

*Original Article*

# The Effectiveness of Acupressure for the Control and Management of Chemotherapy-Related Acute and Delayed Nausea: A Randomized Controlled Trial

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## Abstract

**Context.** Both positive and negative results have been reported in the literature from the use of acupressure at the P6 point, providing evidence of highly suggestive but not conclusive results.

**Objectives.** To clarify whether acupressure is effective in the management of chemotherapy-related nausea and vomiting.

**Methods.** A randomized, three-group, sham-controlled trial was designed. Patients with cancer receiving chemotherapy were randomized to receive standardized antiemetics and acupressure wristbands, sham acupressure wristbands, or antiemetics alone. Primary outcome assessment (nausea) was carried out daily for seven days per chemotherapy cycle over four cycles. Secondary outcomes included vomiting, psychological distress, and quality of life.

**Results.** Five hundred patients were randomized. Primary outcome analysis (nausea in Cycle 1) revealed no statistically significant differences between the three groups, although nausea levels in the proportion of patients using wristbands (both real and sham) were somewhat lower than those in the proportion of patients using antiemetics-only group. Adjusting for gender, age, and emetic risk of chemotherapy, the odds ratio of lower nausea experience was

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1.18 and 1.42 for the acupressure and sham acupressure groups, respectively. A gender interaction effect was evident ( $P = 0.002$ ). No significant differences were detected in relation to vomiting, anxiety, and quality-of-life measures.

**Conclusion.** No clear recommendations can be made about the use of acupressure wristbands in the management of chemotherapy-related nausea and vomiting as results did not reach statistical significance. However, the study provided evidence of encouraging signals in relation to improved nausea experience and warrants further consideration in both practice and further clinical trials.

**Trial Registration.** This trial is registered with the ISRCT register, number ISRCTN87604299. *J Pain Symptom Manage* 2013;■:■-■. © 2013 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.

### Key Words

*Acupressure, nausea, vomiting, chemotherapy*

## Introduction

Significant developments in antiemetic therapy over the past two decades have improved the control of chemotherapy-related vomiting. By contrast, chemotherapy-related nausea, both acute and delayed, is still a significant problem in clinical practice, with 42%–52% of patients experiencing nausea on any one day in routine practice.<sup>1</sup> Surprisingly, despite improvements in the management of vomiting, postchemotherapy nausea seems to have increased.<sup>2</sup> Furthermore, clinicians often underestimate the experience of nausea, especially with regard to delayed nausea.<sup>3,4</sup>

Chemotherapy-induced nausea and vomiting can have a profound effect on the cancer treatment experience<sup>5</sup> and is associated with negative effects on daily life and overall quality of life, including effects on food intake, weight loss, social interactions, dehydration, difficulty with sleeping, and anxiety.<sup>5,6</sup> In a qualitative study of patients' experiences, unmanaged nausea was constant in some patients and made them exhausted for long periods after chemotherapy, making recovery between cycles longer.<sup>5</sup> The impact of nausea is greater than that of vomiting,<sup>7</sup> and nausea has proven to be more difficult to control. The direct and indirect costs of the experience of nausea and vomiting, especially of delayed symptoms, are considerable.<sup>8</sup> Antiemetic trials have traditionally focused primarily on vomiting and emetic episodes, on which the effectiveness of many antiemetic drugs is judged. Little attention has been directed to the concept of

chemotherapy-induced *nausea* despite the fact that it is increasingly recognized that nausea and vomiting are related but separate entities.<sup>9,10</sup> The need for these two symptoms to be treated as two separate entities is strongly advocated.<sup>10</sup>

As antiemetic medications do not fully control nausea during chemotherapy, non-pharmacologic interventions in addition to antiemetics have been tested over the years, especially in the 1980s. Acupuncture and its non-invasive form of acupressure have been tested several times after the classic early work by Dundee et al.<sup>11,12</sup> In a literature search between 1990 and May 2005, we identified 10 studies specific to oncology, reported elsewhere,<sup>13</sup> with seven of 10 studies showing positive results and another two approaching statistical significance. These studies have used a variety of acupressure methods, such as the ReliefBand® (a small battery-operated transcutaneous electrical nerve stimulation device designed to stimulate the P6 acupoint),<sup>14–16</sup> an acupressure wristband (a small elastic band with a round plastic button applying constant mild pressure on the P6 acupoint),<sup>17–19</sup> and direct pressure on acupoint P6<sup>20</sup> or P6 and ST36 points together.<sup>21</sup> We also carried out a two-arm pilot study of 36 patients with breast cancer using acupressure wristbands (plus antiemetics) vs. standard antiemetics only.<sup>13</sup> Although this study was limited, key findings suggested that acupressure improved the *nausea experience* as well as *nausea and vomiting occurrence* and *distress* across the first five days of chemotherapy.

Nevertheless, improvements were higher in relation to nausea than vomiting. The largest study to date ( $N = 739$ ) testing acupressure and acustimulation showed improvements in nausea and vomiting in men, whereas there was a similar trend in women to reduce acute symptoms only, although the latter did not reach statistical significance.<sup>22</sup> No improvement in nausea/vomiting was shown in a small study by Roscoe et al.<sup>23</sup> in women with breast cancer using acustimulation (ReliefBand) wristbands. The latter two studies are suggestive of a possible gender effect. However, most past studies are hampered by small sample sizes, the wide variety of (nonstandardized) antiemetics used, differences in the risk factors for nausea and vomiting in these samples, the range of emetogenicity of chemotherapy regimens used, and sampling issues. A recent Cochrane systematic review of the literature highlights that acupressure reduces acute nausea but not delayed nausea and has no benefit for vomiting.<sup>24</sup> However, the review was primarily focused on acupuncture rather than acupressure, all different methods of acupressure were examined together and the results specifically regarding vomiting are questionable (as many of the studies included in the review had samples with little, if any, vomiting across experimental and control groups).

### *Research Objectives*

The primary objective of our study was to assess the clinical effectiveness of self-acupressure using wristbands in addition to standard care in the management of chemotherapy-induced (acute and delayed) *nausea* compared with patients receiving standard care with sham acupressure wristbands and standard care alone. A similar assessment focus on quality of life, psychological distress, and vomiting alongside patient treatment and demographic characteristics were the secondary outcomes of the trial.

## **Methods**

### *Study Design*

The study was a randomized controlled trial with three arms. Each arm comprised usual care plus 1) acupressure wristbands, 2) sham acupressure wristbands, or 3) no additional treatment. The duration of the patients'

involvement was for four cycles of chemotherapy. Participants were allocated to the trial groups through computer-generated randomization carried out remotely by the Trials Unit of the Christie Hospital NHS Foundation Trust. Randomization was independent, and the randomization method used consisted of minimization with a random element (stochastic minimization), balancing for gender,<sup>25,26</sup> age (16–24, >24–50, and >50 years),<sup>25,27</sup> and three levels of emetogenic chemotherapy (low, moderate, and high according to American Society of Clinical Oncology [ASCO] and Multinational Association of Supportive Care in Cancer [MASCC] international classifications).<sup>28,29</sup>

### *Sample*

Recruitment took place in a large cancer hospital in the U.K. and 14 cancer units or centers of district general hospitals and university hospitals. The target population was a heterogeneous group of cancer patients meeting the inclusion criteria and about to receive chemotherapy of high, moderate, and low emetogenic potential. Heterogeneity is important to address issues of response to different types of emetogenic chemotherapy, as are gender and age; past literature highlights that these are important in assessing the effectiveness of treatments for chemotherapy-related nausea and vomiting.

In the acupressure group, in addition to standard antiemetics, patients were provided with a pair of widely available acupressure wristbands. These bands are elastic wristbands with a 1-cm protruding round plastic button (stud). They are available in two sizes: a standard one and a larger one. Patients wear the wristband with the stud pressing the P6 acupoint, which is located on the anterior surface of the forearm, approximately three-finger widths up from the crease of the wrist between the tendons of the palmaris longus and flexor carpi radialis. Patients were provided with a pair of acupressure wristbands and were instructed to wear them on both arms and take them off only when showering or bathing. An instruction sheet with a picture of point P6 and how to locate the point also was provided to patients. Patients were instructed to wear the wristbands from the morning before chemotherapy administration and for the subsequent six days (total, seven days). No other

complementary therapy use was recommended during the course of acupressure (although any such use was documented).

In the sham acupressure group, in addition to standard antiemetics, patients were provided with a pair of the identical appearing wristbands, with the only difference being that the sham wristband had the button on the exterior of the wristband, and patients were instructed to wear the wristband with the button away from what is the P6 point. An assessment of blinding at the end of the trial was not conducted as patients had not been informed of the use of both sham and real acupressure bands during the trial but had instead been informed that two different types of wristbands were being evaluated in the trial, with the approval of the Ethics Committee. Clinicians did not know the patients' group allocation.

The control group received standard antiemetics alone. Standard antiemetics for all the three groups were based on ASCO and MASCC international antiemetic guidelines,<sup>28,29</sup> with the exception of NK1 receptor antagonists (i.e., aprepitant) recommended in highly emetic chemotherapy, which were not widely used in U.K. hospitals. All patients received rescue antiemetics if nausea and/or vomiting was persistent and failed to respond to the antiemetic treatment (i.e., severe nausea or more than five vomiting episodes), based on the experience of each clinician.

*Inclusion Criteria.* The inclusion criteria include patients scheduled to receive their first chemotherapy cycle; patients scheduled to receive highly, moderately, and low emetogenic chemotherapy (as per ASCO and MASCC classifications); patients scheduled to receive a chemotherapy regimen given as a single or multiple administration repeated in two, three, or four week cycles; patients who were acupressure wristband naive (in terms of never having tried a wristband for themselves, although they may have seen or heard about such wristbands); patients of either gender and older than 16 years of age; patients with any cancer diagnosis receiving chemotherapy without concurrent use of radiotherapy; patients receiving chemotherapy as outpatients or inpatients; and patients who were willing

to participate in the study and be randomized into one of the three study groups.

*Exclusion Criteria.* The exclusion criteria include patients scheduled to receive radiotherapy concurrently with chemotherapy and during the assessment period of four cycles for each patient, patients unable to provide self-care (i.e., unable to use wristbands appropriately and mental incapacity preventing continuous and optimal use of wristbands) as judged by the investigators, patients with liver disease (as nausea is a common presenting symptom), patients with metabolic risk factors for nausea (i.e., electrolyte imbalances causing nausea/vomiting), patients with mechanical risk factors for nausea (i.e., intestinal obstruction), patients experiencing nausea and/or vomiting as a result of use of opioids, patients with lymphedematous arms, and patients with chronic alcohol use (chronic alcohol use is associated with minimal levels of nausea and/or vomiting).

*Sample Size.* In our pilot study,<sup>13</sup> the mean score for nausea experience averaged over five days was 2.79 (weighted average standard deviation [SD] 3.15) and 1.45 (weighted average SD 2.76) in the control and intervention groups, respectively. At least 135 participants per arm would be required to detect this pairwise difference between arms using a *t*-test with a conservative Bonferroni-adjusted significance level of  $0.05/3 = 0.017$  at a power of 90%. The pilot study suggested an attrition rate of 33%; hence, initially at least 202 participants would be required per arm. As SDs were much larger than the means in the pilot data, they were suggestive of highly skewed distributions; hence, the equivalent nonparametric test (Mann-Whitney *U*-test) would be used. The asymptotic relative efficiency of the Mann-Whitney *U*-test is at worst 0.864, so the sample size for a Mann-Whitney *U*-test is, in the worst case, equal to the sample size for the *t*-test divided by 0.864, which is 156 participants per arm (233 including attrition), totaling 699 participants across the three arms. Because of a slower recruitment rate than initially envisioned, a rethinking of the sample size requirements was necessary. The first 141 cases with data on the primary outcome were examined, and the SD was roughly in line

with the value used in the initial calculation, but the attrition rate was lower at about 20%. The sample size was recalculated as above but with revised power of 80% and attrition of 25%, resulting in a total of 489 (366 after attrition) participants. The final recruitment was 500 participants, and there were 361 cases with data on the primary outcome, which provided power of approximately 80% for the same standardized effect sizes as originally specified.

#### *Primary Outcome Measure*

The Rhodes Index of Nausea, Vomiting and Retching (Rhodes Index) was used as the primary outcome measure.<sup>30</sup> This is an eight-item validated scale measuring nausea and vomiting experience, incidence, and severity. In this study, the nausea experience subscale has been used for power calculations of the sample size, using the mean score across all assessment days in each cycle as the end point. The index was completed daily from the day before chemotherapy (to capture any anticipatory nausea) up to seven days after chemotherapy, that is, eight assessments per cycle.

#### *Secondary Outcomes*

*MASCC Antiemesis Tool.* This eight-item scale assesses in a simple way both acute and delayed nausea and vomiting incidence and extent and was designed specifically for chemotherapy-related nausea and vomiting.<sup>31</sup> The MASCC Antiemesis Tool (MAT) is designed to be used once-per-cycle with retrospective patient recall of events, minimizing the patient burden. The scale was completed on Day 10 of each cycle (four assessments).

#### *Functional Assessment of Cancer Therapy-General.*

This is a well-validated quality-of-life scale focusing on functional assessment.<sup>32</sup> This scale was completed at baseline and then on Day 10 of each cycle (five assessments).

*Hospital Anxiety and Depression Scale*<sup>33</sup>. This is a 14-item scale assessing anxiety with seven items and depression with a further seven items. There are separate scores for anxiety and depression;<sup>33</sup> the Hospital Anxiety and Depression Scale was completed on Day 10 of each cycle.

*Patient Expectations of Nausea/Vomiting.* As this is a key risk factor identified in the literature,<sup>25,34</sup> a two-item tool was developed assessing the patient's expectation for nausea and vomiting, measured on a 11-point ordinal scale. Patients also were asked how much they believed this method had helped them alleviate nausea and how much faith they had in complementary therapies, using 11-point scales.

#### *Sociodemographic and Treatment Characteristics.*

These characteristics were obtained from the patients' records and the patients themselves. These included gender, age, educational level, marital status, experience with nausea in the past (e.g., during pregnancy, motion sickness, or nausea when eating certain foods), use of/experience with other complementary therapies in the past, cancer diagnosis, stage of disease, and chemotherapy protocol used and dosage. Side effects also were elicited from the patients.

Assessment scales were provided to patients for self-completion at home; completed forms were returned to researchers using a prepaid self-addressed envelope. Reminder phone calls also were made. Patients were asked to complete their daily assessments of nausea at the same time in the evening to have a consistent time frame for measuring change.

#### *Statistical Analysis*

Descriptive statistics have been estimated for all baseline sociodemographic and clinical variables by arm and outcome variables (scores on nausea and vomiting subscales) by arm. Primary outcome variables have been compared between the arms using Mann-Whitney *U*-tests and Kruskal-Wallis tests. Ordinal regression models were used to permit covariate-adjusted analyses of a grouped version of the primary outcome. An extension of the proportional odds regression model was used for longitudinal analyses over cycles, and this was fitted with a generalized estimating equation (GEE) approach. An intention-to-treat analysis model has been followed. As the primary outcome variable was repeatedly assessed over several days, an aggregate score of all assessments in each cycle was calculated before any modeling analysis.

The effect of missing values was assessed by comparing the numbers and percentages of participants with missing values in the three arms of the study, differences in baseline variables between participants with observed and missing outcomes in each arm, and for participants with observed outcomes and differences in baseline variables between the three arms. There were no clear associations between known predictors of nausea and cases missing the nausea primary outcome. This fact along with the highly nonnormal distribution of the primary response (for which imputation methods are not so well developed) informed our decision to not apply multiple imputation analyses.

## Results

Five hundred cases were randomized (166 standard care [none], 166 sham acupuncture [sham], and 168 acupuncture [acu] groups). A participant flow diagram (Fig. 1) shows the number of participants recruited and randomly assigned to the three trial arms and who received the intended interventions and were analyzed for the primary outcome.

### *Descriptive Statistics by Trial Arm*

The majority of the participants were females, married, and older than 50 years of age. The key diagnoses of the sample included breast and colorectal cancer, and the majority had received moderately emetogenic chemotherapy (including anthracycline-based chemotherapy). Other sociodemographic and clinical data are shown in Table 1.

### *Assessment of Missing Data for the Primary Outcome*

Five hundred cases were randomized, but data were only available for 361 of these for the primary outcome, that is, about 28% of cases were missing the primary outcome. Table 2 illustrates the proportion of cases missing the primary outcome by various factors thought to influence nausea propensity. There were no marked associations for any of these factors with the probability of missing the primary outcome.

### *Nausea Experience*

Table 3 shows the mean nausea experience of the patients using the Rhodes Index. Scores can range from 0 to 12, with higher scores indicating higher levels of nausea. Both the sham and the acupuncture arms had less nausea experience compared with the standard care arm, although this did not reach statistical significance. The observed mean values represent very low levels of nausea.

### *Primary Outcome Analysis*

The primary outcome was the mean Rhodes Index nausea experience (Days 0–6) for Cycle 1. The possible range for values is 0–12, but in fact, 111 of 361 (31%) cases were exactly zero, and around half of all values were less than one. No transformation would be successful in normalizing such a distribution. The distribution by trial arm is shown in Fig. 2. Because of the highly skewed distribution, the nonparametric Kruskal-Wallis test was used for the primary comparison of the trial arms. This overall test was nonsignificant ( $P = 0.14$ ). Provision for pairwise comparisons (Mann-Whitney  $U$ -tests) with a Bonferroni adjustment was made in the trial design: none vs. acupuncture ( $P = 0.23$ ), none vs. sham acupuncture ( $P = 0.05$ ), and sham vs. acupuncture ( $P = 0.40$ ). It should be noted that the reference value for statistical significance is 0.017; therefore, none of these pairwise comparisons are statistically significant. We also carried out primary outcome analysis for Days 0–3, when chemotherapy-induced nausea and vomiting is expected to be more intense. The Kruskal-Wallis test showed again a nonsignificant result ( $n = 361$ ,  $P = 0.22$ ).

### *Regression Analyses for the Nausea Primary Outcome Data*

The approach adopted for this analysis was to group the values into five ordered categories and use regression methods for ordinal data. The first category “zero” was chosen as it represented no nausea at all, and there was a large fraction of cases that fell into such a category (31%). The choice of the other categories was somewhat arbitrary. Five categories are fairly typical for ordinal regression models in the literature, and it is desirable that no category has a very small frequency. Category

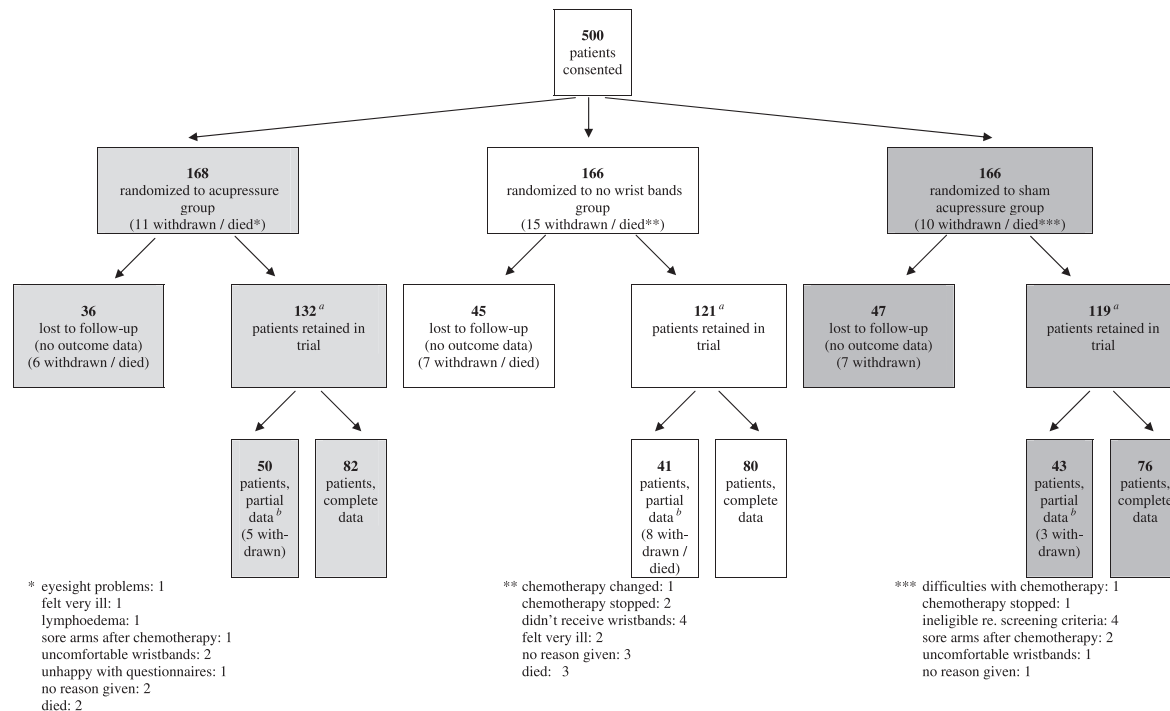


Fig. 1. Patient recruitment CONSORT diagram. <sup>a</sup>Although a complete data set for primary outcome is available from 361 participants, this number includes cases with primary outcome available but no baseline data (total of 11 cases). <sup>b</sup>Partial data indicate data collected from less than the complete data set (baseline plus four cycles of chemotherapy), that is, in which at least one assessment was missing.

5 has a broad range but only 8% cases; subdividing it further would be counterproductive. Having chosen the lowest and highest categories, the remaining three were simply selected to have equal width. The main tool used was the proportional odds regression model.<sup>35</sup>

An unadjusted fit model using all the available data ( $n = 361$ ) showed that the likelihood ratio test for the trial arm effects was nonsignificant ( $P = 0.34$ ). Furthermore, the estimated odds ratio of a lower (i.e., better) score for acupressure compared with control was  $e^{0.2418} = 1.27$  (95% confidence interval [CI] 0.80–2.03) and the estimated odds ratio of a lower (i.e., better) score for sham acupressure compared with control was  $e^{0.3354} = 1.40$  (95% CI 0.87–2.24).

An adjusted fit model (for age, gender, and emetogenic risk) using all the available data ( $n = 361$ ) showed that, irrespective of arm allocation, participants who were older than 50 years of age ( $P = 0.0005$ ) and male ( $P = 0.005$ ) had a better nausea outcome. The emetogenicity of the chemotherapy also

was a significant factor to the nausea outcome ( $P = 0.013$ ). The estimated odds ratio of a lower (i.e., better) score for sham acupressure compared with control (for identical age group, gender, and emetogenic risk groups) was  $e^{0.3520} = 1.42$  (95% CI 0.88–2.30) and for the acupressure arm was 1.18 (95% CI 0.74–1.90).

It is of interest to consider the impact of adding a trial arm  $\times$  term interaction effect to the fitted model for each of age, gender, and emetogenic risk groups in turn. A regression analysis indicated that there is evidence to suggest that treatment effects may vary with gender ( $P = 0.002$ ) (Table 4).

An extended model (age, gender, emetogenic risk, cycle frequency, anxiety, and nausea expectation) of all the available data ( $n = 315$ ) showed that older than 50 years of age ( $P = 0.025$ ), male gender, ( $P = 0.038$ ), and lower expectation of nausea ( $P = 0.002$ ) are significantly linked with lower levels of nausea. The role of the emetogenicity of the chemotherapy in this analysis was borderline nonsignificant ( $P = 0.067$ ). Only gender exhibited

Table 1  
Demographic and Clinical Data of the Sample

Data	Sham Acu		
	None	Bands	Bands
Gender			
Male	38	37	39
Female	128	129	129
Age group (years)			
≤50	51	55	54
>51	115	111	114
Marital status			
Single	18	15	24
Married	85	83	88
Divorced or separated	20	27	21
Widowed	13	16	11
Missing	30	25	24
Educational attainment			
Primary school	0	3	2
Secondary school	68	74	69
College/diploma	37	26	43
University/degree	20	14	17
Postgraduate	6	12	8
Missing	35	37	29
Ethnic origin			
Caucasian	111	110	121
Black	0	1	2
Asian/Chinese	2	2	2
Mixed	1	3	0
Missing	52	50	43
Religious affiliation			
Christian	114	106	122
Muslim	1	2	3
Hindu	0	1	0
None	17	18	12
Prefers not to say	1	4	2
Other	5	8	7
Missing	28	27	22
Occupational group			
Professional	40	44	36
Managerial and technical	17	16	23
Skilled nonmanual	14	11	16
Skilled manual	14	12	11
Unskilled	14	16	15
Not applicable	28	33	43
Missing	39	34	24
Occupational status			
Employed full-time	50	36	33
Employed part-time	22	17	26
Retired	46	50	51
Unemployed	2	4	3
Casual worker	0	0	1
Not working because of ill health	10	20	17
Housewife	5	11	10
Other	2	3	4
Missing	29	25	23
Smoking history			
Never	63	62	66
Previously	56	51	62
Current	20	25	18
Missing	27	28	22
Diagnosis			
Breast	89	90	82
Bowel (colon and rectum)	25	27	19
Gynecologic	20	15	21
Lung	7	10	21
Lymphoma	6	2	7
Esophagus	4	5	2

(Continued)

Table 1  
Continued

Data	Sham Acu		
	None	Bands	Bands
Stomach	2	3	1
Pancreas	1	1	4
Melanoma	2	2	1
Bladder	1	1	2
Gall bladder	0	1	1
Head and neck	1	1	0
Endocrine/thymus	0	1	1
Prostate	1	0	1
Child: Ewing sarcoma	1	1	0
Child: Non-Hodgkin lymphoma	0	1	0
Missing	6	5	5
Emetogenic risk			
Low	13	11	12
Moderate	107	111	111
High	46	44	45

a significant interaction with trial arm ( $P = 0.023$ ).

#### Longitudinal Regression Analyses of Mean Rhodes Index Nausea Experience Scores

The mean Rhodes Index nausea experience (Days 0–6) scores also were calculated for Cycles 2–4. Once again, the scores for each cycle were grouped in the same manner as previously to a five-point ordinal scale. These repeated ordinal data were analyzed using an extension of the proportional odds regression model described previously, this time fitted using a GEE approach.<sup>36</sup>

First, a trial arm by cycle model was fitted and the interaction term was tested for significance (Wald test Chi square on 6 df,  $P = 0.25$ ). There being no formal evidence for different treatment effects with cycle, the simpler trial arm + cycle model was fitted. This analysis showed borderline significance for the trial arms ( $P = 0.07$ ). The estimated odds ratio of a lower (i.e., better) score for acupuncture compared with control was  $e^{0.4255} = 1.53$  (95% CI 1.12–2.09) and the estimated odds ratio of a lower (i.e., better) score for sham acupuncture compared with control was  $e^{0.3823} = 1.47$  (95% CI 1.06–2.02). An extended model adjusting for age, gender, and emetogenic risk once again showed evidence of an arm × gender interaction (Table 4).

#### MASCC MAT: Acute and Delayed Nausea

These were both scored 0–10 and were highly skewed, with large proportions on the



Table 2  
Proportion of Cases Missing the Primary Outcome by Trial Arm

Factors	Level	Missing Primary Outcome (%)	P-value <sup>a</sup>
Trial arm	None	46/163 (28) <sup>b</sup>	0.69
	Sham	48/166 (29)	
Age (years)	Acupressure	42/168 (25)	0.78
	≤50	42/160 (26)	
Gender	>51	94/337 (28)	0.43
	Male	35/114 (31)	
Emetogenic risk	Female	101/383 (26)	0.69
	Low	12/36 (33)	
	Moderate	87/327 (27)	
CT every 2 weeks	High	37/134 (28)	0.75
	No	122/451 (27)	
	Yes	14/46 (30)	
Baseline anxiety (83 missing)	Normal (0–7)	50/250 (20)	0.16
	Borderline (8–10)	22/76 (29)	
	Case (11–21)	24/88 (27)	
Nausea expectation (84 missing)	0–3	24/100 (24)	0.80
	4–6	52/224 (23)	
	7–10	18/89 (20)	

CT = chemotherapy administration.

<sup>a</sup>Chi-square tests of equal proportions.

<sup>b</sup>Three cases were all allocated to “no acupressure,” but there are no records in the trial database for these three cases, that is, no completed screening forms and no returned data forms. These three cases are the discrepant ones between  $n = 500$  and  $n = 497$ .

0 extreme. For regression analysis, new ordered factors with five levels were created. The regression analyses followed a similar approach to that used for the Rhodes Index nausea experience described earlier. For both outcomes, there was no evidence of an arm × cycle interaction, but both outcomes exhibited evidence of an arm × gender interaction. Table 5 shows the arm effect estimates.

#### MASCC MAT: Acute and Delayed Vomiting

The mean (Days 0–6) Rhodes Index vomiting experience data were highly skewed. These were grouped 0, 0–1, 1–2, 2–3, and >3. When analyzed with a longitudinal proportional odds model, there was no evidence of any trial arm effects ( $P = 0.47$ , Wald test). The MASCC MAT-acute vomiting data were recorded as the number of times in the 24 hours since chemotherapy. Descriptively, there was no difference between the trial arms. The MASCC MAT-delayed vomiting data were recorded as

the number of days in which vomiting occurred, 0–4. When analyzed with a longitudinal proportional odds model, there was no evidence of any trial arm effects ( $P = 0.69$ , Wald test).

#### Hospital Anxiety and Depression Scale and Functional Assessment of Cancer Therapy- General Results

These were assessed at baseline and at Cycles 1–4. Longitudinal linear models were fitted (GEE using unstructured covariance matrices) to the Cycles 1–4 data using the relevant baseline variable as a covariate along with factors representing cycle and arm. There was no evidence of any trial arm effects on mean values, as can be seen in Table 6.

#### Wristband Compliance Audit

An audit of compliance with wristband use took place over a period of four months at four sites. In total, 35 “wrist pairs” were

Table 3  
Mean Rhodes Index Nausea Experience (Days 0–6)

Cycles	None	Sham	Acupressure
1	1.43 (0, 0, 3.71, 8.57), $n = 117$	0.57 (0, 0, 2.64, 9.17), $n = 118$	1.0 (0, 0, 2.97, 7.50) $n = 126$
2	1.71 (0, 0, 3.43, 10.14), $n = 109$	0.71 (0, 0, 2.14, 10.29), $n = 105$	0.93 (0, 0, 3.43, 9.57), $n = 114$
3	1.14 (0, 0, 3.86, 11.86), $n = 96$	0.71 (0, 0, 2.29, 9.71), $n = 88$	0.43 (0, 0, 3.00, 10.14), $n = 103$
4	1.14 (0, 0, 4.00, 9.14), $n = 81$	0.43 (0, 0, 2.43, 8.57), $n = 77$	0.00 (0, 0, 1.82, 9.86), $n = 90$

Entries are median (minimum, lower quartile, upper quartile, maximum).

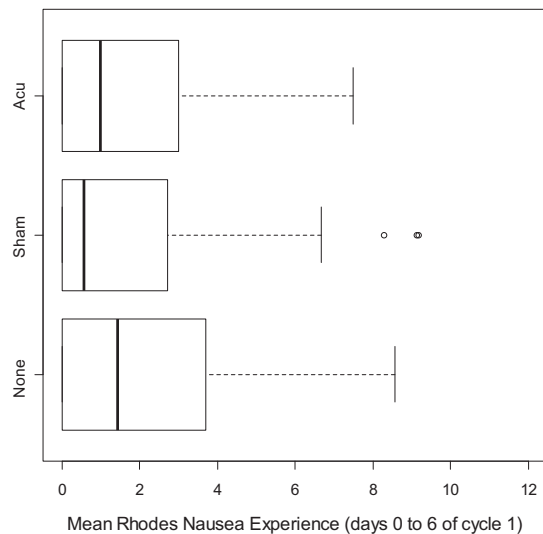


Fig. 2. Box and whisker plot of the primary outcome by trial arm.

observed; the vast majority of observations indicated that both wristbands (i.e., on both left and right wrists) were being worn correctly, with only four of the 68 wristbands observed (i.e., for left and right wrists) positioned incorrectly. Eight patients were not wearing their wristbands: one patient had swollen hands and the remaining seven patients stated that they intended to wear their wristbands after chemotherapy had been administered.

## Discussion

Despite the higher proportion of patients showing no nausea in the acupressure group,

the results of the trial show that there were no statistically significant differences between the three trial arms in relation to nausea experience. Patients in both wristbands arms had a higher odds ratio in improving their nausea experience compared with the standard care arm, with the sham arm having a higher odds ratio than the acupressure arm. There was a significant gender effect, with females in both wristband groups showing significant improvements compared with males.

Other trials in the past also have shown no significant changes from the use of acupressure in relation to nausea and vomiting management during chemotherapy administration. A review by Lee and Frazier<sup>37</sup> examined the results of seven trials of acupressure, in which four trials had positive results and three trials had negative results, highlighting that the overall effect of acupressure is strongly suggestive but not conclusive. No significant differences were reported in another trial of 160 women with regard to acute nausea and vomiting, although significant differences were reported with regard to delayed nausea and vomiting.<sup>38</sup> In the largest trial of its kind ( $n = 739$ ), Roscoe et al.<sup>22</sup> showed that patients in the acupressure arms experienced less nausea on the first day of chemotherapy, but there were no significant differences in relation to delayed symptoms. Also, the authors identified a strong gender effect, with men in an acustimulation arm improving but not women, the opposite of the results of the current trial. Roscoe et al.<sup>15</sup> also showed that, in a small sample of 27 patients (25 women and two men), no statistically significant

Table 4  
Outcomes and Gender Interactions

Cycle 1 (Primary Outcome)		
Effect	Odds Ratio Estimate <sup>a</sup>	95% CI
Sham to none (males)	0.35	0.12–1.03
Sham to none (females)	2.02	1.19–3.42
Acupressure to none (males)	1.27	0.40–4.08
Acupressure to none (females)	1.17	0.70–1.95
Longitudinal Outcomes (i.e., Cycle-Averaged Effects)		
Effect	Odds Ratio Estimate <sup>b</sup>	95% CI
Sham to none (males)	0.66	0.29–1.48
Sham to none (females)	1.71	1.10–2.65
Acupressure to none (males)	1.47	0.59–3.68
Acupressure to none (females)	1.44	0.93–2.23

<sup>a</sup>From a proportional odds model adjusting for gender, age group, and emetogenic risk group.

<sup>b</sup>From a proportional odds model (generalized estimating equation fit) adjusting for gender, age group, emetogenic risk group, and cycle.

Table 5  
Longitudinal Outcomes (i.e., Cycle-Averaged Effects for MASCC MAT-Acute and Delayed Nausea)

Effect	Odds Ratio Estimate <sup>a</sup>	95% CI
Cycle-averaged effects for MAT-acute nausea		
Sham to none (males)	0.32	0.12–0.82
Sham to none (females)	1.62	1.04–2.53
Acupressure to none (males)	0.63	0.21–1.96
Acupressure to none (females)	1.27	0.82–1.96
Cycle-averaged effects for MAT-delayed nausea		
Sham to none (males)	0.54	0.21–1.40
Sham to none (females)	1.74	1.12–2.68
Acupressure to none (males)	0.99	0.37–2.69
Acupressure to none (females)	1.49	0.97–2.28

MASCC MAT = Multinational Association of Supportive Care in Cancer Antiemesis Tool.

<sup>a</sup>From a proportional odds model (generalized estimating equation fit) adjusting for gender, age group, emetogenic risk group, and cycle.

differences in average severity of nausea were observed between acustimulation of the P6 point, sham acustimulation, and the standard care arms. However, the data showed a difference close to statistical significance in the severity of delayed nausea reported during active acustimulation compared with no acustimulation ( $P = 0.06$ ). In addition, patients took fewer anti-nausea pills during the active acustimulation cycle of this experiment compared with the no acustimulation phase ( $P < 0.05$ ). Negative results have been shown in relation to acupressure and nausea/vomiting symptoms in a large trial of 340 women during labor and delivery<sup>39</sup> and in a trial of acupuncture vs. sham acupuncture during radiotherapy.<sup>40</sup>

Key issues in most of the past studies showing positive results include the lack of standardized antiemetic use in the trial participants and inclusion of only or mostly female subjects. If our trial included only the female subsample, the results also would have been positive in our case. Also, it seems that the vast majority of positive studies in the literature include

small sample sizes (less than 100 participants), whereas the negative studies (or partly negative) have much larger sample sizes; this suggests that effects observed in methodologically weaker studies cannot always be sustained when larger and more robust trials are done. Furthermore, other studies in the past have shown that expectancy,<sup>22,41</sup> age, and anxiety<sup>25,42</sup> together with the antiemetic potential of the chemotherapy are important predictors of and can affect the outcome of acupressure, but in our trial, although unidimensionally these also were important, in a multivariate model, only gender showed significant effect.

Our findings suggest a placebo or nonspecific effect of the intervention arms. Placebo effects are viewed as a form of interpersonal healing, distinct from spontaneous natural healing or technological healing that depends on physiologically active pharmacologic products or procedures.<sup>43</sup> Alkaissi et al.<sup>44</sup> have suggested that acupressure does indeed have a placebo effect in relation to nausea after 24 hours, although correct stimulation of the P6 point is needed

Table 6  
Analysis of HADS and FACT-G Data by Trial Arm

Variables	Scale	Cycle × Arm $P$ -value <sup>a</sup>	Arm $P$ -value <sup>b</sup>	Sham	Acupressure
Anxiety	0–21	0.34	0.48	0.11 (0.38)	−0.35 (0.37)
Depression	0–21	0.15	0.40	0.02 (0.37)	0.45 (0.36)
PWB	0–28	0.07	0.71	0.48 (0.67)	0.02 (0.66)
SFWB	0–28	0.37	0.82	−0.13 (0.46)	−0.24 (0.39)
EWB	0–24	0.80	0.77	0.05 (0.39)	0.26 (0.38)
FWB	0–28	0.39	0.86	0.11 (0.68)	0.35 (0.65)
FACT-G	0–108	0.71	0.81	0.92 (1.67)	−0.06 (1.62)

HADS = Hospital Anxiety and Depression Scale; FACT-G = Functional Assessment of Cancer Therapy-General; PWB = physical well-being; SFWB = social well-being; EWB = emotional well-being; FWB = functional well-being.

The last two columns show the estimated difference in means from the “none” group from Model 2 with standard errors in parentheses. These effects are very small and nonsignificant.

<sup>a</sup>Wald test from a  $y$ .baseline + cycle × arm model.

<sup>b</sup>Wald test from a  $y$ .baseline + cycle + arm model.

to observe decreased rescue antiemetic use and decreased vomiting. Research also suggests that there are different placebo responses, each of which may be influenced by different psychological and neurobiological mechanisms depending on the context in which the placebo is given.<sup>45</sup> The literature also shows that placebos have actual biological effects on the brain and body and are more than response biases. Price et al.<sup>45</sup> (p. 586) conclude in their review that placebo effects reflect mind-brain-body relationships, and as such, we should not “resort to eliminative materialism or forms of dualism that completely divide the mind from the body.”

Trials of acupressure pose a specific problem with regard to blinding and the choice of placebo, particularly when outcome measures are subjective. We have chosen to use the same wristbands in both the real and the sham groups so that they can look identical, with the real acupressure group instructed to have the button pressing the P6 point, and the sham group instructed to have the button facing away from the P6 point in the other side of the arm. We have observed during interviews carried out concurrently with the trial that some patients (two of nine in the sham group) used the wristbands as in the real group because they had looked on the Internet or saw others wearing them properly. This may have contaminated our results. It was not possible to create a different wristband that would look identical with the real ones but would have no button nor exert pressure as they were elastic bands. As reported by Singha et al.<sup>39</sup> (through observations from their colleagues in the Department of Industrial and Manufacturing Engineering, Penn State University), elastic bands result in some pressure. This suggests that the pressure of the band in the area proximal to the P6 point, irrespective of the presence of a button pressing the P6 point, may have produced some positive results.

Our sample had generally low levels of nausea and/or vomiting. This may be a result of the fact that we had standardized antiemetic use in our study, and an inclusion criterion was receiving antiemetics as per MASCC antiemetic guidelines. This low level of experienced symptoms may be a reason for not showing significant differences in the current trial as we have shown in another observational study of nearly 1000 patients that use of

antiemetics during chemotherapy according to MASCC guidelines is associated with significantly improved nausea/vomiting symptoms.<sup>46</sup>

A limitation of the trial may be the missing data for the primary outcome. However, the proportion of cases missing the primary outcome (28%) is of similar order compares with that anticipated at the design stage (33%). The attained power that the final sample size with complete data for the primary outcome ( $n = 361$ ) delivered was 80% for a standardized difference in means of 0.46. Also, another limitation, which needs to be carefully considered in future trials, is the choice of sham wristbands, which in our case may not have been the most optimal design.

### *Conclusions and Research Recommendations*

Despite several acupressure antiemetic trials suggesting a beneficial effect, the trial heterogeneity and inconsistent findings prevented any definitive conclusions being drawn. Our study, using a strong methodological design and standardization of antiemetics, showed no significant differences in the use of acupressure wristbands for the management of nausea and vomiting during chemotherapy. However, clinically, the improved levels of nausea in both wristband arms need some attention as patients in both arms tended to show some improvement. However, as minimally important differences in relation to chemotherapy-related nausea and vomiting are currently not established, some caution is necessary with this comment. Also, the use of wristbands led to lower health care utilization (although this did not reach statistical significance). Bands are well accepted and are low cost and safe additions to antiemetic drugs, but the ethical aspects of suggesting the use of potentially noneffective interventions that lead to lower health care costs and health care utilization need some careful consideration. There is a sufficiently encouraging signal and a suggestion of potential health resource use benefits to justify exploration of acupressure in further trials using both no intervention and sham acupressure controls. Questions that need to be answered in the future include whether other forms of acupressure, such as regular finger acupressure or Korean hand acupressure, could be more effective than wristband acupressure. A meta-analysis of existing data on acupressure wristbands

may be an appropriate way to provide a more concrete answer as to whether acupressure wristbands are effective in managing nausea and/or vomiting during chemotherapy.

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### ***References***

1. Glaus A, Knipping C, Morant R, et al. Chemotherapy-induced nausea and vomiting in routine practice: a European perspective. *Support Care Cancer* 2004;12:708–715.
2. Roscoe JA, Morrow GR, Hickok JT, et al. Nausea and vomiting remain a significant clinical problem: trends over time in controlling chemotherapy-induced nausea and vomiting in 1413 patients treated in the community. *J Pain Symptom Manage* 2000;20:113–121.
3. Grunberg SM. Chemotherapy-induced nausea and vomiting: prevention, detection, and treatment—how are we doing? *J Support Oncol* 2004;2(Suppl 1):1–10.
4. Liao CT, Chu NM, Liu HE, Deuson R, Chen JS. Incidence of chemotherapy-induced nausea and vomiting in Taiwan: physicians' and nurses' estimation vs. patients' reported outcomes. *Support Care Cancer* 2005;13:277–286.
5. Bergkvist K, Wengstrom Y. Symptom experiences during chemotherapy treatment—with focus on nausea and vomiting. *Eur J Oncol Nurs* 2006;10:21–29.
6. Foubert J, Vaessen G. Nausea: the neglected symptom? *Eur J Oncol Nurs* 2005;9:21–32.
7. Griffin AM, Butow PN, Coates AS, et al. On the receiving end. V: patient perceptions of the side effects of cancer chemotherapy in 1993. *Ann Oncol* 1996;7:189–195.
8. Ihbe-Heffinger A, Ehlken B, Bernard R, et al. The impact of delayed chemotherapy-induced nausea and vomiting on patients, health resource utilization and costs in German cancer centers. *Ann Oncol* 2004;15:526–536.
9. ASHP therapeutic guidelines on the pharmacologic management of nausea and vomiting in adult and pediatric patients receiving chemotherapy or radiation therapy or undergoing surgery. *Am J Health Syst Pharm* 1999;56:729–764.
10. Miller M, Kearney N. Chemotherapy-related nausea and vomiting—past reflections, present practice and future management. *Eur J Cancer Care* 2004;13:71–81.
11. Dundee JW, Ghaly RG, Fitzpatrick KT, Abram WP, Lynch GA. Acupuncture prophylaxis of cancer chemotherapy-induced sickness. *J R Soc Med* 1989;82:268–271.
12. Dundee JW, Ghaly RG, Fitzpatrick KT, Lynch GA, Abram WP. Acupuncture to prevent cisplatin-associated vomiting. [letter]. *Lancet* 1987;1:1083.
13. Molassiotis A, Helin AM, Dabbour R, Hummerston S. The effects of P6 acupressure in the prophylaxis of chemotherapy-related nausea and vomiting in breast cancer patients. *Complement Ther Med* 2007;15:3–12.
14. Pearl ML, Fischer M, McCauley DL, Valea FA, Chalas E. Transcutaneous electrical nerve stimulation as an adjunct for controlling chemotherapy-induced nausea and vomiting in gynecologic oncology patients. *Cancer Nurs* 1999;22:307–311.
15. Roscoe JA, Morrow GR, Bushunow P, Tian L, Matteson S. Acustimulation wristbands for the relief of chemotherapy-induced nausea. *Altern Ther Health Med* 2002;8:56–63.
16. Treish I, Shord S, Valgus J. Randomised double-blind study of the Reliefband as an adjunct to standard antiemetics in patients receiving moderately-high to highly emetogenic chemotherapy. *Support Care Cancer* 2003;11:516–521.
17. Dundee JW, Yang J. Prolongation of the antiemetic action of P6 acupuncture by acupressure in patients having cancer chemotherapy. *J R Soc Med* 1990;83:360–362.
18. Dundee JW, Yang J, McMillan C. Non-invasive stimulation of the P6 (Neiguan) antiemetic acupuncture point in cancer chemotherapy. *J R Soc Med* 1991;84:210–212.
19. Wright LD. The use of motion sickness bands to control nausea and vomiting in a group of hospice patients. *Am J Hosp Palliat Care* 2005;22:49–53.

20. Shin YH, Kim TI, Shin MS, Juon HS. Effect of acupressure on nausea and vomiting during chemotherapy cycle for Korean postoperative stomach cancer patients. *Cancer Nurs* 2004;27:267–274.
21. Dibble SL, Chapman J, Mack KA, Shih AS. Acupressure for nausea: results of a pilot study. *Oncol Nurs Forum* 2000;27:41–47.
22. Roscoe JA, Morrow GR, Hickok JT, et al. The efficacy of acupressure and acustimulation wrist bands for the relief of chemotherapy-induced nausea and vomiting. A University of Rochester Cancer Center Community Clinical Oncology Program multicenter study. *J Pain Symptom Manage* 2003;26:731–742.
23. Roscoe JA, Matteson SE, Morrow GR, et al. Acustimulation wrist bands are not effective for the control of chemotherapy-induced nausea in women with breast cancer. *J Pain Symptom Manage* 2005;29:376–384.
24. Ezzo JM, Richardson MA, Vickers A, et al. Acupuncture-point stimulation for chemotherapy-induced nausea or vomiting. *Cochrane Database Syst Rev* 2006;2:CD002285.
25. Molassiotis A, Yam BM, Yung H, Chan FY, Mok TS. Pretreatment factors predicting the development of postchemotherapy nausea and vomiting in Chinese breast cancer patients. *Support Care Cancer* 2002;10:139–145.
26. du Bois A, Meerpohl HG, Vach W, et al. Course, patterns, and risk-factors for chemotherapy-induced emesis in cisplatin-pretreated patients: a study with ondansetron. *Eur J Cancer* 1992;28:450–457.
27. Morrow GR, Lindke J, Black PM. Predicting development of anticipatory nausea in cancer patients: prospective examination of eight clinical characteristics. *J Pain Symptom Manage* 1991;6:215–223.
28. Roila F, Hesketh PJ, Herrstedt J. Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer. Prevention of chemotherapy- and radiotherapy-induced emesis: results of the 2004 Perugia International Antiemetic Consensus Conference. *Ann Oncol* 2006;17:20–28.
29. Kris MG, Hesketh PJ, Somerfield MR, et al. American Society of Clinical Oncology guideline for antiemetics in oncology: update 2006. *J Clin Oncol* 2006;24:2932–2947.
30. Rhodes VA, McDaniel RW. The Index of Nausea, Vomiting, and Retching: a new format of the Index of Nausea and Vomiting. *Oncol Nurs Forum* 1999;26:889–894.
31. Molassiotis A, Coventry PA, Stricker CT, et al. Validation and psychometric properties of a short clinical scale to measure chemotherapy-induced nausea and vomiting: the MASCC antiemesis tool (MAT). *J Pain Symptom Manage* 2007;34:148–159.
32. Fairclough DL, Cella DF. Functional Assessment of Cancer Therapy (FACT-G): non-response to individual questions. *Qual Life Res* 1996;5:321–329.
33. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; 67:361–370.
34. Andrykowski MA, Gregg ME. The role of psychological variables in post-chemotherapy nausea: anxiety and expectation. *Psychosom Med* 1992;54: 48–58.
35. Venables WN, Ripley BD. *Modern applied statistics with S*, 4th ed. New York: Springer, 2002.
36. Parsons NR, Edmondson RN, Gilmour SG. A generalized estimating equation method for fitting autocorrelated ordinal score data with an application in horticultural research. *Appl Stat* 2006;55: 507–524.
37. Lee EJ, Frazier SK. The efficacy of acupressure for symptom management: a systematic review. *J Pain Symptom Manage* 2011;42:589–603.
38. Dibble SL, Luce J, Cooper BA, et al. Acupressure for chemotherapy-induced nausea and vomiting: a randomized clinical trial. *Oncol Nurs Forum* 2007;34:813–820.
39. Singha A, Paech MJ, Thew ME, et al. A randomised, double-blinded, placebo-controlled study of acupressure wristbands for the prevention of nausea and vomiting during labour and delivery. *Int J Obstet Anesth* 2011;20:110–117.
40. Enblom A, Lekander M, Hammar M, et al. Getting the grip of nonspecific treatment effects: emesis in patients randomised to acupuncture or sham compared to patients receiving standard care. *PLoS One* 2011;6:e14766.
41. Roscoe JA, O'Neill M, Jean-Pierre P, et al. An exploratory study on the effects of an expectancy manipulation on chemotherapy-related nausea. *J Pain Symptom Manage* 2010;40:379–390.
42. Olver I, Molassiotis A, Apro M, et al. Antiemetic research: future directions. *Support Care Cancer* 2011;19(Suppl 1):S49–S55.
43. Miller FG, Colloca L, Kaptchuk TJ. The placebo effect: illness and interpersonal healing. *Perspect Biol Med* 2009;52:518–539.
44. Alkaissi A, Stalner M, Kalman S. Effect and placebo effect of acupressure (P6) on nausea and vomiting after outpatient gynaecological surgery. *Acta Anaesthesiol Scand* 1999;43:270–274.
45. Price DD, Finiss DG, Benedetti F. A comprehensive review of the placebo effect: recent advances and current thought. *Annu Rev Psychol* 2008;59:565–590.
46. Apro M, Molassiotis A, Dicato M, et al., on behalf of the PEER investigators. The effect of guideline-consistent antiemetic therapy on chemotherapy-induced nausea and vomiting (CINV): the Pan European Emesis Registry (PEER). *Ann Oncol* 2012;23:1986–1992.