

Auricular Point Acupressure (APA) to Manage a Symptom Cluster of Pain, Fatigue, and Disturbed Sleep in Breast Cancer Patients: A Pilot Study

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Abstract

Purpose: To examine the feasibility of an auricular point acupressure (APA) to manage a symptom cluster of pain, fatigue, and sleep disturbance; to explore the potential utility of APA for reducing these symptoms in breast cancer patients.

Design/Research approach: This was an open-pilot trial, with repeated observational research design.

Setting: Participants were recruited from cancer outpatient clinics in an urban setting.

Sample: Breast cancer patients undergoing adjuvant treatment (n=31).

Methods: The APA treatment protocol was designed to manage a pre-selected symptom cluster of pain, fatigue, and sleep disturbance in breast cancer patients. Participants received one in-person APA treatment, and the participants were taught to press the seeds three times a day for 3 minutes each time for 7 days to allow them to continue the treatment on their own at home to manage symptoms.

Main Research Variables: Symptom severity, analgesic use, and functional status.

Findings: The retention and adherence rate was 93%. After 7 days of APA treatment, pain, fatigue, sleep, and other symptoms decreased by a clinically significant amount (symptom severity decrease $\geq 30\%$). Analgesic use was a statistically significant predictor for the symptom cluster of pain, fatigue, and sleep disturbance. However, functional status and perceived efficacy of APA treatment had no statistically significant influence on the symptom cluster.

Conclusions: APA may provide an inexpensive and effective complementary approach for the management of specific symptom cluster of pain, fatigue, and sleep disturbance for breast cancer patients receiving cancer treatment; further study is warranted.

Implication for Nursing: APA is a non-invasive method which can be used to self-manage cancer symptoms. Nurses without formal training in acupuncture easily can be trained to administer APA.

Keywords: Auricular therapy; Acupressure; Breast cancer; Symptom cluster; Pain; Fatigue; Sleep disturbance

Introduction

Symptom management is a crucial element of healthcare for cancer patients, delivered by physicians, nurses, and other health care professionals [1-3]. Despite the remarkable strides in cancer care and survival, patients continue to suffer many poorly managed and distressing symptoms as a result of the cancer itself or the treatment protocols. Severe symptom distress may delay scheduled treatments, decrease the effectiveness of treatment protocols, and delay the rehabilitation process [2,4]. An increasing number of studies demonstrate that cancer patients suffer not just one, but an array of symptoms, and typically suffer from multiple symptoms simultaneously [5-8]. This phenomenon is known as a symptom cluster, according to, when symptoms "are both related to one another and occurring concurrently. When multiple symptoms of a symptom cluster are individually treated with pharmaceuticals, polypharmacy may aggravate symptoms even further and lead to additional problems such as adverse drug reactions and drug interactions [9,10]. Among common symptoms, cancer-related pain (CRP) is one of the most challenging that patients experience [11]. CRP often co-occurs with fatigue and insomnia, which together constitute one of the most common symptom clusters among breast cancer patients [6,12]. However, to date, few interventions have been tested to manage specific symptom clusters in cancer patients [13].

Auricular Point Acupressure (APA) is a form of acupuncture, based

on traditional Chinese medicine (TCM) that uses specific acupoints (hereafter, points) on the inner and outer ear lobe to treat disease and illness [14,15]. APA is similar to acupuncture, but points on the ear are stimulated without using needles. Instead, an acupuncture-like stimulation (e.g., small seeds are taped to ear points and pressed with the index finger and thumb) is used to treat symptoms [14,15]. Auricular therapy originated in China more than 2,000 years ago and was redeveloped by the French neurosurgeon Dr. Paul Nogier in 1957 [16-18]. By 1990, the WHO had established a standardized, internationally accepted nomenclature of ear points and their location [19]. The underlying theory of auricular therapy posits that nerves in the outer ear correspond to specific areas of the brain, and these

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areas have a reflex connection with specific parts of the body [14,15]. The correlation of ear points and brain activity has been validated by functional MRI [20,21]. The treatment of ear points can stimulate the brain to correct its pathological reflex centers [20,21], change levels of serum pro- and anti-inflammatory biomarkers [22,23], and induce reflex reactions to relieve body pathology [14-16]. Some auricular points can treat multiple symptoms [14,15] and APA may significantly lower the risk of polypharmacy and resultant systemic toxicities [14,15].

Despite its long history in TCM, APA is a relatively new treatment in Western medicine and has not yet been researched as extensively as other pain treatments. A recent meta-analysis of auricular therapy for pain management demonstrates that it can indeed deliver significant pain relief when compared to sham or control groups [24]. The overall standardized mean differences (SMD) was 1.59 (95% CI [-2.36, -0.82]) across the 13 trials (total subject number=806), indicating that, on average, the mean decrease in pain score for the auricular therapy group was 1.59 standard deviations greater than the mean decrease for the sham control [24]. Importantly, the use of APA was supported by the most robust evidence for pain relief, followed by auricular acupuncture [24]. However, no single study has examined the effectiveness of APA for concurrently treating multiple symptoms. Therefore, we proposed to examine an APA treatment protocol was designed to treat a symptom cluster that occurred in breast cancer patients, which include pain, fatigue, and sleep disturbance. The purpose of the study was to (1) examine the feasibility of an APA treatment protocol for the management of a symptom cluster of pain, fatigue, and sleep disturbance and (2) explore the effects of APA for reducing these symptoms in breast cancer patients undergoing cancer treatment.

Methods

This study employed an open-pilot trial with repeated observational research design. The APA treatment protocol was designed to manage a pre-selected symptom cluster of pain, fatigue and sleep disturbance in breast cancer patients. Participants received one in-person APA treatment, and the seeds applied to the points during the treatment remained on the participants' ears for 7 days to allow them to continue the treatment on their own at home to manage their symptoms. Participants were called daily by telephone to collect the symptom data during the APA treatment.

Participants and setting

Participants were recruited if they (1) were over age 18, (2) had been diagnosed with breast cancer, (3) reported all three symptoms (pain, fatigue, and sleep) in the previous week, and the severity of at least two of the three symptoms were rated as 3 or more on a 0-10 numeric rating scale (NRS), (4) were currently receiving adjuvant cancer treatment (including chemotherapy or radiotherapy), (5) had completed at least the first cycle of cancer treatment, and (6) had not previously received any acupuncture or acupressure treatments in the previous 3 months. Participants were recruited from cancer outpatient clinics in an urban setting in the northeastern United States.

Measures

MD Anderson Symptom Inventory (MDASI) [25]. The MDASI was used to assess the participants' severity of symptoms during the previous 24 hours. The MDASI utilizes a 0-10 NRS, with 0 indicating not present and 10 indicating as bad as you can imagine. The MDASI measures symptom severity subscale and interference subscale. A component score for the MDASI symptom severity scale is obtained by taking the average of the 13 items together. The MDASI is

widely used to measure cancer symptoms and has known reliability and validity [25].

Eastern Cooperative Oncology Group Performance Status (ECOG PS) [26]. This one-item, 0-4 scale was used to assess the functional status of patients (i.e., the impact of disease on daily living ability when a patient's disease is progressing). The ECOG PS has demonstrated better discriminative ability for patient's prognosis than Karnofsky's index of performance status (KPS) [27].

Perceived Therapeutic Efficacy Scale. This scale was administered to examine participants' expectations regarding the benefit of acupressure. The scale was adapted from the Perceived Treatment Efficacy: Assessment in Rheumatoid Arthritis scale [28]. Cronbach's alpha for the original scale was 0.97, while test-retest reliability was 0.87 [28].

Medication Quantification Scale Version III (MQS) [29]. The MQS was used to assess medication use by computing a single numeric value for a subject's pain medication profile used in the previous 24 hours, according to drug class, dosage, and detriment (risk). This score was based on the subject use of WHO level 1-3 analgesic drugs, coanalgesic drugs (e.g., tricyclic antidepressants and antiepileptics), and other drugs such as benzodiazepines or muscle relaxants. The decreasing MQS was correlated with improved patient outcomes and decreases in adverse side effects [29-31].

Study booklet. Each participant received a booklet containing information about the acupressure technique, which included the intensity and duration of pressure applied to the points using the thumb and index finger. A research assistant telephoned the participants daily by to assess their symptom intensity and the time (frequency) and duration of point stimulation.

Demographic data. The demographic questionnaire used in this study provided information on the participants' gender, age, marital status, education level, living arrangements, ethnicity, disease diagnosis, and treatment status.

Intervention protocol

The APA treatment protocol specifically targeted the management of pain, fatigue, and sleep disturbance. The points selected are listed in Table 1, and Figure 1 shows the locations of the points on the ear. The selection of points addressed both (1) the reflex reaction of points related to the symptomatic body in reflex theory [16-18] and (2) zang organ disharmony and meridian disturbances from TCM theory [14,32]. This dual approach not only corrects pathological reflex centers in the brain, but also regulates qi to alleviate target symptoms (i.e., pain, fatigue, and sleep disturbances). The number of points treated and their specific locations on the ears of each patient varied slightly because each patient experienced pain in different body locations, and that pain is projected onto different corresponding points according to somatic topography. In general, bilateral points were identified for treatment; if the pain was located only on one side, only that side was tested and treated. Between eight and 12 total points were used for each participant. Vaccaria seeds (natural, non-toxic botanical seeds of no medical value, ≈ 2 mm in diameter) were placed on these points and held in place on the ears with small strips of flesh-colored, water-resistant tape ($\approx 6\text{mm}^2$, manufactured by the Auricular Medicine International Research and Training Center). Participants were told to stimulate the points by pressing the seeds between the thumb and index finger three times per day (suggested times were morning, noon, and evening) for 3 minutes each time (i.e., 9 minutes total), even if they were not experiencing any target symptoms. Seeds and tape were kept on the points for 7 days, and patients were instructed to remove them on day eight.

Acupuncture point	Rationale for Selection
Master points (used for each participant)	
Shenmen	Promotes inhibition (tranquilizing) effects
Sympathetic	Relieves pain, promotes relaxant effects on internal organs
Occiput	Promotes inhibition (tranquilizing) effects
Subcortex nervous	Harmonizes excitement and inhibition of the cortex
Neurasthenia points; neurasthenia area	Improves sleep, alleviates stress
Anxious	Promotes relaxation and decreases anxiety
Corresponding points related to body pain location (varied for each participant)	Relieves pain based on reflex theory

Table 1: Ear acupuncture points selected for participants.

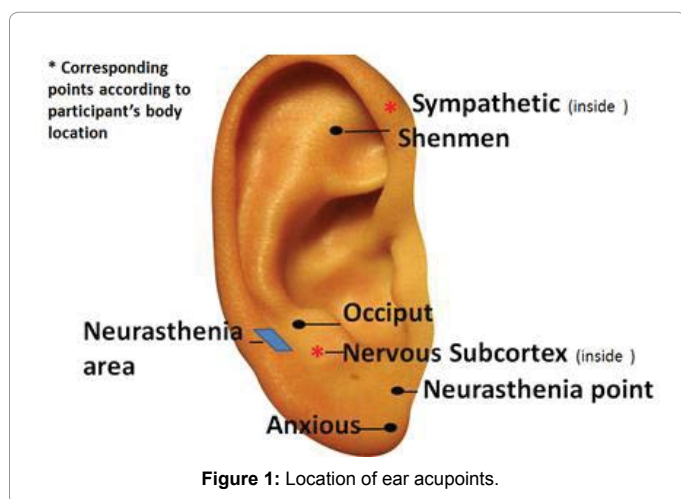


Figure 1: Location of ear acupoints.

Study procedures

Following institutional review board guidelines, potential participants were approached by a member of the research team, who provided introductory information about the study and determined their willingness to meet with the primary investigator (PI-the first author). The PI explained the study in detail to the participants, obtained their signed consent, and scheduled a time to meet for data collection. During the APA treatment, participants were asked to sit in a comfortable chair in an outpatient clinic. Points on each ear were identified using both an electronic point locator and systematic auricular strategies, which including visual inspection (i.e., identifying palpation on the ear) [33,34]. The point locator has two probes: one was held by the participant, and the other was used by the PI to locate the points [35]. The locator makes a sound when the probe makes contact with points corresponding to the particular target symptoms or pain in particular parts of the body. When the locator sounded, participants were then asked if they were experiencing pain in that particular part of the body or asked to describe the symptom they were experiencing.

Once the points were identified, the outer ear, including the ear lobe, was cleaned with 75% alcohol. Vaccaria seeds were then carefully taped onto each selected point. The PI demonstrated the technique for applying pressure to the points with the thumb and index finger and then asked the participants to perform the technique to verify that they could. Moderate stimulation was used for the therapy featured in this study. Patients were instructed that they should press the seeds with increasing pressure until they felt either slight discomfort or a tingling sensation. In addition to the three scheduled times each day, participants were told they could press the seeds whenever they experienced pain or other target symptoms. Seeds were kept taped on

the points for 7 days. Patients were instructed to remove them on day eight. Participants were called daily by the project coordinator to collect MDASI data during the study.

Data analysis

Descriptive statistics were conducted for the demographic characteristics of the participants. Data collected at different time points were coded as day 0 (baseline) and day 1 to 7 after APA treatment, for a total of eight data points. As each symptom was measured on the same 10-point scale, no standardization was necessary. For the further analysis of APA effects on the symptom cluster, only the items of pain, fatigue, and sleep disturbance were reported. In this study, pain, fatigue, and sleep disturbance were treated as a symptom cluster; moreover, we expected that each item could contribute differently to the cluster. Therefore, the score for each item was calculated using the factor scores obtained from a single-factor analysis. A multivariate mixed-effects model (using the MIXED Procedure in SAS) was used to capture the longitudinal outcome measures (modelling covariance across time) as well as the high correlation of symptoms within the cluster (modelling covariance across the multivariate observations, such as pain, fatigue, and sleep disturbance).

To account for the multivariate nature of the data (multiple correlated symptoms over time within the symptom cluster), we used a direct-product covariance structure (UN@AR(1)), available in PROC MIXED. The model included fixed effects for time, physical function (measured by ECOG), previous day pain medication used (measured by MQS daily), and perceived APA efficacy (EFF). All unknown parameters were estimated by the maximum likelihood method. Model effects were tested at a significance level of 0.05. All analyses were performed with SAS software, version 9.2 (SAS Institute Inc., NC) [36].

Results

Characteristics of the participants

Thirty-one patients received the APA treatment. The majority were white (n=29, 94%), married or partnered (n=22, 71%), and employed (n=13, 42%). More than half (n=20, 65%) had education beyond high school. The majority of the patients were treated for stage II and III breast cancer (n=2 [7%] stage I, n=13 [42%] stage II, n=10 [32%] stage III, n=6 [19%] stage IV). No patients were receiving radiotherapy at the time of recruitment. The mean age was 58.32 years (SD=10.93, range=29-84 years).

The feasibility of APA treatment

To recruit participants, 40 outpatients with breast cancer undergoing chemotherapy were approached, and 31 participated in the study. The reasons for declining participation included needing more time to think about it (n=6) and lack of interest (n=3). Thus, the recruitment rate was 78%. During the study, two patients reported that

the tape and seed(s) fell off their ears before the 7 days had passed (i.e., day 4 and day 5). There was no seed replacement for these two patients, but they completed all of the data assessment. The most common side effects of the APA therapy were itchiness (n=3, 10%) and soreness (n=7, 23%) of the ear, and the soreness subsided on day 3 or day 4. The retention and adherence rate was 93%.

Mean change of symptoms

Table 2 presents the basic descriptive findings (i.e., mean and standard deviation) and the mean score changes of each symptom measured at pre-APA treatment (i.e., day 0) and post-APA treatment (i.e., day 7). At the baseline assessment, pain, fatigue, disturbed sleep, distress, dry mouth, sadness, and numbness were reflected by mean scores higher than 4 (on a 0–10 point scale; a higher score indicating more severe symptom). After 7 days of APA treatment, the mean percentage change scores from the 7 days to baseline for the symptom cluster of pain, fatigue, and sleep disturbance ranged from 34% (fatigue) to 51% (pain), which were clinically significant (i.e., the symptom score decreased at least 30%). Other symptoms, including lack of appetite, distress, dry mouth, sadness, and numbness also displayed decreases that were clinically significant ($p < 0.05$).

At baseline, the correlations among symptoms in the symptom cluster ranged from 0.31 to 0.50, indicating a moderate level of

correlation (Table 3). Distress and sadness also displayed moderate correlations with pain, fatigue, and sleep disturbance. On day 7 of APA, the change score from the completion of APA treatment to baseline ranged from 0.54 to 0.61 (Table 3), indicating a moderate relationship among the symptoms within the cluster. Distress and sadness displayed moderate correlation with pain and fatigue (the Pearson correlation coefficient ranged from 0.33 to 0.54).

Predictors of the symptom cluster change

The estimated coefficients show that analgesic use was a statistically significant predictor, suggesting each point increase of analgesic use during the APA treatment was associated with an increase in (1) pain scores by 0.71 (SE=0.13, $p < 0.001$), (2) fatigue scores by 0.52 (SE=0.14, $p < 0.01$), and (3) sleep scores by 0.35 (SE=0.16, $p < 0.05$). Functional status and perceived efficacy of APA treatment had no statistically significant influence on the symptom cluster. Figure 2 shows the trajectory of time variations of the symptom cluster of pain, fatigue, and sleep disturbance. The estimated symptom scores for pain, fatigue, and sleep disturbance had similar trajectories, with high scores (a mean of 8.43 points for pain; 6.83 points for fatigue; 6.20 points for sleep disturbance) at baseline followed by decrements reaching their lowest levels at day 3 (3.07 points for pain; 3.54 points for fatigue; 3.01 points for sleep disturbance) and stabilization during the APA

Label	Baseline		Completion of APA		Percentage of Change
	Mean	SD	Mean	SD	
Pain	8.43	1.28	4.13	2.94	-51%
Fatigue	6.83	2.88	4.52	3.29	-34%
Distress	6.37	3.07	2.96	3.07	-54%
Sleep	6.20	3.12	3.17	3.17	-49%
Sadness	5.20	4.19	3.04	3.72	-42%
Dry mouth	5.00	4.03	3.17	3.49	-37%
Lack of appetite	3.93	3.63	2.26	2.82	-43%
Drowsy (sleepy)	3.87	3.17	3.78	2.94	-2%
Remembering things	3.80	3.34	2.91	2.89	-23%
Shortness of breath	3.43	3.33	2.43	2.71	-29%
Nausea	2.00	2.95	1.61	2.61	-20%
Vomiting	1.23	2.45	1.39	2.62	+13%
Numbness	4.13	4.04	3.39	3.80	-18%

Note. SD: Standard Deviation.

Table 2: Descriptive characteristics of each symptom.

	Pain	Fatigue	Sleep	Distress	Dry mouth	Sadness	Numbness
Pain	1.00	0.50	0.31	0.40	0.42	0.40	0.40
Fatigue	0.76	1.00	0.23	0.68	0.10	0.59	0.23
Sleep	0.50	0.61	1.00	0.53	0.33	0.38	0.47
Distress	0.42	0.54	0.01	1.00	0.26	0.75	0.21
Dry mouth	-0.17	-0.02	0.38	0.33	1.00	0.15	0.54
Sadness	0.33	0.51	0.10	0.82	0.35	1.00	0.29
Numbness	-0.13	0.02	0.11	0.02	0.45	0.77	1.00

Note. Data in the triangular region to the right (shaded in pink) reflects pre-APA treatment; data in the triangular region to the left (shaded in green) reflects the mean score change from pre- to post-APA treatment.

Table 3: Correlations (pearson correlation coefficient) among selected symptoms scored equal to or greater than 4 points at baseline assessment.

intervention. In particular, the pain score decreased sharply during the APA treatment, becoming lower than the fatigue score on day 2. After day 3, both symptoms slowly increased but did not exceed 5 points by the completion of APA treatment (Table 4).

Discussion

This is the first study to examine the feasibility and effects of APA to manage a symptom cluster (including pain, fatigue, and sleep disturbance) and related symptoms in breast cancer patients receiving adjuvant cancer-treatment. During the study, we were able to identify points on the ear(s) for treatment for every participant. Our study had a recruitment rate of 78%, and the retention and adherence rate was 93%. After 7 days of APA treatment, pain, fatigue, sleep, and other symptoms (i.e., lack of appetite, distress, dry mouth, sadness, and numbness) displayed a clinically significant decrease (i.e., $\geq 30\%$). These findings demonstrate not only that the 7-day APA is feasible (in terms of recruitment, retention, and adherence), but also preliminary evidence that the treatment can manage symptoms for breast cancer among patients receiving chemotherapy. However, before interpreting the findings, several limitations of the study must be acknowledged, which include (1) the small sample size due to the nature of the pilot study, (2) the lack of a placebo-control group (i.e., we are not able to differentiate the true effects of APA from the possible psychological effects), (3) only one APA treatment was administered, (4) assessments were not continued post-treatment for the follow-up (therefore, the lasting effects of APA were not assessed), and (5) the decreasing severity of symptoms after chemotherapy may be due to the effects of the chemo drugs naturally subsiding. However, we did not collect detail chemotherapy drug used by the study participants in which the pain and symptoms may be induced by the different antineoplastic drug.

Additionally, non-cancer related pain (e.g., arthritis or fibromyalgia) were also included which may have confounded our findings. These shortcomings should be addressed in future studies.

During participant recruitment, none of the patients had ever heard about APA. Although some patients were hesitant to participate when we contacted them, 78% enrolled in the study. The reason for the hesitation was that they never had heard about APA and, therefore, were skeptical of its effects. Compared to pharmaceutical treatment, APA is a relatively safe treatment, and minimal adverse effects were reported by the participants. The most common side effects were soreness ($n=7$, 23%) and itchiness of the ear ($n=3$ [10%] of 31 total patients), yet no one dropped out of the study due to this, which implies that these were tolerable side effects.

In this study, we tested a 7-day APA treatment. The effects of this treatment reached their maximal reduction values for the symptom cluster of pain, fatigue, and sleep disturbance on day 3. The immediate symptom relief is very encouraging. In addition to increasing the sample size and adding a control group, a future study of this type will need to feature a longer APA treatment to test for the duration of treatment benefits. However, there is insufficient data concerning the optimal duration of treatment to achieve maximum APA effects in the literature. Studies that have examined the sustained effects of auricular therapy for pain relief have varied in duration from one session [37] to up to 6 months [38], and their findings are limited by small sample sizes [24,39]. In our pilot studies using APA to treat chronic low back pain, 1 week of APA has reduced pain intensity by 45% [35], and 4 weeks of therapy have achieved even more pain relief (75% reduction), and this has been maintained at 1-month follow-up [40]. With acupuncture, six treatments over 3 weeks yield better pain relief than fewer than six treatments [41]. Therefore, further study should examine a longer APA treatment duration to determine the optimal amount of time necessary to maximize patient benefit.

To date, although researchers and clinicians have recognized the co-occurrence of symptoms among cancer patients, few interventions have been tested to manage the symptom cluster for cancer patients [13]. The preliminary findings reported here strongly suggest that APA has the potential to effectively manage the symptom cluster of pain, fatigue, and sleep disturbance simultaneously. If confirmed in controlled randomized trials, our APA approach certainly would be worthy of recommendation. For example, the non-invasive nature (i.e., no needles are used and patients need not disrobe) of APA treatment and immediate effects were viewed very positively by the breast cancer patients that participated in this study.

Implications for clinical practice and research

We are aware of the limitations of the study described in this paper; however, we maintain that the characteristics of our APA therapy are well suited to the practice of nursing professionals for three reasons: (1) our protocol has standardized auricular nomenclature [19]; (2) points on the ear can be located easily using an electronic finder, skin changes upon visual inspection, and/or associated tenderness when probed [33,34]; (3) applying seeds to points on the ear can be done by non-acupuncturists [42,43]. Nurses without formal training in acupuncture and TCM can be taught to incorporate APA into their practice to provide symptom relief and augment the effects of other symptom interventions without difficulty. APA is similar in effect to acupuncture, but does not use needles. The most significant advantage of APA is that it is non-invasive. Once seeds are taped to points on the ear by a trained therapist, patients can then stimulate these points by pressing on the taped seeds with the index finger and thumb as directed

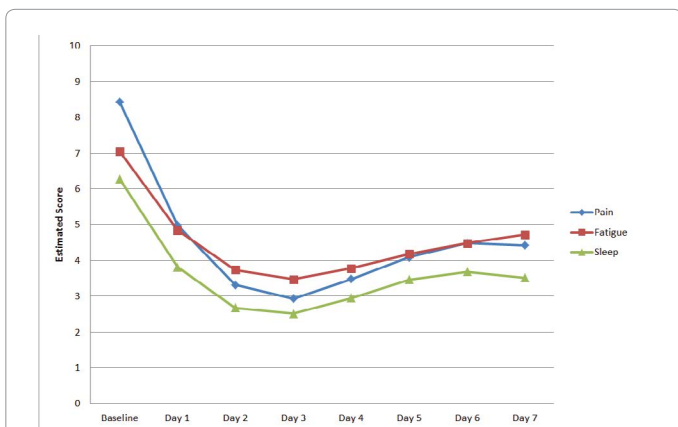


Figure 2: Predicted mean score change patterns for the symptom cluster of pain, fatigue, and sleep disturbance.

	Pain	Fatigue	Sleep
	Estimate (SE)	Estimate (SE)	Estimate (SE)
Functional status	-0.01 (1.05)	-1.11 (1.08)	-1.32 (1.13)
MQS [‡]	0.71 (0.13) [‡]	0.52 (0.14) [‡]	0.35 (0.16) [‡]
Perceived efficacy	-0.18 (0.13)	-0.18 (0.14)	-0.21 (0.15)

[‡]p<0.05, [‡]p<0.01, [‡]p<0.001, SE: Standard Error, [‡]MQS: Medication Quantification Scale.

Table 4: The estimated coefficients and standard errors of the symptom cluster of pain, fatigue, and sleep disturbance.

to achieve acupuncture-like effects. The seeds and tape can remain on the ear for 1 to 4 weeks, depending on the skin condition of the ear, which, therefore requires fewer office visits [40,44]. Patient involvement in the practice of APA to alleviate symptoms provides patients with a greater sense of control over their symptoms. APA practice includes teaching the patients the treatment rationale (i.e., the use of APA alleviates symptoms, and patients can practice APA in managing their own symptoms), skill training (i.e., learning how to press the seeds to practice APA at home), and the application and maintenance of learned skills (adherence to the treatment regimen). Training the participants in the skills necessary for APA practice can be completed within 15 minutes, which is potentially cost-effective [40,44].

In order to confirm the effects of APA, a large scale, randomized clinical trial, including a sham group and the tracking of long-term effects, will be required. In addition, continued research will be needed to understand the underlying biological mechanisms responsible for the effects of APA on specific symptom clusters, which may include neuroendocrine, immunologic, and/or other physiological processes related to symptom relief.

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Disclosure Statement

The authors affirm that there are no conflicts of interest regarding the publication of this article.

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