Novel Local Anesthetics in Clinical Practice: Pharmacologic Considerations and Potential Roles for the Future

Alan D. Kaye, Amber N. Edinoff, Justin Y. Yan, Aaron J. Kaye, Michael A. Alvarado, Alex D. Pham, Azem A. Chami, Rutvij J. Shah, Bruce M. Dixon, Amineh Shafeinia, Elyse M. Cornett and Charles Fox

Abstract

The treatment of pain, both acute and chronic, has been a focus of medicine for generations. Physicians have tried to develop novel ways to effectively manage pain in surgical and post-surgical settings. One intervention demonstrating efficacy is nerve blocks. Single-injection peripheral nerve blocks (PNBs) are usually preferred over continuous PNBs, since they are not associated with longer lengths of stay. The challenge of single injection PNBs is their length of duration, which at present is a major limitation. Novel preparations of local anesthetics have also been studied, and these new preparations could allow for extended duration of action of anesthetics. An emerging preparation of bupivacaine, exarel, uses a multivesicular liposomal delivery system which releases medication in a steady, controlled manner. Another extended-release local anesthetic, HTX-011, consists of a combination of bupivacaine and low-dose meloxicam. Tetrodotoxin, a naturally occurring reversible site 1 sodium channel toxin derived from pufferfish and shellfish, has shown the potential to block conduction of isolated nerves. Neosaxitoxin is a more potent reversible site 1 sodium channel toxin found in shellfish that can also block nerve conduction. These novel formulations show great promise in terms of the ability to prolong the duration of single injection PNBs. This field is still currently in development, and more researchers will need to be done to ensure the efficacy and safety of these novel formulations. These formulations could be the future of pain management if ongoing research continues to prove positive effects and low side effect profiles.

Keywords: Exarel, Neosaxitoxin, Tetrodotoxin, HTX-011, Meloxicam, Novel Local Anesthetics, Peripheral Nerve Blocks, Postoperative Pain

1. Context

The treatment of pain, both acute and chronic, has been a focus of medicine for generations. Opiate medications have been the mainstay of pain management, but for the past 30 years, their use and abuse have risen dramatically (1-3). Scientists and clinicians have attempted to develop novel ways to battle pain in surgical and post-surgical settings (4-7). Chronic pain can result from surgery in about 10% of patients (8). At present, it is believed that pain can transition from acute post-surgical to chronic if not well controlled after surgery (9). Research into this transition has led to new pharmacological interventions to try to better control pain after surgery (10, 11).
of this chronic pain at the donor site (16). They found that persistent pain at the donor site was reported in only 4.3% of all patients at six months and 6.5% at 12 months (16).

This raises the question of whether a peripheral nerve block (PNB) can help with acute and chronic pain management. The results of the above studies show that it can be useful, but how long should the block last? In this regard, there are single injection PNBs and continuous PNBs. Continuous PNBs involve the insertion of a catheter to deliver the anesthetic to its intended target (12). This can be associated with a longer time to discharge, so single injection PNBs are generally preferred (17). The challenge of single injection PNBs is their length of duration, which is their major limitation. Most have a duration of only 24-48 hours (17).

Researchers have worked to find ways to prolong the length of duration of single-shot PNBs (18). This has led to looking at adjuvants that could be added to the local anesthetic to increase the length of their block provided (19). Adjuvants are useful at reducing pain after the surgical operation, additional analgesic requirements, duration of hospitalization, and total health cost (20-24). Many adjuvants are still not FDA approved for use, and more research is needed to determine their safety.

Novel preparations of local anesthetics have also been studied. These new preparations allow for the extended duration of action of local anesthetics (25). One example is the preparation of bupivacaine with a liposomal bilayer, which allows for sustained release of local anesthetic for at least 72 hours after the injection, and this has the potential for decreasing opioid consumption in the postoperative period (25). This manuscript, therefore, aims to look at these novel preparations and their potential role to help reduce postoperative pain and the development of chronic pain states.

1.1. Exparel

Bupivacaine is a commonly used local anesthetic delivered by local infiltration or pain pump (6, 7). The efficacy of this anesthetic method is limited by its short duration of action and nonstandard management approaches (26). Increasing the dose to prolong drug activity is not recommended due to the increased risk of toxicity (27). An emerging technique for administering bupivacaine, called exparel, uses a multivesicular liposomal delivery system that releases medication in a steady, controlled fashion. The liposomal structure is formed in a way that allows slow degradation, as mentioned in the introduction (27). The FDA approved exparel for use in local infiltration analgesia. Its use in numerous peripheral and neuraxial nerve blocks is still under investigation (28). This new technique can increase bupivacaine’s duration of action from 10 hours to 72-96 hours (29, 30). Exparel has been shown, especially in a multimodal pain control strategy, to provide adequate relief during recovery after surgery and during post-op visits (31). When compared to a bupivacaine pain pump, liposomal bupivacaine increases time of pain relief (31, 32). Liposomal bupivacaine also provides similar or better safety and side effect profiles when compared to standard bupivacaine (28). Local anesthetic toxicity is still a risk when using exparel. Patients must be monitored for cardiotoxicity and neurotoxicity. However, the slow-release mechanism of exarel allows it to subvert some of the risks involved with bupivacaine toxicity (33). Caution must be used when using exparel in patients with hepatic disease, a primary site of its metabolism (33).

1.2. HTX-011

Another extended-release local anesthetic, HTX-011, consists of a combination of bupivacaine and low-dose meloxicam. Meloxicam is added to decrease local inflammation and stabilize the pH of bupivacaine. This is thought to enhance bupivacaine’s effectiveness (34). The polymer used to encapsulate HTX-011 is a polymer designed to be hydrolyzed slowly, thus releasing bupivacaine and meloxicam at a gradual and sustained rate (35). HTX-011 provides better pain relief when compared to bupivacaine (36). In Study 301/EPOCH 1, 29% of patients did not require additional opioids for 72 hours post-surgery. Total opioid use was decreased by 25%, and pain scores were decreased by 18% in comparison to bupivacaine (37). In Study 302/EPOCH 2, 51% of patients given HTX-011 did not need opioid in the first 72 hours. This is in comparison to 40% in the bupivacaine group. Pain scores were reduced 23% when compared to the standard of care (36). A study on open inguinal herniorrhaphy showed opioids were not used in 90% of patients given HTX-011 in the first 72 hours. Common side effects include nausea, hypoxia, and headache (34). Safety has been shown to be equivalent to either bupivacaine or placebo (36, 37).

1.3. Tetrodotoxin

Tetrodotoxin, a naturally occurring reversible site 1 sodium channel toxin derived from pufferfish and shellfish, has shown the potential to block conduction of isolated nerves. Tetrodotoxin has been shown in preliminary animal studies to significantly prolong block duration when used in conjunction with bupivacaine (38). Other similar studies show tetrodotoxin, usually known to cause muscle paralysis, to have minimal commonly seen local anesthetic adverse effects of myotoxicity and neurotoxicity (39). A polymer conjugate of tetrodotoxin can further broaden its therapeutic index to further safety (40). Mechanical hyperalgesia has also been shown to be inhibited...
Their findings demonstrate that liposomal bupivacaine did not cause significant difference in nausea, vomiting, and narcotic consumption between the two groups, demonstrated not significant difference (48).

The pain control and also length of stay were improved in patients who received the periarticular injection (PAI) including a mixture of ropivacaine, ketorolac, methylprednisolone and morphine during surgery. The case group received the same injection but containing liposomal bupivacaine. The number of physical therapy sessions required for discharge, total opioid consumption, pain scores, and adverse events were not difference between two groups (49).

Vandepitte et al. showed that adding liposomal bupivacaine to interscalene block reduced the pain score in the first postoperative week (50). However, they note these findings were only modest and did not show significant data in pain compared to baseline, reductions in opioid consumption, or sleep quality (50).

Furthermore, Namdari et al. examined pain scores and analgesic consumption after shoulder arthroplasty performed by adding intraoperative liposomal bupivacaine to preoperative interscalene nerve block (51). The pain score was not significant between these groups (51). Surprisingly, postoperative total narcotic consumption was more than interscalene nerve block alone (51). They further explain this may be due to a “dual rebound” phenomenon in which patients experienced rebound pain both after the effect of the interscalene nerve block eliminated and after the effect of the liposomal bupivacaine reduced, leading to increased opioid consumption (51).

Optimal postoperative pain management remains to be a concern in heart operation (52, 53). In the study done by Lee et al., they looked at the efficacy of liposomal bupivacaine as a single dose in a multi-level parasternal nerve block. The median postoperative pain scores were not significant reductions among two groups (53). However, overall pain scores in the case group showed less pain scores. Additionally, required analgesic reported in morphine equivalents did not show a significant reduction in opioid consumption (53).

2. Clinical Studies: Safety and Efficacy

2.1. Exparel

In a study by Surdam et al., they compared 20 mL of 1.3% liposomal bupivacaine mixed with 40 mL of saline injected into the periaricular tissues versus femoral nerve block (FNB) consisting of 40 mL of 0.5% bupivacaine with epinephrine for total knee arthroscopy (TKA). The initial target was inpatient pain management, and latter target included range of motion, nausea and vomiting, narcotic consumption, and length of stay. The pain control and also nausea, vomiting, and narcotic consumption between the two groups, demonstrated not significant difference (48). Their findings demonstrate that liposomal bupivacaine provided equal pain relief compared to femoral block while not affecting inpatient rehabilitation after arthroplasty (48).

Another study done by Hyland et al. examined patients undergoing TKA with the use of liposomal bupivacaine (49). In their study, those in the control group received a periarticular injection (PAI) including a mixture of ropivacaine, ketorolac, methylprednisolone and morphine during surgery. The case group received the same injection but containing liposomal bupivacaine. The number of physical therapy sessions required for discharge, total opioid consumption, pain scores, and adverse events were not difference between two groups (49).

Vandepitte et al. showed that adding liposomal bupivacaine to interscalene block reduced the pain score in the first postoperative week (50). However, they note these findings were only modest and did not show significant data in pain compared to baseline, reductions in opioid consumption, or sleep quality (50).

Furthermore, Namdari et al. examined pain scores and analgesic consumption after shoulder arthroplasty performed by adding intraoperative liposomal bupivacaine to preoperative interscalene nerve block (51). The pain score was not significant between these groups (51). Surprisingly, postoperative total narcotic consumption was more than interscalene nerve block alone (51). They further explain this may be due to a “dual rebound” phenomenon in which patients experienced rebound pain both after the effect of the interscalene nerve block eliminated and after the effect of the liposomal bupivacaine reduced, leading to increased opioid consumption (51).

Optimal postoperative pain management remains to be a concern in heart operation (52, 53). In the study done by Lee et al., they looked at the efficacy of liposomal bupivacaine as a single dose in a multi-level parasternal nerve block. The median postoperative pain scores were not significant reductions among two groups (53). However, overall pain scores in the case group showed less pain scores. Additionally, required analgesic reported in morphine equivalents did not show a significant reduction in opioid consumption (53).

2.2. HTX-011

In a recent double-blinded, randomized, placebo-controlled, and active-controlled phase 3 study (EPOCH I), they examined the safety and efficacy of HTX-011. A three-arm group undergoing a bunionectomy with group (A) receiving HTX-011 (bupivacaine 60 mg/ meloxicam 1.8 mg), (B) bupivacaine 0.5%, 50 mg, and (C) saline placebo. The primary outcome examined the mean area under the curve of the pain intensity (numeric rating scale) within three days (37). The first group showed a reduction in mean
pain scale over three days compared with saline and bupivacaine group (37). Total analgesic utilization was significantly reduced in those who received HTX-011 when compared with placebo and vs. those who received bupivacaine (23, 37). Overall, 29% of HTX-011 patients were opioid-free in the first 72 hours compared with 11% in the bupivacaine and in the control group.

In the EPOCH 2 study, they examined patients undergoing herniorrhaphy. A double-blinded, randomized, placebo-controlled, and active-controlled phase 3 study (EPOCH 2) was designed to assess the pain relief effect of HTX-011 administered at the surgical site compared with bupivacaine and placebo (36). Group A receiving HTX-011, 300 mg/9 mg (bupivacaine/meloxicam), (B) bupivacaine 0.25%, 75 mg, and (C) placebo. The primary outcome again was the mean area under the curve of the numeric pain score within three days for each group (36). Subjects in the first group showed reduction in mean pain score over three days compared with both placebo and bupivacaine groups (36). Total analgesic utilization within three days in the first group was significantly decreased compared to the saline when compared with bupivacaine (36). Even more significantly, 51% of HTX-011 cases did not need opioid within three vs 40% for second and 22% for placebo groups.

2.3. Tetrodotoxin

In a study done by Brau et al., they examined a variety of drugs used to treat chronic pain in rats. Na+ currents were studied mainly from dorsal root ganglion cells (54). At E of -90 mV, mexiletine, lidocaine, carbamazepine, amitriptyline, and memantine, reversibly inhibited tetrodotoxin-resistant Na+ current (54). Current inhibition was dependent to concentration and at high concentrations was complete (54).

Furthermore Berde et al examined dose-duration following local nerve block with tetrodotoxin with bupivacaine 0.25% with or without epinephrine in rats (55). Thermal nociception blocked was evaluated using a hot plate test (55). This method raised the rat upright and lowered the rat, so the lateral aspect of a single hind paw was touching a hot plate at 56°C (55). The time it took the animal to pull out its paw was calculated with a stopwatch.

The combination of bupivacaine and tetrodotoxin showed a prolonged block duration. With the addition of epinephrine to tetrodotoxin and bupivacaine, the block was prolonged by 1.6 - 1.9 fold for 50% recovery and 1.7-2-fold for 100% recovery (55).

2.4. Neosaxitoxin

A study conducted by Rodriguez-Navarro et al. comparing neosaxitoxin to bupivacaine for laparoscopic cholecystectomy. The neosaxitoxin group was given 100 µg of neosaxitoxin, and in the bupivacaine group, they were given 50 mg for wound infiltration before insertion of working ports (56). Patients in the neosaxitoxin group reported lower scores for incisional pain versus bupivacaine, and with movement (56).

2.5. SABER-bupivacaine

In another trial, the safety and efficacy of SABER-bupivacaine in patients undergoing open inguinal hernia repair were evaluated. SABER-bupivacaine was found to be safe without significant complications compared with placebo. SABER-bupivacaine in the dose of 5 mL decreased the area under the curve (AUC) for mean pain score on movement from 1 to 72 hours and decreased the number of patients requiring supplemental opioids when compared to SABER-Placebo. However, the 2.5 mL dose did not achieve the same results (57).

To date, the above-mentioned study is the only published randomized controlled trial that examines the use of SABER-bupivacaine (25). Currently it remains an experimental medication and it is not used in clinical practice. In 2013 FDA did not approve Saber-bupivacaine due to incomplete evidence of safety.

2.6. INL-001 (Bupivacaine Collagen Implant)

In two phase III double-blind studies MATRIX-1 and MATRIX-2 studies. Patients undergoing surgical inguinal herniorrhaphy were divided to receive three INL-001 100-mg bupivacaine HCl collagen-matrix implant or three placebo collagen-matrix implants during surgery. When compared to placebo, in both studies patients who received INL-001 had significant less pain score and analgesic within the first post-operative day. In both studies, most patients who received INL-001 did not take any opioid during the first three post-operative days. Among patients who required analgesic, subjects in the INL-001 arm received lesser opioids than those in the placebo arm.

Most of the reported side effects were mild or moderate, and bupivacaine toxicity was not observed (58).

In another study patients which scheduled for surgical inguinal hernioplasty, received three INL-001 implants, and 16 patients received local infiltration of 0.25% bupivacaine HCl 175 mg.

INL-001 plasma kevel showed a longer time to maximum plasma level and terminal elimination half-life. Maximum plasma level with INL-001 was comparable to bupivacaine and much lower than the levels related to systemic toxicity (59).

There were no side effects associated to the implant. Most of the reported adverse events were associated with general anesthesia and post-surgical care (59).
3. Conclusions

In clinical studies, exarel was not found to improve pain measurements, opioid consumption, PT sessions needed, or time to mobilization. HTX-011 improves pain scores and opioid consumption in groups that received saline or bupivacaine. Tetrodotoxin has shown some promise in animal studies as it has been shown to prolong nerve blocks when used with bupivacaine. Neosaxitoxin has shown the same prolonging effects when used with bupivacaine.

There was only one published study for SABER-bupivacaine and even though it has shown good efficacy, it has failed to demonstrate a complete evidence of clinical safety. Bupivacaine collagen matrix INL-001, two independent phase 3 studies have demonstrated statistical and clinical significance in pain intensity reduction in addition to lowering opioids requirement. A third study has shown good tolerability in patients with no major adverse events.

These novel formulations show great promise in terms of the ability to prolong the duration of single injection PNBs. This field is still currently in development, and more clinical trials will necessary to be done to ensure the efficacy and safety of these novel formulations. These formulations could be the future of pain management if more research continues to prove their positive effects and low side effect profiles.

Footnotes

Authors’ Contribution: Study concept and design: ADK, ANE, EMC, CJF; Analysis and interpretation of data: AJK, MAA, ADP, AAC, RJS; Drafting of the manuscript: ANE, JYY, EMC, CJF; Critical revision of the manuscript for important intellectual content: ADK, ANE, JYY, AS, EMC, CJF; Statistical analysis: AAC, RJS, BMD.

Conflict of Interests: The authors have no conflicts of interest to disclose.

Funding/Support: No funding was received for the completion of this manuscript.

References

1. Malik KM, Imani F, Beckerly R, Chovatiya R. Risk of opioid use disorder from exposure to opioids in the perioperative period: A systematic review. Anesth Pain Med. 2020;30(1). doi: 10.5812/aapm.101397. [PubMed Central: PMC7582482].
2. Rupniowska-Ladyko A, Malek-Milewska M. A High Dose of Fentanyl May Accelerate the Onset of Acute Postoperative Pain. Anesth Pain Med. 2019;9(5). e94498. doi: 10.5812/aapm.e94498. [PubMed Central: PMC613250].
3. Edinoff AN, Kaplan IA, Khan S, Petersen M, Sauce E, Causey CD, et al. Full Opioid Agonists and Tramadol: Pharmacological and Clinical Considerations. Anesth Pain Med. 2021;11(4). doi: 10.5812/aapm.19956. [PubMed Central: PMC8408288].
4. Noroozi V, Ghazi A, Amani F, Bakhshipoori P. Effectiveness of Sublingual Buprenorphine and Fentanyl Pump in Controlling Pain After Open Cholecystectomy. Anesth Pain Med. 2021;11(3). e113909. doi: 10.5812/aapm.i113909. [PubMed Central: PMC8438705].
5. Koning MV, van der Sijp M, Stolker RJ, Niggebrugge A. Intrathecal Morphine Is Associated with Less Delirium Following Hip Fracture Surgery: A Register Study. Anesth Pain Med. 2020;10(4). e106076. doi: 10.5812/aapm.e106076. [PubMed Central: PMC7539054].
6. Gousheh M, Akhondzadeh R, Rashidi M, Olapour A, Mofzakh F. Comparison of Dexmedetomidine and Morphine as Adjuvants to Bupivacaine for Epidural Anesthesia in Leg Fracture Surgery: A Randomized Clinical Trial. Anesth Pain Med. 2019;9(4). doi: 10.5812/aapm.e94480. [PubMed: 31803587]. [PubMed Central: PMC6829278].
7. Ismail AA, Mohamed Hamza H, Ali Gado A. Efficacy of Dexmedetomidine Versus Morphine as an Adjunct to Bupivacaine in Caudal Anesthesia for Pediatric Thoracic Surgeries: A Randomized Controlled Trial. Anesth Pain Med. 2021;11(2). e112296. doi: 10.5812/aapm.e112296. [PubMed: 34336615]. [PubMed Central: PMC8140901].
8. Glare P, Aubrey KR, Myles PS. Transition from acute to chronic pain after surgery. Lancet. 2019;393(10180):1537–46. doi: 10.1016/s0140-6736(19)30526-4.
9. Berger AA, Liu Y, Possio H, Rogers AG, Moore W, Gress K, et al. Dorsal Root Ganglion (DRG) and Chronic Pain. Anesth Pain Med. 2021;11(2). doi: 10.5812/aapm.e113020. [PubMed: 34336621]. [PubMed Central: PMC814077].
10. Tully J, Jung JW, Patel A, Tukan A, Kandula S, Doan A, et al. Utilization of Intravenous Lidocaine Infusion for the Treatment of Refractory Chronic Pain. Anesth Pain Med. 2020;10(6). e112290. doi: 10.5812/aapm.e112290. [PubMed: 34150583]. [PubMed Central: PMC8207897].
11. Urits I, Jung JW, Angalang A, Fortiier L, Anya A, Wesp B, et al. Utilization of Magnesium for the Treatment of Chronic Pain. Anesth Pain Med. 2021;11(6). doi: 10.5812/aapm.e112348. [PubMed: 34221945]. [PubMed Central: PMC8236838].
12. Sukosompong S, von Bornm S, von Bornm B. Regional Catheters for Postoperative Pain Control: Review and Observational Data. Anesth Pain Med. 2020;10(1). e99745. doi: 10.5812/aapm.e99745. [PubMed: 32137707]. [PubMed Central: PMC7582441].
13. Edinoff AN, Girma B, Trettin KA, Horton CC, Kaye AJ, Cornett EM, et al. Novel Regional Nerve Blocks in Clinical Practice: Evolving Techniques for Pain Management. Anesth Pain Med. 2021;11(4). doi: 10.5812/aapm.e118278. [PubMed: 34692466]. [PubMed Central: PMC8207897].
14. Maniar A, Macachor J, Chiew WA, Kumar CM, Imani F, Rokhtabnak F. Nuts and Bolts of Peripheral Nerve Blocks for Pain Management. Anesth Pain Med. 2019;9(11). e112333. doi: 10.5812/aapm.e112333. [PubMed Central: PMC8207897].
15. Sasso RC, LeHuec JC, Shaffrey C, Spine Interbody Research G. Iliac crest bone graft donor site pain after anterior lumbar interbody fusion: a prospective patient satisfaction outcome assessment. J Spinal Disord Tech. 2005;18 Suppl S77–81. doi: 10.1097/01.bsd.0000112045.36255.83. [PubMed: 15099860].
16. Black ND, Malhas L, Jin R, Bhatia A, Chan VWS, Chin KJ. The analgesic efficacy of the transversalis fascia plane block in iliac crest bone graft harvesting: a randomized controlled trial. Korean J Anesthesiol. 2019;72(1):336–43. doi: 10.4090/kja.d.2018.00332. [PubMed: 30886031]. [PubMed Central: PMC6576022].
17. Joshi G, Gandhi K, Shah N, Gadsden J, Corman SL. Peripheral nerve blocks in the management of postoperative pain: challenges and opportunities. J Clin Anesth. 2016;35:524–9. doi: 10.1016/j.jclinane.2016.08.041. [PubMed: 2787587].

Anesth Pain Med. 2022;12(1):e123112.
26. J Chandran G, H Lalonde D. A Review of Pain Pumps in Plastic Surgery. Anesth Pain Med. 2020;20(3). doi: 10.5812/aapm.103141. [PubMed: 32494562]. [PubMed Central: PMC7472790].

27. Coppens SJR, Zawodny Z, Dewinter G, Neyrinck A, Balocco AL, Rex SG, et al. Adjuvant Drugs for Peripheral Nerve Blocks: The Role of Alpha-2 Agonists, Dexamethasone, Midazolam, and Non-steroidal Anti-inflammatory Drugs. Anesth Pain Med. 2021;21(3). doi: 10.5812/aapm.17197. [PubMed: 34540647]. [PubMed Central: PMC8438706].

28. Edinoff AN, Houk GM, Patil S, Bangalore Siddiah A, Kaye AJ, Iyengar PS, et al. Adjuvant Drugs for Peripheral Nerve Blocks: The Role of NMDA Antagonists, Neostigmine, Epinephrine, and Sodium Bicarbonate. Anesth Pain Med. 2021;21(3). doi: 10.5812/aapm.17846. [PubMed: 34540646]. [PubMed Central: PMC8438706].

29. Cohen SM. Extended pain relief trial utilizing infiltration of Exparel(R), a long-acting, multivascular liposomal formulation of bupivacaine: A Phase IV economic health trial in adult patients undergoing open colectomy. Pain Res Clin. 2020;3(2):338–46. doi: 10.1213/00000539-199807000-00009. [PubMed: 11490800].

30. Baxter R, Bramlett K, Onel E, Daniels S. Impact of local administration of liposomal bupivacaine to control postoperative pain after abdominoplasty. Aesthet Surg J. 2013;33(3):5184–53. doi: 10.1097/ASP.0b013e3182310720. [PubMed: 24241950].

31. Butz DR, Shenoy DS, Rundell VL, Kepler B, Liederbach E, Thiel J, et al. Postoperative Pain and Length of Stay Lowered by Use of Exparel in Immediate, Implant-Based Breast Reconstruction. Plast Reconstr Surg Glob Open. 2015;3(5). e391. doi: 10.1097/GOX.0000000000000355. [PubMed: 26099028]. [PubMed Central: PMC4457254].

32. Kaye AD, Novitch MB, Carlson SF, Fuller MC, White SW, Haroldson AR, et al. The Role of Exparel Plus Meloxicam for Postoperative Pain Management. Curr Pain Headache Rep. 2020;24(3). doi: 10.1007/s11916-020-00372-7. [PubMed: 32003876].

33. Singla N, Winkle P, Bertoch T, Hu J, Beaton A, Redan J. Opioid-free recovery after herniorrhaphy with HTX-011 as the foundation of a multimodal analgesic regimen. Surgery. 2020;168(5):915–20. doi: 10.1016/j.surg.2020.06.036. [PubMed: 32943200].

34. Keller J, Barr J. Biochromon technology. Expert Opin Drug Deliv. 2005;2(2):169–83. doi: 10.1517/17424247.2.1.149. [PubMed: 16296743].

35. 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(6):1071–80. doi: 10.1007/s12109-019-02023-6. [PubMed: 31429023]. [PubMed Central: PMC6918470].

36. Viscusi E, Gimbel J, Pollack RA, Hu J, Lee GC. HTX-011 reduced pain intensity and opioid consumption versus bupivacaine HCl in burn excision: phase III results from the randomized EPOCH I study. Reg Anesth Pain Med. 2019;44(7):700–6. doi: 10.1016/j.rapm.2019.04.053. [PubMed: 31183810].

37. Kohane DS, Yieh J, Lu NT, Langert R, Strichartz GR, Berde CR. A re-examination of tetrodotoxin for prolonged duration local anesthesia. Anesthesiology. 1998;89(9):319–31. doi: 10.1097/00000542-199807000-00009. [PubMed: 9667702].

38. Sakura S, Bollen AW, Ciriales R, Drasner K. Local Anesthetic Neuropathy Does Not Result from Blockade of Voltage-Gated Sodium Channels. Anesth Analg. 1995;81(2):338–46. doi: 10.1213/00000539-199508000-00021.

39. Zhao C, Liu A, Santamaria CM, Shomorony A, Ji T, Wei T, et al. Polymer-tetrodotoxin conjugates to induce prolonged duration local anesthesia with minimal toxicity. Nat Commun. 2019;10(1):2566. doi: 10.1038/s41467-019-02969-9. [PubMed: 31889915]. [PubMed Central: PMC6569191].

40. Alvarez P, Levine JD. Antihyperalgesic effect of tetrodotoxin in rat models of persistent muscle pain. Neuroscience. 2015;311:499–507. doi: 10.1016/j.neuroscience.2015.10.059. [PubMed: 26548414]. [PubMed Central: PMC4679288].

41. Shomorony A, Santamaria CM, Zhao C, Rwei AY, Mehta M, Zurakowski D, et al. Prolonged Duration Local Anesthesia by Combined Delivery of Capsaicin- and Tetrodotoxin-Loaded Liposomes. Anesth Analg. 2019;129(3):709–17. doi: 10.1213/ANE.0000000000004108. [PubMed: 31425210].

42. Santamaria CM, Zhan C, McAlvin JB, Zurakowski D, Kohane DS. Tetrodotoxin, Epinephrine, and Chemical Permeation Enhancer Combinations in Peripheral Nerve Blockade. Reg Anesth Pain Med. 2017;42(4):380–4. doi: 10.1097/AAP.0000000000000272. [PubMed: 28452816]. [PubMed Central: PMC5438287].

43. Walker JR, Novick PA, Parsons WH, Mcgregor M, Zahlocki J, Pando VS, et al. Marked difference in saxitoxin and tetrodotoxin affinity for the human nociceptive voltage-gated sodium channel (Nav1.7) [corrected]. Proc Natl Acad Sci USA. 2012;109(4):1802–7. doi: 10.1073/pnas.1206952109. [PubMed: 23072750]. [PubMed Central: PMC3497785].

44. Rathmell JP, Strichartz G, Wanderer J. Neosaxitoxin versus Tetrodotoxin for Postoperative Pain Management: Role of Alpha-2 Agonists, Dexamethasone, Midazolam, and Nonsteroidal Anti-Inflammatory Drugs. Anesth Pain Med. 2022;12(1):e23121. [PubMed: 36460987].

45. Rathmell JP, Strichartz G, Wanderer J. Neosaxitoxin versus Tetrodotoxin for Postoperative Pain Management: Role of Alpha-2 Agonists, Dexamethasone, Midazolam, and Nonsteroidal Anti-Inflammatory Drugs. Anesth Pain Med. 2022;12(1):e23121. [PubMed: 36460987].
47. Dinges HC, Wiesmann T, Otremba B, Wulf H, Eberhart LH, Schubert AK. The analgesic efficacy of liposomal bupivacaine compared with bupivacaine hydrochloride for the prevention of postoperative pain: a systematic review and meta-analysis with trial sequential analysis. Reg Anesth Pain Med. 2021;46(6):490–8. doi: 10.1136/rapm-2020-102427. [PubMed: 33837139].

48. Surdam JW, Licini DJ, Baynes NT, Arce BR. The use of exparel (liposomal bupivacaine) to manage postoperative pain in unilateral total knee arthroplasty patients. J Arthroplasty. 2015;30(2):325–9. doi: 10.1016/j.arth.2014.09.004. [PubMed: 25282071].

49. Hyland SJ, Deliberato DG, Fada RA, Romanelli MJ, Collins CL, Wasielewski RC. Liposomal Bupivacaine Versus Standard Periarticular Injection in Total Knee Arthroplasty With Regional Anesthesia: A Prospective Randomized Controlled Trial. J Arthroplasty. 2019;34(3):488–94. doi: 10.1016/j.arth.2018.11.026. [PubMed: 30554925].

50. Vandepitte C, Kuroda M, Witvrouw R, Anne L, Bellemans J, Corten K, et al. Addition of Liposome Bupivacaine to Bupivacaine HCl Versus Bupivacaine HCl Alone for Interscalene Brachial Plexus Block in Patients Having Major Shoulder Surgery. Reg Anesth Pain Med. 2017;42(3):488–94. doi: 10.1097/AAP.0000000000000560. [PubMed: 28157798].

51. Namdari S, Nicholson T, Abboud J, Lazarus M, Steinberg D, Williams G. Interscalene Block with and without Intraoperative Local Infiltraion with Liposomal Bupivacaine in Shoulder Arthroplasty: A Randomized Controlled Trial. J Bone Joint Surg Am. 2018;100(16):e1377–8. doi: 10.2106/JBJS.17.01416. [PubMed: 30086188].

52. Hadipourzadeh F, Moussavi S, Heydarpur A, Sadeghi A, Farasat-Kish R. Evaluation of the Adding Paracetamol to Dexmedetomidine in Pain Management After Adult Cardiac Surgery. Anesth Pain Med. 2022;11(1):e123112. doi: 10.5812/apam.110274. [PubMed: 34540629]. [PubMed Central: PMC8438704].

53. Lee CT, Robinson DA, Johnson CJ, Zhang Y, Wong J, Joshi DJ, et al. A Randomized Controlled Trial of Liposomal Bupivacaine Parasternal Intercostal Block for Sternotomy. Ann Thorac Surg. 2019;107(1):128–34. doi: 10.1016/j.athoracsur.2018.06.081. [PubMed: 30700012].

54. Brau ME, Dreimann M, Olschewski A, Vogel W, Hempelmann G. Effect of drugs used for neuropathic pain management on tetrodotoxin-resistant Na(+) currents in rat sensory neurons. Anesthesiology. 2001;94(1):137–44. doi: 10.1097/00000542-200101000-00024. [PubMed: 11157573].

55. Berde CB, Athiraman U, Yahalom B, Zurakowski D, Corfas G, Bogner C. Tetrodotoxin-bupivacaine-epinephrine combinations for prolonged local anesthesia. Mar Drugs. 2011;9(12):2717–28. doi: 10.3390/md9122717. [PubMed: 2363247]. [PubMed Central: PMC3280572].

56. Rodriguez-Navarro AJ, Berde CB, Wiedmaier G, Mercado A, Garcia C, Iglesias V, et al. Comparison of neosaxitoxin versus bupivacaine via port infiltration for postoperative analgesia following laparoscopic cholecystectomy: a randomized, double-blind trial. Reg Anesth Pain Med. 2011;36(2):303–9. doi: 10.1097/aap.0b013e3182030662. [PubMed: 21425506].

57. Hadj A, Hadj A, Hadj A, Rosenfeldt F, Nicholson D, Moodie J, et al. Safety and efficacy of extended-release bupivacaine local anaesthetic in open hernia repair: a randomized controlled trial. ANZ J Surg. 2012;82(4):251–7. doi: 10.1111/j.1445-2197.2011.05754.x. [PubMed: 22510185].

58. Velanovich V, Rider P, Deck K, Minkowitz HS, Leiman D, Jones N, 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(1):200–16. doi: 10.1007/s12325-018-0836-4. [PubMed: 30467808]. [PubMed Central: PMC5631844].

59. Leiman D, Niebler G, Minkowitz HS. Pharmacokinetics and Safety of INL-001 (Bupivacaine HCl) Implants Compared with Bupivacaine HCl Infiltration After Open Unilateral Inguinal Hernioplasty. Adv Ther. 2021;38(1):691–706. doi: 10.1007/s12325-020-01565-x. [PubMed: 33237534]. [PubMed Central: PMC7854444].