

Benefits and Limitations of Local Anesthetics in Postoperative Pain

Eugene R Viscusi, MD

Sidney Kimmel Medical College at Thomas Jefferson University



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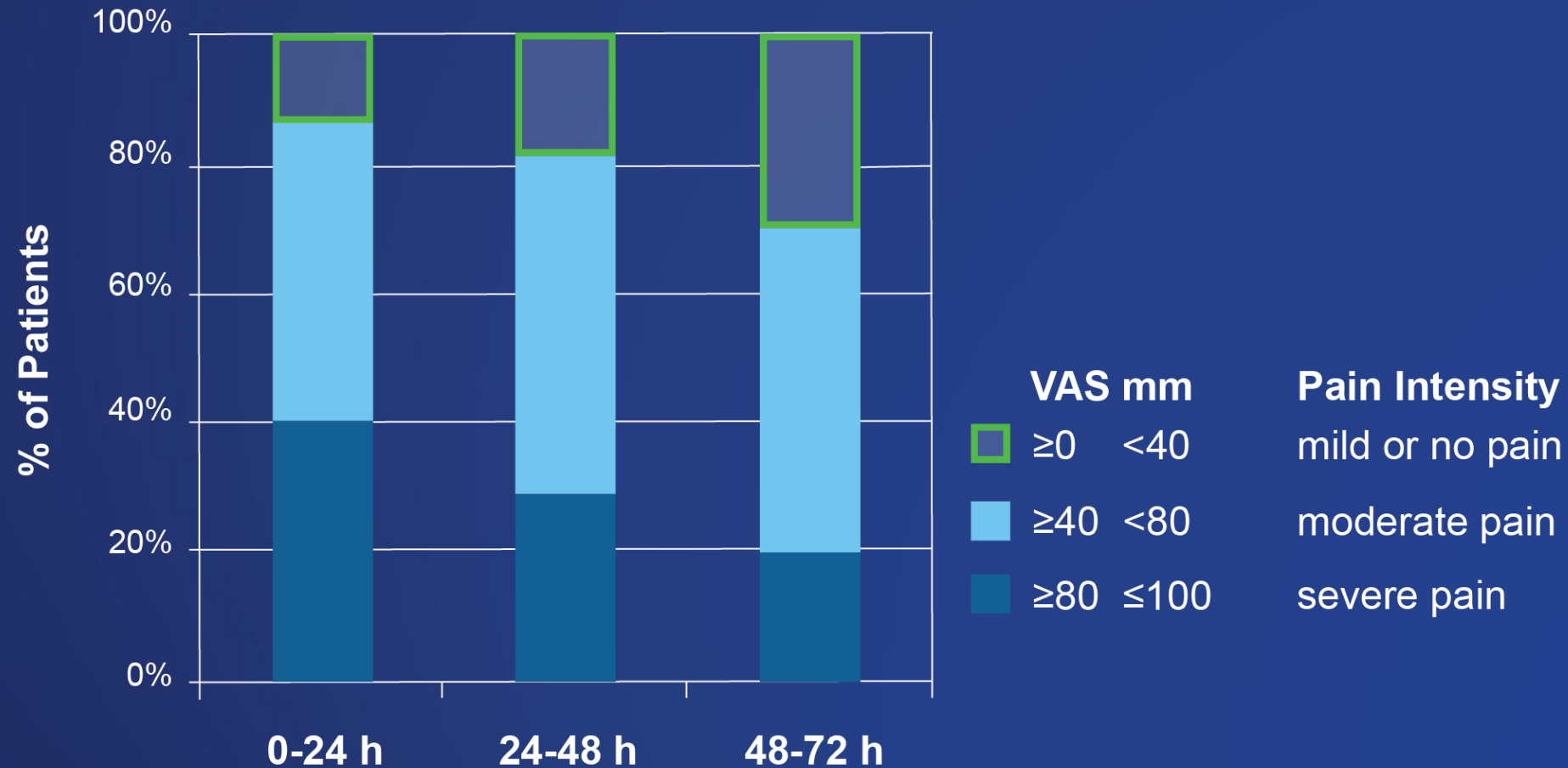
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Discussion Topics

- Managing Severe Pain and Inflammation in the First 72 Hours Postoperatively
- Local Anesthetics: Benefits and Limitations
- Opioids Are Not the Optimal Solution
- Are There Opportunities for Improvement?

Managing Pain and Inflammation in the First 72 Hours Postoperatively

The first 72 hours after surgery are the most painful



Reference: 1. Svensson I, Sjöström B, Haljamäe H. Assessment of pain experiences after elective surgery. *J Pain Symptom Manage*. 2000;193-201.

Uncontrolled postoperative pain impedes patient recovery



Negative impact on physical activity, sleep, and cognitive function¹



Less likely to ambulate²



Delayed discharge²



Decreased patient satisfaction³

References: 1. Aasvang EK, Luna IE, Kehlet H. Challenges in postdischarge function and recovery: the case of fast-track hip and knee arthroplasty. *Br J Anaesth*. 2015;861-866. 2. Morrison RS, Magaziner J, McLaughlin MA, et al. The impact of post-operative pain on outcomes following hip fracture. *Pain*. 2003;103:303-311. 3. Chan EY, Blyth FM, Nairn L, Fransen M. Acute postoperative pain following hospital discharge after total knee arthroplasty. *Osteoarthritis Cartilage*. 2013;21(9):1257-1263.

Types of postoperative pain



**Nociceptive
pain**



**Inflammatory
pain**



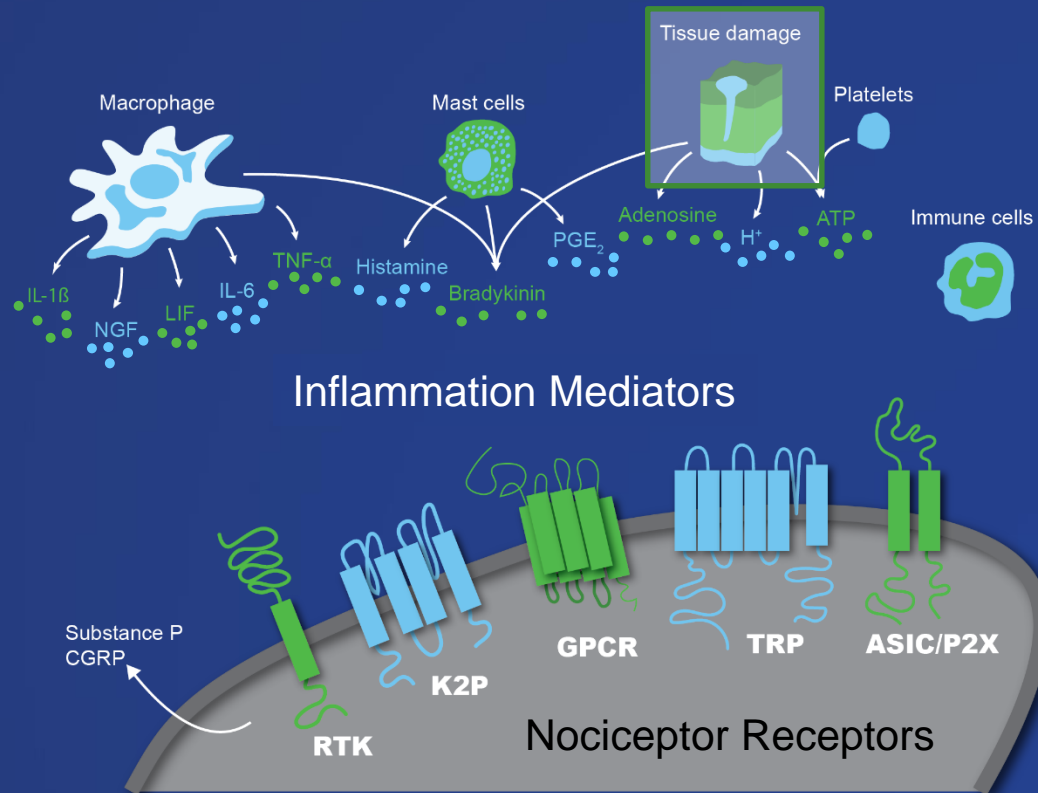
**Neuropathic
pain**

Inflammatory pain: peripheral sensitization

Local tissue damage activates a variety of cells, which release inflammatory mediators^{1,2}

- Inflammation can also modify the activity of the central nervous system's pain pathways¹
- Inflammation is known to result in hyperalgesia²

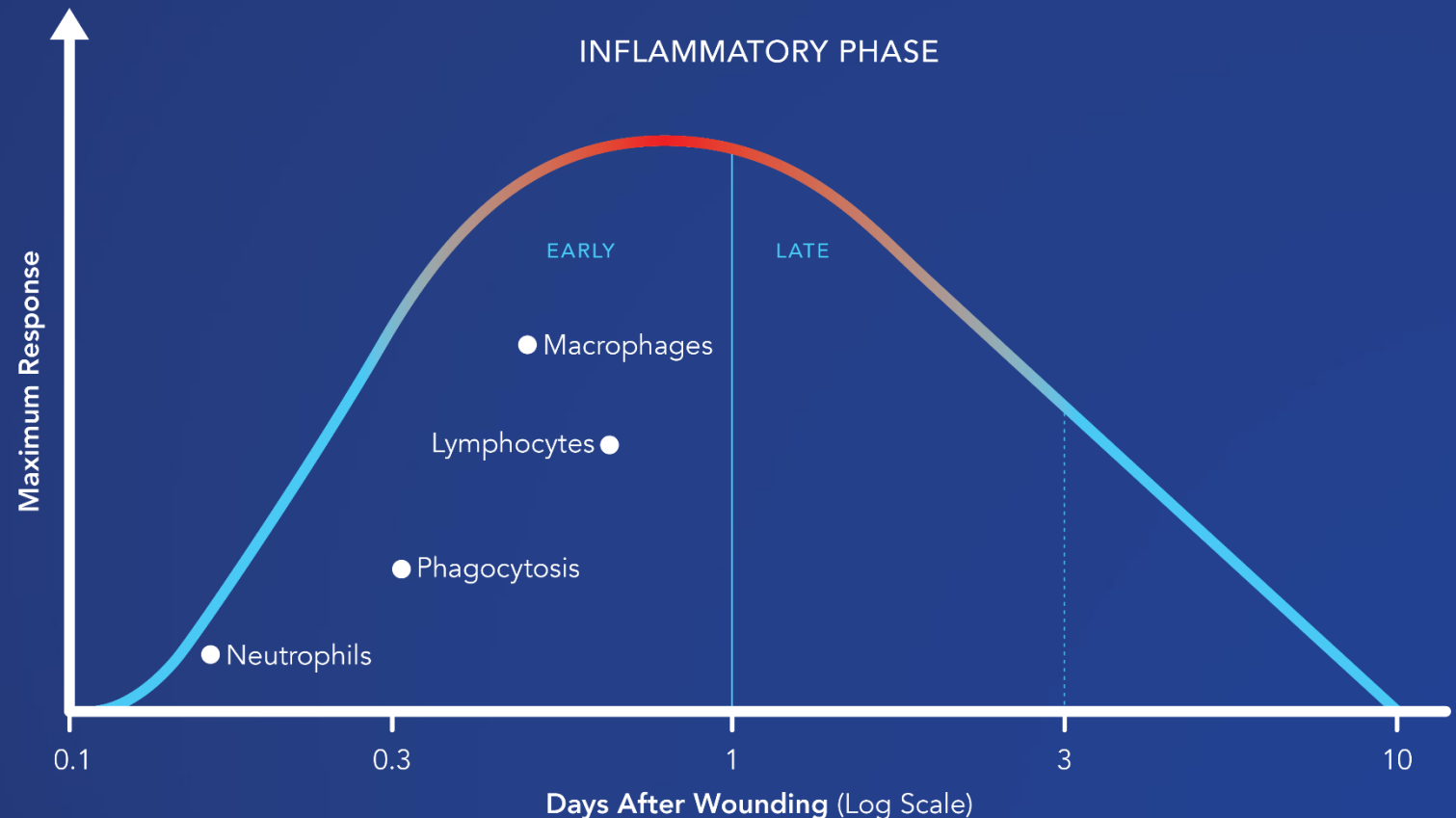
Peripheral mediators of inflammation



References: 1. Woolf CJ. Pain: moving from symptom control toward mechanism-specific pharmacologic management. *Ann Intern Med.* 2004;140(6):441-451. 2. Basbaum AI, Bautista DM, Scherrer G, Julius D. Cellular and molecular mechanisms of pain. *Cell.* 2009;139(2): 267-284.

Inflammation is most active during the first 72 hours postoperatively

Inflammation peaks around 24 hours postoperatively and remains relatively high through the first 72 hours—and it is a significant component of postoperative discomfort.^{1,2}



References: 1. Enoch S, Leaper DJ. Basic science of wound healing. *Surgery (Oxford)*. 2007;31-37. 2. Woolf CJ. Pain: moving from symptom control toward mechanism-specific pharmacologic management. *Ann Intern Med*. 2004;441-451.

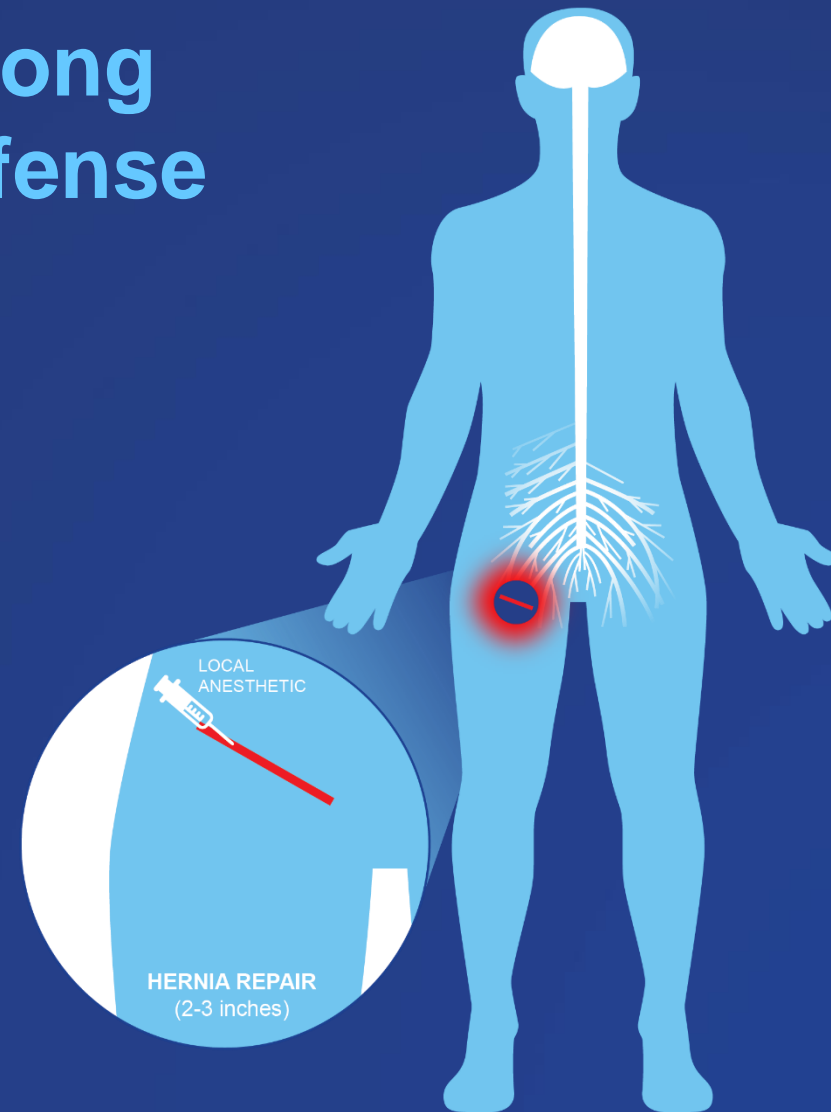
**Adequate treatment
of pain and inflammation
during the first 72 hours
following surgery
is critical**

Local Anesthetics:

Benefits and Limitations

Local anesthetics can be a strong foundation and first line of defense

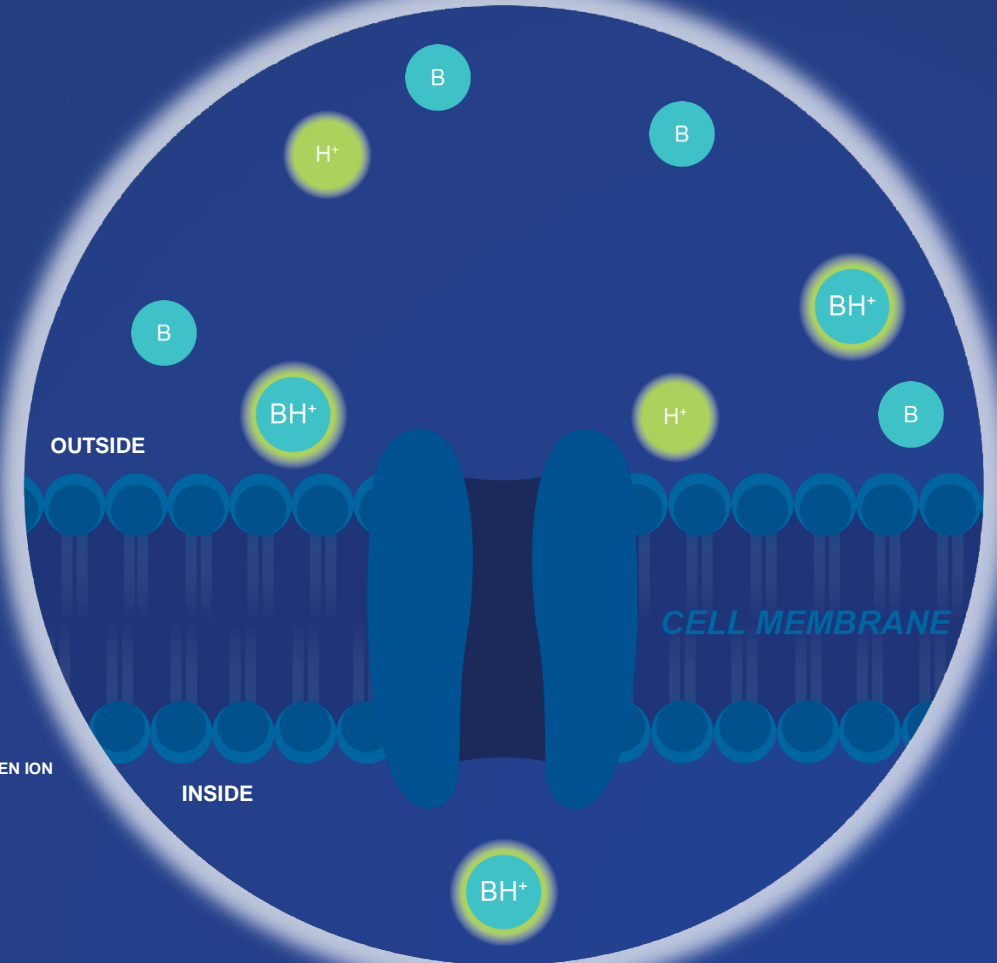
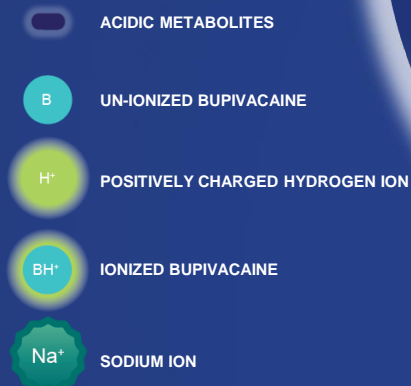
- By allowing patients to come out of surgery with less severe pain, local anesthetics can provide a strong foundation for postoperative pain management.¹
 - Generic local anesthetics are not designed to provide pain relief beyond 8 to 12 hours¹
 - Longer-acting local anesthetics exhibit limited and inconsistent efficacy beyond 24 hours in part because the inflammatory process inhibits their ability to penetrate the nerve cell membrane²⁻⁶



References: 1. Berde CB, Strichartz GR. Local anesthetics. In: Miller RD, et al, eds. *Miller's Anesthesia*. 2015:1012-1054.e4. 2. Gorfine SR, Onel E, Patou G, Krivokapic ZV. Bupivacaine extended-release liposome injection for prolonged postsurgical analgesia in patients undergoing hemorrhoidectomy: a multicenter, randomized, double-blind, placebo-controlled trial. *Dis Colon Rectum*. 2011:1552-1559. 3. Brown L, Weir T, Shasti M, et al. The efficacy of liposomal bupivacaine in lumbar spine surgery. *Int J Spine Surg*. 2018:434-440. 4. Ali A, Sundberg M, Hansson U, Malmvik J, et al. Doubtful effect of continuous intraarticular analgesia after total knee arthroplasty: a randomized, double-blind study of 200 patients. *Acta Orthopaedica*. 2015:373-377. 5. Carvalho B, Clark DJ, Yeomans DC. Continuous subcutaneous instillation of bupivacaine compared to saline reduces interleukin 10 and increases substance P in surgical wounds after cesarean delivery. *Anesth Analg*. 2010:1452-1459. 6. Kim J, Burke SM, Kryzanski JT, et al. The role of liposomal bupivacaine in reduction of postoperative pain after transforaminal lumbar interbody fusion: a clinical study. *World Neurosurg*. 2016:460-467.

Inflammation can inhibit the efficacy of local anesthetics such as bupivacaine

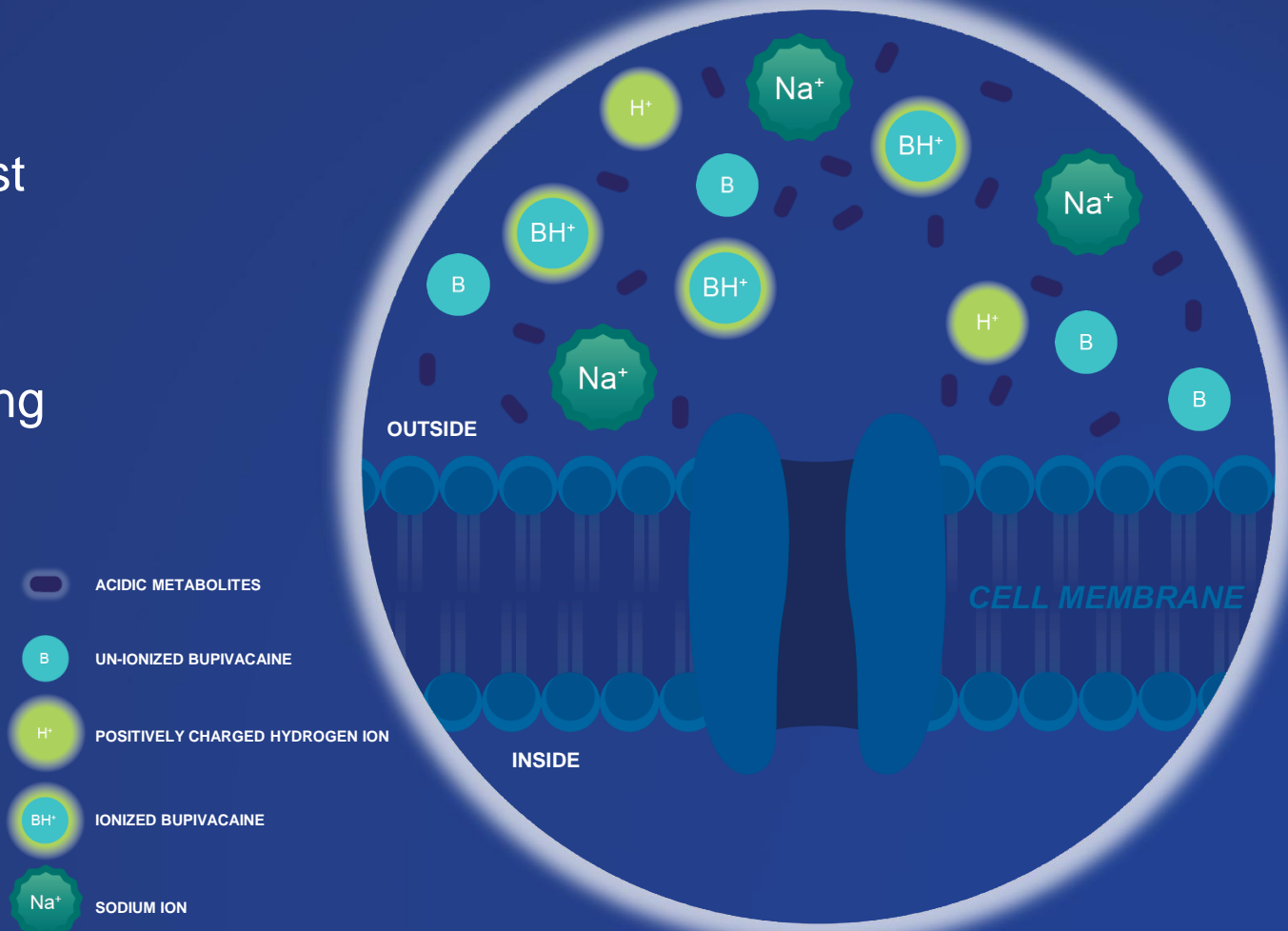
- To stop pain signals, bupivacaine must penetrate the nerve cell membrane¹
- The inflammatory process floods the wound with acidic metabolites, lowering pH at the surgical site^{2,3}
- Bupivacaine becomes ionized²
- Ionized bupivacaine cannot penetrate and therefore cannot block pain signals²



References: 1. Berde CB, Strichartz GR. Local anesthetics. In: Miller RD, Cohen NH, Eriksson LI, Fleisher LA, Wiener-Kronish JP, Young WL, eds. *Miller's Anesthesia*. 2015:1012-1054.e4. 2. Hargreaves KM, Keiser K. Local anesthetic failure in endodontics: mechanisms and management. *Endod Topics*. 2002;1(1):26-39. 3. Becker DE, Reed KL. Essentials of local anesthetic pharmacology. *Anesth Prog*. 2006:98-109.

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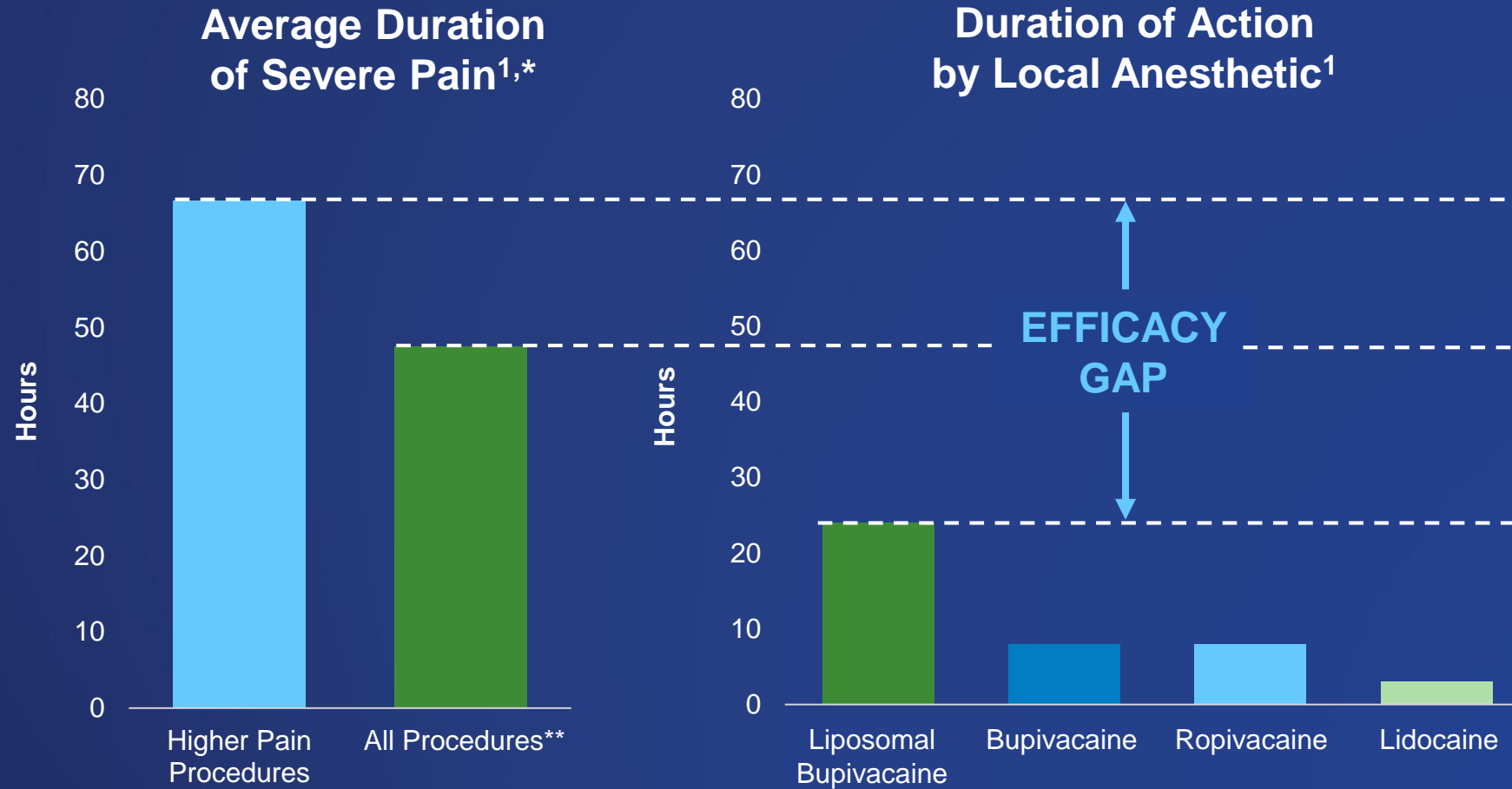
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The failure of local anesthetics to consistently manage pain beyond 24 hours has contributed to the extensive use of opioids¹⁻⁹

References: 1. Berde CB, Strichartz GR. Local anesthetics. In: Miller RD, et al, eds. *Miller's Anesthesia*. Vol 2. 8th ed. Philadelphia, PA: Saunders; 2015:1012-1054.e4. 2. Gorfine SR, Onel E, Patou G, Krivokapic ZV. Bupivacaine extended-release liposome injection for prolonged postsurgical analgesia in patients undergoing hemorrhoidectomy: a multicenter, randomized, double-blind, placebo-controlled trial. *Dis Colon Rectum*. 2011:1552-1559. 3. Ali A, Sundberg M, Hansson U, Malmvik J, Flivik G. Doubtful effect of continuous intraarticular analgesia after total knee arthroplasty: a randomized, double-blind study of 200 patients. *Acta Orthopaedica*. 2015:373-377. 4. Carvalho B, Clark DJ, Yeomans DC, Angst MS. Continuous subcutaneous instillation of bupivacaine compared to saline reduces interleukin 10 and increases substance P in surgical wounds after cesarean delivery. *Anesth Analg*. 2010:1452-1459. 5. Hill MV, McMahon ML, Stucke RS, Barth RJ Jr. Wide variation and excessive dosage of opioid prescriptions for common general surgical procedures. *Ann Surg*. 2017:709-714. 6. Lee M, Silverman SM, Hansen H, Patel VB, Manchikanti L. A comprehensive review of opioid-induced hyperalgesia. *Pain Physician*. 2011:145-161. <http://www.painphysicianjournal.com/current/pdf?article=MTQ0Ng%3D%3D&journal=60>. Accessed October 1, 2018. 7. Kessler ER, Shah M, Gruschus SK, Raju A. Cost and quality implications of opioid-based postsurgical pain control using administrative claims data from a large health system: opioid-related adverse events and their impact on clinical and economic outcomes. *Pharmacotherapy*. 2013:383-391. 8. Becker DE, Reed KL. Essentials of local anesthetic pharmacology. *Anesth Prog*. 2006:98-109. 9. Hargreaves KM, Keiser K. Local anesthetic failure in endodontics: mechanisms and management. *Endod Topics*. 2002:26-39.

Opioids Are Not the Optimal Solution

The efficacy gap in postoperative pain management

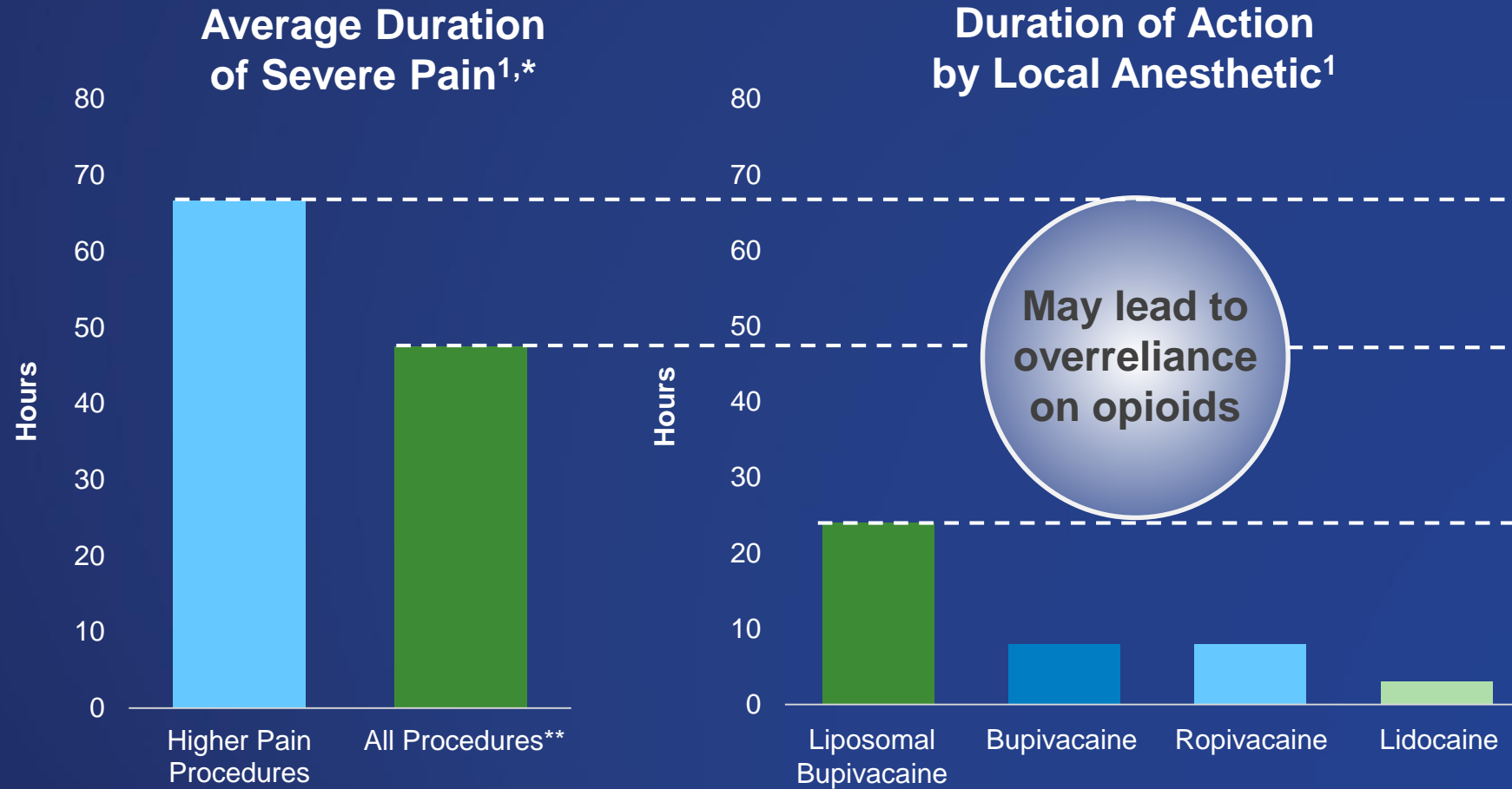


*Defined as pain of >5 on 1-10 scale.

** ~50 of the top procedures requiring post-op pain management (selected for analysis based on real-world post-op pain management usage).

Reference: 1. Data on file. DRG Physician Survey. Heron Therapeutics; 2016.

The efficacy gap in postoperative pain management



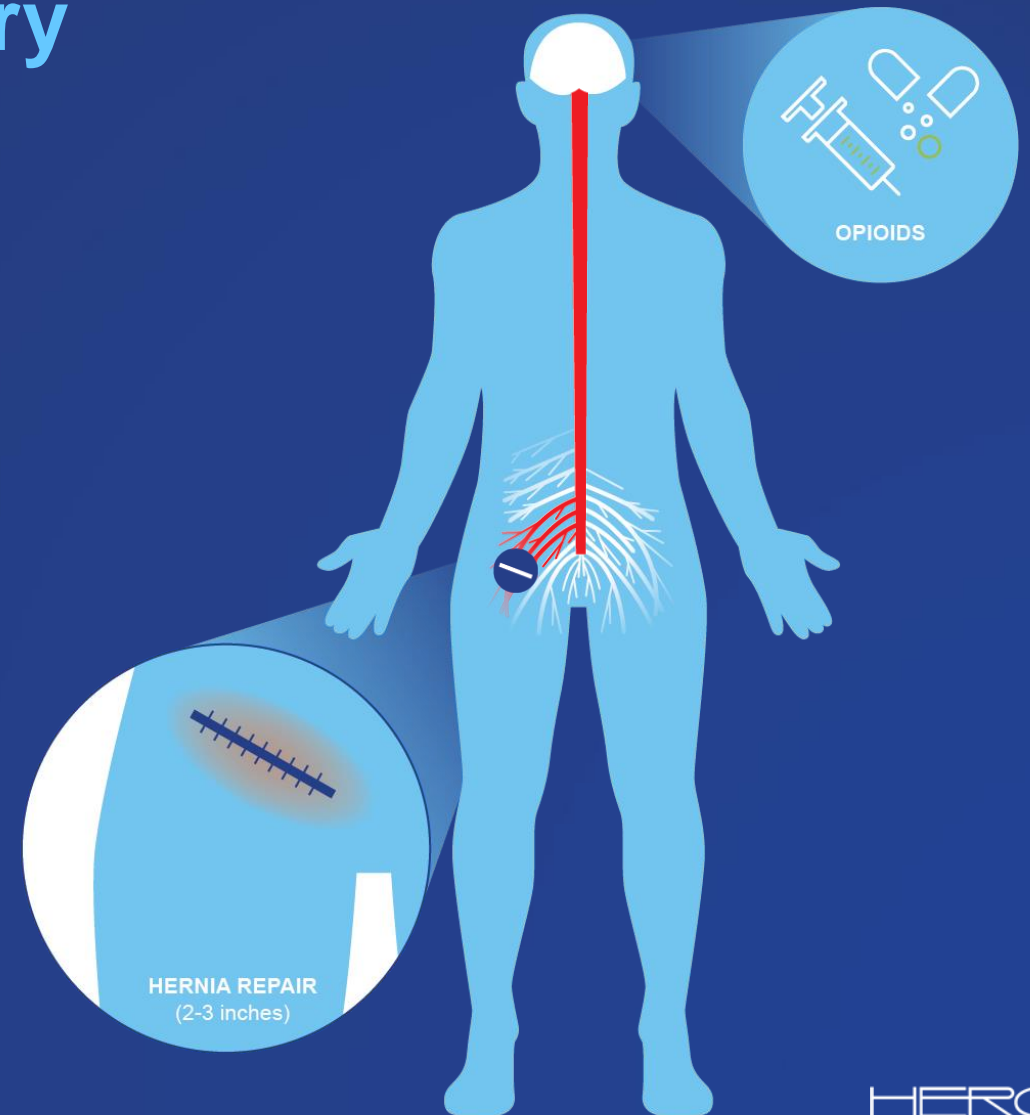
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Opioids work in the central nervous system—not at the site of injury

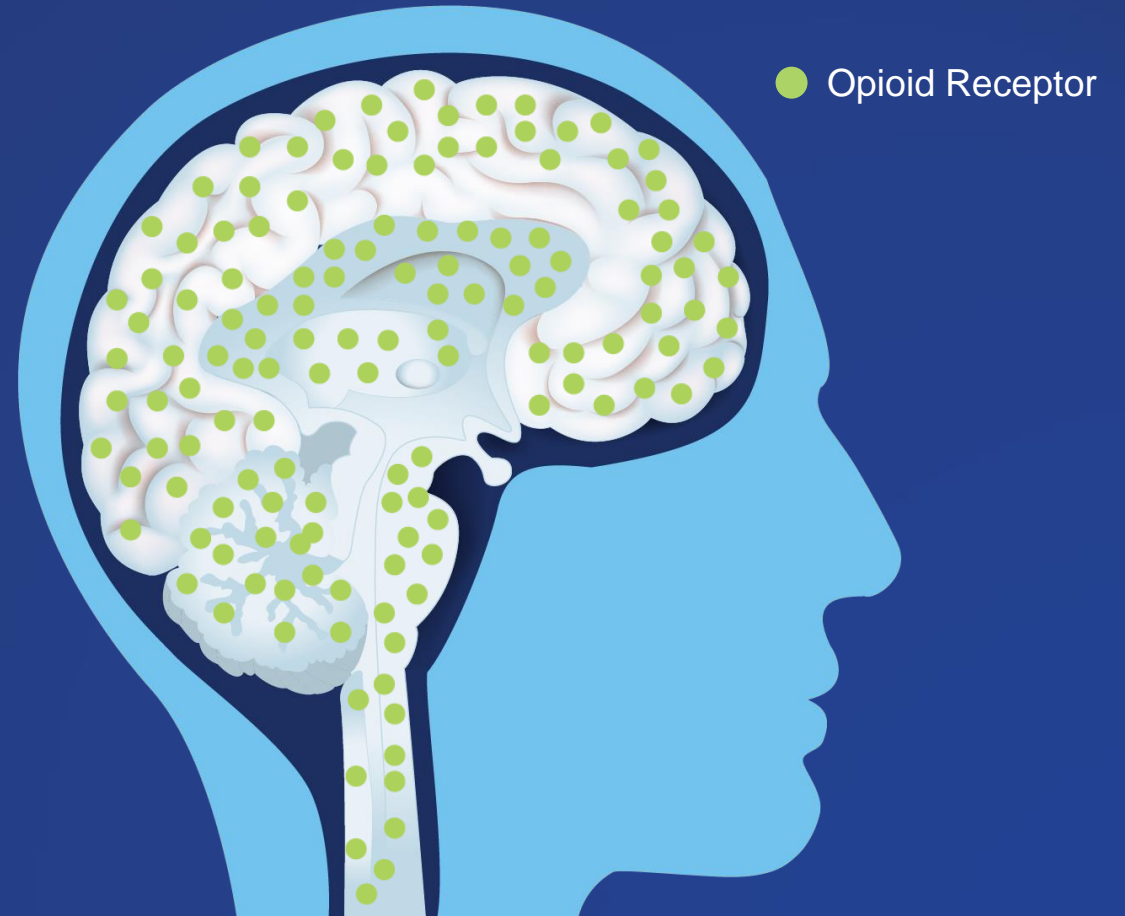
- 90% of patients are treated with opioids after surgery¹
- Opioids block pain centrally (at the brain), but they do not block transmission of the pain signals at the source²
- Opioids can exacerbate postoperative pain, resulting in opioid-induced hyperalgesia and allodynia³



References: 1. Hill MV, McMahon ML, Stucke RS, Barth RJ Jr. Wide variation and excessive dosage of opioid prescriptions for common general surgical procedures. *Ann Surg.* 2017:709-714. 2. Al-Hasani R, Bruchas MR. Molecular mechanisms of opioid receptor-dependent signaling and behavior. *Anesthesiology.* 2011:1363-1381. 3. Lee M, Silverman SM, Hansen H, Patel VB, Manchikanti L. A comprehensive review of opioid-induced hyperalgesia. *Pain Physician.* 2011:145-161. <http://www.painphysicianjournal.com/current/pdf?article=MTQ0Ng%3D%3D&journal=60>. Accessed October 1, 2018.

Opioids can have unintended consequences

- Opioids can cause serious adverse events (AEs), including respiratory depression¹
- Opioid-related AEs may increase length of hospital stay^{2,3}
- Opioids mask pain but cannot prevent the transmission of pain signals from the site of injury⁴



References: 1. Kessler ER, Shah M, Gruschus SK, Raju A. Cost and quality implications of opioid-based postsurgical pain control using administrative claims data from a large health system: opioid-related adverse events and their impact on clinical and economic outcomes. *Pharmacotherapy*. 2013;383-391. 2. Pizzi LT et al. *Pharmacotherapy*. 2012;32(6):502-514. 3. Oderda GM et al. *J Pain Palliat Care Pharmacother*. 2013;27(1):62-70. 4. Al-Hasani R, Bruchas MR. Molecular mechanisms of opioid receptor-dependent signaling and behavior. *Anesthesiology*. 2011:1363-1381.

How postoperative pain may contribute to the opioid crisis

MORE THAN 50 MILLION

surgical procedures happen in the United States.¹

90%

of patients undergoing a surgical procedure are prescribed opioids for pain management.²



As many as

6.5%

of patients who take opioids to manage pain after surgery may become persistent opioid users.¹



Of these 2.6 million persistent opioid users, approximately

440,000

will become addicted to opioids.^{1,3}



That equals about
2.6 MILLION PEOPLE.¹



In addition, opioid discharge prescriptions filled by recovering surgical patients result in more than

1 billion unused pills.^{1,2}

70% of prescription opioids go unused by the patient.²

90% of these pills remain inside the home.⁴

32% of all opioid addicts report first opioid exposure through leftover pills.⁵

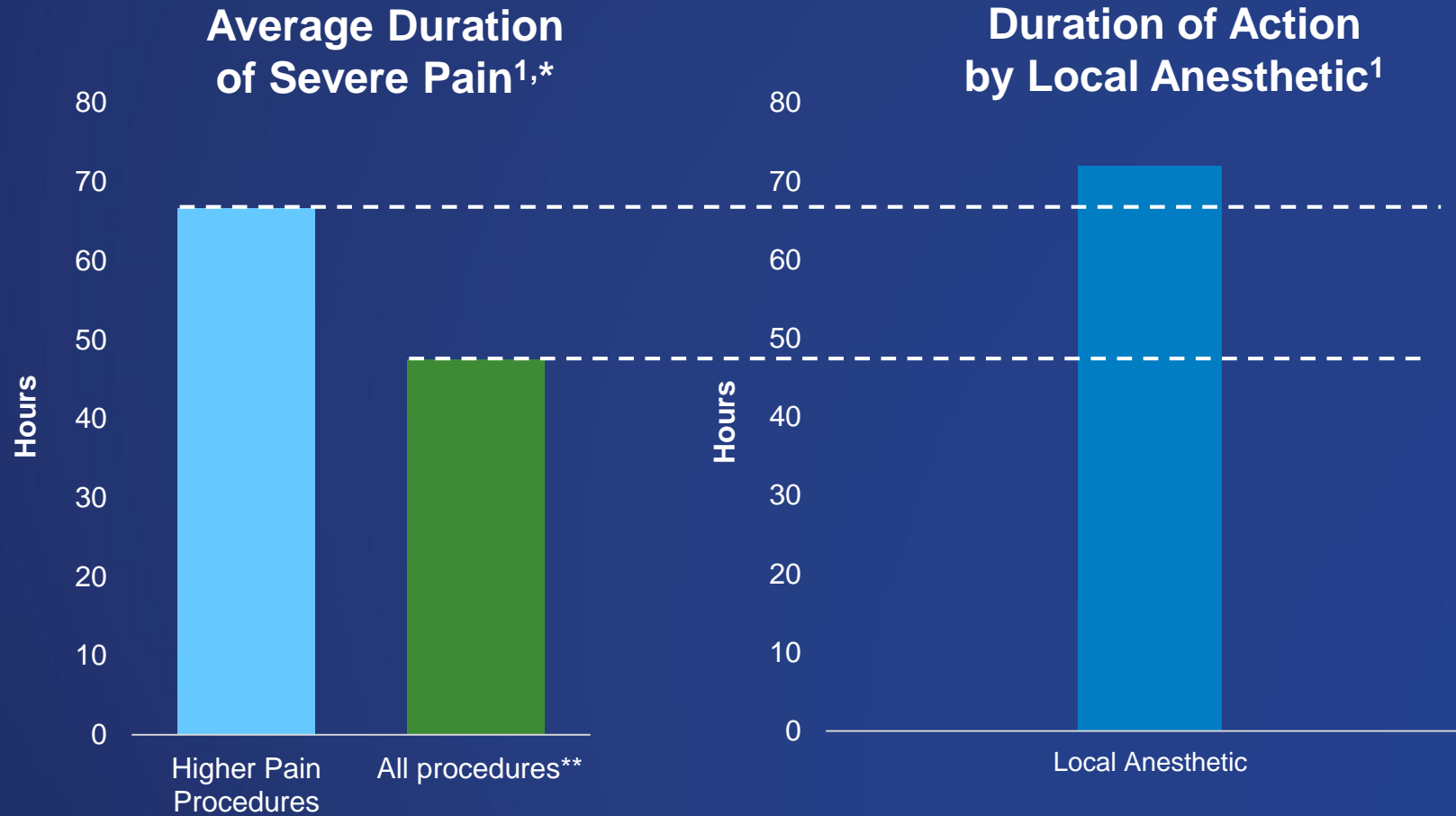
More than
\$13 billion of the annual healthcare costs associated with addiction can be attributed to postoperative pain management.^{1,3,6}



References: 1. Brummett CM, Waljee JF, Goesling J, et al. New persistent opioid use after minor and major surgical procedures in US adults. *JAMA Surg.* 2017;152(6):e170504. doi:10.1001/jamasurg.2017.0504 2. Hill MV, McMahon ML, Stucke RS, Barth RJ Jr. Wide variation and excessive dosage of opioid prescriptions for common general surgical procedures. *Ann Surg.* 2017;265(4):709-714. doi:10.1097/SLA.0000000000001993 3. Banta-Green CJ, Merrill JO, Doyle SR, Boudreau DM, Calsyn DA. Opioid use behaviors, mental health and pain: development of a typology of chronic pain patients. *Drug Alcohol Depend.* 2009;104(1-2): 34-42. doi:10.1016/j.drugalcdep.2009.03.021 4. Bates C, Laciak R, Southwick A, Bishoff J. Overprescription of postoperative narcotics: a look at postoperative pain medication delivery, consumption and disposal in urological practice. *J Urol.* 2011;185(2):551-555. doi:10.1016/j.juro.2010.09.088 5. Canfield MC, Keller CE, Frydrych LM, Ashrafioun L, Purdy CH, Blondell RD. Prescription opioid use among patients seeking treatment for opioid dependence. *J Addict Med.* 2010;4(2):108-113. doi:10.1097/ADM.0b013e3181b5a713 6. The Council of Economic Advisers. The underestimated cost of the opioid crisis. <https://www.whitehouse.gov/briefings-statements/cea-report-underestimated-cost-opioid-crisis/>. Published November 20, 2017. Accessed December 16, 2018.

Are There Opportunities for Improvement?

A longer-acting local anesthetic could reduce the treatment gap



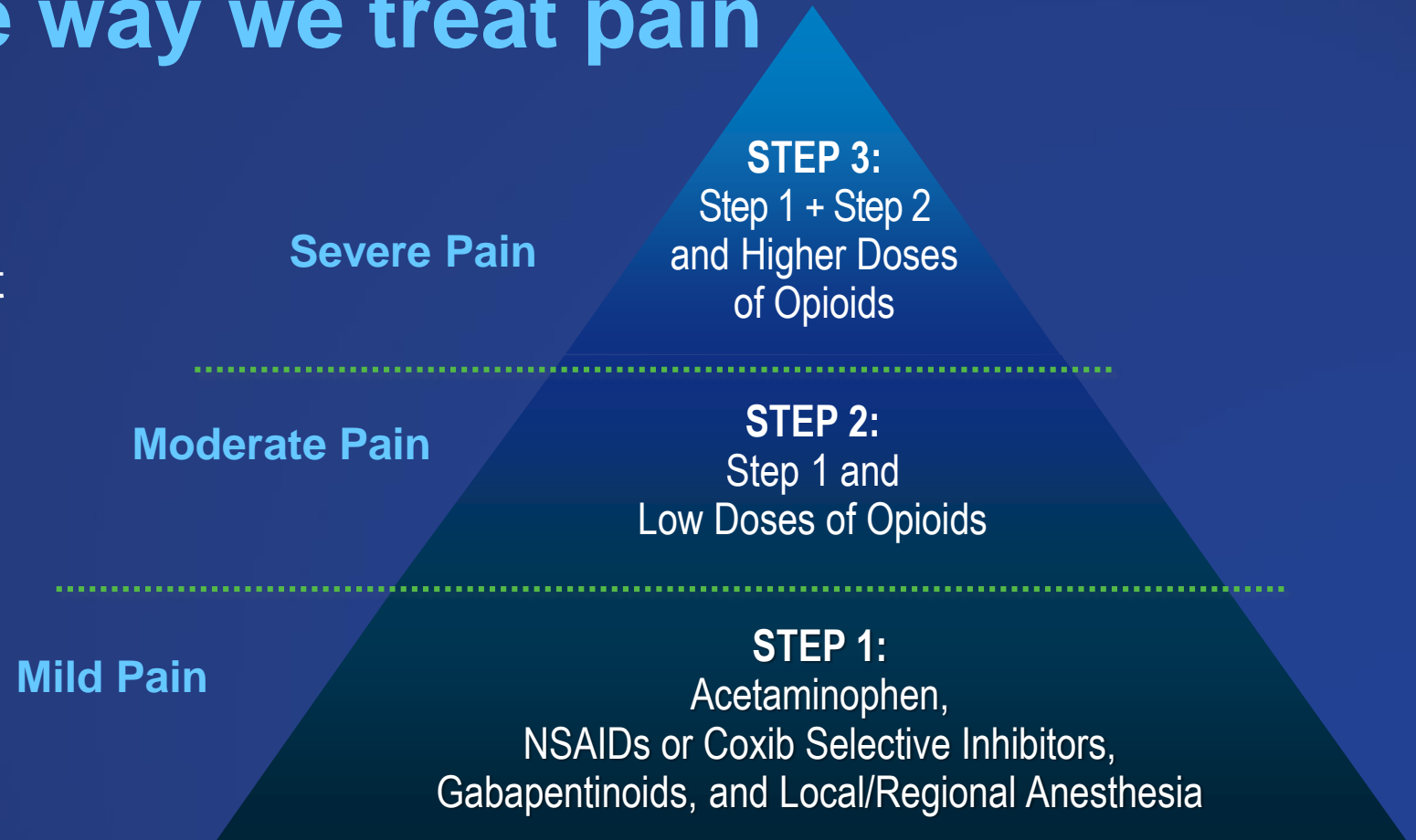
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A longer-acting local anesthetic could impact the way we treat pain

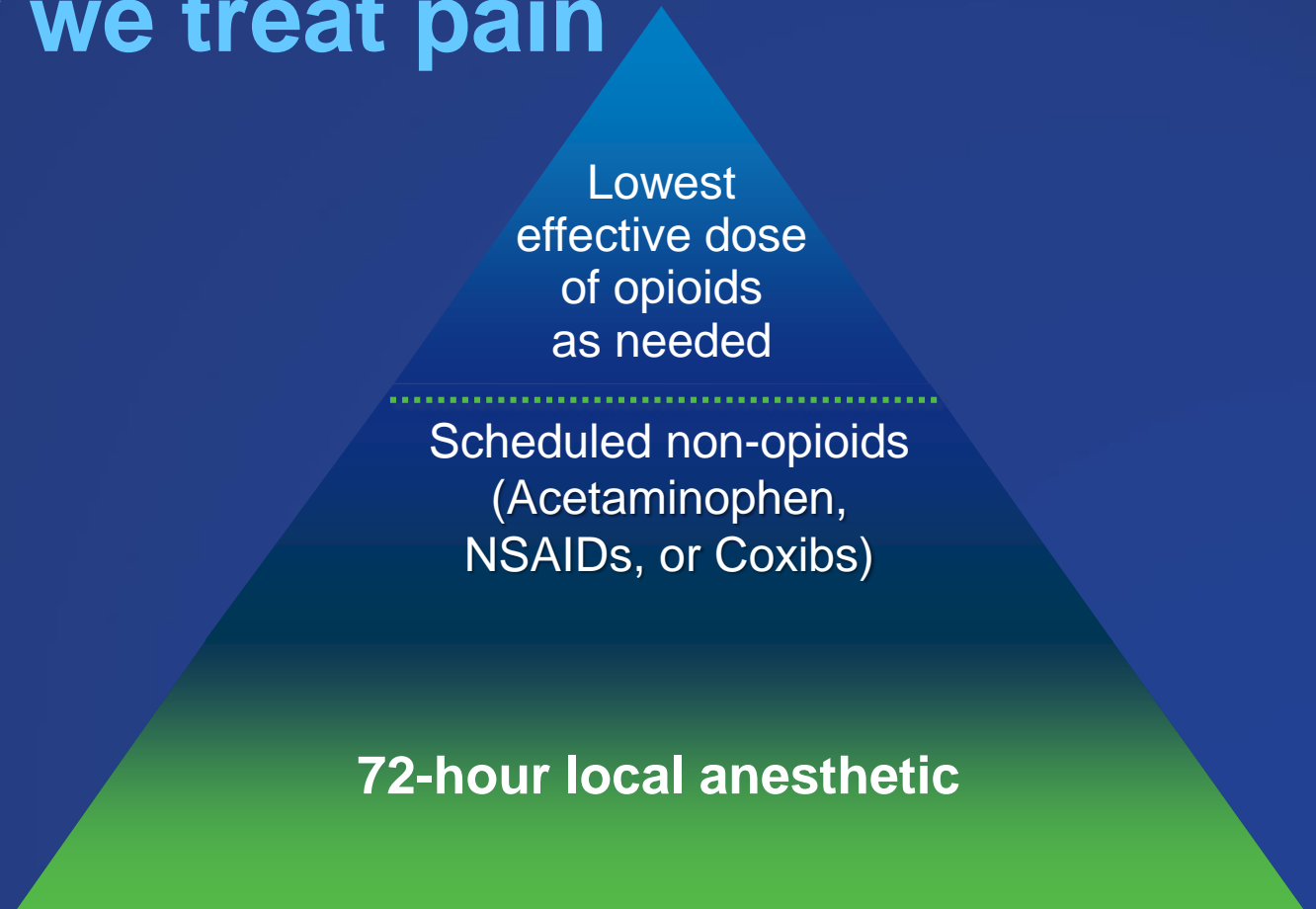
- **Many experts agree:**
It's time to update the current WHO analgesic ladder¹⁻³



References: 1. Vargas-Schaffer G. Is the WHO analgesic ladder still valid? Twenty-four years of experience. *Can Fam Physician*. 2010;514-517. 2. Vargas-Schaffer G, Cogan J. Patient therapeutic education: placing the patient at the centre of the WHO analgesic ladder. *Can Fam Physician*. 2014;235-241. 3. Pergolizzi JV, Paladini A, Varrassi G, Raffa RB. Change pain: ever evolving—an update for 2016. *Pain Ther*. 2016;127-133. doi:10.1007/s40122-016-0058-x. 4. Crews JC. *JAMA*. 2002;629-632.

A longer-acting local anesthetic could impact the way we treat pain

- A new proposed algorithm addresses the need for acute pain relief to avoid adverse outcomes and lowers risks associated with opioids¹



References: 1. Vargas-Schaffer G. Is the WHO analgesic ladder still valid? Twenty-four years of experience. *Can Fam Physician*. 2010;514-517. 2. Crews JC. *JAMA*. 2002;288(5):629-632.

In conclusion



- Surgery causes nociceptive, inflammatory, and neuropathic pain¹
- Postoperative pain and inflammation are most severe in the first 72 hours following surgery^{2,3}
- Improperly managed postoperative pain can lead to delayed recovery⁴



- Local anesthetics stop pain signals at the source⁵
- Many products exhibit limited and inconsistent efficacy beyond 12 to 24 hours⁶
- The inflammatory process inhibits current local anesthetics⁷



- Many local anesthetic options fail after 24 hours, contributing to the extensive use of opioids for postoperative pain management⁸
- Opioids are associated with adverse events and addiction^{8,9}
- Opioids do not stop pain signals at the source¹⁰



THE IDEAL SOLUTION:

- Longer-acting local anesthetic
- Reduction in opioid exposure

References: 1. Woolf CJ. Pain: moving from symptom control toward mechanism-specific pharmacologic management. *Ann Intern Med.* 2004;441-451. 2. Svensson I, Sjöström B, Haljamäe H. Assessment of pain experiences after elective surgery. *J Pain Symptom Manage.* 2000;193-201. 3. Enoch S, Leaper DJ. Basic science of wound healing. *Surgery (Oxford).* 2007;31-37. 4. Morrison RS, Magaziner J, McLaughlin MA, et al. The impact of post-operative pain on outcomes following hip fracture. *Pain.* 2003;103:303-311. 5. Berde CB, Strichartz GR. Local anesthetics. In: Miller RD, Cohen NH, Eriksson LI, Fleisher LA, Wiener-Kronish JP, Young WL, eds. *Miller's Anesthesia.* 2015;1012-1054.e4. 6. Gorfine SR, et al. *Dis Colon Rectum.* 2011;54:1552-1559. 7. Hargreaves KM, Keiser K. Local anesthetic failure in endodontics: mechanisms and management. *Endod Topics.* 2002;26-39. 8. Hill MV, McMahon ML, Stucke RS, Barth RJ Jr. Wide variation and excessive dosage of opioid prescriptions for common general surgical procedures. *Ann Surg.* 2017;709-714. 9. Kessler ER, Shah M, Gruschus SK, et al. Cost and quality implications of opioid-based postsurgical pain control using administrative claims data from a large health system: opioid-related adverse events and their impact on clinical and economic outcomes. *Pharmacotherapy.* 2013;383-391. 10. Al-Hasani R, Bruchas MR. Molecular mechanisms of opioid receptor-dependent signaling and behavior. *Anesthesiology.* 2011;1363-1381.

Thank You

