

Efficacy of acupuncture in the management of fatigue related to breast cancer antineoplastic treatment: a systematic review

Eficácia da acupuntura no manejo da fadiga relacionada com o tratamento antineoplástico do câncer de mama: uma revisão sistemática

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RESUMO | INTRODUÇÃO: O câncer de mama é o câncer mais prevalente entre as mulheres em todo o mundo. Semelhante à quimioterapia, o tratamento antineoplástico está associado a muitos efeitos colaterais, sendo o cansaço um dos mais comuns. É importante investigar possíveis tratamentos, especialmente alternativas não farmacológicas, para controlar os sintomas que afetam diretamente a qualidade de vida das mulheres. **OBJETIVO:** O objetivo deste estudo foi fornecer evidências científicas para verificar a eficácia da acupuntura no manejo da fadiga em pacientes com câncer de mama. **MÉTODOS:** Este estudo envolveu uma revisão sistemática baseada na metodologia Preferred Reporting Items for Systematic Reviews e Meta-Analysis (PRISMA). Ensaios clínicos randomizados publicados em revistas científicas indexadas foram compilados. A pesquisa bibliográfica foi realizada utilizando as bases de dados eletrônicas, PubMed, PEDro e BIREME, utilizando os descritores “câncer de mama”, “fadiga”, “acupuntura” e “ensaio randomizado”. Os critérios de inclusão incluíram artigos on-line totalmente disponíveis que foram classificados como ensaios clínicos randomizados publicados de 2012 a 2017 em inglês ou português. A elegibilidade dos estudos baseou-se na estratégia PICO, onde a População representou mulheres com câncer de mama e idade entre 18-65 anos, a Intervenção foi a acupuntura, o Controle compreendeu o uso de medidas de cuidado padrão ou acupuntura “sham” e o desfecho foi o desenvolvimento de fadiga. A escala de qualidade PEDro e o escore definido no WebQualis foram usados para avaliar os artigos e os periódicos. **RESULTADOS:** No total, 66 artigos foram selecionados, mas apenas quatro preencheram todos os critérios de inclusão, totalizando uma amostra de 620 mulheres. Todos os estudos avaliaram o efeito da acupuntura na fadiga e outros sintomas relacionados ao tratamento do câncer de mama com diferentes durações de tratamento. Três artigos relataram resultados estatisticamente significativos, e todos os artigos descreveram melhora clínica da fadiga após a aplicação da acupuntura. A média do escore da escala PEDro foi 6.25. Todos os artigos foram publicados em periódicos estrangeiros e o Web Qualis variou de B2 to A1. **CONCLUSÃO:** Evidências científicas confirmam a eficácia da acupuntura no manejo da fadiga relatada por mulheres com câncer de mama. A acupuntura foi eficaz na redução da fadiga nos estudos selecionados para esta revisão.

PALAVRAS-CHAVE: Terapia por acupuntura. Revisão sistemática. Fadiga. Neoplasias da mama.

ABSTRACT | INTRODUCTION: Breast cancer is the most prevalent cancer among women worldwide. Similar to chemotherapy, antineoplastic treatment is associated with many side effects, with fatigue being one of the most common. It is important to investigate potential treatments, especially non-pharmacological alternatives, to control symptoms that directly affect women's quality of life. **OBJECTIVE:** The objective of this study was to provide scientific evidence to verify the efficacy of acupuncture in the management of fatigue in patients with breast cancer. **METHODS:** This study involved a systematic review based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) methodology. Randomized clinical trials published in indexed scientific journals were compiled. The literature search was performed using the electronic databases, PubMed, PEDro, and BIREME, using the descriptors ‘breast cancer’, ‘fatigue’, ‘acupuncture’, and ‘randomized trial’. Inclusion criteria included fully available online articles that were classified as randomised clinical trials published from 2012 to 2017 in either English or Portuguese. Study eligibility was based on the Population, Intervention, Control, Outcome, and Study (PICO) design criteria, in which the (1) population included women 18–65 years of age with breast cancer, (2) intervention was acupuncture, (3) comparison referred to standard care or sham acupuncture, and (4) outcome was the evaluation of fatigue. The PEDro scale was applied to evaluate the quality of the studies. WebQualis was also used to evaluate the quality of the journals of the selected articles. **RESULTS:** In total, 66 articles were selected, but only four fulfilled all inclusion criteria, giving a total sample size of 620 women. All trials evaluated the effect of acupuncture on fatigue and other symptoms related to the treatment of breast cancer with different treatment durations. Three articles reported statistically significant results, and all articles described clinical improvement in fatigue after the application of acupuncture. The average PEDro score of the manuscripts was 6.25. All articles were published in non-Brazilian journals with WebQualis scores that ranged from B2 to A1. **CONCLUSION:** Scientific evidence confirms the efficacy of acupuncture in the management of fatigue reported by women with breast cancer. Acupuncture was effective in reducing fatigue in the studies selected for this review.

KEYWORDS: Acupuncture therapy. Review. Fatigue. Breast neoplasms.

Introduction

Breast cancer is a type of neoplasm that develops in the breast tissue and, to a large extent, arises from the ducts or lobes of the mammary gland^{1,2}. It may be classified as non-invasive carcinoma or carcinoma in situ when it has not yet infiltrated the basal membrane separating the ducts and lobules from adjacent tissues, which presents a lower risk for metastasis. Invasive or infiltrative carcinoma refers to a tumour that spreads to other tissues, and may grow and infiltrate the skin, pectoral muscles, and axillary lymph nodes^{1,3}.

Breast cancer is the most prevalent cancer in women¹ and represents 25% of all cancer cases worldwide. In 2017, a total of 252,710 cases were reported in the United States; death occurred in 40,610 cases⁴. Excluding non-melanoma skin tumours, breast cancer is the most common neoplasia in women from all regions of Brazil, except the north, where cervical cancer is the most common. The mortality rate from breast cancer is increasing worldwide. In Brazil, breast cancer represents the primary cause of cancer death in the female population, with 13.03 deaths per 100,000 women. The regions with the highest mortality rates in Brazil are the south and southeast, with 14.21 and 14.60 deaths per 100,000 women, respectively. The incidence and mortality rate of breast cancer progress with age, increasing significantly in those older than 40 years of age. In men, breast cancer accounts for 1% of malignant neoplasms³.

Breast cancer does not have a single aetiology, and its heterogeneity is reflected by its different clinical manifestations⁵. Generally, treatments incorporate two or more approaches, taking into account not only disease staging, but also individual characteristics (i.e., clinical and psychological) to provide better quality of life for the patient^{6,7}.

Fatigue is a common side effect that may be present in cancer patients from initial to advanced phases

of treatment. The fatigue experienced by healthy individuals differs from the fatigue resulting from cancer treatment. In healthy individuals, it is often described as an acute tiredness that improves with rest or sleep. In cancer patients, fatigue is considered to be chronic because it persists for a long period and does not improve with rest or sleep⁸. It can be defined as a persistent feeling of tiredness that interferes with the function of certain organs and organ systems. It is multidimensional and subjective since patients may perceive and describe it as physical exhaustion, reduced activity, less motivation, or mental fatigue⁹. Consequently, it has a negative impact on self-esteem and affects social interactions.

Fatigue has a negative impact on many areas, including work, leisure, domestic activities, mood, social interaction, and cognitive performance. It is reported by patients using adjectives such as "tired", "weak", "exhausted", "heavy", or "slow". Among health professionals, commonly used terms for fatigue include "asthenia", "lassitude", "prostration", "exercise intolerance", or "weakness"¹⁰. Fatigue is associated with several physical, psychological, social, cognitive, and behavioural factors. Depression, physical disability, and the need for sleep and rest during the day are common symptoms of fatigue, which significantly increases the severity of each other symptom and, in turn, results in limitations to daily activities in patients with breast cancer¹⁰.

There are several therapeutic approaches indicated for the treatment of fatigue. Classical therapies include modifications to lifestyle habits, medication, psychological intervention, and integrative therapies^{11,12}. Acupuncture is a component of traditional Chinese medicine and is considered to be a complementary and alternative medicine¹³. It has been practiced in China and other Asian countries for over 4,000 years. Acupuncture literally means to 'pierce with a needle'; however, it is not limited to the use of needles. It is often used in combination with moxibustion, which involves burning of selected herbs on the skin; the use of glass

domes with vacuum suction; and other techniques that stimulate specific body points, such as laser therapy¹⁴. Although the exact mechanisms of action of acupuncture remain unclear, it is known that, for pain control, opioid system activation and release of neurotransmitters and neurohormones occur¹⁵. However, for other symptoms, such as fatigue, the mechanisms may be different¹⁶. Acupuncture affects both the HPA axis and sympathetic nervous system, which are downregulated in women with breast cancer¹⁷.

This systematic review aims to provide scientific evidence to verify the efficacy of acupuncture in the management of fatigue in breast cancer patients undergoing antineoplastic treatment.

Methods

The present systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) methodology. Randomized clinical trials published in indexed scientific journals were selected for this review. Only scientific articles available in electronic databases, PubMed, PEDro, and BIREME, from November to December 2017, were searched. The last search was performed in December 31st 2017. Keywords, including 'breast cancer', 'fatigue', 'acupuncture', and 'randomized trial', and the combination of these terms by means of the Boolean operator 'AND' were used in the same way for all electronic databases searching. Both authors individually analysed the abstracts of the articles to determine which studies would be pertinent to the central question of this systematic review, namely, is the use of acupuncture effective for the treatment of fatigue in women with breast cancer?

Inclusion criteria included full articles available online and classified as randomised clinical trials, published in 2012–2017 in either English or Portuguese. Only studies that included women with breast cancer were eligible. Studies found using these databases that did not meet the establish criteria or reported on another alternative combined treatment or type of cancer were excluded. The selection process for the articles used in this systematic review is illustrated in Flowchart 1.

Study eligibility was based on the Population, Intervention, Control, Outcome, and Study (PICO) design criteria, in which the (1) population included women 18–65 years of age with breast cancer, (2) intervention was acupuncture, (3) comparison referred to standard care or sham acupuncture, and (4) outcome was the evaluation of fatigue. The type of study selected was randomised controlled trial.

The PEDro scale was applied to evaluate the quality of the studies. WebQualis was also used to evaluate the quality of the journals of the selected articles. Flowchart 1 describes the main findings. The scores of articles as assessed using the PEDro scale, are described in Table 1.

To evaluate the risk of bias on each study, it was used the ROBIS tool.

Flow chart 1. Search strategy of manuscripts according PRISMA STATMENT

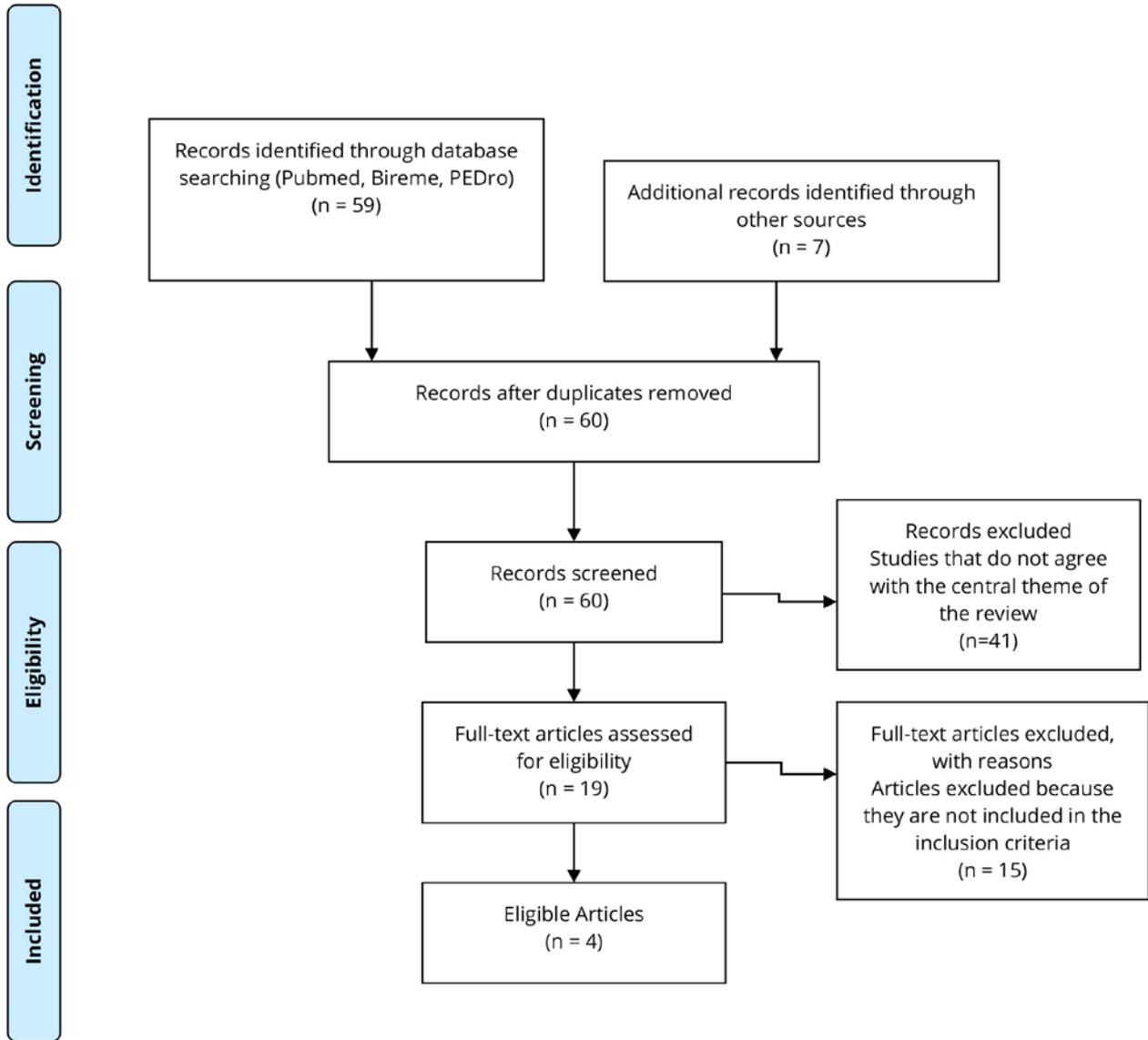


Table 1. Scores of the manuscripts described by PEDro Scale

Manuscripts	SCORE											FINAL
	1*	2	3	4	5	6	7	8	9	10	11	
Molassiotis et al., 2012	X	X		X					x	x	x	5/10
Smith et al., 2013	X	X	x	X	x			x	x	x	x	8/10
Molassiotis et al., 2013	X	X								x	x	3/10
Mao et al., 2014	X	X	x	X	x		x	x	x	x	x	9/10

(* Note: this criterion is not used to calculate the PEDro score)

Results

Of the 66 articles retrieved from the literature search and review, only four were eligible for inclusion in the present study. A description of each article and its WebQualis and PEDro scores are shown in Table 2. The average PEDro score of the manuscripts was 6.25. All articles were published in non-Brazilian journals with WebQualis scores that ranged from B2 to A1.

The total sample included 620 women. Molassiotis et al. (2012) analysed 302 women divided into two groups receiving standard care and acupuncture treatment. Smith et al. (2013) analysed a sample of 84 women allocated to three groups: acupuncture, sham acupuncture, and wait list (control). In a study by Molassiotis et al. (2013), 97 women were evaluated in three groups classified by the type of treatment received: acupuncture, auto-acupuncture, and control. A study by Mao et al. (2014) included 67 women allocated to electroacupuncture, sham acupuncture, and standard care groups. All the authors selected the patients for each study group randomly, in order to avoid any possible bias.

All included studies evaluated the effect of acupuncture on fatigue and other symptoms related to breast cancer treatment over different time intervals. Smith et al. (2013) and Molassiotis et al. (2012) evaluated acupuncture effects over shorter periods of two and four weeks, respectively, whereas Mao et al. (2014) and Molassiotis et al. (2013) evaluated acupuncture effects over longer periods of 12 and 18 weeks, respectively.

The authors used a number of scales for symptom assessment. The 14-item Hospital Anxiety and Depression Scale (HADS) as well as the Functional Assessment of Cancer Therapy-General (FACT-G), Functional Assessment of Cancer Therapy-Breast Cancer (FACT-B), and Multidimensional Fatigue Inventory (MIF) scales were used by Molassiotis et al. (2012, 2013). The HADS scale was also used by Mao et al. (2014). The authors used the BWI, Brief

Fatigue Inventory (BFI), Pittsburgh Sleep Quality Index (PSQI), and Brief Pain Inventory (BPI). The BFI was also used by Smith et al. (2013), along with other scales, including the Wellbeing Questionnaire (W-BQ12) and Measure Yourself Concerns and Wellbeing Questionnaire (MYCaW).

In these studies, the use of two scales for fatigue evaluation was described. The nine-question BFI evaluated the severity and impact of physical, affective, cognitive, perceptive, and social fatigue on daily activities. The 20-question MIF was also used to assess the cognitive, emotional, motivational, and physical activities of patients^{18,19,20}.

Molassiotis et al. (2012) evaluated fatigue, quality of life, anxiety, and depression. On all scales, the acupuncture group demonstrated significant improvement after six weeks of treatment ($p < 0.05$). Smith et al. (2013) reported that, after two weeks of treatment, the acupuncture group had already experienced decreased fatigue and, after six weeks of treatment, this group also exhibited improvement in general well-being ($p > 0.05$). In the study by Molassiotis et al. (2013), the acupuncture group experienced improvement in fatigue after 18 weeks of treatment ($p > 0.05$). Mao et al. (2014) demonstrated that electroacupuncture was effective for the clinical improvement of fatigue after eight weeks of treatment. Moreover, electroacupuncture was shown to be effective for controlling anxiety and depression ($p < 0.05$).

There was a great variation of acupuncture points in the studies and one of them didn't inform the application points. Although all the authors mentioned favourable results, it is important to consider risk of bias in selecting the points of acupuncture.

The ROBIS tool was used to estimate the risk of bias. It was seen that the potential risk of bias in relation to the methods used to identify and/or select the studies was classified as low, since all questions were answered as "Yes" or "Probably Yes".

Table 2. Data of the selected manuscripts: breast cancer, fatigue, acupuncture, and randomized trial, dec/2017

Title, Author, Periodical, Year	Type of Study	Intervention	Sessions	Duration	Points	Sample	Outcome	Conclusion	Qualis	PEDro
Molassiotis et al., 2012	Randomized Clinical Trial	Acupuncture x Usual Care	1 session per week for 6 weeks	20 minutes	ST36, SP6 and LI4 (alternative lymphoedema points: GB34 and SP9)	302 women (75 Usual Care x 227 Acupuncture)	Acupuncture group presented improvement in fatigue and quality of life at the end of the 6-week treatment (p <0.001)	Acupuncture was effective in managing fatigue and improving the quality of life of patients. Acupuncture promoted improvement of symptoms, but the authors suggest that it is necessary to perform clinical trials with greater power and larger sample.	A1	5/10
Smith et al., 2013	Clinical Trial Randomized Controlled	Acupuncture x Sham Acupuncture x Waiting List	2 sessions per week for 3 weeks and then 1 week per week for 3 weeks.	20 minutes of application n(45 minutes of complete session)	ST36, SP6, bilateral KI3, KI27, unilateral CV4, e CV6	30 women (10 Acupuncture x 10 Sham x 10 Waiting List)	Acupuncture group showed improvement in wellbeing, fatigue, mood and sleep after 2 weeks. (p = 0.006)	There was no statistically significant difference between groups at the end of 4 weeks of treatment. But a clinical improvement was scored. (p = 0.07)	B2	8/10
Molassiotis et al., 2013	Randomized Clinical Trial	Acupuncture x Auto Acupuncture x Control	1 time per week for 6 weeks	20 minutes	ST36, SP6 e LI4	197 women (65 Acupuncture x 67Auto x 65 Control)	Electroacupuncture produced significant improvements in fatigue, anxiety, and depression and a non-significant improvement in sleep disturbance during the 12-week intervention and follow-up period. Acupuncture sham had a significant improvement in depression. (p <0.001)	Maintenance of acupuncture did not produce major improvements beyond those observed after an initial clinical-acupuncture course. Electroacupuncture demonstrated efficacy in improving fatigue, sleep, depression and pain. The authors recommend further research with a longer follow-up time.	A1	3/10
Mao et al., 2014	Clinical Trial Randomized Controlled	Electroacupuncture x Sham Acupuncture x Usual Care	2 times a week for 2 weeks, then once a week for 6 weeks weeks.	30 minutes	Uninformed	67 women (22 Electroacupuncture x 22Sham x 23Usual Care)	Electroacupuncture produced significant improvements in fatigue, anxiety, and depression and a non-significant improvement in sleep disturbance during the 12-week intervention and follow-up period. Acupuncture sham had a significant improvement in depression. (p <0.001)	Electroacupuncture demonstrated efficacy in improving fatigue, sleep, depression and pain. The authors recommend further research with a longer follow-up time.	A1	9/10

Discussion

Given the increasing prevalence and incidence of breast cancer worldwide, new challenges related to the management of symptoms arising from oncological treatment have emerged. These include complaints of fatigue, which may negatively affect the emotional, psychological, and social health of patients with breast cancer. All the manuscripts included in this systematic review strongly suggested the use of acupuncture as an efficient therapeutic method for the management of fatigue related to breast cancer. The use of all available therapeutic resources, such as acupuncture, to treat effectively these symptoms is relevant to physiotherapeutic and medicine practice. This therapeutic tool has low cost and could be used easily in public health service.

Treatment of breast cancer involves the use of chemo- or radiotherapy. Patients may experience side effects from these treatments that interfere with their quality of life and daily activities. Pain, nausea, anxiety, depression, insomnia, and fatigue are just a few of the symptoms associated with cancer therapy. According to Servaes et al. (2007), 40% of patients with breast cancer complain of fatigue²¹. In a clinical study by Goldstein et al. (2012), 31% of patients with breast cancer complained of fatigue after oncological treatment. Among these women, 11% reported episodes of fatigue lasting up to six months and 6% complained of fatigue lasting up to 12 months²².

Several terms are used to describe non-invasive therapies that 'complement' the therapeutic strategy chosen for each cancer patient. 'Complementary therapy' and 'alternative therapy' are terms that describe any medical practice, system, or product that is not part of traditional medical care. A more current and comprehensive term that has been used is 'integrative medicine', which is defined as the coordinated use of evidence-based complementary practices²³. Acupuncture, hypnosis, and meditation may be included in the latter category.

Some studies have suggested the use of integrative medicine practices, such as acupuncture, to improve and control undesirable symptoms caused by the use of drugs, regardless of whether they are radiochemotherapeutic. A positive outcome of acupuncture reported by the study populations of the clinical trials evaluated was that it contributed to a decrease in the use of drugs used to control chronic fatigue. In addition to improving

fatigue, the authors described reductions in insomnia, depression, and anxiety.

Although there is a favourable consensus in the scientific literature for the use of acupuncture, in some situations, it is difficult to quantitatively measure the efficacy of this therapeutic method. Molassiotis et al. (2013) reported that there was no significant outcome; however, their patients reported perceived clinical improvement.

No other methods of fatigue assessment were reported besides the scales described. However, some authors have evaluated fatigue associated with other types of cancer using different scales and patient reports. In 2009, Balk et al.²⁴ used the Functional Assessment of Chronic Illness Therapy-Fatigue Subscale (FACIT-F), which is a scale derived from the Functional Assessment of Cancer Therapy-General (FACT-G) scale, which analyses the impact of fatigue on physical, social, emotional, and functional domains. It was used in a randomised, double-blind, controlled pilot study of 27 women who were treated with acupuncture for cancer-related fatigue. The authors reported that there were no significant results; however, the patients described clinical improvement in their quality of life.

In 2013, He et al.²⁵ published a systematic review and meta-analysis that sought to assess the efficacy of acupuncture and moxibustion. In 2018, Zhang et al.²⁶ published a systematic review and meta-analysis investigating the effect of acupuncture on fatigue associated with various types of cancer. The authors reported similar results and stated that although the exact mechanism of action of acupuncture was unclear, it was shown to be effective in addressing cancer-related fatigue in general. These results corroborate those described in the present systematic review; however, our investigation only focussed on breast cancer.

Although all articles included in this systematic review were published in international journals of high impact within the scientific community, two articles had a score equal to or less than five on the PEDro scale. This can be explained by some aspects of the methodology that could have been more explicitly and adequately described. Unlike the other two articles with PEDro scores greater than eight, the evaluators for these studies were not blinded and there was no follow-up after treatment.

In 2006, Ordinance 8536 included acupuncture in the Integrative and Complementary Practices in the Services and Classifications Table of the National Registry System of Health Establishments (SCNES) of the Health Unique System (SUS), enabling health specialists to perform acupuncture in Brazil. The demand for acupuncture from SUS users is increasing; however, the number of acupuncturists in SUS areas remains low. Greater access to this therapy could be provided by the Family Health Support Centre (NASF), where women with breast cancer could have greater opportunity to receive acupuncture therapy²⁷. Since acupuncture is an inexpensive and accessible integrative practice that does not require a special environment or complex and expensive materials, it can serve as a therapeutic option for basic care and be integrated into public health policies. The adoption of acupuncture could reduce medical consultations and the financial costs of medications, as well as accelerate the return of patients to work activities.

This study has some limitations. Specifically, a limited number of articles met the inclusion criteria and, in the articles selected, the methodologies included different acupuncture points and treatment protocols.

It would be useful for health professionals, patients and politicians to amplify their knowledge about acupuncture and its indication for fatigue treatment because the number of cancer patients has been increasing everywhere.

Conclusion

There is increasing evidence that acupuncture is effective in women with breast cancer for controlling cancer therapy-related fatigue. In particular, the present study found a reduction in fatigue-related complaints with acupuncture treatment. However, in accordance with the practice of evidence-based medicine, the observed clinical improvement associated with acupuncture must be supported by stronger scientific evidence to promote its use for fatigue associated with other types of cancer.

Author contributions

Costa ACMP was responsible for the bibliographical survey, selection of articles and drafting of the systematic review. Medrado AP was responsible for critical analysis of the manuscript and writing of the study.

Competing interests

No financial, legal or political competing interests with third parties (government, commercial, private foundation, etc.) were disclosed for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.).

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