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"Post Mastectomy Pain Syndrome: A Systematic Review of Prevention Modalities"

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ABSTRACT

Background: Post-mastectomy pain syndrome (PMPS) is a surgical complication of breast surgery characterized by chronic neuropathic pain. The development of PMPS is multifactorial and research on its prevention is limited. The objective of this systematic review is to synthesize the existing evidence on interventions for lowering the incidence of persistent neuropathic pain after breast surgery.

Methods: Using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, we performed a comprehensive search of the electronic databases of MEDLINE, Cochrane Library, Embase, CINAHL, PsycINFO, Web of Science, and ClinicalTrials.gov using a combination of database-specific controlled vocabulary and keyword searches. Two reviewers independently screened all unique records. Publications on chronic (>3-month duration) pain after breast cancer-related surgery were included. Studies were classified by modality.

Results: Our literature search yielded 7092 articles after deduplication. We identified 45 studies that met final inclusion criteria for analysis, including 37 randomized-controlled trials. These studies revealed seven major intervention modalities for prevention of

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PMPS: physical therapy, mindfulness-based cognitive therapy, oral medications, surgical intervention, anesthesia, nerve blocks, and topical medication therapy.

Conclusion: High-quality data on preventative techniques for PMPS are required to inform decisions for breast cancer survivors. We present a comprehensive assessment of the modalities available that can help guide breast and reconstructive surgeons employ effective strategies to lower the incidence and severity of PMPS. Our review supports the use of multimodal care involving both a peripherally targeted treatment and centrally acting medication to prevent the development of PMPS.

BACKGROUND

Persistent pain is a postoperative complication estimated to affect between 20% and 50% of mastectomy patients with considerable negative influence on quality of life.[1] Post-mastectomy pain syndrome (PMPS) is a neuropathic condition defined as pain located in the anterior surface of the chest axilla, shoulder or upper half of the arm that persists for longer than 3 months after surgery.[2,3] As treatment and diagnostic strategies advance, more women are expected to survive breast cancer, growing the population at risk for developing PMPS. Interventions are needed to prevent the development of this long-term, costly, and painful complication of breast cancer procedures.

The pathophysiology of PMPS involves unrelieved inflammation and neuropathic pain. Possible contributors include sensitization of peripheral nociceptors and their primary afferent neurons, growth of neuromas on pain-sensing fibers, and sensitization of nerve cells in the brain.[4] Further, severe acute postoperative pain results in increased incidence of persistent postoperative pain.[5,6] Consequently, preventive and perioperative forms of analgesia and pharmacological agents may reduce the development of, or transition to, PMPS.

Previous studies have reviewed associated risk factors for PMPS, including preoperative pain, axillary lymph node dissection (ALND), anxiety, younger age, and radiation therapy.[7,8] Pharmacotherapy for prevention of general chronic pain after surgery has also been a focus of literature.[4] However, a comprehensive review of interventions for the prevention of post-mastectomy neuropathic pain is lacking. In this study, we review the available modalities for prevention of the development of PMPS and assess their outcomes in order to guide optimal care for breast cancer patients.

MATERIALS AND METHODS

Our systematic review was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines as a framework to assess quality of evidence and risks of bias in the included studies.[9] The protocol was registered with the National Institutes of Health Research database PROSPERO (ID = CRD42020167225).

Literature search and Study Appraisal

A research librarian (ABW) worked in collaboration with the review authors (SY, AC) to create a comprehensive search for identifying literature related to the neuropathic pain associated with breast cancer surgery. A search was developed for MEDLINE (PubMed), which was then translated for Cochrane Library databases (Wiley), Embase (Elsevier), CINAHL (Ebsco), PsycINFO (Ebsco), Web of Science (Clarivate), and ClinicalTrials.gov. All searches were conducted using a combination of database-

Table 1
Inclusion and Exclusion Criteria for Abstract and Full-Text Screening

Inclusion criteria
Full-text, original articles
Written in the English language
Reporting outcomes for interventions to prevent chronic pain after breast cancer-related surgery
Observational studies (case-control studies and cohort studies)
Intervention studies, including RCTs
Exclusion criteria
Review articles
Case reports, case series, conference abstracts, book chapters, and letters to editor
Animal studies, cell studies, and cadaver studies
Articles with follow-up <3 months
Articles regarding only treatment of chronic postoperative pain

RCTs – randomized-controlled trials

specific controlled vocabulary and keyword searches without limits for date or publication type. English language filters were applied. Results were exported to a citation management software (EndNote) for deduplication. An example of the search strategy for PubMed is provided in **Appendix A**. References of eligible studies and review articles were reviewed to include studies not previously captured by the original search terms. To avoid selection bias, inclusion and exclusion criteria were agreed upon before data extraction and analysis (Table 1). Definition of the terms "chronic pain," and "breast cancer-related procedures" was critical in creating the selection criteria (**Appendix B**). All unique records were uploaded into an online screening platform (Rayyan) for blinded independent screening by two reviewers, first through title and abstract screen and then through full-text review[10]; disagreements were resolved by the senior author (MFE).

Data Extraction

Types of data extracted from each study included: (i) pain prevention modality, (ii) study design, (iii) number of patients, (iv) follow-up time, (v) outcome metrics, and (vii) major outcomes of intervention. Primary outcomes were limited to patient-reported pain characteristics, both quantitative and qualitative, and quality of life scores. Studies were organized based on thematic analysis of each pain prevention modality.

RESULTS

The initial literature search in the seven electronic databases yielded 7092 articles from the years 1946–2020 after deduplication. Following two rounds of screening, 45 studies fulfilled the eligibility criteria for inclusion, of which 37 were randomized-controlled trials (RCTs). Seven unique intervention modality groups were identified, with a range of reported outcomes (Table 2).

Physical Therapy

Two double-blinded RCTs evaluated the effects of physical therapy (PT) on incidence and severity of PMPS in women undergoing breast cancer surgery with ALND, with little effect.[11,12] The follow-up time in both studies was 12 months, and the total study population was 301 patients. Ammitzbøll et al. reported that a 1-year progressive resistance training program initiated at 3 weeks after breast cancer surgery with ALND conferred no benefit over usual care in reducing chronic pain incidence or intensity.[11] Similarly, an 8-week myofascial therapy program had no added benefit compared with standard PT.[12]

Cognitive Therapy

Two studies on the efficacy of cognitive behavioral therapy in the prevention of PMPS met inclusion criteria, one of which was an RCT.[13,14] The mean follow-up time for both studies was 26 months,

Table 2
Study characteristics of all included studies

Treatment Modality	Reference	Design, N (# of patients)	Intervention
Physical Therapy	Ammitzbøll et al., 2020[11]	Double-blinded RCT, 158	1-year progressive resistance training
	De Groef et al., 2010[12]	Double-blinded RCT, 143	8 sessions of myofascial therapy
Cognitive Therapy	Lacroix et al., 2019[13]	Prospective non-randomized study, 42	Perioperative hypnosedation
	Garssen et al., 2010[14]	RCT, 70	Pre-surgical stress management training
Nerve Blocks	Besch et al., 2010[19]	Retrospective comparative study, 191	GA with pectoral nerve block
	Fujii et al., 2018[20]	Double-blinded RCT, 80	PECS II Block
	De Cassai et al., 2019[18]	Prospective observational comparative study, 132	PECS II block
	Strazisar et al., 2014[15]	Prospective randomized study, 60	Wound catheter with continuous infusion of local anesthetic
	Mohamed et al., 2018[17]	Double-blinded RCT, 90	Wound irrigation with bupivacaine plus 5, 10, or 15 mg morphine
	Albi-Feldzer et al., 2000[16]	Double-blinded RCT, 236	Wound infiltration with repeated injections of local anesthetic
	Shimizu et al., 2015[23]	Retrospective cohort study, 46	Perioperative ultrasound-guided TPVB
	Karmakar et al., 2017[24]	Double-blinded RCT, 177	Single injection or continuous infusion with catheter of TPVB
	Kamal et al., 2019[25]	Double-blinded RCT, 80	TPVB of bupivacaine with 0.5 mg/kg or 1 mg/kg ketamine
	Kairaluoma et al., 2006[26]	Double-blinded RCT, 59	Pre-incisional PVB
	Elkaradawy et al., 2012[28]	RCT, 50	Ultrasound-guided TPVB with GA
	Ilfeld et al., 2018[27]	Double-blinded RCT, 60	Ultrasound-guided continuous PVB catheter
	Gacio et al., 2018[21]	Non-randomized prospective observational study, 66	GA and single-injection PVB
	Qian et al., 2019[22]	Double-blinded RCT, 184	Ultrasound-guided single-injection multilevel TPVB
Anesthesia	Cho et al., 2012[29]	Retrospective comparative study, 228	Propofol vs. sevoflurane anesthesia
	Lefebvre-Kuntz et al., 2015[32]	Prospective cohort study, 328	Halogenated anesthetic vs. propofol
	Grigoras et al., 2013[30]	Double-blinded RCT, 36	Perioperative IV lidocaine
	Terkawi et al., 2017[38]	Double-blinded RCT, 61	Intraoperative IV lidocaine infusion
	Kim et al., 2017[37]	Double-blinded RCT, 116	Intraoperative systemic lidocaine vs. magnesium
	Kendall et al., 2018[34]	Double-blinded RCT, 121	Perioperative IV lidocaine
	Khan et al., 2019*[35]	Double-blinded RCT, 100	Perioperative pregabalin and lidocaine infusion
	Jain et al., 2012[36]	Double-blinded RCT, 69	Intraoperative IV dexmedetomidine
	Kang et al., 2020[33]	Double-blinded RCT, 168	Perioperative IV ketamine
	Sun et al., 2012[31]	Double-blinded RCT, 60	Perioperative IV flurbiprofen axetil
Oral medications	Fassoulaki et al., 2002[39]	Double-blinded RCT, 67	Perioperative oral mexiletine vs. gabapentin capsules
	Lee et al., 2013[40]	Single-blinded RCT, 51	Multimodal analgesia (perioperative pregabalin and PVB catheter of local anesthetic)
	Vig et al., 2019[42]	Double-blinded RCT, 71	Perioperative pregabalin
	Reyad et al., 2019[43]	Double-blinded RCT, 181	Perioperative pregabalin
	Fassoulaki et al., 2001[44]	Double-blinded RCT, 96	Perioperative mexiletine and regional ropivacaine block

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Table 2 (*continued*)

Treatment Modality	Reference	Design, N (# of patients)	Intervention
	Amr et al., 2009[46]	Double-blinded RCT, 150	Perioperative gabapentin and venlafaxine
	Khan et al., 2019*[35]	Double-blinded RCT, 100	Perioperative pregabalin and lidocaine infusion
	Hah et al., 1996[45]	Double-blinded RCT, 41	Perioperative gabapentin
	Van Helmond et al., 2016[41]	Double-blinded RCT, 94	Perioperative parecoxib injection and celecoxib
	Fassoulaki et al., 2005[47]	Double-blinded RCT, 44	Multimodal analgesia (Gabapentin, EMLA cream near incision, irrigation of brachial plexus block)
	Na et al., 2018[48]	Double-blinded RCT, 83	Intraoperative IV nefopam
Surgical interventions	Salmon et al., 1998[55]	Double-blinded RCT, 128	Preservation of ICBN
	Torresan et al., 2007[51]	Double-blinded RCT, 85	Preservation of ICBN
	Freeman et al., 2003[53]	Double-blinded RCT, 73	Preservation of ICBN
	Taira et al., 2014[54]	Non-blinded RCT, 140	Preservation of ICBN
	Tasmuth et al., 1999[50]	Retrospective observational study, 221	High-volume surgical units vs. small-volume units
	Yang et al., 2012[52]	Double-blinded RCT, 99	Spray of HA–CMC gel onto surface of pectoralis major and serratus anterior muscles
Topical medications	Fassoulaki et al., 2000[56]	Double-blinded RCT, 45	Intraoperative EMLA on sternal area

***Included in two categories**
RCT – Randomized controlled trial
GA – Generalized anesthesia
TPVB – Thoracic paravertebral block
ICBN – Intercostal-brachial nerve
HA–CMC – Hyaluronic acid–carboxymethyl cellulose
IV – Intravenous

and the total study population was 112 patients. Lacroix et al. reported that in 42 patients undergoing mastectomy with ALND, perioperative hypnosedation led to significantly lower incidence of PMPS at 4 years postoperatively compared with general anesthesia (GA) ($P = 0.008$).[13] Pre-surgical stress management training (SMT) did not significantly influence postoperative pain or anxiety after 3 months compared with control.[14]

Nerve Blocks

Fourteen studies on the efficacy of perioperative nerve blocks in the prevention of PMPS met inclusion criteria (Table 3). [15–20] Eight of these were double-blinded RCTs, while the rest comprised two retrospective cohort studies, two prospective randomized studies, and two prospective observational comparative studies. The mean follow-up time across all studies was 8 months, and the total study population involved 1511 patients.

Wound infiltration with local analgesia, whether through continuous infusion with a wound catheter or through repeat injections, was ineffective across two double-blinded RCTs. [15,16] In a third study by Mohamed et al., higher doses of morphine for wound irrigation were more effective in decreasing intensity of chronic pain ($P < 0.006$).[17]

Three studies with a total of 403 patients investigated the utility of pectoral nerve blocks (PECS) in preventing chronic pain after breast cancer-related surgery. [18–20] While PECS administered with GA was ineffective, [19] the results of PECS II were equivocal; one study found its benefit versus GA to be limited to 3 months, and another found that it reduced incidence of moderate/severe chronic pain when compared to serratus plane block ($P = 0.02$).[18, 20]

Table 3
Nerve Block Studies

Reference	Procedure	Intervention	Follow-up (mo), Avg (Range)	Outcome measures	Findings
Besch et al., 2010[19]	Breast cancer surgery	Perioperative GA with pectoral nerve block	6	Presence of pain (Breast Cancer Pain Questionnaire), Pain intensity	Pectoral block had no effect on incidence nor severity of persistent post-surgical pain
De Cassai et al., 2019[18]	Mastectomy or lateral quad-rantectomy	PECS II block	12	Presence of pain, intensity of pain (NRS)	PECS II decreased incidence of chronic pain only for 3 months compared to GA alone (**P = 0.039**). It did not decrease pain intensity.
Fujii et al., 2018[20]	Mastectomy	PECS II block	6	Presence of pain, pain intensity (NRS), health-related QOL (EQ-5D-3L questionnaire)	PECS II reduced incidence of moderate and severe chronic pain compared to serratus plane block (**P = 0.02**).
Strazisar et al., 2014[15]	Breast cancer surgery with ALND	Wound catheter with continuous infusion of local anesthetic	6	Presence of pain	Infusion of local anesthetic did not significantly decrease incidence of neuropathic pain compared to standard IV analgesia (20% vs. 40%, P = 0.09)
Mohamed et al., 2018[17]	Modified radical mastectomy with ALND	Wound irrigation with bupivacaine plus 5, 10 or 15 mg morphine	3	Location, intensity, nature and duration of pain, analgesic medication use, LANSS Pain Scale	The lowest mean LANSS score was recorded in the Morphine 15 group compared with Morphine 5 and Morphine 10 (**P < 0.006**).
Albi-Feldzer et al., 2000[16]	Breast cancer surgery	Wound infiltration with repeated injections of local anesthetic	12	Presence of pain, pain intensity at rest and movement, pain interference (BPI), neuropathic pain (DN4)	Ropivacaine wound infiltration did not decrease chronic pain intensity or incidence.
Gacio et al., 2018[21]	Major resection for breast cancer Pain intensity at rest and with movement in ipsilateral arm (VAS), neuropathic pain (DN3), QOL (EORTC QLQ-C30)	Single TPVB injection Single-injection PVB had no effect on intercosto-brachial neuralgia (P = 0.3).	6		

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Table 3 (*continued*)

Reference	Procedure	Intervention	Follow-up (mo), Avg (Range)	Outcome measures	Findings
Kairaluoma et al., 2006[26]	Conservative breast surgery for cancer with SENTINEL lymph node biopsy	Single TPVB injection	12	Presence of pain, pain intensity at movement and rest (NRS), pain characteristics	PVB lowered pain incidence (**P = 0.003),** intensity at rest (**P = 0.011**) and movement (**P = 0.003**).
Shimizu et al., 2015[23]	Breast cancer surgery	Ultrasound-guided single TPVB injection	15 (13, 17)	Pain intensity (VRS)	TPVB significantly lowered incidence of chronic pain (**P = 0.039**).
Karmakar et al., 2017[24]	Modified radical mastectomy with ALND	Single injection or continuous infusion with catheter of TPVB	6	Incidence of pain, pain severity (VRS) at rest and during movement, health-related QOL, Chronic Pain Symptom and Sign Score	No difference in incidence of chronic pain between groups (P = 0.79). Patients receiving TPVB had lower chronic pain scores (**P < 0.05)** and had fewer symptoms of chronic pain (**P ≤ 0.01).**
Elkaradawy et al., 2012[28]	Conservative breast surgery for cancer	Ultrasound-guided TPVB with GA	9	Neuropathic pain (NPS), Pain intensity (NRS)	TPVB decreased pain intensity **(P ≤ 0.05)**.
Ilfeld et al., 2018[27]	Uni- or bilateral mastectomy	Ultrasound-guided continuous PVB catheter	12	Presence of pain, pain intensity and interference (BPI)	PVB catheter significantly decreased incidence (**P = 0.011**) and intensity of pain (**P = 0.007**).
Qian et al., 2019[22]	Unilateral partial mastectomy	Ultrasound-guided single-injection multilevel TPVB	6	Presence of pain, pain intensity and interference (BPI)	PVB significantly reduced severity (**P < 0.001**). and incidence **(P = 0.03**) of chronic pain.
Kamal et al., 2019[25]	Modified radical mastectomy and ALND	Ultrasound-guided multilevel TPVB with 0.5 mg/kg or 1 mg/kg ketamine	3	DN4 questionnaire for chronic neuropathic pain	No difference in mean DN4 scores between control, 0.5 mg/kg and 1 mg/kg ketamine (P = 0.132)

NRS – Numerical rating scale
QOL – Quality of life
LANSS- Leeds Assessment of Neuropathic Symptoms and Signs
BPI – Brief Pain Inventory
DN4 – Douleur neuropathique 4
TPVB – Thoracic paravertebral block
VAS – Visual analogue scale
DN3 – Douleur neuropathique 3
VRS – Verbal rating scale

Eight studies with a total of 722 patients investigated the effects of thoracic paravertebral blocks (TPVBs) on reducing chronic pain after breast cancer.[21–28] Five of these studies used ultrasound guidance for TPVB administration. While one study found no effect on intercostobrachial neuralgia, [21] six studies found that TPVBs reduced incidence and intensity of chronic pain. Single injection versus continuous infusion with a catheter did not differ in efficacy. [24] Ketamine administration with TPVB had no effect.[25]

General Anesthesia

Ten studies on the efficacy of anesthesia in the prevention of PMPS met inclusion criteria (Table 4).[29–38] These included one retrospective study, one prospective study, and eight double-blinded RCTs. The mean follow-up time for all ten studies was 9 months, and the total study population was 1287 patients.

A retrospective study found that incidence of chronic pain was significantly higher in the sevoflurane anesthesia group compared with the propofol anesthesia group ($P = 0.007$).[29] However, a multicenter prospective study by Lefebvre-Kuntz et al. with a greater sample size found no difference between propofol and other halogenated agent anesthetics.[32] Neither study found an effect of anesthesia type on pain intensity.

Across five studies, intravenous (IV) lidocaine infusion significantly decreased chronic pain incidence, intensity, or both.[30,34,35,37,38] Pregabalin and magnesium were both comparatively ineffective. [35,37]

The remaining three studies in this cohort investigated several other anesthetic agents. Intraoperative low-dose ketamine reduced pain incidence at 3 months postoperatively compared with a control, but these results did not continue through 6 months.[33] IV flurbiprofen axetil significantly decreased both incidence of pain and pain scores at 6 months postoperatively compared with a control.[31] Perioperative infusion of dexmedetomidine significantly decreased the incidence and intensity of chronic pain.[36]

Oral Medications

Eleven RCTs regarding the efficacy of oral medications met inclusion criteria (Table 5).[37,39–48] Of these, ten were double-blinded RCTs. Across all studies, the mean follow-up time was 5 months, and there were 978 total patients.

Four studies testing the efficacy of gabapentin showed negative results, whether it was administered alone, with another medication, or as part of a multimodal analgesia course.[39,45–47] Four studies evaluated the efficacy of pregabalin.[37,40,42,43] While it had no effect on incidence or intensity of chronic pain in three studies, Reyad et al. found that the medication decreased both incidence and intensity of chronic pain at 6 months postoperatively.[43]

Various other medications had mixed results in reducing PMPS incidence. Mexiletine and COX2 inhibitors were both ineffective, while venlafaxine, a selective serotonin and norepinephrine reuptake inhibitor (SSNRI), significantly reduced incidence and intensity of chronic pain at 6 months postoperatively.[41,44,46,49] Preventative IV nefopam significantly decreased the incidence, but not intensity, of chronic pain.[48]

Surgical Techniques

Six articles focusing on the potential role of surgical techniques in prevention of chronic neuropathic pain after breast cancer-related surgery were included (Table 6).[50–55] These consisted of four double-blinded RCTs, one non-blinded RCT, and one retrospective observational study. Across all studies, the mean follow-up time was 16 months and a total of 746 patients were included.

Preservation of the intercostal-brachial nerve (ICBN) was discussed in four RCTs. [51,53–55] Three of these studies concluded that preserving the ICBN conferred no significant differences in incidence or intensity of chronic pain. [53–55] However, Torresan et al. found that ICBN preservation decreased overall incidence of anesthesia, hypoesthesia, or hyperesthesia. [51]

Table 4
Anesthesia Studies

Reference	Procedure	Intervention	Follow-up (mo), Avg (Range)	Outcome measures	Findings
Cho et al., 2012[29]	Breast cancer surgery	Propofol vs. sevoflurane anesthesia	39 (30, 48)	Presence of pain, pain intensity (NRS), pain interference with daily life	Sevoflurane resulted in higher incidence of chronic pain compared to propofol (**P = 0.007**), but not pain intensity.
Lefebvre-Kuntz et al., 2015[32]	Breast cancer surgery	Propofol vs. halogenated anesthetic	6	Presence of pain, Neuropathic pain (DN4, Neuropathic Pain Symptom Inventory), pain intensity (VAS),	Type of general anesthetic had no effect on incidence nor intensity of pain.
Grigoras et al., 2013	Mastectomy or wide local excision with ALND	IV lidocaine infusion	3	Presence of pain, intensity of pain (SF-MPQ, VAS) character of pain, interference with daily life	Lidocaine resulted in lower pain incidence (**P = 0.031**) and intensity (**0.025**) compared to control.
Terkawi et al., 2017[38]	Mastectomy	IV lidocaine infusion	6	Presence of pain, pain intensity (NRS), pain characteristics	Lidocaine was associated with a 20-fold decrease in incidence of CPSP compared to control (**P = 0.013**).
Kim et al., 2017[37]	Breast cancer surgery	Systemic lidocaine infusion vs. magnesium	3	Presence of pain, pain intensity and quality (Korean SF-MPQ)	Lidocaine significantly decreased pain intensity compared to control (**P = 0.046**), but had no effect on chronic pain incidence. Magnesium had no effect.
Kendall et al., 2018[34]	Breast cancer surgery	IV lidocaine infusion	6	Presence of pain, pain intensity (NRS, BPI, SF-MPQ), neuropathic pain (S-LANSS)	Lidocaine reduced pain incidence (**P = 0.04**) compared to control and had no effect on intensity.
Khan et al., 2019*[35]	Unilateral or bilateral mastectomy or lumpectomy	Perioperative pregabalin and lidocaine infusion	3	Presence of pain, pain intensity (BPI, SF-MPQ2), neuropathic pain (DN4)	Lidocaine decreased incidence of persistent neuropathic pain (**P = 0.049**) compared to control, but not intensity. Pregabalin had no effect.
Sun et al., 2012[31]	Mastectomy with ALND	Perioperative IV flurbiprofen axetil	12	Presence of pain, pain intensity (NRS), nature of pain	Flurbiprofen axetil resulted in lower pain incidence for 6 months postoperatively, but not 12 months. It significantly lowered pain intensity (**P < 0.05**).
Kang et al., 2020[33]	Unilateral breast cancer surgery	IV ketamine	6	Presence of pain, pain intensity at rest and movement (NRS), Neuropathic pain (DN4)	Ketamine did not reduce pain intensity compared with control. Pain incidence was lower at 3 months, but not 6.

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Table 4 (*continued*)

Reference	Procedure	Intervention	Follow-up (mo), Avg (Range)	Outcome measures	Findings
Jain et al., 2012[36]	Breast cancer surgery	IV dexmedetomidine	3	Presence of pain, pain intensity (BPI, SF-MPQ2)	Dexmedetomidine decreased pain intensity (**P < 0.001**) and incidence (**P < 0.001**) compared with control.

NRS – Numerical rating scale
DN4 – Douleur neuropathique 4
VAS – Visual analogue scale
SF-MPQ – Short-form McGill Pain Questionnaire
BPI – Brief Pain Inventory
S-LANSS – Self-administered Leeds Assessment of Neuropathic Symptoms and Signs
QOL – Quality of life
IV – Intravenous

A mixed solution of sodium hyaluronate and carboxymethylcellulose (HA–CMC) on the surface of the pectoralis major and serratus anterior muscles resulted in significantly lower pain intensity related to flexion and horizontal abduction at 6 months postoperatively. [52] According to an observational study, pain at 1 year was less common in patients receiving breast cancer surgery at high-volume surgical units than low-volume ones ($P < 0.05$).[50]

Topical Medication Therapy

A double-blinded RCT of 45 patients evaluating topical medication for prevention of PMPS concluded that perioperative application of eutectic mixture of local anesthetics (EMLA) cream on the sternal, supraclavicular, and axillary area significantly decreased incidence ($P = 0.002$) and intensity ($P = 0.003$) of pain in the chest wall and axilla 3 months postoperatively.[56]

DISCUSSION

Summary of main results

This systematic review aimed to identify effective interventions for prevention of PMPS. Interventions were categorized into seven unique modalities that could, in turn, be categorized based on pathophysiologic targets that are either peripherally or centrally mediated. Peripheral nerve sensitization is caused by iatrogenic injury and compression by scar tissue, which reduce firing thresholds of nociceptors' terminals in the axilla and chest wall and their associated primary afferent neurons.[57] Other interventions target the central nervous system (CNS) by interfering with neurotransmission. This prevents maladaptive central sensitization caused by repeated stimulation of nociceptive pathways.[58]

Interventions for peripheral sensitization (*topical medication, systemic and local anesthesia, peripheral nerve surgery*)

Of all forms of anesthesia, perioperative IV lidocaine showed the most positive results in our review, with multiple RCTs demonstrating its efficacy in reducing incidence and severity of PMPS. Systemic administration of local anesthetics has analgesic, anti-inflammatory, and anti-hyperalgesic effects, simultaneously targeting peripheral nociceptors and central sensitization. [30,59] However, Kendall et al. hypothesize that relying on a binary yes/no criterion to detect persistent pain rather than a validated pain instrument, as all but one of these studies do, may lead to overestimation of lidocaine's efficacy.[34]

Administration of local anesthetic suppresses afferent nociceptive signals and inflammatory reaction after nerve injury, but appears limited in its capacity to prevent chronic pain. This indicates that

Table 5
Oral Medication Studies

Reference	Procedure	Intervention	Follow-up (mo), Avg. (Range)	Outcome measures	Findings
Fassoulaki et al., 2001[44]	Modified radical mastectomy or lumpectomy with ALND	Mexiletine and regional ropivacaine block	3	Presence of pain, pain intensity	Oral mexiletine, regional block nor their combination decreased incidence or intensity of chronic pain compared with control.
Fassoulaki et al., 2002[39]	Breast surgery for cancer	Mexiletine vs. gabapentin	3	Presence of pain, pain intensity (NRS)	Neither mexiletine nor gabapentin affected pain incidence or intensity compared with control.
Hah et al., 1996[45]	Unilateral/ bilateral mastectomy or breast lumpectomy	Gabapentin	12	Presence of pain, pain intensity (BPI)	Gabapentin did not decrease incidence of pain compared with control.
Amr et al., 2009[46]	Partial or radical mastectomy with ALND	Gabapentin and venlafaxine	6	Presence of pain, pain intensity (VAS), pain characteristics	Venlafaxine decreased pain intensity (**P < 0.0001**) and incidences of burning and stabbing pain compared with gabapentin and control.
Fassoulaki et al., 2005[47]	Breast cancer surgery	Multimodal analgesia (oral gabapentin, EMLA cream near incision, irrigation of brachial plexus block)	6	Presence of pain, pain intensity	Multimodal analgesia intervention did not decrease incidence of chronic pain.
Vig et al., 2019[42]	Modified radical mastectomy	Pregabalin	3	Presence of pain, pain intensity (NRS)	Pregabalin did not decrease incidence nor intensity of chronic pain compared with control.
Reyad et al., 2019[43]	Modified radical mastectomy or conservative breast surgery with ALND	Pregabalin	6	Presence of pain, neuropathic pain (GSNP), pain intensity at rest and movement (VAS)	Pregabalin decreased incidence (**P < 0.001**) and intensity (**P = 0.002**) of neuropathic pain compared with control.
Khan et al., 2019*[35]	Unilateral or bilateral mastectomy or lumpectomy	Pregabalin and lidocaine infusion	3	Presence of pain, pain intensity (BPI, SF-MPQ2), neuropathic pain (DN4)	Lidocaine decreased incidence of persistent neuropathic pain (**P = 0.049**) compared with control, but not severity. Pregabalin had no effect.
Lee et al., 2013[40]	Breast surgery with ALND	Multimodal analgesia (pregabalin and PVB catheter of local anesthetic)	3	Presence of pain, pain characteristics (SF-MPQ)	Multimodal analgesic regimen did not decrease pain incidence compared with control.

(*continued on next page*)

Table 5 (*continued*)

Reference	Procedure	Intervention	Follow-up (mo), Avg. (Range)	Outcome measures	Findings
Van Helmond et al., 2016[41]	Breast cancer surgery	Parecoxib injection and oral celecoxib	12	Presence of pain, pain intensity at rest and during movement (VAS), electric pain and pressure pain tolerance thresholds	COX-2 inhibition had no effect on pain intensity compared with control.
Na et al., 2018[48]	Lumpectomy with ALND or SLNB	IV nefopam	3	Pain intensity (NRS)	Nefopam decreased
incidence of chronic pain (**P = 0.04**), but had no effect on pain intensity compared with control.					

NRS – Numerical rating scale
BPI – Brief Pain Inventory
VAS – Visual analogue scale
GSNP- Grading system for neuropathic pain
SF-MPQ – Short-form McGill Pain Questionnaire
DN4 – Douleur neuropathique 4

while there is ample evidence for severe acute postoperative pain being a risk factor for development of PMPS,[1] modulation of acute pain alone is not sufficient to prevent chronic pain. Meanwhile, topical EMLA seems to significantly reduce the incidence and severity of PMPS, whether through anesthetic effect on cutaneous areas where injured nerves project, or due to systemic uptake.[56]

Intercostobrachial neuralgia due to sectioning of the ICBN is the most common cause of post-mastectomy chronic pain, and a common consequence of ALND.[60,61] Across multiple studies, ALND increases the incidence of chronic pain compared to sentinel lymph node biopsy (SLND) and no axillary procedures.[62–66] While the efficacy of ICBN preservation is widely debated in the literature, it has no effect on PMPS based on the findings of this review. Importantly, evidence has shown that breast reconstruction, whether implant or autologous, does not increase the incidence of PMPS despite additional tissue dissection and potential donor site morbidity.[67] Long-term prospective cohort studies with standardized pain management among patients to compare different approaches to breast reconstruction are necessary.

Interventions for central sensitization (psychiatric treatment, oral medications)

Cortical reorganization plays an essential role in neuropathic pain after mastectomy. Anxiety, depression, and pain catastrophizing increase intensity of pain perception in the acute postsurgical period and are associated with development of PMPS.[68–70] Behavioral cognitive therapy may help alter perception of noxious stimuli. Accordingly, perioperative hypnosis and pre-surgical stress management performed appear to be effective in preventing PMPS.

Medications targeting central sensitization showed variable benefits in this review, with wide ranges of drug doses and administration duration across studies. Nefopam and venlafaxine were both effective. Despite its efficacy in treatment of PMPS, gabapentin was ineffective in pain prevention, while results of pregabalin studies were equivocal. Gabapentinoids, such as gabapentin and pregabalin, interfere with afferent pain signals by inhibiting glutamate release in the dorsal horn of the spinal cord. Nefopam has properties of a monoamine reuptake inhibitor and an NMDA receptor antagonist,

Table 6
Surgical Intervention Studies

Reference	Procedure	Intervention	Follow-up (mo), Avg (Range)	Outcome measures	Findings
Salmon et al., 1998[55]	Mastectomy or conservative breast cancer surgery	Preservation of ICBN	16 (10, 22)	Presence of pain or sensitivity in region of the ICBN	ICBN preservation had no effect on pain.
Torresan et al., 2007[51]	Axillary lymphadenectomy	Preservation of ICBN	3	Presence, intensity and type of sensitivity deficits and pain	ICBN preservation decreased incidence of anesthesia, hypoesthesia or hyperesthesia (**P < 0.01**).
Freeman et al., 2003[53]	Breast cancer surgery	Preservation of ICBN	36 (32-38)	Sensation for light touch, presence of neuromas	Preservation of ICBN had no effect on pain.
Taira et al., 2014[54]	Breast cancer surgery	Preservation of ICBN	24	Presence of dysesthesia, paresthesia and pain sensation in upper arm, health related QOL (FACT-B)	Preservation of ICBN had no effect on incidence or severity of pain compared to dissection.
Yang et al., 2012[52]	Total mastectomy	Spray of HA-CMC gel onto surface of pectoralis major and serratus anterior muscles	6	Presence of motion-related pain and intensity of pain (NRS), DASH questionnaire	HA-CMC decreases pain intensity related to flexion **(P < 0.001)** and abduction **(P = 0.034)** compared to control.
Tasmuth et al., 1999[50]	Unilateral breast cancer surgery with axillary clearance	High-volume surgical units (HVU) vs. small-volume units (LVU)	12	Presence of pain, pain intensity (VAS, Finnish MPQ), interference with sleep	Patients in LVU had higher incidence of chronic pain (**P < 0.05**).

ICBN - Intercostal-brachial nerve
QOL – Quality of life
FACT-B – Functional Assessment of Cancer Therapy – Breast
NRS – Numerical rating scale
DASH – Disabilities of the arm, shoulder, and hand
VAS – Visual analogue scale
MPQ- McGill Pain Questionnaire

preventing pain signal transmission to secondary afferent neurons. Tricyclic antidepressants (TCAs), SSNRIs, such as venlafaxine, and SSNRIs inhibit pain transmission by: 1) binding to α2-adrenergic receptors in the dorsal horn of the spinal cord, preventing release of excitatory neurotransmitters that lead to pain perception and 2) increasing noradrenaline levels at the locus coeruleus of the brainstem, improving the function of an impaired descending noradrenergic inhibitory system.[71] While our review found COX-2 inhibitors to be ineffective, IV flurbiprofen axetil, a nonselective COX inhibitor with a high affinity for inflammatory tissues due to its composition as emulsified lipid microspheres, effectively reduced pain incidence, indicating that blocking inflammatory responses plays a role in preventing PMPS.[31] This supports the idea that therapy limited to pre- and intraoperative periods are likely to be insufficient for pain prevention due to the inflammatory reaction of damaged tissue providing a source of sensory signals that could induce central sensitization, even if it was prevented during the operation.

Given the close link between acute postoperative pain and chronic pain, medications that reduce perioperative anxiety may play a role in PMPS prevention. Ketamine has both mood stabilization and analgesic effects achieved through NMDA receptor blockade and decreased reuptake of serotonin and

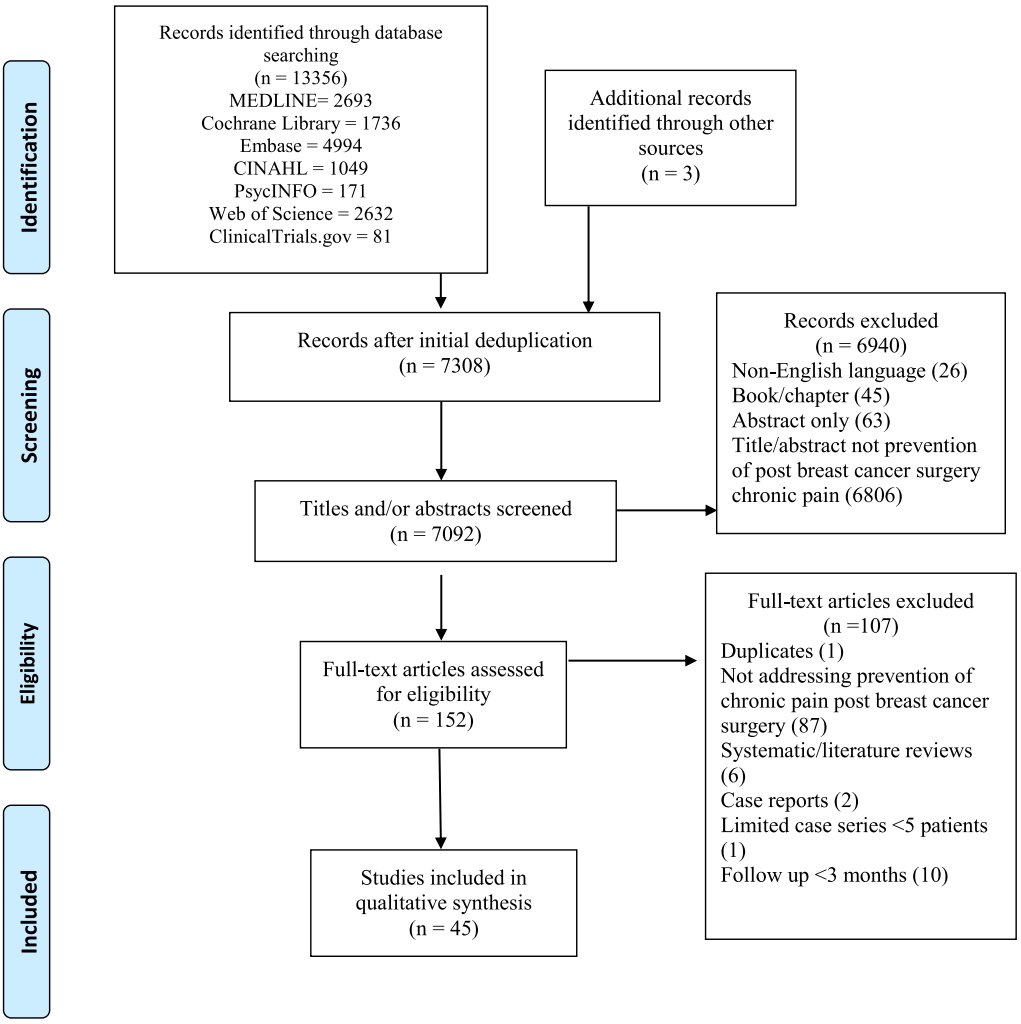

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram illustrating the flow of information through phases of the systematic review.

norepinephrine. [33] However, it was shown to be ineffective for PMPS prevention in this review, both alone and when administered with TPVB, indicating that targeting central sensitization alone is insufficient.

Interventions for central sensitization (nerve blockade)

Nerve blocks prevent integration of nociceptive impulses to the CNS, preventing the development of hyperalgesia and chronic pain.[72] We conclude that single injection and continuous TPVB are effective in reducing severity and incidence of chronic pain.

Ultrasound-guided thoracic interfascial plane blocks are alternatives to PVBs. The PECS II block entails two interfascial injections of local anesthetic between the pectoralis major and minor muscles, while the serratus plane block is a single injection between the serratus anterior and latissimus dorsi muscles. As found in our review, PECS II was effective compared with serratus plane block; however,

its efficacy compared with that of GA was not significant after 3 months. Considering the apparent positive results of nerve blocks for chronic pain, RCTs are necessary to compare the efficacy of PVB with PECS II block, and future work is needed to elucidate the exact medications and dosages necessary for optimal results.

Interventions for musculoskeletal dysfunction

Breast surgery often results in a decrease in motility of myofascial tissues relative to each other, creating trigger points (TrPs) and contributing to chronic postoperative upper limb pain.[73] The aim of PT is to manually release these TrPs and tissue adhesions. However, our review found no benefit of myofascial therapy. Progressive resistance training was similarly ineffective. These results indicate a need to identify subgroups of patients for whom PT would be effective, specifically those whose pain is contributed to by myofascial dysfunctions. While pectoralis tightness and pain from adhesion can be prevented by stretching exercises, this intervention poses a risk for seroma formation.[74] The effectiveness of HA–CMC as an alternative seen in our review shows promise in attenuating early postoperative adhesions that may evolve into chronic pain.

Limitations of this study

Lack of access to potentially negative studies that remain unpublished may be a source of publication bias that our review strategy was unable to overcome. Another potential limitation of this study is reviewer bias. To minimize this bias, two independent reviewers screened articles in the method supported by the PRISMA-P systematic review protocol.[9] Due to the heterogeneity of patient populations, follow-up times and treatments across studies, subgroup analysis was not feasible. Future studies are necessary to guide treatment recommendations tailored to specific patient profiles.

CONCLUSION

This comprehensive review of strategies for prevention of chronic pain after breast cancer-related surgery highlights several effective intervention modalities. As PMPS is a phenomenon mediated through multiple mechanisms, our review supports the use of a multimodal intervention involving preoperative nerve block, intraoperative lidocaine infusion and postoperative medications to prevent the onset of pain hypersensitivity. Future research should evaluate the potential of personalized and multimodal prevention strategies that utilize combination therapy to more effectively prevent chronic post-mastectomy pain. Further, that many medications are effective for treatment of acute postoperative pain, but not prevention of chronic neuropathic pain after breast cancer surgery highlights the need for further investigation into the pathogenesis of post-mastectomy pain and novel pharmacological targets of prevention.

Fig. 1.

Declaration of Competing Interest

Dr. Ellis, Ms. Yuksel, Dr. Chappell, Dr. Jackson and Ms. Wescott have nothing to disclose.

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