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Review Article

Post-mastectomy pain syndrome: mechanisms, prevention, and management strategies

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ABSTRACT

Post-mastectomy pain syndrome (PMPS) affects a significant proportion of breast cancer survivors and represents a challenging consequence of surgical treatment. It is primarily characterized by chronic neuropathic pain in the chest wall, axilla, or upper arm that persists beyond the expected healing period. The underlying mechanisms involve a combination of peripheral nerve injury, central sensitization, inflammatory processes, and maladaptive neuroplasticity. Surgical disruption of nerves such as the intercostobrachial and thoracodorsal plays a critical initiating role, while changes within the central nervous system sustain and amplify the pain experience over time. Preventive strategies span the entire surgical timeline. Preoperative psychological screening and education can reduce risk by addressing anxiety and pain sensitivity. Intraoperative nerve-sparing techniques and regional anesthesia such as paravertebral or pectoral nerve blocks help to blunt nociceptive signaling. Postoperative care focuses on controlling acute pain, early mobilization, and maintaining functions to limit the transition to chronic pain. Despite these interventions, a subset of patients continues to experience persistent symptoms that interfere with daily activities and quality of life. Therapeutic management is often multidisciplinary, incorporating pharmacologic agents like tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and gabapentinoids, along with physical therapy and psychological interventions. The variability in patient response remains a clinical hurdle. Newer approaches such as neuromodulation, ketamine infusions, and noninvasive brain stimulation are being explored for refractory cases. Persistent gaps in early identification, consistent treatment pathways, and personalized care models continue to limit progress. Addressing PMPS requires a comprehensive understanding of its biological and psychosocial components, along with strategies that evolve alongside advances in surgical and pain science. Effective care hinges on early intervention, tailored treatment, and improved integration across specialties involved in breast cancer recovery.

Keywords: Post-mastectomy pain syndrome, Neuropathic pain, Nerve injury, Chronic postoperative pain, Pain management

INTRODUCTION

Breast cancer is the most commonly diagnosed malignancy among women worldwide, and surgical intervention remains a central component of curative treatment. Mastectomy, particularly when accompanied by axillary lymph node dissection, is associated with a high incidence of chronic postoperative pain. This condition, commonly termed Post-Mastectomy Pain Syndrome (PMPS), is recognized as a form of chronic neuropathic pain that persists beyond the normal healing period, often defined as lasting longer than three months after surgery.[1] Despite advances in surgical techniques and anesthetic protocols, PMPS continues to affect a substantial proportion of breast cancer survivors, with reported prevalence ranging from 20 to 60 percent.[2] The pain is frequently localized to the chest wall, axilla, and upper arm, and may present as burning, stabbing, or shooting in nature, often accompanied by sensory abnormalities such as allodynia or hyperalgesia.

The pathophysiology of PMPS is multifactorial and complex, involving peripheral nerve injury, central sensitization, and inflammatory responses. During mastectomy, nerves such as the intercostobrachial, medial and lateral pectoral, and long thoracic nerves may be inadvertently damaged, leading to abnormal nociceptive signaling.[3] In some cases, neuroma formation and maladaptive neuroplasticity further exacerbate pain perception. Additionally, psychological factors including anxiety, depression, and catastrophizing have been shown to influence the risk and severity of chronic pain following breast surgery. This biopsychosocial model of PMPS highlights the need for an integrated understanding of its mechanisms in order to develop effective prevention and treatment strategies.

Preventive measures for PMPS span preoperative, intraoperative, and postoperative domains. Regional anesthesia techniques, such as paravertebral blocks or pectoral nerve blocks, have demonstrated efficacy in reducing the incidence of chronic pain when administered perioperatively.[4] Minimally invasive surgical approaches and nerve-sparing techniques also play a critical role in mitigating nerve damage. Postoperative interventions including early physiotherapy, multimodal analgesia, and psychosocial support are essential components of a comprehensive care plan. However, current preventive strategies are not uniformly applied across clinical settings, and evidence on their long-term benefits remains variable.

REVIEW

PMPS presents a persistent clinical challenge due to its complex and multifactorial nature. While nerve injury during surgery remains a primary cause, increasing evidence points to the role of central sensitization and maladaptive plasticity in sustaining chronic pain states. This evolving understanding supports the integration of both peripheral and central mechanisms into pain management strategies. For instance, studies have shown that preventive regional anesthesia techniques, such as pectoral nerve blocks, can not only reduce acute postoperative pain but may also lower the risk of chronic neuropathic pain development by attenuating central sensitization early in the surgical process.[5] Moreover, patient-specific risk factors such as younger age, higher BMI, and pre-existing anxiety or depression have been consistently associated with increased PMPS risk, suggesting the value of preoperative psychological screening and intervention.[6]

NEUROBIOLOGICAL PATHWAYS UNDERLYING POST-MASTECTOMY PAIN

The persistence of pain following mastectomy is rooted in distinct but interconnected neurobiological disruptions. Peripheral nerve injury remains a central initiating event. During surgical resection, especially when axillary lymph node dissection is involved, there is a high likelihood of trauma to sensory nerves such as the intercostobrachial nerve, long thoracic nerve, or thoracodorsal nerve. Even with meticulous surgical techniques, damage to these nerves is often unavoidable. Transection or stretching of these nerves initiates a cascade of abnormal electrical activity and molecular signaling that contributes to the onset of neuropathic pain. Damaged nerve endings may develop ectopic discharges and increased expression of sodium channels, which heighten the excitability of nociceptors and lead to spontaneous pain or increased sensitivity to external stimuli.[7]

Once peripheral sensitization sets in, spinal mechanisms begin to play a dominant role. Central sensitization involves enhanced responsiveness of dorsal horn neurons to sensory input, even in the absence of ongoing peripheral damage. Repetitive nociceptive input from the injured site induces long-term potentiation in spinal cord pathways, especially within lamina I and II of the dorsal horn. The result is amplification of pain signaling, reduced inhibitory control, and expansion of receptive fields. These changes are mediated by the upregulation of excitatory neurotransmitters such as glutamate and substance P, as well as by the activation of N-methyl-D-aspartate (NMDA) receptors, which are key to synaptic plasticity in pain pathways.[8] Furthermore, glial activation in the spinal cord contributes to the maintenance of central sensitization. Microglia and astrocytes, once activated, release pro-inflammatory cytokines such as interleukin-1β and tumor necrosis factor-alpha, reinforcing the state of hyperexcitability and perpetuating pain.

Neuroimaging studies have expanded our understanding of central involvement in post-mastectomy pain. Functional MRI and PET imaging have revealed structural and functional alterations in brain regions involved in pain processing, including the thalamus, anterior cingulate cortex, insula, and prefrontal cortex.

These changes reflect the brain's adaptation to chronic pain and are indicative of central reorganization. In patients with PMPS, heightened activity in these areas correlates with pain intensity and altered emotional responses to pain stimuli. There is growing interest in how emotional regulation circuits intersect with nociceptive networks, suggesting that the emotional burden of mastectomy may intensify central sensitization. This supports the involvement of descending modulatory systems that fail to inhibit pain, such as impaired function of the periaqueductal gray and rostroventromedial medulla, leading to disinhibition of nociceptive input at the spinal level.[9]

At the molecular level, evidence from genetic and transcriptomic studies indicates that individual susceptibility to PMPS may be linked to polymorphisms in genes encoding for cytokines, ion channels, and enzymes related to inflammatory and pain pathways. Single nucleotide polymorphisms in the COMT gene, which influences catecholamine metabolism, have been associated with greater pain sensitivity and higher risk for chronic postoperative pain. Likewise, increased expression of voltage-gated calcium channels and chemokine receptors in dorsal root ganglia neurons has been identified in models of neuropathic pain after surgical injury, offering potential targets for future interventions.[10]

PREVENTIVE APPROACHES ACROSS THE SURGICAL TIMELINE

The emergence of PMPS is closely tied to events before, during, and after surgery, making a timeline-based preventive strategy both logical and necessary. Preoperative screening provides a valuable opportunity to identify patients at higher risk. Psychological distress, particularly anxiety and catastrophizing tendencies, has been associated with increased postoperative pain and chronicity. Patients with high baseline pain sensitivity or history of chronic pain are also more susceptible. Preoperative education that prepares patients for the surgical experience and postoperative recovery has demonstrated benefits not only in anxiety reduction but also in pain outcomes.[1] Incorporating psychological assessments and supportive interventions into pre-surgical planning could shift the risk profile for PMPS significantly.

Intraoperatively, nerve preservation is a central concern. Surgical approaches that avoid unnecessary traction or transection of nerves such as the intercostobrachial or thoracodorsal nerves have shown promise in reducing neuropathic complications. However, anatomical variation and the need for oncologic completeness sometimes make this difficult. For this reason, anesthetic techniques have become an area of active interest. Regional nerve blocks administered intraoperatively, such as thoracic paravertebral or pectoral nerve blocks (Pecs I and II), have been associated with decreased acute postoperative pain and reduced incidence of chronic pain syndromes. These techniques help inhibit nociceptive input at the spinal cord level, potentially preventing central sensitization and long-term pain memory encoding. Use of total intravenous anesthesia and minimizing intraoperative opioids may also contribute to better outcomes by reducing opioid-induced hyperalgesia.[11]

Postoperative pain management forms the final layer of this timeline. Effective control of acute pain is not only essential for comfort and mobility but may also reduce the transition to persistent pain. Multimodal analgesia, combining non-opioid medications such as NSAIDs, acetaminophen, and gabapentinoids, has gained traction as a safer and more comprehensive method than opioid monotherapy. The role of gabapentinoids remains debated due to mixed evidence and concerns about sedation, but when appropriately used, they appear to reduce hyperexcitability in the dorsal horn. Postoperative physiotherapy and early mobilization protocols have also been shown to contribute to lower pain scores. Immobility following breast surgery can cause shoulder dysfunction, myofascial pain, and muscular stiffness, which in turn may fuel chronic pain patterns. Encouraging structured movement within safe limits can break this cycle.[12]

Pharmacologic interventions with disease-modifying potential are also being investigated. Perioperative use of ketamine has shown benefit in some studies, possibly due to its NMDA receptor antagonism and its ability to attenuate central sensitization. Corticosteroids have been evaluated for their anti-inflammatory effects during surgery, though their role in chronic pain prevention is still being clarified. Beyond drugs, early psychosocial support has emerged as a protective factor. Pain catastrophizing, depressive symptoms, and social isolation can amplify pain experience and hinder recovery. Behavioral therapy techniques introduced shortly after surgery may offer longer-term benefit by improving coping strategies and decreasing somatic focus.[13]

EVOLVING THERAPEUTIC STRATEGIES AND CLINICAL CHALLENGES

Management of PMPS remains clinically demanding due to the wide variability in symptoms, individual pain trajectories, and inconsistent response to treatment. The therapeutic approach is rarely linear. For many patients, pain persists despite conventional interventions, requiring a layered strategy that integrates pharmacologic, physical, and psychological care. Among pharmacologic options, tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors have demonstrated utility in reducing neuropathic symptoms. Nortriptyline and duloxetine, in particular, are often favored due to their better tolerability profiles compared to older agents. These drugs modulate descending inhibitory pain pathways and help balance

neurotransmitter activity in the central nervous system. Although results vary, randomized trials support their use in reducing pain intensity in chronic postsurgical conditions.[14]

Gabapentinoids like pregabalin have also been frequently prescribed, especially in the early phase following surgery. Their ability to inhibit calcium channel subunits in hyperexcitable neurons is thought to dampen ectopic discharges from damaged nerves. Yet, concerns about sedation and dependency have prompted a more cautious application. Long-term efficacy remains under debate, especially in populations with comorbid fatigue or cognitive impairment. Topical agents such as lidocaine patches and capsaicin cream provide localized relief for patients with cutaneous hypersensitivity, although benefits are often limited to superficial symptoms without deeper neural involvement. Interventional pain procedures, including trigger point injections and nerve blocks, offer short-term reprieve but are not consistently effective in breaking the cycle of central sensitization.[15]

Physical therapy forms an essential part of the recovery process, particularly in addressing secondary myofascial pain and restoring upper limb function. Techniques such as myofascial release, nerve gliding, and progressive stretching have shown clinical benefit in improving range of motion and reducing mechanical contributors to pain. Limitations in access to specialized physical therapy and inconsistent adherence reduce the overall impact of these programs. Moreover, patients frequently present late for physiotherapy referral, often after maladaptive movement patterns have already developed. Early engagement with structured rehabilitation, ideally within weeks of surgery, appears more effective in preventing long-term disability than retrospective intervention.

Psychological therapy, especially cognitive-behavioral approaches, plays a crucial role in modifying the pain experience. Pain catastrophizing, fear avoidance behaviors, and mood disturbances can significantly influence both the intensity and duration of pain. Interventions targeting these processes have demonstrated promise in reducing perceived pain severity and improving emotional functioning. Despite this, referrals to psychological support services are often delayed or underutilized. Stigma, limited provider availability, and lack of integrated care pathways remain major barriers. Telemedicine-based delivery of pain psychology has emerged as a potential solution, although its long-term outcomes in the PMPS population are not yet fully characterized.[16]

Emerging modalities like neuromodulation and ketamine infusions are under active investigation. Spinal cord stimulation has been explored for refractory cases, though evidence remains limited and cost concerns are substantial. Low-dose ketamine, due to its NMDA receptor antagonism, offers a mechanistic match for central sensitization, yet its psychoactive side effects and inconsistent protocols have limited routine use. More recently, interest in noninvasive brain stimulation techniques and virtual reality–assisted pain distraction has highlighted the need to move beyond pharmacology alone.[17]

CONCLUSION

Post-mastectomy pain syndrome remains a complex clinical issue rooted in neurobiological, surgical, and psychosocial factors. Timely prevention and tailored therapeutic strategies are essential to reduce long-term morbidity and improve patient outcomes. Advances in perioperative care, neuroplasticity research, and integrated pain management continue to shape evolving treatment models. Greater emphasis on individualized approaches and early intervention may hold the key to reducing chronic pain burden in breast cancer survivors.

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