Acupuncture and Acupressure for Chemotherapy-Induced Nausea and Vomiting: A Systematic Review

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ABSTRACT

Background: Control of chemotherapy-induced nausea and vomiting (CINV) has improved with advances in antiemetics, such as NK[1] antagonists. Despite these advances, patients still experience these symptoms, and expert panels encourage additional methods to reduce these symptoms. Objectives: The objective was to assess the effectiveness of acupuncture and acupressure on acute and delayed CINV in cancer patients. Search strategy: The following databases were searched: AMED, MEDLINE, CINAHL, PubMed, Cochrane Controlled Trials Registry, and Science Direct. The search was undertaken from the inception of the database to January 2012. Selection criteria: Randomised controlled trials and systematic reviews of acupoint stimulation by needles, electrical stimulation or acupressure (excluding laser, point injection and non-invasive electrostimulation) and assessing chemotherapy-induced nausea or vomiting, or both. Data collection and analysis: Data was provided by publications of original trials and pooled. Standardised mean differences with confidence incidences were calculated. Main results: Seven trials were pooled for acupuncture and six for acupressure. Acupuncture reduced the frequency of acute vomiting (mean difference [MD] -7.40, 95% confidence interval [CI] -9.07 to -5.72), but did not reduce acute nausea severity or frequency compared to control. Delayed symptoms for acupuncture were not reported. Acupuncture showed a reduction in the dose of rescue medication (MD -5.52, 95% CI -7.45 to -3.58). Acupressure showed a decrease in frequency of nausea (MD -0.32, 95% CI -0.59 to 0.06) but not acute vomiting or delayed symptoms. All trials used state-of-the-art combination antiemetics, except for the early electroacupuncture trials. Authors' conclusions: Acupuncture has demonstrated some benefit for chemotherapy-induced acute vomiting by reducing the frequency of vomiting and reducing the use of rescue medication, while acupressure has shown a decrease in the frequency of nausea. Further trials of acupuncture and acupressure for chemotherapy-induced nausea and vomiting in patients with refractory symptoms are needed before recommendations for clinical practice can be made. Future trials must be sufficiently powered, as this remains a major flaw with the majority of studies to date.

KEYWORDS acupuncture points, nausea/chemically induced, electroacupuncture, vomiting/chemically induced, cancer, antineoplastic agents/adverse effects

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Introduction

Nausea is defined as an unpleasant feeling in the throat or stomach that may or may not lead to expulsion of stomach contents; vomiting is a motor reflex resulting in the expulsion of stomach contents.[1] Nausea and vomiting are among the most distressing and debilitating adverse effects identified by patients receiving chemotherapy treatment.[2,3] These symptoms continue to be a major concern for patients despite new and improved antiemetic therapy.[4–6] Patients have expressed a fear of developing these adverse effects.[7] Chemotherapy-induced nausea and vomiting (CINV) is defined as acute (occurring within the first 24 hours post treatment) and delayed (occurring from 24–120 hours post treatment). Acute and delayed CINV are identified as two different clinical aetiologies. Acute CINV is related to serotonin release, whereas delayed CINV is related in part to substance P.[8] The prevalence of acute and delayed CINV is approximately 40%–60% and 40%–80% respectively.[2]

Another type of CINV is defined as anticipatory. This is thought to be a conditioned reflex as a result of poor prior control of emesis[8] and affects approximately 25% of patients after four cycles of chemotherapy.[1,9]

The current management of CINV involves the use of 5-HT_3 receptor antagonists such as ondansetron, granisetron and palonsetron. 5-HT_3 antagonists are more effective against acute CINV, being minimally to moderately effective in delayed CINV. Their effect is increased when combined with a corticosteroid, normally dexamethasone.[10] Anticipatory CINV is linked to psychological processes and management is aimed at providing good control of acute and delayed CINV, and subsequently introducing behavioral interventions such as progressive muscle relaxation, other relaxation techniques and systematic desensitisation.[1,9]

A more recently developed antiemetic used in chemotherapy is aprepitant, a neurokinin-1-receptor antagonist, which has particularly increased the control of delayed CINV and has also shown benefit in acute CINV. However, despite advances in antiemetic therapy, there are still individuals who experience some form of CINV, most commonly delayed nausea.

Reviews on the control of CINV identified that non-pharmacological methods are a useful addition to standard treatment with antiemetics.[7] A growing number of studies have shown a benefit from electroacupuncture for CINV. Although acupuncture for CINV has been investigated previously, further high quality research is needed.[11–20] Since the publication of a review in 2006[21] on acupoint stimulation for CINV, several clinical trials have been published. The objective of this review is to examine the effectiveness of acupuncture and acupressure with the management of acute and delayed CINV.

Methods: Criteria for considering studies for this review

TYPES OF STUDIES

Systematic reviews and randomised controlled trials (RCTs), including parallel and crossover designs, were included. In the crossover trials, data from the first phase only was analysed, as the sufficiency of the washout period was unknown. Quasi-experimental trials were excluded.

TYPES OF PARTICIPANTS

Adults and children (aged 6–18 years old) receiving chemotherapy for any cancer were included.

TYPES OF INTERVENTIONS TO BE INCLUDED

Acupuncture involving stimulation using manual acupuncture, electroacupuncture and acupressure (pressure applied to acupoints) were included. Styles of acupuncture practised included traditional Chinese medicine (TCM), medical, auricular and Japanese. Laser acupuncture, point injection and non-invasive electrostimulation were excluded.

Control groups included: placebo acupuncture (defined as non-penetrating needles at same acupoints or non-acupoints, minimal invasive needling or sham acupuncture with no or little stimulation with a non acupoint, electroacupuncture inert position and no electrical stimulation) and placebo acupressure (defined as acupressure at non-acupoint or acupressure band with no button). Other control groups include standard care, including pharmacological interventions or other active intervention.

TYPES OF OUTCOME MEASURES

Frequency and severity of acute or delayed CINV, as measured by numbered rating scales, visual analogue scales, Rhodes Index of Nausea, Vomiting and Retching (RINV) and the Morrow Assessment of Nausea and Emesis (MANE) tool. Other measures include quality of life, use of rescue medications and breakthrough antiemetics.

SEARCH STRATEGY

The following databases were searched: AMED, MEDLINE, CINAHL, PubMed, Cochrane Controlled Trials Registry and Science Direct. The search was undertaken from the inception of the database to January 2012. Reference lists were reviewed for any possible missed trials.

The search strategy was limited to randomised controlled trials, reviews and systematic reviews only. Terms utilised include

acupuncture, acup*, electroacup*, electro-acup*, acupuncture therapy, traditional Chinese medicine, nausea, vomiting, cytotoxic, antineoplastic, chemotherapy, sham acupuncture and MESH headings.

Only English language texts were considered. Unpublished data was included in the analysis if obtainable.

Methods of the review

STUDY SELECTION

One reviewer performed the literature search and reviewed the citation list. Two reviewers independently reviewed all articles for study inclusion or exclusion and any disagreement not resolved by discussion was referred to the third reviewer for resolution.

DATA EXTRACTION

Following an assessment of study eligibility, two reviewers extracted data.

For each trial, the data extracted included the number of treatments, the number of needles utilised, the style of point selection and the time of needle retention. For the acupressure studies, data was collated on the duration of acupressure stimulation and type of stimulation, and the number of times points were stimulated. The following characteristics of the trial were documented including the number of participants, details of the control arms, study setting and the country of the trial. The authors were contacted to obtain additional information for unclear reporting or for primary data.

ASSESSMENT OF RISK OF BIAS

To assess the risk of bias for clinical trials a modified ten-point scale developed by Joanna Briggs Institute (JBI)[22] was used.

The scale assessed bias in relation to:

- Randomisation
- Control design
- Blinding
- Attrition: dropouts and withdrawals.

The quality of systematic reviews was assessed using the Critical Appraisal Skills Programme (CASP)[23] tool adapted from Oxman.[24]

MEASURES OF TREATMENT EFFECT

Data entry and statistical analysis was performed using Review Manager[25] software.

A statistical summary of the data was undertaken with continuous data expressed as mean difference (MD) with 95% confidence intervals (CI) and no missing scores being input.

Results

SYSTEMATIC REVIEW

Only one systematic review was identified: a Cochrane systematic review published in 2006.[21]

The Cochrane systematic review[21] was of a high methodological quality.

- The review asked a clearly focused question in relation to the population, interventions and outcomes considered and included randomised controlled trials (RCT) only.
- The method of the review clearly stated the databases used, follow-up of references and the limitations of not including unpublished studies or non-English language studies in the search.
- A clearly defined strategy was used for assessing the quality of the included studies, looking at antiemetic regimens, acupoint stimulation procedure and methodological quality of the studies.
- Data meta-analysis for each study was displayed clearly as relative risks, standardised mean difference and 95% confidence intervals.
- The authors identified heterogeneity in some trials in their analysis.
- The treated population was varied, allowing the ability to generalise study findings.
- The review clearly identified the implications for practice, concluding the practice is safe with minimal side effects, and identifying a need for further research.

The Cochrane review[21] identified a total of 1 247 participants from a total of 11 RCTs. Four were acupuncture or electroacupuncture trials, three used a form of acupressure and the remaining four used noninvasive electrostimulation. The review identified some benefit from acupoint stimulation (manual and electroacupuncture, acupressure and non-invasive electrostimulation) on acute vomiting (RR = 0.82; 95% CI 0.69 to 0.99; P = 0.04) but not acute or delayed nausea severity. Acupressure appeared to have a protective effect on acute nausea (MD = -0.19; 95% CI -0.37 to -0.01; P = 0.04). Acupuncture reduced the proportion of patients experiencing acute vomiting, but the electroacupuncture trials did not use state-of-the-art antiemetics (RR = 0.74%; 95% CI 0.58 to 0.94; P = 0.01). Acupressure was effective in reducing mean and worst acute nausea scores when used in conjunction with state-of-the-art antiemetic therapy.

RANDOMISED CONTROLLED TRIALS

The results of the current search identified trials included in the Cochrane systematic review[21] (a total of seven) as well as new trials published since 2005. In total 19 trials were identified for eligibility in this review, including the seven trials from the

Cochrane review. Twelve trials were included and seven trials were excluded.

Included trials were Dibble,[26] Dibble,[27] Dundee,[13] Dundee,[12] Gottschling,[14] Jones,[28] Melchart,[17] Molassiotis,[29] Reindl,[18] Roscoe,[30] Shen,[19] and Streitberger.[20]

Seven trials were included in the acupuncture group[12–14,17–20] and six in the acupressure group.[17,26–30] One trial[17] was included in both the acupuncture and acupressure interventions compared to standard treatment. A description of the trials is presented in Table 1.

EXCLUDED STUDIES

Seven trials were excluded. Three were excluded due to insufficient data availability or inability to contact the author.[31–33] One trial was not a randomised controlled trial.[11] One trial utilised transcutaneous stimulation bands,[34] one trial was not acupressure or acupuncture but used a herbal formula.[35] Two trials reported on exploratory analysis of data from previous trial.[36,37]

EXCLUDED REVIEWS

Six reviews were excluded. Two reviews[38,39] were excluded as they encompassed all symptoms of cancer treatment and were descriptive reviews. One systematic review addressed only breast cancer patients[40] with no meta-analysis and another examined all types of nausea and vomiting.[41] One publication was excluded because it was a narrative review of acupressure only.[42] One review was excluded due to a focus on moxibustion for symptom control in cancer patients.[43]

CHARACTERISTICS OF THE STUDIES

(SEE TABLE 1)

Four acupuncture trials were conducted in Germany, two in Northern Ireland and one in the United States of America (USA). Four trials were single centre only and three were conducted in a multicentre format. Five trials were undertaken in an inpatient setting, one in an outpatient setting and one in an inpatient and outpatient setting.

Four acupressure studies were conducted in the USA, one in Germany and one in the United Kingdom (UK). Two trials were single centre only and four trials were conducted in multicentres. Three trials were conducted in an inpatient setting and three in an outpatient and inpatient setting.

Sample sizes ranged from 10–739 participants with only five trials[19,20,27,29,30] having more than 50 participants, the majority having less than 30 participants. Acupuncture trial sample sizes ranged from 10–104, and acupressure trials from 18–739 participants; three trials[17,26,28] had fewer than 30 participants.

DESCRIPTION OF THE INTERVENTIONS

The acupuncture intervention varied significantly in the point selection, frequency of treatments and total numbers of treatments between trials. The majority of the trials (five of seven) utilised a formula approach to point selection and point selection using only one or two points (PC 6 *Neiguan* and ST 36 *Zusanli*).

In the acupressure trials, only one trial[26] used two points (PC 6 *Neiguan* and ST 36 *Zusanli*). All other trials stimulated one point only (PC 6 *Neiguan)*.

The duration of needling varied from 20–40 minutes in one trial[14] with four trials[17–20] reporting a needling duration of 20 minutes. Two trials[12,13] did not report on the duration of stimulation. The number of treatment sessions varied from 1–10, with three trials[13,14,19] having 5–6 treatments. One trial[18] reported administering 8–10 sessions, one trial[20] reported two sessions and two trials[12,17] reported one session only.

Acupressure stimulation method was either by digital pressure[26,27] or acupressure bands.[17,28–30] Acupressure stimulation varied from three minutes,[26,27] to 72 hours[17] to five days,[30] with one trial[28] not clearly stating the duration. The number of sessions varied greatly from one session[17,29,30] to ≥28 sessions.[26,27] One trial[28] did not clearly state the number.

OUTCOME MEASURES

ACUPUNCTURE OUTCOMES

Primary outcome measures varied between trials. Two trials[12,13] measured acute vomiting on a four-point scale (very good [no sickness], some benefit [marked reduction in sickness], no change [no benefit] and worse [worse than before]), two trials measured rescue antiemetic use,[14,18] two assessed the number of vomits[19,20] and one measured nausea only.[17] Secondary outcome measures also varied. Three trials[14,18,20] measured number of vomits, two trials[18,20] measured nausea intensity, two trials[17,19] measured rescue antiemetic use, one trial[19] measured vomiting-free days, one trial[17] frequency and duration of nausea and vomiting and one trial[20] perception of benefit.

Acupressure primary outcomes varied between the trials. Two trials measured nausea scores,[17,26] two assessed nausea and vomiting scores,[27,30] one used the Morrow scale[28] and one the Rhodes Index of Nausea, Vomiting and Retching (RINV).[29] Secondary outcomes measured included nausea intensity (three trials),[26,27,29] expectations of benefit(two trials),[28,30] and anxiety states(two trials).[27,29.] One trial each measured satisfaction with treatment,[28] quality of life[30] and a chemotherapy problem checklist.[26]

TABLE 1 Characteristics of studies

Dibble 2000	
Methods	Design: Parallel – Acupressure plus medication vs medication only Duration: One cycle 21–28 days
Participants	Setting: Outpatient oncology clinic teaching hospital and private outpatient oncology practice, USA Mean age (±SD or range): 49.5 (SD = 6.0) Men/Women (*n*/*n*): 0/18 Recruitment method: Research assistants approached patients or by their physicians Inclusion criteria: Receiving CMF (cyclophosphamide, methotrexate and fluorouracil) or a regimen containing doxorubicin, nausea from previous cycle or first cycle of chemotherapy, ability to communicate in English Exclusion criteria: None stated
Interventions	Intervention group: Acupressure Number allocated to acupressure = 9 Points stimulated: PC 6 and ST 36 Total length of treatment period: 21–28 days, one cycle of chemotherapy Number of sessions: Daily and when necessary; minimum of 21 Number of points used: 2 points Duration: Maximum 3 min or until point 'released' Method of stimulation: Digital acupressure Control group: Standard care Number allocated to control = 9 Total length of treatment period: 21–28 days
Outcomes	Nausea – daily score from nausea experience subscale from the INVR and daily intensity scale Reported as *p*-values and mean with SD
Attrition bias	Dropouts/withdrawals: No dropouts or withdrawals
Selection bias	Unclear, stated random but not method, unclear if allocation of treatment was concealed from allocator and both groups were comparable at entry
Performance bias	Attempt to confirm patient blinding for sham control? Not applicable Participants not blinded, unclear if assessors we blinded
Measurement bias	Low risk bias, both groups treated same, *p*-value analysis reported
Dibble 2007	
Methods	Design: Parallel – Acupressure plus medication vs sham acupressure plus medication vs medication only Duration: 21–28 days
Participants	Setting: Multicentre, total 19 settings throughout USA in clinical oncology centres Mean age (±SD or range): 49.3 (SD = 9.4) Men/Women (*n*/*n*): 0/160 Recruitment method: Not stated Inclusion criteria: Women receiving cyclophosphamide with or without 5-FU, doxorubicin with paclitaxel or docetaxel, or 5-FU, epirubicin and cyclophosphamide for breast cancer, had moderate nausea on previous chemotherapy cycle (per MANE scale) Exclusion criteria: Seeing acupuncturist, unable to communicate in English

TABLE 1 Characteristics of studies cont.

Dibble 2007 cont.	
Interventions	Intervention group: Acupressure to PC6 Number allocated to acupressure = 53 Style of acupressure: Self acupressure Points stimulated: PC6 Total length of treatment period: 21–28 days, depending on chemotherapy cycle Number of sessions: Minimum of one daily Number of points used: One Duration: 3 min each point Method of stimulation: Digital Control sham group: Acupressure to SI3 Number allocated to control: 53 Style of acupressure: Self acupressure Points stimulated: PC6 Total length of treatment period: 21–28 days depending on chemotherapy cycle Number of sessions: Minimum of one daily Number of points used: One Duration: 3 min each point Method of stimulation: Digital Control group: Standard treatment Number allocated to control = 54 Total length of treatment period: 21–28 days
Outcomes	Acute nausea and vomiting day 1 Delayed emesis days 2 to 11 Delayed nausea days 2 to 11
Selection bias	Yes, participant's allocation concealed Randomised to group, method not stated so unclear and both groups were comparable at entry
Attrition bias	Dropouts/withdrawals: Yes (13 withdrew reasons not stated) not included in analysis
Performance bias	Attempt to confirm patient blinding for sham control? Yes Participants blinded to group, not clear if outcome assessors where blinded, research assistants blinded to active point
Measurement bias	Type of analysis reported: Mean SD, consistent both groups
Dundee 1987	
Methods	Design: Crossover within cycle – Acupuncture plus medication vs sham acupuncture plus medication Duration: 3 days
Participants	Setting: Inpatient, Belfast, Northern Ireland Mean age (±SD or range): Not provided Men/Women (*n*/*n*): 10/0 Recruitment method: Unclear Inclusion criteria: Previous severe sickness after treatment despite metoclopramide Exclusion criteria: None identified

TABLE 1 Characteristics of studies cont.

Dundee 1987 cont.

Interventions	Intervention group: Antiemetics and electroacupuncture to PC6 Number allocated to acupuncture = 10 Style of acupuncture: Traditional Chinese medicine (TCM) Point selection: Formula Points stimulated: PC6 Total length of treatment period: 3 days Number of sessions: 5 or 6 Number of points used: One Insertion depth: Not stated Was *deqi* reportedly sought: Yes Duration: Not stated Method of stimulation: DC stimulator frequency 10 Hz, pulse width 0.25 ms Control group: Antiemetics and sham electroacupuncture to point near right elbow Number allocated to sham acupuncture = 10 Total length of treatment period: 3 days Number of sessions: Maximum one sham treatment in 3 days Number of points used: One Insertion depth: Not stated Was *deqi* reportedly sought: Not stated Duration: Not stated Method of stimulation: Electroacupuncture was applied via DC stimulator (10 Hz, pulse width 0.25 ms)
Outcomes	Acute vomiting Outcome measured by 4-point scale: very good (no sickness), some benefit (marked reduction in sickness), no change (no benefit) and worse (worse than before) Significant less sickness for PC6 than sham ($p<0.001$) Control from previous study showed 52 of 54 patients on cisplatin who had distressing symptoms after first treatment had just as severe the subsequent treatment
Selection bias	Stated that patients were unaware of allocation. Random selection but methods not clear. Unclear if allocator blinded to treatment group allocation and unsure if both groups were comparable at entry
Attrition bias	No dropouts or withdrawals, low risk of bias
Performance bias	Attempt to confirm patient blinding for sham control? No Participants were blinded, unclear if outcome assessors blinded, observers not always blinded as patient conveyed site of acupuncture
Measurement bias	Type of analysis reported: *p*-value same for both groups
Notes	Did not identify time of stimulation Drop reasons not identified Older study, not using modern antiemetics

Dundee 1988

Methods	Design: Parallel – Acupuncture vs medication only Duration: 5 min

TABLE 1 Characteristics of studies cont.

Dundee 1988 cont.	
Participants	Setting: Outpatients clinic, Belfast, Northern Ireland Mean age (±SD or range): Not stated Men/Women (*n*/*n*): Not stated 20 total Recruitment method: Not stated Inclusion criteria: First cycle chemotherapy Exclusion criteria: None stated
Interventions	Intervention group: Antiemetics and electroacupuncture to PC 6 Number allocated to acupuncture = 10 Style of acupuncture: TCM Point selection: Formula Points stimulated: PC 6 Total length of treatment period: One
Outcomes	Acute vomiting measured at 8–10 hr post chemotherapy administration Scale moderate or slight – though improvement not statistically significant
Selection bias	Unclear – randomised from previously prepared list – unsure who and how list was generated or if allocation to group concealed from the allocator and unsure if both groups were comparable at entry
Attrition bias	No dropouts or withdrawals, low risk of bias
Performance bias	Attempt to confirm patient blinding for sham control? Not applicable Blinding: Patients not blinded, observer was blinded
Measurement bias	Not clearly stated if outcome measure carried out in reliable way
Notes	Older study, not using modern antiemetics
Gottschling 2008	
Methods	Design: Crossover – Acupuncture plus medication vs medication only Duration: Varied from 4–5 days depending on chemotherapy treatment. Offered first day then succeeding days depending on patient's decision. Two cycles were observed, one with acupuncture and one without. Total time 4 weeks.
Participants	Setting: 5 paediatric inpatient settings, Germany Mean age (±SD or range): 13.6 ± 2.9 Men/Women (*n*/*n*): (10/13) Recruitment method: Not clearly stated Inclusion criteria: Receiving 3 identical courses of highly emetogenic chemotherapy (relating to type amount of antineoplastic agents) for solid tumours Exclusion criteria: Patients with full control of CINV without the need for rescue medications in first cycle, age under 6 and over 18 years, cerebral metastasis
Interventions	Intervention group: Standard antiemetics and acupuncture day 1 prior to chemotherapy and following 4 or 5 days depending on patient's request Number allocated to acupuncture = 23 Style of acupuncture: TCM Point selection: Flexible, practitioner decision based on TCM principles Points stimulated: Most commonly used points, PC 6, ST 36, CV 12 and LI 4

TABLE 1 Characteristics of studies cont.

Gottschling 2008 cont.	
Interventions cont.	Total length of treatment period: 4 weeks including washout period of two weeks between cycles Number of sessions: Maximum of 6 Number of points used: Not stated, stated could be unilateral or bilateral Insertion depth: Not stated Was *deqi* reportedly sought: Yes Duration: 20–40 min Method of stimulation: Manual acupuncture Control group: Standard antiemetics only Number allocated to control = 23 Total length of treatment period: 4 weeks in total, control was one cycle either 4 or 5 days
Outcomes	Primary outcome – antiemetic rescue medication use, obtained from chart documentation Secondary outcome – number of episodes of retching and vomiting, obtained from chart documentation
Selection bias	Patient randomised by computer generation sequencer and notified by phone. Allocation of treatment was concealed from allocator and both groups were comparable at entry
Attrition bias	No dropouts or withdrawals, low risk of bias
Performance bias	Attempt to confirm patient blinding for sham control? Not applicable. Participants not blinded due to study design. Unclear if outcome assessors blinded
Measurement bias	Type of analysis reported: Period effects both mean and standard error and treatment effects and treatment effect being equal in both periods
Notes	Patients also documented their subjective experience of acupuncture in a short open-form essay
Jones 2008	
Methods	Design: Crossover – Acupressure plus medication vs sham acupressure plus medication vs medication only Duration: 1–5 days for each cycle and total 3 cycles
Participants	Setting: Children's inpatient hospital USA Mean age (±SD or range): 5–19 (two sequence 11.7 ± 4.2 and 12.5 ± 3.6) Men/Women (*n*/*n*): 9/9 Recruitment method: Not stated Inclusion criteria: Patients receiving chemotherapy that included one of the following: an alkylating agent, an antitumour antibiotic or high dose cytarabine Exclusion criteria: Not receiving 3 cycles of chemotherapy, more than 7 years of age and did not assent, or not English-speaking
Interventions	Intervention group: Acupressure wrist band Number allocated to acupressure = 18 Point selection: Formula Points stimulated: PC6 Total length of treatment period: Time of chemotherapy treatment, not clearly stated as varied Number of sessions: One session Number of points used: One Duration: Not clear, could be hours to days Method of stimulation: Sea-Bands, elastic wrist band with plastic button Control group 1: Sham acupressure wrist band

TABLE 1 Characteristics of studies cont.

Jones 2008 cont.	
Interventions cont.	Number allocated to control = 18 Total length of treatment period: Unclear, could be hours to days Method of stimulation: Sea-Bands, elastic wrist band with no plastic button Control group 2: No acupressure Number allocated to control: 18 Total length of treatment period: Unclear
Outcomes	Modified Morrow with questions written in age appropriate language. Nausea measured with 11-point Likert scale. Previous knowledge and experience with acupuncture/acupressure, expectations of nausea prevention, episodes of emesis, degree of nausea at various time points, side effect, satisfaction and perceived differences acupressure and placebo bands
Selection bias	Patient randomised, method unclear and unclear if allocation of treatment was concealed from allocator and both groups were comparable at entry
Attrition bias	Dropouts/withdrawals: Yes (1 died, 1 incomplete data and 1 changed chemotherapy) but not included in analysis
Performance bias	Attempt to confirm patient blinding for sham control? Not applicable Participants were blinded, unclear if the outcome assessors were blinded
Measurement bias	Type of analysis reported: Mean and SD and consistent in both groups
Melchart 2006	
Methods	Design: Crossover – Acupuncture plus acupressure plus medication vs sham acupuncture plus sham acupressure plus medication Duration: Two cycles of chemotherapy, not clearly stated
Participants	Setting: 1 hospital, Munich, Germany Mean age (±SD or range): 57 (17–72) Men/Women (*n*/*n*): 18/9 Recruitment method: Not stated Inclusion criteria: Scheduled for moderately or highly emetogenic chemotherapy regimes, standard antiemetics and additional medication for two chemotherapy cycle and ages between 18–75 Exclusion criteria: Anticipatory nausea and vomiting, chemotherapy within past 3 months, cerebral metastases, chronic ileus or sub ileus, lymphoedema of arms
Interventions	Intervention group: Antiemetics and acupuncture followed by acupressure bands Number allocated to acupuncture = 10 Style of acupuncture: TCM Point selection: Formula Points stimulated: PC6 Total length of treatment period: 7 days for each cycle, total 2 cycles Number of sessions: One Number of points used: One Insertion depth: 0.5–1 cm Was *deqi* reportedly sought: Yes Duration: 20 min acupuncture, 72 hr acupressure bands and further 4 days if needed Method of stimulation: Manual and acupressure band Control group: Antiemetics and sham acupuncture and acupressure bands Number allocated to acupuncture = 11

TABLE 1 Characteristics of studies cont.

Melchart 2006 cont.	
Interventions cont.	Points stimulated: Sham point located 3–4 cm proximal to wrist crease; insertion of needle under the radius Total length of treatment period: 7 days for each cycle, total 2 cycles Number of sessions: One Number of points used: One Insertion depth: 0.5 cm Was *deqi* reportedly sought: Not sought, needle not manipulated Duration: 20 min for acupuncture followed by 72 hr with acupressure band Method of stimulation: Manual sham acupuncture and sham acupressure band
Outcomes	Nausea and vomiting, antiemetic rescue medication Daily diary completed for 7 days, (intensity scale 0–6) documenting frequency and duration of nausea and vomiting and use of additional antiemetic medication. Shortened version of the MANE (Morrow Assessment of Nausea and Vomiting) Main outcome was the intra-individual difference of the nausea score (sum of intensity rating for nausea in the diary range 0–48) between acupuncture and sham acupuncture Secondary outcome measures were: No nausea at all No vomiting Complete control (no vomiting and nausea score <9) Hours with nausea Number of vomiting episodes Use of rescue medication Acupuncture/acupressure helped a lot Preference Adverse effects
Selection bias	Participants randomised with computer random generation and concealed envelopes and allocator blinded to allocation of treatment group and unclear if both groups were comparable at entry
Attrition bias	Dropouts/withdrawals: Yes (3 change chemotherapy/death, 1 time problems, 1 ineffective and 1 no data) but not included in analysis
Performance bias	Attempt to confirm patient blinding for sham control? Not applicable Assessors of outcomes blinded to allocation – nursing staff and oncologist were blinded to allocation arm
Measurement bias	Type of analysis reported: Relative risks or mean difference
Molassiotis 2006	
Methods	Design: Parallel – Acupressure plus medication vs medication only Duration: 5 days
Participants	Setting: Two centres in the UK, one cancer centre at general hospital and one a specialist cancer hospital Mean age (±SD or range): 51 (±12.2) Men/Women (*n*/*n*): 0/54 Recruitment method: Not stated Inclusion criteria: Diagnosis breast cancer, chemotherapy naïve, receiving doxorubicin and cyclophosphamide or equivalent epirubicin protocols Exclusion criteria: Palliative chemotherapy, less than 3 months to live, metastatic disease, suffered from bowel obstruction, having concurrent radiotherapy or had lymphoedema of the arms

TABLE 1 Characteristics of studies cont.

Molassiotis 2006 cont.	
Interventions	Intervention group: Acupressure bands Number allocated to acupressure = 17 Point selection: Formula Points stimulated: PC 6 Total length of treatment period: 5 days Number of sessions: 1 Number of points used: 1 Duration: 5 days Method of stimulation: Sea-Band wrist bands Control group: No acupressure Number allocated to control = 19 Total length of treatment period: 5 days
Outcomes	Revised Rhodes Index of Nausea, Vomiting and Retching (INVR), number of times wristband stud was pressed, antiemetic use
Attrition bias	Dropouts/withdrawals: Yes (18 not competed study reasons not stated, 6 control group and 12 experimental group) not included in analysis
Selection bias	Patient effectively randomised, allocation of group concealed from allocator and both groups comparable at entry
Performance bias	Attempt to confirm patient blinding for sham control? Not applicable Participants not blinded, unclear if outcome assessors where blinded
Measurement bias	Type of analysis reported: *p*-value, utilised on both groups
Reindl 2006	
Methods	Design: Crossover – Acupuncture plus medication vs medication only Duration: Total of 3 cycles, time not specified
Participants	Setting: 4 inpatient paediatric centres, Germany Mean age (±SD or range): 15.2 (10.0–16.8) Men/Women (*n*/*n*): 4/7 Recruitment method: Not stated Inclusion criteria: Patients aged 6–18 years who receive several courses of highly emetogenic chemotherapy treating Ewing's sarcoma, rhabdomyosarcoma and osteosarcoma having $5HT_3$ antagonists as basic antiemetic medication Exclusion criteria: No exclusion criteria listed
Interventions	Intervention group: Standard antiemetics and acupuncture on day 1 prior to chemotherapy and subsequent 4 or 5 days Number allocated to acupuncture = 11 Style of acupuncture: TCM Point selection: Flexible, practitioner decision based on TCM principles Points stimulated: Most common points used PC 6, ST 36, CV 12 and LI 4 Total length of treatment period: Three cycles with third cycle not evaluated Number of sessions: 4 or 5 depending on chemotherapy protocol per session, total of 8 or 10 Number of points used: Not stated, points could be unilateral or bilateral Insertion depth: Not stated Was *deqi* reportedly sought: Not stated Duration: 20 min

TABLE 1 Characteristics of studies cont.

Reindl 2006 cont.	
Interventions cont.	Method of stimulation: Manual stimulation Control group: Standard antiemetics alone Number allocated to control = 11 Total length of treatment period: Two cycles of chemotherapy
Outcomes	Rescue antiemetic use, episodes of vomiting, nausea and weight loss Rescue antiemetic use obtained from medical chart, reported as mg/day Vomiting episodes recorded as a number per day for each cycle Weight loss was recorded by kg/cycle lost Nausea score using evaluated tool (Memorial Symptom Assessment Scale (MSAS)), concerning sensations of nausea, vomiting and appetite
Selection bias	Participants randomised, method unclear, allocation of treatment was concealed from allocator and both groups were comparable at entry
Attrition bias	No dropouts or withdrawals, low risk of bias
Performance bias	Attempt to confirm patient blinding for sham control? Not applicable Participants not blinded to treatment group due to trial design, unclear if outcome assessors were blinded
Measurement bias	Type of analysis reported: *p*-value, consistent with both groups
Roscoe 2003	
Methods	Design: Parallel – Acupressure plus medication vs medication only Duration: 5 days
Participants	Setting: 17 cancer centres in Rochester USA Mean age (±SD or range): Not reported Men/Women (*n*/*n*): 55/645 Recruitment method: Not clear Inclusion criteria: Chemotherapy naïve, chemotherapy containing cisplatin or doxorubicin Exclusion criteria: Concurrent radiotherapy or interferon, bowel obstruction, symptomatic brain metastases or cardiac pacemaker
Interventions	Intervention group: Acupressure band Number allocated to acupuncture = 231 (not stated) Points stimulated: PC6 Total length of treatment period: 5 days Number of sessions: 1 Number of points used: 1 Duration: 5 days Method of stimulation: Sea-Bands acupressure bands Control group: No treatment Number allocated to control = 226 Total length of treatment period: 5 days
Outcomes	Patient report diary developed by Burish et al and Carey and Burish measuring nausea and emesis in 4 time points each day. Nausea measured on 7-point scale. QOL measured by FACT-G (Functional Assessment of Cancer Therapy – General), expected efficacy assess on 5-point scale

TABLE 1 Characteristics of studies cont.

Roscoe 2003 cont.	
Selection bias	Participants randomised method unclear, unclear if allocator was blinded to group allocation, unclear if both groups were comparable at entry
Attrition bias	Dropouts/withdrawals: Yes reasons not stated, not utilised in analysis
Performance bias	Attempt to confirm patient blinding for sham control? Not applicable Not clear if outcome assessors blinded to group
Measurement bias	Type of analysis reported: Mean and SD, *p*-value, consistent with both groups
Shen 2000	
Methods	Design: Parallel – Acupuncture plus medications vs sham acupuncture plus medications vs medication only Questionnaire at the end of day 5 study period Duration: 14 days
Participants	Setting: 1 inpatient hospital, USA Mean age (±SD or range): 45.5(7.4) electroacupuncture, 43.8(8.0) minimal needling and 48.0(6.8) pharmacotherapy only Men/Women (*n*/*n*): 0/104 Recruitment method: Patients approached at clinics Inclusion criteria: Female patients 18–62 years of age, breast cancer, receiving myeloablative chemotherapy and for bone marrow transplantation, life expectancy at least 6 months Exclusion criteria: Patients with brain metastases, life-threatening concurrent non-malignant conditions, active infections, cardiac pacemaker
Interventions	Intervention group: Standard antiemetics and electroacupuncture for total 5 days Number allocated to acupuncture = 37 Style of acupuncture: TCM Point selection: Formula Points stimulated: PC 6 and ST 36 Total length of treatment period: 5 days Number of sessions: 5 Number of points used: 2 Insertion depth: 1–1.5 body inch Was *deqi* reportedly sought: Yes Duration: 20 min Method of stimulation: Electroacupuncture – 2–10 Hz, 0.5–0.7 ms pulse width, under a variable DC output with square waveform balanced alternating polarity of less than 26 mA maximal voltage 15 V Control group 1: Standard antiemetics and minimal acupuncture for total 5 days Number allocated to acupuncture = 33 Point selection: Formula Points stimulated: Near LU 7 and GB 34 Total length of treatment period: 5 days Number of sessions: 5 Number of points used: 2 Insertion depth: Minimal with no stimulation Was *deqi* reportedly sought: No Duration: 20 Method of stimulation: Electrostimulator was connected but no current was passed to the needles Control group 2: Standard antiemetics Number allocated to acupuncture = 34 Total length of treatment period: 5 days

TABLE 1 Characteristics of studies cont.

Shen 2000 cont.	
Outcomes	Emesis, emesis-free days, adverse events and concurrent antiemetic use Emesis measured and recorded daily by nursing staff, emesis as defined as projection of gastric contents not dry retching Proportion of emesis-free days was calculated Patients identified any adverse events they thought were attributed to the study Concurrent antiemetic use was identified from documentation All staff were unaware of patient's group allocation
Selection bias	Patient effectively randomised by concealed envelope system, allocation of group concealed from allocator and both groups were comparable at entry
Attrition bias	No dropouts or withdrawals, low risk of bias
Performance bias	Attempt to confirm patient blinding for sham control? Yes. Participants blinded. Outcome assessors were blinded to treatment group, nursing staff and other staff were blinded to patient allocation.
Measurement bias	Type of analysis reported: Analysed according to the intention-to-treat principle. *P*-value and confidence interval, consistent both groups
Streitberger 2003	
Methods	Design: Parallel – Acupuncture plus medication vs sham acupuncture plus medications Duration: 2 days
Participants	Setting: One hospital Haematology and Oncology unit, Heidelberg, Germany Mean age (±SD or range): 54.9 (9.0) acupuncture and 53.3(9.3) placebo group Men/Women (*n*/*n*): 41/39 Recruitment method: Not clearly stated Were people with history of acupuncture treatment excluded? Yes, no acupuncture for past 6 months Inclusion criteria: 18 years or older, patients receiving high dose chemotherapy and autologous peripheral blood stem cell transplantations Exclusion criteria: Patients suffering nausea and vomiting past 24 hours, receiving antiemetic drugs 24 hours before chemotherapy, receiving benzodiazepines (exception for one application at night), had received an antiemetic therapy before the start of chemotherapy exception of steroids if part of the chemotherapy treatment or a physiological supplement therapy, eczematous skin changes at acupuncture point PC 6, plaster allergy, opioid therapy starting or coagulopathy
Interventions	Intervention group: Standard antiemetics and acupuncture Number allocated to acupuncture = 41 Style of acupuncture: TCM Point selection: Formula Points stimulated: One Total length of treatment period: 2 days Number of sessions: 2 Number of points used: 1 Insertion depth: Not stated Was *deqi* reportedly sought: Yes Duration: 20 min Method of stimulation: Manual stimulation, initial *deqi* sensation obtained then left in situ for 20 min Control group: Standard antiemetics and placebo acupuncture Number allocated to acupuncture = 39

TABLE 1 Characteristics of studies cont.

Streitberger 2003 cont.	
Interventions cont.	Style of acupuncture: TCM Point selection: Formula Points stimulated: PC6 Total length of treatment period: 2 days Number of sessions: 2 Number of points used: 1 Insertion depth: Zero Was *deqi* reportedly sought: Not sought Duration: 20 min Method of stimulation: Use of Streitberger placebo needle (blunted, telescopic placebo needle)
Outcomes	Vomiting, rescue medications, nausea, side effects of acupuncture, credibility of treatment Vomiting assessed by number of patients who had one episode of vomiting in the evening of each day by use of patients' diary Use of rescue medications assessed on first and second day Nausea assessed by 4-point scale (none = 0, mild = 1, moderate = 2, severe = 3) Episodes of vomiting and retching
Selection bias	Participants randomised but method unclear, allocator was blinded to treatment groups and both groups were comparable at entry
Attrition bias	No dropouts or withdrawals, low risk of bias
Performance bias	Attempt to confirm patient blinding for sham control? Yes assessed with tool developed by Vincent Outcome assessors were blinded to allocation and patients were blinded to treatment group
Measurement bias	Type of analysis reported: *p*-values (t-test for continuous variable, Fisher's exact test for categorical variables), consistent for both groups

An assessment of the risk of bias

ACUPUNCTURE TRIALS

Five trials were at a low to moderate risk of bias.[17–20] Only one trial was at a low risk of bias,[20] four trials[14,17–19] were of moderate risk of bias and the remaining two trials[13,14] were at a high risk of bias (see Table 2).

SELECTION BIAS

Three trials[14,17,19] reported the method of generating the randomisation sequence to the treatment or control arms, and were assessed as low risk. Two trials[14,17] used a computer program and one trial[19] used a table to generate the randomisation. Four trials[12,13,18,20] didn't state how the randomisation sequence was generated and were assessed as risk unclear. Two trials[12,13] were published prior to the CONSORT Statement outlining the reporting of RCTs.

Five trials[14,17–20] identified the randomisation allocation as concealed from the allocator ensuring a low risk of bias. Three trials[14,18,20] concealed allocation by phone, while two trials[17,19] used sealed opaque envelopes. Again the two older trials[12,13] did not identify if this occurred.

Three trials[12,18,20] reported the control and treatment groups were comparable at entry and were assessed as low risk, while one did not report patient characteristics and it was unclear if there was bias.[13] Two trials[14,17] used crossover trials and the risk of bias was assessed as low. One trial[19] was assessed at a low risk of bias as there was no difference in groups at entry in relation to ethnicity, emesis with prior chemotherapy and alcohol use.

ATTRITION BIAS

Four trials[14,18–20] had no withdrawals and were assessed at a low risk of bias. Two early trials[12,13] did not detail reasons for withdrawal and were assessed as having an unclear risk of bias. The remaining trial[17] reported a 25% loss due to withdrawals, but did not include them in the analysis, and was assessed at a low to moderate risk of attrition bias.

PERFORMANCE BIAS

Four trials addressed performance bias in relation to blinding of outcome assessors.[13,17,19,20] Two trials[12,18] did not conceal the allocation from the assessors and were identified as moderate to high risk of bias. The remaining trial[14] was unclear.

MEASUREMENT BIAS

Six trials[13,14,17–20] used the same outcome measures for both groups and utilised reliable measures, ensuring a low risk of bias. The remaining trial[12] did not clearly state how the outcome measurements were assessed.

ACUPRESSURE TRIALS

Five trials[17,26–29] were assessed at a low risk of bias and the remaining trial[30] was assessed at a high risk of bias.

SELECTION BIAS

One trial[17] was assessed as low risk of bias because a randomisation sequence generation was stated. Another trial[29] using computer generation used simple random selection and was of low risk of bias. The remaining trials[26–28,30] were categorised as unclear risk of bias.

Four trials[26–29] reported that control and treatment groups were comparable at entry and were assessed as low risk. One trial[17] used a crossover design trial and was assessed at a low risk of bias. The other trial[30] was assessed as unclear.

ATTRITION BIAS

Only one trial[26] reported withdrawals and was assessed at a low risk of bias. The remaining trials[17,27–30] identified the withdrawals but did not include withdrawals in the analysis and were assessed at a low to moderate risk of bias. Levels of withdrawal were: Dibble et al[26] 8%, Jones et al[28] 14%, Melchart et al[17] 25%, Molassiotis et al[29] 34% and Roscoe et al[30] 34%.

PERFORMANCE BIAS

Three trials[17,27,28] reported that outcome assessment was blind to group allocation. Three trials[26,29,30] were assessed as unclear.

Two trials[17,29] ensured the allocation of treatment was concealed from the allocator with staff collecting the information blind to group allocation, and were assessed at a low risk of bias. The remaining trials[26–28,30] were assessed as unclear.

MEASUREMENT BIAS

All six trials[17,26–30] measured outcomes the same way for both groups and utilised reliable measures and were assessed at low risk of bias.

TABLE 2 Assessment of bias

Criteria	Acupuncture articles						
	Dundee 1987	Dundee 1988	Shen 2000	Streitberger 2003	Melchart 2006	Reindl 2006	Gottschling 2008
Assignment to groups truly random	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes
Were participants blinded to treatment allocation	Yes	No	No	Yes	Yes	No	No
Was allocation to treatment groups concealed from the allocator	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes
Were the outcomes of people who withdrew described and included in the analysis	No	Unclear	Yes	Yes	No	Yes	Yes
Were those assessing the outcomes blind to the treatment allocation	No	Yes	Yes	Yes	Yes	No	Unclear

TABLE 2 Assessment of bias cont.

Criteria	Acupuncture articles cont.						
	Dundee 1987	Dundee 1988	Shen 2000	Streitberger 2003	Melchart 2006	Reindl 2006	Gottschling 2008
Were control and treatment groups comparable at entry	Unclear	Unclear	No	Yes	Unclear	Yes	Unclear
Were groups treated identically other than for the named interventions	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes
Were outcomes measured in the same way for all groups	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were outcomes measured in a reliable way	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Was appropriate statistical analysis used	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Score out of 10	4	2	8	10	8	8	7

TABLE 2 Assessment of bias cont.

Criteria	Acupressure articles					
	Dibble 2000	Roscoe 2003	Melchart 2006	Dibble 2007	Molassiotis 2007	Jones 2008
Assignment to groups truly random	Yes	Yes	Yes	Yes	Yes	Yes
Were participants blinded to treatment allocation	No	Unclear	Yes	Yes	No	Yes
Was allocation to treatment groups concealed from the allocator	Unclear	Unclear	Yes	Unclear	Yes	Unclear
Were the outcomes of people who withdrew described and included in the analysis	Yes	No	No	No	No	No
Were those assessing the outcomes blind to the treatment allocation	Unclear	Unclear	Yes	Yes	Unclear	Yes
Were control and treatment groups comparable at entry	Yes	Unclear	Unclear	Yes	Yes	Yes
Were groups treated identically other than for the named interventions	Yes	Yes	Yes	Yes	Yes	Yes
Were outcomes measured in the same way for all groups	Yes	Yes	Yes	Yes	Yes	Yes

TABLE 2 Assessment of bias cont.

Criteria	Acupressure articles cont.					
	Dibble 2000	Roscoe 2003	Melchart 2006	Dibble 2007	Molassiotis 2007	Jones 2008
Were outcomes measured in a reliable way	Yes	Yes	Yes	Yes	Yes	Yes
Was appropriate statistical analysis used	Yes	Unclear	Yes	Yes	Yes	Unclear
Score out of 10	7	4	8	8	7	7

Meta-analysis

(SEE APPENDIX 1)

1. ACUPUNCTURE PLUS MEDICATION VS MEDICATION ONLY

1.1 FREQUENCY OF VOMITING

The frequency of vomits was reported in two trials.[14,19]A reduction in vomiting frequency was shown in the acupuncture plus medication group, mean difference (MD -7.40, 95% CI -9.07 to - 5.72, 94 participants).

1.2 DOSE OF RESCUE MEDICATION

The dose of rescue medication was reported in one trial[14] and showed a reduction in the dose of rescue medication in the acupuncture plus medication group (MD -5.52, 95% CI -7.45 to -3.58, 23 participants).

2. ACUPUNCTURE PLUS MEDICATIONS VS SHAM ACUPUNCTURE PLUS MEDICATIONS

2.1 FREQUENCY OF VOMITING

The frequency of vomits was reported in three trials[13,17,20] and showed no difference between groups (MD 0.70, 95% CI 0.38 to 1.29, 138 participants).

2.2 FREQUENCY OF NAUSEA

The frequency of nausea was reported in two trials[17,20] and showed no difference between groups (MD 1.01, 95% CI 0.67 to 1.50, 128 participants).

2.3 DOSE OF RESCUE MEDICATION

The dose of rescue medication was reported in two trials.[17,20] There was no difference between groups (MD 1.03, 95% CI 0.64 to 1.67, 128 participants).

2.4 HELPFULNESS OF ACUPUNCTURE

The helpfulness of acupuncture was reported in one trial[20] with 80 participants. There was no difference between groups (MD 1.11, 95% CI 0.71 to 1.74, 80 participants).

3. ACUPRESSURE PLUS MEDICATION VS MEDICATION ONLY

3.1 FREQUENCY OF VOMITING

Frequency of vomiting was reported in one trial.[29] No difference was found between groups (MD 0.13, 95% CI -1.46 to 1.20, 94 participants).

3.2 FREQUENCY OF NAUSEA

Frequency of nausea was reported in three trials.[26,29,30] There was a decrease in the frequency of nausea in the acupressure plus medication group. (MD -0.32, 95% CI -0.59 to 0.06, 510 participants).

4. ACUPRESSURE PLUS MEDICATION VS SHAM ACUPRESSURE PLUS MEDICATION

4.1 FREQUENCY OF VOMITING

Frequency of vomits was reported in one trial.[17] There was no difference between groups (MD 1.24, 95% CI 0.34 to 4.43, 48 participants).

4.2 FREQUENCY OF NAUSEA

Frequency of nausea was reported in one trial.[17] There was no difference between groups (MD -0.10, 95% CI -5.52 to 5.02, 48 participants).

4.3 USE OF RESCUE MEDICATION

The dose of rescue medication was reported in one trial.[17] There was no difference between groups (MD 1.03, 95% CI 0.64 to 1.67, 48 participants).

Discussion

Twelve trials were included in the review: seven acupuncture trials and six acupressure trials. The trials included a total of 1381 participants, 1133 in acupressure studies and 275 in acupuncture studies. One trial[17] was included in both acupuncture and acupressure analysis.

The meta-analysis showed a reduction in the frequency of acute chemotherapy-induced nausea in the acupressure plus

medication group compared with the medication only group (MD -0.10, 95% CI 0.34 to 4.43). In addition, there was a reduction in frequency of vomiting (MD -7.40, 95% CI -9.07 to -3.58), and a reduction in the dose of rescue medication (MD -5.52, 95% CI -7.45 to -3.58) in the acupuncture plus medication group versus medication only.

The limitations of the primary studies relate to whether an adequate dose of acupuncture or acupressure was administered. It has been suggested that a minimum of six treatments is needed to constitute adequate treatment.[44] Five of seven of the acupuncture trials used a formula for point selection with just one or two points. Two of the acupuncture trials used a flexible point selection process, with TCM practitioners selecting points based on TCM principles rather than acupuncture stimulation of a particular point or set of points. The use of sham controls within acupuncture remains controversial, as some studies indicate physiological activity with many of the techniques of sham acupuncture.[45–47] Ethical concerns have also been raised about the use of a sham control in the evaluations of acupuncture in cancer care.[48,49]

The most recent acupuncture trials are beginning to reflect modern practice by the use of more than one or two points and individualised treatments rather than a formula of points. Research is moving away from investigating the effects of a specific acupuncture point to investigating acupuncture as a 'whole person' intervention, including the specific and non-specific effects of an acupuncture treatment and the acupuncturist.[50–52] In these instances, researchers reported the most common points utilised in the intervention. This may help guide further research and guide practitioners in their clinical practice but the heterogeneity will make it difficult to compare studies.

The quality of the trials in relation to risk of bias could and should be improved. Four of the seven acupuncture trials[14,17–19] had a low to moderate risk of bias; only one[20] had a low risk of bias. Five of the six[17,26–29] acupressure trials had a low to moderate risk of bias.The bias in the other trial was assessed as moderate to high as it did not clearly state many of the criteria. There was slight improvement in addressing bias in the acupuncture and acupressure trials following the Cochrane review.

Overall the methodology of recently published acupuncture studies has not greatly improved from that in the trials identified in the Cochrane review.[21] In addition, the reporting of trials has improved only slightly despite the publication of the Standards for Reporting Interventions in Controlled Trials of Acupuncture (STRICTA)[53] guidelines. With improved reporting, a more accurate assessment of the risk of bias can be obtained. The studies remain small, with most being pilot studies, which is a common occurrence and a major weakness. There has been a tendency to utilise crossover designs for the most recent trials. The issue raised by this design is that the washout period for acupuncture or acupressure treatment has not been clearly identified through research. Overall, few studies remain at a low risk of bias.

The one other systematic review of acupuncture in the literature was published by Ezzo et al.[21] This review included 11 trials, and included one other form of acupoint stimulation: non-invasive electrostimulation, which was excluded from this review. This review found some benefit with respect to acute nausea for acupressure (MD -0.32, 95% CI -0.59 to 0.06, 510 participants) and there was evidence of a decrease in frequency of vomiting (MD -7.40, 95% CI -9.07 to - 5.72, 94 participants) and dosage of rescue medication (MD -5.52, 95% CI -7.45 to -3.58, 23 participants) in those receiving acupuncture.

Characteristics of the participants in these trials varied. Some of the recent acupuncture trials included children with cancer. This patient group is not often seen by acupuncture practitioners, but does have relevance to the growing number of practitioners who work in integrative oncology clinics. Some trials included patients with more than one cancer type. This mixed patient group is more representative of the type of patient acupuncture practitioners would treat in their clinics.

The review showed persistent weaknesses in the design and implementation of acupuncture trials. The main flaw is small sample sizes, resulting in underpowered studies from which no definitive recommendation can be made. Another issue is the lack of a consensus as to what is the most appropriate control.[54]

Implications for research

Further research trials should use appropriate sample sizes and adequate power. Future researchers need to ensure that when designing trials, outcome measures are both clinically relevant and patient-centred.[57–59] Trials should also allow the treating acupuncturist the flexibility to decide the appropriate acupuncture treatment to ensure the trials have clinical relevance and help direct practice.[50,51] The adoption of broad trial inclusion and exclusion criteria will also ensure the findings of the study are more generalisable and representative of the usual care situation.[52,60] This will help the research reflect more closely what occurs in clinical practice.

Conflict of interest

No known conflict of interest.

Clinical Commentary

There is some evidence to support the use of the two major points (PC6 *Neiguan* and ST36 *Zusanli*) for acute CINV, although less evidence for delayed CINV. These points are commonly used in clinical practice, especially for treating nausea and vomiting arising from other causes, including post-operative and pregnancy-induced nausea and vomiting.[55,56] There is less evidence for the use of other points such as CV12 *Zhongwan* and LI4 *Hegu*, which can not be recommended for use until more high-quality research is conducted. Acupressure on PC6 *Neiguan* and ST36 *Zusanli* has shown some benefit for acute chemotherapy-induced nausea. Although the research is not conclusive, the intervention is inexpensive, low-risk and easy for patients to learn and perform, and could be included for patients experiencing CINV.[42]

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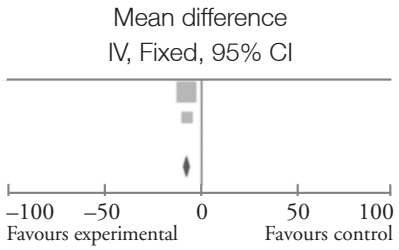
APPENDIX 1

1: ACUPUNCTURE + MEDICATION VS MEDICATION ONLY

1.1 Frequency of Vomiting

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight %	Mean difference IV, Fixed, 95% CI
Gottschling 2008	3.83	2.41	12	11.36	2.56	11	67.5	-7.53 [-9.57, -5.49]
Shen 2000	6.29	4.16	37	13.41	7.77	34	32.5	-7.12 [-10.06, -4.18]
Total (95% CI)			**49**			**45**	**100.00**	**-7.40 [-9.07, -5.72]**

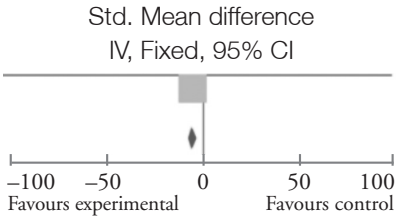
Heterogeneity: Chi² = 0.05, df = 1 (P = 0.82); I² = 0%
Test for overall effect: Z = 8.66 (P < 0.00001)



1.2 Dose of Rescue Medications

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight %	Std. Mean difference IV, Fixed, 95% CI
Gottschling 2008	13.47	6.07	12	48.95	6.34	11	100.00	-5.52 [-7.45, -3.58]
Total (95% CI)			**12**			**11**	**100.00**	**-5.52 [-7.45, -3.58]**

Heterogeneity: Not applicable
Test for overall effect: Z = 5.59 (P < 0.00001)

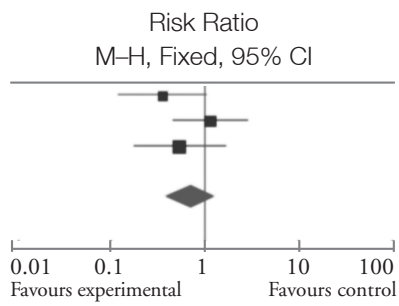


2: ACUPUNCTURE PLUS MEDICATIONS VS SHAM PLUS MEDICATIONS

2.1 Frequency of Vomiting

Study or Subgroup	Acupuncture plus Meds Events	Acupuncture plus Meds Total	Control Events	Control Total	Weight %	Risk Ratio M–H, Fixed, 95%
Dundee 1987	2	7	3	3	26.2	0.36 [0.12, 1.06]
Melchart 2006	7	24	6	24	33.6	1.17 [0.46, 2.96]
Streitberger 2003	4	41	7	39	40.2	0.54 [0.17, 1.71]
Total (95% CI)		**72**		**66**	**100.00**	**0.70 [0.38, 1.29]**
Total events	13		16			

Heterogeneity: Chi² = 2.81, df = 2 (P = 0.25); I² = 29%
Test for overall effect: Z = 1.13 (P = 0.26)

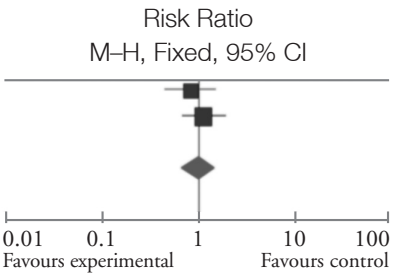


2: ACUPUNCTURE PLUS MEDICATIONS VS SHAM PLUS MEDICATIONS CONT.

2.2 Frequency of Nausea

Study or Subgroup	Acupuncture plus Meds		Sham plus meds			Risk Ratio
	Events	Total	Events	Total	Weight %	M–H, Fixed, 95%
Melchart 2006	10	24	12	24	43.8	0.83 [0.45, 1.55]
Streitberger 2003	18	41	15	39	56.2	1.14 [0.67, 1.93]
Total (95% CI)		**65**		**63**	**100.00**	**1.01 [0.67, 1.50]**
Total events	28		27			

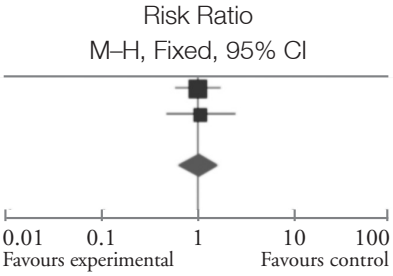
Heterogeneity: $Chi^2 = 0.58$, df = 1 (P = 0.45); $I^2 = 0\%$
Test for overall effect: Z = 0.03 (P = 0.98)



2.3 Use of Rescue Medications

Study or Subgroup	Experimental		Control			Risk Ratio
	Events	Total	Events	Total	Weight %	M–H, Fixed, 95%
Melchart 2006	12	24	12	24	59.4	1.00 [0.57, 1.76]
Streitberger 2003	9	41	8	39	40.6	1.07 [0.46, 2.49]
Total (95% CI)		**65**		**63**	**100.00**	**1.03 [0.64, 1.67]**
Total events	21		20			

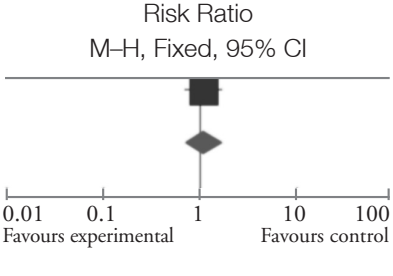
Heterogeneity: $Chi^2 = 0.02$, df = 1 (P = 0.89); $I^2 = 0\%$
Test for overall effect: Z = 0.11 (P = 0.91)



2.4 Helpfulness of Acupuncture

Study or Subgroup	Acupuncture plus Meds		Sham plus Meds			Risk Ratio
	Events	Total	Events	Total	Weight %	M–H, Fixed, 95%
Streitberger 2003	21	41	18	39	100.00	1.11 [0.71, 1.74]
Total (95% CI)		**41**		**39**	**100.00**	**1.11 [0.71, 1.74]**
Total events	21		18			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.45 (P = 0.65)

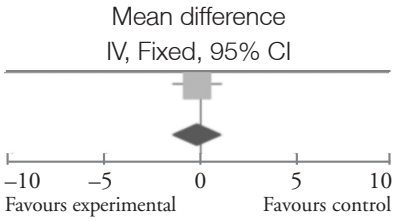


3: ACUPRESSURE PLUS MEDICATION VS MEDICATION ONLY

3.1 Frequency of Vomiting

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight %	Mean difference IV, Fixed, 95% CI
Molassiotis 2006	0.53	2.1	17	0.66	1.94	19	100.00	-0.13 [-1.46, -1.20]
Total (95% CI)			**17**			**19**	**100.00**	**-0.13 [-1.46, -1.20]**

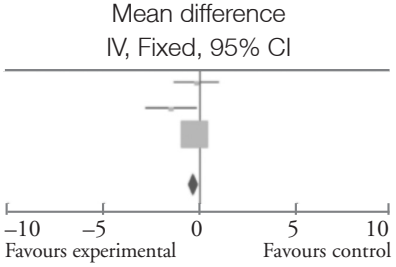
Heterogeneity: Not applicable
Test for overall effect: Z = 0.19 (P = 0.85)



3.2 Frequency of Nausea

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight %	Mean difference IV, Fixed, 95% CI
Dibble 2000	2.83	1.6	8	3	0.58	9	5.1	-0.17 [-1.34, -1.00]
Molassiotis 2006	0.66	1.6	17	2.16	2.4	19	4.0	-1.50 [-2.82, -0.18]
Roscoe 2003	1.99	1.47	231	2.27	1.55	226	90.9	-0.28 [-0.56, -0.00
Total (95% CI)			**256**			**254**	**100.00**	**-0.32 [-0.59, -0.06]**

Heterogeneity: $Chi^2 = 3.21$, df = 2 (P = 0.20); $I^2 = 38\%$
Test for overall effect: Z = 2.40 (P = 0.02)

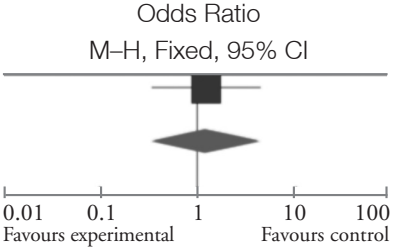


4: ACUPRESSURE PLUS MEDICATION VS SHAM ACUPRESSURE PLUS MEDICATION

4.1 Frequency of Vomiting

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight %	Odds Ratio M–H, Fixed, 95% CI
Melchart 2006	7	24	6	24	100.00	1.24 [0.34, 4.43]
Total (95% CI)		**24**		**24**	**100.00**	**1.24 [0.34, 4.43]**
Total events	7		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.32 (P = 0.75)

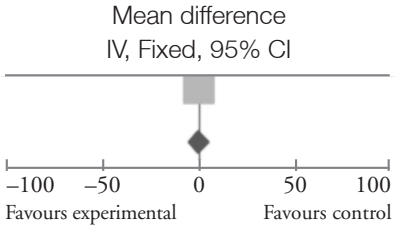


4: ACUPRESSURE PLUS MEDICATION VS SHAM ACUPRESSURE PLUS MEDICATION CONT.

4.2 Frequency of Nausea

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight %	Mean difference IV, Fixed, 95% CI
Melchart 2006	6.2	9	24	6.3	9.1	24	100.00	-0.10 [-5.22, 5.02]
Total (95% CI)			**24**			**24**	**100.00**	**-0.10 [-5.22, 5.02]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.04 (P = 0.97)



4.3 Use of Rescue Medication

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight %	Odds Ratio M–H, Fixed, 95% CI
Melchart 2006	12	24	12	24	100.00	1.00 [0.32, 3.10]
Total (95% CI)		**24**		**24**	**100.00**	**1.00 [0.32, 3.10]**
Total events	12		12			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)