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Attention Dysregulation in Breast Cancer Patients Following a Complementary Alternative Treatment Routine: A Double-Blind Randomized Trial

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Abstract

Introduction: Breast cancer patients and survivors frequently report fatigue, emotional, and cognitive disturbances, which reduce performance at all levels of occupation and make life quality issues a considerable clinical concern. The aim of this study is to evaluate attention and emotion regulation across radiotherapy period and the possible effects of complementary alternative medicine (CAM). **Methods:** Fifty-seven patients with unilateral breast cancer underwent surgery and systemic chemotherapy before participating in this double-blind randomized study. Two thirds were given CAM (n = 38) while the rest received placebo (carrier only, n = 19). Patients' attention and anxiety were physiologically tested at baseline, 2 and 4 weeks during the radiation period as well as 1-month after the end of radiation session. **Results:** Both groups showed similar levels of anxiety with no significant differences at baseline nor post-radiotherapy. Long-term significant recovery of attention performance was observed in the CAM patients, accompanied by a similar tendency in anxiety level, measured by the eye-blink probability. **Conclusions:** This study physiologically validates the attention impairment reported among breast cancer survivors; also, it depicted a beneficial late-effect of a routine CAM on attention dysregulation. The suggested non-invasive physiological measures can physiologically monitor patients' psychological and cognitive well-being as well as evaluate the beneficial effect of CAM in breast cancer patients by assessing their coping ability to support the treatment plan. Thus, the results have potential clinical implications on patients' and survivors' quality of life. **Trial Registration:** NIH, NCT02890316. Registered July 2016, http://www.ClinicalTrials.gov

Keywords

breast cancer, radiotherapy, fatigue, attention, anxiety, emotion, dysregulation, complementary alternative medicine, homeopathy

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Introduction

Breast cancer is a chronic medical condition frequently associated with fatigue, cognitive disturbances, and psychological distress according to subjective reports among patients and survivors.[1-8]

Fatigue and tiredness symptoms are experienced by up to 60% of breast cancer patients[9-12] during and after their treatment trajectory.[13-15] These symptoms may persist for years post treatment,[16-20] and therefore negatively impact quality of life,[11,21,22] even compared with the impact of

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pain.[23] A strong association between fatigue and patients' objective cognitive performance may propose the existence of functional reciprocal relations.[24]

Breast cancer survivors commonly report deficits in attention span and memory functions before, during, and after treatments, which reduce confidence and performance at all levels of occupation.[7,25] As opposed to fatigue, cognitive impairments are not only subjectively reported as perceived symptoms, but also objectively supported in the literature up to 20 years after completion of radiotherapy and chemotherapy.[26] Accordingly, animal studies of chemotherapy-induced cognitive impairment have confirmed learning and memory alterations.[27] Human neuroimaging studies validate how chemotherapy and psychological distress potentially influence hemodynamic activity in attention network brain areas which reduces attention performance in breast cancer patients[28] after treatments are over, even for months.[29] Thus, treatment-induced attentional dysfunction may contribute to subjective and objective memory and concentration complaints in breast cancer survivors; emphasizing the importance of sensitive objective measures for subjective complaints of treatment-related attention impairments.[7,25,30]

Accordingly, both fatigue and cognitive dysfunction have been observed as post-treatment outcomes of chemotherapy and/or radiotherapy;[20,31] and a strong association between fatigue and cognitive performance suggests they are functionally related.[32] This association has been studied mainly in the context of sleep deprivation. Indeed, fatigue, low alertness, and sleep deprivation are suggested as candidates in altering[33,34] and impairing[35-37] cognitive functions, attention, and behavioral performance.[38]

Breast cancer patients are also at high risk for developing psychiatric disorders such as anxiety and depression.[39] Accordingly, in a study among survivors, the prevalence rates 5-years post-diagnosis were 26.3% and 9.6%, respectively.[40] Since anxiety and depression negatively affect quality of life, there is a need to assess the mental health of patients[41] for maintaining their psychological well-being. Notably, level of anxiety is a more significant psychological state than depression in contributing to the feeling of distress experienced by patients, thus should be evaluated and monitored.[42]

The pre-pulse inhibition (PPI) is a physiological operational measure associated with pre-attentional mechanisms[43] based on a neurological sensorimotor reflexive phenomenon, in which a weaker acoustic pre-pulse inhibits the reaction to a subsequent strong startling pulse. The reduction of response amplitude reflects the ability of the nervous system to temporarily adapt to a strong sensory stimulus when a preceding weaker signal is given. It has been suggested by us[44,45] that such reflexive inhibition of response is modulated by attention mechanisms, thus can be referred to as an Auditory Sustained Attention Test (ASAT). In the present study, we investigate the impact of breast cancer following surgery, chemotherapy, and during radiotherapy on patients' attention functioning. We used the ASAT, which comprised of objective physiological measures for both attention and emotional dysregulation mechanisms.

The approach for fatigue, cognitive functions, and quality of life management during and after radiotherapy is yet to be defined[20] and the use of CAM for this purpose, such as herbal, vitamin, and nutritional supplements, has increased over the past decade.[46] Homeopathy is one of the most popular CAM modalities for cancer patients in 7 European countries.[47] Clinical studies have shown homeopathy to potentially reduce many toxic effects of oncology treatments, while improving global health and well-being.[48,49] In a double-blind study of lung cancer patients, homeopathy was found to positively influence not only quality of life but also survival time.[50,51]

Cancer-treatments significantly reduced mortality,[52] but at the same time they increased fatigue, emotional changes, and cognitive impairments among cancer patients during treatment and into survivorship, making quality of life issues a considerable clinical concern. Therefore, additional evidence-based management strategies to objectively measure and reduce the fatigue-induced cognitive and emotional burden are required.

Accordingly, the current study aims are 2-fold. First, to physiologically evaluate attention and emotion dysregulation across radiotherapy period. Second, to evaluate the possible effects of a routine CAM compared with placebo effects on radiotherapy related cognitive and emotional functions. We hypothesize that all patients will endure cancer-induced attention and emotion dysregulation at baseline and throughout radiotherapy sessions as well as after treatments are done. However, the experimental group is assumed to benefit from the CAM and demonstrate a more balanced cognitive and emotional performance during and after radiation compared to the control-placebo group.

Methods

We used the CONSORT Reporting Guidelines

Participants: 70 female patients participated in a double-blind parallel group trial design.[53] All participants were patients at the medical cancer center and recruited by their treating physicians after signing a written informed consent form. Eligible participants were over the age of 18, with unilateral breast cancer following surgery and chemotherapy, and were planned to receive adjuvant radiation therapy to the breast or chest wall as well as to the lymphatic drainage area. The radiation dose was 50 Gy in 2 Gy daily doses, for 25 days, 5 treatments every week for 5 weeks. Some patients received a consecutive short course of mastectomy scar dose, 5 daily treatments.

Inclusion criteria: female patients with biopsy proven breast cancer, following breast conserving surgery or mastectomy, receiving adjuvant chemo, and radiation therapy. Exclusion criteria: unable to sign informed consent, uncontrolled hypertension, active chest wall infection, connective tissue disorder, participating in another clinical study with active treatment, substance abuse, hearing problem or intellectual disabilities.

Procedure: The study was conducted in a double-blind randomized manner. Research was approved by the Sheba Medical Center Institutional Review Board and conducted according to the World Medical Association Declaration of Helsinki. Informed written consent to participate in the study was obtained from all participants. Recruitment started in March 2017 following obtaining the Institutional Review Board approval (2370-15-SMC) and ended in August 2018 after completion. Female patients, who underwent chemotherapy and started receiving adjuvant 50 Gy whole breast/chest wall radiation according to the standard departmental protocol, were physiologically examined for attention regulation and anxiety level. Patients were assessed at the beginning of radiation as baseline, after 2, 4 weeks, and after 1-month following cessation of radiotherapy. Exams were conducted after the daily radiotherapy session and data were collected in a quiet room at the medical center. Demographics and characteristics data were collected.

In advance, a random list was generated using a random generator (*Random.org*) and was transferred in a blind labeling to a pharmacist. Accordingly, a pharmacist prepared and provided serial numbered sets of Homeopathic Medicinal Product (HMP) from 111 to 175 which were given to each patient by the treating doctor, according to the recruitment order. Two-thirds of the HMP sets contained a routine homeopathic treatment and the rest contained the carrier only, in the same size, color, and shape (ie, placebo). Each serial number of the HMP was identified as treatment or placebo in a list that was kept in a sealed envelope and opened only after data collection was over. Thus, both patients and researchers were blinded to the assigned treatment. Homeopathy treatment was administered to 38 participants during the radiotherapy period while the rest received placebo (n = 19). Since no special reaction/side-effects were observed or reported during the research period, the code of treatment/placebo was revealed only after the study was over.

Complementary alternative treatment (CAM): The HMP are produced by serial dilution and vigorous shaking (called successions) between every dilution.[46]

The preparation of the homeopathic treatment (5 gr of 100% sucrose granules containing the homeopathic dilution) was performed in a licensed pharmacy. To prepare the HMP: 1 g of the raw material is triturating with 99 g of lactose for 1 to 3 hours to create 1 ch (Centesimal Hahnemann) potency of the raw material. To prepare 2 ch: 1 gr of the 1 ch is triturating with 99 g of lactose.[54] Raising up the potency of the established HMP can be continued in the same manner or it can be done by dissolving 1 g of the established ch potency in 99 cc of 70% alcohol following 40 successions. To raise the potency of the dissolved HMP, every 1 cc of the former solution dissolved in 99 cc of 70% alcohol following 40 successions makes the following ch potency, until it reaches desired potency.[55] Sixty granules of sugar are wetted in the final diluted solution, dried for several minutes and packed in the pharmacy to be consumed by the patients. Placebo treatment is 1% sugar globule, similar in form and hedonic value to the aforementioned granules. The HMP used in the study are:

Cadmium sulphuratum - Cd SO4, 4H2 O (Cadm-s; 30 ch)[55]

Phosphoricum acidum - HPO3 (Phos-ac; 30 ch)[55]

Radium Bromide -Ra br2, 2H2O (Rad-br; 30 ch)[56]

X-ray (6 ch)[57]

Carcinosinum burnett (Carc; 30 ch)[58]

Dosage:

Carc 30 ch – 1 granule once a day every morning for 8 weeks.

Phos ac, Rad-br, X-ray and Cadm-s – 1 granule every morning, noon and evening for 8 weeks.

Patients were instructed to make no break between the different HMPs

Physiological testing:

ASAT and Startle: A computerized human startle response monitoring system (SR-HLAB STARTLE REFLEX, San Diego Instruments, SD, CA) is used to deliver acoustic stimuli via headphones while recording the electromyographic activity from the orbicularis oculi muscle (ie, eye-blinks). Two electrodes (sensor area 12 mm^2) are placed approximately 0.75 to 1 cm below the pupil on the orbicularis oculi muscle and third reference electrode on the mastoid bone. The skin at the electrode site is prepared using "Skin prep" (3M, Red Dot, Cat. #2236).

The session starts with a 3-minute acclimatization period with 60 dB background noise level that is delivered continuously throughout the session. The session is comprised from 98 pseudo-randomly delivered trials at 10 seconds average Inter-Trial-Interval ranging from 8 to 12 seconds. Forty startle trials comprised of single 40 ms 96, 102, 108, or 114 dB "pulse alone" startle stimuli (10 trials per intensity) to evaluate both the individual startle response (ie, the amplitude level following startle stimuli) and the eye-blink

probability (ie, the relative frequency of response occurrence following startle stimuli) that form together the emotional dysregulation measure.[59] Ten "No stimulus" trials were recorded in order to evaluate baseline noise levels. In order to evaluate Pre pulse inhibition (PPI), 40 "pre + pulse" trials consisted of a single 114 dB pulse preceded (100 ms inter-stimulus-interval) by a 30 ms pre-pulse of 6, 12, 18, or 24 dB above background noise (ie, 66, 72, 78, or 86 dB), in addition to 8 "pre alone" stimuli trials (66, 72, 78, or 86 dB). The PPI is calculated as percent of the habituated/inhibited response as follows: 100-(max response to "pre + pulse" trial/max response to "pulse alone" trial × 100),[45] using the Mindtension software (Mindtension, Ltd, NirAm, Israel).

Electro-Dermal Activity (EDA): Activity monitored by skin conductance changes. Two 5-mm-diameter Ag-AgCl electrodes (Mindlife, Jerusalem, Israel) were applied to the fingertips of the second and fourth digits and secured with a velcro band, as described previously.[60] Electrodes were connected to a sensor and to an amplified receiver to record the Electro-Dermal Response (EDR). An isolated skin conductance coupler (Mindlife) applied a constant 0.5V (DC) potential across the electrode pair at sample rate of 10 samples per sec. Different parts of skin may show different resistance change due to stress related sweating. In minimizing the variance that may arise due to this effect, it is suggested to record from the non-dominant hands of the subjects.[61]

Statistical methods: A double blind randomized mixed design with 2 treated groups as between subject's factor (CAM treatment vs placebo) and testing time points as within subject factor (4 levels). Results were analyzed with 2-way ANOVA for mixed design (2 × 4) with interaction analysis using One-way ANOVA followed by post Hoc Tukey's tests (SPSS, IBM, v21). For binary outcomes we used Chi-Square test analysis. All results were used with a confidence interval of 95%. Sample size calculation was made to provide statistical power of more than 85%. The analysis was performed by the original assigned groups (ie, 38 treatment vs 19 placebo participants were included).

Results

All participants were unequally randomized with an allocation ratio of 2:1 (treatment vs placebo). Fifty-seven completed the study after 9 losses to the experimental group and 4 losses to the control group. The reasons were lack of motivation, sudden occurrence of hearing deterioration and other medical conditions such as Herpes zoster, personal preference to participate in another simultaneous clinical trial and schedule related personal inconvenience issues (Figure 1). Chi-Square test analysis revealed that treated and placebo groups did not differ in their characteristics relative to their group size except for estrogen receptor measurement which was found to be significantly higher in the treated group (Table 1).

Auditory Sustained Attention Test (ASAT)

Performance on the ASAT was comprised of the following measures:

Emotional Dysregulation was assessed by the level of startle response together with skin conductance level. At baseline, both treated and placebo groups showed similar levels of anxiety. There was no significant effect in startle response during and after radiotherapy (Figure 2). Similar results were demonstrated by the level of skin conductance response; indicating no significant effect in the level of emotional response in both groups (Figure 3). However, we recently suggested the eye-blink probability as a more sensitive measure of anxiety.[59] Indeed, though at baseline and during radiotherapy, no significant difference was observed between the treated and placebo groups, at recovery a non-significant tendency for decrease was observed in the placebo group while the homeopathic treatment preserved baseline performance level ($P<0.058$; Figure 4).

Attention performance was assessed by detected changes in the level of inhibition amplitude of the startle response (ie, PPI). At baseline, both groups had similar attention results. No significant difference was found between the groups nor for the test during the radiation period. Nevertheless, a significant treatment and test time interaction was found (F [3, 141] = 2.776, [$P < .044$]) and indicated a long-term (8 weeks) preventive effect in the treated group compared to the placebo group ($P < .035$); Figure 5, which deteriorated as a sign for the significant impairing effect of radiation on attention functioning 1-month after the end of treatment period. In other words, the homeopathic treatment prevented the cognitive disturbance back to baseline performance level. Representative signals of the mean response amplitude in both groups are also presented (Figure 6). To note, this finding is also supported by the aforementioned finding of no significant effect in startle response between groups, in a way that emotional state could not explain the long-term attention effect after the end of radiation (Figure 2).

Discussion

The aim of the present study was to monitor cognitive (ie, attention) and emotional (ie, anxiety) dysregulation that commonly occurs in breast cancer patients for a variety of psychological conditions and medical factors that disrupt quality of life.[62,63] Generalized cognitive disturbances are commonly reported by cancer patients and evident following chemotherapy and radiotherapy.[64] Specifically, more than 60% of cancer survivors reported difficulties with concentration and attention.[65]

As expected, the physiological measure of attention indicated a significant late adverse effect due to radiotherapy as observed by the deterioration in performance of the placebo

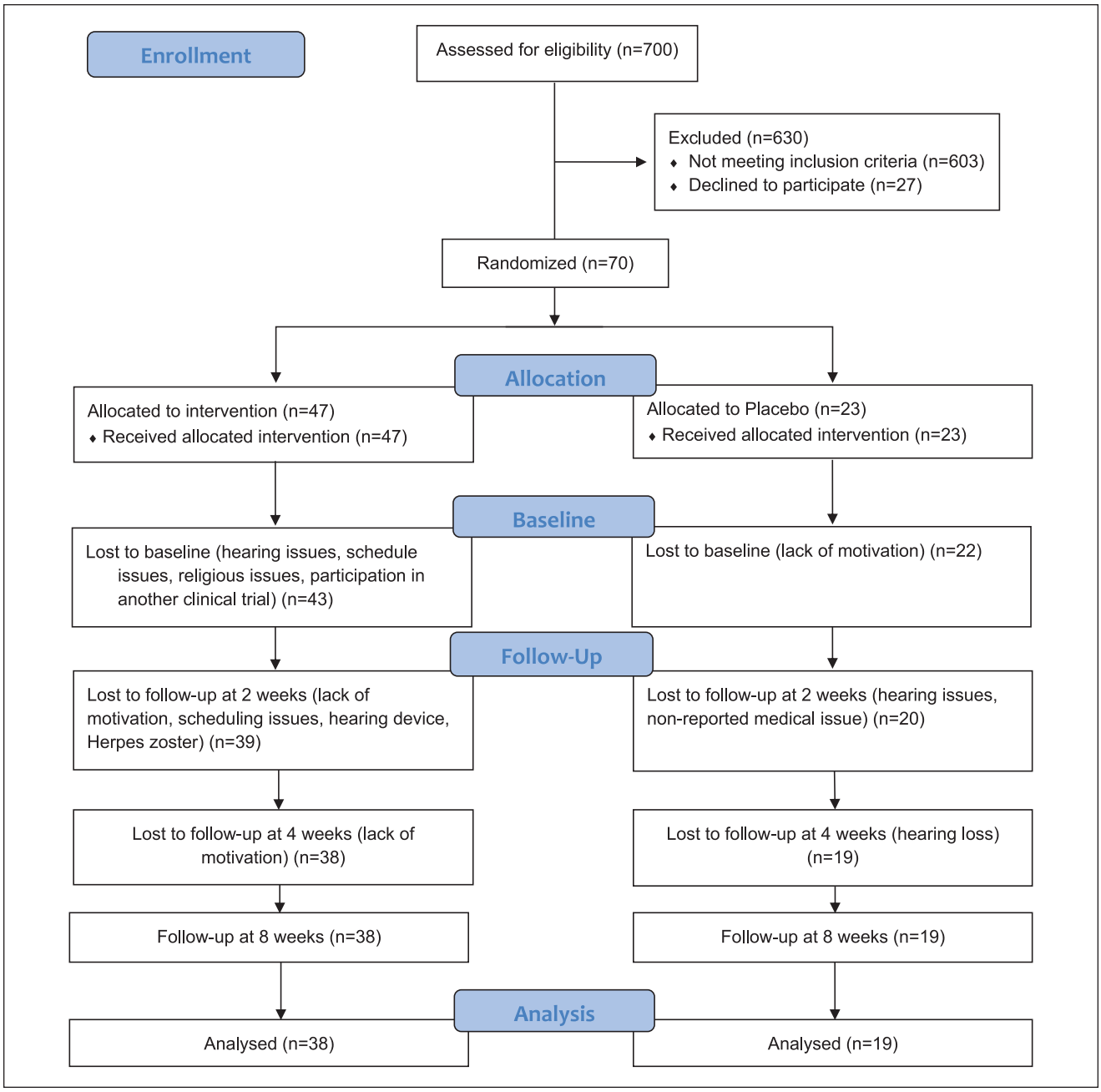

Figure 1. Enrollment flow chart.

group. Furthermore, although it was not an individualized homeopathic study following the "Law of Similars," the routine complementary homeopathic treatment yielded a beneficial effect as it maintained baseline attention function level in the treated group. Note, these effects were revealed at the recovery phase, 1-month post completion of radiotherapy treatment.

Neuroimaging findings offer indications for structural[66] and functional[67] alterations in brain areas related to cognition (eg, prefrontal cortex) compared to untreated controls. Moreover, the ability of radiotherapy to generate late effects is supported by earlier studies.[17,19,20] For further support, breast cancer chemotherapy treated patients had significant selective deficits in alerting and executive control but not in orienting attention networks, compared to breast cancer patients who had not received treatment as well as healthy controls. Their memory and information processing abilities were also damaged.[68] Furthermore, breast cancer survivors demonstrated an abnormal pattern of sustained attention and resource allocation compared to healthy controls.[30]

Table 1. Patient Characteristics.

		Treated group		Placebo group		Significance
		Mean		Mean		*P* value
	Age (y)	47.5000		43.6316		.203
	BMI	26.1485		24.7629		.353
	Tumor size (cm)	3.2013		3.1316		.889
		Frequency	Percent	Frequency	Percent	*P* value
Tumor side	Left/right	23/15	60.5/39.5	11/8	57.9/42.1	.849
Estrogen receptor	Positive	28	73.7	9	47.4	.050*
HER 2	Positive	9	23.7	8	42.1	.152
Protocol	AC-T	22	57.9	9	47.4	.316
	ACTC	7	18.4	2	10.5	
	AC TPH-H	9	23.7	7	36.8	
	THP	0	0	1	5.3	
BRCA	BRCA 1	4	10.5	5	26.3	.193
	BRCA 2	1	2.6	2	10.5	
Cannabis	Yes	6	15.8	1	5.3	.254
	No	32	84.2	18	94.7	
Aromatase inhibitors	Yes	9	23.7	2	10.5	.235
	No	29	76.3	17	89.5	
Antidepressants	Yes	9	23.7	2	10.5	.235
	No	29	84.2	17	89.5	
Antihypertensive	Yes	6	15.8	1	5.3	.254
	No	32	84.2	18	94.7	

No demographic differences were found between the groups except estrogen receptor measurement which was significantly higher in the treated group.
Abbreviations: A, adriamycin; C, cyclophosphamide; T, paclitaxel; H, Trastuzumab (Roche); P, pertuzumab (Roche).
*$P < .05$.

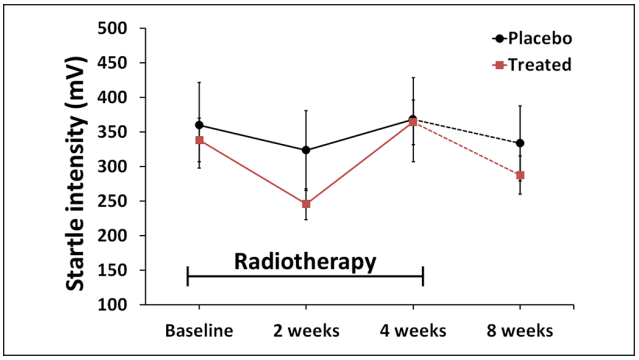

Figure 2. Startle response intensity during and post-radiations. No emotional dysregulation effect was found in both treated and non-treated groups according to the startle response during and post-radiation period.

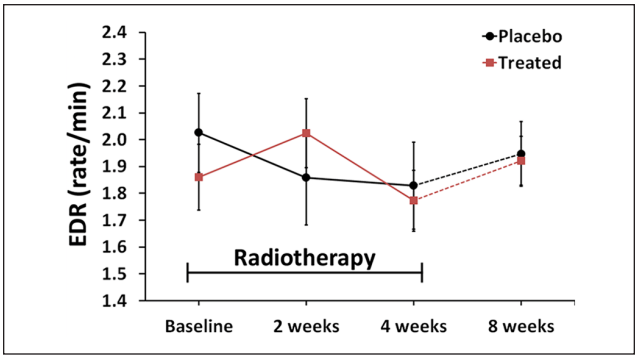

Figure 3. Electro-dermal activity during and post-radiations. No emotional effect over anxiety level was found in both treated and non-treated groups according to the EDR during and post radiation period.

Fatigue in cancer patients is strongly associated with high levels of anxiety.[69] Also, fatigue is considered related to emotional state and even suggested as a complex emotion itself instead of a physical event, which is affected by motivation and other emotions like anger or fear. Further, emotional states such as anger and fatigue involve physiological changes which can be scientifically measured.[70,71]

Surprisingly, the startle reflex and EDA measures had no evidence for emotional effect in both groups. Another study which revealed negative lasting cognitive impairments among breast cancer patients also did not find a significant difference in their profile of mood states.[72] Further, previous study which evaluated the emotional state of breast cancer patients, before, during and after chemotherapy, found a

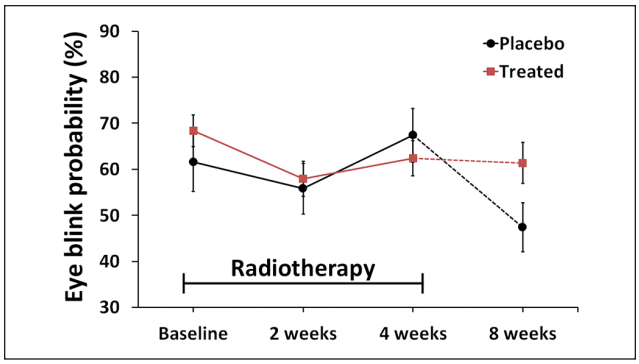

Figure 4. Startle response probability during and post-radiations. Radiotherapy had a non-significant tendency to decrease the probability of producing eye-blinks following an acoustic startling pulse as observed in the placebo group, while the homeopathic treatment preserved baseline performance level.

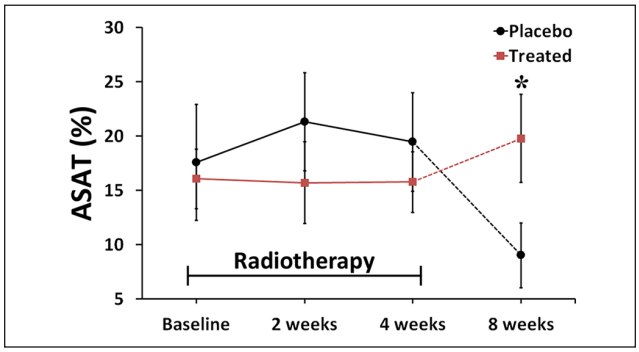

Figure 5. Response inhibition during and post-radiation. Homeopathic treatment ameliorated the radiotherapy-induced decrease in cognitive performance back to baseline level as observed 1-month after the end of radiation period.
*$P < .035$.

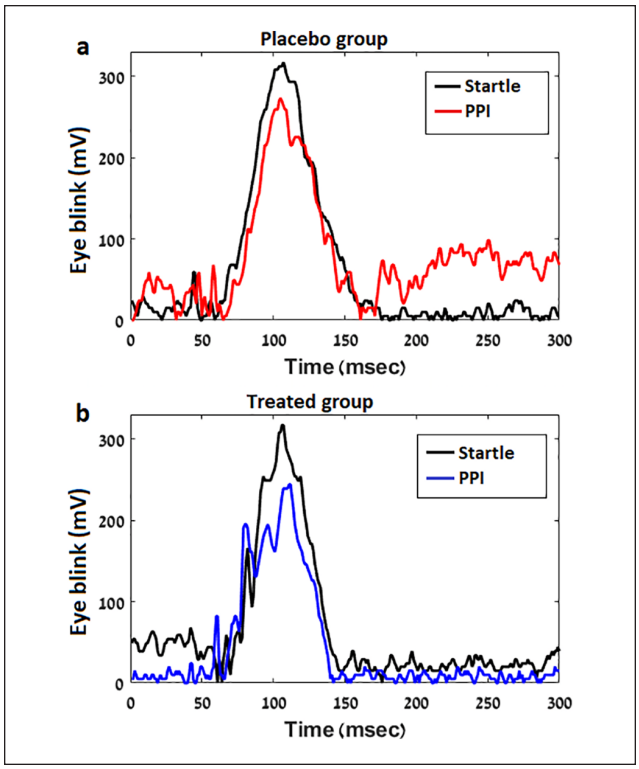

Figure 6. Representative signals of the startle response inhibition between groups. The placebo-control group (a) inhibited 9% of the baseline startle response while the treated group (b) inhibited 19% of the baseline startle response intensity.

progressive reduction in anxiety level throughout the testing points and suggested it may result from a better understanding of the treatment steps and acquired ability to face the illness compared to the recent awareness of having cancer at the first assessment before treatment.[64] Accordingly, in the present study, subjects were emotionally assessed for the first time after they have already completed chemotherapy and the cancer was gone; therefore, a long time has passed since they received their initial diagnosis and they have had enough time to mentally process the fact of facing illness. Hence, at the time points measured, the homeopathic treatment did not affect anxiety level. Noteworthy, to our current knowledge, this is the first study to use both measuring techniques on cancer patient population.

Interestingly, although cancer treatment-induced fatigue had no effect over the startle response amplitude (ie, eye-blink intensity), the eye-blink probability showed tendency toward significant decrease. This result provides additional support for the importance of response probability as a measure of fatigue in human model.[59] Furthermore, it has been demonstrated before how sleep deprivation potentiates loss of reflexivity and reduction in responsiveness to environmental stimuli induced by anesthetics.[73] Therefore, it could be suggested that the radiation induced-fatigue may serve as an explanation for the observed decrease in producing reflexive response (ie, eye-blink probability) in the placebo group. If so, the homeopathic treatment prevented this tendency as the treated group maintained baseline level of eye-blink probability which may indicate lower level of fatigue and better alertness.

Limitations

Anxiety level might have become significantly different if a larger sample size was used. Also this study addressed breast cancer patients during radiotherapy only; thus, it highlights female patients with this type of cancer and treatment trajectory. Future studies should address additional types of cancer.

Conclusions

The present results serve as addition to the growing research emphasizing the need for symptom management study as essential for decreasing distress among cancer survivors.[62,63,74] Accordingly, in this randomized double-blind placebo-controlled study, results provide evidence-based support for the effectivity of CAM in reducing treatment-induced cognitive disturbance and therefore improving life quality of breast cancer patients. Taking into consideration the high prevalence of anxiety and depression in cancer patients and survivors, future research can fully determine if the suggested non-invasive physiological measures may serve as a monitoring tool for patients' psychological and cognitive well-being as indicated by the results, and thus support the treatment plan.

Authors' Note

The authors Merav Ben-David and Yaakov Freed have moved to new institutions since completing the research. Dr. Ben-David's new affiliation is Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel; Assuta Medical Center, Ramat-Hahayal, Tel-Aviv. Dr. Freed's new affiliation is Oncology Division, Sourasky Medical Center, Tel-Aviv, Israel.

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Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Avi Avital discloses a patent (16/541,517) of the ASAT "an EMG-based method to evaluate attention". All other authors declare that they have no competing interests.

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References

1. Byar KL, Berger AM, Bakken SL, Cetak MA. Impact of adjuvant breast cancer chemotherapy on fatigue, other symptoms, and quality of life. *Oncol Nurs Forum*. 2006;33:E18-E26. doi:10.1188/06.ONF.E18-E26
2. So WKW, Marsh G, Ling WM, et al. Anxiety, depression and quality of life among Chinese breast cancer patients during adjuvant therapy. *Eur J Oncol Nurs*. 2010;14:17-22. doi:10.1016/j.ejon.2009.07.005
3. Lim CC, Kamala Devi M, Ang E. Anxiety in women with breast cancer undergoing treatment: a systematic review. *Int J Evid Based Healthc*. 2011;9:215-235. doi:10.1111/j.1744-1609.2011.00221.x
4. Cheung YT, Shwe M, Tan YP, Fan G, Ng R, Chan A. Cognitive changes in multiethnic Asian breast cancer patients: a focus group study. *Ann Oncol*. 2012;23:2547-2552. doi:10.1093/annonc/mds029
5. Van Esch L, Roukema JA, Ernst MF, Nieuwenhuijzen GAP, De Vries J. Combined anxiety and depressive symptoms before diagnosis of breast cancer. *J Affect Disord*. 2012;136:895-901. doi:10.1016/j.jad.2011.09.012
6. Cheung YT, Lee HHL, Chan A. Exploring clinical determinants and anxiety symptom domains among Asian breast cancer patients. *Support Care Cancer*. 2013;21:2185-2194. doi:10.1007/s00520-013-1769-8
7. Root JC, Ryan E, Barnett G, Andreotti C, Bolutayo K, Ahles T. Learning and memory performance in a cohort of clinically referred breast cancer survivors: the role of attention versus forgetting in patient-reported memory complaints. *Psychooncology*. 2015;24:548-555. doi:10.1002/pon.3615
8. Cheung YT, Ong YY, Ng T, et al. Assessment of mental health literacy in patients with breast cancer. *J Oncol Pharm Pract*. 2016;22:437-447. doi:10.1177/1078155215587541
9. Jacobsen PB, Hann DM, Azzarello LM, Horton J, Balducci L, Lyman GH. Fatigue in women receiving adjuvant chemotherapy for breast cancer: characteristics, course, and correlates. *J Pain Symptom Manage*. 1999;18:233-242. doi:10.1016/S0885-3924(99)00082-2
10. Servaes P, Verhagen C, Bleijenberg G. Fatigue in cancer patients during and after treatment: prevalence, correlates and interventions. *Eur J Cancer*. 2002;38:27-43. doi:10.1016/S0959-8049(01)00332-X
11. Lawrence DP. Evidence report on the occurrence, assessment, and treatment of fatigue in cancer patients. *J Natl Cancer Inst Monogr*. 2004;2004:40-50. doi:10.1093/jncimonographs/lgh027
12. Bower JE. Behavioral symptoms in patients with breast cancer and survivors. *J Clin Oncol*. 2008;26:768-777. doi:10.1200/JCO.2007.14.3248
13. Andrykowski MA, Curran SL, Lightner R. Off-treatment fatigue in breast cancer survivors: a controlled comparison. *J Behav Med*. 1998;21:1-18. doi:10.1023/A:1018700303959
14. Graydon JE. Women with breast cancer: their quality of life following a course of radiation therapy. *J Adv Nurs*. 1994;19:617-622. doi:10.1111/j.1365-2648.1994.tb01131.x
15. Schmidt ME, Chang-Claude J, Vrieling A, Heinz J, Flesch-Janys D, Steindorf K. Fatigue and quality of life in breast cancer survivors: temporal courses and long-term pattern. *J Cancer Surviv*. 2012;6:11-19. doi:10.1007/s11764-011-0197-3
16. Cella D, Davis K, Breitbart W, Curt G. Cancer-related fatigue: prevalence of proposed diagnostic criteria in a United States sample of cancer survivors. *J Clin Oncol*. 2001;19:3385-3391. doi:10.1200/JCO.2001.19.14.3385
17. Bower JE, Ganz PA, Desmond KA, et al. Fatigue in long-term breast carcinoma survivors. *Cancer*. 2006;106:751-758. doi:10.1002/cncr.21671
18. Servaes P, Gielissen MFM, Verhagen S, Bleijenberg G. The course of severe fatigue in disease-free breast cancer patients:

a longitudinal study. *Psychooncology*. 2007;16:787-795. doi:10.1002/pon.1120
19. Reinertsen KV, Cvancarova M, Loge JH, Edvardsen H, Wist E, Fosså SD. Predictors and course of chronic fatigue in long-term breast cancer survivors. *J Cancer Surviv*. 2010;4:405-414. doi:10.1007/s11764-010-0145-7
20. Noal S, Levy C, Hardouin A, et al. One-year longitudinal study of fatigue, cognitive functions, and quality of life after adjuvant radiotherapy for breast cancer. *Int J Radiat Oncol Biol Phys*. 2011;81:795-803. doi:10.1016/j.ijrobp.2010.06.037
21. Poulson MJ. Not just tired. *J Clin Oncol*. 2003;21:112s-113s. doi:10.1200/JCO.2003.01.191
22. Crosswell AD, Lockwood KG, Ganz PA, Bower JE. Low heart rate variability and cancer-related fatigue in breast cancer survivors. *Psychoneuroendocrinology*. 2014;45:58-66. doi:10.1016/j.psyneuen.2014.03.011
23. Jereczek-Fossa BA, Marsiglia HR, Orecchia R. Radiotherapy-related fatigue. *Crit Rev Oncol Hematol*. 2002;41:317-325. doi:10.1016/S1040-8428(01)00143-3
24. Gullett JM, Cohen RA, Yang GS, et al. Relationship of fatigue with cognitive performance in women with early-stage breast cancer over 2 years. *Psychooncology*. 2019;28:997-1003. doi:10.1002/pon.5028
25. Frank JS, Vance DE, Jukkala A, Meneses KM. Attention and memory deficits in breast cancer survivors. *J Neurosci Nurs*. 2014;46:274-284. doi:10.1097/JNN.0000000000000078
26. Van der Willik KD, Koppelmans V, Hauptmann M, Compter A, Ikram MA, Schagen SB. Inflammation markers and cognitive performance in breast cancer survivors 20 years after completion of chemotherapy: a cohort study. *Breast Cancer Res*. 2018;20:135. doi:10.1186/s13058-018-1062-3
27. Seigers R, Fardell JE. Neurobiological basis of chemotherapy-induced cognitive impairment: a review of rodent research. *Neurosci Biobehav Rev*. 2011;35:729-741. doi:10.1016/j.neubiorev.2010.09.006
28. Chen X, He X, Tao L, et al. The attention network changes in breast cancer patients receiving neoadjuvant chemotherapy: evidence from an arterial spin labeling perfusion study. *Sci Rep*. 2017;7:42684. doi:10.1038/srep42684
29. Shen CY, Chen VCH, Yeh DC, et al. Association of functional dorsal attention network alterations with breast cancer and chemotherapy. *Sci Rep*. 2019;9:104. doi:10.1038/s41598-018-36380-6
30. Kam JWY, Brenner CA, Handy TC, et al. Sustained attention abnormalities in breast cancer survivors with cognitive deficits post chemotherapy: an electrophysiological study. *Clin Neurophysiol*. 2016;127:369-378. doi:10.1016/j.clinph.2015.03.007
31. Minton O, Stone PC. A comparison of cognitive function, sleep and activity levels in disease-free breast cancer patients with or without cancer-related fatigue syndrome. *BMJ Support Palliat Care*. 2012;2:231-238. doi:10.1136/bmjspcare-2011-000172
32. McGhie A, Chapman J. Disorders of attention and perception in early schizophrenia. *Br J Med Psychol*. 1961;34:103-116. doi:10.1111/j.2044-8341.1961.tb00936.x
33. Schmitz R, Deliens G, Mary A, Urbain C, Peigneux P. Selective modulations of attentional asymmetries after sleep deprivation. *Neuropsychologia*. 2011;49:3351-3360. doi:10.1016/j.neuropsychologia.2011.08.009
34. Benwell CSY, Harvey M, Gardner S, Thut G. Stimulus- and state-dependence of systematic bias in spatial attention: additive effects of stimulus-size and time-on-task. *Cortex*. 2013;49:827-836. doi:10.1016/j.cortex.2011.12.007
35. Van der Linden D, Massar SAA, Schellekens AFA, Ellenbroek BA, Verkes RJ. Disrupted sensorimotor gating due to mental fatigue: preliminary evidence. *Int J Psychophysiol*. 2006;62:168-174. doi:10.1016/j.ijpsycho.2006.04.001
36. Alhola P, Polo-Kantola P. Sleep deprivation: impact on cognitive performance. *Neuropsychiatr Dis Treat*. 2007;3:553-567.
37. McCoy JG, Strecker RE. The cognitive cost of sleep lost. *Neurobiol Learn Mem*. 2011;96:564-582. doi:10.1016/j.nlm.2011.07.004
38. Curcio G, Ferrara M, De Gennaro L. Sleep loss, learning capacity and academic performance. *Sleep Med Rev*. 2006;10:323-337. doi:10.1016/j.smrv.2005.11.001
39. Tsaras K, Papathanasiou I V., Mitsi D, et al. Assessment of depression and anxiety in breast cancer patients: prevalence and associated factors. *Asian Pacific J Cancer Prev*. 2018;19:1661-1669. doi:10.22034/APJCP.2018.19.6.1661
40. Faye-Schjøll HH, Schou-Bredal I. Pessimism predicts anxiety and depression in breast cancer survivors: a 5-year follow-up study. *Psychooncology*. 2019;28:1314-1320. doi:10.1002/pon.5084
41. Kugbey N, Oppong Asante K, Meyer-Weitz A. Depression, anxiety and quality of life among women living with breast cancer in Ghana: mediating roles of social support and religiosity. *Support Care Cancer*. 2020;28:2581-2588. doi:10.1007/s00520-019-05027-1
42. Ng CG, Mohamed S, Kaur K, Sulaiman AH, Zainal NZ, Taib NA. Perceived distress and its association with depression and anxiety in breast cancer patients. Ho Y-S, ed. *PLoS One*. 2017;12:e0172975. doi:10.1371/journal.pone.0172975
43. Molina V, Montes C, Tamayo P, et al. Correlation between prepulse inhibition and cortical perfusion during an attentional test in schizophrenia. A pilot study. *Prog Neuro-Psychopharmacol Biol Psychiatry*. 2009;33:53-61. doi:10.1016/j.pnpbp.2008.10.011
44. Avital A, Dolev T, Aga-Mizrachi S, Zubedat S. Environmental enrichment preceding early adulthood methylphenidate treatment leads to long term increase of corticosterone and testosterone in the rat. Burne T, ed. *PLoS One*. 2011;6:e22059. doi:10.1371/journal.pone.0022059
45. Zubedat S, Aga-Mizrachi S, Cymerblit-Sabba A, et al. Human-animal interface: the effects of handler's stress on the performance of canines in an explosive detection task. *Appl Anim Behav Sci*. 2014;158:69-75. doi:10.1016/j.applanim.2014.05.004
46. Frass M, Friehs H, Thallinger C, et al. Influence of adjunctive classical homeopathy on global health status and subjective wellbeing in cancer patients - a pragmatic randomized controlled trial. *Complement Ther Med*. 2015;23:309-317. doi:10.1016/j.ctim.2015.03.004
47. Molassiotis A, Fernández-Ortega P, Pud D, et al. Use of complementary and alternative medicine in cancer patients: a

European survey. *Ann Oncol*. 2005;16:655-663. doi:10.1093/annonc/mdi110
48. Samuels N, Freed Y, Weitzen R, et al. Feasibility of homeopathic treatment for symptom reduction in an integrative oncology service. *Integr Cancer Ther*. 2018;17:486-492. doi:10.1177/1534735417736133
49. Rostock M, Naumann J, Guethlin C, Guenther L, Bartsch HH, Walach H. Classical homeopathy in the treatment of cancer patients - a prospective observational study of two independent cohorts. *BMC Cancer*. 2011;11:19. doi:10.1186/1471-2407-11-19
50. Frass M, Lechleitner P, Gründling C, et al. Homeopathic Treatment as an add-on therapy may improve quality of life and prolong survival in patients with non-small cell lung cancer: a prospective, randomized, placebo-controlled, double-blind, three-arm, multicenter study. *Oncologist*. 2020;25:e1930-e1955. doi:10.1002/onco.13548
51. Gleiss A, Frass M, Gaertner K. Re-analysis of survival data of cancer patients utilizing additive homeopathy. *Complement Ther Med*. 2016;27:65-67. doi:10.1016/j.ctim.2016.06.001
52. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin*. 2019;69:7-34. doi:10.3322/caac.21551
53. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMC Med*. 2010;8:18. doi:10.1186/1741-7015-8-18
54. Hahnemann S. *Organon of Medicine*. W.F. Wakeman; 2002. Accessed November 26, 2019. https://books.google.com/books?hl=en&lr=&id=EGphHjIE2U4C&oi=fnd&pg=PR6&ots=zWcaGs3r4C&sig=JNkBD3aLgw1Tmo_z086gHkfFNy8
55. O'Connor JT. *American Homoeopathic Pharmacopoeia*. Boericke & Tafel; 1896.
56. Clarke J. *A Dictionary of Pratical Materia Medica*. Homoeopathic Publishing Company; 1902.
57. Association IH. *Proceedings*. The Association; 1897.
58. Templeton W, Hom F. The British Homoeopathic Journal. 1954;44. Accessed November 26, 2019. https://www.thieme-connect.com/products/ejournals/pdf/10.1016/S0007-0785(45)80025-X.pdf
59. Zubedat S, Havkin E, Maoz I, Aga-Mizrachi S, Avital A. A probabilistic model of startle response reveals opposite effects of acute versus chronic Methylphenidate treatment. *J Neurosci Methods*. 2019;327:108389. doi:10.1016/j.jneumeth.2019.108389
60. Shapiro M, Melmed RN, Sgan-Cohen HD, Eli I, Parush S. Behavioural and physiological effect of dental environment sensory adaptation on children's dental anxiety. *Eur J Oral Sci*. 2007;115:479-483. doi:10.1111/j.1600-0722.2007.00490.x
61. Okkesim Ş, Kara S, Kaya MG, Asyali MH. Analysis of coronary angiography related psychophysiological responses. *Biomed Eng Online*. 2011;10:71. doi:10.1186/1475-925X-10-71
62. Portenoy RK, Itri LM. Cancer-related fatigue: guidelines for evaluation and management. *Oncologist*. 1999;4:1-10.
63. Mock V, Atkinson A, Barsevick A, et al. NCCN practice guidelines for cancer-related fatigue. *Oncology (Williston Park)*. 2000;14:151-161.
64. Biglia N, Bounous VE, Malabaila A, et al. Objective and self-reported cognitive dysfunction in breast cancer women treated with chemotherapy: a prospective study. *Eur J Cancer Care (Engl)*. 2012;21:485-492. doi:10.1111/j.1365-2354.2011.01320.x
65. Wagner L, Sweet J, Butt Z, Lai J, Oncol DC-JS, 2009 U. Measuring patient self-reported cognitive function: development of the functional assessment of cancer therapy-cognitive function instrument. *J Support Oncol*. 2009;7:W32-W39.
66. Inagaki M, Yoshikawa E, Matsuoka Y, et al. Smaller regional volumes of brain gray and white matter demonstrated in breast cancer survivors exposed to adjuvant chemotherapy. *Cancer*. 2007;109:146-156. doi:10.1002/cncr.22368
67. Silverman DHS, Dy CJ, Castellon SA, et al. Altered frontocortical, cerebellar, and basal ganglia activity in adjuvant-treated breast cancer survivors 5-10 years after chemotherapy. *Breast Cancer Res Treat*. 2007;103:303-311. doi:10.1007/s10549-006-9380-z
68. Chen X, Li J, Ren J, et al. Selective impairment of attention networks in breast cancer patients receiving chemotherapy treatment. *Psychooncology*. 2014;23:1165-1171. doi:10.1002/pon.3539
69. Valentine AD, Meyers CA. Cognitive and mood disturbance as causes and symptoms of fatigue in cancer patients. *Cancer*. 2001;92:1694-1698. doi:10.1002/1097-0142(20010915)92:6+<1694::AID-CNCR1499>3.0.CO;2-S
70. St. Clair Gibson A, Baden DA, Lambert MI, et al. The conscious perception of the sensation of fatigue. *Sport Med*. 2003;33:167-176. doi:10.2165/00007256-200333030-00001
71. Noakes TD. Fatigue is a brain-derived emotion that regulates the exercise behavior to ensure the protection of whole body homeostasis. *Front Physiol*. 2012;3:82. doi:10.3389/fphys.2012.00082
72. Lohrisch C. Cognition effects of chemotherapy. *Breast Cancer Res*. 2000;2:66696. doi:10.1186/bcr-2000-66696
73. Tung A, Szafran MJ, Bluhm B, Mendelson WB. Sleep deprivation potentiates the onset and duration of loss of righting reflex induced by propofol and isoflurane. *Anesthesiology*. 2002;97:906-911. doi:10.1097/00000542-200210000-00024
74. Marciel kelli K. National institute of health state-of-the-science conference statement: symptom management in cancer: pain, depression, and fatigue, July 15-17, 2002. *J Natl Cancer Inst*. 2003;95:1110-1117. doi:10.1093/jnci/djg014