IRECONSTRUCTIVE

Putting It All Together: Managing Pain in Autologous and Implant-Based Breast Reconstruction

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Background: Appropriate pain management in breast reconstruction improves outcomes and patient satisfaction. The purpose of this study is to review the current methodology and paradigms in pain management following breast reconstruction.

Methods: A review of the scientific literature was performed. The protocols used at our institution were further examined and contrasted in the context of this published literature.

Results: Pain following breast reconstruction is multifactorial and patient specific. Pain can originate from the mastectomy alone, from the donor site, or from tissue expansion. Counseling a patient is of upmost importance. The armamentarium to address pain includes narcotic analgesics, nonnarcotic analgesics, local anesthesia, and other nontraditional regimens. Each of these methods has an evidence-based efficacy and patient selection factors for application.

Conclusions: The data contained herein provide a review of perioperative pain management following autologous and implant-based breast reconstruction. (*Plast. Reconstr. Surg.* 134: 120S, 2014.)

btaining adequate pain control following breast reconstruction is paramount to ensuring optimal outcomes and patient satisfaction. Failure to ameliorate postoperative pain is associated with increased physiological and psychological stress with corresponding increased hospital admissions and cost.^{1,2} Multiple components of intraoperative care can contribute to postoperative discomfort. The surgeon and treatment team must recognize each of these components. Given the wide breadth of reconstructive options and immense interpatient variability, pain regimens must be well tailored to the individual patient.

When tailoring a pain regimen, the surgeon must first recognize the different types of pain and corresponding available treatment modalities. Postsurgical pain can be divided according to its duration (acute vs chronic) and nature (nociceptive vs neuropathic). Chronic pain is often defined according to the International Association for the Study of Pain as occurring after the normal time of healing.³

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Prior studies of breast reconstruction pain have considered this period to be approximately 120 days.⁴ Nociceptive pain refers to pain resulting from injury to somatic structures including skin, muscle, and fat. By contrast, neuropathic pain is that pain resulting from direct injury or inflammation of the central or peripheral nervous system. Surgeons are primarily concerned with management of postsurgical nociceptive pain; however, neuropathic pain resulting from local nerve injury and regeneration can be present and should be recognized. In our experience, the treatment of neuropathic pain and/or chronic pain requires the assistance of a pain specialist.

Current treatment modalities following breast reconstruction include narcotic analgesia, nonnarcotic analgesia [nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen], local anesthesia, regional anesthesia, muscle relaxants, and nontraditional neuropathic regimens. Each treatment modality has an associated riskto-benefit ratio, and all should serve as part of the available armamentarium for postoperative pain management. Despite the many interventions now at the surgeon's disposal, perioperative

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patient counseling and expectation management remain the first and, arguably, the most critical step toward achieving success.

COUNSELING

Before mastectomy and reconstruction, patients must be thoroughly counseled by both the extirpative and reconstructive surgeons. Patients should be advised that acute postoperative pain is a certainty with variability depending on reconstructive methods. Preoperative candidates should also understand the risk of progression to a chronic pain condition. Reconstruction aside, mastectomy alone is associated with postprocedural pain. Most notably, the risk of postmastectomy pain syndrome (PMPS) should be discussed. PMPS is a chronic yet poorly understood condition affecting up to 40%of patients and requires specific management.⁵⁻¹⁰ Recent prospective studies have illustrated that risk factors for PMPS include axillary node dissection, transection of the intercostal brachial nerve, and younger age at the time of surgery.^{6,11} Despite current treatment regimens, complete resolution is generally difficult to achieve.

More germane to reconstruction, there are notable differences between autologous and implant-based reconstruction. Implant-based reconstruction may be associated with less initial postoperative pain. The pain in implant reconstruction is limited to the reconstructive site as there is of course no donor site. Patients may have increased pain in the breast than those undergoing free-tissue transfer; this pain may be worsened with higher starting fill volumes.¹² Additionally, pain will be associated with each subsequent increase in tissue expander volume and the eventual exchange for a permanent implant. This must be discussed with the patient before undergoing implant reconstruction.

In contrast to implant reconstruction, autologous reconstruction is complicated by the need to control pain at the breast and the donor site. When anticipating potential acute pain, the surgeon must appreciate that postoperative pain is typically commensurate with the degree of flap dissection. Regarding abdominally based flaps, studies have demonstrated that the degree of pain is directly proportional to the amount of fascia and muscle harvested.^{13,14} Traditionally, pain is expected to be greatest with abdominally based flaps; however, there is recent evidence to suggest that patients undergoing extended latissimus muscle flap reconstruction may experience greater pain than those undergoing abdominally based flap reconstruction.¹³

Finally, patients should be counseled as to the potential for chronic pain after surgery. Up to 25% of patients may have insufficient response to narcotic analgesia, resulting in a prolonged inpatient admission.¹⁵ Some of these patients may progress to chronic pain. An institutional review of patients treated with abdominally based autologous tissue transfer found that 17% experienced chronic pain postoperatively. The risk of such chronic pain was found to be related to preoperative factors, specifically preexisting pain, rather than perioperative or postoperative factors.⁴

NARCOTIC ANALGESICS

Narcotics are the mainstay of pain control in breast reconstruction. Typically, a parenteral pain regimen is initiated using either morphine or hydromorphone. Patient-controlled analgesic (PCA) pumps are a safe and convenient method of delivery.¹⁶ As a patient's parenteral requirement diminishes, they are advanced to an oral regimen of either oxycodone or hydromorphone. A small subset of patients, usually implant-based reconstruction, is started on an oral regimen immediately with parenteral breakthrough. Studies have demonstrated that a direct to oral regimen is less effective than a PCA for pain control, but may be appropriate in select patients.¹¹

Narcotic medications are nearly a universal necessity in treating the postreconstructive patient, but the well-established side effects include nausea, vomiting, constipation, ileus, pruritus, lethargy, changes in mental status, respiratory depression with subsequent hypercapnea, and physical dependence. Given the significant side-effect profile and predilection for dependence, both the physician and patient should strive for rapid wean of narcotics while still balancing the continued need for pain control.

NONNARCOTIC ANALGESICS

NSAIDs and acetaminophen are frequently used in the perioperative setting. NSAIDs affect both COX-1 and COX-2 resulting in down regulation of cyclooxygenase and the local inflammatory response. NSAIDs have further action in the glomerular apparatus, gastric lining, and on platelet aggregation. Nonspecific NSAIDs are therefore associated with a decreased glomerular filtration rate and increased risk of gastric ulcer formation with theoretical increased risk of bleeding. COX-2 inhibitors, developed specifically for anti-inflammatory properties, were found to have an increased risk of heart attack and stroke.^{17,18} Accordingly, COX-2 inhibitors have largely been discontinued with celecoxib (Celebrex) standing as one of the few exceptions. Given the availability, efficacy, and general tolerability of nonspecific NSAIDS, these are more commonly used in the immediate postoperative period.

Controversy surrounding the use of NSAIDs in the perioperative setting persists. Surgeons have been traditionally hesitant to prescribe NSAIDs and most often cite an increased risk of postoperative bleeding. The long-standing resistance among surgeons to use NSAIDs has been somewhat disparate with the published evidence. Studies have demonstrated that the risk of bleeding is minimal and that the belief of significantly increased bleeding risk is largely unfounded.¹⁹⁻²¹ Nonetheless, NSAIDs must still be used with caution given the well-established risk of acute kidney injury in the elderly and under-resuscitated patients and risk of gastrointestinal bleeding with prolonged use.²² Ketorolac is the parenteral NSAID most often available for postoperative pain control. The side-effect profile of Ketorolac is similar to that of other NSAIDs and likewise suffers from underutilization. Ketorolac has been associated with decreased narcotic intake, improved pain control, and has not been demonstrated to increase the risk of bleeding or renal failure in patients with otherwise normal renal function.^{19,23}

Acetaminophen is an alternative nonnarcotic analgesic with a minimal side-effect profile and demonstrated efficacy comparable to NSAIDs in some settings. The primary risk associated with acetaminophen is dose-dependent liver toxicity. The total amount of acetaminophen should not exceed 4 g over a 24-hour period. Acetaminophen should be avoided in patients with liver failure or alcohol dependence. Acetaminophen can be administered as a stand-alone. Alternatively, acetaminophen can be used in conjunction with NSAIDs and narcotic regimens for adjunctive effect.²⁴ In the setting of breast reconstruction, acetaminophen should be routinely used for most patients.

CONTINUOUS LOCAL ANALGESICS

Efforts to reduce narcotic use and mitigate narcotic-associated side effects following reconstruction have resulted in the use of elastomeric pain catheters that can be placed in the reconstructed breast and donor sites.²⁵ Pain catheters function by continuously infusing the surgical site with local anesthetic (typically bupivacaine). The infusion rate is dependent on body temperature and fill volume of the pump. Multiple trials have demonstrated a proven benefit to the continuous infusion of local anesthesia. Local pain pumps have been shown to improve pain and reduce narcotic use. There is an associated increase in patient satisfaction, and as such, these systems have become widely accepted in the management of perioperative pain.²⁶⁻³²

Liposomal bupivacaine under the trademark Exparel (Pacira Pharmaceuticals, San Diego, Calif.) has recently received Food and Drug Administration approval for postoperative analgesia.^{33,34} Liposomal bupivacaine is injected once during a procedure and acts as a continuous depot of bupivacaine for up to 72 hours. Like elastomeric pumps, clinical trials have demonstrated that liposomal bupivacaine decreases initial pain and postoperative narcotic use.³⁵ Unlike traditional bupivacaine, liposomal bupivacaine does not require external catheter placement, which can be both bothersome to the patient and challenging to the staff. Liposomal bupivacaine has been successfully implemented for management following both abdominoplasty and breast augmentation; It should be noted, however, that there are limited data regarding liposomal bupivacaine specifically in the setting of breast reconstruction.^{36,37} Thus, a pointed evidence-based recommendation for the use of liposomal bupivacaine in breast reconstruction is not possible at this time; nonetheless, it seems as though this modality may serve an important role in the future.

NONTRADITIONAL

The use of epidural analgesia can be considered in abdominally based free flap breast reconstruction. The surgical literature has consistently demonstrated that epidural analgesia significantly reduces post laparotomy pain and allows for expedited recovery with a shorter inpatient admission.^{16,38–40} Epidural analgesia does require increased time and patient discomfort for placement. It also introduces risk of urinary retention, lower extremity weakness, and even paralysis. Epidural analgesia is not routinely used in the setting of free flap reconstruction, but this may be a worthwhile consideration for patients with a known high narcotic requirement. Paravertebral blocks (PVBs) are used often in the management of pain following thoracotomy, video-assisted thoracoscopic surgery, and mastectomy.⁴¹⁻⁴³ Much like epidural analgesia, their drawbacks include increased time for placement, but PVBs are not associated with a risk of paralysis or urinary retention. Studies have consistently illustrated the

benefit of PVBs following mastectomy including decreased nausea and faster return to work.⁴⁴⁻⁴⁶ Given the abovementioned data purporting the benefits of PVBs following mastectomy, this modality may be underutilized in breast reconstruction and warrants further clinical investigation.

Other nontraditional methods of pain management include benzodiazepines, gabapentin, and related drugs, that is, pregabalin (Lyrica) or tricyclic antidepressants. Benzodiazepines, serving as both anxiolytics and spasmolytics, are often used as adjuncts to mediate pain.⁴⁷ Most often, these drugs are used in the early stages following implant reconstruction when muscle irritation and contractions may be a large component of postoperative pain. Caution is advised with the use of benzodiazepines and narcotics together given the increased risk of respiratory failure and mental status alteration. Gabapentin and other gabapentinoid agents are traditionally used in the setting of chronic postsurgical pain. There is limited evidence to suggest the use of gabapentin as a onetime treatment for acute postoperative pain management.⁴⁸ In our experience, gabapentin/gabapentinoids are not used without the accompanying assistance of a pain specialist.

INSTITUTIONAL PRACTICE

Below, we briefly review our routine pathways for both implant-based and autologous reconstruction. These pathways conform to current evidence-based recommendations and serve as general guidelines for pain management. There is deviation from the below-mentioned pathways as individual patient care dictates.

Implant-Based Reconstruction

At our institution, implant-based reconstruction is most often performed as a 2-stage procedure with subpectoral/subserratus tissue expansion followed by implant insertion. Patients most often require an inpatient admission lasting 1–2 nights. Intraoperatively, elastomeric pain catheters are placed over the pectoralis muscles bilaterally. On postoperative day 1, patients are maintained on a PCA along with standing 5 mg dose of diazepam every 8 hours. If patient is less than 65 years old with appropriate renal function and no contraindications, standing NSAIDS are prescribed, usually ketorolac. Following the first 12–24 hours, patients are advanced to a combined oral narcotic regimen and acetaminophen. The standard narcotic dosage is as follows: 5 mg of oxycodone every 4 hours or 2 mg of hydromorphone every 3 hours. Unless contraindicated, all patients are prescribed

650 mg of acetaminophen every 6 hours. Following discharge, patients return for outpatient tissue expansion at which time prescriptions for narcotics and benzodiazepines are refilled if needed.

Autologous Reconstruction

The donor site for harvest in free tissue reconstruction (eg, abdominal wall, TUG, and IGAP) varies; however, the standard pain management pathway remains similar. Continuous pain catheters are placed in the donor site. All patients are provided a hydromorphone or morphine PCA for 48 hours postoperatively. Patients are then concurrently advanced to an oral pain regimen and a regular diet. Patients are then discharged with instructions to wean narcotic usage over 2-4 weeks. The precise wean depends on patient pain tolerance, use of adjunctive medications, and prior pain conditions. Given prolonged procedures and concomitant likely hypovolemic state, NSAIDs are not routinely used for inpatients following autologous breast reconstruction. Following adequate volume resuscitation, we have often found NSAIDs to be a helpful additional measure in treating refractory postoperative pain.

CONCLUSIONS

Adequate pain control is a critical component of achieving optimal clinical outcomes with corresponding patient satisfaction following breast reconstruction. Surgeons should adequately counsel patients as to the nature and course of pain including the risk of chronic pain syndromes. In accordance with much of the abovementioned evidence-based guidelines, postreconstruction pain control should be approached using multiple treatment modalities. By implementing a variety of methods to achieve postoperative pain control, the surgeon can individualize a treatment regimen for each patient and ensure optimal pain control following breast reconstruction.

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REFERENCES

Bonnet F, Marret E. Influence of anaesthetic and analgesic techniques on outcome after surgery. Br J Anaesth. 2005;95:52–58.

- Tsui SL, Law S, Fok M, et al. Postoperative analgesia reduces mortality and morbidity after esophagectomy. *Am J Surg.* 1997;173:472–478.
- 3. American Society of Anesthesiologists Task Force on Acute Pain Management. Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. *Anesthesiology* 2004;100:1573–1581.
- 4. Nelson JA, Fischer JP, Pasick C, et al. Chronic pain following abdominal free flap breast reconstruction: a prospective pilot analysis. *Ann Plast Surg.* 2013;71:278–282.
- 5. Bruce J, Thornton AJ, Powell R, et al; Recovery Study Group. Psychological, surgical, and sociodemographic predictors of pain outcomes after breast cancer surgery: a populationbased cohort study. *Pain* 2014;155:232–243.
- 6. De Oliveira GS Jr, Chang R, Khan SA, et al. Factors associated with the development of chronic pain after surgery for breast cancer: a prospective cohort from a tertiary center in the United States. *Breast J.* 2014;20:9–14.
- Gahm J, Wickman M, Brandberg Y. Bilateral prophylactic mastectomy in women with inherited risk of breast cancerprevalence of pain and discomfort, impact on sexuality, quality of life and feelings of regret two years after surgery. *Breast* 2010;19:462–469.
- 8. Hickey OT, Burke SM, Hafeez P, et al. Severity of acute pain after breast surgery is associated with the likelihood of subsequently developing persistent pain. *Clin J Pain* 2010;26:556–560.
- 9. Hovind IL, Bredal IS, Dihle A. Women's experience of acute and chronic pain following breast cancer surgery. *J Clin Nurs.* 2013;22:1044–1052.
- Wilson GC, Quillin RC III, Hanseman DJ, et al. Incidence and predictors of neuropathic pain following breast surgery. *Ann Surg Oncol.* 2013;20:3330–3334.
- 11. Legeby M, Segerdahl M, Sandelin K, et al. Immediate reconstruction in breast cancer surgery requires intensive post-operative pain treatment but the effects of axillary dissection may be more predictive of chronic pain. *Breast* 2002;11:156–162.
- Roth RS, Lowery JC, Davis J, et al. Persistent pain following postmastectomy breast reconstruction: long-term effects of type and timing of surgery. *Ann Plast Surg.* 2007;58:371–376.
- 13. Misra A, Chester D, Park A. A comparison of postoperative pain between DIEP and extended latissimus dorsi flaps in breast reconstruction. *Plast Reconstr Surg.* 2006;117:1108–1112.
- 14. Kroll SS, Sharma S, Koutz C, et al. Postoperative morphine requirements of free TRAM and DIEP flaps. *Plast Reconstr Surg.* 2001;107:338–341.
- 15. Bar-Meir ED, Yueh JH, Hess PE, et al. Postoperative pain management in DIEP flap breast reconstruction: identification of patients with poor pain control. *Eplasty* 2010;10:pii:e59.
- 16. American Society of Anesthesiologists Task Force on Acute Pain Management. Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. Anesthesiology 2012;116:248–273.
- 17. Baron JA, Sandler RS, Bresalier RS, et al. Cardiovascular events associated with rofecoxib: final analysis of the APPROVe trial. *Lancet* 2008;372:1756–1764.
- Bresalier RS, Sandler RS, Quan H, et al; Adenomatous Polyp Prevention on Vioxx (APPROVe) Trial Investigators. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med. 2005;352:1092–1102.

- Strom BL, Berlin JA, Kinman JL, et al. Parenteral ketorolac and risk of gastrointestinal and operative site bleeding. A postmarketing surveillance study. *JAMA* 1996;275:376–382.
- 20. Lewis SR, Nicholson A, Cardwell ME, et al. Nonsteroidal antiinflammatory drugs and perioperative bleeding in paediatric tonsillectomy. *Cochrane Database Syst Rev.* 2013;7:CD003591.
- 21. Lee A, Cooper MG, Craig JC, et al. Effects of nonsteroidal anti-inflammatory drugs on postoperative renal function in adults with normal renal function. *Cochrane Database Syst Rev.* 2007;2:CD002765.
- Feldman HI, Kinman JL, Berlin JA, et al. Parenteral ketorolac: the risk for acute renal failure. *Ann Intern Med.* 1997;126:193–199.
- 23. Gillis JC, Brogden RN. Ketorolac. A reappraisal of its pharmacodynamic and pharmacokinetic properties and therapeutic use in pain management. *Drugs* 1997;53:139–188.
- 24. Derry CJ, Derry S, Moore RA. Single dose oral ibuprofen plus paracetamol (acetaminophen) for acute postoperative pain. *Cochrane Database Syst Rev.* 2013;6:CD010210.
- Man D, Plosker H. The pain-control infusion pump for postoperative pain control in plastic surgery. *Plast Reconstr Surg.* 2002;109:2169–2170.
- 26. Rawlani V, Kryger ZB, Lu L, et al. A local anesthetic pump reduces postoperative pain and narcotic and antiemetic use in breast reconstruction surgery: a randomized controlled trial. *Plast Reconstr Surg.* 2008;122:39–52.
- 27. Baroody M, Tameo MN, Dabb RW. Efficacy of the pain pump catheter in immediate autologous breast reconstruction. *Plast Reconstr Surg.* 2004;114:895–898; discussion 899–900.
- Giordano S, Veräjänkorva E, Koskivuo I, et al. Effectiveness of local anaesthetic pain catheters for abdominal donor site analgesia in patients undergoing free lower abdominal flap breast reconstruction: a meta-analysis of comparative studies. *J Plast Surg Hand Surg*: 2013;47:428–433.
- Heller L, Kowalski AM, Wei C, et al. Prospective, randomized, double-blind trial of local anesthetic infusion and intravenous narcotic patient-controlled anesthesia pump for pain management after free TRAM flap breast reconstruction. *Plast Reconstr Surg.* 2008;122:1010–1018.
- Losken A, Parris JJ, Douglas TD, et al. Use of the infusion pain pump following transverse rectus abdominis muscle flap breast reconstruction. *Ann Plast Surg.* 2005;54:479–482.
- 31. Strazisar B, Besic N, Ahcan U. Does a continuous local anaesthetic pain treatment after immediate tissue expander reconstruction in breast carcinoma patients more efficiently reduce acute postoperative pain—a prospective randomised study. *World J Surg Oncol.* 2014;12:16.
- 32. Cheong WK, Seow-Choen F, Eu KW, et al. Randomized clinical trial of local bupivacaine perfusion versus parenteral morphine infusion for pain relief after laparotomy. *BrJ Surg.* 2001;88:357–359.
- 33. Vogel JD. Liposome bupivacaine (EXPAREL®) for extended pain relief in patients undergoing ileostomy reversal at a single institution with a fast-track discharge protocol: an IMPROVE Phase IV health economics trial. J Pain Res. 2013;6:605–610.
- 34. Marcet JE, Nfonsam VN, Larach S. An extended paIn relief trial utilizing the infiltration of a long-acting Multivesicular liPosome foRmulation Of bupiVacaine, EXPAREL (IMPROVE): a Phase IV health economic trial in adult patients undergoing ileostomy reversal. J Pain Res. 2013;6:549–555.
- 35. Gorfine SR, Onel E, Patou G, et al. Bupivacaine extendedrelease liposome injection for prolonged postsurgical analgesia in patients undergoing hemorrhoidectomy: a

multicenter, randomized, double-blind, placebo-controlled trial. *Dis Colon Rectum* 2011;54:1552–1559.

- 36. Smoot JD, Bergese SD, Onel E, et al. The efficacy and safety of DepoFoam bupivacaine in patients undergoing bilateral, cosmetic, submuscular augmentation mammaplasty: a randomized, double-blind, active-control study. *Aesthet Surg J.* 2012;32:69–76.
- Minkowitz HS, Onel E, Patronella CK, et al. A two-year observational study assessing the safety of DepoFoam bupivacaine after augmentation mammaplasty. *Aesthet Surg J.* 2012;32:186–193.
- Wu CL, Cohen SR, Richman JM, et al. Efficacy of postoperative patient-controlled and continuous infusion epidural analgesia versus intravenous patient-controlled analgesia with opioids: a meta-analysis. *Anesthesiology* 2005;103: 1079–1088; quiz 1109–1110.
- Chestnut DH. Efficacy and safety of epidural opioids for postoperative analgesia. *Anesthesiology* 2005;102:221–223.
- 40. Mann C, Pouzeratte Y, Boccara G, et al. Comparison of intravenous or epidural patient-controlled analgesia in the elderly after major abdominal surgery. *Anesthesiology* 2000;92:433–441.
- 41. Fibla JJ, Molins L, Mier JM, et al. The efficacy of paravertebral block using a catheter technique for postoperative

analgesia in thoracoscopic surgery: a randomized trial. *Eur J Cardiothorac Surg.* 2011;40:907–911.

- 42. Vogt A, Stieger DS, Theurillat C, et al. Single-injection thoracic paravertebral block for postoperative pain treatment after thoracoscopic surgery. *Br J Anaesth.* 2005;95:816–821.
- 43. Buckenmaier CC III, Kwon KH, Howard RS, et al. Doubleblinded, placebo-controlled, prospective randomized trial evaluating the efficacy of paravertebral block with and without continuous paravertebral block analgesia in outpatient breast cancer surgery. *Pain Med.* 2010;11:790–799.
- 44. Pusch F, Freitag H, Weinstabl C, et al. Single-injection paravertebral block compared to general anaesthesia in breast surgery. *Acta Anaesthesiol Scand*. 1999;43:770–774.
- 45. Naccache N, Jabbour H, Nasser-Ayoub E, et al. Regional analgesia and breast cancer surgery. *J Med Liban*. 2009;57:110–114.
- Naja MZ, Ziade MF, Lönnqvist PA. Nerve-stimulator guided paravertebral blockade vs. general anaesthesia for breast surgery: a prospective randomized trial. *Eur J Anaesthesiol.* 2003;20:897–903.
- Howard P, Twycross R, Shuster J, et al. Benzodiazepines. J Pain Symptom Manage. 2014;47:955–964.
- Straube S, Derry S, Moore RA, et al. Single dose oral gabapentin for established acute postoperative pain in adults. *Cochrane Database Syst Rev.* 2010;5:CD008183.