs associated with managing the epidural infusion/catheter, etc. and length of stay was lessened by one day. However, since two methods of analgesia were compared (local infiltration and posterior intercostal nerve block with LBup vs. TEA with SBup) and the study was retrospective, the findings may be considered as hypothesis generating. Hutchins, et al. randomized 58 patients having robotic assisted hysterectomy to LBup administered as a bilateral subcostal transverse abdominis plane

(TAP) block or bilateral TAP block with SBup.¹⁴ In this trial, opioid use was less in the 72-hour postoperative period (24.9 mg vs. 51.7 mg) and nausea was also less in the LBup group. There were no differences in length of stay or patient satisfaction between groups. In another trial of 60 women undergoing total abdominal hysterectomy (TAH), local wound infiltration with LBup was compared to bilateral TAP blocks with SBup.¹⁵ Pain scores at rest and with coughing were lower in the local infiltration with LBup group vs. TAP block and opioid use was lower in the first 24 hours. There were no differences in incidence of nausea/vomiting, use of rescue medications and all patients resumed oral intake and were discharged home within 48-60 hours. The limitation of this trial is comparing two different modes of analgesia (local infiltration vs. TAP block) with two different local anesthetic agents (LBup vs. SBup) so it is difficult to discern whether the differences were due to the method of analgesia or local anesthetic. In this study, the authors discussed that TAP blocks may not alter the peritoneal contribution to pain since the spread of local anesthetic may not be uniform because of the anatomic variation and certain nerves have varied origin which may influence the efficacy of TAP. In the final study, 34 women undergoing breast augmentation were randomized to receive LBup in one breast pocket and SBup in the other.¹⁶ Pain scores were lower in the LBup group vs. SBup with differences ranging from 0.08-0.98 on VAS. However, when patients were asked if they would be willing to pay an additional cost (\$250) for the improved pain control, nearly 70% stated that they would not pay the additional amount. The authors question whether the differences were clinically significant.

Limitations of these studies include comparing different methods of analgesia and retrospective study design in a single study.¹³ From the evidence in non-orthopedic surgeries, there is limited evidence to support a minimal advantage of LBup over SBup administered as a TAP block. However, it is unclear if these differences are clinically meaningful. In one retrospective study, length of stay was lessened by one day when local infiltration and intercostal nerve block with LBup was compared with TEA with SBup. Although this is an important finding, the study was retrospective and compared two different methods of analgesia (local infiltration + posterior intercostal nerve block vs. TEA) using two different local anesthetics.

TABLE 1. SUMMARY OF STUDIES OF BUPIVACAINE, LIPOSOME INJECTION (Additional details in Appendix A)

Study	Study Design/	Intervention	Results (Main Outcomes)	Comments
JOINT ARTHROPLASTY				
Bagsby 2014³ N=150 TKA	Retrospective, cohort	LBup PAI vs. Ropi+epi+MS PAI	Post-op pain and use of opioids: No improvement in post-op pain was observed in LBup vs. Ropi and no difference in use of opiates between LBup and Ropi PAI. <i>LBup=Ropi PAI</i>	Retrospective
Surdam 2015⁴ N=80 TKA	Prospective, randomized	LBup PAI vs. FNB with Ropi and tetracaine	Post-op pain control: No difference between groups. <i>LBup PAI=FNB</i>	Comparing 2 different modes of pain control: PAI vs. FNB.
Broome 2014⁵ N=200, 100 consecutive cases LBup vs. 100 controls TKA	Retrospective case-control.	LBup by local injection vs. FNB	Pain scores, ambulation, range of motion and LoS: <ul style="list-style-type: none"> • Resting pain scores were lower for LBup vs. FNB on POD 1 and 2 (Diff. in VAS=0.6-0.9) • NS diff in IV or oral opioids 	Comparing 2 different modes of pain control: local injection vs. FNB. Retrospective

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			<ul style="list-style-type: none"> LoS: LBup 53 hrs vs. FNB 60 hrs No statistics provided <p><i>LBup lower resting pain scores vs. FNB but NS for use of opioids or LoS</i></p>	
<p>Barrington 2015⁶ N=>1000 cases vs. >1000 controls</p> <p>TKA or THA</p>	<p>Retrospective, case-control.</p> <p>4 surgeons</p>	LBup PAI vs. SBup PAI	<p>Average VAS pain scores and % of pts reporting no pain: VAS pain scores: Hip: LBup 1.67 vs. 2.3 Knee: LBup 2.21 vs. 2.52 All combined: LBup 1.98 vs. 2.43 (All differences p<0.0001) <i>*The effect on VAS varied by surgeon with largest differences reported for surgeon 1 and 4. (Performed 68% of operations). Surgeons 2 and 3 performed 32% of surgeries and no differences were reported in pain scores for their patients.</i></p> <p><u>Percentage of pts reporting no pain:</u> Hip: LBup 57.3% vs. 43.4% Knee: LBup 47.2% vs. 42.1% (Both p<0.0001).</p> <p>LoS and patient satisfaction were not different.</p> <p><i>LBup slightly better pain scores vs. SBup PAI for 2/4 surgeons, mainly hip. Pain scores low in all groups overall. LoS and patient satisfaction were not different</i></p>	<p>Although differences were statistically significant, overall pain scores were low in all groups and differed by 0.3-0.6 pts on VAS.</p> <p>Significant differences were limited to 2/4 surgeons and mostly for hip.</p> <p>Retrospective, case-control.</p>
<p>White 2015⁷ N=120</p> <p>TKA</p>	<p>Retrospective, case-control</p> <p>No COI found</p>	LBup intra-op vs. those who did not	<p>AUC NRS pain scores, opioid use 0-48 hrs post-op, ambulation and LoS: NS difference in any endpoint measured but use of non-opioid analgesics was higher in the non LBup group (continuous regional Ropi infusion, celecoxib and pregabalin)</p> <p><i>LBup=no LBup but non-LBup group received more non opioid analgesics which</i></p>	<p>Retrospective</p> <p>No active control</p> <p>Use of more non-opioid analgesics in the non-LBup group.</p>

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			<i>may explain the NS findings</i>	
Schoerer⁸ N=111 TKA	Prospective, randomized, active control	LBup PAI+SBup vs. SBup PAI	Pain scores POD 1-3, opioid use and range of motion: NS in pain scores POD 1-3 NS is opioid use, LoS, knee range of motion and post-op nausea <i>LBup+SBup PAI=SBup PAI</i>	N/A
Collis 2016⁹ N=105 TKA	Prospective, randomized, active control	LBup PAI vs. Ropi+epi+ketorolac+0.8 mg clonidine PAI (Modified Ranawat's)	Pain scores and use of opioids: NS in pains scores at any timepoint, knee range of motion or ambulation distance. <i>LBup=Modified Ranawat's</i>	N/A
Schwarzkopf 2016¹⁰ N=38 TKA in chronic opioid users	Prospective, randomized active control	LBup PAI + SBup vs. PAI (ropivacaine, clonidine, ketorolac, epinephrine and saline).	Pain scores (VAS), opioid consumption: NS is daily pain score, use of opioids. No difference in LoS, post-op complications, readmissions, etc. <i>LBup PAI+SBup=Ropi PAI</i>	N/A
Domb 2014¹¹ N=58 THA	Retrospective, case-control	LBup local infiltration of hip vs. SBup local infiltration of hip	Pain scores, opioid use, LoS: NS in pain scores, opioid use was < in first 24 hrs in LBup but not POD 2 or 3 and LoS was 1.93 days in LBup vs. 2.47 days in SBup <i>LBup=SBup in pain scores, opioid use POD 2 and 3 but slightly improved LoS and less opioid use in first 24 hrs with LBup.</i>	Retrospective
Yu 2016¹² N=1272, THA	Retrospective, case-control	LBup PAI vs. no PAI injection	Pain scores, opioid use, PT milestones: <ul style="list-style-type: none"> The only difference in pain scores that was statistically improved for the LBup group was in the first 8 hrs after surgery (p=0.03). All other times pain scores was not different. Less opioids were used on POD 1 in LBup vs. control (p<0.001) but more opioids were used by LBup on POD 2 vs. control (p=0.016) For the entire hospital stay, LBup recipients received 15.49 mg less of morphine vs. control. LoS was less in LBup vs. 	Retrospective, lack of active PAI control Unclear whether differences are clinically meaningful

			<p>control (2.62 days vs. 2.93 days, p<0.001).</p> <ul style="list-style-type: none"> LBup pts were reported to have improved PT milestones vs. control. Discharge to home occurred in 5.19% greater number of LBup vs. control <p>LBup PAI>no PAI in pain scores in first 8 hrs post-op, less opioids on POD 1.</p>	
OTHER SURGICAL PROCEDURES				
<p>Rice 2015¹³ N=108</p> <p>Major thoracic surgery (Pulmonary resection)</p>	Retrospective, case-control	<p>Intra-op posterior intercostal nerve block plus local wound infiltration with LBup vs. TEA SBup 0.075% with hydromorphone or fentanyl.</p> <p>2 surgeons used LBup while 3 did not</p>	<p>Perioperative morbidity, pain scores (VAS 0-10) and narcotic use: NS differences in post-op pain scores or opioid use between groups. LoS was 3.5 days in LBup vs. 4.5 days in TEA</p> <p>LBup=TEA in post-op pain or opioid use but LoS was less in LBup.</p>	Retrospective. Authors comment that nerve block with LBup is equal to TEA in post-op pain and opioid use but may require less nursing time, etc.
<p>Hutchins 2015¹⁴ R, DB N=58, 28 LBup vs. 30 SBup</p> <p>Robotic assisted hysterectomy</p>	Prospective, randomized, active control	<p>LBup was administered using bilateral TAP blocks vs. SBup 0.25% (75 mg) with epi bilateral TAP block.</p> <p>TAP blocks administered by 1 of 4 anesthesiologists</p>	<p>Total opioid use 0-72 hours post-op. Secondary: pain intensity, use of pain meds, LoS, nausea/vomiting, and pt satisfaction with pain control:</p> <ul style="list-style-type: none"> <u>Opioid use 0-72 hrs post-op:</u> LBup: 24.9 mg SBup: 51.7 mg, p=0.002 Differences primarily 0-24 hrs and 24-48hrs. Nausea was also less in LBup vs. SBup (25% vs. 56.7%, respectively, p=0.014) No difference in use of acetaminophen or ibuprofen, LoS or patient satisfaction <p>LBup TAP > SBup TAP in opioid use. NS difference in use of non-opioid analgesics. LoS or patient satisfaction.</p>	<ul style="list-style-type: none"> Was the dose of SBup used in this study standard for RAH? If so, should pain control be similar early post-op? Was similar in PACU. Duration of surgery was about 4 hrs. TAP blocks last between 6-24 hrs. Limited trials using TAP blocks for RAH. One trial evaluating unilateral TAP blocks with SBup did not show a difference vs. sham. Although opioids consumed was the primary endpoints, authors indicated that no protocol existed for opioid admin. Patient recall was used to count other

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				medications taken and study was not powered for secondary outcomes.
<p>Gasanova 2015¹⁵ N=60</p> <p>Total abdominal hysterectomy</p>	Prospective, randomized	LBup infiltrated into the surgical site (preperitoneal, subfascial and subcutaneous planes) vs. SBup 0.5% (100 mg on each side) as bilateral TAP blocks using ultrasound.	<p>Pain scores while coughing at 6 hrs post-op.</p> <p>Secondary outcomes: Pain scores, opioid use, nausea/vomiting, need for rescue analgesics:</p> <ul style="list-style-type: none"> • Pain scores at rest and with coughing were lower with the local infiltration/LBup group vs. TAP block with SBup across time. • Morphine PCA: • LBup/local infiltration 33.6 mg vs. SBup/TAP block 47.7 mg in first 24 hrs (p=0.0497) • Hydromorphone/acetaminophen tabs: • LBup 1.90 vs. SBup 3.55 (p=0.009) • NS difference in nausea/vomiting, use of rescue medications and all pts resumed oral intake and discharge home within 48-60 hrs post-op. <p><i>LBup local infiltration > SBup TAP blocks in pain scores and opioid use in first 24 hrs. NS diff. in nausea/vomiting, rescue meds, etc.</i></p>	<p>Comparing 2 different modes of local anesthesia, TAP block with SBup vs. local infiltration with LBup. Difficult to discern whether the local infiltration was a better mode of local anesthesia vs. TAP block or whether the LBup outperformed the SBup.</p> <p>Authors discussed that TAP blocks with local anesthetics may not alter the peritoneal contribution to pain perception since the spread of local anesthetics may not be uniform because of anatomic variation and certain nerves may have varied origin influencing the efficacy of TAP.</p>
<p>Nadeau 2016¹⁶ N=34</p> <p>Breast augmentation</p>	Randomized, double-blind, active control	Breast augmentation. LBup in one breast implant pocket vs. SBup in the other.	<p>Pain scores post-op in each breast (VAS)</p> <p>Secondary outcomes: whether the added cost of LBup is justifiable:</p> <p>Pain scores were lower in the LBup vs. SBup group at each time point measured. Differences in VAS pain scores (0-10) ranged from 0.08-0.98.</p> <p>Patients were contacted to determine if improved pain control was worth the extra charge of \$250. Authors were able to contact 23/34 pts (67.6%). Of those, 16/23 (69.6%) said the pain relief was not worth the added cost.</p> <p><i>LBup marginally better in improving pain scores vs. SBup but over 2/3 of pts did not feel it was worth the added cost.</i></p>	Pain scores differed by <1 point on VAS and authors question the clinical importance of that difference. Also, nearly 70% of pts did not feel the benefit was worth the added cost.

AUC=area under the curve, COI=conflict of interest, FNB=femoral nerve block, LBup=liposomal bupivacaine, LoS=length of stay, MS=morphine sulfate, NRS=numeric rating scale, PAI=peri-articular injection, POD=post-op day, PT=physical therapy, RAH=robotic assisted hysterectomy, Ropi=ropivacaine, SBup=standard bupivacaine, TAP=subcostal transversus abdominis plane, TEA=thoracic epidural analgesia, THA=total hip arthroplasty, TKA=total knee arthroplasty

CONCLUSION

In the fourteen studies reviewed for this update, seven were retrospective case-control studies and seven were prospective randomized trials. The dose of liposomal bupivacaine was 266 mg given by local infiltration or PAI or TAP blocks compared to other local anesthetics (e.g., SBup or ropivacaine) given as local infiltration or PAI, FNB, TAP blocks or TEA. In a few studies, the method of LBup analgesia was compared to another method of analgesia as the active control, making it difficult to determine if any differences were due to the drug/intervention or due to the different method of analgesia. In the studies involving patients having TKA, statistical differences were limited to studies with a retrospective study design while the prospective randomized trials did not show a difference in the main outcomes measured. There were minimal differences in favor of LBup in some outcomes measured in studies of patients having THA, robotic assisted or total abdominal hysterectomy or breast augmentation. Statistical differences in pain scores on VAS were limited to <1 point on a 0-10 point scale. Other differences (opioid use, length of stay), although statistically different, were relatively small and inconsistent across studies and it is uncertain if the differences are clinically meaningful that will translate into improved patient care. In most of the studies, there were no differences in length of stay or patient satisfaction. There were no safety concerns with LBup that were identified in this review. From the evidence reviewed, there does not appear to be substantive or consistent advantages to the use of LBup over other local anesthetics when compared using the same method of analgesia.

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APPENDIX A

CLINICAL TRIALS: BUPIVACAINE LIPOSOME VS. PLACEBO OR STANDARD BUPIVACAINE

Clinical Trial	Population/Intervention	Outcomes	Results	Comments
JOINT ARTHROPLASTY				
Bagsby 2014³ N=150, Cohort, retrospective	TKA, consecutive pts given intra-op PAI with R 400 mg w epi (n=85) or LBup 266 mg (n=65). Multimodal analgesia same in both groups (pre and post-op)	Mean post-op opiates Pt reported pain scores; mean anti-emetic doses or naloxone doses.	No difference in any outcome measure in the first 24 hours, during the remaining stay or at discharge between groups. Only difference was the mean pain score was lower in the R vs. LBup group (4.4 vs. 4.9, respectively, p=0.04) after first 24 hr. Also, after the initial 24 hrs, 81.5% of patients reported their pain as moderate on LBup vs. 46.5% on R. And, 16.9% of pts on LBup reported pain as mild vs. 47.6% on R.	No revision or reoperation in R vs. 3/65 pts on LBup had wound drainage at 3-4 wks post-op and wound infection requiring reoperation. Retrospective design is a limitation. However, no improvement in post-op pain was observed and no difference in use of opiates. Further study is warranted.
Surdam 2014⁴ N=80 consecutive pts, P, R	TKA, LBup (266 mg [20 ml mixed with 40 ml saline) vs. FNB with R (40 ml 0.5% w epi [200 mg] with 30 mg tetracaine). LBup injected into tissues surrounding joint.	Inpatient pain control ROM, N and V, opioid use, ambulation distance and LoS	Pain control: NS (p=0.07) Mean pain score in FNB with R 2.92 vs. 3.42 LBup during the entire stay. Biggest difference between groups was on POD 0 (2.91 FNB with R vs. 3.84 LBup) which was significant. After first 24 hrs, pain scores were nearly identical. Passive ROM was better in the FNB with R vs. LBup (p=0.001) N and V=NS, Total opioid consumption=NS, Opioid use on POD 0 and 1 favored the FNB with R vs. LBup (13.9 mg vs. 25.5 mg, respectively), POD favored LBup (3.9 mg vs. 9.1 mg), POD 2 and 3=NS Significantly higher percentage of patients ambulating day of surgery in LBup vs. FNB. LoS: 2.36 LBup vs. 2.65 FNB (p=0.03). Ability to perform straight leg raise was significantly greater in the LBup vs. FNB group and several patients were discharged on POD 1 in the LBup (n=5) vs. none in the FNB group (? Statistically significant or not?)	FNB contributes to femoral weakness and potential falls. Approximately 10% vs. 62% ambulated day of surgery in FNB vs. LBup (?diff). Only 17% of the FNB pts were able to perform straight leg raise vs. 100% with LBup. And quadriceps weakness/buckling was noted during therapy on POD 0 in FNB group. Finally, a knee immobilizer was needed in 10% of FNB on POD 1 to prevent buckling. No difference in total opioid consumption or pain control between groups. More patients ambulated on POD 0 in LBup group and more patients in FNB experienced quadriceps weakness/buckling on POD 0. And, knee immobilizers were used in 10% of FNB. Further studies are needed to assess utility of LBup as part of a multi-modal pain protocols.
Broome 2014⁵	TKA, 100 consecutive	Pain scores-scale	Detail results and statistics were	Detail results and statistics

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<p>N=200, 100 consecutive vs. 100 historical cohort</p> <p>(Case-control)</p>	<p>pts given LBup by local injection vs. 100 historical pts receiving FNB.</p> <p><u>Both groups received:</u> Pre-op: celecoxib, ondansetron, famotidine and optional oxycontin Intra-op: IV acetaminophen, dexamethasone Post-op: ketorolac, IV/oral acetaminophen, celecoxib, tramadol for breakthrough pain and oxycodone or IV hydromorphone for rescue pain.</p>	<p>used not specified. Discharge to home, opioid use, range of motion and length of stay.</p>	<p>not provided.</p> <p><u>Resting pain scores:</u> LBup: 4 vs. FNB: 4.9 (POD 1) LBup: 4.7 vs. FNB: 5.3 (POD 2)</p> <p>NS differences in IV or oral opioid use.</p> <p><u>LoS:</u> LBup 53 hrs vs. FNB 60 hrs</p> <p><u>Range of motion:</u> LBup: 109° 3 wks and 121° 9 wks FNB: 100° 3 wks and 105° 9 wks</p> <p>Unknown if differences are statistically significant</p>	<p>were not provided, unclear if differences reported were statistically significant, other than IV/oral rescue opioids and pain scores.</p> <p>Dose of LBup is not provided in article and whether it was given as a periarticular injection or other.</p> <p>Authors compared LBup to FNB. FNB is effective for reducing pain post op after TKA but can impair quadriceps functioning, delay walking and may increase risk for falls.</p> <p>Lack of PAI control</p>
<p>Barrington⁶ 2015 >1000 cases and >1000 historical controls</p> <p>(Case-control)</p>	<p>TKA or THA cases Pre-group: 1124 cases (12-2011 to 10-2012) received PAI with SBup with or without ketorolac and morphine and therapy protocols (not specified) Post-group: 1125 cases (10-2012 to 8-2013) LBup replaced established PAI and therapy protocols. Unclear if PAI with LBup included ketorolac or morphine</p>	<p>Average VAS pain score and the percentage of scores that were zero during hospitalization.</p>	<p><u>VAS pain scores:</u> Hip: LBup 1.67 vs. 2.3 Knee: LBup 2.21 vs. 2.52 All combined: LBup 1.98 vs. 2.43 (All differences p<0.0001) <i>*The effect on VAS varied by surgeon with largest differences reported for surgeon 1 and 4. (Performed 68% of operations). Surgeons 2 and 3 performed 32% of surgeries and no differences were reported in pain scores for their patients.</i></p> <p><u>Percentage of pts reporting no pain:</u> Hip: LBup 57.3% vs. 43.4% Knee: LBup 47.2% vs. 42.1% (Both p<0.0001).</p> <p>LoS and patient satisfaction were not different.</p>	<p>4 surgeons performed the operations; differences in pain scores were reported for surgeons 1 and 4 but not 2 and 3.</p> <p>Power calculations were done post-hoc as well as effect size differences in VAS</p> <p>Unclear if differences in VAS were clinically important to pts, for what time point they are reported and at what point did patients have no pain (e.g., POD 1, 2?).</p> <p>LoS and patient satisfaction did not differ statistically</p>
<p>White 2015⁷ N=120, 55 LBup and 65 no LBup</p> <p>(Retrospective cohort)</p>	<p>TKA, 266 mg LBup vs. no LBup (control)</p> <p>Pts with opioid use of 60 mg or > before surgery were excluded.</p>	<p>Post-op pain (AUC NRS pain scores up to 48 hrs after surgery), opioid use, ambulation, and LoS.</p>	<p><u>Post-op pain (AUC-NRS) 48 hr:</u> LBup: 199.59 vs. C 192.94 (NS) <u>Post-op pain (AUC-NRS) 24 hr:</u> LBup: 80.6 vs. C 79.8 (NS) <u>Opioid Use (mg):</u> LBup: 239.2 vs. C 229.1 (NS) LoS: LBup: 72.3 hr vs. C 67.9 hr (NS) <u>Max Ambulation (Ft):</u> LBup: 124.3 vs. C 127.4 (NS)</p> <p>Use of non-opioid analgesics was higher in control vs. LBup</p>	<p>Use of non-opioid analgesics was higher in the control group (Non LBup), which may explain the NS differences. Nearly all control pts received ropivacaine infusions.</p> <p>Retrospective design, small sample size, lack of standard times for collection of pain ratings.</p>

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			(celecoxib, pregabalin, continuous regional ropivacaine infusions-almost all pts in the non-LBup group).	
<p>Schoer 2015⁸ R, DB N=111, 58 LBup and 53 Bup</p> <p>(Prospective, randomized, active control)</p>	<p>TKA, 266 mg LBup + 75 mg 0.25% SBup PAI vs. 150 mg 0.25% SBup PAI</p> <p>On day before surgery, pts took: 400 mg celecoxib, 20 mg oxycontin and 6 mg scopolamine patch. Post-op, pts received: celecoxib 400 mg daily, oxycontin 10 mg every 12 hrs for 2 doses and prn hydrocodone or oxycodone and PCA with morphine for breakthrough pain.</p> <p>(1 surgeon)</p>	<p>Pain scores (VAS) POD 1-3, opioid use, range of motion,</p>	<p>No difference in pain scores POD 1, 2 or 3. Majority of patients discharged home, 1 LBup and 2 Bup were discharged to rehab facility. No difference in LoS No difference in opioid use in hospital No difference in knee range of motion No difference in post-op nausea</p>	<p>No difference between LBup and SBup recipients in any outcome measured.</p> <p>The authors concluded that LBup PAI had no significant benefit over SBup PAI in TKA patients.</p> <p>SBup was included in LBup PAI injection to ensure rapid release of SBup for early pain control prior to initiation of the effect of LBup (obviating the potential window of breakthrough pain with LBup).</p> <p>This author expresses concern of other study methodologies that have been used by other authors. Retrospective, case-control, lack of PAI control, comparing dissimilar pain management modalities (FNB, regional ropivacaine infusions, etc.). Additionally, concern with regard to conflict of interest of other authors whose studies show positive results, stating that entire journal supplements are funded by industry. Authors also note prior investigations in orthopedic surgery found that positive studies are more likely to be published vs. negative studies, when COI exist.</p>
<p>Collis 2016⁹ R, DB N=105, 54 LBup and 51 Ranawat Soln.</p> <p>(Prospective, randomized, active control)</p>	<p>TKA, 266 mg LBup PAI vs. Modified Ranawat Soln (ropivacaine 246 mg, epinephrine, 30 mg ketorolac and 0.8 mg clonidine) PAI</p> <p>Both groups had same post-op pain regimen:</p>	<p>Pain scores (VAS), cumulative IV and oral opioids, active range of motion, walking distance, and need for assistance devices</p>	<p>No difference in pain via VAS at rest or activity at any time period recorded. No difference in IV or oral opioids at any timepoint (24, 48 or 72 hrs, 2 weeks or 4-8 weeks) No difference in active range of knee motion. No difference in walking</p>	<p>No statistical difference in any outcomes measured. However, author comments on the convenience of LBup whereas the Modified Ranawat's solution requires compounding by pharmacy.</p>

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	acetaminophen 1000 mg q8h, tramadol 50 mg q8h x 24hrs, PCA and oxycodone oral 5-10 mg prn. (1 surgeon)		distance.	
Schwarzkopf 2016¹⁰ R, DB N=38, 20 LBup vs. 18 PAI Prospective, randomized active control)	TKA in <u>opioid dependent patients</u> . 266 LBup + SBup vs. PAI (ropivacaine, clonidine, ketorolac, epinephrine and saline). (1 surgeon)	Pain scores (VAS), opioid consumption Pre-op and post-op multimodal analgesics were the same in both groups.	Pain was reported to be higher in the LBup group on POD 1 but no differences on POD 2 or 3. When baseline levels of opioid use were considered prior to surgery, the differences had disappeared. No difference in first use of opioid in recovery 4 LBup vs. 24 min control PAI, no differences in daily opioid use at all time points evaluated. No difference in LoS, post-op complications, readmissions, etc.	LBup+SBup PAI vs. standard PAI, containing ropivacaine did not result in difference in pain scores, daily opioid use, LoS or other measures studied. Authors concluded that LBup was not found to be superior to standard PAI in opioid dependent pts undergoing TKA.
Domb 2014¹¹ N=58, 28 LBup vs. 30 SBup (Case-control retrospective)	THA or hip resurfacing (n=28 patients on LBup, 266 ml (20 ml) mixed with 40 ml of 0.25% SBup with epi infiltrated throughout the hip capsule and surrounding tissues; n=30 receiving 60 ml of 0.25% SBup with epi [150 mg]). As part of a multi-modal pain control approach.	LoS recorded in days Post op opioid use and separated into 24 hr increments. Pain scores were also assessed at 24 hr increments.	LoS: 1.93 days LBup+SBup vs. 2.47 days SBup (p<0.05). Opioid use was less in first 24 hrs in the study group but during the second and third 24 hr interval, there were no differences. Pain scores did not differ during any of the 24 hr intervals.	More hip resurfacings were done in the control group. More patients in the control group were assessed for pain control and for opioid use vs. study group. Potentially since they were discharged sooner. Limitations: retrospective, case-control, SBup was used in both groups. LoS reduced by 0.54 days in the LBup+SBup group vs. SBup alone as part of a multimodal pain control approach. Also, opioid use was statistically reduced in study group in first 24 hr after surgery but not thereafter. Also, no difference in pain scores between groups at any time.
Yu 2016¹² N=1272, 586 LBup and 686 cohort non-LBup (Retrospective, case-control)	THA, 586 pts received 266 mg LBup PAI vs. no PAI injection in 686 pts (historical cohort) All pts received the same pre-op analgesics, same spinal anesthesia, LBup PAI vs. no PAI, intraoperative-superficial injection of bupivacaine,	Pain scores, opioid use, physical therapy (PT) milestones (ambulation, stairs, etc.)	The only difference in pain scores that was statistically improved for the LBup group was in the first 8 hrs after surgery (p=0.03). All other times pain scores were not different. Less opioids were used on POD 1 in LBup vs. control (p<0.001) but more opioids were used by LBup on POD 2 vs. control	No PAI control group. Evidence supports improved post-op pain control with PAI. Would results differ if active PAI control were used?

	morphine and ketorolac and same post-op analgesics		(p=0.016) For the entire hospital stay, LBup recipients received 15.49 mg less of morphine vs. control LoS was less in LBup vs. control (2.62 days vs. 2.93 days, p<0.001). LBup pts were reported to have improved PT milestones vs. control. Discharge to home occurred in 5.19% greater number of LBup vs. control	
OTHER SURGICAL PROCEDURES				
Rice 2015¹³ N=108, 54 LBup vs. TEA (Retrospective, case-control) (COI not noted)	Major thoracic surgery (Pulmonary resection): 54 pts intraoperative posterior intercostal nerve block plus local wound infiltration with LBup 266 mg vs. 54 pts thoracic epidural analgesia (TEA) (SBup 0.075% with hydromorphone or fentanyl.	Perioperative morbidity, pain scores (VAS 0-10) and narcotic use 2 surgeons used LBup while 3 did not	<u>Mean pain score using VAS did not differ on any post-op day neither did the use of opioids.</u> <u>Subgroups</u> -Minimally invasive surgery-NS difference in pain scores or opioid use -Thoracotomy-Mean pain scores were lower POD1-3 in LBup vs. TEA group and use of opioids was also lower on these days. No difference at POD 4. *Use of non-opioid analgesics was significantly more common in LBup vs. TEA group (Acetaminophen and gabapentin/pregabalin) <u>Mean LoS:</u> LBup: 3.5 days vs. 4.5 days TEA, p=0.004 NS difference in post-op hypotension (which is a concern with TEA) Median duration of epidural infusions was 88 hrs for thoracotomy and 63 hrs for video assisted thoracic surgery (VATS) No difference in post-op complications	Retrospective, case-control, 2 surgeons choosing to use LBup vs. those not. Although not a prospective, randomized study, authors conclude that LBup appeared to be an effective alternative to TEA and may require less nursing staff, etc. than what is required for epidural infusions.
Hutchins 2015¹⁴ R, DB N=58, 28 LBup	Pts undergoing RAH. LBup 133 mg (10 mL) was administered using	Total opioid use 0-72 hours post-op.	<u>Opioid use 0-72 hrs post-op:</u> LBup: 24.9 mg SBup: 51.7 mg, p=0.002	In general authors stated that pts having RAH are sent home the day of

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<p>vs. 30 SBup (Prospective, randomized, active control) (Primary author on speaker's bureau, consultant and received grant funding from Pacira)</p>	<p>bilateral TAP blocks vs. SBup 0.25% (75 mg) with epi bilateral TAP block. TAP blocks administered by 1 of 4 anesthesiologists</p>	<p>Secondary: pain intensity, use of pain meds, LoS, nausea/vomiting, and pt satisfaction with pain control.</p>	<p>Differences primarily 0-24 hrs and 24-48hrs. <u>Max and Min pain scores:</u> <u>MAX:</u> LBup 5 vs. SBup 6 (0-24 hr) (p=0.002) LBup 4 vs. SBup 5 (24-48 hr) (p=0.044) LBup 3 vs. SBup 5 (48-72 hr) (p=0.047) <u>MIN:</u> LBup 1.5 vs. SBup 3 (0-24 hr) (p=0.003) LBup 2 vs. SBup 2 (24-48 hr) NS LBup 2 vs. SBup 2 (24-48 hr) NS Nausea was also less in LBup vs. SBup (25% vs. 56.7%, respectively, p=0.014) No difference in use of acetaminophen or ibuprofen, LoS or patient satisfaction</p>	<p>surgery and depends upon: adequate pain control, nausea/vomiting controlled and ability to void without problems. Is the dose of SBup used in this study standard for RAH? If so, should pain control be similar early post-op? Was similar in PACU, not sure how long pts in PACU. Duration of surgery was about 4 hrs. TAP blocks last between 6-24 hrs. There are limited trials using TAP blocks for RAH. One trial evaluating unilateral TAP blocks with SBup did not show a difference vs. sham. Although opioids consumed was the primary endpoints, authors indicated that no protocol existed for opioid administration. Patient recall was used to count other medications taken and study was not powered to find differences in all secondary outcomes measured. Authors call for larger trials to confirm their findings.</p>
<p>Gasanova 2015¹⁵ R, DB N=60, 30 LBup vs. 30 SBup (Majority of authors disclose no COI)</p>	<p>Total abdominal hysterectomy (TAH) LBup 266 mg infiltrated into the surgical site (preperitoneal, subfascial and subcutaneous planes) vs. SBup 0.5% (100 mg on each side) as bilateral TAP blocks using ultrasound. Both groups received 1-gram acetaminophen IV and ketorolac 30 mg IV intra-op. 24 hr post-op: each group received ketorolac 30 mg IV q6h+acetaminophen 1 mg oral q6h and PCA</p>	<p>Pain scores while coughing at 6 hrs post-op Secondary outcomes: Pain scores, opioid use, nausea/vomiting, need for rescue analgesics.</p>	<p>Pain scores at rest and with coughing were lower with the local infiltration/LBup group vs. TAP block with SBup across time. Morphine PCA: LBup/local infiltration 33.6 mg vs. SBup/TAP block 47.7 mg in first 24 hrs (p=0.0497) Hydromorphone/acetaminophen tabs: LBup 1.90 vs. SBup 3.55 (p=0.009) NS difference in nausea/vomiting, use of rescue medications and all pts resumed</p>	<p>Comparing 2 different modes of local anesthesia, TAP block with SBup vs. local infiltration with LBup makes it difficult to discern whether the local infiltration was a better mode of local anesthesia vs. TAP block or whether the LBup outperformed the SBup. Authors discussed that TAP blocks with local anesthetics may not alter the peritoneal contribution to pain perception since the spread of local anesthetics may not be uniform because</p>

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	24-48 hrs post-op: each group received ibuprofen 800 mg and acetaminophen 1 gm orally q8h plus hydrocodone/acetaminophen 1-2 tabs prn.		oral intake and discharge home within 48-60 hrs post-op.	of anatomic variation and certain nerves may have varied origin influencing the efficacy of TAP.
Nadeau 2016 ¹⁶ R, DB N=34 (Authors disclose no COI)	Breast augmentation. LBup (? Dose) in one breast implant pocket vs. SBup 0.5% (10 mL or 50 mg) in the other.	Pain scores post-op in each breast (VAS) Secondary outcomes: whether the added cost of LBup is justifiable	Pain scores were lower in the LBup vs. SBup group at each time point measured. Differences in VAS pain scores (0-10) ranged from 0.08-0.98. Patients were contacted to determine if improved pain control was worth the extra charge of \$250. Authors were able to contact 23/34 pts (67.6%). Of those, 16/23 (69.6%) said the pain relief was not worth the added cost.	Pain scores were improved by a difference of 0.08-0.98 in favor of LBup vs. SBup. Authors question whether the dose of SBup was comparable to the dose used for LBup since differences were noted in pain immediately post-op. Also, authors questioned whether the differences were clinically significant. They concluded that although there was a statistical difference in post-op with LBup vs. SBup, this may not result in an substantive benefit that requires additional costs to pts.

AUC=area under the curve, C=control, COI=conflict of interest, FNB=femoral nerve block, LBup=liposomal bupivacaine, LoS=length of stay, NRS=numeric rating scale, N and V=nausea and vomiting, P=placebo, PACU=post anesthesia care unit, PAI=periarticular injection, PCA=patient controlled analgesia, POD=post-operative day, R=ropivacaine, RAH=robotic assisted hysterectomy, ROM=range of motion, SBup=standard bupivacaine, TAH=total abdominal hysterectomy, TAP=subcostal transversus abdominis plane, TEA=thoracic epidural analgesia (TEA), THA=total hip arthroplasty, TKA=total knee arthroplasty, VAS=visual analog scales.