UNIVERSITY OF ROCHESTER CANCER CENTER

Protocol

for

Alternative Approaches for Nausea Control
UCCS1202

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Abstract

Nausea remains a significant clinical problem despite the use of the best available antiemetic medications. Several studies have shown that expectations of developing nausea are a significant determinant of whether patients actually develop treatment-induced nausea. For example, we found that breast cancer patients (N = 194) about to begin their first chemotherapy regimen containing doxorubicin who believed that they were "very likely" to experience severe nausea were five times more likely to experience severe nausea than those who believed that they were "very unlikely" to do so. In addition, studies have shown that expectations of efficacy are largely responsible for the placebo effect and for many of the benefits derived from some CAM therapies. For example, in a multicenter study (N = 465) examining acupressure wristbands for control of chemotherapy-induced nausea, we found that patients who expected the bands to be effective in nausea control experienced significantly less nausea than patients who did not expect them to be effective.

As a test of whether the effectiveness of acupressure bands in reducing nausea could be enhanced by boosting patients' expectations of the bands' efficacy, we conducted a double-blind, randomized R21 pilot study examining the efficacy of acupressure bands with and without expectancy-enhancing supplementary materials in breast cancer patients beginning chemotherapy. **Patients were stratified by expected nausea (high, low)**. Patients in the active condition received a handout with expectancy-enhancing materials and a 12-minute relaxation CD that included a 30-second "suggestion" concerning the acupressure bands' effectiveness. Patients in the control group received a handout that had only neutral materials concerning the bands' likely effectiveness and a relaxation CD that was identical to the active one except additional music was substituted for the 30-second suggestion concerning the bands' effectiveness. **For the 26 patients expecting nausea, peak nausea on the 1-7 scale was an average of 1.2 points less in the patients randomized to the active condition of expectancy-enhancing supplementary materials** compared to the control condition with neutral supplementary materials; **this represents a large effect size of 0.78 (Cohen's D)**.

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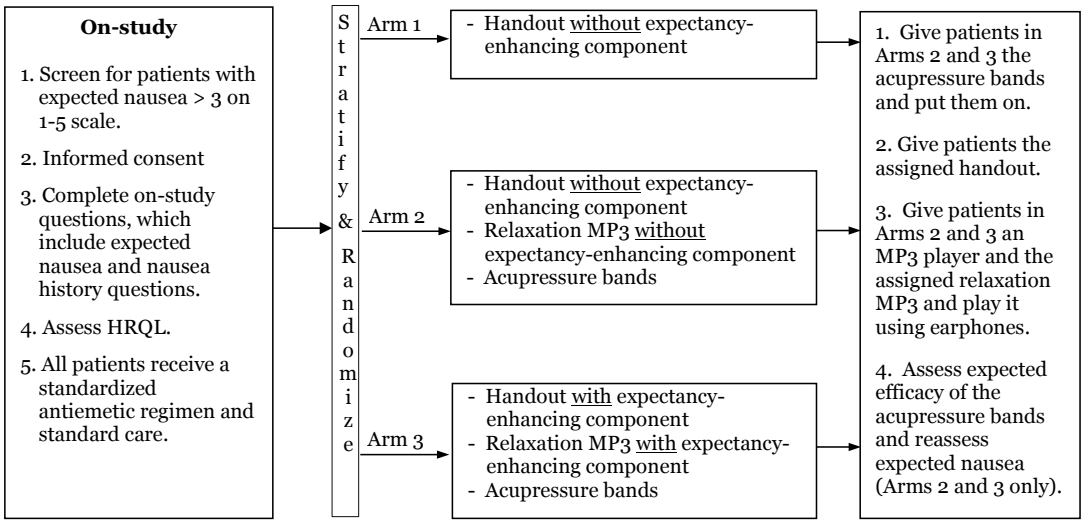
The present study seeks to confirm and extend these findings in a multi-site, 3-arm, randomized, controlled study of 252 breast cancer patients beginning chemotherapy who expect to have nausea. All patients will receive a standardized antiemetic regimen. **Arm 1**: Neutral handout; **Arm 2**: Neutral handout + control relaxation MP3 + acupressure bands; **Arm 3**: Active handout + active relaxation MP3 + acupressure bands. We hypothesize that acupressure bands provided with efficacy-enhancing materials will be more effective in controlling chemotherapy-induced nausea than acupressure bands provided with neutral materials. We build upon a successful R21 study that was designed to refine methods and provide an effect size estimate for this application.

Prior to patient's first chemotherapy treatment

Schema



Following patient's first and second chemotherapy treatment

1. Assess nausea, emesis, and antiemetic and concomitant therapy use for nausea, for 5 days by diary.
2. Record the number of hours the acupressure bands were worn and the number of times the MP3 was listened to for five days by diary.
3. Assess HRQL on Day 5.
4. Feedback questions on Day 5.

1.0 Background

The shift towards patient-centered care has increasingly made communication between caregiver and patient a two-way street. Healthcare professionals need to impart information about treatment to the patient while listening to the patient's fears, hopes, and wishes. Working together, a treatment plan is developed. Patient and caregiver communication is crucial in the development of patients' expectancies for treatment outcomes, termed "response expectancies." This anticipation can influence physical, emotional, and mental outcomes throughout the treatment process.[1-4]

The effect of response expectancies can be considerable, and they frequently account for variance in chemotherapy-induced nausea above and beyond the emetogenicity of the chemotherapeutic agent and other known predictive factors for nausea such as gender and age.[2-11] For example, Roscoe et al. studied 194 breast cancer patients about to begin chemotherapy with a doxorubicin-based regimen and found that **patients who believed that they were "very likely" to experience severe nausea were five times more likely to experience severe nausea** than those who believed that they were "very unlikely" to do so.[8]

Although expectancies may represent an acknowledgement of one's propensity to develop nausea based on past experience (e.g., nausea during pregnancy or susceptibility to motion sickness), these expectancies are also influenced by socio-cultural factors and what patients are told to expect from the range of information they receive from clinicians, hospital staff, other patients, family, friends, and the world at large. Thus, nausea

expectancies can be considered to have both internal and external sources, and it is these external sources that might provide a way of reducing chemotherapy-induced nausea. Unlike other risk factors for nausea, nausea expectancies are malleable and provide an opportunity for intervention.

Acupressure Bands and Expectancy: Research done by our group and others provides evidence that acupressure bands are efficacious in reducing treatment-related nausea,[12-17] and that **acupressure bands are particularly effective for patients who expect nausea.**[18] Expectancy appears to play a dual role in the bands' effectiveness, with research also showing that their effectiveness in controlling nausea can largely be accounted for by patients' expectations of efficacy, i.e., a placebo effect.[11,13,19,20] In this regard, in addition to any intrinsic efficacy for relieving nausea they may have, the **acupressure bands can be considered an inert device/remedy that facilitates a change in nausea expectancies.** The interplay between patients' expectations for developing nausea and their propensity to respond favorably to an intervention designed to increase positive expectations for nausea control leads to a logical question—can the effectiveness of acupressure bands in reducing nausea be enhanced by boosting patients' expectations of the bands' efficacy? Stated another way, can the placebo effect be maximized and utilized for enhanced nausea control?

We tested that question in an R21 pilot study of acupressure bands, with and without expectancy-enhancing supplementary materials, for control of nausea in breast cancer patients beginning chemotherapy (Preliminary Study 1).[11] The **active condition** consisted of a handout and a specially made 12-minute relaxation CD, each with components to enhance patients' expectations of the usefulness of the acupressure wristbands. Patients in the **control condition** received acupressure bands along with a neutral handout concerning the bands' likely effectiveness and a relaxation CD that had no information concerning the acupressure bands. For the 26 patients expecting nausea, peak nausea on the 1-7 scale was an average of 1.2 points less in the patients randomized to the active condition compared to the control condition. The present study seeks to confirm and extend these findings in a multi-site, 3-arm, randomized, controlled study.

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Overview of Proposed Study: 252 Chemotherapy-naïve, female breast cancer patients about to begin chemotherapy without concurrent radiotherapy or interferon, treated at the University of Rochester James P. Wilmot Cancer Center (URCC), Rochester General Hospital's Lipson Cancer and Blood Center (RGH-LCC), Roswell Park Cancer Institute (RPCI), or at Hematology-Oncology Associates of Central New York (HOACNY), and **who expect to have nausea,** will be entered. Participants will be randomized to one of three study arms: **Arm 1**: Neutral handout; **Arm 2**: Neutral handout + control relaxation MP3 + acupressure bands; **Arm 3**: Active handout + active relaxation MP3 + acupressure bands.

Four common chemotherapy regimens will be allowed. They are doxorubicin and cyclophosphamide with or without docetaxel, docetaxel with cyclophosphamide, and docetaxel with carboplatin. Only patients receiving the antiemetic regimen described below will be eligible. All patients will receive a standardized antiemetic regimen. All ancillary treatments, as appropriate for control of symptoms caused by the cancer or its treatment, may be administered as clinically indicated and will be recorded. As part of the consent process, patients will be told that we are studying the use of acupressure bands and a relaxation MP3 and how information is delivered. At no point will we inform patients we are examining the role of expectancy and that we are testing an expectancy manipulation.

Hypothesis: Acupressure bands with efficacy-enhancing supplementary material will be more effective in controlling chemotherapy-induced nausea than acupressure bands with neutral supplementary material.

2.0 Aims

2.1 Primary Aim: To determine whether acupressure bands provided with efficacy-enhancing supplementary material are more effective in controlling chemotherapy-induced nausea than acupressure bands provided with neutral supplementary material. (Arm 2 vs. Arm 3)

2.2 Secondary Aim: To determine whether acupressure bands combined with a relaxation MP3 and supplementary material are a helpful adjunct to standard antiemetics in controlling nausea. (Arm 1 vs. Arm 3)

3.0 Subject Eligibility

Study Patients Must:

3.1 Be female.

3.2 Have a diagnosis of breast cancer, any stage.

3.3 Be chemotherapy naïve and about to begin her first course of chemotherapy.

3.4 Be scheduled to receive one of the following four common chemotherapy regimens* with the specified antiemetic regimen.**[ab] They are:

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1. Chemotherapy regimen: Doxorubicin/cyclophosphamide
   Antiemetic regimen: Aprepitant (125 mg p.o.) + palonosetron ** (0.25 mg I.V.) + dexamethasone on Day 1 and aprepitant (80 mg p.o.) + dexamethasone on Days 2 & 3.[a]
   Note: Fosaprepitant (150 mg I.V.) on Day 1 will be allowed in place of the three days of oral aprepitant.

2. Chemotherapy regimen: Doxorubicin/cyclophosphamide/docetaxel
   Antiemetic regimen: Aprepitant (125 mg p.o.) + palonosetron ** (0.25 mg I.V.) + dexamethasone on Day 1 and aprepitant (80 mg p.o.) + dexamethasone on Days 2 & 3.[a]
   Note: Fosaprepitant (150 mg I.V.) on Day 1 will be allowed in place of the three days of oral aprepitant.

3. Chemotherapy regimen: Docetaxel/carboplatin
   Antiemetic regimen: Palonosetron ** (0.25 mg I.V.) + dexamethasone on Day 1 + dexamethasone on Days 2 & 3.[ab]

4. Chemotherapy regimen: Docetaxel/cyclophosphamide
   Antiemetic regimen: Palonosetron ** (0.25 mg I.V.) + dexamethasone on Day 1 + dexamethasone on Days 2 & 3.[ab]

* In the study, Herceptin® (trastuzumab) is not classified as a chemotherapy agent and will be allowed at the oncologist's discretion.

** Granisetron or ondansetron, on one or more days, will be allowed in place of palonosetron. Note: both granisetron and ondansetron may be given to the same patient if provided on different days.

[a] Providing dexamethasone on Day 2 and/or Day 3 is optional at the discretion of clinic personnel.

[b] Aprepitant or fosaprepitant, as described in regimens 1 and 2 above, may be provided with this antiemetic regimen at the discretion of clinic personnel.

3.5. Have a response of > 3 on a question assessing expected nausea as assessed on a 5-point Likert-scale anchored at one end by 1 = "I am certain I WILL NOT have this," and at the other end by 5 = "I am certain I WILL have this."

3.6 Be able to read English (since the assessment materials are in printed format).

3.7 Be 18 years of age or older and give written informed consent.

Study Patients Must Not:

3.8 Have clinical evidence of lymphedema, current bowel obstruction, or symptomatic brain metastases, as determined by their treating oncologist.

3.9 Be receiving concurrent radiotherapy or interferon.

4.0 Randomization

4.1 Patients who meet the eligibility criteria and who have signed the consent form will be randomized to one of three trial arms as described below.

4.2 Randomization will be stratified by whether or not patients receive a doxorubicin-based chemotherapy (yes, no) because it is more emetogenic than other chemotherapy regimens.[10] We will also stratify by site (i.e., URCC, RGH-LCC, RPCI, HOACNY) as is customary in multicenter cancer studies.

4.3 A total enrollment of 252 patients is planned, with 84 patients in each treatment condition.

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4.3.1 Each of the four sites will have an accrual target range from 48 to 96 patients.

4.3.2 Accrual at a given site will halt only when (1) at least 96 subjects have been enrolled at the site or (2) enrollment at all sites is closed since at least 252 subjects have been enrolled in the study.

4.4 Treatment Arms

Arm 1: Neutral handout that has no mention of acupressure bands.
Arm 2: Neutral handout concerning acupressure bands + control relaxation MP3 + acupressure bands.
Arm 3: Active handout concerning acupressure bands + active relaxation MP3 + acupressure bands.

4.5 Because patients must actually receive the intervention prior to their initial chemotherapy, which is an extraordinarily busy and hectic time in cancer clinics, an expedited randomized system will be used which involves providing the study coordinator with the correct study materials for any given patient in advance of that patient providing consent. Details for implementation are as follows:

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4.5.1 Research associates of Dr. Roscoe who will not be involved in study analyses and will not have patient contact will create **randomization envelopes** and **study packets** for each site in advance of patient recruitment.

Rev 1/9/15 4.5.2 324 **Study packets** will be created and numbered sequentially with each packet containing the necessary questionnaires for the study with preprinted study ID numbers (i.e., 1-324) on all of the Teleform questionnaires within that packet.

4.5.21 Study packets will be grouped in sequential blocks of 18, i.e., 1-18, 19-36, 37-54, etc.

4.5.22 Each block of 18 study packets will be randomly assigned to Study Arms by means of a computer-generated random table using the Mersenne-Twister (Ref: Matsumoto, M. and Nishimura, T. (1998) Mersenne Twister: A 623-dimensionally equidistributed uniform pseudo-random number generator, ACM Transactions on Modeling and Computer Simulation, 8, 3–30.) with a random block size of 3 or 6.

4.5.3 All study packets randomized to study **Arm 1 will be yellow in color** and will have the neutral handout with no mention of acupressure bands added.

4.5.4 All study packets randomized to study **Arm 2** will have an opaque, sealed, **study-materials envelope** added with the **expectancy neutral handout** and a piece of paper the same size as a prescription which says, "Use the acupressure bands in addition to your regular medication" inside. The sealed study-materials envelope will also have a flash drive with the control relaxation MP3 on it.

4.5.5 All study packets randomized to study **Arm 3** will have an opaque, sealed, **study-materials envelope** added with the **expectancy enhanced handouts** inside. The sealed study-materials envelope will also have a flash drive with the active relaxation MP3 on it.

4.5.6 All study packets for study arms 2 and 3 from each randomization block of 18 packets will be placed in sequential order and included in a box with study arm 1 packets. There will be a total of 18 study packets per box.

4.5.61 Each site will initially receive two of these boxes, one with the additional marking, **For Patients Receiving Doxorubicin**, and the other with the additional marking, **For Patients Not Receiving Doxorubicin**.

4.5.62 The remaining boxes will be stored at the URCC until needed at one of the sites. These remaining boxes can later be marked either For Patients Receiving Doxorubicin or For Patients Not Receiving Doxorubicin, as necessary, and can go to any site.

4.5.63 Note: This procedure will keep the study materials for these two conditions blinded from anyone with patient contact up to this point in the study. Arm 1 is not blinded in this study.

Rev 1/9/15 4.5.7 Additional sealed, opaque, **randomization envelopes** will be created for each of the four study sites (150 for RPCI, 150 for HOACNY, 114 for RGH-LCC, and 78 for URCC). For **stratification purposes**, half of the randomization envelopes for each site will be marked "doxorubicin-based chemotherapy" on the outside, will have some red coloring (because doxorubicin is red), and will be labeled sequentially, i.e., 1-38 or 1-75. The remaining half will be marked "non doxorubicin-based chemotherapy" and will also be labeled sequentially. Two thirds of the envelopes in each group will have a sheet of paper saying "**Active**" inside. The remaining envelopes will have a sheet of paper saying "**Control"** inside. The information in the envelopes will be randomized using the procedure outlined in Section 4.5.2 and adapted as

appropriate for the 2-1 randomization. The envelopes in each group will then be numbered sequentially and placed in a **doxorubicin box** or **a non-doxorubicin box** as appropriate.

4.5.8 To randomize a patient who meet the eligibility criteria and who have signed the consent form, the study coordinator will take the next sealed randomization envelope out of the appropriate doxorubicin or non-doxorubicin box. If the randomization envelope says **Control,** the study coordinator will take the next study packet labeled control for that patient from the box labeled **Doxorubicin** or from the box labeled as **Not Receiving Doxorubicin**, depending on the chemotherapy regimen the patient receives. If the randomization envelope says **Active,** the study coordinator will take the study packet for that patient from the box labeled **Doxorubicin** or from the box labeled as **Not Receiving Doxorubicin**, depending on the chemotherapy regimen the patient receives.

4.6 Documentation of IRB approval and a copy of the institution's IRB-approved informed consent document form must be on file with Dr. Roscoe prior to entering participants on this protocol.

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4.7 Within 24 hours following randomization, the following information needs to be sent to Dr. Roscoe:

4.7.1 Site, i.e., URCC, RGH-LCC, RPCI, HOACNY

4.7.2 Name of person consenting the study participant

4.7.3 Verification that participants meet all eligibility requirements listed in Section 3.0

4.7.4 Whether or not the patient will receive doxorubicin-based chemotherapy

4.7.5 Verification that the consent form has been signed

4.7.6 Initials of patient

4.7.7 Ethnicity

4.7.8 Race

4.7.9 Age

4.7.10 Randomization envelope number

4.7.11 Study packet number

4.7.12 Whether or not the patient will receive Herceptin® (trastuzumab).

5.0 Treatment Protocol

5.1 All ancillary treatments, including antiemetic medications, as appropriate for control of symptoms caused by the cancer or its treatment may be administered as clinically indicated to all patients.

5.1.1. The chemotherapy and/or antiemetic regimens may be altered at the patient's second and subsequent chemotherapy cycles.

5.2 Recruitment and Informed Consent: All data will be gathered from patients, 18 years of age or older, who are undergoing chemotherapy for breast cancer and who are able to read and understand English. Subjects will be recruited from the URCC, HOACNY, RPCI, and RGH-LCC. Study personnel will monitor the clinic schedule. If the study is deemed appropriate for the patient, and if the patient agrees to discuss it, a member of the research team will then explain the project to the potential subject and answer all questions. After they sign the consent form, patients will be given a copy of the document, along with the phone numbers to call in case questions arise.

5.3 Procedures: Prior to first chemotherapy, all patients will complete the on-study questionnaires (see Schema) and be given the handout appropriate for their randomization assignment. The remaining procedures vary according to randomization assignment.

5.3.1 **Arm 1:** Patients receive a neutral handout with no mention of acupressure bands.

5.3.2 **Arms 2 and 3:** Patients will receive two acupressure wrist bands to be put on at that time. Patients will be told they are allowed to wear or remove the bands throughout the study period at their own discretion. While still wearing the acupressure bands, patients will be given a sealed envelope with their assigned handout and asked to read the contents without letting any research or clinical personnel know the contents. Patients will also be given, to keep, a portable MP3 player and the assigned relaxation MP3. They will listen to the MP3 at that time using provided earphones to ensure they hear it at least once. Patients will also be encouraged to listen to the MP3 later if they found it helpful and to record how many times they did so. The same procedures regarding the relaxation MP3 used for Arm 2 will then be followed. A reassessment of expected nausea, including questions regarding expected efficacy of the acupressure bands, will then be completed. Note: Patients will be instructed not to share information provided in the handouts and on the MP3 with the researcher or other patients.

5.3.3 All patients, regardless of study arm, will be given a diary (Five-Day Home Record) to complete at home following their first and second treatments to assess frequency and severity of NV and use of antiemetic medications and concomitant therapies for nausea. They will also receive a HRQL measure to complete on Day 5 following their first and second treatments. In addition, logs, as appropriate, will be used to assess use of the wristbands and MP3s, as well as the effect of the intervention on patients' levels of apprehension regarding treatment-related side effects, their sense of control over side effects, and the perceived credibility of the intervention following their first and second treatments.

5.3.4 Patients will be contacted two to four days after their first and second chemotherapy treatments (i.e., Days 3, 4 or 5 of the cycle) to ask them to complete and return the questionnaires in the provided stamped, pre-addressed envelope.

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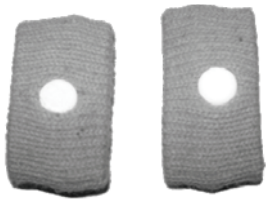
5.3.4.1 Day 4 is preferred for patient contact. However, if Day 4 falls on a weekend or holiday, contact may be made on the weekday corresponding most closely to Day 4.

5.3.5 The study will be double-blinded for the Primary Aim, i.e., Arm 2 vs. Arm 3. Researchers with patient contact and the treating physicians will be blinded as to randomization condition for these two study arms by the judicious use of sealed envelopes, earphones, and carefully worded descriptions of the study. In addition, an expectancy-neutral script will be followed when consenting and enrolling patients. The handouts and MP3 will be prepared for each patient and group assignment recorded by study personnel who do not have patient contact. In order to assure blinding for these two study arms, we will perform a blinding check by asking the study personnel with patient contact what arm they think the patients were assigned to.

5.3.6 The trial ends when the completed measures have been returned following the participant's second chemotherapy treatment.

5.4 Intervention Materials:

5.4.1 Bilateral acupressure wrist bands (Sea-Band International, England), given to patients in trial **Arms 2 and 3**, are widely available and inexpensive (under $6.00 a pair). The acupressure bands are worn on the ventral portion of each wrist (approximately 2 inches proximal to the distal skin crease of the wrist joint). The protruding round plastic button is used to apply pressure to the Neiguan (P6) acupoint which is centered between the tendons of the palmaris longus and flexor carpi radialis muscles at this location.


Seabands

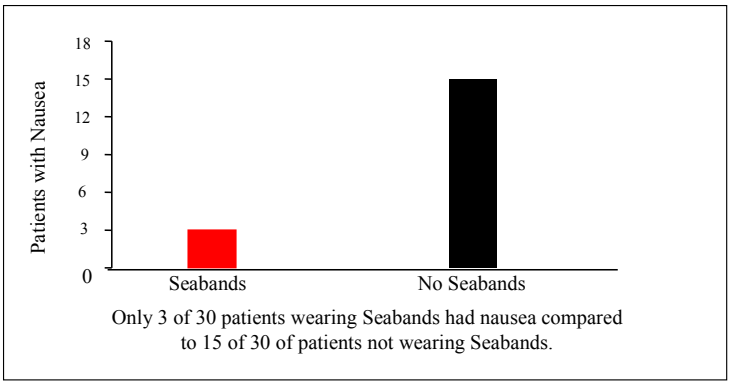
5.4.2 The two parts of the expectancy enhancing handout that will be given to patients in trial **Arm 3** to enhance expected acupressure band efficacy are shown on the next page. The information provided in the first part of the handout is accurate and is intended to provide evidence that the bands may be helpful for reducing nausea. It will be printed on Cancer Center letterhead and signed by a medical oncologist. We give a very positive (and truthful) interpretation of the data from these studies. For example, the caption under the graph reads, "Only 3 patients wearing Seabands had nausea compared to 15 patients not wearing Seabands."

The prescription for the acupressure bands, that is the second part of this handout, is not intended to imply that they are prescription only devices. It will be made clear to all patients that they are sold over-the-counter. Rather, it is included as part of the efficacy enhancing handout because individualized print communication has been found to be more effective for influencing health-related behaviors than non-tailored written information. In addition, personalized information is perceived as more credible, read more, and remembered better.[21]

The prescription is signed by a medical oncologist and has the instruction, "Wear Seabands for up to five days as needed to prevent or alleviate nausea." In order to make it clear that the acupressure bands were to be used in addition to their antiemetic regimen and not in place of it, there will a sticker on the prescription with the wording, "Use the acupressure bands in addition to your regular medication." Patients' names are not on the prescription.

Part 1 of the expectancy enhancing handout for patients in **Arm 3.**

Thank you for taking part in this study. We are excited about this study because we think it might help stop or reduce the nausea that could result from your treatments. Previous studies show that the Seabands have been able to reduce nausea, and we are hopeful the Seabands will help you. As you can see from the graph below, results from a previous study of 60 surgical patients show that only 3 of the 30 patients wearing Seabands had nausea. Many more patients (15 out of 30) had nausea without them.

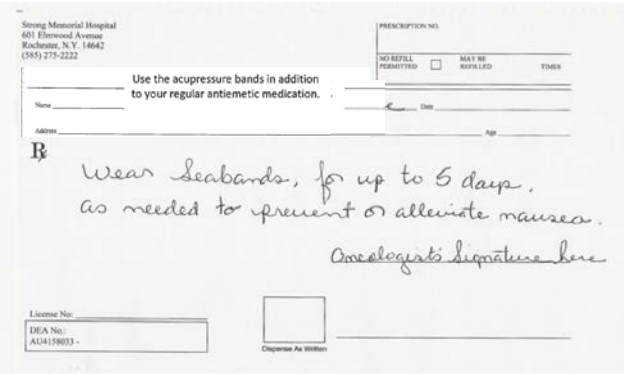


Only 3 of 30 patients wearing Seabands had nausea compared to 15 of 30 of patients not wearing Seabands.

In another study involving 386 chemotherapy patients, patients wearing the Seabands had much less nausea on the day they received their chemotherapy than patients who did not wear Seabands.

The promising findings from these two studies suggest that the Seabands are well worth trying and that they may be very helpful to patients receiving chemotherapy.

Part 2 of the expectancy enhancing handout for patients in **Arm 3.**


Strong Memorial Hospital
601 Elmwood Avenue
Rochester, N.Y. 14642
(585) 275-2222

PRESCRIPTION NO.

NO REFILL PERMITTED ☐ MAY BE REFILLED TIMES

Use the acupressure bands in addition to your regular antiemetic medication.

Name Date

Address Age

℞

Wear Seabands, for up to 5 days, as needed to prevent or alleviate nausea.

Oncologist's Signature here

License No:

DEA No.:
AU4158033 -

Dispense As Written

The prescription (shown above) will be paper clipped to the above handout and is intended to augment the efficacy enhancing potential of the handout.

5.4.3 The expectancy neutral handout given to patients in **Arms 1 and 2** will simply thank patients for participating in the study. Handouts provided to these patients will not have a prescription attached and will not contain information on the efficacy of the acupressure bands nor positive statements concerning them. The text is shown below and it will be printed on the appropriate Cancer Center letterhead and signed by a medical oncologist. In addition, patients in Arm 2 will receive a piece of paper the size of a prescription that says, "Use the acupressure bands in addition to your regular medication."

> Thank you for agreeing to participate in this study regarding the use of acupressure bands to control chemotherapy-related nausea. The information you will provide is extremely valuable. It is only with the assistance of individuals like you, who are willing to give their time, that we can learn new ways to better control the side effects of cancer treatment. We are very appreciative of your contribution to this study.

5.4.4 Expectancy enhancing and expectancy neutral MP3s: The basic script used in both the expectancy neutral and expectancy enhancing MP3s is about 12 minutes in length and utilizes guided imagery in which the individual visualizes pleasant, soothing images or scenes while relaxed. It is based upon a published script.[22,23] The MP3s differ from one another only in that the expectancy enhancing MP3 (for subjects randomized to **Arm 3)** will have additional language inserted concerning efficacy of the acupressure bands and control of nausea. This additional language is under one minute in length and is intended to strengthen patients' beliefs that the acupressure bands will be effective by focusing patients' attention on how effective the acupressure bands have been in reducing or eliminating nausea for other patients. We believe that this focusing of attention will serve to more deeply imbed the idea that the acupressure bands will be helpful. In addition, it will be suggested that since the acupressure bands were helpful to others, "we think that they will be helpful to you, as well." This use of a suggestion is a technique borrowed from suggestive/hypnosis therapy and is a non-deceptive psychological procedure to alter expectancy.[24] Evidence suggests that both hypnotic and placebo effects share the common mechanism of response expectancy and that they are therapeutic because they change patients' expectations of outcome.[25] Both can be viewed as instances of the broader phenomenon of suggestion.[26] Interventions that make use of suggestions (with or without the induction of a hypnotic trance) have been used successfully to control nausea related to chemotherapy,[27-31] during pregnancy,[32,33] and after anesthesia.[34] In the proposed study, a hypnotic trance will not be induced. We will simply make use of the therapeutic technique of providing a suggestion as a method that may be efficacious in increasing positive expectancies concerning the acupressure bands.

The actual language that has been inserted in the expectancy enhancing MP3, but not in the control MP3, is as follows:

"I'd like you to imagine feeling this way as you begin your treatment, and receive it …and then afterwards…you can call up these calm, pleasant feelings at any time…return whenever you wish to this special, safe place…and I wonder, too, if you might be able to use the wristband you now have as a reminder of these relaxed, pleasant sensations you are now experiencing…free of stress, nausea or other unpleasant sensations…I wonder if directing your attention to the

wristband in the future can call up these feelings for you…of being quiet, relaxed, with no queasiness…others who have had chemotherapy have found the wristbands useful in providing relief of that unpleasant feeling, and I wonder if you will too…knowing you can use the bands to call up the peace you feel now, the feeling of being free of nausea that you are hopefully feeling …and regain the sense of calm...peace and relaxation you have now."

5.4.5 Patients will be told that they may wear or remove the bands throughout the five days at their own discretion and to record when they were worn in the provided five-day diary. Although patients will be given two acupressure bands, they may choose to wear only one band. In this case, the band may be worn on either wrist or alternated between wrists, as the patient desires.

5.4.6 Patients will be given the MP3, and an MP3 player, if necessary, to take home and told they may listen to it as much or as little as they would like.

5.5 No side effects are associated with use of the Seabands. Patients susceptible to lymphedema, however, will be cautioned not to wear the band on the affected arm.

5.6 No side effects are associated with use of the MP3s.

5.7 Any adverse event (AE) that is possibly, probably, or definitely related to the study intervention will be reported according to the guidelines below:

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5.7.1 A SAE refers to any event in which the outcome results in any of the following: death*, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability, incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

* This includes all deaths within 30 calendar days of ending study participation regardless of attribution.

5.7.1.1 Only SAEs that are possibly, probably, or definitely related to the study intervention will be recorded in this study.

5.7.2 An AE is any untoward medical occurrence in a subject during participation in the clinical study or with use of the experimental device being studied. An adverse finding can include a sign, symptom, abnormal assessment (laboratory test value, vital signs, electrocardiogram finding, etc.), or any combination of these.

5.7.2.1 Only AEs that are possibly, probably, or definitely related to the study intervention will be recorded in this study.

5.7.3 The MedWatch form found at http://www.fda.gov/Safety/MedWatch/default.htm will be used for reporting any AEs or SAEs that are possibly, probably, or definitely related to the study intervention.

5.7.4 The NCI Common Terminology Criteria for Adverse Events version 4.0 will be utilized to describe and grade any AEs or SAEs that are possibly, probably, or definitely related to the study intervention.

5.7.5 SAEs and AEs at HOACNY, RPCI, and RGH-LCC will be reported according to the following guidelines:

5.7.5.1 SAEs that are that are possibly, probably, or definitely related to the study intervention must be reported to the URCC by phone (585 275-9962 or 585 276-3559) within 24 hours of learning of the event with a written report to follow within 5 calendar days.

5.7.5.2 Any AE that is possibly, probably, or definitely related to the study intervention must be reported to the URCC within 10 calendar days.

5.7.5.3 SAEs and AEs should be reported to the local IRB as per their requirements.

5.7.5.4 SAE and AE reports should be submitted to the URCC in one of the following ways:

- Mail:
  Joseph A. Roscoe, Ph.D.
  Department of Radiation Oncology
  University of Rochester Medical Center
  265 Crittenden Blvd
  CU 420658
  Rochester, NY 14642-0658
- Fax: 585-461-5601.
- Email: joseph_roscoe@urmc.rochester.edu

5.7.6 All MedWatch forms received by the URCC will be reviewed upon receipt by Drs. Roscoe, Shayne, and/or Morrow to confirm toxicity, grade, expectedness, relatedness, sequelae, follow-up required, risk to current or future subjects, and for possible expedited reporting.

5.7.7 Expedited reporting: Any SAE that is possibly, probably, or definitely related to the study intervention will be reported within 15 calendar days to the NCCAM Program Officer and within 10 calendar days to the DSMC, the RSRB, and study investigators at HOACNY, RPCI, and RGH-LCC. The DSMC Chair will determine whether further action is required, and when patient safety is of concern, an interim meeting may be called.

5.7.7.1 In addition, SAEs that are that are possibly, probably, or definitely related to the study intervention AND are also either life threatening or result in death will also be reported within 24 hours via phone to the University of Rochester Research Subjects Review Board and within 7 calendar days to the NCCAM Program Officer.

5.8 Rev 5/23/13 Clinical Trials Data Safety Monitoring Committee (DSMC): The DSMC provides oversight of study progress and safety by review of accrual and events at regularly scheduled meetings. Based on the size, risk, and complexity of this study, the URCC Protocol Review Committee has scheduled this study for annual review. The PI will submit annual progress reports of these data to the DSMC for review. The report will include the number of patients enrolled, withdrawals, and all SAEs and AEs that are possibly, probably, or definitely related to the study intervention. The PI maintains a database of all adverse events that are at least possibly related with description of event, toxicity, expectedness, grade, attribution, and information regarding treatment required complications, or sequelae. The adverse event summary sheet, including any SAEs previously reported, will be reviewed by the DSMC at the annual meeting.

5.8.1 Reports regarding the study from the Clinical Trials Data Safety Monitoring Committee at the University of Rochester Cancer Center will be sent to RGH-LCC, RPCI, HOACNY and NCCAM.

5.9 Fidelity of the Intervention: To ensure the fidelity of the intervention, all study packets and all of the intervention elements (i.e., the acupressure bands, the two versions of the MP3, and the two versions of the handout) will be created at the URCC in an identical fashion. These packets will be appropriately coded for randomization purposes and distributed to the study sites as needed. In addition, we will provide the research coordinators with a script on how to present the study and the intervention materials to patients. A checklist to document that key elements of the script were followed for each patient accrued will be signed by the research coordinators and kept as a study document. Finally, the research coordinator from the URCC will make three site visits to each study location during each year of the study—as well as an additional visit to each site to set up the study—to assure uniformity across treatment sites and over time.

6.0 Treatment Evaluation

Measures:

6.1 The On-Study Data questionnaire is used to record demographic and clinical information and patient's history of nausea from various causes. It also includes questions concerning the information sources for expectations concerning nausea and expected acupressure band efficacy.

6.2 The measure of patients' expectations for side effects is based on a questionnaire used previously by our group,[7,35] as well as by others.[36,37] Expectations of developing specific side effects (e.g., nausea, vomiting) are assessed on separate 5-point Likert-scales that are anchored at one end by 1 = "I am certain I WILL NOT have this" and at the other end by 5 = "I am certain I WILL have this." Questions concerning the expected efficacy of the acupressure wrist bands and whether this expectation was changed by the information materials have been added to the post-intervention version of the questionnaire.

6.3 Nausea and emesis will be measured by a patient report diary developed by Burish[38] and Carey[39] and completed by patients over a five-day period. Each day is divided into four segments (morning, afternoon, evening, night) in which patients report the severity of nausea and number of vomiting episodes for each period of the day (20 total reporting times for each five-day period). Severity of nausea is assessed on a 7-point rating scale, anchored at one end by 1 = "Not at all nauseated" and at the other end by 7 = "Extremely nauseated." Vomiting episodes will be recorded for the same time intervals as part of the five-day diary for later exploratory analyses. We have used this scale in previous studies,[7,13,40] so we will be able to compare current findings with results of our previous research.

6.4 Logs will be used to assess use of the wristbands, MP3s, antiemetic medications, and concomitant therapies for nausea, as well as the effect of the intervention on patients' levels of apprehension regarding treatment-related side effects, their sense of control over side effects, and the perceived credibility of the intervention.

6.5 Health-Related Quality of Life will be assessed using the Functional Assessment of Cancer Therapy Scale – General (FACT–G). The FACT–G is a 28-item scale developed specifically for use in cancer clinical trials.[41] It was developed by Cella and his group through extensive interviews with patients experiencing symptoms of cancer and with oncology professionals and has been validated in a series of studies of 542 cancer patients. It has shown very good test-retest reliability as well as validity.[42,43] Along with a total score representing HRQL, there are psychometrically validated subscales of physical,

functional, social, and cognitive-emotional status. It has become one of the most commonly used measures in oncology, and we have used this scale in our previous studies.

6.6 Demographic and treatment information will be abstracted from patients' charts or obtained from patients in a brief interview.

6.6.1 Data on white blood cell counts (i.e., lymphocytes, monocytes, neutrophils, basophils, and eosinophils) from CBC blood work done within a week of patients' first chemotherapy and/or within a week of patients' second chemotherapy will be abstracted from patients' charts. We note that a CBC is not required for the study and will not be paid for by study funds. We are collecting this data, if it is available, for exploratory analyses to see whether there is an effect of the relaxation MP3 on cell counts.

7.0 Statistical Considerations

7.1 Data Handling and Statistical Considerations:

7.1.1 Data will be entered on scannable forms (Teleform) and electronically sent to an Access Database. After scanning, data is audited visually for errors. R, SPSS, and SAS statistical packages will be used for the analyses. Every effort will be made to encourage and facilitate patients' completion of questionnaires.

7.1.2 Unless otherwise stated, all statistical tests will be performed at the two-tailed 5% level of significance. Likewise, 95% confidence intervals will be constructed to quantify uncertainty of effect estimates. Data will be analyzed on an "intent-to-treat" basis; participant data will be included in the treatment group to which the participant was randomized, regardless of any subsequent changes to the treatment. No interim analyses of efficacy data from the trial are planned.

7.1.3 Assumptions and Outliers: The assumptions underlying all statistical analyses will be thoroughly checked using appropriate graphical and numerical methods.[44,45] In the case of serious violations of the assumptions, appropriate nonparametric methods or transformations will be attempted.[46,47] Outlying data are a potential concern in the collection of data on nausea severity in a diary format, such as we propose. This concern did not materialize in a study we concluded that assessed nausea severity in 96 breast cancer patients.[48] Patients completed the same 5-day nausea diary as in the study proposed herein. No patients were considered outliers in this prior dataset. For the present study, we will consider observations that are more than 3 standard deviations above or below the mean as outlying, where the mean and standard deviation are calculated based on data without the observation under consideration. Should any be present, we will carefully check the data and make corrections if necessary. If no errors are found, we will conduct analyses both with and without the outlying data and report both results.

7.2 <u>Calculation of the Primary Outcome Variable, Handling of Missing Data, and ITT:</u>

7.2.1 The primary outcome variable will be Peak Nausea (measured on a 7-point scale anchored by "Not at all Nauseated" and "Extremely Nauseated") defined as the highest nausea rating across the 20 nausea assessment points (i.e., four measuring points on each of the five days). If scored outcomes are missing, we will evaluate if they are missing at random (MAR) with respect to treatment arm and key prognostic variables. Under the MAR assumption, we will use multiple imputation to assess significance and

uncertainty of the key analysis parameters.[49] In the unlikely event we suspect the missing values are not missing at random (MNAR), we will use selection and pattern-mixture models to assess the sensitivity of the results to missing data.[49]

7.2.2 All analyses evaluating the interventions will follow the Intent to Treat (ITT) principle, and all subjects will be included in the analysis regardless of compliance or outlier status. Separate analyses will be performed after removing noncompliant subjects. These analyses will be considered exploratory and the results will be treated with caution; we note that the power will be reduced because of the smaller sample size.

7.3 Potential Covariates to be Added to the Statistical Analyses Below: Variables that may be related to nausea report, (i.e., age, doxorubicin-based chemotherapy or not, susceptibility to motion sickness or not, morning sickness or not, ethnicity, race, educational level, receiving trastuzumab or not, receiving palonosetron or not, receiving a first generation 5HT-3 on Day 1 only or not, baseline FACT-G scores, receiving dexamethasone on Day 2 or not, receiving dexamethasone on Day 3 or not, and receiving optional aprepitant or fosaprepitant as part of antiemetic regimens 3 or 4 or not) will be tested as potentially meaningful covariates to the analyses below by using ANCOVA. Only covariates testing at $P < 0.05$ will be left in the final model.

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7.4 **Primary Analysis:** The Primary Aim to determine whether acupressure bands provided with efficacy-enhancing supplementary material are more effective in controlling chemotherapy-induced nausea than acupressure bands provided with neutral supplementary material will be examined using ANCOVA with Peak Nausea after the first chemotherapy as the response, Arm (Arms 2 and 3) as the factor and expectancy of acupressure bands as the covariate (in addition to any covariates identified as stated above).

7.5 **Secondary Analysis:** Study Arm 1 and Study Arm 3 will be compared to determine whether acupressure bands combined with a relaxation MP3 and supplementary material are a helpful adjunct to standard antiemetics in controlling nausea. The analysis will be the same as the one used in the primary analysis with Arms 1 and 3 as the factor.

7.6 **Additional Analyses**: The following will be interpreted very cautiously. It is our intention to use them solely to support findings from the Primary and Secondary analyses and to generate information to be used in the design of further randomized controlled investigations.

7.6.1 ANCOVA analyses the same as those used for the primary and secondary aims will be used with Average Nausea and HRQL as the responses.

7.6.2. Analyses will be conducted to see if the intervention positively affects patients' pre-randomization expectations of developing nausea (EXPN) using ANOVA with EXPN as the response and Arm as the factor. Using only the Arms 2 and 3 subjects (i.e. those that received acupressure bands) an ANOVA will be conducted with pre-randomization expectations of how effective the acupressure bands (EXPAB) as the response, and Arm (2 vs 3) as the factor.

7.6.3 Analyses will be conducted to see how patients' pre-randomization expectations of developing nausea (EXPN) as well as their pre-randomization expectations of how effective the acupressure bands (EXPAB) will be in controlling nausea mediate the effect of the interventions on Peak Nausea. Specifically, we will fit a linear model with Peak Nausea as the response, and Arm, EXPN, EXPAB, Arm*EXPN, Arm*EXPAB as the factors. The two-way interactions will be used to assess how the expectancies moderate the effect of the interventions.

7.6.4 The effects of the intervention following patients' second chemotherapy on Peak and Average nausea, and HRQOL will be examined in the same manner as the primary and secondary analyses, also including Peak Nausea after the first chemotherapy (PN1) and Arm*PN1 as additional factors to assess how PN1 affects Peak Nausea and the effect of the interventions after the second treatment.

7.6.5 We will use a linear mixed model to assess the growth/persistence of the intervention effects over the first and second chemotherapy. Peak nausea from both times will be the response. Arm (all three arms for this analysis), Cycle (1 or 2), and expectancy (in addition to any covariates identified) will be the fixed effects. Subject and within-subject will be the random effects. REML estimation will be used, and F-Tests will be used to test significance.[50] We will test whether the intervention effect is stable over the course of the two interventions (i.e. the effects at each assessment are the same) using the appropriate contrast test.

7.6.6 Interactions in any of the above models will be retained only if there are statistically significant at the 0.05 level.

7.7 S**ample Size:** The Primary Aim is to evaluate whether a difference exists between Study Arm 2 and Study Arm 3 in Peak Nausea. Using the data from our multicenter study of delayed nausea in breast cancer patients conducted by the URCC CCOP, the SD of peak nausea was 1.89. Conservatively assuming a correlation of 0.5 between baseline and post-intervention, a sample size of 64 subjects per arm will have 80% power to detect a difference between the arms of 0.82, using ANCOVA with a 0.05 two-sided significance level. Based upon these figures and assuming approximately 24 patients (11%) fail to provide evaluable information, our accrual target will be 72 patients per group or 216 total patients. Based upon our R21 study, we anticipate being able to recruit 72 patients at the Rochester, N.Y. site. This is approximately one patient every 4 weeks during the 54-month recruitment period. We also anticipate a total recruitment of 72 patients each at HOACNY and RPCI.

Rev 1/9/15 7.7.1 The total accrual target has been increased from 216 to 252 i.e., 84 patients per group, with the additional 36 subjects coming from RGH-LCC.

Comment [PDR1]: Usually, this section would also be updated to justify and better reflect any revisions to the targeted sample size(s).

8.0 Records To Be Kept

8.1 Completed questionnaires from RPCI, HOACNY, and RGH-LCC will be photocopied with originals sent immediately by mail to Rochester and copies placed in the patients' study folders at HOACNY, RPCI, and RGH-LCC. The Case Summary should accompany ALL data submissions. Once forms arrive in Rochester, they will be scanned and audited for missing or out-of-range data. Queries for missing or out-of-range data will be relayed to the study coordinator in the three off-site locations to be rectified.

8.2 All completed forms should be sent to:

Tsige Temanu
Department of Radiation Oncology
University of Rochester Medical Center
265 Crittenden Blvd.
CU 420658
Rochester, NY 14642-0658

8.3 Personnel from Rochester will also conduct a yearly site audit of HOACNY, RPCI, and RGH-LCC using the procedures already in place for our CCOP site audits. The auditors will review source documentation on randomly selected patients.

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8.4 All questionnaires will be kept confidential, locked in the private office of the research coordinator and identified only by ID numbers.

	Schedule Of Data Collection			
Measure	Prior to randomization (pre-randomization)	After intervention materials are provided to patient but prior to chemotherapy (post-randomization)	After first chemotherapy	After second chemotherapy
On Study Data	X			
Expectation Questionnaire (pre- randomization)	X			
Expectation Questionnaire (post- randomization)		X		
5-Day Patient Report Diary			X	X
FACT-G (HRQL)	X		X	X
Medication Log			X	X
Wristband Log (with feedback)			X	X
MP3 Log (with feedback)			X	X
Data on white blood counts if available			X	X

9.0 Patient Consent and Peer Judgment

9.1 All investigational, FDA, NCI, State, Federal, and Institutional regulations concerning informed consent and peer judgment will be fulfilled.

10.0 References

1. Crow R, Gage H, Hampson S, Hart J, Kimber A, Thomas H. The role of expectancies in the placebo effect and their use in the delivery of health care: A systematic review. *Health Technology Assessment (Rockville, Md)* 1999;3:1-96.

2. Colagiuri B, Roscoe JA, Morrow GR, Atkins JN, Giguere JK, Colman LK. How do patient expectancies, quality of life, and postchemotherapy nausea interrelate? *Cancer* 2008;113:654-61.

3. Olver IN, Taylor AE, Whitford HS. Relationships between patients' pre-treatment expectations of toxicities and post chemotherapy experiences. *Psychooncology* 2005;14:25-33.

4. Roscoe JA, Jean-Pierre P, Shelke AR, Kaufman ME, Bole C, Morrow GR. The role of patients' response expectancies in side effect development and control. *Current Problems in Cancer* 2006;30:40-98.

5. Montgomery GH, Bovbjerg DH. Pre-infusion expectations predict post-treatment nausea during repeated adjuvant chemotherapy infusions for breast cancer. *British Journal of Health Psychology* 2000;5:105-19.

6. Rhodes VA, Watson PM, McDaniel RW, Hanson BM, Johnson MH. Expectation and occurrence of postchemotherapy side effects: Nausea and vomiting. *Cancer Pract* 1995;3:247-53.

7. Roscoe JA, Hickok JT, Morrow GR. Patient expectations as predictor of chemotherapy-induced nausea. *Annals of Behavioral Medicine* 2000;22:121-6.

8. Roscoe JA, Bushunow P, Morrow GR, et al. Patient expectation is a strong predictor of severe nausea after chemotherapy: A University of Rochester Community Clinical Oncology Program study of patients with breast carcinoma. *Cancer* 2004;101:2701-8.

9. Booth CM, Clemons M, Dranitsaris G, et al. Chemotherapy-induced nausea and vomiting in breast cancer patients: a prospective observational study. *The Journal of Supportive Oncology* 2007;5:374-80.

10. Roscoe JA, Morrow GR, Colagiuri B, et al. Insight in the prediction of chemotherapy-induced nausea. *Support Care Cancer* 2010;18:869-76.

11. 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;40:379-90.

12. Roscoe JA, Matteson SE. Acupressure and acustimulation bands for control of nausea: A brief review. *Am J Obstet Gynecol* 2002;186:S244-S247

13. 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 URCC CCOP multicenter study. *J Pain Symptom Manage* 2003;26:731-42.

14. Roscoe JA, Bushunow P, Jean-Pierre P, et al. Acupressure bands are effective in reducing radiation therapy-related nausea. *J Pain Symptom Manage* 2009;38:381-9.

15. Fan CF, Tanhui E, Joshi S, Trivedi S, Hong Y, Shevde K. Acupressure treatment for prevention of postoperative nausea and vomiting. *Anesthesia & Analgesia* 1997;84:821-5.

16. Taspinar A, Sirin A. Effect of acupressure on chemotherapy-induced nausea and vomiting in gynecologic cancer patients in Turkey. *European Journal of Oncology Nursing* 2010;14:49-54.

17. 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. *Complementary Therapies in Medicine* 2007;15:3-12.

18. Roscoe JA, Jean-Pierre P, Morrow GR, et al. Exploratory analysis of the usefulness of acupressure bands when severe chemotherapy-related nausea is expected. *Journal Of The Society For Integrative Oncology* 2006;4:16-20.

19. Ferrara-Love R, Sekeres L, Bircher NG. Nonpharmacologic treatment of postoperative nausea. *J Perianesth Nurs* 1996;11:378-83.

20. Alkaissi A, Stalnert M, Kalman S. Effect and placebo effect of acupressure (P6) on nausea and vomiting after outpatient gynaecological surgery. *Acta Anaesthesiologica Scandinavica* 1999;43:270-4.

21. Skinner CS, Campbell MK, Rimer BK, Curry S, Prochaska JO. How effective is tailored print communication? *Annals of Behavioral Medicine* 1999;21:290-8.

22. Montgomery GH, Weltz C, Seltz M, Bovbjerg DH. Brief pre-surgery hypnosis reduces distress and pain in excisional breast biopsy patients. *Int J Clin Exp Hypn* 2002;50:15-30.

23. Rhue JW, Lynn SJ, Kirsch I. Handbook of Clinical Hypnosis. Washington, DC.: American Psychological Association, 1993.

24. Kirsch I. Clinical hypnosis as a nondeceptive placebo. In: Kirsch I, Capafons A, et al., eds. Clinical hypnosis and self-regulation: Cognitive-behavioral perspectives. Dissociation, trauma, memory, and hypnosis book series. Washington, DC: American Psychological Association, 1999:211-25.

25. Krassner AM. Hypnotherapy. In: Strohecker J., ed. Alternative medicine: The definitive guide. Fife, Washington: Future Medicine Publishing, 1994:306-12.

26. Kirsch I. Hypnosis and placebos: Response expectancy as a mediator of suggestion effects. *Anales de Psicologia* 1999;15:99-110.

27. Redd WH, Andresen GV, Minagawa RY. Hypnotic control of anticipatory emesis in patients receiving cancer chemotherapy. *J Consult Clin Psychol* 1982;50:14-9.

28. Marchioro G, Azzarello G, Viviani F, et al. Hypnosis in the treatment of anticipatory nausea and vomiting in patients receiving cancer chemotherapy. *Oncology (Huntingt)* 2000;59:100-4.

29. Jacknow DS, Tschann JM, Link MP, Boyce WT. Hypnosis in the prevention of chemotherapy-related nausea and vomiting in children: a prospective study. *Journal of Developmental & Behavioral Pediatrics* 1994;15:258-64.

30. Zeltzer LK, Dolgin MJ, LeBaron S, LeBaron C. A randomized, controlled study of behavioral intervention for chemotherapy distress in children with cancer. *Pediatrics* 1991;88:34-42.

31. Walker LG, Dawson AA, Pollet SM, Ratcliffe MA, Hamilton L. Hypnotherapy for chemotherapy side effects. *British Journal of Experimental and Clinical Hypnosis* 1988;5:79-82.

32. Giorlando S, Mascola R. The treatment of hyperemesis gravidarum with hypnotherapy. *Am J Obstet Gynecol* 1957;73:444-7.

33. Kroger W, DeLee S. The psychosomatic treatment of hyperemesis gravidarum by hypnosis. *Am J Obstet Gynecol* 1946;51:544-52.

34. Williams AR, Hind M, Sweeney BP, Fisher R. The incidence and severity of postoperative nausea and vomiting in patients exposed to positive intra-operative suggestions. *Anaesthesia* 1994;49:340-2.

35. Roscoe JA, Morrow GR, Hickok JT, et al. Expectations of nausea, but not trait optimism, predict chemotherapy-induced nausea severity. *Supportive Care in Cancer, 13th International Symposium* 2001;9:291.

36. Andrykowski MA, Gregg ME. The role of psychological variables in post-chemotherapy nausea: Anxiety and expectation. *Psychosom Med* 1992;54:48-58.

37. Jacobsen PB, Andrykowski MA, Redd WH, et al. Nonpharmacologic factors in the development of posttreatment nausea with adjuvant chemotherapy for breast cancer. *Cancer* 1988;61:379-85.

38. Burish TG, Carey MP, Krozely MG, Greco FA. Conditioned side effects induced by cancer chemotherapy: Prevention through behavioral treatment. *J Consult Clin Psychol* 1987;55:42-8.

39. Carey MP, Burish TG. Etiology and treatment of the psychological side effects associated with cancer chemotherapy: A critical review and discussion. *Psychol Bull* 1988;104:307-25.

40. Hickok JT, Roscoe JA, Morrow GR, King DK, Atkins JN, Fitch TR. Nausea and emesis remain significant problems of chemotherapy despite prophylaxis with 5-hydroxytryptamine-3 antiemetics: A University of Rochester James P. Wilmot Cancer Center Community Clinical Oncology Program Study of 360 cancer patients treated in the community. *Cancer* 2003;97:2880-6.

41. Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: Development and validation of the general measure. *J Clin Oncol* 1993;11:570-9.

42. Ward WL, Hahn EA, Mo F, Hernandez L, Tulsky DS, Cella D. Reliability and validity of the Functional Assessment of Cancer Therapy-Colorectal (FACT-C) quality of life instrument. *Quality of Life Research* 1999;8:181-95.

43. Winstead-Fry P, Schultz A. Psychometric analysis of the Functional Assessment of Cancer Therapy-General (FACT-G) scale in a rural sample. *Cancer* 1997;79:2446-52.

44. Atkinson AC. Plots, Transformations and Regression. Oxford: Oxford University Press, 1985.

45. Cook RD, Weisberg S. Residuals and Influence in Regression. London: Chapman and Hall, 1982.

46. Conover WJ, Iman RL. On some alternative procedures using ranks for the analysis of experimental designs. *Comm Statist A* 1976;5:1349-68.

47. Conover WJ, Iman RL. Rank transformations as a bridge between parametric and nonparametric statistics. *American Statist* 1981;35:124-33.

48. 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. *Journal of Pain & Symptom Management 29(4):376-84,* 2005;

49. Little RJA, Rubin DB. Statistical Analysis with Missing Data. In: AnonymousNew York: Wiley, 1987:

50. Diggle PJ, Heagerty P, Liang KY, Zeger. Analysis of Longitudinal Data. Oxford, UK: Oxford University Press, 2002.