

# An Interdisciplinary Approach to Post-Surgical Pain Management Secondary to Breast Cancer Treatment

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## Abstract

The realm of limb lengthening has undergone significant evolution, propelled by advancements in surgical methodologies and technologies. This article delves into the historical progression of limb lengthening procedures, tracing their origins back to the 19th century. Early techniques emerged as solutions for addressing diverse challenges such as war-related injuries, improperly healed fractures, and deformities, laying the groundwork for contemporary approaches. The evolution of external fixation devices and recent strides in internal lengthening technologies have collectively propelled limb lengthening into a highly sophisticated practice. Notably, the applications of limb lengthening have expanded beyond remedying pathological conditions to encompass cosmetic enhancements, amplifying the prominence of ethical considerations in contemporary discussions surrounding this medical discipline.

**Key words:** exclusive breastfeeding; knowledge; instruction; feeding; breastfeeding; breastfeeding techniques

## Introduction

The post-mastectomy pain syndrome (PMPS) or post-breast surgery pain (PBSPS) is defined as a chronic pain with neuropathic qualities, located in the ipsilateral breast/chest wall, axilla, and/or medial arm which lasts at least six months following breast surgery [1, 2]. This underdiagnosed yet widespread condition impacts the quality of life of those patients. Over 1.7 million new cases of breast cancer are diagnosed every year world-wide [3], and approximately 25%-60% of women will suffer from chronic pain after breast cancer related surgery [4].

Current medical management of PMPS/PBSPS is often ineffective, and no standard treatment protocol exists other than addressing neuropathic pain with options ranging from pharmaceutical and surgical management to alternative medicine modalities. PMPS is a complex condition influenced by multiple factors, including nerve damage, surgical trauma, and psychological distress. The diverse components of PMPS necessitate a comprehensive and collaborative method aimed toward patient betterment. Applying multidisciplinary approaches in the diagnosis and treatment of PMPS and understanding the multi-faceted course of this condition will improve the long-term prognosis and well-being of those affected.

## PMPS

PMPS is a complication that follows the removal of cancerous or potentially cancerous tissue in the breast or axilla region and is commonly associated with nerve fiber injury to the intercostobrachial nerve. The prevalence of this condition is expected to increase associated with an increase in breast cancer survival rates. The chronic neuropathic pain that typifies PMPS is often

localized to the axilla, medial upper arm, breast and/or chest wall, and is characterized as an intermittent, dull pain by most patients [5].

Breast cancer survivors with persistent postoperative pain have increased anxiety and depression symptoms compared to breast cancer survivors without postoperative pain [11]. The presence of pain is also predictive of increased anxiety and depression scores in patients with PMPS [13]. These psychological factors are another negative contributor that patients with PMPS may experience, diminishing their post-cancer life and general well-being.

Along with affecting overall quality of life, patients with PMPS have increased clinic visits to manage their symptoms, further contributing to the limitations of resources within the healthcare system to help alleviate symptoms of these individuals. This condition may also delay a patient's return to baseline activities of daily living and increase the amount of time spent in a hospital or doctor's office [6].

## Signs and Symptoms

Normal post-mastectomy recovery may often involve pain from the operation site, however, if symptoms persist longer than three months after surgery, further evaluation is warranted. Patients typically describe the pain as burning, tingling, or stabbing feeling localized to the axillary and breast region that radiates to the upper medial aspect of the arm unilaterally.

On physical exam, patients may present with either heightened or diminished sensation and weakness on the affected upper extremity. Patients may also present with musculoskeletal changes in anatomy to the affected side, such

as a tilted scapula, signs of shoulder impingement, rotator cuff pathologies, or asymmetric gait [18].

### Pathophysiology

Many factors can produce pain in patients with PMPS, making it difficult to attribute the pain to one cause. Post-operative pain is most commonly defined as mixed pain that includes a combination of nociceptive, neuropathic and nociplastic types [15].

Many nerves are located along the axillary and breast region where breast cancer treatments occur including the long thoracic nerve, brachial plexus, intercostobrachial nerve, lateral pectoral nerves and lateral cutaneous branch of the 2<sup>nd</sup> intercostal nerve. PMPS and associated neuropathic pain can be caused by direct or indirect injury to nerve fibers during a mastectomy or during the post-operative healing process as a result of unresolved inflammation.

The skin overlying breast tissue is innervated by the anterior and lateral cutaneous branches of the intercostal nerves. The lateral cutaneous branch crosses the axillary area, innervating the upper medial arm and anterolateral chest. Pain in the breast is associated with arm movements for this reason. Another element of PMPS that may contribute to chronic pain includes the increased sensitization of peripheral and central nociceptors that can develop during and after treatment. Central sensitization is an increased response of nociceptive neurons in the central nervous system to normal stimuli causing pain hypersensitivity. Patients with PMPS have significantly higher preoperative and 1-month postoperative central sensitization inventory (CSI) scores than patients without PMPS [12, 13].

Women with PMPS have higher levels of inflammatory markers such as C-reactive protein and pro-inflammatory cytokines. IL-6, IL-8, and TNF- $\alpha$  levels were found to be increased in post-operative women with PMPS [14].

### Risk factors

Currently, an association has not been found between BMI and PMPS. However, younger women were more common to report increased pain after surgery [6]. A possible cause for this observation is that younger patients often present with higher-grade tumors and undergo aggressive treatments, such as chemotherapy and multiple lymph node dissection which entail a higher risk for nerve injury. Another possibility is that younger patients may have an enhanced central nervous system response to treatment.

PMPS is more likely to occur in patients who have undergone axillary lymph node removal which suggests damage to the intercostal brachial nerves may be an underlying consideration contributing to this condition [8].

Psychological factors are also a risk factor and predictor of overall pain outcomes. Psychological robustness and emotional resilience when faced with a breast cancer, a life-threatening illness, found that a more robust coping strategy significantly produced more favorable acute postoperative outcomes [10]. Breast cancer patients with increased psychological distress experience increased acute and chronic pain after breast cancer treatment, further exhibiting the power of psychological factors, such as catastrophizing and anxiety, that influence the level of pain experienced by patients.

### Diagnosis

PMPS is diagnosed clinically after other potential causes of pain are ruled out, making it a diagnosis of exclusion. Differential diagnoses to consider include post-operative site infection, metastatic cancer to the humerus, lymphedema, musculoskeletal disorders, phantom breast sensation and pain, post-radiation and chemotherapy effects or cervical radiculopathy. Imaging and labs do not show significant findings in a patient with PMPS.

### Treatment

The management of PMPS is unclear, primarily associated with a limited patient pool as most breast cancer survivors who develop PMPS go undiagnosed. However, patients with chronic musculoskeletal pain of any type frequently use healthcare resources to effectively manage their pain, and

pain management programs may be used as an alternative and effective way to treat patients with PMPS [7]. Pain management programs have focused on including medications, physical therapy, exercise programs, cognitive-behavioral therapy, and interventional procedures to improve symptoms.

### Exercise Interventions

Exercise has been shown to decrease inflammatory markers by increasing antioxidative activity and decreasing reactive oxidative species circulating in the body. Adequately active breast cancer patients had decreased inflammatory markers and post-surgical pain compared to non-active and sedentary patients [14]. Incremental increases in exercise including stretching, low intensity aerobic activity, and postural modification as soon as tolerated after surgery should be integrated into post-operative and cancer treatment to result in more favorable patient outcomes.

Yoga, Pilates, and water aerobics also provided improvements to pain by increasing shoulder and neck range of motion, decreasing the occurrence of lymphedema, along with improving overall mood. [18]. Participation in these activities also introduces patients to an increased community of support and socialization, which is a beneficial part to healing.

Additionally, a combination of resistance training and aerobic exercise significantly improved the quality of life of patients with PMPS [16, 17]. Exercise works as a non-invasive tool for increasing quality of life for breast cancer patients, and implementing these practices may be considered in a clinical setting to manage and treat patients with PMPS. Exercise also provides the benefit of psychosocial treatment, reducing levels of anxiety and depression in this patient population, furthering its clinical use in the management of PMPS.

### Ultrasound-Guided Nerve Blocks

Ultrasound-guided regional blocks are a form of anesthetic techniques that are low risk and have shown to be effective in the management of PMPS. Pain is mediated by tissue injury, and nerve blocks inhibit nociceptive input responding to the inflammation and tissue damage which contribute to chronic pain.

### Serratus Anterior Nerve Block

One form of this technique is a serratus anterior nerve block. Patients are placed in a lateral decubitus position with the affected side pointing upwards. Using ultrasound, the serratus anterior muscle is identified under the latissimus dorsi muscle, and the anesthetic is injected into the intermuscular space between the two identified muscles.

A case report showed the use of an ultrasound-guided superficial serratus plane block on patients with bilateral mastectomy suffering from PMPS. The nerve block significantly improved these patient's symptoms indefinitely after three treatments in 4 months. The patients who reported the feeling of tightness in the affected region were particularly good candidates for this form of treatment [19]. Another study used a similar technique, however targeted both the superficial and deep nerves of the serratus anterior muscle. They found that the superficial block was more effective in providing anesthetic relief in patients with anterior chest wall pain. This case report also included two different groups of patients; those who had undergone a mastectomy and those who had undergone a lumpectomy. Patients with a mastectomy without radiation had improved pain after two nerve block treatments as needed. Patients with a lumpectomy and radiation showed to have improvement of symptoms up to 20% 3-months post-procedure [20]. A superficial serratus anterior nerve block showed to have beneficial results on those who had gone through a mastectomy without radiation.

### Thoracic Paravertebral Nerve Block with Continuous Infusion

Another location for nerve blocks between third and fourth thoracic paravertebral space. In a triple-masked trial, patients who received a 3-day ropivacaine paravertebral nerve block infusion immediately after surgery had lower occurrence of 1-year post-mastectomy pain compared to the placebo group. There was no statistical difference in acute development of

pain between the two groups 3-months post-mastectomy [21]. Treatment results may take longer than the patient is expecting and hoping for. Providing reassurance and foresight about treatment timeline can be beneficial for overall treatment outcomes as patients are less discouraged about their progress, or lack of progress, in the first few months.

### Thoracic Peripheral Nerve Block

A study identified trigger points along the inframammary fold in patients with PMPS. These trigger points were found at the 3- and 6-o'clock region of the left breast and 6- and 9-o'clock region of the right breast, which involve the T4 and T5 cutaneous nerve branches. 65% of patients who received a single bupivacaine nerve block injection reported improved pain at their 3-month follow up visit. Patients who did not receive complete relief from the 1<sup>st</sup> injection were offered a 2<sup>nd</sup> injection, after which 91.2% of patients experienced complete relief of pain [22].

### Autologous Fat Graft

Autologous fat grafting is a safe and minimally invasive treatment for PBPS and those who have undergone lumpectomy with radiation. It uses a single injection of mesenchymal multipotent stem cells which triggers remodeling in the affected area. It can relieve compressed nerves affected by breast cancer treatment and reduce scarring of the damaged tissue by reducing inflammation in the area. This technique also has regenerative properties and can act as filler to restore breast shape, further reinforcing the idea that this a favorable technique for those who have had a lumpectomy. A case study showed that in patients with PBPS and who had undergone lumpectomy, autologous fat grafting was effective in reducing overall pain [24].

Another study identified risk factors in patients who had undergone mastectomy for developing PMPS and pathologic scarring. Affected patients who smoked had unfavorable treatment outcomes possibly due to the vasoconstriction and endothelial damage smoking inherently produces in the body. As adipose grafts are unable to proliferate with inadequate vascularization, which may be a reason smoking is associated with these negative results. Additionally, patients who had undergone axillary lymph node dissection reported higher levels of pain and reduced improvement of their symptoms with treatment [25]. These risk factors should be considered when choosing the most effective treatment for the patient.

Considering a patient's individual care in breast cancer treatment is an important factor in choosing the therapy that will result the most satisfactory outcomes. For instance, the effectiveness of autologous fat grafting in patients with PMPS who had undergone mastectomy without reconstruction was called into question when a study found no significant difference between the control and treatment group after one treatment in a 6-month period [26]. Patients who develop PBPS from lumpectomy may respond better to autologous fat grafting than those with PMPS from mastectomy and should be recognized when discussing treatment options and shared decision making with patients.

### Laser Therapy

Laser therapy has been used for a number of conditions, such as fibromyalgia, osteoarthritis, and carpal tunnel syndrome, because it is a non-invasive and painless method to reducing pain. Laser therapy has shown to have anti-inflammatory and pain-relieving effects by reducing total serum prostaglandin levels, making it a practical option for patients with PMPS. A double-blind study used pulsed high-intensity laser therapy on patients with PMPS and lymphoedema who had undergone axillary lymph node dissection. They looked at shoulder range of motion and patient-reported pain scores before and after treatment and found that 12 sessions of pulsed laser therapy over four continuous weeks had significant lasting therapeutic benefits in the patient population [27]. Benefits to this technique are that patients feel immediate relief of pain and improved quality of life without the tradeoff of experiencing adverse effects from treatment. Continue physical therapy and exercise should be used in adjunct as a part of patient's daily routine to maintain treatment outcomes.

### Medications

PMPS involves injury to peripheral nerves, central sensitization, and neuropathic pain. Medication aimed at these pathways have been used for persistent pain prevention and treatment. The goal of alleviating symptoms long-term will also improve quality of life for affected patients, however, with all mediations, there are side-effects that may affect quality of life. Utilizing whole-person care and individualization of treatment plans will optimize what is best for each patient and their specific treatment goals.

Historically, excess use of NSAIDs and opioids have been used long-term for immediate relief. Although there is application for these medications in certain situations, there are more effective alternatives for long-lasting relief that hold less harmful outcomes for patients. Utilizing the pathophysiology of PMPS and targeting these pathways peri- and post-operatively can provide greater continued benefit to patients.

### Gabapentin

Gabapentin is an anticonvulsant under the class of gabapentinoids that mimics the neurotransmitter, gamma aminobutyric acid (GABA) and inhibits presynaptic voltage-gated calcium channels to calm excitatory neurons. Excitatory neurons involve the neurotransmitter, glutamate, which activates N-methyl-D-aspartate (NMDA) receptors and modulates pain. Gabapentin has been traditionally used off-label to treat diabetic neuropathy and fibromyalgia, the highest dosing for neuropathic pain being 1200 mg three times daily.

A double-blind study found that at 24-hours post-surgery, patients who received 400 mg oral gabapentin 2-hours before their radical mastectomy had significantly less pain than those who received placebo 2-hours before surgery. They also found that the treatment group consumed less opioids postoperatively [33]. Using gabapentin perioperatively can aid in decreasing opioid consumption and well as make patients feel more comfortable with less pain after their major surgery to beat cancer.

The long-term effects of gabapentin to treat PMPS have also been reviewed. A retrospective study found that 1135 mg gabapentin for 14 weeks significantly reduced pain in patients diagnosed with PMPS (34). At this higher dose of the medication, however, there comes the risk of common side-effects such as sedation and dizziness. These adverse effects may be not tolerable and a reason to not continue to take this medication for patients.

### Pregabalin

Pregabalin is an anticonvulsant and under the class of gabapentinoids which has also been effective to treating neuropathic pain such as diabetic neuropathy and spinal cord associated injury as it modifies pain perception. The medication targets calcium channels through inhibition and decreases nociceptive sensitization to pain. The highest dose recommended for neuropathic pain is 300 mg twice daily, although studies show that there is not much relief after 300 mg administered per day. Similarly, to gabapentin, common side-effects are dizziness and sedation.

A double-blind study used a moderate-dose of 75 mg pregabalin twice daily for one week immediately post-mastectomy. A moderate dose of the medication was used to avoid the most associated side-effects of dizziness and sedation. Researchers followed up with patients after 24 weeks and found that the emergence of PMPS was reduced in those who were treated with pregabalin the week of surgery compared to the control [28]. Using pregabalin within 24 hours of surgery may have advantageous effects for patients at increased risk of developing PMPS, including those who have undergone axillary lymph node dissection and total mastectomy.

### Duloxetine

Duloxetine is a serotonin-norepinephrine reuptake inhibitor (SNRI) that has also been shown to treat neuropathic pain when dosed at 60 mg per day. A double-blind study gave patients who had undergone a radical mastectomy with axillary dissection 60 mg duloxetine post-mastectomy 2 days before surgery and continued this for 2 weeks, followed by 30 mg duloxetine for

the remainder of the study. Patients reported decreased occurrence of PMPS at their three- and six-month follow up appointment compared to the placebo group [29]. Another study looked at the effectiveness of different doses of duloxetine and found that starting 60 mg duloxetine 2 days before surgery was optimal for recovery and presented to fewer side-effects such as sedation and vomiting. It was also found that patients who received 60 mg or 90 mg duloxetine required less morphine 24 hours post-mastectomy [30]. This is an effective way to reduce opioid use while also successfully managing pain levels in breast cancer patients.

### Memantine

Gabapentinoids and SNRIs are more well-known for treating neuropathic pain, however, new medications are being released to help treat affected patients. Traditionally, memantine has been used as a treatment for moderate to severe Alzheimer disease. This medication helps slow the progression of memory loss by blocking NMDA receptors. Blocking this receptor has also been shown to reduce neuropathic pain and has recently been studied as a treatment for PMPS. A study showed that patients who received 20 mg memantine 2 weeks before surgery and who continued taking the medication 2 weeks after surgery, significantly had lower occurrence of PMPS at their 3- and 6-month follow up appointment compared to those who only received placebo [35]. It is important to have different medications that can be used for patients that fits their individual needs. Some medications have less tolerable adverse effects, and some patients may not have the same response to certain medications as others do. This makes it important to be aware of the different medications that are effective and available to this patient population.

### Acupuncture

Acupuncture is a form of alternative medicine that has been used as a tool for pain management and has newly been used to treat PMPS. Fine needles are placed along a meridian throughout the body to restore balance. The benefit of acupuncture is that it is minimally invasive and relatively safe. The most severe adverse event reported, is bruising and pain from the needles. A case report showed that the patient who had undergone bilateral mastectomy with PMPS experienced complete resolution of pain after eight treatments over the course of 6-months [23]. This treatment option can be aimed at individuals who prefer a more natural method to improving the pain they experience from breast cancer treatment, especially after aggressive treatments patients have to undergo to beat cancer.

### Osteopathic Manipulative Treatment

Osteopathic manipulative therapy (OMT) uses a holistic and non-invasive approach to treatment. It is effective in reducing pain associated with cancer treatment because of its patient-centered focus in restoring body function even in individuals who may not have their peak strength to engage in physical activity. It is an alternative to medication if patients have missed their optimal treatment window or if patients are looking for another way to restore their health as it restores the musculoskeletal framework of patients. A study showed that 4 weeks of mixed and individualized OMT, including cranial, fascial, and articular techniques, lowered pain scores in patients with PMPS [36]. Different techniques and their application will be discussed below.

### Muscle Energy

Chemotherapy and radiation may yield musculoskeletal dysfunctions, such as muscle spasms or tightness, which cause patients pain and decreased range of motion. PMPS may be exacerbated by reduced shoulder range of motion and surrounding muscle tightness. A study showed that 3-weeks of muscle energy combined with physical therapy on the shoulder of a breast cancer survivor with PMPS who also underwent bilateral mastectomy, significantly decreased the patient's pain [31]. Correcting musculoskeletal dysfunctions is an easy and successful way to relieve pain instantaneously for patients. This form of treatment can also yield long-term results as patients' complete chemotherapy and the surgery needed to be in remission.

### Lymphatic Pump

Lymphedema in the upper extremity may be further exacerbated by scar formation in the treated area and can be a common issue in patients who develop PMPS. Studies show that manual lymphatic drainage of the upper extremity improves lymph circulation provide benefits and decreased pain levels and pain sensitivity in those with PMPS [18]. Using OMT and treating patients with upper extremity effleurage may relieve symptoms and compartment pressure associated with the developed lymphedema.

### Myofascial Trigger Points

Patients with PMPS can also experience a pressure-like pain associated with their breast cancer treatment. Due to the region that surgery occurs, myofascial trigger points are more likely to arise in the pectoralis major, infraspinatus, and upper trapezius muscles which cause chronic neck and chest pain if left untreated [32].

Using treatments in adjunct and employing healthy habits through regular exercise, that patients can implement at home results in favorable long-term outcomes.

### Final Takeaways

PMPS is increasing in prevalence as breast cancer survival increases. Although there is no standard treatment to alleviate the symptoms that affect these patient's general quality of life, more options are becoming available to prevent PMPS from occurring as it is being researched more. Being familiar with these options, such as laser therapy, OMT, medications, autologous fat grafting and others, while also catering the best treatment plan to each individual patient will improve overall healthcare outcomes and patient satisfaction. Understanding each breast cancer survivor's goals is especially important since this is a population who has already been faced with a life-threatening disease and the repercussions of issues that arise after being placed in remission. Reducing pain can alleviate anxiety and depression patients may experience and effectively treating this concern is one less difficulty survivor has to be reminded of as they continue their path towards healing. Therefore, implementing a multidisciplinary approach is fundamental for the management of PMPS to improve overall patient outcomes and quality of life.

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