



# Updates on the preventions and management of post-mastectomy pain syndrome beyond medical treatment: a comprehensive narrative review

Eriko Narusawa<sup>1</sup>, Sarina Sadeghi<sup>2</sup>, Kaori Tane<sup>3</sup>, Muna Alkhaifi<sup>2</sup>, Yuichiro Kikawa<sup>4</sup>

<sup>1</sup>Department of Breast and Endocrine Surgery, NHO Takasaki General Medical Center, Gunma, Japan; <sup>2</sup>Department of Medical Oncology & Malignant Hematology, Sunnybrook Health Sciences Centre, Toronto, Canada; <sup>3</sup>Department of Breast Surgery, Hyogo Cancer Center, Hyogo, Japan; <sup>4</sup>Department of Breast Surgery, Kansai Medical University, Osaka, Japan

**Contributions:** (I) Conception and design: M Alkhaifi; (II) Administrative support: Y Kikawa; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: S Sadeghi, E Narusawa; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

**Correspondence to:** Eriko Narusawa, MD. Department of Breast and Endocrine Surgery, NHO Takasaki General Medical Center, 36, Takamatsucho, Takasakishi, Gunma 370-0829, Japan. Email: nishiki1992@gmail.com.

**Background and Objective:** With the significant advances in breast cancer treatment, the survival rates have improved. Consequently, improving the quality of life for breast cancer survivors has emerged an important issue. In this study, we examined the management of post-mastectomy pain syndrome (PMPS) in breast cancer patients thorough a comprehensive literature review. We introduce the preventive measures and pharmacotherapy for PMPS in breast cancer patients and discuss the effectiveness of psychosocial interventions.

**Methods:** We conducted a literature search for relevant articles in Medline ALL, Cochrane Database of Systematic Reviews, Cochrane CENTRAL, Embase, and nine other databases from October 2023 to January 2024. Chronic pain was defined as pain persisting for more than 3 months after breast cancer surgery. The search included terms related to PMPS, psychological interventions, and breast cancer. Data extraction was done independently by two reviewers, and any discrepancies will be discussed to ensure consensus or by a third reviewer.

**Key Content and Findings:** Studies have investigated surgical anesthetics, postoperative medications, and surgical procedures for PMPS prevention, but few have focused on treatment. Our literature search about the usefulness of psychosocial interventions yielded two articles, one was about the usefulness of mindfulness and the other was about the efficacy of yoga.

**Conclusions:** Mindfulness and yoga show potential efficacy for PMPS treatment, but the evidence is limited. More research is needed to confirm these findings and to explore other psychosocial interventions.

**Keywords:** Post-mastectomy pain syndrome (PMPS); psychosocial intervention; breast cancer

Submitted Apr 25, 2024. Accepted for publication Jul 26, 2024. Published online Aug 16, 2024.

doi: 10.21037/apm-24-73

View this article at: <https://dx.doi.org/10.21037/apm-24-73>

## Introduction

### Background

Breast cancer is the most prevalent cancer among women. The mortality rate from breast cancer is decreasing, due to advances in early detection and remarkable treatment

methods. Consequently, the number of breast cancer survivors is growing (1). Therefore, it's crucial to focus on enhancing the quality of life for these survivors.

In this article, we address the management of post-mastectomy pain syndrome (PMPS), focusing on preventive measures, pharmacotherapy, and psychosocial interventions.

This review aims to fill gaps in current research by evaluating the effectiveness of psychosocial interventions which have shown promise but are not well-studied in the context of PMPS. We present this article in accordance with the Narrative Review reporting checklist (available at <https://apm.amegroups.com/article/view/10.21037/apm-24-73/rc>).

### **What is PMPS?**

The treatment of breast cancer mainly consists of surgery, drug therapy, and radiation therapy. A study by Wang *et al.* revealed that between 2% and 78% of breast cancer patients experience chronic pain for more than 3 months after surgery, with a median occurrence rate of 37% (2). Chronic postoperative pain following breast cancer surgery was initially described as “intercostobrachial nerve entrapment syndrome” by Wood *et al.* in 1978 (3). Currently, this condition is known as PMPS. Waltho *et al.* characterized PMPS as pain that develops after any breast surgery, which is moderately severe or more intense, exhibits neuropathic characteristics, and occurs on the same side as the surgery in the breast/chest wall, axilla, or arm (4). This pain persists for at least 6 months, is present at least 50% of the time, and may worsen with shoulder movements (4). Previous studies identified preoperative pain, axillary lymph node dissection, anxiety, young age, and radiation therapy as risk factors for PMPS (5). It is known that PMPS has a considerable negative influence on the quality of life. Gong *et al.* showed that patients with PMPS had worse body image and sexual enjoyment (6).

### **How to prevent PMPS**

The development of PMPS involves inflammation and neuropathic pain. Additionally, severe acute postoperative pain can worsen the development of PMPS. Therefore, prophylactic analgesia and perioperative pharmacotherapy could reduce the onset of PMPS. Yuksel *et al.* conducted a systematic review on preventing, identifying seven primary intervention methods for its prevention (7). They found physical therapy, cognitive therapy, nerve blocks, anesthesia, oral medications, surgical interventions, and topical medication therapy to be effective in preventing of PMPS. Notably, a significant amount of research has focused on nerve blocks, anesthesia, oral medications, and surgical interventions (7). Nerve blocks including thoracic nerve blocks and paraspinal blocks, have been emphasized for preventing PMPS. Anesthesia approaches such as

intravenous lidocaine has shown promise in reducing chronic pain, alongside intravenous flurbiprofen axetil and preoperative dexmedetomidine (7). Perioperative pregabalin, venlafaxine, and selective serotonin reuptake inhibitor and serotonin noradrenaline reuptake inhibitor may also be useful for medical therapy. Regarding surgical techniques, there’s a debate over the effectiveness of preserving intercostal nerves (7). A study reported that applying a mixture of sodium hyaluronate and carboxymethylcellulose to the surfaces of the pectoralis major and serratus anterior muscles reduced pain intensity (7).

### **How to treat PMPS (Table 1)**

#### **Pharmacotherapy for PMPS**

The Canadian Pain Society recommends gabapentin, tricyclic antidepressants, and serotonin-norepinephrine reuptake inhibitors as initial treatment for chronic neuropathic pain (8). Belfer *et al.* reported the efficiency of gabapentin on PMPS (9). While numerous studies have focused on the pharmacological prevention of PMPS, reports on that after PMPS are limited.

#### **Nerve block for PMPS**

Ultrasound-guided peripheral nerve block might be effective not only as prevention of PMPS but also as treatment. Yang *et al.* performed a retrospective investigation and they reported that peripheral nerve block reduced postoperative chronic pain significantly (10).

#### **Physical intervention for PMPS**

A meta-analysis by Kannan *et al.* found that exercise improved the quality of life and alleviated pain in breast cancer patients with PMPS (11). The study also highlighted that myofascial release and acupuncture significantly reduced pain severity (11).

#### **Psychological intervention for PMPS**

Pain is a multifaceted phenomenon that includes psychological and social factors, suggesting that psychosocial interventions might be effective in managing pain (12). Systematic reviews have supported the effectiveness of psychosocial interventions for chronic pain among various populations, including those without cancer (13), and specifically cognitive therapy for chronic pain in breast cancer patients (14). Johannsen *et al.* published a systematic review in 2013 assessing psychosocial interventions for

**Table 1** Summary of treatment

| Treatment modality    | Reference                        | Design                              | Intervention  | Findings   |
|-----------------------|----------------------------------|-------------------------------------|---|--|
| Pharmacotherapy       | Mu <i>et al.</i> , 2017 (8)      | Systematic review                   | Gabapentin, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors | These 3 are the first-line agents of chronic pain  |
|                       | Belfer <i>et al.</i> , 2017 (9)  | Proof of principle open label study | 8-week treatment with gabapentin  | A significant positive change was found in pain intensity, pain impact, and sleep  |
| Nerve block           | Yang <i>et al.</i> , 2021 (10)   | Single center retrospective review  | Ultrasound guided peripheral nerve block  | The mean baseline pain score was 7, compared with the post-treatment mean score of 3 (95% confidence interval: 3.58 to 3.98; P=0.0001)   |
| Physical intervention | Kannan <i>et al.</i> , 2022 (11) | Systematic review                   | Exercise, myofascial release, acupuncture   | Meta-analyses of six exercise trials, two myofascial release trials, and two acupuncture trials revealed a significant improvement in pain severity in the treatment group than in the control group |

chronic pain in breast cancer patients and survivors. Although this meta-analysis showed a statistically significant difference in the usefulness of psychosocial interventions, the results were considered preliminary due to potential publication bias (15).

### Objective of this narrative review

Although various psychosocial interventions for breast cancer-related pain have been reported, assessing their effectiveness is challenging due to the ambiguous distinction among cancer pain, postoperative pain, and chemotherapy-induced neural pain. Furthermore, the diversity of pain assessment scales used across studies complicates the analysis. In this study, we narrowed our focus to chronic postoperative pain specifically, and examined the effectiveness of psychosocial interventions.

### Methods

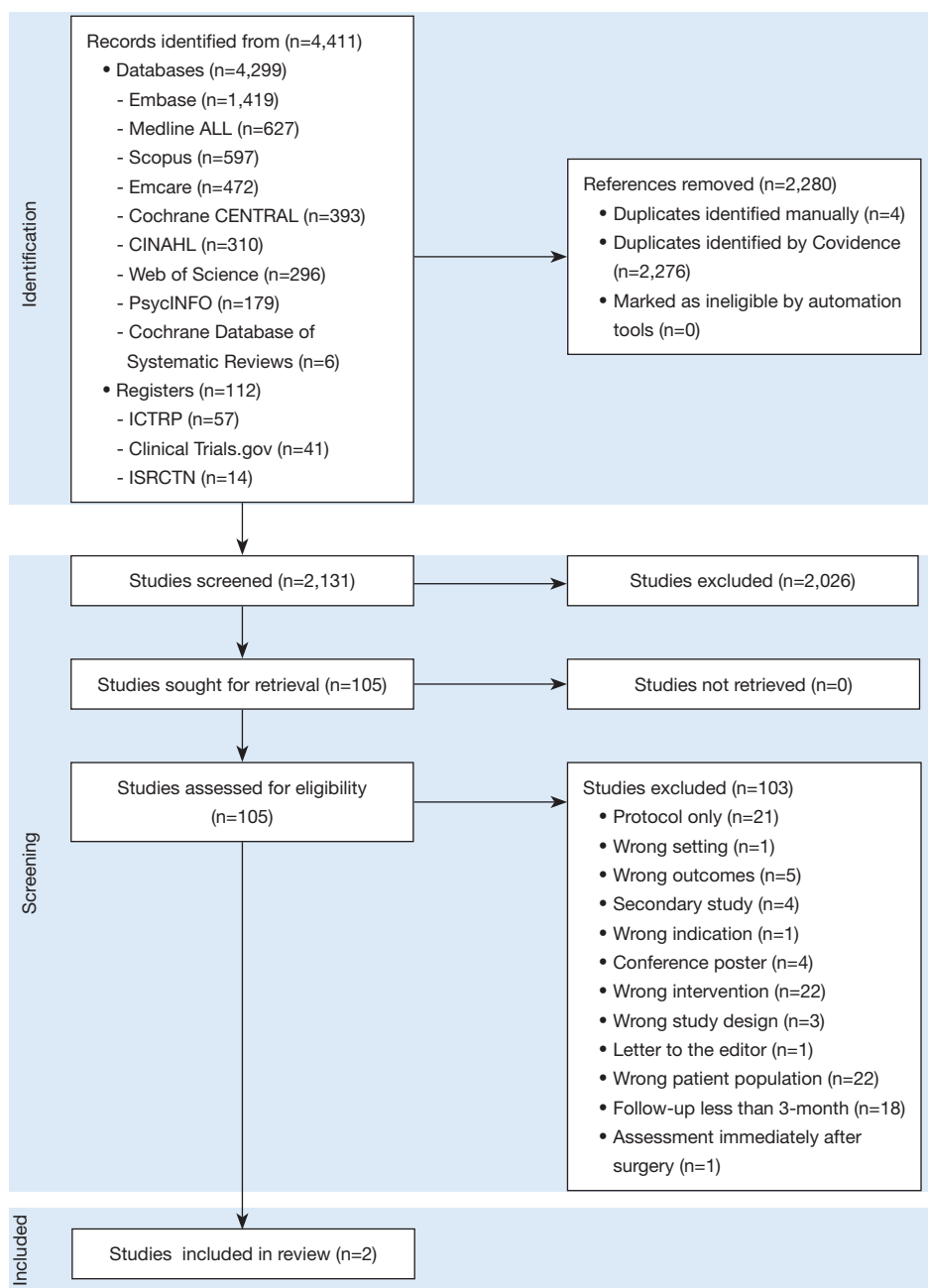
A literature search was conducted from October 2023 to January 2024 to identify studies on psychological intervention for chronic postoperative pain following breast cancer surgery. We used databases such as Medline ALL, Cochrane Database of Systematic Reviews, Cochrane CENTRAL, Embase, Emcare, PsycINFO, CINAHL, Scopus, and Web of Science. The search terms included “breast neoplasms”, “pain”, “postmastectomy pain syndrome”, “psychological intervention”, “mindfulness”,

and “yoga”. For this research, chronic pain was defined as pain that persisted for more than 3 months post-surgery. The psychosocial interventions examined included cognitive behavioral therapy, psychotherapy, group psychotherapy, talk therapy, couple counseling, mindfulness-based interventions, education, hypnosis, self-hypnosis, meditation, relaxation, guided imagery, and yoga. Studies are eligible if they: (I) report pain outcome of a psychological intervention tested in breast cancer survivors who have undergone surgery; (II) include both baseline and post-intervention measures of pain; (III) include pain that has been persistent for more than 3 months post-surgery; (IV) reports data on interventions done post-operatively and not pre-operatively or peri-operatively; and (V) are peer-reviewed. We excluded studies that do not meet the inclusion criteria and: (I) include preventative interventions conducted before cancer treatment, i.e., prior to surgery; (II) articles with follow-up <3 months; (III) are published as conference abstracts, posters, meetings, dissertations, theses, case reports, case series, book chapters, and letters to editor; and (IV) are animal studies, cell studies, and cadaver studies.

Details of the literature search strategy are summarized in Table S1.

### The efficiency of mindfulness and yoga for PMPS

Our review identified only two relevant studies; one randomized controlled trial (RCT) assessing the efficacy of



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

mindfulness (1) and one cohort study evaluating yoga (16) (Figure 1). These studies are summarized in Table 2.

### **Mindfulness**

Mindfulness-based stress reduction (MBSR) is a therapeutic

intervention that enhances awareness and acceptance of personal thoughts and feelings, which include physical discomfort and negative emotions. Central to this practice is meditation aimed at heightening sensations, emotion, and thoughts awareness, fostering self-regulation, and adapting to stress (1). A meta-analysis by Ledesma and

**Table 2** Summary of psychological intervention

| Parameters        | Johannsen, 2016 (12)  | Sudarshan, 2013 (16)  |
|-------------------|---|---|
| Nation            | Denmark   | Canada  |
| Participants      | 129   | 14  |
| Sex               | Female  | Female  |
| Age (years), mean | Intervention group: 56.6<br>Control group: 56.7               | 55  |
| Intervention      | Mindfulness-based cognitive therapy                           | Yoga  |
| Control           | Wait-list   | NR  |
| Tools             | SF-MPQ-2, PPI, 11-point NRS                                   | DPQ   |
| Result            | Statistically significant effect was found for pain intensity | There was a consistent trend in decreased scores on the DPQ |

SF-MPQ-2, Short Form McGill Pain Questionnaire 2; PPI, The Present Pain Intensity; NRS, Numeric Rating Scale; DPQ, The Dallas Pain questionnaire.

Kumano concluded that MBSR significantly improved the mental and physical health status of cancer patients (17). Additionally, a meta-analysis by Veehof *et al.* found that MBSR not only reduced chronic pain but also decreased symptoms of depression and anxiety, and enhanced the physical well-being and quality of life in non-cancer populations (13).

One pivotal RCT, conducted by Johannsen *et al.*, investigated MBSR's effectiveness for PMPS among breast cancer survivors (12). The study included 129 participants who were assigned to groups of 13–17 patients each. Over eight weekly sessions, the groups engaged in mindfulness exercises and psychological education tailored to manage current pain symptoms. Additionally, participants were advised to practice mindfulness for 45 minutes daily at home. The results showed significant reductions in pain intensity (as measured by the 11-point Numeric Rating Scale), present pain intensity ratings, and neurogenic pain assessments using the Short Form McGill Pain Questionnaire 2. These benefits were maintained during a 6-month follow-up period, especially in terms of pain intensity. The study also utilized the World Health Organization-5 Well-Being Index as a secondary measure, noting significant improvements in the intervention group's quality of life (12).

### Yoga

Originating from ancient Indian philosophy, yoga integrates spiritual practices, physical postures, and ethical lifestyle

advice, aiming to unite the mind, body, and spirit. In North America and Europe, yoga is commonly associated with physical exercises, breathing techniques, and meditation (18).

According to a systematic review by Cramer *et al.*, yoga enhances the quality of life as well as the social and emotional well-being of breast cancer patients (18). However, the review noted no significant benefits for post-treatment breast cancer patients (18).

From our literature search, a cohort study conducted by Sudarshan *et al.* explored the effects of yoga on PMPS (16). This study involved 14 postoperative breast cancer patients who participated in weekly yoga classes over a 12-week period. The Hospital Anxiety and Depression Scale and the Dallas Pain Questionnaire were utilized to evaluate the outcomes. The results indicated a positive trend in pain improvement within the yoga group, although the differences were not statistically significant. Similarly, trends in anxiety and depression levels showed improvements but were not statistically significant (16).

### Discussion

The effectiveness of psychosocial interventions, such as mindfulness and yoga, for PMPS is based on limited studies. These studies have small sample sizes and potential methodological biases. For instance, the mindfulness study by Johannsen *et al.* had a follow-up period of only 6 months, which may not capture long-term effects (12). The yoga study by Sudarshan *et al.* showed positive trends but lacked statistical significance, possibly due to the small

sample size of 14 participants (16). Future research should aim for larger, more diverse sample sizes and longer follow-up periods to better assess the long-term benefits of these interventions. Additionally, standardizing pain assessment tools across studies would facilitate more accurate comparisons and meta-analyses.

## Conclusions

The potential efficacy of mindfulness therapy and yoga for treating PMPS has been suggested. However, there were limited studies assessing PMPS beyond 3 months post-operatively, and a clear distinction between immediate postoperative pain and PMPS was lacking. Although we have defined PMPS as pain persisting for more than 3 months in this review, the appropriateness of this 3-month benchmark was uncertain. Additionally, there was no standardized method for evaluating PMPS.

Further studies are required to establish a standardized evaluation method and to verify the long-term benefits of these treatments. Therefore, clinicians should consider incorporating these psychosocial strategies into PMPS management plans, while researchers should continue exploring and refining these approaches to improve the quality of life for breast cancer survivors.

## Acknowledgments

*Funding:* None.

## Footnote

*Provenance and Peer Review:* This article was commissioned by the editorial office, *Annals of Palliative Medicine* for the series “Supportive Care After Breast Cancer: Challenges and Opportunities”. The article has undergone external peer review.

*Reporting Checklist:* The authors have completed the Narrative Review reporting checklist. Available at <https://apm.amegroups.com/article/view/10.21037/apm-24-73/rc>

*Peer Review File:* Available at <https://apm.amegroups.com/article/view/10.21037/apm-24-73/prf>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://apm.amegroups.com/article/view/10.21037/apm-24-73/coif>).

The series “Supportive Care After Breast Cancer: Challenges and Opportunities” was commissioned by the editorial office without any funding or sponsorship. M.A. served as the unpaid Guest Editor of the series. Y.K. received payment or honoraria for lectures, presentations, speaker bureaus, manuscript writing or education events from Eisai, Lilly, Chugai, Pfizer, Daiichi Sankyo, Astra Zeneca, and Taiho. The authors have no other conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

*Open Access Statement:* This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

## References

1. Shergill Y, Rice DB, Khoo EL, et al. Mindfulness-Based Stress Reduction in Breast Cancer Survivors with Chronic Neuropathic Pain: A Randomized Controlled Trial. *Pain Res Manag* 2022;2022:4020550.
2. Wang L, Cohen JC, Devasenapathy N, et al. Prevalence and intensity of persistent post-surgical pain following breast cancer surgery: a systematic review and meta-analysis of observational studies. *Br J Anaesth* 2020;125:346-57.
3. Wood KM. Intercostobrachial nerve entrapment syndrome. *South Med J* 1978;71:662-3.
4. Waltho D, Rockwell G. Post-breast surgery pain syndrome: establishing a consensus for the definition of post-mastectomy pain syndrome to provide a standardized clinical and research approach - a review of the literature and discussion. *Can J Surg* 2016;59:342-50.
5. Wang L, Guyatt GH, Kennedy SA, et al. Predictors of persistent pain after breast cancer surgery: a systematic review and meta-analysis of observational studies. *CMAJ* 2016;188:E352-61.
6. Gong Y, Tan Q, Qin Q, et al. Prevalence of



- postmastectomy pain syndrome and associated risk factors: A large single-institution cohort study. *Medicine (Baltimore)* 2020;99:e19834.
7. Yuksel SS, Chappell AG, Jackson BT, et al. "Post Mastectomy Pain Syndrome: A Systematic Review of Prevention Modalities". *JPRAS Open* 2021;31:32-49.
  8. Mu A, Weinberg E, Moulin DE, et al. Pharmacologic management of chronic neuropathic pain: Review of the Canadian Pain Society consensus statement. *Can Fam Physician* 2017;63:844-52.
  9. Belfer I, Pollock NI, Martin JL, et al. Effect of gastroretentive gabapentin (Gralise) on postmastectomy pain syndrome: a proof-of-principle open-label study. *Pain Rep* 2017;2:e596.
  10. Yang A, Nadav D, Legler A, et al. An Interventional Pain Algorithm for the Treatment of Postmastectomy Pain Syndrome: A Single-Center Retrospective Review. *Pain Med* 2021;22:677-86.
  11. Kannan P, Lam HY, Ma TK, et al. Efficacy of physical therapy interventions on quality of life and upper quadrant pain severity in women with post-mastectomy pain syndrome: a systematic review and meta-analysis. *Qual Life Res* 2022;31:951-73.
  12. Johannsen M, O'Connor M, O'Toole MS, et al. Efficacy of Mindfulness-Based Cognitive Therapy on Late Post-Treatment Pain in Women Treated for Primary Breast Cancer: A Randomized Controlled Trial. *J Clin Oncol* 2016;34:3390-9.
  13. Veehof MM, Trompetter HR, Bohlmeijer ET, et al. Acceptance- and mindfulness-based interventions for the treatment of chronic pain: a meta-analytic review. *Cogn Behav Ther* 2016;45:5-31.
  14. Tatrow K, Montgomery GH. Cognitive behavioral therapy techniques for distress and pain in breast cancer patients: a meta-analysis. *J Behav Med* 2006;29:17-27.
  15. Johannsen M, Farver I, Beck N, et al. The efficacy of psychosocial intervention for pain in breast cancer patients and survivors: a systematic review and meta-analysis. *Breast Cancer Res Treat* 2013;138:675-90.
  16. Sudarshan M, Petrucci A, Dumitra S, et al. Yoga therapy for breast cancer patients: a prospective cohort study. *Complement Ther Clin Pract* 2013;19:227-9.
  17. Ledesma D, Kumano H. Mindfulness-based stress reduction and cancer: a meta-analysis. *Psychooncology* 2009;18:571-9.
  18. Cramer H, Lange S, Klose P, et al. Yoga for breast cancer patients and survivors: a systematic review and meta-analysis. *BMC Cancer* 2012;12:412.

**Cite this article as:** Narusawa E, Sadeghi S, Tane K, Alkhaifi M, Kikawa Y. Updates on the preventions and management of post-mastectomy pain syndrome beyond medical treatment: a comprehensive narrative review. *Ann Palliat Med* 2024;13(5):1258-1264. doi: 10.21037/apm-24-73

**Table S1** The search strategy summary

| Items                                | Specification   |
|--------------------------------------|---|
| Date of search                       | Oct 4th, 2023   |
| Databases and other sources searched | Medline ALL, Cochrane Database of Systematic Reviews, Cochrane CENTRAL, Embase, Emcare, PsycINFO, all from OvidSp platform, CINAHL from EBSCOhost, Scopus from Elsevier, and Web of Science from Clarivate, ClinicalTrials.gov, International Clinical Trials Registry Platform, and International Standard Randomised Controlled Trial Number Registry   |
| Search terms used                    | “Breast Neoplasms”[MeSH] AND (pain[tiab] OR neuropathy[tiab]) AND (lumpectomy[tiab] OR mastectomy[tiab] OR surgery[tiab] OR operation[tiab]) AND “Behavior Therapy” [MeSH] OR Emoton-Focused Therapy [MeSH] OR “Feedback, Psychological” [MeSH] OR “Feedback, Sensory” [MeSH] OR “Hypnosis” [MeSH] OR “Imagery, Psychotherapy” [MeSH] OR Interpersonal Psychotherapy [MeSH] OR “Mentalization-Based Therapy” [MeSH] OR “Narrative Therapy” [MeSH] OR “Person-Centred Psychotherapy” [MeSH] OR “Psychoanalytic Therapy” [MeSH] OR “Psychosocial Intervention” [MeSH] OR “Psychtherapy, Brief” [MeSH] OR “Psychotherapy, Multiple” [MeSH] OR “Psychotherapy, Psychodynamic” [MeSH] OR “Psychotherapy, Rational-Emotive” [MeSH] OR “Schema Therapy” [MeSH] OR (Psychosocial[tiab] OR Psychologic*[tiab] OR yoga[Title/Abstract] OR mindfulness[Title/Abstract] OR meditation[Title/Abstract] OR hypnosis[Title/Abstract] OR psycho-education[Title/Abstract] OR psychotherapy[Title/Abstract] OR counseling[Title/Abstract] OR counselling[Title/Abstract] OR “Talk Therapy”[Title/Abstract] OR “Mental health services”[tiab] OR “Group psychotherapy”[tiab] OR “Psychiatric rehabilitation”[tiab] OR “Social work”[tiab] OR “Psychoanalytic interpretation”[tiab] OR intervention[tiab]) OR “postmastectomy pain syndrome”[tiab] |
| Timeframe                            | From Oct 2023 to Jun 2024   |
| Inclusion and exclusion criteria     | <p>Studies are eligible if they:</p> <ul style="list-style-type: none"> <li>(I) Report pain outcome of a psychological intervention tested in breast cancer survivors who have undergone surgery</li> <li>(II) Include both baseline and post-intervention measures of pain</li> <li>(III) Include pain that has been persistent for more than 3 months post-surgery</li> <li>(IV) Reports data on interventions done post-operatively and not pre-operatively or peri-operatively</li> <li>(V) Are peer-reviewed</li> </ul> <p>We excluded studies that do not meet the inclusion criteria and:</p> <ul style="list-style-type: none"> <li>(I) Include preventative interventions conducted before cancer treatment, i.e., prior to surgery</li> <li>(II) Articles with follow-up &lt;3 months</li> <li>(III) Are published as conference abstracts, posters, meetings, dissertations, theses, case reports, case series, book chapters, and letters to editor</li> <li>(IV) Are animal studies, cell studies, and cadaver studies</li> </ul>  |
| Selection process                    | Data extraction was done independently by two reviewers, and any discrepancies will be discussed to ensure consensus or by a third reviewer   |