

Acupuncture and Related Therapies for Symptom Management in Palliative Cancer Care

Systematic Review and Meta-Analysis

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Abstract: Available systematic reviews showed uncertainty on the effectiveness of using acupuncture and related therapies for palliative cancer care.

The aim of this systematic review and meta-analysis was to summarize current best evidence on acupuncture and related therapies for palliative cancer care.

Five international and 3 Chinese databases were searched. Randomized controlled trials (RCTs) comparing acupuncture and related therapies with conventional or sham treatments were considered. Primary outcomes included fatigue, paresthesia and dysesthesias, chronic pain, anorexia, insomnia, limb edema, constipation, and health-related quality of life, of which effective conventional interventions are limited.

Thirteen RCTs were included. Compared with conventional interventions, meta-analysis demonstrated that acupuncture and related therapies significantly reduced pain (2 studies, $n = 175$, pooled weighted mean difference: -0.76 , 95% confidence interval: -0.14 to -0.39) among patients with liver or gastric cancer. Combined use of acupuncture and related therapies and Chinese herbal medicine improved quality of life in patients with gastrointestinal cancer (2 studies, $n = 111$, pooled standard mean difference: 0.75 , 95% confidence interval: 0.36 – 1.13). Acupressure showed significant efficacy in reducing fatigue in lung

cancer patients when compared with sham acupressure. Adverse events for acupuncture and related therapies were infrequent and mild.

Acupuncture and related therapies are effective in reducing pain, fatigue, and in improving quality of life when compared with conventional intervention alone among cancer patients. Limitations on current evidence body imply that they should be used as a complement, rather than an alternative, to conventional care. Effectiveness of acupuncture and related therapies for managing anorexia, reducing constipation, paresthesia and dysesthesia, insomnia, and limb edema in cancer patients is uncertain, warranting future RCTs in these areas.

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Abbreviations: CI = confidence interval, CIPN = chemotherapy-induced peripheral neuropathy, NRS = numerical rating scale, PSQI = Pittsburgh Sleep Quality Index, RCT = randomized controlled trial, RR = relative risk, SR = systematic review, TFRS = Tang Fatigue Rating Scale, VAS = visual analog scale.

INTRODUCTION

Acupuncture is one of the major treatment modalities in Chinese medicine. It refers to a group of therapeutic techniques characterized by needle insertion into the skin, followed by either manual manipulation or electrical stimulation. Related therapies like acupoints injection and needleless procedures like moxibustion and transcutaneous electrical nerve stimulation are also often used separately or together with acupuncture. Acupuncture and related techniques have been widely used in managing various diseases and symptoms for more than 2000 years. Multiple theories were proposed to explain the mechanisms of actions, the most widely studied theory is the endorphin theory, where acupuncture stimulated release of neurotransmitter such as endorphin at spinal and supraspinal levels to modulate various physiological responses,^{1,2} which the physiological effects with acupuncture could be demonstrated by functional magnetic resonance imaging studies.³ On the other hand, 1 theory suggested possible association of acupuncture points with loose connective tissue anatomically.⁴ However, the exact mechanism remains unclear.^{5–7}

Multidimensional factors contribute to various symptoms in cancer patients, including tumor invasion or metastasis, anemia, polypharmacy, treatment side effects, hypogonadism in male patients, autonomic dysfunction, and release of inflammatory cytokines.^{8–14} Fatigue is the most common complaint in palliative cancer patients. Limited pharmaceutical agents such as glucocorticoid had proved their efficacy but they were associated with profound side effects. Available evidence suggests that acupuncture and related therapies are generally

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safe treatment modalities when they are delivered by adequately trained practitioners.^{5–7} Acupuncture and related therapies are widely used in palliative cancer care among Chinese populations,¹⁵ and are gaining popularity globally. Effectiveness of these treatments, especially in the management of symptoms for which conventional medicine has limited to offer, would be of high interest among clinicians in palliative medicine. For instance, the National Institute for Health stated that acupuncture is a proven effective treatment modality for adult post-operative and chemotherapy nausea and vomiting.¹⁶ Clinical evidence on the potential effectiveness of acupuncture and related therapies for controlling fatigue, paresthesia and dysesthesias, chronic pain, anorexia, insomnia, limb edema, and constipation should be synthesized. Currently, 10 systematic reviews (SRs) have been conducted to assess the role of acupuncture and related therapies in palliative cancer care. One meta-analysis showed effectiveness of acupuncture and patient education on cancer-related fatigue.¹⁷ An SR demonstrated that acupuncture is an effective treatment for chemotherapy-induced nausea and vomiting, but its effectiveness for other areas with unmet needs is uncertain.¹⁸ Results from SRs by Lee et al¹⁹ and Bardia et al²⁰ on treatment of cancer-related pain showed insufficient evidence to support or refute the effectiveness of acupuncture. One SR by O'Regan et al²¹ identified potential roles of acupuncture in treatment of pain, nausea and vomiting, xerostomia, hot flushes, fatigue, anxiety, depression, and insomnia. Nevertheless, firm conclusion could not be drawn as well.

The applicability of these available SRs is limited for a number of reasons. First, some SRs had less restrictive inclusion criteria for the study design, which included randomized controlled studies (RCTs), observational studies, and even case series studies.^{19,22} Including studies with less rigorous designs may jeopardize trustworthiness of the conclusion. Second, details on the baseline treatment, as well as interventions used in control groups were often not provided by either the SR authors or the primary study authors.²² Poor reporting makes it difficult to generalize evidence to clinical practice, even when the intervention is found to be effective. Lastly, many of these SRs were conducted more than 5 years ago. New primary studies have been published during the last 5 years, and an up-to-date SR focusing on this area is urgently needed.

We have conducted an updated SR on acupuncture and related therapies for symptom management in palliative cancer care. The objective of this study is to evaluate current best evidence on the potential role of acupuncture and related therapies in managing common cancer symptoms that pose substantial challenges to conventional care, including fatigue, paresthesia and dysesthesias, chronic pain, anorexia, insomnia, limb edema, constipation, and health-related quality of life. In order to overcome the shortcomings of previous SRs, strict inclusion criteria on study design and reporting quality were adopted in the current SR. Evidence from this SR may support the development of pragmatic collaboration model between conventional and complementary medical practice.

METHODS

This SR and meta-analysis was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist. Ethical approval was not necessary since all the analyses were conducted based on data retrieved from previous published SRs and trials.

Inclusion Criteria

To be included, the primary studies have to satisfy the following criteria:

- (1) Randomized controlled trials comparing acupuncture and/or related therapies with a valid comparison that allows evaluation of the net effect of acupuncture and/or related therapies.
- (2) Patients who are diagnosed with any type of cancer.
- (3) Any form of acupuncture or related techniques were considered, including needle-based acupuncture (including electroacupuncture), as well as other techniques, including auricular acupuncture, laser acupuncture, acupressure, acupoints injection, moxibustion, and transcutaneous electrical nerve stimulation.
- (4) Randomized controlled trials with control groups that have used any type of interventions without acupuncture or related treatments listed above. Control interventions may include conventional treatment, behavioral therapies, Chinese herbal medicine treatment, sham acupuncture, waiting list, or no treatment.
- (5) Randomized controlled trials reporting 1 or more of the following predefined primary outcomes measured with validated instruments were included: fatigue, paresthesia and dysesthesias, chronic pain, anorexia, insomnia, limb edema, constipation, and health-related quality of life.
- (6) Randomized controlled trials that reported details on treatment prescription and follow-up duration for both acupuncture and control group to ensure the usefulness of synthesized evidence.

Literature Search

Comprehensive literature search was conducted by searching both international and Chinese databases, including the Cochrane Central Register of Controlled Trials, MEDLINE, Embase, CINAHL Plus, the Allied and Complementary Medicine Database,²³ Chinese Biomedical Databases, Wanfang Digital Journals, and Taiwan Periodical Literature Databases. Specialized search filter for clinical trials were used in MEDLINE²⁴ and Embase.²⁵ Detailed search strategies and related results for each database are reported in Appendix 1, <http://links.lww.com/MD/A726>. No language restriction was set during the literature search.

Literature Selection, Data Extraction, and Risk of Bias Assessment

All the retrieved citations were screened and assessed for their eligibility according to the inclusion criteria. The following data were extracted from each included RCT: characteristics of the study, including first author's name, year of publication, country in which the trial was conducted, eligibility criteria, and sample size; details on patient characteristics, acupuncture and related therapies, and control interventions and outcomes; effect on each interested outcomes and adverse effects related to acupuncture and related therapies; and information on risk of bias.

Risk of bias of included RCTs were assessed with the latest version of the Cochrane risk of bias tool,²⁶ which assessed risk of bias in the domains of sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, incomplete outcome data, and selective outcome reporting. Each domain was judged to have low,

high, or unclear risk of bias according to information provided by RCT authors.

Literature selection, data extraction, and risk of bias assessment were performed by 2 researchers (XW, XL) independently, with disagreement resolved by discussion and consensus. A third reviewer (VCC) was consulted if disagreement could not be resolved, and his judgment was used as the final decision.

Data Analysis

Effectiveness was measured with relative risk (RR) for dichotomous data and standardized mean difference, or weighted mean difference for continuous data. Total 95% confidence interval (CI) was used to account for the uncertainty of the estimation. Random effects model was used to account for the variations across trials²⁷ during meta-analysis. I^2 statistic was used to measure the heterogeneity across trials. $I^2 < 25%$ was considered as low level of heterogeneity, 25% to 50% as moderate level, and larger than 50% as high level.²⁸ Funnel plot would be used to detect the potential presence of publication bias if more than 10 trials were available for 1 outcome.²⁹ Stata Version 13.0 (STATA Corporation, College Station, TX) was

used for the data analyses, with a 2-tailed significance level of 0.05. The protocol of this SR has been registered in PROSPERO (<http://www.crd.york.ac.uk/PROSPERO/DisplayPDF.php?ID=CRD42015023934>).

RESULTS

Study Selection

A total of 1704 citations were retrieved from the databases. Total 237 duplicates and 1402 citations were excluded based on title and abstract screening, and 65 citations were left for full-text assessment. Fifty-two were excluded for the following reasons: did not report prespecified outcomes (n=20); the add-on effect of acupuncture could not be evaluated as it was not separated from other treatments (n=7); no details reported on baseline or acupuncture treatment (n=7); no acupuncture prescribed in the treatment group (n=3); not a RCT (n=5); did not use validated instruments for outcome assessment (n=3); no details reported on time point for outcome measurement (n=4); and recruited both cancer and noncancer patients (n=2). At last, 13 RCTs³⁰⁻⁴² were included. Details on the study selection process can be found in Figure 1.

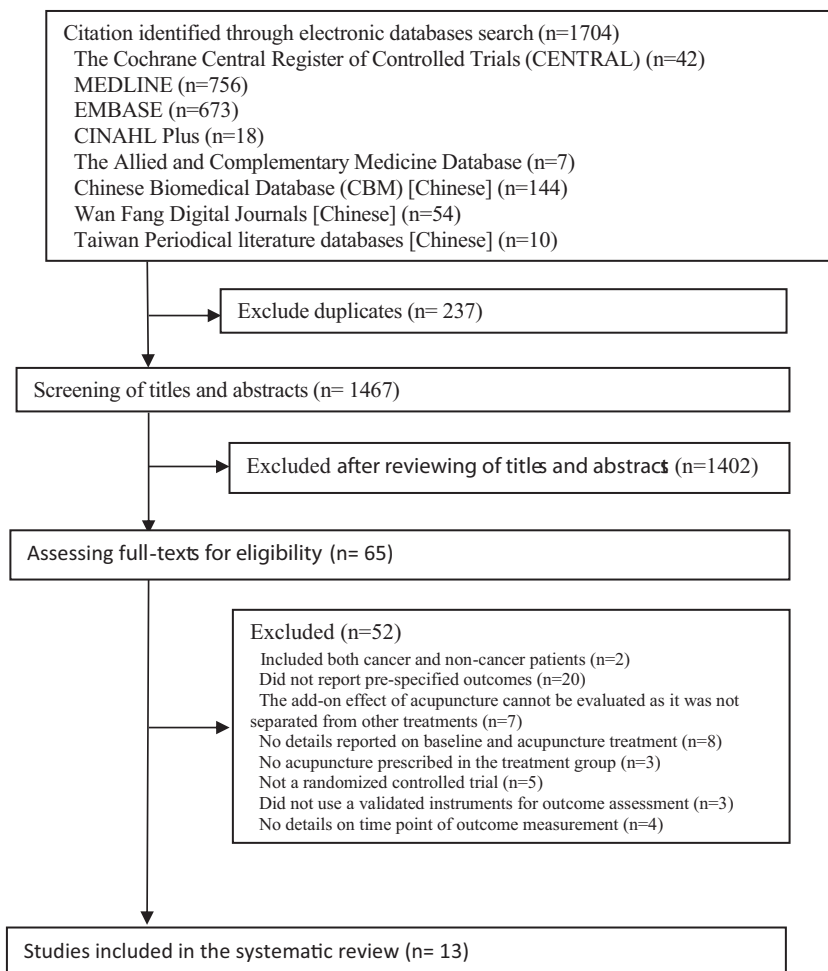


FIGURE 1. Flowchart of literature selection on randomized controlled trials of acupuncture for symptom management for cancer palliative care.

Characteristics of Included Randomized Controlled Trials

The 13 RCTs were published between 2005 and 2014, with 11 of them conducted in Mainland China, 1 in Taiwan and 1 in Germany. Eight RCTs included various types of cancer patients, and the remaining 5 RCTs were conducted in patients with gastric cancer (n = 2), liver cancer (n = 1), lung cancer (n = 1), and nonsmall cell lung cancer (n = 1). Various acupuncture modalities were used among the 13 RCTs, including acupoint injection (n = 4), needle acupuncture (n = 2), electroacupuncture (n = 2), and moxibustion (n = 1), the remaining 4 trials included more than 1 acupuncture modalities. As for the comparisons, 7 RCTs assessed the effectiveness of acupuncture and related therapies by comparing them with conventional interventions, 5 investigated the effect of acupuncture and related therapies as an add-on to conventional care, and the remaining trial assessed the efficacy of acupuncture by comparing it to sham acupuncture.

The most frequently reported outcome was pain (8 trials), followed by quality of life (3 trials). Respectively, 1 RCT reported evidence on constipation, anorexia, paresthesia and dysesthesia, fatigue, and insomnia. Details on characteristics of included RCTs are shown in Table 1.

Risk of Bias of Included Randomized Controlled Trials

Majority of included RCTs had low risk of bias in the domains of sequence generation (8 trials), incomplete outcome data (9 trials), and selective outcome reporting (12 trials). However, methods on allocation concealment and blinding were poorly reported. Only 2 RCTs were judged to have low risk of bias for allocation concealment, whereas the remaining 11 had unclear risk of bias. Due to difficulties in blinding and subjective nature of interested outcomes, we judged 12 RCTs as having high risk of bias for blinding of participants and personnel, and 8 as having high risk of bias for blinding of outcome assessment. Only 1 RCT had low risk of bias for the 2 blinding-related domains. Details are reported in Table 2.

EFFECTS OF ACUPUNCTURE AND RELATED THERAPIES

Pain

Eight RCTs assessed the effect of acupuncture for reducing pain in cancer patients. Two RCTs^{31–36} measured pain with numerical rating scale (NRS), which measured pain with a 0 (no pain) to 10 (most intolerable pain) scale. Meta-analysis showed that, compared with conventional medicine (morphine sulfate controlled-release tablets or World Health Organization's 3-step ladder for cancer pain relief), acupuncture and related therapies significantly reduced pain (n = 175, weighted mean difference: -0.76 , 95% CI: -0.14 to -0.39 , $I^2 = 0.0\%$) (Figure 2). Two RCTs^{31,41} also suggested that acupuncture and related therapies had significantly shorter analgesic onset time as compared with conventional medicine (morphine) (Table 3). An RCT⁴¹ reported data on analgesic duration has shown that, when compared with intramuscular injection of morphine, acupoint injection of morphine had 7 additional hours of analgesic duration (n = 115, mean difference [MD]: 7.29 hours, 95% CI: 6.27–8.31 hours) in patients with advance cancer (Table 3). Among the remaining 5 RCTs,^{32,35,37,38,40} although pain was measured with visual analog scale (VAS) or NRS, results were reported as proportion of patient achieving

satisfactory relief instead of VAS or NRS changes. Better effectiveness was described in acupuncture groups among all 5 studies, but no statistical significance was reached. Due to differences in the cutoff used to define satisfactory relief, data were not pooled in those 5 studies (Table 4).

Quality of Life

Four RCTs provided evidence on the effectiveness of acupuncture and related therapies for improving quality of life in cancer patients. Two studies^{34,42} reported quality of life-related scores measured with validated scales (Karnofsky Performance Status and Quality of Life Scale for cancer patients). Meta-analysis showed that the combination use of acupuncture and related therapies and Chinese herbal medicine slightly improved quality of life in patients with gastrointestinal cancer (n = 111, standardized mean difference: 0.75, 95% CI: 0.36–1.13) (Figure 3). Another RCT³² (n = 32) reported that nonsmall cell lung cancer patients who received the combination of acupoints injection of *Astragalus* extract with 3-step analgesic ladder medications had a significantly better quality of life than patients who received 3-step analgesic ladder medications only (33.3% versus 14.3%, RR: 2.00, 95% CI: 1.46–8.70) (Table 4). Another RCT³³ (n = 60) failed to find any difference in quality of life among cancer patients who received electroacupuncture, hydroelectric baths, vitamin B or vitamin B placebo.

Anorexia

One RCT³⁴ (n = 50) assessed the add-on effect of needle acupuncture on top of compounds Kushen injection for anorexia in patients with advanced gastrointestinal cancer. After 4 weeks treatment, a higher proportion of patients in the combined treatment group showed improvement on anorexia (59.3%) as compared with those who only received compounds Kushen injection (17.4%). However, the difference did not reach statistical significance (RR: 2.51, 95% CI: 0.94–6.72).

Constipation

An RCT³⁹ (n = 100) assessed the effectiveness of acupoint injection with vitamin B as compared with oral phenolphthalein for reducing constipation caused by slow-release morphine tablets. A higher proportion of patients in the acupoint injection group showed improvement (92.0% versus 70.0%). However, the difference was of no statistical significance (RR: 1.16, 95% CI: 0.84–1.63).

Fatigue

A 3-arm RCT⁴³ (n = 57) explored the efficacy of acupressure plus essential oil, and acupressure alone for cancer-related fatigue by comparing them with sham acupressure in lung cancer patients. Fatigue was measured with Chinese versions of the 37 items Tang Fatigue Rating Scale.⁴⁴ Each item is rated on a Likert scale ranging from 1 to 10, with higher scores indicating more severe fatigue. Data from the acupressure plus essential oil group and acupressure only groups were combined during data analysis. After 5 months of treatment, patients in the acupressure plus essential oil group and acupressure group showed significantly lower fatigue score (MD: -0.63 , 95% CI: -1.22 to -0.04). We conducted sensitivity analysis within study by excluding the acupressure group that had a high lost to follow-up. Significant difference was still observed between acupressure plus essential oil and sham acupressure group (Table 3).

TABLE 1. Basic Characteristic of Included Randomized Controlled Trials on Acupuncture and Related Therapies for Symptom Management in Cancer Palliative Care

First Author, Year of Publication, Country	Study Design Sample Size	Cancer Cite (Tumor Stage)	Characteristics of patients: M/F Mean Age, y	Intervention in the Treatment Group Details of Acupuncture	Intervention in the Treatment Group Details in Compared Intervention	Outcome	Time of Outcome Assessment
Chen, 2005 ¹⁷ China	2 arms RCT 32	Nonsmall cell lung cancer (TNM III–IV)	T: 16/2, 57.5 C: 12/2, 59.9	Acupoint injection + chemotherapy + 3-step analgesic ladder. Acupoint injection: ST36 (Zusanli), BL23 (Shen Shu), astragalus injection, 1 mL for each acupoint, 1 time/d for 56 days	Chemotherapy + 3-step analgesic ladder. Chemotherapy: NP: DDP 40 mg/m ² iv drip d1, d2, NVB 2.5 mg/m iv drip d1, d8; or CE: CBP 300 mg/m iv drip d1; VP-16 100 mg/m iv drip d1–d5; plus 3-step analgesic ladder; for 56 days	Pain and quality of life	Day 56
Yang, 2005 ²⁰ China	2 arms RCT 52	Gastrointestinal cancer (moderate to advanced stage)	T: NR, NR C: NR, NR	Acupoint injection: ST36 (Zusanli), tramadol, 0.05 g	Intramuscular injection. Intramuscular injection: tramadol, 0.1 g	Pain	30 minutes after the treatment
Li, 2006 ¹⁹ China	2 arms RCT 50	Gastrointestinal cancer in (advanced stage)	T: 17/10, 54.8 C: 14/9, 54.3	Needle acupuncture + conventional care. Acupuncture: ST36 (Zusanli), ST37 (Shangjuxu), ST39 (Xiajuxu), and GB34 (Yanglingquan), double; 20 minutes/session, 6 sessions/week for 4 weeks	Conventional care alone. Compounds Kushen injection 20 mL + 0.9% NS injection 250 mL, 1 time/d; 20% middle to long-chain fat milk 250 mL, 1 time/2 d for 4 weeks	Anorexia and quality of life	Day 28
Liu, 2007 ²¹ China	2 arms RCT 60	Liver cancer (NR)	T: 28/2, 52.35 ± 8.16 C: 18/12, 50.12 ± 7.72	Acupoint injection + needle acupuncture + moxibustion. Needle acupuncture: LR8 (Ququan), BL18 (Ganshu), BL15 (Hsinshu), and GV14 (Dazhui); 30 minutes; 1 session/d; acupoint injection: LR8 (Ququan), BL18 (Ganshu), and BL15 (Hsinshu); danshen injection 2 mL for each acupoint; 1 session/2 d; moxibustion: CV4 (Guanyuan), 5–7 minutes/session, 1 session/d, for 14 days	3-step analgesic ladder. 3-step analgesic ladder: pain in level I: indometacin 25–50 mg/time, 3 times/d; pain in level II: bucliperazine 50–100 mg/time, 3–4 times/d; and pain in level III: pethidine 50–100 mg/time, 4–6 times/d, for 14 days	Pain	Day 14
Chen, 2008 ²² China	2 arms RCT 66	Various types of cancer (advanced stage)	T: 15/19, NR C: 15/17, NR	Needle acupuncture: acupoints were select according to Ashi points, 30 minutes/session, 1 session/d, for 7 days	3-step analgesic ladder. 3-step analgesic ladder: pain in level I: aspirin 25–100 mg/time, 4–6 times/d; pain in level II: codeine 30–60 mg/time, 4–6 times/d; and pain in level III: morphine 5–30 mg/time, 4–6 times/d, for 7 days	Pain	Day 7
Wang, 2010 ¹⁶ China	2 arms RCT 60	Gastric cancer (advanced stage)	T: 28/12, 50.0 (median) C: 20/10, 52.5 (median)	Acupoint injection + needle acupuncture. Acupoint injection: ST34 (Liangqiu), compound angelica injection, 4 mL/time, 1 time/d. Needle acupuncture: CV12 (Chungwan), ST21 (Liangmen), P6 (Neiguan), ST36 (Zusanli), and BL21 (Weishu), 40–60 minutes/session, 1 session/d, for 7 days	Morphine. Morphine sulfate controlled-release tablets (MS Contim), 10–30 mg/time, 2 times/d, for 7 days	Pain	Day 7
Qin, 2010 ²⁴ China	2 arms RCT 100	Various types of cancer (NR)	T: NR, NR C: NR, NR	Acupoint injection: ST36 (Zusanli), BL25, S25; vit B1 6 mL, 1–2 mL for each acupoint, 1 session/d, for 12 days	Phenolphthalein tablets. Phenolphthalein tablets, 1–2 tablets/d, for 12 days	Constipation	Day 12
Yang, 2011 ²³ China	2 arms RCT 120	Various types of cancer (moderate to advanced stage)	T: 34/26, NR C: 31/29, NR	Electroacupuncture + morphine. Electroacupuncture: 25–30 minutes/session, 2 sessions/d, for 7 days	Morphine alone morphine hydrochloride tablets, 30–60 mg, 2/d, for 7 days	Pain	Day 7

First Author, Year of Publication Country	Study Design Sample Size	Cancer Cite (Tumor Stage)	Characteristics of patients: M/F Mean Age, y	Intervention in the Treatment Acupuncture	Intervention in the Treatment Group Details in Compared Intervention	Outcome	Time of Outcome Assessment
Li, 2011 ²⁵ China	2 arms RCT 133	Various types of cancer (NR)	T: 40/32, 61.36 ± 11.28 C: 36/25, 60.46 ± 12.18	Catgut implantation at acupoint + acupuncture + 3-step analgesic ladder. Catgut implantation at acupoint: CV12 (Chungwan), V10 (Hsiawan), CV6 (Qihai), CV4 (Guanyuan), ST24 (Huaroumen), and ST26 (Wailling); acupuncture: acupoints were selected according to Ashi points, 30 minutes/session, 1 session/d, for 10 days	3-step analgesic ladder. 3-step analgesic ladder: pain in level I: aspirin 25–100 mg/time, 4–6 times/d; pain in level II: codeine 30–60 mg/time, 4–6 times/d; and pain in level III: morphine 5–30 mg/time, 4–6 times/d, for 10 days	Pain	Day 10
Liu, 2013 ²⁶ China	2 arms RCT 115	Various types of cancer (TNM IV)	T: 30/29, 56.37 ± 11.62 C: 29/27, 58.12 ± 12.41	Acupoint injection: ST36 (Zusanli), morphine, 5 mg, injection when pain occurred, for 14 days	Intramuscular injection. Intramuscular injection: morphine, 10 mg, injection when pain occurred, for 14 days	Pain	Day 14
Pan, 2013 ²⁷ China	2 arms RCT 64	Gastric Cancer (TNM I-III)	T: 17/14, 57 C: 16/14, 58	Moxibustion + Weichang'an. Moxibustion: ST36 (Zusanli), 10–15 minutes/session, 1 session/2 d, for 6 months	Weichang'an alone. Weichang'an (WCA, a Chinese traditional medicine), 1 time/d, for 6 months	Quality of life	6 months later
Rostock, 2013 ¹⁸ Germany	4 arms RCT 60	Various types of cancer (NR)	T: 4/10, 49.9 ± 9.6 C1: 1/12, 52.3 ± 11.3 C2: 5/10, 56.3 ± 11.1 C3: 3/14, 52.0 ± 8.1	T: EA: LV3 (Taichong), SP9 (Xiongxiang), GB41 (Zulinqi), GB34 (Yanglingquan) (in patients with chemotherapy-induced peripheral neuropathy (CIPN) symptoms in the lower extremities), and LI4 (Hegu), LI11 (Quchi), SI3 (Houxu), and HT3 (Shaohai) (in patients with CIPN symptoms in the upper extremities), 15 minutes of electrostimulation (50 Hz) for each session, 8 ± 1 sessions for 3 weeks	C1: hydroelectric bath (HB); C2: vit B complex; C3: placebo of vit B. HB: The patients dipped their arms and feet into a special water basin with water at a temperature of about 35 °C. Each treatment lasted for 15 minutes with cross-galvanization of each individual extremity by low-frequency (50 Hz) faradic current (direct current impulses) up to the individual's sensitive threshold. For 3 weeks vit B: high-dosage vit B1/B6, 3 capsules/time, 1 time/d, for 3 weeks. Placebo: lactose capsules identical in form, taste, and odor to the vit B capsules, 3 capsules/time, 1 time/d, for 3 weeks	Paresthesia and dysesthesia; quality of life	Day 21 day 84
Tang, 2014 ²⁸ Taiwan	3 arms RCT 57	Lung cancer (TNM I–IV)	T1: 9/8, 53.9 ± 9.8 T2: 12/12, 54.8 ± 9.5 C: 12/4, 66.1 ± 8.0	T1: acupressure with essential oils; T2: acupressure only. Acupressure with essential oils: LI4 (Hegu), ST36 (Zusanli), and SP6 (Sanyingjiao); 5% essential oil, 1 minute/point, 1 session/d; acupressure only: LI4 (Hegu), ST36 (Zusanli), and SP6 (Sanyingjiao), 1 minute/point, 1 session/d for 5 months	C: sham acupressure. Sham acupressure: first metacarpal head, patella, and inner ankle, 1 minute/point, 1 session/d for 5 months	Fatigue and insomnia	Day 1 of the third chemotherapy; and day 1 of the sixth chemotherapy

C = control, CBP = carboplatin, CE = cisplatin, DDP = cisplatin, EA = electroacupuncture F = female, iv = intravenous, M = male, NP = cisplatin + vinorelbine, NR = not reported, NS = normal saline, NVB = Navelbine, RCT = randomized controlled trial, T = treatment, TNM = tumor node metastasis stage, vit B = vitamin B, VP = etoposide.

TABLE 2. Risk of Bias of Included Randomized Controlled Trials on Acupuncture and Related Therapies for Symptom Management in Cancer Palliative Care

First Author and Year of Publication	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Researchers	Blinding of Outcome Assessment	Incomplete Outcome Data Addressed	Selective Outcome Reporting
Chen, 2005 ¹⁷	Unclear risk quote: "32 advanced lung cancer patients were randomly divided into the observed group and the control group"	Unclear risk [*]	High-risk acupoint injection is difficult to accomplish blinding without sham control	High risk [†]	Low risk [§]	Low risk
Yang, 2005 ²⁰	Unclear risk quote: "Patients were randomly divided into the observed group and the control group"	Unclear risk [*]	High-risk acupoint injection is difficult to accomplish blinding without sham control	High risk [†]	Low risk [§]	Low risk
Li, 2006 ¹⁹	Low-risk quote: "50 cases were allocated to 2 groups using a table of random numbers"	Unclear risk [*]	High risk-acupuncture is difficult to accomplish blinding without sham control	Unclear risk [‡]	Low risk [§]	Low risk
Liu, 2007 ²¹	Unclear risk quote: "Patients were randomly allocated to treatment and control groups based on sequence of admission"	Unclear risk [*]	High-risk acupoint injection, acupuncture, and moxibustion are difficult to accomplish blinding without sham control	High risk [†]	Low risk [§]	Low risk
Chen, 2008 ²²	Low-risk quote: "66 cases of patients were first divided in to 3 different degrees of pain, each degree were randomly divided into using a table of random number"	Unclear risk [*]	High-risk acupuncture is difficult to accomplish blinding without sham control	High risk [†]	Low risk [§]	Low risk
Wang, 2010 ¹⁶	Low-risk quote: "Patients were randomly allocated into 2 groups using a table of random number"	Unclear risk [*]	High-risk acupoint injection and acupuncture are difficult to accomplish blinding without sham control	High risk [†]	Low risk [§]	Low risk
Qin, 2010 ²⁴	Unclear risk quote: "Patients were randomly divided into the observed group and the control group"	Unclear risk [*]	High-risk acupoint injection is difficult to accomplish blinding without sham control	High risk [†]	Low risk [§]	Low risk
Yang, 2011 ²³	Unclear risk quote: "Patients who meet the inclusion criteria were randomly allocated to treatment and control groups"	Unclear risk [*]	High-risk electroauricular acupuncture is difficult to accomplish blinding without sham control	High risk [†]	High risk no lost to follow-up in the treatment group, whereas 10 (16.7%) patients were lost to follow-up in the control group	Low risk
Li, 2011 ²⁵	Low-risk quote: "Patients were randomly allocated into 2 groups using a table of random numbers"	Unclear risk [*]	High-risk catgut implantation at acupoint and acupuncture are difficult to accomplish blinding without sham control	High risk [†]	Low risk [§]	Low risk

First Author and Year of Publication	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Researchers	Blinding of Outcome Assessment	Incomplete Outcome Data Addressed	Selective Outcome Reporting
Liu, 2013 ²⁶	Low-risk quote: "Patients were randomly divided into the observed group and the control group by drawing lots"	Unclear risk [*]	High-risk acupoint injection is difficult to accomplish blinding without sham control	High risk [†]	Unclear risk number of subjects included in the data analysis was not reported	High-risk pain score before and after intervention was listed in method; however, only effective rate for pain relief was reported instead of pain score. Low risk
Pan, 2013 ²⁷	Low-risk quote: "Patients were randomly allocated to 2 groups using a table of random number"	Unclear risk [*]	High-risk moxibustion is difficult to accomplish blinding without sham control	Unclear risk [‡]	Low risk lost to follow-up are 1/32 = 3.1% in the treatment group and 2/32 = 6.2% in the control group	Low risk
Rostock, 2013 ¹⁸	Low-risk quote: "Patients were allocated to one of the four treatment groups by a non-stratified block randomization with randomly varying block lengths"	Low-risk quote: "The biometrician prepared sealed, opaque, and sequentially numbered envelopes containing the treatment assignments"	High-risk electroacupuncture is difficult to accomplish blinding without sham control	Unclear risk [‡]	High risk lost to follow-up were 1/14 = 7.1%, 0/13 = 0.0%, 4/15 = 26.7%, and 3/17 = 17.6% in the 4 groups respectively.	Low risk
Tang, 2014 ²⁸	Low-risk quote: "Those who agreed to participate were randomly allocated to three groups by flipping a coin twice"	Low-risk quote: "to avoid bias, different personnel were responsible for randomizing, for implementing/teaching acupressure, and for collecting data. To maintain a double-blind design, data collectors and patients were unaware of group assignment"	Low-risk quote: "to avoid bias, different personnel were responsible for randomizing, for implementing/teaching acupressure, and for collecting data. To maintain a double-blind design, data collectors and patients were unaware of group assignment"	Low-risk quote: "to avoid bias, different personnel were responsible for randomizing, for implementing/teaching acupressure, and for collecting data. To maintain a double-blind design, data collectors and patients were unaware of group assignment"	High risk according to the study result, lost to follow-up were 2/17 = 11.8%, 8/24 = 33.3%, and 2/16 = 12.5% for acupuncture + essential oil, acupuncture alone and sham acupuncture group, respectively. Rates are imbalanced	Low risk

* = insufficient information reported.

† = no information on this domain was reported.

‡ = no information on who were the outcome assessors.

§ = no lost to follow-up.

|| = all the outcomes listed in the method section were completely reported.

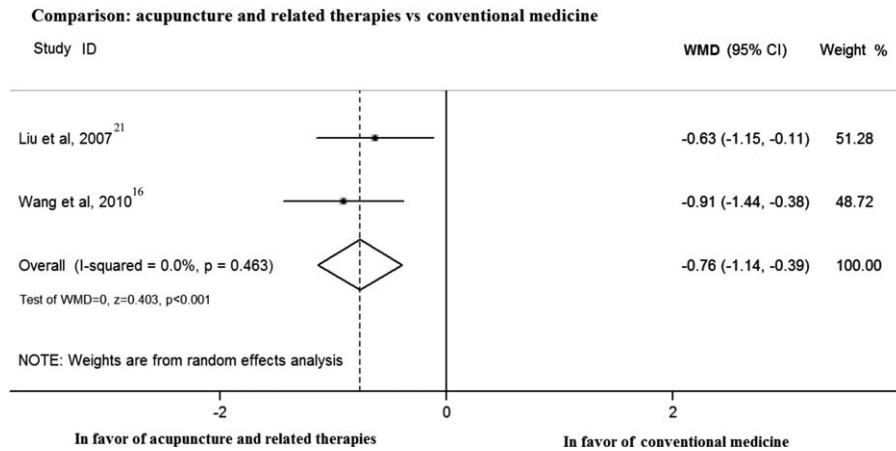


FIGURE 2. Meta-analysis on the effectiveness of acupuncture and related therapies for reducing pain score in cancer patients as compared with conventional medicine (comparison: acupuncture and related therapies versus conventional medicine).

Insomnia

The same 3-arm RCT⁴³ also investigated the efficacy of acupressure plus essential oil, and acupressure alone for insomnia in lung cancer patients. Sleep quality was measured with the 19-item Pittsburgh Sleep Quality Index.⁴⁵ With each item rated on a 0 to 3 Likert scale, a lower total score indicates better sleep

quality. Results showed that after 5-month treatment, patients in the acupressure plus essential oil and acupressure only group had better quality of sleep than that of patients in the sham acupressure group (Pittsburgh Sleep Quality Index score: 7.5 versus 10.1). However, this difference did not reach statistical significance (MD: -0.57, 95% CI: -1.16 to 0.02) (Table 3).

TABLE 3. Effectiveness of Acupuncture and Related Therapies for Symptom Management in Cancer Palliative Care: Outcomes Measured as Continuous Data

Author and Year of Publication	Comparison	Outcome Measurement	Treatment Group		Control Group		MD (95% CI)
			Mean (SD)	Number of Patients	Mean (SD)	Number of Patients	
Pain							
Analgesic onset time							
Wang, 2010 ¹⁶	Acupoint injection + needle acupuncture versus morphine	Day	2.03 (0.53)	30	3.69 (0.76)	30	-2.53 (-3.22, -1.85)
Liu, 2013 ²⁶	Acupoint injection versus intramuscular injection	Minutes	5.31 (4.98)	59	13.56 (3.47)	56	-1.91 (-2.36, -1.47)
Analgesic duration							
Liu, 2013 ²⁶	Acupoint injection versus intramuscular injection	Hours	19.21 (1.44)	59	10.35 (0.92)	56	7.29 (6.27, 8.31)
Fatigue							
Tang, 2014 ²⁸	Acupressure or acupressure + essential oil versus sham acupressure	Chinese version of the TFRS	130.0 (71.5)	41	175.7 (75.0)	16	-0.63 (-1.22, -0.04)
	Acupressure + essential oil versus sham acupressure	Chinese version of TFRS	122.9 (73.3)	17	175.7 (75.0)	16	-0.71 (-1.42, -0.01)
Insomnia							
Tang, 2014 ²⁸	Acupressure or acupressure + essential oil versus sham acupressure	PSQI	7.50 (4.47)	41	10.09 (4.76)	16	-0.57 (-1.16, 0.02)
	Acupressure + essential oil versus sham acupressure	PSQI	7.53 (4.29)	17	10.09 (4.76)	16	-0.57 (-1.26, 0.13)
Paraesthesias and dysesthesias							
Rostock, 2013 ¹⁸	Electroacupuncture versus (hydroelectric bath or vitamin B)	CIPN perceived severity score, day 21	3.2 (1.9)	14	3.5 (2.4)	28	-0.13 (-0.78, 0.51)
	Electroacupuncture versus (hydroelectric bath or vitamin B)	CIPN perceived severity score, day 84	3.4 (1.9)	14	3.7 (3.9)	28	-0.09 (-0.73, 0.55)

CI = confidence interval, CIPN = chemotherapy-induced peripheral neuropathy MD = mean difference, PSQI = Pittsburgh Sleep Quality Index, SD = standard deviation, TFRS = Tang Fatigue Rating Score.

TABLE 4. Effectiveness of Acupuncture and Related Therapies for Symptom Management in Cancer Palliative Care: Outcomes Measured as Dichotomous Data

First Author and Year of Publication	Comparison	Number of Patients in Treatment Group		Number of Patients in Control Group		RR (95% CI)
		Rated as Effective	Total	Rated as Effective	Total	
Pain						
Chen, 2005 ¹⁷	Acupoint injection + chemotherapy + 3-step analgesic ladder versus chemotherapy + 3-step analgesic ladder	12	18	3	12	2.00 (0.66, 6.03)
Yang, 2005 ²⁰	Acupoint injection versus intramuscular injection	26	26	22	26	1.09 (0.72, 1.64)
Chen, 2008 ²²	Needle acupuncture versus 3-step analgesic ladder	32	34	28	32	1.04 (0.72, 1.50)
Yang, 2011 ²³	Electroauricular acupuncture + morphine versus morphine alone	57	60	44	50	1.04 (0.79, 1.38)
Li, 2011 ²⁵	Catgut implantation at acupoint + acupuncture + 3-step analgesic ladder versus 3-step analgesic ladder alone	61	72	43	61	1.11 (0.83, 1.49)
Quality of life						
Chen, 2005 ¹⁷	Acupoint injection + chemotherapy + 3-step analgesic ladder versus chemotherapy + 3-step analgesic ladder	15	18	6	14	2.00 (1.46, 8.70)
Anorexia						
Li, 2006 ¹⁹	Needle acupuncture + conventional care versus conventional care alone	26	27	16	23	2.51 (0.94, 6.72)
Constipation						
Qin, 2010 ²⁴	Acupoint injection versus phenolphthalein tablets	46	50	35	50	1.16 (0.84, 1.63)

CI = confidence interval, RR = relative risk.

Paresthesia and Dysesthesia

A 4-arm RCT³³ compared electroacupuncture with hydroelectric baths, vitamin B and vitamin B placebo in managing chemotherapy-induced peripheral neuropathy (CIPN) including paresthesia among cancer patients. Severity of CIPN was measured with a NRS, scoring from 0 to 10, with a higher score indicating higher severity of CIPN. During analysis, data from hydroelectric baths and vitamin B groups were combined.

When compared with electroacupuncture group, no significant difference was found at follow-up on 21 days (MD: -0.13, 95% CI: -0.78 to 0.51) or 84 days (MD: -0.09, 95% CI: -0.73 to 0.55).

Adverse Events

Four RCTs^{31,35,41,42} reported information on adverse events. Patients in control group generally had more adverse

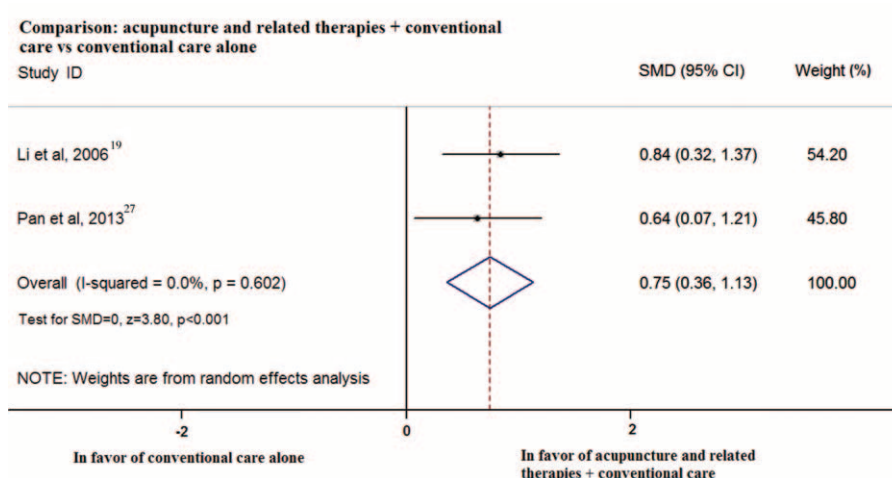


FIGURE 3. Meta-analysis on the add-on effect of acupuncture and related therapies for improving quality of life score in cancer patients as compared with conventional care alone (comparison: acupuncture and related therapies + conventional care versus conventional care alone).

events than those in the acupuncture group. However, only 2^{31,42} RCTs reported acupuncture induced side effects, including dizziness during needle insertion (5/30), subcutaneous bleeding (3/30), and mild burn, which was observed in few cases when moxibustion was inappropriately conducted, which was judged by the original RCT.²⁷

DISCUSSION

Results from 13 RCTs with 969 cancer patients were summarized in this SR. Acupuncture and related therapies significantly reduced pain in cancer patients with a quicker analgesic effect and longer analgesic duration when compared with conventional medicine. Acupressure or acupressure plus essential oil showed significant efficacy in reducing fatigue in lung cancer patients when compared with sham acupressure. Existing evidence also suggested that the additional use of acupuncture and related therapies with conventional or Chinese herbal medicine might improve quality of life in cancer patients. Overall, acupuncture and related therapies only caused minor side effects. On the other hand, available evidence did not show any differences on the following comparisons: the combined use of acupuncture and conventional care versus conventional care alone for treating anorexia; acupuncture and related therapies versus conventional medicine for reducing constipation, paresthesia and dysesthesia; and acupressure or acupressure plus essential oil versus sham acupressure for improving insomnia.

This SR has presented an updated view on the clinical applicability of acupuncture and related therapies for symptom management, especially in controlling pain and fatigue. Previous SRs^{19,20,46} showed inconclusive results for the efficacy of acupuncture and related therapies in cancer pain control due to a lack of “high quality” studies. Results from our SR suggested clinicians may consider acupuncture and related therapies for cancer related pain, in particular when pain control is unsatisfactory under conventional care, or when patients are experiencing significant side effects induced by analgesic medications. Regarding alleviation of cancer-related fatigue, 1 previous meta-analysis¹⁷ demonstrated statistical significant improvement with acupuncture and patient education when compared with conventional care. However, whether the effect was attributable to acupuncture or patient education could not be well delineated. Fatigue is a well acknowledged undertreated symptom in cancer patients due to lack of effective options in conventional medicine.⁴⁷ Our results suggest the practice of acupressure alone or in combination with essential oil can be an alternative or adjuvant treatment for cancer-related fatigue.

Risk of bias among the included RCTs should be carefully assessed. The majority of them did not provide information on how allocation concealment and blinding were ensured, results in high risk of ascertainment bias. On the other hand, bias could be further reduced if the outcomes were assessed by blinded²⁹ investigators.²⁹ Unfortunately, the majority of included RCTs did not specify whether the investigators analyzing outcomes were blinded except for 1 trial on fatigue and insomnia.³⁰ These reflected poor adherence of the Consolidated Standards of Reporting Trials reporting requirements⁴⁸ among these RCTs.³⁰

Another limitation of the reviewed evidence is that, due to small number of included studies for each outcome, we are unable to evaluate the presence or absence of publication bias. The majority of the included studies were conducted in Chinese populations either from Mainland China or Taiwan. Evidence users should consider potential heterogeneity among different

ethnicities and settings when adopting acupuncture and related therapies for their own practice.

Based on limitations of the included RCTs, several recommendations are made for further research. First, with the emergence of integrative medicine, acupuncture and related therapies are usually used as an adjuvant therapy on top of conventional care in real clinical settings. Hence, comparing acupuncture alone with standard care or sham acupuncture alone may only generate results with limited external validity. Conducting pragmatic trials that compare acupuncture plus standard care versus standard care alone may provide results that can directly inform clinical practice.⁴⁶ Second, future RCTs should use validated instruments for measuring outcomes. Amendments of instruments were not uncommon among included trials and this practice should be discouraged. For example, although all the 8 RCTs that reported data on pain used VAS or NRS, 5 of them summarized their results as dichotomous data according to self-developed rules. This reduces the interpretability of their results, and reporting bias of the outcomes is highly suspected. Third, future trials should evaluate the effect of acupuncture and related therapies in managing other important symptoms, including limb edema of which we did not locate any RCTs. Lastly, future RCTs should report adverse effect comprehensively so as to facilitate the safety assessment.

In conclusion, our meta-analyses demonstrated that acupuncture and related therapies showed a significant analgesic effect in terms of reducing pain score, providing quicker analgesic effect, and longer analgesic duration in cancer patients when compared with conventional medicine alone. However, these results are not in line with the rest of the evidence body in the area.⁴⁹ Acupuncture and related therapies can be considered as an adjunct, instead of a replacement to, conventional pain management protocol for cancer palliative care patients.

Acupressure or acupressure plus essential oil showed efficacy in improving fatigue in lung cancer patients. The combined use of acupuncture and related therapies with conventional medications or Chinese herbal medicine can improve quality of life among cancer patients. The effectiveness of acupuncture and related therapies in treating anorexia, constipation, paresthesia and dysesthesia, insomnia, and limb edema in cancer patients is unclear. As a relatively safe modality, acupuncture could be considered as an adjuvant options for the management of pain, fatigue, and improving quality of life in cancer patients. On the other hand, safety of acupoint injection and moxibustion would require further investigation. Future research should pay attention on: choosing appropriate control interventions that reflect real clinical practice; using validated outcome measurement instrument without unwarranted amendments; blinding the outcome assessors to reduce potential bias; and reporting the RCTs in accordance to the Consolidated Standards of Reporting Trials statement.⁴⁸

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