ERASing Postoperative Pain

An Update on Recently Approved Non-Opioid Analgesics

A presentation for HealthTrust Members | October 7, 2021

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Speaker Disclosures

The presenter and their preceptor have no financial relationships with any commercial interests pertinent to this presentation.

This program may contain the mention of drugs, brands or suppliers presented in a case study or comparative format using evidence-based research. Such examples are intended for educational and informational purposes and should not be perceived as an endorsement of any particular drug, brand or supplier.

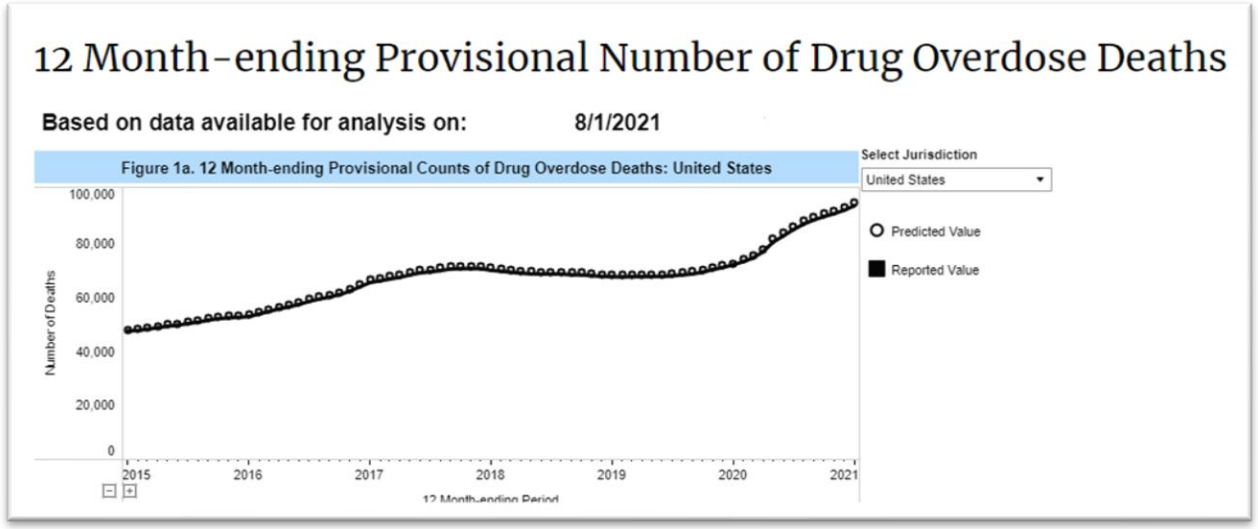
Learning Objectives

1. Define Enhanced Recovery After Surgery (ERAS)
2. Recognize the current pharmacological non-opioid agents in a multimodal approach to treating postoperative pain
3. Identify the place in therapy for recently approved non-opioid analgesics

The Opioid Epidemic

Overdose deaths accelerated during the COVID-19 pandemic

- Primarily caused by synthetic opioids
- Concern for Opioid Use Disorder development with legally prescribed opioids



https://www.cdc.gov/media/releases/2020/p1218-overdose-deaths-covid-19.html
https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm

Lane Stadium – 66,233 capacity

https://wset.com/news/local/virginia-techs-lane-stadium-to-open-at-100-capacity-this-fall-2021

Enhanced Recovery After Surgery (ERAS)

- **Develop** patient-centered, evidence-based and multidisciplinary team pathways
- **Reduce** patient's surgical stress response
- **Optimize** physiologic function
- **Facilitate** recovery

https://www.aana.com/practice/clinical-practice-resources/enhanced-recovery-after-surgery

ERAS Protocol

Preoperative

- Carbohydrate beverage up to 2 hours preoperative
- Patient/family education
- Multimodal analgesia and/or regional block placement ★

Intraoperative

- Normovolemia/Normothermia/Normoglycemia
- Avoid tubes and drains when possible
- Opioid sparing, multimodal analgesia ★

Postoperative

- Early nutrition / Early mobilization
- Fluid restriction or judicious IV fluid management
- Multimodal analgesia ★

https://www.aana.com/practice/clinical-practice-resources/enhanced-recovery-after-surgery

Multimodal Analgesia

Benefits include:

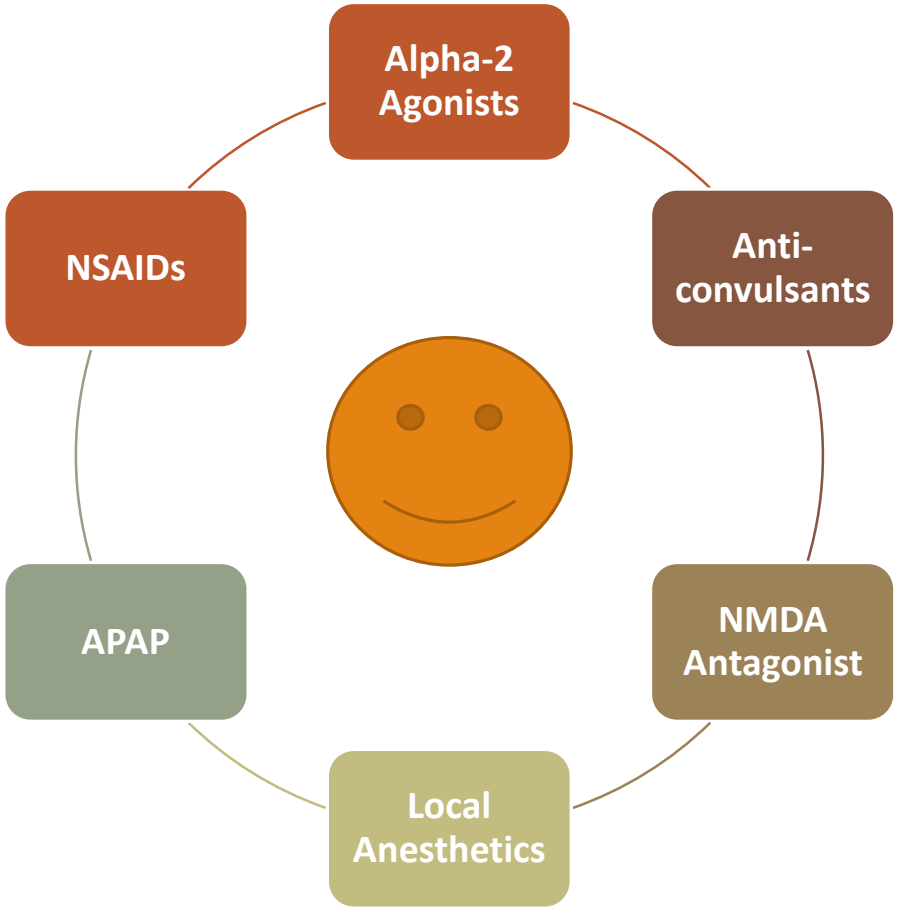
- Reduced opioid use and associated side effects, tolerance and diversion
- More effective pain control strategy

Results of poor pain control:

- Impedes postoperative rehabilitation
- Reduces patients' health-related quality of life
- Causes significant personal burden
- Adds to national health care expenditure
- Development of chronic pain

https://www.apsf.org/article/multimodal-analgesia-and-alternatives-to-opioids-for-postoperative-analgesia/

Multimodal Analgesia



https://www.apsf.org/article/multimodal-analgesia-and-alternatives-to-opioids-for-postoperative-analgesia/

Alpha-2-Agonists

- **MoA:** Direct stimulation of alpha-2-adrenoreceptors in CNS and spinal cord
  - Inhibits cAMP → ↓ K^+ efflux / Ca^+ influx → hyperpolarization state → ↓ NE release
  - Inhibits nociceptive neuronal firing → ↓ substance P release
- **May significantly reduce opioid consumption**, postoperative nausea/vomiting, anxiety, postoperative shivering, and stress responses intraoperative

	Dexmedetomidine	Clonidine
Dose	**IV LD:** 0.5-1 mcg/kg over 10 min **Infusion:** 0.2-1.7 mcg/kg/hr	**Oral:** 0.2 mg twice daily **Epidural:** 30-40 mcg/hr
Important Considerations	• Severe bradycardia and hypotension • Severe hypertension during LD • Consider dose ↓ in geriatric patients	• Severe hypotension • Withdrawal • Epidural (severe cancer pain)

MoA = mechanism of action
CNS = central nervous system
cAMP = cyclic adenosine monophosphate
NE = norepinephrine
PO = by mouth
LD = loading dose

https://www.apsf.org/article/multimodal-analgesia-and-alternatives-to-opioids-for-postoperative-analgesia/

Anticonvulsants

- **MoA:** Bind voltage-gated calcium channels
  - Inhibit excitatory neurotransmitter release → promotes antinociceptive actions
- **Originally for chronic neuropathic pain**
  - May also prevent/reduce acute pain and opioid consumption

	Gabapentin	Pregabalin
Dose	**PO:** 300-1200 mg three times a day	**PO:** 150-600 mg/day in 2-3 divided doses
Important Considerations	• Given preoperatively to reduce postoperative pain • Dizziness, drowsiness, water retention • Discontinue over 1 week	• 90% bioavailability compared to gabapentin

https://www.apsf.org/article/multimodal-analgesia-and-alternatives-to-opioids-for-postoperative-analgesia/

Ketamine

- **MoA:** N-methyl-D-aspartate (NMDA) Receptor Antagonist
- Non-barbiturate dissociative anesthetic with hypnotic, analgesic and amnestic effects
- Sub-anesthetic doses for treatment of neuropathic, acute and chronic pain

	Ketamine
Dose	**IV bolus:** 0.3-0.5 mg/kg **Infusion:** Start at 0.1-0.2 mg/kg/hr
Important Considerations	Side effects include increased sympathetic activity, elevated intracranial pressure, increase salivation, nystagmus and hallucinations

https://www.apsf.org/article/multimodal-analgesia-and-alternatives-to-opioids-for-postoperative-analgesia/

Lidocaine

- **MoA:** Local anesthetic
- Can be administered subcutaneously, intravenously and used in peripheral nerve blocks and neuraxial anesthetics

	Lidocaine
Dose	**IV bolus:** 1.5 mg/kg **Infusion:** 1-2 mg/kg/hr
Important Considerations	Can cause conduction block, dizziness, seizures and bradycardia

https://www.apsf.org/article/multimodal-analgesia-and-alternatives-to-opioids-for-postoperative-analgesia/

Acetaminophen

- **QUESTION -** What is acetaminophen's mechanism of action for treating pain?
- **MoA:** Unknown but may be due to inhibition of central prostaglandin synthesis and an elevation in pain threshold
- Potential for liver toxicity

	Acetaminophen
Dose	**PO:** 325-650 mg every 4-6 hr **PO:** 1000 mg every 6 hr **IV:** 1000 mg every 6 hr (if >50 kg) **IV:** 15 mg/kg every 6 hr (if <50 kg)
Important Considerations	• Max 4 grams in 24 hr • Chronic alcohol use: limit to max 2 gram per day • Potentiates warfarin anticoagulation

https://www.apsf.org/article/multimodal-analgesia-and-alternatives-to-opioids-for-postoperative-analgesia/

NSAIDs

	Dose	Important Considerations
Diclofenac	**PO:** 100-200 mg/day in 2-3 divided doses	• Dose-dependent relief • Start at lowest possible dose • Prolonged use predisposes to GI, CV and renal dysfunction • **Ketorolac (IV or PO):** limit use to 5 days • **Ketorolac (PO):** Only use to continue therapy after IV initiation • Increases lithium levels • Prone to gastric ulceration with bisphosphonates
Ibuprofen	**IV:** 400 mg, then 100-200 mg every 4-6 hr **PO:** 1.2-3.2 g/day in 3-4 divided doses	
Ketorolac	**IM/IV:** 15-30 mg every 4-6 hr **PO:** 10 mg every 4-6 hr	
Meloxicam	**PO:** 7.5-15 mg daily	
Celecoxib	**PO:** 50-200 mg/day in 1-2 divided doses	

NSAIDS = nonsteroidal anti-inflammatory drugs
GI = gastrointestinal
CV = cardiovascular

https://www.apsf.org/article/multimodal-analgesia-and-alternatives-to-opioids-for-postoperative-analgesia/

Recently Approved Non-Opioid Analgesics

Bupivacaine Liposome Injection (Exparel®) – October 2011

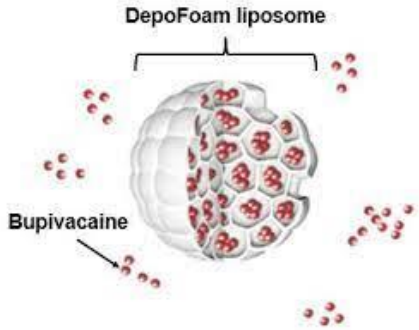
Pharmacological Class	Local Anesthetic
Manufacturer	Pacira
Mechanism of Action	Blocks initiation and conduction of nerve impulses → Inhibits depolarization → Conduction blockade
Indication	1. Postsurgical local analgesia via infiltration 2. Postsurgical regional analgesia via interscalene brachial plexus nerve block in adults
Operations	Suspension for injection in single-dose vials • 133 mg/10 mL or 266 mg/20 mL **After withdrawal from vial:** stable for 4 hours at RT **Unopened vials:** refrigeration recommended, but may be stored at RT up to 30 days

RT = room temperature

https://www.exparel.com/
Exparel [package insert]. San Diego, CA: Pacira Pharmaceuticals, Inc.: November 2018.

Bupivacaine Liposome Injection (Exparel®) – October 2011

Dosing	**Infiltration:** up to 266 mg (20 mL) → **$454.40** **Nerve Block:** 133 mg (10 mL) → **$227.20**
Dose Adjustments	Caution should be used in patients with hepatic or renal impairment
Contraindications	Obstetrical paracervical block anesthesia
Considerations	Exparel® is not bioequivalent to other bupivacaine formulations



Source: https://www.exparel.com/

Exparel [package insert]. San Diego, CA: Pacira Pharmaceuticals, Inc.: November 2018.
Lexicomp Online, Pricing: US. Waltham, MA: UpToDate, Inc.; July 30, 2021. https://online.lexi.com. Accessed September 2, 2021.

Clinical Effectiveness of Liposomal Bupivacaine Administered by Infiltration or Peripheral Nerve Block to Treat Postoperative Pain

- Narrative review published to ***Anesthesiology*** in February 2021
- Comprehensive summary of 76 randomized, controlled trials
- Studies were compared by:
  - Administration type
  - Placebo vs active comparator
- Evaluated using the Cochrane Risk of Bias tool

Conclusion: Whether introduced by surgical infiltration or as part of a peripheral nerve block, the preponderance of current evidence **fails to support** the routine use of liposomal bupivacaine over standard local anesthetics when treating postoperative pain.

Source: Ilfeld BM, Eisenach JC, Gabriel RA: Clinical effectiveness of liposomal bupivacaine administered by infiltration or peripheral nerve block to treat postoperative pain: A narrative review. ANESTHESIOLOGY 2020; 134:283–344

Perineural Liposomal Bupivacaine Is Not Superior to Nonliposomal Bupivacaine for Peripheral Nerve Block Analgesia

Design: Systematic review/meta-analysis evaluating effectiveness of peripheral nerve block analgesic

Intervention: Liposomal bupivacaine (LB) vs non-liposomal anesthetics (non-LB)

Primary Outcome: The difference in area under the receiver operating characteristics curve (AUC) of the pooled 24- to 72-h rest pain severity scores

Results Measure	**Non-LB** (mean±SD)	**LB** (mean±SD)	**Mean Difference** (95% CI)	**P-value**
AUC pain scores over 24-72h	7.6 ± 4.9	6.6 ± 4.6	1.0 (0.5-1.6)	0.003

Conclusion: Perineural liposomal bupivacaine provided a **statistically significant but clinically unimportant** improvement in the AUC of postoperative pain scores compared with plain local anesthetic**.**

Source: Hussain N, Brull R, Sheehy B, Essandoh MK, Stahl DL, Weaver TE, Abdallah FW: Perineural liposomal bupivacaine is not superior to nonliposomal bupivacaine for peripheral nerve block analgesia: A systematic review and meta-analysis. ANESTHESIOLOGY. 2021; 134:147–64

IV Meloxicam (Anjeso®) – February 2020

Pharmacological Class	Analgesic, NSAID
Manufacturer	Baudax Bio
Mechanism of Action	COX-1 and 2 reversible inhibitor → Decreased prostaglandin precursor formation
Indication	Management of moderate to severe pain, alone or in combination with non-NSAID analgesics
Operations	• Solution for injection in single-dose vials (1 mL) • No reconstitution or dilution required • Stored at 15-25°C (59-77°F)

Source: Anjeso (meloxicam), injection [package insert]. Malvern, PA: Baudax Bio; February 2020.
https://www.empr.com/home/news/anjeso-approved-for-management-of-moderate-to-severe-pain/

IV Meloxicam (Anjeso®) – February 2020

Dosing	30 mg IV push over 15 seconds (once per 24 hours) → **$112.80**
Dose Adjustments	<u>Renal Impairment</u> • Mild: no adjustment • Moderate-severe: use NOT recommended <u>Hepatic impairment</u> • Mild-moderate: no adjustment • Severe: use with caution and monitor for adverse events <u>CYP2C9 poor metabolizer or concomitant CYP2C9 inhibitor</u> • Consider dose adjustment
Black Box Warnings	Risk of severe cardiovascular events; risk of severe gastrointestinal events
Pregnancy	Avoid use in pregnant women starting at 30 weeks gestation • Risk of premature closure of fetal ductus arteriosus

Sources: Lexicomp Online, Pricing: US. Waltham, MA: UpToDate, Inc.; July 30, 2021. https://online.lexi.com. Accessed September 2, 2021. and Anjeso (meloxicam), injection [package insert]. Malvern, PA: Baudax Bio; February 2020.
https://www.empr.com/home/news/anjeso-approved-for-management-of-moderate-to-severe-pain/

IV Meloxicam (Anjeso®)

Study 1: Bunionectomy Surgery (n=201)

Intervention:

- IV meloxicam 30 mg every 24h for up to 3 doses (n=100)
- IV placebo every 24h for up to 3 doses (n=101)

Population:

- 18-75 years, undergoing bunionectomy repair
- Moderate-severe pain on 4-point categorical pain rating sale and NPRS score $\geq$ 4/10 within 9 hrs popliteal block d/c on post-op day 1

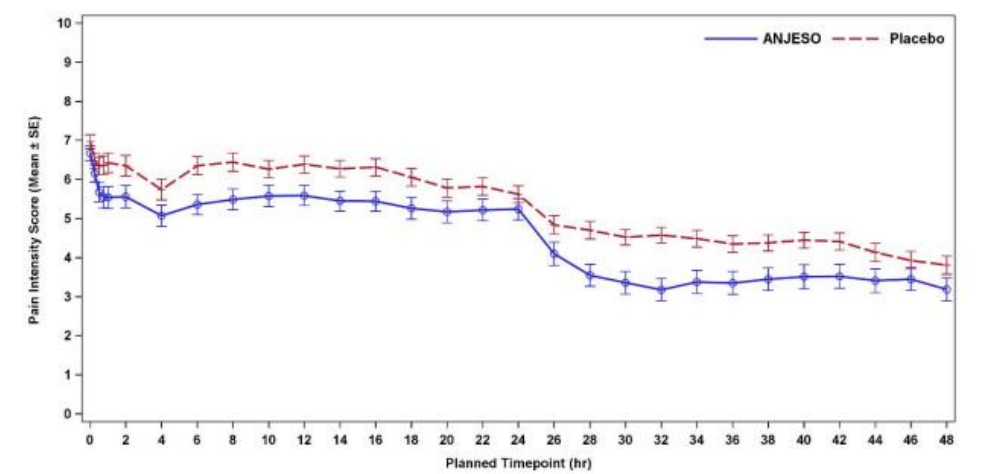
Primary Outcome:

- Pain reduction: the summed pain intensity difference from Hr0-Hr 48 (SPID48)

NPRS = numeric pain rating scale

Source: Pollak RA, Gottlieb IJ, Hakakian F, et al. Efficacy and safety of intravenous meloxicam in subjects with moderate-to-severe pain following bunionectomy: a randomized, double-blind, placebo-controlled trial. Clin J Pain. 2018;34:918-26.

Study 1: Bunionectomy Surgery (n=201)



Safety:

- IV meloxicam was well tolerated with no deaths; no treatment d/c due to AEs and no serious AEs
- Most events in IV meloxicam group were mild (39% IV meloxicam vs 43.6% placebo) or moderate (14% IV meloxicam vs 20.8% placebo) in severity
- Most common TEAEs in IV meloxicam vs placebo subject: **nausea** (20% vs 25.7%, **headache** (8% vs 11.9%), **pruritus** (8% vs 3%), **constipation** (4% vs 5%), **vomiting** (3% vs 8.9%), **dizziness** (3% vs 4%), **somnolence** (3% vs 2%) and **flushing** (3% vs 1%)

Conclusion: Treatment with IV meloxicam provided pain relief within 30 minutes and was observed for 24 hours with a well-tolerated safety profile.

d/c = discontinue
AE = adverse event
TEAE = treatment emergent adverse effect

Source: Pollak RA, Gottlieb IJ, Hakakian F, et al. Efficacy and safety of intravenous meloxicam in subjects with moderate-to-severe pain following bunionectomy: a randomized, double-blind, placebo-controlled trial. Clin J Pain. 2018;34:918-26.

IV Meloxicam (Anjeso®)

Study 2: Abdominoplasty Surgery (n=219)

Intervention:

- IV meloxicam 30 mg every 24h for 2 doses (n=110)
- IV placebo every 24h for 2 doses (n=109)

Population:

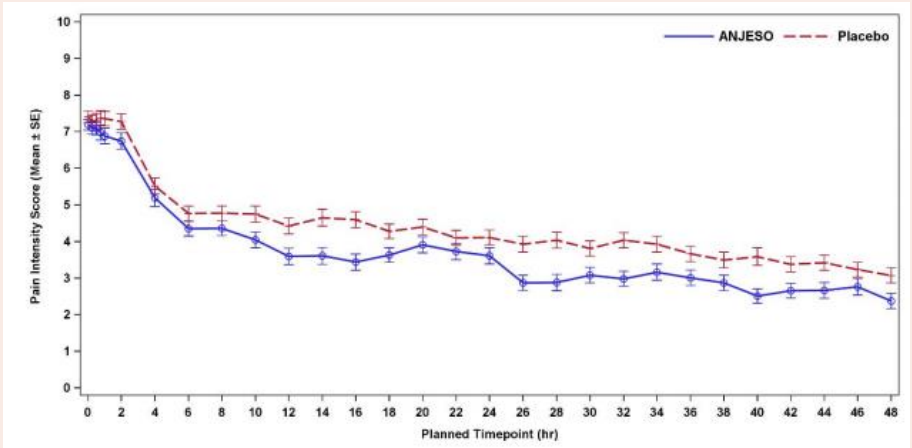
- 18-75 years, undergoing abdominoplasty surgery
- Moderate-severe pain on 4-point categorical pain rating sale and NPRS score $\geq$ 4/10 within 3 hrs of the end of surgery

Primary Outcome:

- Pain reduction: the summed pain intensity difference from Hr0-Hr24 (SPID24)

Source: Singla N, Binderwald M, Singla S, et al. Efficacy and safety of intravenous meloxicam in subjects with moderate to severe pain following abdominoplasty. Plast Reconstr Surg Glob Open. 2018;6:e1846.

Study 2: Abdominoplasty Surgery (n=219)



Safety:

- IV meloxicam was well tolerated with no deaths; no treatment d/c due to AE
- Serious AEs – 3 in placebo, 1 in IV meloxicam
  - **Both groups:** 1 case of bleeding in each group (post procedural hemorrhage)
  - **Placebo group:** 1 postop wound infection and 1 post procedural PE
- Most common TEAEs in IV meloxicam vs placebo subjects: **nausea** (20% vs 25.7%, **headache** (8% vs 11.9%), **pruritus** (8% vs 3%), **constipation** (4% vs 5%), vomiting (3% vs 8.9%), dizziness (3% vs 4%), somnolence (3% vs 2%) and flushing (3% vs 1%)

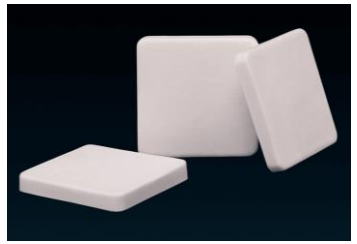
Conclusion: Treatment with IV meloxicam resulted in a **statistically significant reduction** in pain from baseline compared to placebo for SPID24. IV meloxicam was generally well tolerated with the majority of TEAEs being mild or moderate in intensity (0 deaths, 1 serious AE, no discontinuations).

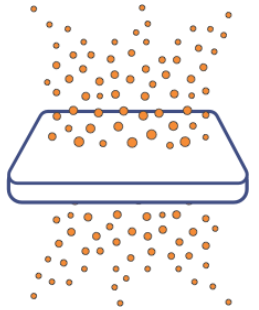
d/c = discontinue
AE = adverse event
TEAE = treatment emergent adverse effect

Source: Singla N, Binderwald M, Singla S, et al. Efficacy and safety of intravenous meloxicam in subjects with moderate to severe pain following abdominoplasty. Plast Reconstr Surg Glob Open. 2018;6:e1846.

Collagen Matrix Impregnated with Bupivacaine (Xaracoll®) – August 2020

Pharmacological Class	Local Anesthetic
Manufacturer	Innocoll
Indication	Postsurgical analgesia for up to 24 hours in adults following open inguinal hernia repair
Operations	• Single-dose cartons (3 implants per carton) • Implants must be cut in half prior to administration • Store at room temperature and keep dry





Source: https://xaracoll.com/

XARACOLL (bupivacaine collagen matrix) [package insert]. Athlone, Ireland: Innocol Pharmaceuticals Limited; August 2020.

Collagen Matrix Impregnated with Bupivacaine (Xaracoll®) – August 2020

Dosing	300 mg, as 3x100 mg implants → **$280.80** • Avoid additional local anesthetic administration within 96 hours following implantation
Dose Adjustments	Renal Impairment: Monitor for adverse reactions and local anesthetic systemic toxicity in any renal disease Hepatic impairment: Monitor for adverse reactions and local anesthetic systemic toxicity in moderate to severe impairment
Contraindications	• Hypersensitivity to any amide-type local anesthetic or any component of the formulation • Patients undergoing obstetrical paracervical block anesthesia (due to risk of fetal bradycardia and death)

Source: XARACOLL (bupivacaine collagen matrix) [package insert]. Athlone, Ireland: Innocol Pharmaceuticals Limited; August 2020.
Lexicomp Online, Pricing: US. Waltham, MA: UpToDate, Inc.; July 30, 2021. https://online.lexi.com. Accessed September 2, 2021.

MATRIX-1 (n=305) and MATRIX-2 (n=319)

Design: Two phase 3, multicenter, double-blind, parallel-group, placebo-controlled (2:1)

Intervention: INL-001 100 mg implant x3 vs Placebo collagen matrix x3

Population: ≥18 years old, undergoing elective open mesh tension-free inguinal hernia repair under general anesthesia between August 2015 and April 2016

Primary Outcome: Sum of pain intensity (SPI) from 0-24 hours (SPI-24, the area under the NRS PI curve from 0 to 24 hours)

Secondary Outcomes:

- SPI from 0-48 hours (SPI-48)
- SPI from 0-72 hours (SPI-72)
- Total use of opioid analgesia (TOpA) from 0-24 hours (TOpA-24), 0-48 hours (TOpA-48), 0-72 hours (TOpA-72) [in mg IV morphine equivalents]
- Safety measures through 30-day study period

INL-001 = collagen matrix impregnated with bupivacaine
SPI = sum of pain intensity
TOpA = total use of opioid analgesia
NRS PI = numeric rating scale-pain intensity

Source: Velanovich C, Rider P, Deck K, et al. Safety and efficacy of bupivacaine HCl collagen-matrix implant (INL-001) in open inguinal hernia repair: results from two randomized controlled trials. Adv Ther. 2019;36:200-16.

Pooled Results of MATRIX-1 and MATRIX-2

	Efficacy Results	INL-001 (n=404)	Placebo (n=206)	P-value
1º	SPI-24, mean (SEM)	87.1 (2.34)	111.6 (3.22)	<0.0001
2º	SPI-48, mean (SEM)	186.1 (4.65)	209.2 (6.44)	0.0033
2º	SPI-72, mean (SEM)	268.0 (6.91)	291.3 (9.55)	0.0441
2º	TOpA-24, median	5.0	12.3	<0.0001
2º	TOpA-48, median	7.0	15.0	<0.0001
2º	TOpA-72, median	9.0	17.0	0.0004

Safety Results	INL-001 (n=411)	Placebo (n=208)
Treatment-related TEAE, n (%)	**14 (3)**	**6 (3)**
Dysgeusia	6 (2)	2 (1)
Dizziness	4 (1)	1 (<1)
Incision-site complication	3 (<1)	0

Conclusions

- The MATRIX-1 and MATRIX-2 pivotal phase 3 studies of INL-001 met its primary end points.
- The analgesic efficacy of INL-001 was further supported by a significantly lower use of opioid analgesics in the INL-001 group compared with the placebo collagen-matrix group through 24 hours.
- INL-001 was well tolerated, and no safety issues emerged during the study related to the use of the collagen-matrix.

SEM = standard error of the mean

Source: Velanovich C, Rider P, Deck K, et al. Safety and efficacy of bupivacaine HCl collagen-matrix implant (INL-001) in open inguinal hernia repair: results from two randomized controlled trials. Adv Ther. 2019;36:200-16.

Bupivacaine & Meloxicam (Zynrelef™) – May 2021

Pharmacological Class	Local anesthetic (bupivacaine); analgesic/NSAID (meloxicam)
Manufacturer	Heron Therapeutics
Indication	Postsurgical analgesia for up to 72 hours (following bunionectomy, open inguinal herniorrhaphy, & TKA)
Operations	• Strengths: 60mg/1.8mg, 200 mg/6mg, 300 mg/9mg, & 400 mg/12mg • Single-dose vials packaged with a kit containing all necessary components for administration • Stored at room temperature and protected from light and moisture

TKA = total knee arthroplasty

Source: https://zynrelef.com/
Zynrelef (bupivacaine/meloxicam), solution for injection. Heron Therapeutics; May 2021.

Bupivacaine & Meloxicam (Zynrelef™) – May 2021

Dosing	Bunionectomy: Up to 2.3 mL (60 mg Bup/1.8 mg meloxicam) →**$52.74** Open inguinal hernia repair: Up to 10.5 mL (300 mg Bup/9 mg meloxicam) → **$240.77** TKA: Up to 14 mL (400 mg Bup/12 mg meloxicam) → **$321.02**
Dose Adjustments	Renal impairment: Monitor for worsening renal function; avoid use in advanced disease Hepatic impairment: Use caution; monitor for toxicity in severe impairment CYP2C9 poor metabolizers: consider dose reduction
Black Box Warnings	Risk of serious cardiovascular and gastrointestinal events
Pregnancy	Avoid use in pregnant women starting at 30 weeks gestation • Risk of premature closure of fetal ductus arteriosus

Source: Zynrelef (bupivacaine/meloxicam), solution for injection. Heron Therapeutics; May 2021.
Lexicomp Online, Pricing: US. Waltham, MA: UpToDate, Inc.; July 30, 2021. https://online.lexi.com. Accessed September 2, 2021

Study 1: Bunionectomy Surgery (n=412)

Design: Multicenter, double-blind, parallel-group, active and placebo-controlled (3:3:2)

Intervention: Bupivacaine & meloxicam 60mg/1.8mg (HTX-011), bupivacaine HCl 50 mg (BUP), or placebo (PBO)

Population: ≥18 years old, primary unilateral, distal, first metatarsal bunionectomy with osteotomy and internal fixation

Exclusion:

- NSAID use within 10 days prior to surgery
- Daily use of opioids for ≥ 7 consecutive days within 6 months prior to surgery
- Opioids within 24 hours prior to surgery
- Long-acting opioids within 3 days prior to surgery
- Bupivacaine use within 5 days prior to surgery
- Systemic steroids within 5 half-lives or 10 days prior to surgery

Primary Outcome: Mean AUC of NPRS of pain intensity scores from 0 to 72 hours post-surgery (AUC0-72) for HTX-011 vs PBO

Source: Viscusi E, Gimbel JS, Pollack RA, Hu J, Lee GC. HTX-011 reduced pain intensity and opioid consumption versus bupivacaine HCl in bunionectomy: phase III results from the randomized EPOCH 1 study. Reg Anesth Pain Med. 2019;44(7):700-6. doi.org/10.1007/s10029-019-02023-6

Study 1: Bunionectomy Surgery (n=412)

	Endpoint	HTX-011 (n=157)	BUP (n=155)	PBO (n=100)	P-value
1º	Mean (SD) of AUC_{0-72} of NPRS	323.3 (182.6)	393.5 (153.8)	445.3 (155.8)	0.0002 vs BUP <0.0001 vs PBO
2º	Mean (SD) of opioid consumption (MME) through 72 hours	18.8 (19.8)	25.09 (21.55)	30.06 (21.01)	0.0022 vs BUP <0.0001 vs PBO
2º	% of patients opioid free through 72 hours	45 (28.7%)	17 (11.0%)	2 (2.0%)	0.0001 vs BUP <0.0001 vs PBO

Conclusion: HTX-011 demonstrated a significant reduction in postoperative pain through 72 hours and a significant reduction in opioid consumption compared to saline placebo and bupivacaine HCl.

SD = standard deviation
MME = Morphine Milligram Equivalent

Source: Viscusi E, Gimbel JS, Pollack RA, Hu J, Lee GC. HTX-011 reduced pain intensity and opioid consumption versus bupivacaine HCl in bunionectomy: phase III results from the randomized EPOCH 1 study. Reg Anesth Pain Med. 2019;44(7):700-6. doi.org/10.1007/s10029-019-02023-6

Study 2: Hernia Repair (n=446)

Design: Multicenter, double-blind, parallel-group, active and placebo-controlled

Intervention: Bupivacaine & meloxicam 300mg/9mg, bupivacaine HCl 0.25% solution 75 mg, or placebo (2:2:1)

Population: ≥18 years old, unilateral open inguinal herniorrhaphy with mesh placement

Exclusion:

- NSAID use within 10 days prior to surgery
- Daily use of opioids for ≥ 7 consecutive days within 6 months prior to surgery
- Opioids within 24 hours prior to surgery
- Long-acting opioids within 3 days prior to surgery
- Bupivacaine use within 5 days prior to surgery
- Systemic steroids within 5 half-lives or 10 days prior to surgery

Primary Outcome:

- Mean AUC of NPRS of pain intensity scores from 0 to 72 hours post-surgery (AUC0-72) for HTX-011 vs PBO

Source: Viscusi E, Minkowitz H, Winkle P, Ramamoorthy S, Hu J, Singla N. HTX 011 reduced pain intensity and opioid consumption versus bupivacaine HCl in herniorrhaphy: results from the phase 3 EPOCH 2 study. Hernia. 2019;23:1071-80. doi.org/10.1007/s10029-019-02023-6

Study 2: Hernia Repair (n=446)

	Endpoint	HTX-011 (n=164)	BUP (n=172)	PBO (n=82)	P-value
1º	Mean (SD) of AUC_{0-72} of NPRS	269.4 (173.72)	341.9 (158.30)	350.8 (171.22)	<0.0001 vs BUP 0.0004 vs PBO
2º	Mean (SD) of opioid consumption (MME) through 72 hours	10.9 (17.06)	14.5 (18.19)	17.5 (18.91)	0.0240 vs BUP 0.0001 vs PBO
2º	% of patients opioid free through 72 hours	84 (51.2%)	69 (40.1%)	18 (22.0%)	0.0486 vs BUP <0.0001 vs PBO
2º	% patients w/severe pain at any time from 0-72 hrs	48.8%	60.5%	81.7%	0.0372 vs BUP <0.0001 vs PBO

Conclusion: HTX-011 demonstrated a statistically significant reduction in postoperative pain through 72 hours and a significant reduction in opioid consumption following inguinal herniorrhaphy.

Viscusi E, Minkowitz H, Winkle P, Ramamoorthy S, Hu J, Singla N. HTX 011 reduced pain intensity and opioid consumption versus bupivacaine HCl in herniorrhaphy: results from the phase 3 EPOCH 2 study. Hernia. 2019;23:1071-80. doi.org/10.1007/s10029-019-02023-6

Study 3: TKA (n=222)

Design: Multicenter, double-blind, parallel-group, active and placebo-controlled

Intervention:

- Bupivacaine & meloxicam 400mg/12mg via periarticular injection (HTX-011)
- Bupivacaine & meloxicam 400mg/12mg via periarticular injection + ropivacaine 50 mg injection into posterior capsule (HTX+ROP)
- Bupivacaine HCl 125 mg via multiple periarticular injections (BUP)
- Saline placebo (PBO)

Population: ≥18 years old, American Society of Anesthesiologists physical status of I, II or III, scheduled to undergo a unilateral TKA

Primary Outcome: Mean AUC of NPRS of pain intensity scores from 0 to 48 hours post-surgery (AUC0-48) for HTX-011 vs PBO

Source: Lachiewicz PF, Lee GC, Pollak RA, Leiman DG, Hu J, Sah AP. HTX-011 reduced pain and opioid use after primary total knee arthroplasty: results of a randomized phase 2b trial. J Arthroplasty. 2020;35:2843-51.

Study 3: TKA (n=222)

Endpoint	PBO (n=53)	BUP (n=55)	HTX-011 (n=58)	HTX + ROP (n=56)
AUC0-48 of the NPRS pain intensity scores (non-adjusted)				
Mean (SD)	267.3 (81.3)	233.7 (85.5)	188.9 (81.6)	194.5 (99.6)
Primary endpoint: p value vs. PBO	-	-	p<0.0001	p<0.0001
Secondary endpoint: p value vs. BUP	-	-	p=0.0070	p=0.0190
AUC0-72 of the NPRS pain intensity scores (non-adjusted)				
Mean (SD)	365.4 (127.2)	319.6 (128.4)	264.56 (123.2)	269.51 (144.8)
Secondary endpoint: p value vs. PBO	-	-	p<0.0001	p=0.0002
Secondary endpoint: p value vs. BUP	-	-	p=0.0269	p=0.0456

Conclusion: HTX-011 (either alone or with additional ropivacaine) demonstrated a **statistically significant reduction** in postoperative pain through 48 and 72 hours compared to saline placebo and bupivacaine HCl following unilateral TKA.

Source: Lachiewicz PF, Lee GC, Pollak RA, Leiman DG, Hu J, Sah AP. HTX-011 reduced pain and opioid use after primary total knee arthroplasty: results of a randomized phase 2b trial. J Arthroplasty. 2020;35:2843-51.

Claims to Fame

October 2011

Bupivacaine Liposome (Exparel®)

"…utilizes the proprietary **DepoFoam®** drug delivery technology to consistently deliver safe levels of bupivacaine"

February 2020

IV Meloxicam (Anjeso®)

"…only approved 24-hour, **IV COX-2 preferential NSAID** that offers once-daily dosing"

August 2020

Bupivacaine Impregnated Collagen Matrix (Xaracoll®)

"First long-acting, opioid-sparing, local analgesic to meet primary endpoints of Phase 3 clinical trials in **hernia repair**"

May 2021

Bupivacaine & Meloxicam (Zynrelef™)

"…first and only FDA-approved extended-release **dual-acting** local anesthetic"

Sources: https://www.exparel.com/hcp/OMFS_FAQs_2021.pdf
https://www.globenewswire.com/news-release/2020/02/20/1988253/0/en/Baudax-Bio-Announces-FDA-Approval-of-ANJESO-for-the-Management-of-Moderate-to-Severe-Pain.html
https://www.innocoll.com/innocoll-announces-xaracoll-bupivacaine-collagen-bioresorbable-implant-meets-primary-endpoint-in-both-pivotal-phase-3-trials-in-postoperative-pain-relief/

Cost Comparison – AWP

IV Meloxicam (Anjeso®)

- Estimated cost per dose: **$112.80**

Bupivacaine & Meloxicam (Zynrelef™)

- Estimated cost per dose: **$52.74 - $321.02**

Bupivacaine Liposome Injection (Exparel®)

- Nerve Block: **$227.20** ; Infiltration: **$454.40**

Bupivacaine Impregnated Collagen Matrix (Xaracoll®)

- Estimated cost per dose: **$280.80**

Meloxicam Oral Tablets

7.5 mg (per each): **$0.05 - $3.17**

15 mg (per each): **$0.06 - $4.85**

Bupivacaine HCl Injection

Nerve Block: **$11.20 - $16.00**

Infiltration: **$4.90 - $7.00**

AWP = average wholesale price

Source: Lexicomp Online, Pricing: US. Waltham, MA: UpToDate, Inc.; July 30, 2021. https://online.lexi.com. Accessed September 2, 2021.

Key Takeaways

- ERAS protocols are **patient-centered**, **evidence-based**, and **multidisciplinary** team developed pathways
- Multimodal analgesia **decreases opioid consumption** and may often provide superior analgesia compared to opioids alone
- Newly approved non-opioid analgesics often use **placebo-controlled trials** for FDA approval
  - Future active-controlled studies are needed to determine cost vs. benefit

Assessment Question 1

What does ERAS stand for?

a. Enhanced Recovery After Surgery
b. Expected Relief After Surgery
c. Elective Rehabilitation After Surgery
d. Encouraged Rest After Surgery

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Assessment Question 2

Which of the following is not an agent used in a multimodal approach in treating postoperative pain?

a. Lidocaine
b. Ketamine
c. Propofol
d. Clonidine

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Assessment Question 3

Which of the following 24-hour intravenous COX-2 preferential NSAID is approved for the treatment of acute postoperative pain?

a. Celecoxib
b. Ibuprofen
c. Diclofenac
d. Meloxicam

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Assessment Question 4

Bupivacaine is available in what formulation?

a. Dry powder inhaler
b. Collagen matrix implant
c. Sublingual tablet
d. Transdermal patch

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Bupivacaine is available in what formulation?

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Thank you!

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