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Acupuncture Treatment in Cancer-related Symptoms

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Dear Editor of

Journal of Acupuncture & Meridian Studies

I am pleased to submit our manuscript entitled: “**Acupuncture Treatment in Cancer-related Symptoms**” for consideration as a review article in *Journal of Acupuncture & Meridian Studies*. This manuscript including related data has not been previously published and is not under consideration in the same or substantially similar form in any other peer-reviewed media. To the best of our knowledge, no conflict of interest, financial or other, exists. I have read and have abided by the statement of ethical standards for manuscripts submitted to **Journal of Acupuncture & Meridian Studies**

Sincerely,

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Acupuncture Treatment in Cancer-related Symptoms

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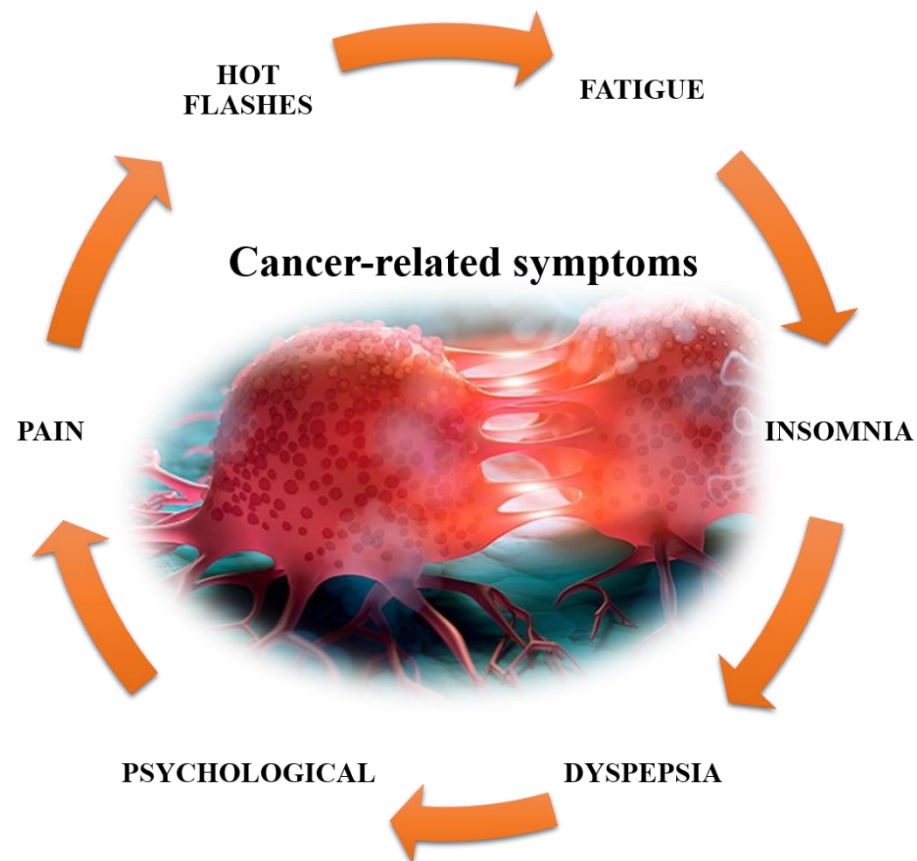
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Abstract

The development of malignancy in tumors and cancerous tissues will have a series of symptoms and side effects that negatively affect the quality of life of people, especially cancer patients, as well as their adherence to treatment and their long-term survival, is negatively affected. Acupuncture is a method of treatment that belongs to the classical methods in traditional Chinese medicine with a wide range of applications in the treatment of various diseases. Recently, the clinical application of acupuncture in cancer patients has received much attention. In this study, we summarized the clinical application of acupuncture in reducing cancer symptoms, reducing cancer-related side effects, and relieving cancer pain. Symptoms and side effects discussed in this study include fatigue, insomnia, chemotherapy dyspepsia syndrome, pain, hot flashes, and psychological symptoms. As a result, acupuncture is beneficial for cancer patients. However, more research is needed to elucidate acupuncture's potential effects and relationships for widespread acceptance in clinical applications.

Keywords: Cancer side-effects; Acupuncture; Fatigue, Insomnia, Dyspepsia Syndrome, Pain.

Graphical Abstract



Introduction

Cancer is a major cause of global mortality[1], so the prevention and treatment of cancer have become a major topic of medical research[2]. In addition to death, the progression of cancer is associated with a series of symptoms and side effects that are not only caused by cancer itself but also by cancer-related treatments such as surgery, chemotherapy, radiotherapy, and so on[3]. Side effects severely affect the quality of life and adherence to the treatment of cancer patients and thus negatively affect their long-term survival[4]. Recently, complementary and alternative medicine, including acupuncture[5], yoga[6], mindfulness[7], and massage therapy[8], have been increasingly used by cancer patients to relieve cancer-related symptoms. Among them,

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4 acupuncture, a well-practiced therapeutic approach in traditional Chinese medicine, has been
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7 proposed as an effective approach to improving cancer-related symptoms [9-11].
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10 Acupuncture is the placement of fine needles at specific acupuncture points in the human body[12].
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12 East Asia has utilized acupuncture to treat various ailments for over 2,500 years[13]. It is
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14 noteworthy that the benefits of acupuncture in the treatment of various diseases are also gradually
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16 recognized in the West. For example, the World Health Organization (WHO) and the National
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18 Institutes of Health (NIH) published a report on acupuncture, showing that more than 100 diseases
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20 and conditions can be treated with acupuncture [14]. NIH issues a consensus statement on
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22 acupuncture for postoperative nausea, asthma, chemotherapy, headache, toothache, low back pain,
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25 obsession, stroke rehabilitation, menstrual cramps, fibromyalgia, myofascial pain, osteoarthritis,
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27 and carpal tunnel syndrome[15]. The approved acupuncture needles have FDA licenses for use by
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30 licensed physicians[16]. 257% increment was seen in the total number of licensed acupuncturists
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32 in the United States (1998-2018). Acupuncture was one of the most common integrative oncology
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35 services in the United States and the European Union[17].
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40 Acupuncture effect on the symptoms and side effects of cancer

41 Cancer and cancer treatment are often associated with many symptoms and side effects, including
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43 fatigue, insomnia, indigestion syndrome of chemotherapy, radiation-induced dry mouth, pain,
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45 vomiting and nausea, cognitive impairment, anxiety, and depression. Since some of these
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47 symptoms and side effects are quite related, we mainly discussed the therapeutic potential of
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50 acupuncture in some of these symptoms and side effects in this review.
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54 Fatigue

55 Cancer-related fatigue is known to be one of the most common cancer-related side effects [18] and
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58 usually cannot be reduced with adequate sleeping or rest[19]. The onset of fatigue usually occurs
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4 before cancer treatment and often worsens during treatment[20]. More importantly, fatigue has
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6 been identified as a risk factor for short survival in cancer patients. Wang and Yu (2021) briefly
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8 summarize the main methods of traditional treatment of cancer-induced fatigue in patients with
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10 colorectal cancer to provide references and recommendations for clinical practice[21]. David et al.
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12 (2021) aimed to evaluate recent data on potentially effective and safe complementary and
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14 integrated drug therapies that could help cancer patients suffering from cancer-related fatigue. The
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16 results suggest that methods may have a potential role in reducing cancer-related fatigue. These
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18 include acupuncture, touch therapy, nutrition, dietary supplements, stress reduction, homeopathy,
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20 and circadian rhythm management. More research is needed to better integrate these methods into
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22 the conventional approach to cancer fatigue[21].
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29 Effective treatment options for fatigue are limited, including non-pharmacological interventions
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31 such as physical activity and psychosocial and mental-physical interventions. Choi et al. (2021)
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33 stated that despite the benefits of acupuncture in improving and safety of fatigue treatment, the
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35 methodological quality of most of these studies is low, limiting our ability to draw definitive
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37 meanings. Further high-quality research is needed to confirm these findings[22]. However,
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39 acupuncture has been shown to improve fatigue in patients with lung cancer. Lung cancer in people
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41 may have a high rate of symptom burden, and cancer-induced fatigue is a mutual and worrying
42
43 problem that can damagingly affect the quality of life and the course of treatment. Biological,
44
45 psychosocial, and medical factors play a role in causing and experiencing fatigue. Treatment of
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47 fatigue includes recognizing and treating underlying diseases and using pharmacological and non-
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49 pharmacological methods[23]. Lv et al. (2022) identified the effect and mechanism of acupuncture
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51 treatment on fatigue. They provided an alternative treatment for fatigue after chemotherapy for
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53 breast cancer, as well as a clinical and theoretical basis for the widespread use of acupuncture in
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tumor rehabilitation[24]. In addition, a meta-analysis study of ten randomized and controlled trials confirmed acupuncture as an effective tool for fatigue[25]. Therefore, acupuncture can be an effective and practical approach to relieving fatigue.

Insomnia

Insomnia is known as the most common sleep problem worldwide. Zhang et al. (2022) identified 690 studies with a specific type of cancer. The majority of breast cancer patients with 22 reviews and six quantitative syntheses were identified as highly heterogeneous in terms of participatory characteristics and study methods. Qualitative evaluation of the available evidence indicated the beneficial effects of acupuncture on sleep without serious side effects in several studies (55%). Manual acupuncture had a similar effective rate to acetazolamide immediately after the intervention and was more effective than acetazolamide at a 1-week follow-up. All reported acupuncture-related adverse events were mild to moderate in severity. Acupuncture has great potential for managing cancer-related insomnia for cancer patients or survivors[26]. Because cancer-related insomnia is often seen as a natural and transient response to cancer itself or cancer treatment, insomnia is often overlooked by physicians and cancer patients, leading to symptoms of chronic insomnia in cancerous patients[27-29]. Insomnia can be treated with both medication and non-medication. Hypnotic agents, including benzodiazepines and non-benzodiazepines, and antidepressants such as amitriptyline, doxepin, mirtazapine, and trazodone are commonly used to treat insomnia[30].

Although medication can improve sleep outcomes in the short term, significant side effects and concerns about drug interactions limit their use. Meanwhile, with the advent of non-pharmacological approaches, acupuncture is effective in treating primary insomnia, post-stroke

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4 insomnia, menopausal insomnia, and chronic pain-related insomnia. Effective treatment of
5
6 insomnia is controversial. In a clinical trial for the treatment of insomnia, Romero et al. (2019)
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8 conducted semi-structured post-treatment interviews with cancer survivors randomly in the
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10 acupuncture group. Participants considered the ability to respond to acupuncture dependent on
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12 treatment, effectively reducing comorbidities that lead to insomnia, supporting sleep hygiene
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14 practices, and providing a lasting therapeutic effect. Acupuncture treatment that does not address
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16 one of these issues often reduces the positive results of treatment and the perceived benefits of
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18 acupuncture[31]. Genovese MPH et al. (2021) performed an exploratory analysis of the genetic
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20 association with the insomnia treatment response in a randomized trial of cognitive-behavioral
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22 therapy for insomnia (CBT-I) versus acupuncture in a heterogeneous group of cancer survivors. In
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24 cancer survivors, specific alternates in the genes of COMT and NFKB2 are possibly connected
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26 with the acupuncture response but not CBT-I. Confirming these preliminary results helps to inform
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28 insomnia management for cancer survivors[32].
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36 Other studies have shown that acupuncture can provide significant and lasting improvements in
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38 insomnia in cancer survivors [32] and patients[33]. However, all of these studies suffer from small
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40 sample size weakness, so stronger clinical trials are needed to elucidate the therapeutic efficacy of
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42 acupuncture in insomnia treatment. On the other hand, Semi-structured interviews with cancer
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44 survivors participating in a randomized, controlled trial comparing the effectiveness of cognitive-
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46 behavioral therapy and acupuncture for the treatment of insomnia showed that three specific
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48 knowledge gaps, including treatment goal, mechanism, and durability, regarding the use of
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50 acupuncture for rescue insomnia Cancer Finders Addressing these gaps by providing appropriate
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52 and timely training on the use of acupuncture to treat insomnia, is essential to increase evidence-
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54 based use of acupuncture and better meet the needs of patients among cancer survivors[34].
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Dyspepsia Syndrome of Chemotherapy (DSC)

Chemotherapy is commonly used in combination with radiotherapy, surgery, hormone therapy, or immunotherapy to treat many types of cancer. Despite effectively reducing tumor burden, chemotherapy inevitably causes irreversible side effects, such as DSC, defined as gastrointestinal symptoms after receiving chemotherapy, including premature satiety, anorexia, diarrhea, nausea, and vomiting[35]. It has been reported that up to 20% of cancer patients had to delay or even discontinue potential chemotherapy for DSC[36]. Although prophylactic administration of antiemetic drugs can reduce nausea and vomiting in 70 to 90% of cancer patients, these antiemetic drugs have limited effects on early satiety, anorexia, and chemotherapy-induced diarrhea. Despite the high prevalence of DSC, its pathophysiology is not well understood, and treatment options are limited and unsatisfactory. In the absence of effective drug therapies for DSC, many physicians and patients with DSC seek non-pharmacological approaches, including reassurance, lifestyle modification, psychotherapy, dietary interventions, medical nutrition, acupuncture, and electrical stimulation and modulation[37, 38].

Acupuncture is a safe and effective function for indigestion, while its effectiveness varies from person to person. Predicting the response of different indigestion patients to acupuncture treatment in advance and thus performing appropriate treatment for the individual is in line with the principle of predictive, preventive, and personalized medicine. In a recent study, Yin et al. (2022) developed individual effectiveness prediction models based on a support vector machine algorithm and common clinical features to predict the effectiveness of acupuncture in the treatment of DSC and identify patients suitable for acupuncture treatment. Predictive models developed based on this promise to assist physicians in judging patients' responses to acupuncture in advance so that they can tailor acupuncture treatment plans for different patients in a forward-looking rather than

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4 reactive manner, which can improve the clinical efficacy of medical treatment and save on medical
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6 expenses[39].
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10 To better understand the therapeutic mechanism of acupuncture, a recent study used functional
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12 brain imaging in DSC patients to assess brain activity response to acupuncture treatment. The
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14 acupuncture treatment reduced DSC symptom scores associated with widespread inactivation of
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16 brain activity in the brainstem, anterior cortex, insula, thalamus, and hypothalamus, suggesting
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18 that the therapeutic mechanism of acupuncture may include modulation of the homeostatic afferent
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20 processing network[40]. Two meta-analyses evaluated the efficacy and safety of acupuncture for
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22 the treatment of DSC patients. Kim et al. [41] included 20 randomized controlled trials and 1423
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24 DSC patients who received either acupuncture or other treatment. The second analysis by Zhou et
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26 al. [42] included 24 randomized controlled trials and 3097 DSC patients who received acupuncture
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28 or electrical acupuncture treatment. Both meta-analyses showed that acupuncture was more useful
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30 than conventional drugs. Both meta-analyses also showed that acupuncture increases the
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32 therapeutic benefits of DSC drugs.
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40 Pains

41 Pain is the most common symptom of cancer and has been reported in 90% of cancer patients at
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43 different stages of progression[43]. In addition, moderate to severe pain has been claimed in less
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45 than 50% of patients with early or moderate-stage cancer and nearly 90% of advanced-stage cancer
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47 patients[44]. More importantly, most cancer pain is not treated[45]. A current study summarized
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49 current evidence on the use of acupuncture to manage pain in cancer patients and described how
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51 acupuncture works and what intervention requires[46]. To evaluate the effectiveness of
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53 acupuncture on pain of cancer patients undergoing chemotherapy and to evaluate changes in the
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55 use of analgesics after using this intervention, a randomized controlled trial was performed on two
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parallel groups, one of which had an acupuncture group to treat pain and another one received a placebo. The results showed that acupuncture effectively reduced pain in patients undergoing chemotherapy[47].

Research on acupuncture and its use for cancer pain is rising, but the findings are contradictory. A total of 17 studies (with 1111 patients) were included in the systematic review to evaluate the available randomized clinical trials for evidence linking acupuncture and acupressure to cancer pain reduction. Also, in 6 randomized clinical trials to reduce pain intensity and two randomized clinical trials to reduce opioid dose, acupuncture and acupressure were combined with analgesic therapy. The degree of evidence was moderate due to the significant heterogeneity between studies[48].

Studies show that acupuncture improves cancer-related symptoms. However, it is not clear whether the patient's characteristics predict the pain response. A retrospective chart review included adult cancer patients who sought palliative care and received acupuncture to manage pain, determined the effect of acupuncture on cancer-related pain, and identified variables related to pain response. It was concluded that acupuncture improves cancer-related pain and other symptoms. Those with higher baseline pain scores and advanced disease were more likely to achieve significant pain relief. Improvements in depression and fatigue were closely related to pain relief[49]. Meng et al. (2018) also conducted a pilot study on acupuncture at pain acupoints for cervical cancer pain. They found that after treatment, patients in the acupuncture group had more results in reducing cervical cancer pain than patients in the control group[50]. A standardized clinical reference manual for the evaluation, diagnosis, and treatment of acupuncture-induced cancer pain in hospitalized cancer patients by Ashby et al. (2022) in east Asian medicine to fill a critical gap in the current literature, support the community and hospital-based acupuncturists as a

standard clinical reference and provide guidance for the management of cancer-related pain, using acupuncture in hospitalized patients[51].

Psychological symptoms

Emerging research suggests that acupuncture may also help treat cancer-related psychological symptoms. Medication for common symptoms such as anxiety, depression, and sleep disturbances can contribute to the high chemical load of cancer patients and cause other side effects. As a result, patients and providers alike are interested in evidence-based non-pharmacological alternatives such as acupuncture for these symptoms[52].

To evaluate the effects of acupuncture in women with breast cancer, focusing on patient-reported outcomes, a comprehensive literature review of randomized and controlled trials was performed on 2,524 identified studies in which the patients treated with acupuncture experienced an improvement in reddening and anxiety scores compared with the control group. In contrast, the improvement in depression was comparable in both groups[53].

While studies on the exact prevalence of depression in cancer vary, a recent study found that up to 15% of cancer patients and survivors and 50% of those in palliative care suffer from depression and acupuncture in addition to massage as an intervention[54]. A randomized clinical trial evaluated acupuncture for depression versus antidepressant drug (fluoxetine) in 80 patients diagnosed with a malignant tumor. The results showed that both acupuncture and fluoxetine effectively reduce depression, but acupuncture was significantly more effective than fluoxetine[33].

To observe the effect of Tiaodu Jieyu acupuncture with sertraline hydrochloride and sertraline hydrochloride alone on cancer-related depression and to discover its mechanism of action, a total

of 120 patients with depression were randomly divided into an observation group and a control group. It was found that Tiaodu Jieyu acupuncture combined with sertraline hydrochloride tablets can effectively reduce depression in patients with depression and has a better therapeutic effect than sertraline hydrochloride tablets. This mechanism may be related to regulating immune-related cytokine expression[55].

Improper management of preoperative anxiety reduces the speed of postoperative recovery in cancer patients. Therefore, preventive management using non-pharmacological interventions is essential to reduce opioid or anti-anxiety substance use, anxiety levels, and postoperative complications and improve hemodynamics and patient satisfaction with care. A recent systematic review in 2021 found that music, aromatherapy, and acupuncture effectively reduced preoperative anxiety in women undergoing breast cancer surgery[56]. Patients with chest cancer have the high health-related quality of life losses. A pilot study evaluated the effects of acupuncture, cognitive-behavioral therapy, and mindfulness on depression, anxiety, and quality of life. A total of 8 patients from this group participated in 5 sessions, and eight patients were followed up as controls. Adherence to treatments was high, and a tendency to improve anxiety, fatigue, pain and shortness of breath was observed in patients receiving acupuncture. However, it was not statistically significant due to the sample size[57].

In 2020, a pragmatic controlled randomized trial with blind assessment in the breast unit of a hospital in Spain was performed on a sample of 40 women receiving acupuncture treatment in addition to standard care or standard care procedures. The main outcome, pain, and secondary outcomes, including anxiety, analgesia use, nausea, side effects, and surgical complications, improved, which helped elucidate the potential role of acupuncture as a low-cost non-pharmacological strategy in controlling postoperative side effects[58]. In 2022, a pilot study aimed

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4 at evaluating the initial effect and feasibility of electrical acupuncture for quality of life and
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6 symptom burden in these gastric cancer patients who experience a reduction in health-related
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8 quality of life during adjuvant chemotherapy after gastrectomy and show promising effects in
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10 improving the quality of life, controlling the burden of symptoms and reducing toxicity during
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12 adjuvant chemotherapy in patients with gastric cancer[59]. Also, a systematic review of the
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14 treatments performed in the articles reported that acupuncture treatment for cancer patients based
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16 on a standard treatment protocol used acupuncture points, LI4, LR3, SP6, and ST36 for the basic
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18 symptoms of fatigue, hot flashes, mood problems, anxiety, depression and sleep problems[60].
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23 24 Hot flashes

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26 Hot flashing, a clinical symptom associated with touch, anxiety, sleep disturbances, and cognitive
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28 impairment, refers to a sudden sensation of fever and sweating on the face, neck, and chest[61-
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30 63]. Prevalence of hot flashing 80% to 90% and 51% to 81%, respectively, are the most common
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32 symptoms among pre- and post-menopausal women and breast cancer survivors[64]. Its related
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34 symptoms severely affect the treatment of sleep disorders and emotional problems or reduce the
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36 quality of daily life because hot flashes can last from 6 months to more than ten years[65-67].
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38 Hormone therapy (HT) is an intervention recommended for hot flashes. However, recent studies
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40 have shown that HT has many side effects and can increase the incidence of cardiovascular disease
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42 or breast cancer. The data show that the US government allocates 339 million annually to research
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44 complementary and alternative medicine, the most important of which is acupuncture.
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46 Acupuncture is now widely accepted by physicians and patients worldwide as a promising
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48 complementary alternative due to its clinically satisfactory therapeutic effect, fewer side effects,
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50 and non-drug resistance[68].
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Acupuncture is a well-known integrated method for managing hot flashes. However, data on predictors of acupuncture response in cancer patients experiencing hot flashes are limited. Randomized trials were conducted between 2019 and 2021 on 158 women with stage 0-3 breast cancer at three sites in the United States, China, and the Republic of Korea. They showed that acupuncture resulted in statistically and clinically significant improvements in hot flashes and endocrine symptoms[69]. In another study, the authors examined the relationship between patient characteristics, including diagnosis of traditional medicine, and response to therapy among cancer patients who received acupuncture to manage hot flashes. The final analysis included 558 acupuncture cases (151 patients) with a majority of women (90%) and 66% breast cancer, which showed that the mean treatment response was a 25% reduction in flushing score. The diagnosis of traditional medicine and other patient characteristics predicted the therapeutic response to acupuncture for hot flashes in cancer patients[70].

Acupuncture remains an effective treatment strategy, especially for fewer or no side effects, to critically evaluate acupuncture's effectiveness and safety in treating hot flashes in breast cancer patients[71, 72]. However, a suspicious attitude has emerged from existing systematic studies and meta-analyses of acupuncture for hot flashes. Although some articles argue that acupuncture can lead to acceptance and encourage effectiveness[71], most articles believe that there was insufficient evidence to determine whether acupuncture was effective or not. Based on quantitative analysis, acupuncture's effects with synthetic or positive drugs are not exceptional[73]. The results show that mock controlled trials failed to show specific effects of acupuncture, [74] acupuncture with venlafaxine reported no significant intergroup differences [75]. It can be assumed that there is insufficient evidence to support the effectiveness of acupuncture[76]. In addition, almost all studies evaluated the previous test process as poor quality. In addition, it is suggested that future

studies should be more accurate and of higher quality. In short, the science of acupuncture is insufficient to support its benefits adequately.

Conclusion

Non-pharmacological therapies can be useful for treating cancer-related symptoms, including reassurance, lifestyle modification, psychotherapy, diet management, medical nutrition, acupuncture, and electrical stimulation. Families and medical providers increasingly seek acupuncture to treat cancer-related symptoms. The non-invasive nature and minimized potential side effects of this non-addictive and non-drug-based treatment method are likely to benefit cancer patients, especially those who have failed conventional treatments. There is currently limited evidence to support the routine use of acupuncture in the symptoms treatment of cancer patients, although some patients respond well to non-pharmacological management. The timing of the integration of acupuncture into standard treatment and its position in the current treatment algorithm for cancer patients is not yet known. It is not yet clear whether it should be used for cancer patients or as an adjunct to acupuncture. Clinical trials are well performed and on a larger scale are needed to confirm the efficacy and identify potential opposing effects of this method on cancer-related symptoms.

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