Chapter

Persistent Breast Cancer Pain

Sachin Sahni and James Khan

Abstract

Fortunately, with advances in screening and management, the prognosis of breast cancer has substantially improved. However, as patients with breast cancer are living much longer, consequences of management are becoming increasingly apparent, particularly persistent pain after breast cancer surgery. This pain disorder, referred to as Post-Mastectomy Pain Syndrome (PMPS) is common and typically presents as pain with neuropathic features around the surgical incision. This pain disorder is associated with negative effects on the patient's social and psychological well-being as well as increased healthcare expenditures. Despite the common occurrence of this disorder, it is vastly under-recognized with a lack of preventative and treatment options. This chapter aims to outline the management of persistent breast surgery pain. The pathophysiology and etiology will be reviewed, followed by tools that clinicians can implement in order to appropriately diagnose neuropathic pain. Pertinent risk factors that are commonly seen in practice will be outlined, followed by non-pharmacological, pharmacological, and interventional therapeutic options that can be offered.

Keywords: persistent pain, chronic pain, neuropathy, post-mastectomy pain syndrome, intercostobrachial neuralgia, intercostal neuralgia, psychological factors, axillary lymph node dissection, postoperative pain, pharmacological therapy, interventional therapy, nerve blocks, neuromodulation

1. Introduction

Breast cancer continues to be the most frequently diagnosed cancer in women worldwide [1] and cases in the United States are expected to rise by 64% between 2011 and 2030 [2]. Nonetheless, with significant progress in prevention and treatment over the past 30 years, survivorship has substantially increased [3], most notably in women ages 20–39 years [4]. The 5-year relative survival rate for breast cancer now approaches 90% [5] and while mortality rates have declined, it presents a unique challenge, as long-term complications of breast cancer management are becoming increasingly apparent, particularly persistent post-surgical pain.

Persistent pain has become a significant area of concern as it appears to afflict up to 50% of women after breast cancer surgery [6]. This pain disorder is typically neuropathic in nature and described as burning, spontaneous, electrical, numbness, tingling, and pinprick pain affecting the area of surgery in the chest, shoulder, axilla, and medial arm [7]. While the literature commonly refers to this presentation as post-mastectomy pain syndrome (PMPS), it is important to note that damage of nerves can occur after all types of breast cancer surgeries, including unilateral or bilateral surgeries, radical mastectomies, lumpectomies, and from axillary lymph node dissection. Thus, in 2016 Waltho et al. proposed the term post-breast surgery pain syndrome (PBSPS) which is not only a more inclusive term but may also help to decrease the wide variation in overall prevalence [8].

The International Association for Study of Pain (IASP) also recently updated their definition to include all types of breast surgeries in the classification. Thus, the term "persistent pain after breast surgery" was chosen, and it is pain which persists for more than 3 months after a surgical incision to the anterolateral chest wall and in some cases in the ipsilateral axillary region [9].

Management of persistent pain after breast cancer surgery can be a challenging task with the lack of effective treatment options [10]. Furthermore, this pain disorder places a financial burden on both patients and the healthcare system with studies showing an estimated cost of approximately $1 billion USD annually to the US healthcare system [11]. Identifying perioperative risk factors associated with the development of persistent pain can help decrease the incidence and the need for ongoing healthcare services.

In this chapter we will provide an outline of the pathophysiology of persistent pain after breast cancer surgery, including a review of pertinent risk factors, clinical features, and various treatment options.

2. Pathophysiology

Pain can originate from a multitude of sources, such as from injury to the overlying skin, tissue, or nerves during surgical intervention, or from the effects of radiation and chemotherapy. Additionally, the origin is frequently multifactorial, with psychosocial factors also playing a role.

2.1 Nerve injury

Surgical factors can cause nerve injuries that contribute to persistent pain after breast cancer surgery. Direct nerve injury, for instance from skin incisions, surgical retractors, or extensive axillary lymph node dissection, can lead to direct nerve transections [12]. This can subsequently lead to the eventual formation of neuromas and scar adhesions. Nerve damage can also be due to indirect injury from postoperative inflammation, hematoma formation, or positioning during surgery (resulting in nerve stretching during the procedure) [12]. The nerves most commonly at risk for injury during breast cancer surgery are the intercostobrachial nerve (ICBN), the thoracic intercostal nerves, medial and lateral pectoral nerves, the thoracodorsal nerve, and the long thoracic nerve [13].

Intercostobrachial neuralgia is a well-known cause of persistent pain after breast cancer surgery and presents as neuropathic pain in the ipsilateral axilla and arm [14]. The ICBN is the lateral cutaneous branch of the second intercostal nerve (T2) and is pure sensory in nature [12]. It innervates areas of the axilla, lateral chest wall, and aspects of the medial arm (**Figure 1**), and due to its trajectory and close relation to the axillary lymph nodes, is at high risk of injury during axillary lymph node dissection and radical mastectomies [16]. Furthermore, a study by Zhu et al. demonstrated that identification, dissection, and preservation of the ICBN during surgery reduced the incidence of persistent pain and improved quality of life for patients after breast cancer surgery [17]. While this finding has been observed in additional studies [18, 19], it is important to note that while sensitivity was preserved, the incidence of reduced pain was not always obtainable [19].

Along with the ICBN, which is a branch of the T2 intercostal nerve, the T3-T6 intercostal nerves are also at high risk for injury and subsequent intercostal neuralgia. These nerves primarily innervate the skin of the breast, and major branches include the rami communicates, the muscular branches, the collateral branch, the lateral cutaneous branch, and the anterior cutaneous branch [20]. Involvement

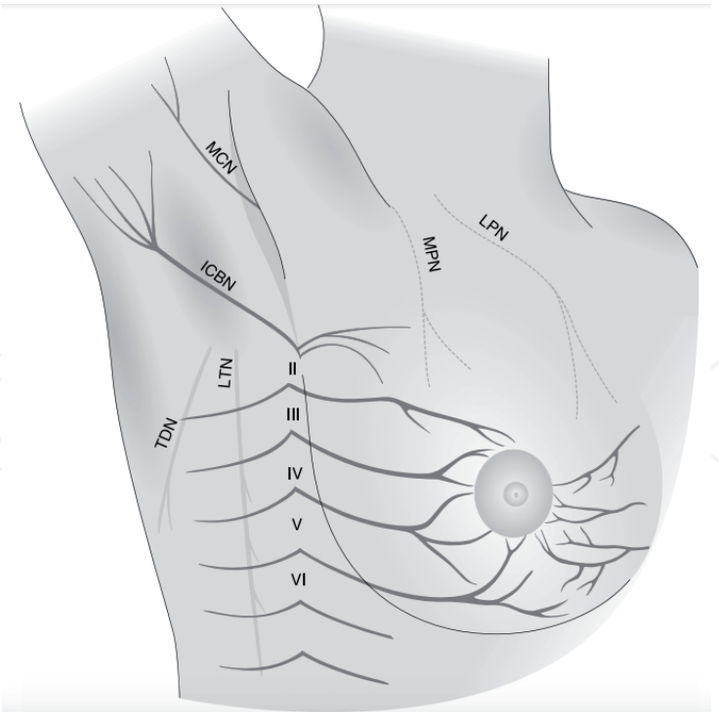

Figure 1.
*Peripheral nerves innervating the breast. *obtained with permission from Dr. Nelun Wijayasinghe from article [15] . II-VI – intercostal nerves II to VI; ICBN – intercostobrachial nerve; LPN – lateral pectoral nerve; LTN – long thoracic nerve; MPN – medial pectoral nerve; MCN – musculocutaneous nerve; TDN – thoracodorsal nerve;*

of intercostal nerves can present as pain originating at the posterior axillary line radiating anteriorly into the chest wall, in the distribution of the affected intercostal nerve. It is not uncommon to have multiple intercostal nerves involved in the presentation of persistent pain after breast cancer surgery.

Another nerve, albeit less commonly involved, is the medial cutaneous nerve of the arm. This nerve branches from the medial cord of the brachial plexus and can form a connection with the ICBN. Damage to this nerve results in sensory loss to the lower medial skin of the upper arm [14]. Additionally, neuromas can develop within the surgical scar and be a problematic source of persistent pain - scar neuromas are an elusive source of pain after any type of surgical procedure.

2.2 Phantom pain

As with other types of amputations, resection of breast tissue is susceptible to the development of phantom pain and sensations. Ahmed et al. enrolled eighty patients undergoing a modified radical mastectomy and at the one-year mark, 13.6% experienced phantom pain, while 17% experienced phantom sensation. Its lower incidence compared to phantom limb pain may be due to the fact that breasts do not involve kinesthetic sensory impulses in the same manner as limbs do [21]. Likewise, there may simply be a lack of widespread knowledge and education for this condition and thus it may be overlooked in clinical practice. Regardless, while less prevalent than neuropathic pain secondary to nerve injury, its importance may be greater as treatment options are even more limited [22].

2.3 Perioperative radiation

Radiation therapy can also lead to nerve damage, producing persistent peripheral neuropathy. While treatment is targeted, radiation therapy may still

cause unavoidable injury to nearby nerves such as the brachial plexus, including proximal and distal branches. The onset and severity of radiation-induced pain can be proportional to the total dose received [23]. A meta-analysis by Wang et al. reviewing thirty studies involving 19,813 patients showed an increased likelihood of PMPS among women who underwent radiotherapy [24]. This is likely secondary to an increased incidence of tissue fibrosis, which can lead to local constriction and compression on nerves and subsequent neural entrapment. Furthermore, lymphedema and impaired glenohumeral motion are other sequelae that can arise after radiation therapy and lead to the formation of persistent pain and morbidity.

2.4 Perioperative chemotherapy

Several commonly used chemotherapy agents such as paclitaxel, vinblastine, and vincristine have all been identified as causing residual neuropathic symptoms [25]. Peripheral neuropathies are the most common presentation with patients experiencing sensations of numbness and tingling usually in a stocking and glove-like formation [25]. Unfortunately, those receiving both radiation and chemotherapy tend to experience enhanced neuropathic symptoms [26]. The mechanism of chemotherapy-induced peripheral neuropathy caused by common antineoplastic agents is multifactorial. For platinum-based drugs such as oxaliplatin and cisplatin, activation of glial cells causes nearby immune cells to release pro-inflammatory cytokines, and altered activity in Na^+ and K^+ ion channels can result in nociceptor sensitization and hyperexcitability of peripheral neurons [27]. Vinca alkaloids also cause the release of pro-inflammatory mediators and influence microtubule polymerization that inhibits axonal transport. This, along with Wallerian degeneration, leads to distal axonopathy [27].

3. Risk factors

PMPS is multifactorial in nature and several risk factors have been evaluated for their association in the development of persistent pain. Risk factors can be categorized broadly into patient demographics, psychological influence, and surgical and anesthetic factors. While an abundance of literature has evaluated risk factors for chronic pain, only some consensus exists. Nonetheless, identifying risk factors and modifying them early in the perioperative period could potentially help in decreasing the risk of persistent pain in high-risk patients.

3.1 Patient demographics

3.1.1 Age

Younger age has been strongly correlated with a higher pain burden index and relationship of younger age with persistent pain is well supported [28–31]. This finding may be secondary to the fact that younger patients usually present with more aggressive, estrogen-receptor negative disease, or higher tumor grade requiring more radical surgeries or adjuvant therapies [32]. Younger patients also tend to have greater levels of perioperative anxiety and a lower threshold to pain, when compared to older patient groups, thus increasing their overall risk [12]. While younger age has been one of the most consistent factors associated with PMPS, some reviews have not always found this to be the case [33].

3.1.2 Body Mass Index (BMI)

Literature also reports that patients with a higher BMI are more likely to experience persistent pain after breast cancer surgery. A study by Spivey et al. found that both a young age and higher BMI correlated with higher pain scores at the six month follow up [34], and Juhl et al. showed that a BMI ≥30 kg/m^2 was significantly associated with persistent pain in both univariate and multivariate models [14]. Surprisingly however, a systematic review and meta-analysis of thirty high-grade observational studies totaling 19,813 patients showed that BMI was not associated with persistent pain [24]. Thus, the correlation may be multifactorial in nature. Surgery in obese patients may be associated with more difficult axillary dissections due to larger breasts, thus placing them at a higher risk for greater tissue and nerve damage. Regardless, as with other surgical disciplines, the risks of perioperative complications such as impaired wound healing and increased blood loss remain higher in patients with a higher BMI [35, 36].

3.2 Psychological

Several studies have shown a significant correlation between high levels of preoperative anxiety [37], catastrophizing symptoms [38], and persistent breast pain following breast cancer surgery [34, 39, 40]. Furthermore, there is also a significant and independent association between PMPS and somatization, depressive symptoms, and sleep disturbance, regardless of the surgical or medical treatment a patient received [33]. Furthermore, pain catastrophizing has been found to intensify the experience of both pain and depression [23, 41]. Patients undergoing breast surgery may expect to have severe pain after the procedure, thus increasing their emotional distress and cause them to excessively focus on only negative aspects such as chronic pain. These negative emotions and beliefs may evolve into catastrophic thoughts and irrational patterns of thinking and become self-fulfilling in producing higher pain levels [42]. In contrast, patients who have a more positive mindset going into surgery, and lower levels of emotional distress, are more likely to experiences less acute pain [43] and therefore experience a lower incidence of PMPS [40].

3.3 Surgical type

With the advancement of surgical management, the association between surgical type and chronic pain development seems to vary in the literature. Both breast-conserving surgery (BCS), with or without lymph node dissection, and radical mastectomy have not consistently shown a positive relationship in the development of PMPS. A study of 475 patients found that patients who underwent breast-conserving surgery were at higher risks of developing moderate to severe chronic pain at rest (OR 2.0, 95% CI = 1.2–3.3) [30]. Some reports however, indicate that more extensive surgery (e.g. radical mastectomies, bilateral procedures, reconstruction) does lead to greater acute postoperative pain, which in turn is a risk factor in developing chronic pain [44]. A prospective, observational study by Spivey et al. with 216 patients, and a systematic review and meta-analysis of thirty observational studies of 19,813 patients by Wang, et al. both did not observe a significant relationship between surgical type and pain at three and six months, respectively [24, 34].

3.4 Axillary lymph node dissection (ALND)

Lymph node dissection can help with the staging and management of breast cancer [45]. Compared to sentinel lymph node biopsy, ALND has been an

associated risk factor with PMPS in several studies [17, 34, 44, 46]. Fabro et al. analyzed ALND on persistent pain, and after controlling for confounding variables they reported that removal of more than fifteen lymph nodes resulted in two times the risk for developing persistent pain [47]. ALND involves more extensive damage to tissues in the axilla, and the intercostobrachial nerve is at most risk during the dissection [48]. As mentioned above, when possible, the ICBN should aim to be preserved during ALND. Abdullah et al. conducted a randomized controlled trial where the ICBN was preserved during ALND and found a decreased incidence of sensory deficits at the three-month follow up. Notably however, preservation could only be obtained in 65% of the patients.

3.5 Acute postoperative pain

Postoperative pain scores in the acute setting have been shown to be a significant risk factor associated with persistent pain across numerous surgical sub-groups, including breast surgeries. Acute surgical injury has been linked to central and peripheral pain sensitization, which can lead to the development of persistent chronic pain [49, 50]. Bruce et al. studied 362 post-mastectomy patients and found that higher levels of postoperative pain increased the odds of developing PMPS at four months (OR 1.34, 95% CI 1.12–1.60) and at nine months (OR 1.17, 95% CI 1.00–1.37) after surgery [51]. Wang et al. also concluded that for every point on a 10-point scale, the level of postoperative pain severity increased the likelihood of PMPS (OR 1.16, 95% CI 1.03–1.30) [24]. Extensive surgical reconstruction, axillary lymph node dissection, high levels of anxiety and pain catastrophizing, and presence of preoperative pain all increase the risk of severe acute postoperative pain [34]. Therefore, acute postoperative pain is a worthy indicator for the development of chronic pain [38] and emphasis should be placed on controlling it early in the postoperative course. Improved postoperative pain control is best managed using a multimodal strategy such as through the use of anti-inflammatories, N-methyl-D-aspartate (NMDA) inhibitors, interventions such as nerve or fascial plane blocks with local anesthetics, or by addressing preoperative psychological factors such as anxiousness or fear of the postsurgical path.

4. Presentation

There are a number of etiologies that can be responsible for pain after breast cancer surgery. Largely, persistent pain is due to neuropathic causes (**Table 1**) [7, 10], such as from trauma or injury to the intercostobrachial nerve and other local peripheral nerves (medial and lateral pectoral nerve, intercostal nerves, etc), but also due to phantom breast pain, scar neuroma formation, and chemotherapy/radiation induced peripheral neuropathy.

Neuropathic pain due to local peripheral nerve injuries typically present as pain in and around the surgical incision, but due to the peripheral nerve distribution, it can be felt as if it also involves the chest wall, medial arm, axilla, and shoulder [7]. Pain is associated with neuropathic pain features which include burning, paresthesia, tingling, as well as allodynia and hyperalgesia [46, 52]. Pain is also typically associated with sensory changes, such as numbness and hypoesthesia. Furthermore, the incision itself may be a source of spontaneous pain and mechanosensitivity, which may indicate the presence of a scar neuroma, which is more common after a lumpectomy than a mastectomy [53].

Other non-neuropathic etiologies can occur after breast cancer surgery and include musculoskeletal impairments such as rotator cuff dysfunction, adhesive

Neuropathic	**Intercostobrachial neuralgia**
	Phantom breast pain
	Neuroma formation
	Local peripheral nerve injuries - medial and lateral pectoral nerves, intercostal nerves, long thoracic, brachial plexopathy
	Chemotherapy-induced peripheral neuropathy
	Radiation-induced peripheral neuropathy
Musculoskeletal	Rotator cuff dysfunction
	Adhesive capsulitis
	Myofascial pain syndrome
	Aromatase inhibitor-associated arthralgia
Others	Axillary web syndrome
	Lymphedema

[*] from previously published article by Dr. James Khan: [10].

Table 1.
Pain disorders after breast cancer surgery.

capsulitis of the glenohumeral joint, myofascial pain syndrome of the pectoral or intercostal muscles, and aromatase inhibitor-associated arthralgias (**Table 1**) [7, 10]. Other potential disorders include axillary web syndrome and lymphedema.

When patients present for evaluation of their pain, the first step involves diagnosing the type of pain being experienced. Origin of pain is broadly categorized as either nociceptive or neuropathic [54]. In the acute postoperative phase, pain after breast surgery is likely to be nociceptive in nature resulting from intraoperative injury and subsequent inflammation to tissue, ligaments, or muscles. In order to help diagnose the type of pain, and track its severity over time, routine use of questionnaire-based assessments are commonly implemented. One that is frequently used is the Douleur Neuropathique en 4 (DN4), which consists of two sections – a set of interview questions and examination findings [55]. The yes/no interview questions ask for the presence of burning, painful cold, or electric shocks, and one or more of tingling, pins and needles, numbness, and itching. The second section assesses if the patient experiences hypoesthesia to touch or pinprick, and if brushing provokes the pain. With each point valued at 1, a total score ≥ 4 signifies a 90% probability of neuropathic pain. The questionnaire is quick and reliable, with a sensitivity of 78.0% and specificity of 81.2% [56].

It is important that a thorough history and physical examination is conducted. History will include an evaluation of the patient's preoperative diagnosis and any adjuvant chemotherapy or radiation. Reviewing surgical records will be important to establish what type of procedure was conducted (mastectomy versus lumpectomy), whether axillary lymph nodes were resected, if ICBN nerve sparing surgery was performed, and if implants or expanders were placed. The anesthesia record will also include helpful information on whether perioperative regional anesthetic techniques (i.e., Serratus plane or Pectoralis blocks) or intravenous lidocaine infusions were administered — these techniques are known to be effective on reducing acute pain but also potentially helpful in preventing persistent pain [10, 57].

Physical examination will include a detailed evaluation of the surgical incision and surrounding area, documenting any sensory changes. An evaluation for upper extremity lymphedema and a comprehensive shoulder exam should also be performed.

5. Treatments

Approach to the treatment of persistent pain after breast surgery should be multimodal and include the use of both non-pharmacological and pharmacological therapeutic modalities. The involvement of a multidisciplinary team, including an oncologist, pain management specialist, physiotherapist, psychologist, palliative care specialist, and social worker should be implemented whenever possible. Furthermore, a preoperative comprehensive and patient-tailored pain management plan should be formulated in advance, which includes education on surgery sequelae, the nature and development of their symptoms, and available treatment options.

5.1 Non-pharmacological

Non-pharmacological interventions should always be included in the pain management plan, regardless of whether medications are employed or not. Moreover, patients should be aware that non-pharmacological treatments are only one part of the overall comprehensive treatment plan. Some patients may actually prefer non-pharmacological modalities to pharmacological, to avoid risks of drug side effects or costs [58].

5.1.1 Physical therapy

The initiation of physical therapy (PT) has repeatedly been shown to be beneficial to patients recovering from breast cancer surgery. Range of motion exercises and active stretching helps to improve upper extremity strength and function, maintain glenohumeral and scapular movement, and allow neuromuscular recruitment with the overall goal of minimizing dysfunction. A systematic review, which evaluated the effectiveness of PT after breast cancer surgery, showed that therapy involving active exercise and stretching was effective in not only improving range of motion but also decreasing postoperative pain [59].

Timing on when to initiate PT has also been studied. Most studies focus on implementing PT early in the postoperative period, with clinical practice guidelines recommending starting gentle range of motion exercises the day after surgery to reduce shoulder dysfunction and pain [60]. Active stretching, followed by strengthening, can then be introduced over the next 6–8 weeks [60]. Several studies however, do report an increase in complications when starting PT too soon after ALND, with Schultz et al. suggesting that a delay of one week can help reduce the incidence of postoperative seromas [61]. Fortunately, patients taking part in early PT after ALND still tend to recover sufficiently by the two-year mark [62].

Besides pain relief, PT has been shown to offer several added benefits to patients after breast surgery. A meta-analysis of 56 studies evaluating the effects of exercise interventions showed significant benefits in fatigue, depression, body image, and health-related quality of life in cancer survivors [63]. As psychological factors play a known role in the incidence of persistent pain [51], long-term benefits can be obtained if practitioners include a PT or exercise course with the hospital discharge plan.

5.1.2 Psychological therapies

As outlined earlier, psychological factors such as anxiety and catastrophizing play a crucial role in the development of persistent pain. Thus, implementing various psychological interventions into the treatment plan not only helps with

pain control [64], but also allows patients to effectively cope during this challenging period in their life. Facing a cancer diagnosis, undergoing invasive treatments, and managing treatment sequelae can all add to the emotional suffering breast cancer patients are faced with. The effectiveness of psychological interventions for non-metastatic breast cancer in women was evaluated in twenty-eight randomized controlled trials involving 3940 patients. The study showed that psychological intervention, in particular cognitive behavioural therapy (CBT), produced favourable effects on anxiety, depression, and mood disturbance [65]. Mindfulness-based stress reduction (MBSR) has also been examined in breast cancer patients, with a recent meta-analysis by Haller et al. evaluating the effectiveness of MBSR in 1709 patients. MBSR was found to have a significant effect on improving health-related quality of life, fatigue, sleep, stress, anxiety, and depression [66].

Perioperative screening questionnaires evaluating psychological stressors, fears, and overall mood, such as the Pain Catastrophizing Scale (PCS) or the Amsterdam Preoperative Anxiety and Information Scale (APAIS) should be implemented both in the pre- and postoperative phase. From this, at-risk patients can be identified and the involvement of psychological interventions can be applied. Moreover, with the advancement of technology and involvement of virtual care into clinical practice, it now allows for easier access and for group therapies to support even larger number of participants per session.

5.2 Pharmacological therapy

Treatment with oral analgesics provides a non-invasive approach to treating pain, and most patients begin here as they transition from acute to chronic pain. Appropriate medication selection relies heavily on obtaining the correct diagnosis, patient comorbidities, drug side-effect profiles, and at times, cost. Furthermore, we must be cognizant of the chronicity of symptoms and the potential long-term consequences of certain therapies, such as with opioids.

A variety of mediation classes have shown to be effective in neuropathic pain, and these same classes are effective in patients with chronic neuropathic pain after breast cancer surgery. Several guidelines are also available to assist prescribers in selecting the most appropriate medication, and second or third line alternatives, if necessary [67–69]. Various medication choices by class are briefly outlined in this section.

5.2.1 Antidepressants

Treatment of neuropathic pain has benefitted from the analgesic properties provided by well-studied and familiar anti-depressants. Tricyclic antidepressants (TCAs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) have become common medication choices when treating neuropathic pain [70], albeit usually at lower doses than that needed for anti-depressant effects.

Tricyclic antidepressants, such as amitriptyline and nortriptyline, inhibit norepinephrine, serotonin, and adenosine re-uptake at nerve terminals. While not fully understood, the increased concentration of these neurotransmitters plays a role in the analgesic effects [71]. Furthermore, TCAs also have an antagonistic action at the N-methyl-D-aspartate (NMDA) receptor [72], which further helps to reduce pain. Doses of TCAs for the treatment of neuropathic pain are much lower than those required for depression [73], and may be the reason that the analgesic properties of TCAs differ from their anti-depressant properties. The effect of amitriptyline was studied in a double-blinded randomized, placebo-controlled crossover trial involving 15 patients with PMPS [74]. A statistically significant improvement in pain, effect on

daily life, and improved sleep was seen, particularly at the 100 mg daily dose. Initial starting dose was at 25 mg once daily, and most common adverse effects included tiredness, dry mouth, and constipation. While these effects may not be ideal, prescribing TCAs to be taken at bedtime may benefit patients who also have difficulty with sleep.

Serotonin-norepinephrine reuptake inhibitors, including duloxetine and venlafaxine, also work by inhibiting neurotransmitter reuptake, with venlafaxine slightly inhibiting the reuptake of dopamine as well [75]. Both medications have been used to treat neuropathic pain and beneficial effects have been reported in the literature [76]. Tasmuth et al. evaluated venlafaxine in neuropathic pain following breast cancer treatment in patients with pain and sensory disturbances in the anterior chest wall, and/or axilla, and/or the median upper arm. While the study only examined 15 patients, average pain relief and the maximum pain intensity were significantly lower with venlafaxine when compared with placebo [77]. When compared to TCAs, venlafaxine has minimal muscarinic and histaminergic activity, and the effect of the two medications has been comparable in some studies [78]. Furthermore, venlafaxine added to gabapentin has shown enhancement in neuropathic pain relief when the therapies are combined [79].

Along with providing benefit for post-surgical neuropathic pain, both duloxetine and venlafaxine also offer pain relief for patient's suffering from chemotherapy induced peripheral neuropathy [80, 81], and even decrease motor neuropathy symptoms [82]. Benefits of these two SNRIs has been their ability to target multiple concerns, such as depression, anxiety, musculoskeletal pain, and neuropathy [83] and thus should be strongly considered as an adjuvant when formulating a comprehensive pain management plan.

5.2.2 Gabapentinoids

Gabapentin and pregabalin are common medications used to treat neuropathic pain. While both have structural resemblance to the gamma-aminobutyric acid (GABA) neurotransmitter, neither acts as a GABA agonist. Gabapentin's primary mechanism of action is its high-affinity binding to the $\alpha_2\delta$ subunit of voltage-activated calcium channels, resulting in a reduction in nerve conduction [84]. A retrospective study of 89 patients with persistent breast cancer pain found a reduction in pain in 80% of patients with an average gabapentin dose of 1135 mg for 14 weeks [85]. Initiating gabapentin at 100-300 mg three times daily, and slowly escalating the dose as tolerated, can provide significant pain relief. While gabapentin continues to be a first line agent for neuropathic pain, certain drawbacks must be considered, such as drowsiness, weight gain, and three times a day dosing.

Pregabalin works similarly to gabapentin by inhibiting voltage-activated calcium channels. It was developed as a successor to gabapentin and has the added benefit of being almost completely absorbed in the body, unlike gabapentin. Thus, with absorption almost three times that of gabapentin, pregabalin reaches peak blood concentrations within one hour after ingestion [86]. Pregabalin has been shown to offer significant decrease in VAS pain scores in patients with PMPS [87, 88], along with significant improvement in quality of life [88].

5.2.3 Opioids

With the general shift away from prescribing narcotics in clinical practice, opioid therapy can still play an important role in pain management when used appropriately. The need for opioid therapy in the acute postoperative period is common and can help decrease nociceptive post-surgical pain. Unfortunately, limited

data supports the use of opioids for neuropathic pain, especially in the long-term [89, 90]. Nonetheless, for cancer patients with continued pain and functional impairment, a trial of opioids in carefully selected patients can be beneficial. Local and national practice guidelines should be reviewed, risks of adverse effects should always be discussed, and signs of tolerance, abuse, addiction, and diversion should continually be assessed.

One major benefit of opioid therapy is its synergistic effect when combined with other medications. For instance, several studies have demonstrated greater pain relief when using gabapentin and an opioid, compared to opioid monotherapy, in the treatment of neuropathic pain [91–93]. Not only did combination therapy allow for greater reduction in overall pain scores, it also allowed for a decrease in the opioid dose. In turn, this helped to decrease the number of adverse effects that arise with chronic opioid therapy.

5.3 Interventional therapy

5.3.1 Nerve blocks

Several peripheral nerves can be directly targeted for perineural injections with local anesthetics, steroids, or even with neurolytic substances such as phenol or alcohol. Once the problematic nerves have been identified by a thorough history and physical exam, ultrasound guidance can help to visualize the nerves.

The intercostobrachial nerve (ICBN) and specific intercostal nerves can be specifically isolated on ultrasound, and medications can be administered under real-time visualization. The ICBN can be identified in the same approach as performing an axillary brachial plexus block - with the shoulder abducted 90° and externally rotated [94]. The ICBN can be seen posterior to the vessels and just deep to the superficial fascia. The medial cutaneous nerve of the arm can also be visualized just anterior to the ICBN [95]. It is important to note that patients experiencing pain in the anterior chest wall may not benefit from an ICBN block.

For chest wall pain, especially pain radiating laterally from the posterior to the anterior chest, intercostal nerve blocks should be considered. Each intercostal nerve branches from the anterior rami of the thoracic spinal nerves and travels on the underside of its corresponding rib [96]. Consecutive intercostal nerves can be blocked simultaneously under ultrasound guidance with the patient lying prone. While the actual nerve may not always be visible on ultrasound, the therapeutic solution can be deposited just inferior to the rib, posterior to the pleura, where the intercostal nerve resides with its corresponding artery and vein. Due to the location, the potential risk of pneumothorax should be explained to the patient, however the use of ultrasound decreases this risk [97].

When the pain is not consistent with a specific nerve, or involves a set of multiple interconnected nerves, various interfascial plane blocks can be an option for pain relief. Due to the complexity of innervation to the breast, the serratus anterior (SA) plane block helps to cover several small nerve branches altogether [98]. This block is approached in a similar manner as individual intercostal nerve blocks, and medication is injected in between the latissimus dorsi muscle and the SA muscle. Branches of the intercostal nerves can be found both above and below the SA [99] and thus some practitioners may choose to deposit additional medication below the SA muscle as well. The ICBN perforates the SA muscle in the mid-axillary line and can be indirectly captured with this plane block as well [10]. Zocca et al. performed the injection on eight patients suffering from PMPS, depositing 0.25% bupivacaine and 40 mg of methyl-prednisolone, and all patients had pain relief ranging from 25% to near complete relief [99].

Other nerve blocks commonly used for patients suffering from pain in the breast region include the thoracic paravertebral block and erector spinae plane block [100]. The true value of these blocks comes mainly in the perioperative period [101, 102]. As mentioned earlier, significant acute postoperative pain is a risk factor for the development of chronic pain. Thus, several studies have shown that the use of these blocks before surgical incision can help decrease the level of acute pain after surgery, and subsequently the prevalence of chronic pain at the six and twelve month follow ups [101, 103]. Furthermore, they have also shown to decrease postoperative opioid use [102, 104].

Regardless of the procedure chosen, the most optimal option should be one that is easy to perform, causes little discomfort to the patient, has reasonable low-risk complications, and allows adequate pain relief.

5.3.2 Neuromodulation

With increasing prevalence in the diagnosis of neuropathic pain, and a shift to decrease use of chronic opioid therapy, the use of neuromodulation has gained significant interest [105]. Both invasive and non-invasive mechanisms of neuromodulation exist and have been used in the treatment of PMPS. A conservative approach to PMPS with neuromodulation is with the use of a transcutaneous electrical nerve stimulation (TENS) unit. TENS has effects on the neurophysiological activities of receptors via the gate theory of pain and can induce the expression of endogenous opioids [106]. EEG changes with use of a TENS unit and decrease in overall pain have been observed particularly in patients with ICBN pain after breast cancer surgery [107]. Due to its low cost, non-invasiveness, and favourable side-effect profile, TENS units have gained attention in treating cancer pain [108].

Peripheral nerve stimulation (PNS) continues to gain growing recognition in the field of pain management due to its less invasive percutaneous approach [109]. PNS allows for direct electrical stimulation of a peripheral nerve to alleviate pain in the distribution of that nerve [110]. This offers targeted therapy and offers pain relief for patients suffering from ICBN or intercostal neuralgia [111]. PNS electrodes can be placed under ultrasound guidance alongside the nerve, avoiding the need for fluoroscopy, and the pulse generator can remain external to the body [112].

Spinal cord stimulators (SCS) are a better-known type of neuromodulation available for chronic neuropathic pain. Technological advancements in SCS throughout the years, such as high frequency SCS, burst stimulation, and dorsal root ganglion (DRG) stimulation, have helped tailor treatment to an individual's pain condition and target specific symptoms [105]. While SCS continues to play a major role in the relief of failed back surgery syndrome and complex regional pain syndrome, new literature has emerged considering SCS for the treatment of PMPS. A case report using DRG stimulation at the T3 nerve roots demonstrated effective pain relief in a patient with severe neuropathic pain [113], and another showed the effectiveness of SCS in treatment of chronic drug-resistant neuropathy in a patient with radiation-induced plexopathy [114]. While these cases are promising, larger studies still need to be conducted in order to evaluate the optimal spinal level for SCS electrode placement and the best neuromodulation programming.

6. Conclusion

Treatment of persistent pain after breast surgery continues to be a challenge and clinical vigilance is needed when caring for this patient population. Neuropathic

pain features can affect nearly half the number of patients who undergo breast cancer surgery, and failure of diagnosis and treatment can lead to a long-term negative decline in mood, quality of life, and overall functioning. While effective treatments still remain areas of active research, identifying patients at risk allows for the implementation of an early multidisciplinary therapeutic approach. Prospective studies on larger populations of breast cancer survivors continue to be performed, and these will help to fill gaps in knowledge and uncover novel therapeutic measures.

Author details

Sachin Sahni* and James Khan
Department of Anesthesia, University of Toronto, Toronto, ON, Canada

*Address all correspondence to: sachin.sahni@uhn.ca

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