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Persistent Post-Mastectomy Pain: Risk Factors and Current Approaches to Treatment

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Abstract

Persistent Post-Mastectomy Pain (PPMP) is a common condition that can follow surgeries for breast cancer, the most common cancer in women. Because of the frequency of PPMP and its potential severity, it has received increasing research attention. This manuscript reviews the recent research literature, beginning with a brief history and then relevant medical, surgical, demographic, and psychosocial risk factors. Subsequently, social, psychological, and functional sequelae that have been linked to PPMPs are considered, as is research on current pharmacological, psychological, and rehabilitative approaches to treatment. The review concludes with a discussion of directions for future research and treatment that might reduce the incidence and impact of PPMP on breast cancer survivors.

Perspective—This article describes current research literature involving mechanisms, risks, and treatments related to persistent post-mastectomy pain. Implications of research findings also are discussed for pre- and post-surgical approaches to pain management, current treatments, and promising research directions.

Keywords

Persistent post-mastectomy pain; post-mastectomy pain syndrome; breast cancer; postsurgical pain; chronic pain; lymphedema

Breast cancer is the most commonly diagnosed form of cancer among women in the U.S., affecting over 250,000 patients per year, although offsetting advances in treatment have led to decreased mortality and increased five-year survival rates (90.8%, 95% CI = 90.5% to 91.1%).⁴⁶ The increase in survivorship underscores the importance of optimizing quality of life for breast cancer patients whose lives are extended by treatment. For many patients, intractable post-mastectomy pain negatively impacts their quality of life.^{64,127}

Pain following mastectomy has long been recognized as a clinically significant post-surgical complication. It initially was described 40 years ago as dull, burning, and aching sensations involving the chest, axilla, and ipsilateral upper extremity.¹⁶⁷ Because it was generally thought to reflect a neuropathy attributed to intercostobrachial nerve (ICBN) damage during surgical dissection, the term, post-mastectomy pain syndrome (PMPS) was coined to refer to these symptoms.⁷³

Post-mastectomy pain initially was thought to be a relatively infrequent complication of breast surgery, but more recently has been estimated to affect from 20% to 50% of post-mastectomy patients.^{5,32,67,127,154,156,161} The wide variation in estimates largely reflects definitional inconsistencies across studies.^{24,163} For example, studies that consider only patients who present with neuropathic symptoms, the classic PMPS constellation, find an incidence at the lower end of the range (e.g., 23.9%)¹⁶¹. Studies that capture not only PMPS, but also other sources of post-mastectomy pain, such as lymphedema^{67,79} and musculoskeletal pain,^{77,97,101} find a higher incidence (e.g., 47%,⁶⁷ 42%,¹²⁷). The broader characterization evident in the latter studies has been termed persistent post-mastectomy pain (PPMP) in order to distinguish it from the narrower PMPS definition referenced above.¹⁶ The clinical features of PPMP are presented in Table 1.

This manuscript reviews literature bearing on the broader PPMP spectrum and is timely for several reasons. First, while several manuscripts have reviewed important elements of the literature (e.g., lymphedema,⁷⁹ risk factors,¹⁶⁴ preemptive analgesia³⁴), a comprehensive review is lacking. Second, recent research on PPMP and, more generally, chronic post-surgery pain (CPSP) has focused on the identification of perioperative risk factors associated with the conversion from acute to chronic pain—a review of this literature is in order. Finally, a large literature has studied the effects of preemptive analgesia protocols aimed at minimizing postoperative pain, both acute and chronic. Thus, the sheer volume of recent research both directly and indirectly relevant to PPMP speaks to the need for a broad review at this time.

We first consider the extensive literature that has arisen around risk factors for PPMP, beginning with preoperative factors and then moving to intraoperative and postoperative risks. This is followed by a review of social, psychological, and functional sequelae linked to PPMP and a discussion of pharmacological, psychological, and rehabilitative approaches to reducing the incidence and/ or the impact of PPMP-related sequelae. Finally, we discuss directions for future research and treatment.

Risk factors

Current Mastectomy Trend

As noted earlier, numerous advances in treatment have enhanced breast cancer survivorship. One advance is linked to the identification of gene mutations (e.g., BRCA1, BRCA2) that confer an elevated cancer risk over a lifetime. Patients with such mutations can undergo prophylactic bilateral mastectomies that significantly reduce cancer risk.¹⁰⁵ While prophylactic mastectomies for BRCA gene mutations have demonstrated clinical value, they account for only a portion of the 21% increase in mastectomies that has occurred between 2005 and 2013.^{153,170} Advances in surgical treatment also account for a portion of the increase in mastectomies. For example, nipple sparing and other breast-conserving approaches have increased in use, procedures that can reduce negative post-surgical sequelae that impact body image and/or sexual intimacy.⁴

While these advances account for some of the increase in mastectomies, the increase also reflects patients' misguided attempts to reduce risk. For example, women without a risk-conferring genetic mutation may choose a bilateral rather than unilateral mastectomy in order to minimize the likelihood of cancer recurrence, even though epidemiologic data show that the likelihood of such a recurrence is low and impacted negligibly by elective surgery.^{15,173} These data suggest that preventative unilateral or bilateral mastectomies may be over-utilized, placing patients at risk of post-surgical sequelae, including PPMP, with little offsetting benefit.¹⁷⁰

Preoperative Risk Factors

Data suggest that several sociodemographic factors, race/ethnicity and age, contribute to PPMP risk. Relative to race/ethnicity, minorities are at increased risk for PPMP.^{56,130} Several factors are cited as reasons for the increased risk, both of which are likely consequences of Black, Hispanic, and other minority patients being diagnosed at more advanced stages of the disease.⁵⁶ Not only does this have negative implications for rates of survival,⁸⁵ but minorities also are more likely to require extensive surgery,¹⁵³ itself a risk factor for PPMP.⁶⁷ Finally, the treatment of later-stage disease also is likely to require more aggressive adjunctive treatment (i.e., chemotherapy), also associated with higher rates of pain.^{7,67}

Younger age also is a preoperative risk factor.^{7,27,106,115} Although the reason for younger age predicting PPMP is not clear, its weight as a risk factor is clear: a recent meta-analysis of 30 studies involving 19,813 post-mastectomy patients showed increased odds of PPMP with younger age (odds ratio for every 10-year decrement = 1.36; 95% CI = 1.24—1.48).¹⁶⁴ Several mechanisms have been proposed, including the increased likelihood of a higher histopathological tumor grade in younger patients and the need for adjuvant chemotherapy in this group. In addition, differences in estrogen receptor status in younger versus older patients and decreased pain receptor sensitivity in older patients have been cited as potential risk-related mechanisms.^{27,94,113} Interestingly, younger age is not just a risk factor for mastectomy patients: younger age also is a risk factor for other post-surgical chronic pain syndromes.^{91,131}

The existence of a preoperative painful condition is another potent risk factor for PPMP. Indeed, the presence of pre-existing pain is one of the most consistent predictors for PPMP, as demonstrated by a recent meta-analysis that showed the odds of PPMP to increase to 1.29 (95% CI = 1.01—1.64) among women with pre-operative pain.¹⁶⁴ This phenomenon appears to apply to pain of any type or location: women who have pre-existing headache and low back pain, conditions unrelated to their breast cancer, are significantly more likely to develop chronic pain related to surgery.⁶⁷ This vulnerability is likely to extend to other pre-existing chronic pain conditions, including such common conditions as fibromyalgia and temporomandibular disorders. That said, the risk for PPMP is heightened further when preoperative pain exists in the area to be operated.^{7,99,117,118} The mechanisms that account for this enhanced vulnerability are unclear, although a number of authors have theorized that pain sensitivity and/or central sensitization may predispose surgical patients to post-operative chronic pain.^{8,13,89,97,118,144,168,172}

Psychological factors constitute a fourth major risk category associated with chronic post-operative pain. Several studies of patients undergoing major joint arthroplasties and/or abdominal hysterectomy have shown that pain catastrophizing (a negative cognitive— affective response to pain)¹³² and illness representations are independent risk factors for chronic postsurgical pain.^{128,129} Such results are consistent with other studies showing that anxiety bestows risk for chronic pain that is independent of pre- and post-operative pain levels.¹¹² Further support for a psychological risk factor also derives from several reviews: 1) a systematic review of 50 studies that found likely correlations between chronic post-surgical pain and depression, stress, and psychological vulnerability,⁸⁰ and 2) a meta-analysis of 29 studies and 6,628 patients that found a pooled odds ratio for chronic post-surgical pain of 1.55 (95% CI = 1.10—2.10) for patients with elevated levels of anxiety and pain catastrophizing.¹⁵⁸

Several large studies suggest that the latter pattern applies to PPMP. For example, a longitudinal study of 410 patients showed that preoperative anxiety and depression were significantly associated with the subsequent development of moderate-to-severe PPMP.¹¹⁹ Similarly, a cross-sectional cohort study that followed 611 patients an average of 3 years showed that anxiety, catastrophizing, sleep disturbance, and somatization were independently associated with PPMP (defined as pain severity $\geq 3/10$).¹⁶ Another study of 970 patients showed associations of both anxiety and depression with subsequent PPMP.¹¹⁷ Interestingly, a recent meta-analysis that pooled effect sizes for 13 studies did not support an association between psychological risk factors and PPMP.⁸⁶ That analysis, however, was complicated by the relatively small number of studies that met inclusion criteria, reducing the power of the analyses, and by heterogeneity in measures of both psychological factors and pain outcomes, further attenuating study power.

While depression is somewhat less studied than anxiety, research has shown that it, too, may be a risk factor for PPMP. The evidence is not quite as compelling as that for anxiety, as it has not been shown to be an independent factor after controlling for other risks, such as age, preoperative pain severity, and post-operative pain severity.^{26,117} Whether a preoperative risk factor or not, a diagnosis of depression after successful breast cancer treatment has been found to predict ongoing pain at 4 year follow-up.¹³⁵

Catastrophizing is a well-documented risk factor for a poor adjustment to chronic pain.^{9,53,69} While less studied than anxiety in the post-surgical pain literature, it has been shown to predict chronic pain after both breast surgery¹⁴⁶ and total knee arthroplasty.²⁹ Further, there is evidence that it contributes above and beyond the effects of anxiety and depression to a poor post-surgical adjustment.⁹ Indeed, in the previously referenced meta-analysis, pain catastrophizing more consistently predicted pain chronicity than did anxiety.¹⁵⁸

Another psychological risk factor that has received attention involves cognitive functioning. A neuropsychological battery that assessed executive function, visual memory, attention, and levels of anxiety, depression, and coping strategies was administered to 189 patients prior to total knee arthroplasty for osteoarthritis or breast surgery for cancer.¹² Patients were then followed for clinically meaningful pain outcomes (pain $\geq 3/10$) at six and twelve months. Results, consistent across surgery types, showed that depression, passive coping, and impaired executive functioning (diminished cognitive flexibility and memory) were associated with poorer pain outcomes.

Not all psychological research has focused on risk factors for poor outcomes. There also is interest in protective factors, such as resilience—a person's ability to "...maintain relatively stable, healthy levels of psychological and physical functioning..." when exposed to highly disruptive events.²¹ The experience of cancer, obviously, is a highly disruptive event that poses acute challenges associated with the cancer diagnosis and recurring challenges associated with ongoing treatment and survivorship.⁴⁸ Several studies have shown that the majority of cancer patients demonstrate resilient responses to disease,⁴⁷ while those lacking in resilience demonstrate poor long-term outcomes.⁹⁶ Relative to breast cancer, the evidence suggests that patients who approach surgery in a resilient manner—with positive affect and lower levels of emotional distress—are likely to report lower levels of acute post-operative pain²⁷ and a lower likelihood of PPMP.^{26,119}

Genetic polymorphisms constitute another preoperative risk factor for PPMP, although the evidence is less abundant than that for previously described factors. OPRM1, the gene responsible for encoding the mu opioid receptor, has been studied relative to its role in pain control after surgery. A meta-analysis of eight studies of 677 carriers of the 118G allele and 1005 wild-type subjects¹⁶² showed no effects for opioid dosing ($d = -0.015$, $p = 0.93$), and only a marginal contribution of the G allele on increased pain reports ($d = 0.27$, $p = 0.074$).¹⁶² Nonetheless, it has been proposed that an understanding of a patient's OPRM1 allele may enhance post-operative pain control by aiding in the choice of the proper opioid agonist.¹⁷ In fact, interest continues in genetic and other biomarkers that may represent risk factors for transitioning from post-surgical acute to chronic pain, as reflected in a recent NIH funding initiative, Helping to End Addiction Long-term.¹²⁰

Intraoperative Risk Factors

Axillary lymph node dissection (ALND) is a well-recognized intraoperative risk factor for the development of PPMP.^{5,67,117} Several recent studies have underscored that risk. One, a study of 475 patients that were followed for one year post-mastectomy, found that women who underwent ALND were 3.1 times more likely ($p = 0.0005$) to experience moderate-to-severe pain at rest.⁷ Another, a meta-analysis, also found that ALND conferred a relative risk

for the subsequent development of PPMP (OR = 2.41, 95% CI = 1.73–3.35).¹⁶⁴ By comparison, sentinel lymph node biopsy, the current standard of care in assessing metastatic disease, is associated with a lower incidence of PPMP.¹⁰⁸ Importantly, patients who had a positive sentinel node biopsy and therefore had to undergo a second ALND procedure fared no worse than those who underwent primary ALND.⁸³

The effects of other intraoperative factors, such as damage to the ICBN, on postoperative pain and subsequent chronic pain are not so clear. There is conflicting evidence as to whether ICBN damage causes neuropathic symptoms in the area of the breast, axilla and upper arm. A recent prospective cohort trial divided ALND patients into subgroups according to whether the ICBN was preserved, partially preserved, or sectioned during surgery, but found no differences among these approaches in pain outcomes one week after surgery.⁶ Another study replicated this finding when outcomes were evaluated 4 and 9 months post-surgically.²⁶ Interestingly, yet another study found that ICBN preservation during surgery was actually a risk factor for continued pain at one year.⁷

The “intact nociceptor hypothesis” has been advanced as a mechanism to explain the contradictory findings described above:³¹ uninjured nerve fibers sharing the same receptive field may become spontaneously active when nearby neurons are damaged. These neighboring, intact nerve fibers preserve the capacity for nociceptive signaling to a greater degree than injured fibers. Regardless of whether this or some other mechanism is involved (e.g., microscopic damage or damage from tension on a nerve during surgery), the relationship between damage to the ICBN and post-mastectomy pain remains poorly understood.

In addition to potential ICBN damage, surgical procedures can occasion pain secondary to musculoskeletal mechanisms. For example, during breast reconstruction surgery, the pectoralis major may be used to create a pouch for an implant¹⁶⁵ or a window may be cut in the muscle to access circulation during a free flap procedure,¹⁴ either of which can shorten the pectoralis muscle, restrict glenohumoral range of motion, and result in musculoskeletal dysfunction.^{35,104}

More broadly, mastectomy patients may be at risk for axillary web syndrome, adhesive capsulitis, myofascial dysfunction, brachial plexopathy, and rotator cuff injury.⁷⁹ All of these can lead to pain and restrictions in shoulder range of motion, strength, and lymphatic function.^{98,99,101} Indeed, a study of pain 6 months post-mastectomy found that 27.2% of patients reported pain in the shoulder and/or scapulothoracic area.⁵ Moreover, guarding and other common responses to pain can lead to reduced upper extremity use and a further decline in function.^{32,49,78}

Other variables related to surgical approaches to the treatment of breast cancer are not as clearly related to pain outcomes. For example, the evidence for mastectomy versus breast conservation therapy, while consistently supporting the quality of life benefits for breast conservation, is conflicting in regard to pain.^{55,76} One study of 475 patients found 2.0 greater odds (95% CI = 1.2–3.3, $p = 0.006$) of moderate-to-severe pain at rest for women who underwent breast conserving surgery, after controlling for the effects of radiotherapy.⁷

Another study, however, found that breast conserving therapy was associated with less pain at one year follow-up.¹⁰⁹

Postoperative Risk Factors

The presence of acute postoperative pain is another strong risk factor consistently associated with the development of PPMP. This has been demonstrated in several large and methodologically rigorous studies. One study of 362 post-mastectomy patients found that higher levels of postoperative pain conveyed increased odds of PPMP at 4 months (OR = 1.34, 95% CI = 1.12–1.60) and at 9 months (OR = 1.17, 95% CI = 1.00–1.37).²⁶ Another study followed 475 mastectomy patients for one year following surgery and also found that higher levels of postoperative pain increased the odds of moderate-to-severe PPMP (OR = 2.8, $p = 0.0018$).⁷ Finally, a recent meta-analysis of 30 studies, involving 19,813 patients, reached a similar conclusion: for every point on a 10-point scale, the level of postoperative pain severity increased the likelihood of PPMP by 1.16 times (95% CI = 1.03–1.30).¹⁶⁴

Radiation therapy, which may be administered in conjunction with surgery for breast cancer, also carries significantly increased risk for PPMP. A cross sectional study followed 3,253 Danish women two to three years after undergoing mastectomies in 2005 and 2006, and 47% reported ongoing pain several years later.⁶⁷ Increased odds of PPMP were associated not only with young age (18–39 years) and ALND, as previously discussed, but also with adjuvant radiotherapy (OR = 1.5, 95% CI = 1.08–2.07, $p = 0.03$). Moreover, patients who received regional radiotherapy also were at increased risk for lymphedema at the time of follow-up (unadjusted OR = 3.37, 95% CI = 2.68–4.23, $p < 0.0001$). Similar results were reported in the meta-analysis cited above:¹⁶⁴ high quality evidence showed an increased likelihood of PPMP among women who underwent radiotherapy (OR = 1.35, 95% CI = 1.16–1.57). This is likely a function of an increased incidence of tissue fibrosis, neural entrapment, and impaired glenohumeral motion,¹³⁶ all of which can lead to higher levels of pain and activity limitations.⁹⁸

Psychosocial Impairments and Quality of Life

Abundant evidence shows that pain increases the general symptom burden experienced by patients with breast cancer, as it negatively impacts mood, cognition, sleep, activities of daily living, social interactions, and overall quality of life.^{90,134,140} As noted previously, advances in cancer treatment have increased survival rates and longevity, underscoring the importance of managing quality of life in cancer survivors. Studies exploring the psychosocial impact of PPMP have examined changes in overall quality of life, depression, anxiety, catastrophizing, sleep, body image, and sexuality. The following sections summarize these issues.

Quality of Life

Numerous studies have revealed the serious impact of PPMP on overall quality of life and customary role functions in women who underwent surgical treatment for breast cancer.^{20,30,90,127,134,151,161} Even in instances where chronic pain severity was mild, women with PPMP reported significant impairment in role functioning, as well as generally negative

effects of pain on physical and mental health.^{113,127} Pain also takes a toll on day-to-day activities that previously were completed with little or no thought. In a study that focused on patients with lymphedema, both increased fear of lymphedema and higher levels of pain were found to interfere with daily function.¹⁸¹ To some degree, functional interference may be mitigated by spouse support: women living with a spouse or partner describe lower levels of disability.⁹⁵ Of course, such support is not available to all: in a sample of women with PPMP, 26% were living alone and therefore lacked the possibility of support from a partner as described above.⁸¹

For a significant number of PPMP patients, pain may be severe enough to impair occupational function. Among women with higher levels of pain, interference with “normal work” is common, such that more than half of the women with PPMP report significant pain-related disability.^{25,60} Among those who were working, 54% reported that they reduced their workload to part-time as a direct result of pain. Of course, secondary to such changes in employment status, many women also report financial insecurity.¹⁵⁴

Despite problems with customary activities, research suggests that most women who cope with pain are resilient, so that post-surgical quality of life generally improves over time.¹⁰⁶ Together, these studies suggest a positive adaptation by women to PPMP: women who are able to mitigate the impact of pain on their participation in customary activities can maintain a good quality of life despite their pain conditions.

Depression and Anxiety

In a study that examined the impact of PPMP on a broad range of psychosocial dimensions, mood was found to be the most affected domain.⁷⁴ Multiple subsequent studies have supported a strong association of PPMP with mood disorders, including both depression and anxiety.^{17,25,42,60,146} While not specific to women with PPMP, estimates of the prevalence of mood disorders in breast cancer patients are high compared to the normal population, ranging from 10% to 25% of patients⁵⁹ to rates as high as 50%.^{28,174} While absolute rates of depression and anxiety appear to decline after active treatment is completed, the burden associated with depression and anxiety appears to escalate in patients who continue to experience those disorders.¹⁴⁰ Such findings are consistent with the broader research literature relevant to mood disorders and chronic pain: multiple studies have shown that depression and anxiety are present in a large proportion of patients who experience chronic pain,^{10,45,139} particularly those experiencing pain at higher levels of severity.^{71,149}

Catastrophizing

As noted previously, catastrophizing is a risk factor for post-surgical pain,¹⁵⁸ including pain after breast surgery.¹⁴⁵ Further, among patients who experience persistent pain following mastectomy, high levels of catastrophizing are common, as are somatization, anxiety, and sleep disturbance.¹⁶ There is evidence, however, that the passage of time post-surgery may attenuate the association between catastrophizing and emotional adjustment as the association appears strongest in the two years following surgery.¹⁵⁸ This trend is consistent with the resilience literature and suggests that interventions aimed at boosting resilience and other self-management strategies may help women cope with the challenges of PPMP.^{22,48}

Sleep and fatigue

Problems with sleep and fatigue are common among patients with cancer, with studies reporting fatigue in 60% to 99% of patients undergoing treatment, as well as up to 40% of cancer survivors.^{155,157} Not surprisingly, many studies also have found sleep impairment among patients with ppmp.^{16,60,106,146,151} Impediments to sleep include breast and neck/shoulder pain, shoulder movement restriction, and upper limb weakness.⁸⁸ While the latter sources of discomfort may be most pronounced immediately post-mastectomy, the negative impact of disturbed sleep on quality of life and interference with daily activities can persist for years after treatment has concluded.¹⁴⁰

Body image and sexuality

Abundant research points to negative effects of mastectomy on body image, as well as negative changes in sexuality in women following mastectomy.^{2,41,54,58,107,126,137} A recent systematic review of 36 studies of body image in breast cancer survivors showed that younger women are especially vulnerable to concerns about sexual dysfunction and body image, concerns that are heightened when treatment involves not only surgery, but also chemotherapy and radiation.¹²⁵

Treatment of PPMP

Because PPMP involves issues associated not only with pain management, but also with psychosocial and functional disruption, the assessment of each of these domains should be addressed routinely so as to enable early detection and treatment.¹²¹ Women also should be educated regarding common post-mastectomy sequelae and the many available treatment options. Indeed, absent education, an unfortunate number of women are exposed to the pernicious effects of PPMP because they are unaware of available treatment options.⁹³ When considering those options, generally, non-pharmacological strategies should be considered prior to or in conjunction with drug therapy. Table 2 provides treatment options targeted to specific clinical issues. These are listed in order of consideration, based upon guidelines found in the literature.^{51,79,138}

Physical therapy

Physical therapy is an integral part of the management of PPMP, especially to preserve glenohumeral and scapulothoracic movement, strength, and normal neuromuscular recruitment patterns, and to minimize upper extremity dysfunction.³⁵ Clinical practice guidelines generally recommend initiation of physical therapy the day after surgery, with gentle range of motion exercises progressing to active stretching once surgical drains are removed, followed by strengthening over 6–8 weeks until full upper extremity range of motion is achieved.⁷⁷ A systematic review provided empirical support for these guidelines:⁴⁴ multimodal interventions consisting of stretching and active exercises,^{37,92} as well as active exercises alone,^{19,23} were shown to be effective in improving shoulder range of motion and decreasing postoperative pain. Patients who underwent physical therapy also had improved upper extremity function and quality of life 3–6 months after completing therapy compared to those who were only given information about exercise.^{19,37}

Although there is good evidence supporting the early implementation of physical therapy following breast surgery, the optimal timing for initiation of physical therapy continues to be investigated. Several studies have reported increased complications in ALND patients who initiated physical therapy within the first week relative to those who delayed treatment: early treatment was associated with increased drainage¹⁵⁹ and increased incidence of seroma formation.^{1,147} Nonetheless, ALND patients who initiated physical therapy early had better 2 year outcomes for upper extremity range of motion.¹⁸

One patient group that demonstrates clear benefit from early intervention involves those experiencing pain secondary to lymphedema. Depending on its stage, lymphedema may require intervention with physical therapy, occupational therapy, or a combination of therapies that target the reduction of swelling. Treatments to address lymphatic system insufficiency include use of compression bandages or sleeve-and-glove compression garments, manual lymph drainage, lymph- reducing exercises, and skin care.^{57,116} Compression garments, worn during the day and sometimes at night, reduce the flow of lymph back into the interstitial space. Manual lymph drainage can offer additive benefit to the use of compression garments, although it can be time intensive and require specialized training. While some studies support individualized exercise programs as a way to stimulate lymph flow and improve functional outcomes,^{142,143} a recent meta-analysis of 25 studies did not find evidence to support an exercise effect for lymphedema or lymphedema-related symptoms, such as pain, heaviness, and tightness.¹⁴⁸ On the other hand, the study found no evidence of harm from exercise, either, so the functional benefits typically derived from exercise may be sufficient to justify an exercise intervention. Appropriate skin hygiene and care is necessary to reduce the risk of skin infection; lymph fluid has high protein content, an ideal environment for bacterial growth. Keeping skin adequately moisturized to protect from skin tears is important, as is the use of low- pH soaps and pH-neutral creams or lotions.⁵⁷

Aside from the functional benefits described above in the post-operative phase of treatment, physical therapy and exercise-related interventions have been shown to benefit survivors who have concluded active cancer treatment. A meta-analysis and review of 56 studies showed that exercise interventions yielded effect sizes (ES) reflecting significant benefits for cancer survivors:⁵² fatigue (ES = -0.315, 95% CI = -0.532–0.098, $p = .004$), depression (ES = -0.262, 95% CI = -0.476–0.049, $p = .016$), body image (ES = 0.280, 95% CI = 0.077–0.482, $p = .007$), and quality of life (ES = 0.298, 95% CI = 0.117–0.479, $p = .001$). For survivors experiencing severe dysfunction the benefits of exercise may be more substantial: a recent study showed that group exercise yielded larger, positive effects for patients whose baseline levels of function were low, as well as those exposed to more aggressive forms of cancer treatment.⁸⁷ Such results suggest that providers should consider a course of exercise-based therapy for those patients who exhibit persistent functional interference beyond the active phase of treatment.

Psychological therapies

Because breast cancer survivorship often involves coping with a complex combination of physical, psychological, and social co-morbidities, it is not surprising that psychological

interventions have been studied extensively. Although the research generally lacks high levels of methodological rigor, it consistently shows that cognitive behavioral techniques, whether delivered individually, in groups, or in some combination thereof, provide moderate benefits for depression, anxiety, and coping skills relative to patients receiving standard care.⁸⁴

Self-management strategies form the core of the psychological interventions that have been studied in PPMP. Typically, self-management programs involve some combination of group and individual formats. Most share some or all of the following features:^{22,68} 1) an educational element (often involving group-based instruction); 2) a cognitive restructuring component that is aimed at modifying thought processes so as to reduce distress and enhance problem-solving; 3) coping skills training (e.g., pacing strategies, communication skills); 4) relaxation training (e.g., hypnosis, mindfulness-based stress reduction);¹⁰² and 5) explicit attention to the generalization of training to the home environment, typically delivered both during active training (e. g., through the use of diaries) and in follow up to that training.

There is significant variability in the format for self-management training. For example, the internet has been used as a medium to deliver low-resource interventions:¹²³ educational materials were posted for participants to access, as was a discussion room and a chat board. Interestingly, the intervention proved to be of interest primarily for patients interested in its social networking element. Most psychosocial interventions, however, involve more labor intensive combinations of group and/or individual training. Evidence from these studies suggests that they yield modest but durable benefits. For example, a meta-analysis of 34 studies involving 4,199 patients with various cancers found moderate average effect sizes (ES) for various psychosocial interventions on pain severity (ES = 0.34, 95% CI = 0.23–0.46, $p < .001$) and pain interference (ES = 0.40, 95% CI = 0.21–0.60, $p < .001$).⁷² Meta-analytic support is also found specifically for breast cancer patients: an analysis of 26 studies involving 1,786 patients found a robust effect for reductions in reported pain severity (Hedges $g = 0.37$, 95% CI = 0.20–0.40, $p < .001$),⁸⁶ while another found benefits of behavior therapies for fatigue (ES = -0.158 , 95% CI = -0.233 – 0.082 , $p < .001$), depression (ES = -0.336 , 95% CI = -0.482 – 0.190 , $p < .001$), anxiety (ES = -0.346 , 95% CI = -0.538 – 0.154 , $p < .001$), and stress (ES = -0.159 , 95% CI = -0.310 – 0.009 , $p = .038$).⁵²

More focused attention has been given to several specific psychosocial interventions, hypnosis and mindfulness-based meditation. Research on hypnosis has been somewhat limited—a systematic review found only three RCTs involving PPMP patients, of which two reported significantly greater reductions in pain associated with hypnosis relative to a comparison group.⁴³ While more studies have examined mindfulness-based interventions in women with breast cancer (10 studies, 1,709 patients),⁷⁵ the sample included patients at many different cancer stages and treatment phases, and none of the studies included pain severity as a primary outcome variable (studies examined anxiety, depression, and quality of life outcomes). On the other hand, a meta-analysis of mindfulness-based interventions involving 25 studies and 1,285 patients with chronic pain, did find evidence supporting small-to-moderate effects of such interventions on pain severity and pain-related interference.¹⁶⁰ Hence, although the results of the PPMP meta-analysis are unclear relative

to the latter variables, there is reason to expect moderate benefits for pain and interference, as well as quality of life, for PPMP patients.

Pharmacologic management

Pharmacological approaches to PPMP fall into two broad categories. The first, an area of high research activity in recent years, involves preemptive analgesia protocols that target reducing the severity of acute post-operative pain and, subsequently, the development of a chronic pain condition. The second category involves management of existing PPMP conditions. The following sections address each of these categories.

Pre-emptive analgesia

Because postoperative pain remains poorly managed,⁶⁶ a large number of studies have looked at preemptive strategies targeting pain reduction. Relative to the effects on post-operative acute pain, the evidence is encouraging. For example, a recent systematic review of 84 studies examining various pre-emptive medication regimens for women undergoing hysterectomy found strong evidence supporting improved post-operative pain control associated with a number of medications:¹⁵² paracetamol, rofecoxib, gabapentin, ketamine, morphine, and fentanyl. A meta-analysis focusing specifically on six studies involving 452 patients who received perioperative pregabalin for acute post-hysterectomy pain control was similarly encouraging:¹⁷¹ relative to controls, pre-treated patients reported lower levels of pain severity (a weighted mean difference—WMD—of -6.20 mm on 0–100-point scales, 95% CI $= -11.83$ – 0.58 , $p = 0.03$), as well as lower opioid requirements (WMD $= -8.50$ mg of morphine equivalent, 95% CI $= -11.29$ – 5.71 , $p < 0.00001$). A meta-analysis of eight randomized controlled trials of 516 mastectomy patients that involved gabapentin and four (209 patients) that involved pregabalin also demonstrated effective acute post-operative pain control.¹³³ On a 0–10 numeric scale, preoperative gabapentin reduced recovery room pain scores by 1.68 points (95% CI $= -2.59$ – 0.77 , $p < 0.001$) and pain at 24 hours post-surgery by 0.52 points (95% CI $= -1.02$ – 1.01); no such reduction was found for pregabalin, although data from only two studies could be pooled for that analysis.

The evidence for mitigating chronic pain following surgery, however, is much more mixed. Indeed, several meta-analyses of the broad surgical literature have yielded conflicting results. An initial systematic review of 11 trials (8 studying gabapentin, 3 pregabalin) showed promising results:^{38,40} four of the gabapentin trials found reductions in the incidence of pain two or more months post-surgery, while all three of the pregabalin trials did so. A subset of these studies (six gabapentin trials, two pregabalin trials) had sufficient data to support a meta-analysis, which showed a moderate reduction in the risk of chronic pain for gabapentin (OR $= 0.52$, 95% CI $= 0.27$ – 0.98 , $p = 0.04$) and a larger reduction for pregabalin (OR $= 0.09$, 95% CI $= 0.02$ – 0.79 , $p = 0.007$).

More recent meta-analyses have not been so positive. A Cochrane review reported a meta-analysis that looked more broadly at 40 published and unpublished clinical trials of differing perioperative medication interventions:³⁴ ketamine (14 trials), gabapentin (10 trials), pregabalin (five trials), corticosteroids (three trials), ibuprofen (two trials), mexilitine (two trials), and various other drugs (four trials). Among these interventions, only ketamine

showed some evidence of benefit; at 6-month follow-up, the data suggested that the incidence of chronic pain was reduced relative to controls (55/285 versus 79/231; OR = 0.50, 95% CI = 0.33–0.76), although methodological considerations tempered that finding. Another meta-analysis of 18 studies and 1,884 patients examined the perioperative administration of pregabalin:¹¹⁰ it found no evidence to support a reduced risk of chronic pain incidence at three months post-surgery (RR = 0.87, 95% CI = 0.66–1.14). Similar results were reported for a meta-analysis that looked at both gabapentin and pregabalin:¹³³ despite the benefits reported for the reduction of acute postoperative pain, none were found for patients followed two or more months after surgery (OR for gabapentin = 0.47, 95% CI = 0.15–1.53, *p* = 0.21; OR for pregabalin = 0.23, 95% CI = 0.02–2.80, *p* = 0.25).

The disconnection between the effectiveness of pre-emptive analgesia for acute versus its lack of effectiveness for chronic pain indications is striking and disconcerting, especially given data cited earlier showing that the severity of post-operative pain is a proven risk factor for chronicity. A number of factors have been cited as possible reasons for the discrepant outcomes:⁷⁰ 1) ectopic nerve discharges from neuroma formation; 2) sensitization of peripheral nerves; 3) sensitization at spinal and supraspinal sites; 4) central nervous system inflammation (e.g., from proliferation of microglia); 5) musculoskeletal changes after surgery; 6) impaired inhibitory modulation of sensory nerves; and 7) enhanced facilitatory modulation through both peripheral and central mechanisms. The multiplicity of potential mechanisms, alone and in combination, is likely to reduce the benefits of any monotherapy, such as those described above, relative to more personalized approaches to treatment.

Persistent pain

As noted above, the identification of optimal approaches to pharmacotherapy is complicated by the multiplicity of potential contributing nociceptive factors, as well as the heterogeneity and variable quality of existing studies, conflicting data regarding benefits, side effect profiles, and drug interactions.¹²² Nonetheless, several general guidelines do apply to effective pharmacologic management: 1) it requires a thorough patient assessment to identify the various factors associated with pain and dysfunction; 2) therapy should target multiple contributing factors, when possible (e.g., venlafaxine and duloxetine can treat depression, anxiety, musculoskeletal pain and neuropathy);^{62,65,150} and 3) pharmacotherapy may be a useful adjuvant to nonpharmacological strategies.

Of course, all pharmacological approaches require consideration of side effect profiles, drug-drug interactions, and drug-disease complications, so that dose titration is likely to inform both initiation and discontinuation. Table 3 describes a range of drug-specific considerations that should be weighed when initiating pharmacotherapy.

Although PPMP encompasses multiple pain mechanisms, a neuropathic element is not only common, but it carries a particularly high disease burden.¹¹ Hence, it is important for practitioners who follow PPMP patients to be familiar with the pharmacological approaches to its treatment. While a thorough review of the literature is beyond the scope of this paper (readers are referred to a recent systematic review and meta-analysis),⁶¹ data relevant to

recommended first, second, and third line treatments are presented in Table 4. The latter recommendations take into account several factors: 1) the number needed to treat (NNT) to realize a treatment effect relative to placebo; 2) the methodologic quality of the studies; 3) the number of patients enrolled in the selected trials; and 4) side effect and other treatment-related complications.

Some commentary is in order regarding the use of opioids. While they are often prescribed perioperatively to manage acute, nociceptive post-surgical pain, limited data support the long-term use of opioids for chronic pain, especially pain of a neuropathic nature.^{36,124} If long-term opioids are used, patients should be monitored carefully in order to comply with recent guidelines offered by the Centers for Disease Control.⁵⁰ Moreover, if used long-term, providers should be sensitive to potential complications such as misuse, cognitive impairment, endocrinopathy, and immunological changes.^{36,124}

Multidisciplinary treatment

For the most part, studies are lacking that evaluate the benefits of multidisciplinary care for chronic postsurgical pain (including PPMP), despite evidence cited earlier in this manuscript that demonstrates consistent, moderate benefits associated with elements that are common in such interventions (e.g., exercise and psychosocial interventions). While there is strong evidence that multidisciplinary treatment for chronic pain is more effective than standard medical treatment,¹⁴¹ there is a need for more studies that target multidisciplinary treatment of post-surgical pain, including PPMP.¹⁶⁹

An exception to the above comments involves recent work on the development of a transitional pain service (TPS) as a model of post-operative care. The TPS model involves pain physicians, nurse practitioners, psychologists, pharmacists, and physical therapists who function as a team to improve pain management post-surgery and post-discharge, to reduce opioid use in the post-discharge phase, and to reduce the risk of developing chronic post-surgical pain.^{39,82} The service follows selected post-surgery patients in the hospital who report intense pain more than four days post-operatively, as well as patients discharged with prescriptions for long-acting opioids, patients admitted on methadone or buprenorphine, and others with complex pain conditions.⁴⁰ Because the TPS model was only developed recently, data supporting its effectiveness have yet to be reported. Nonetheless, given the relative risk of PPMP described previously, a strong argument could be made for considering such a service for post-mastectomy patients.

Discussion

Clearly, numerous advances have been made in our understanding of risk factors for PPMP, as well as its physical, psychosocial, and functional sequelae. One of these advances has been the identification of ALND as a risk factor for PPMP. Consequently SLND has become the standard of care for assessing metastatic disease. Another involves pre-emptive approaches to reducing acute post-surgical pain severity, yielding persuasive evidence that a range of medication regimens can be effective. Several other areas stand out, however, where opportunities exist for further advances.

While yet to yield a treatment pathway, one area of significant advance and opportunity involves our understanding preoperative factors that confer added risk for PPMP. Multiple studies have shown that pre-existing pain, especially at the surgical site, is a robust predictor of PPMP, as is severe post-operative pain.^{7,26,99,118,164} The latter work has yielded a proposed risk index for PPMP that is constituted of four risk factors: ALND, preoperative pain in the operative area, severe acute postoperative pain, and a high body mass index.¹¹⁷ The model, derived from a Finnish sample, demonstrates promising sensitivity and specificity when applied retrospectively to mastectomy patients from Denmark (N = 453) and Scotland (N = 231). Prospective studies of this index are needed to test the predictive utility of the model.

Of course, the latter risk index does not include psychological predictors, despite studies that suggest that preoperative psychological factors (e.g., anxiety, depression, pain catastrophizing) constitute an increased risk for PPMP,^{3,112,119,145} possibly through a common pathway that reflects “pain sensitivity” and vulnerability to PPMP.^{89,172} Nor does the model include “psychological robustness,” a function of optimistic attitudes, positive affect, and low levels of emotional distress, that may protect against PPMP.²⁶ Nonetheless, these psychological variables have sufficient empirical support to merit consideration when assessing a patient’s vulnerability to PPMP.

Despite the lack of proven predictive models, the available literature suggests that preoperative pharmacological (e.g., duloxetine) and psychological (e.g., coping skills training) interventions, each aimed at reducing pain sensitivity among vulnerable patients, may mitigate PPMP risk. High sensitivity patients, patients with preoperative pain at the operative site, and patients scheduled to undergo mastectomy with ALND might receive training to strengthen problem solving capacities or another psychological intervention (e.g., mindfulness training, self-hypnosis) to enhance pain coping skills, alone or in combination with a pharmacological agent,. Those patients, as well as other patients who experience intense post-operative pain, also might benefit from enhanced post-operative follow-up, possibly through a mechanism such as an acute pain service¹⁶⁶ or a TPS-like, post-discharge service focused on reducing the risk of developing chronic pain and opioid use.

The preceding pages also have described enormous perioperative efforts aimed at reducing the severity of post-operative pain and, potentially, the risk of subsequent development of chronic pain. The evidence relative to the inhibition of chronic pain is mixed, with several meta-analyses that have found only weak evidence that supports that approach, despite its obvious value for reducing acute pain. Of course, it is likely that persistent post-surgery pain is a phenomenon mediated through multiple mechanisms,^{70,114} so it is possible that multimodal pharmacologic perioperative interventions may yield more promising results than suggested by the current literature.

On the other hand, it may be that PPMP and other chronic post-surgical pain conditions are not consistently associated with histological or biochemical mediators, but are predicted, instead, by clinical markers.¹¹¹ If so, increased attention is needed to patient centered care aimed at “secondary prevention,” reducing the negative impacts of PPMP on mood, function, and quality of life. While several approaches seem to have promise for patients

with established PPMP,¹⁰⁰ a surgical procedure, autologous fat grafting, has yielded particularly interesting results: patients have reported reductions in pain severity of 3.2 points on a 0–10 scale, reductions that persisted over a 13-month follow up.³³ While not so dramatic, the benefits of rehabilitative, psychosocial, and pharmacologic interventions for various PPMP sequelae are well established, although increased attention is needed to their multidisciplinary implementation. Further, the timeliness of interventions to address the physical, psychological, and functional sequelae of PPMP also needs attention. Evidence from the occupational medicine literature suggests that treatment effectiveness is likely to be greater if interventions are initiated early, rather than long after pain onset.⁶³

We would be remiss if we did not also comment on issues related to health disparities, a broad societal issue and one with particular implications for PPMP. Because breast cancer is diagnosed at a later stage for minorities than for white Americans and often requires more extensive surgery, minorities also are at higher risk of developing PPMP.⁷ Such data point to the need for increased engagement with minority communities so that women are educated to the need for early identification and timely treatment of breast cancer and present for care at earlier stages of the disease.¹³⁰

In summary, while considerable progress has been made, especially in identifying factors that constitute vulnerability to PPMP and to the sequelae commonly associated with PPMP, much work remains if the incidence of this disorder and its adverse sequelae are to decrease. Not surprisingly, such gains are likely to require further research into factors that contribute to risk and/or protect against its development. Equally important, significant efforts should be made to educate the provider community about the range of options that can be arrayed so that appropriate interventions are initiated in a timely manner and quality of life of cancer survivors is optimized. Educational efforts also should be directed at the community at large, not only to promote the early identification and treatment of breast cancer so as to reduce mortality, but also to enhance the quality of life of those who survive.

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Table 1.**Persistent Post-Mastectomy Pain: Common Characteristics**

ELEMENT	CHARACTERISTICS
Distribution	Axilla, breast/chest wall, medial upper extremity
Descriptors	Shooting, stabbing, pulling, tight, burning, aching
Exacerbating factors	Movement, straining, overhead activity, cold weather
Potential mechanisms	Neuropathy, lymphedema, neuromuscular, mechanical
Comorbidities	Disability, quality of life, emotional distress

Table 2.

Symptom-Specific Treatment Strategies for PPMP

	NON-PHARMACOLOGICAL	PHARMACOLOGICAL *
Lymphedema	Weight loss (if necessary) Physical and/or occupational therapy Lymphedema specialist Surgery (for severe, refractory cases)	None
Depression & Anxiety	Cognitive Behavior Therapy Hypnosis Mindfulness-based therapies Meditation (e.g., yoga)	Selective serotonin-norepinephrine reuptake inhibitors (SNRIs) - e.g., duloxetine, venlafaxine extended-release Selective serotonin reuptake inhibitors (SSRIs) - e.g., escitalopram, paroxetine
Fatigue	Referral to mental health resource Treat other contributing factors (e.g., anemia, thyroid dysfunction, etc.) Encourage physical activity as tolerated or consider yoga	
Pain & Neuropathy	Encourage physical activity as tolerated Massage therapy Acupuncture	Acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs) Duloxetine (for neuropathy) Opioids generally not recommended
Sexual Health	Nonhormonal water-based lubricants Moisturizers for vaginal dryness Psychoeducational support (e.g., group therapy, sexual or marital counseling, etc.)	
Premature Menopause	Lifestyle and environmental modifications	Selective serotonin-norepinephrine reuptake inhibitors (SNRIs) - e.g., venlafaxine, desvenlafaxine Selective serotonin reuptake inhibitors (SSRIs) - e.g., paroxetine Gabapentin, pregabalin

* With consideration of convenience of use, cost, side effects and drug-drug, drug-disease interactions

Table 3.**Drug-Specific Considerations^{#103}**

AGENT	STATUS	TOLERABILITY/SIDE EFFECTS	MAJOR DRUG-DRUG INTERACTIONS	DRUG-DISEASE CONSIDERATIONS
Acetaminophen	Over-the-counter	Well tolerated within dosing limits		
Non-steroidal antiinflammatory drugs (NSAIDs)	Over-the-counter	Well tolerated within dosing limits	Increased bleeding risk with anticoagulants	
Selective serotonin-norepinephrine reuptake inhibitors (SNRIs)	Prescription	Possibly better tolerated than SSRIs but drug specific	Some are inducers, inhibitors or substrates of CYP pathways which enhance or reduce metabolism of applicable drugs May enhance effect of anticoagulants	Can elevate heart rate and blood pressure May cause or exacerbate sexual dysfunction
Selective serotonin reuptake inhibitors (SSRIs)	Prescription	Not well-tolerated overall	Some are inducers, inhibitors or substrates of CYP pathways which enhance or reduce metabolism of applicable drugs May enhance effect of anticoagulants	May cause or exacerbate sexual dysfunction
Gabapentin/Pregabalin	Prescription	Not well-tolerated (somnolence, sedation, peripheral edema, dizziness); dose at bedtime	Additive to other drugs that suppress the CNS (e.g., alcohol, opioids)	
Opioids	Prescription	Not well-tolerated (pruritus, sedation, constipation, risk of misuse/abuse)	Additive to other drugs that suppress the CNS (e.g., alcohol, gabapentin). Avoid concomitant use of benzodiazepines.	

* Consult with a pharmacist for full evaluation of considerations of any particular drug

Table 4.

Drugs or drug classes with strong or weak recommendations for treating neuropathic pain, based on the GRADE classification⁶¹

	TOTAL DAILY DOSE AND DOSE REGIMEN	NUMBER NEEDED TO TREAT (95% CI)	RECOMMENDATIONS
Strong recommendations for use			
Gabapentin	1200–3600 mg, in three divided doses	7.2 (5.9–9.1)	First line
Gabapentin extended release or encarbil	12–3600 mg, in two divided doses	7.2 (5.9–9.1)	First line
Pregabalin	300–600 mg, in two divided doses	7.7(6.5–9.4)	First line
Serotonin-noradrenaline reuptake inhibitors (duloxetine or venlafaxine)	60–120 mg, once a day (duloxetine) 150–225 mg, once a day (venlafaxine extended release)	6.4 (5.2–8.4)	First line
Tricyclic antidepressants	25–150 mg, once a day or in two divided doses	3.6 (3.0–4.4)	First line
Weak recommendations for use			
Capsaicin 8% patches	One to four patches to the painful area for 30–60 min every 3 months	10.6(7.4–18.8)	Second line (peripheral neuropathic pain)
Lidocaine patches	One to three patches to the region of pain once a day for up to 12 h	Insufficient data	Second line (peripheral neuropathic pain)
Tramadol	200–400 mg, in two (tramadol extended release) or three divided doses	4.7 (3.6–6.7)	Second line
Botulinum toxin A (subcutaneously)	50–200 units to the painful area every 3 months	1.9 (1.5–2.4)	Third line; Third line; specialist use (peripheral neuropathic pain)
Strong opioids	Individual titration	4.3 (3.4–5.8)	Third line