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Bilateral transcutaneous auricular vagus nerve stimulation for the treatment of insomnia in breast cancer

Melissa Do[1], Alexandra Evancho[2,3] & William J. Tyler[1,4]✉

Substantial diagnostic and therapeutic advances have been made in medicine to address breast cancer. There remain unmet needs to translate solutions for addressing insomnia and mental health concerns in breast cancer patients. In this open-label, pilot clinical trial, we evaluated the safety and efficacy of nightly, bilateral, transcutaneous auricular vagus nerve stimulation (taVNS) on insomnia and mental health outcomes in breast cancer patients across a two-week treatment period. Our results demonstrate that noninvasive vagus nerve stimulation can significantly reduce insomnia severity, improve sleep quality, decrease sleep onset latency, and enhance sleep efficiency. Treatment with taVNS also significantly reduced the number of nightly awakenings, cancer-related fatigue, and depression scores while increasing heart rate variability. These observations demonstrate that auricular vagus nerve stimulation holds promise for improving sleep quality and mental health in patients diagnosed with breast cancer. Future investigations aimed at more thoroughly investigating the safety profile and clinical impacts of taVNS on the quality of life in patients with breast cancer are warranted.

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Keywords Neuromodulation, Vagus nerve stimulation, Breast cancer, Insomnia, Mental health, Cancer, Fatigue

Studies investigating new and aggravated cases of insomnia in cancer patients estimate that insomnia incidence is two to three times more prevalent in cancer patients compared to the general population[1,2]. Notably, breast cancer patients report the highest rates of insomnia and fatigue, with prevalence estimates ranging from 38 to 70%, compared to other cancers[3,4]. Insomnia and cancer-related fatigue are critical concerns for breast care clinicians, as both are associated with poorer treatment outcomes, slower recovery, decreased overall health, and potentially reduced survival. Highlighting this importance, actigraphy monitored sleep quality in women with advanced breast cancer has been shown to be a survival predictor[5].

Behavioral and psychological comorbidities frequently emerge or intensify during cancer treatment and may persist long after its completion, contributing to a diminished overall quality of life[6]. Sleep disturbances further exacerbate these issues, placing patients at increased risk for fatigue, mood instability, poor treatment adherence, and systemic inflammation. These factors are closely linked to mood disorders, such as anxiety and depression. Studies have shown that insomnia in cancer populations is strongly associated with elevated rates of depression and anxiety[7], as well as impaired immune function and reduced survival. The consequences of poor sleep are complex and multifaceted, adversely affecting both physical and psychological health outcomes.

The increased risk of the development or worsening of insomnia is further elevated by the adverse effects of cancer treatments and adjuvant therapies[2,8,9]. For example, aromatase inhibitors and tamoxifen, which are common hormonal therapies used to improve survival in women with breast cancer, are frequently associated with sleep disturbances[8]. The most common and severe side effects reported from hormone therapy treatment includes sleep disturbances, depression, and fatigue[10]. Depression in breast cancer patients has been linked to poor clinical outcomes, including lower quality of life, reduced adherence to treatment, and increased risks

[1]Center for Neuroengineering and Brain Computer Interfaces, Schools of Engineering and Medicine, The University of Alabama at Birmingham (UAB), Birmingham, USA. [2]Center for Engagement in Disability Health and Rehabilitation Sciences, UAB School of Health Professions, Birmingham, USA. [3]Department of Physical Therapy, UAB School of Health Professions, Birmingham, USA. [4]Department of Biomedical Engineering, UAB Schools of Engineering and Medicine, Birmingham, AL, USA. ✉email: wjpt@uab.edu

of recurrence and mortality[11,12]. A large-scale analysis involving 282,203 breast cancer patients found that depression was associated with increased risks of cancer recurrence, all-cause mortality, and cancer-specific mortality[13]. Similarly, a prospective study of 578 women with early-stage breast cancer reported that depressive symptoms significantly predicted reduced five-year survival[14]. More recent studies associated pre-diagnosed depression with a 26% higher risk of death and post-diagnosed depression with a 50% higher risk of death[15].

These adverse effects not only impair quality of life but also serve as predictors of poor treatment adherence[16]. Disruptions in sleep may also be mediated by the bidirectional relationship between sleep and immune function[17]. Inflammatory processes appear to play a central role in the symptom cluster of sleep difficulties, fatigue, and depression, while poor sleep has been consistently associated with elevated inflammatory markers[17–20]. This broader link between cancer and inflammation is well investigated and supports the development of targeted interventions addressing sleep disturbances in breast cancer populations to improve clinical outcomes and quality of life in the treatment of insomnia in breast cancer patients and survivors[21,22].

Although women with breast cancer experience disproportionately high rates of sleep disturbances, fatigue, and inflammation, current treatment options remain limited. Clinical guidelines for the treatment of insomnia typically include cognitive behavioral therapy for insomnia (CBT-I) and pharmacological interventions[2,3,23,24]. Among these, studies have shown that CBT-I is as effective and more long lasting than pharmacological therapies and is considered an efficacious and safe treatment for chronic insomnia. It combines cognitive restructuring, behavioral therapy, and healthy sleep habits for an evidence-based approach to address insomnia without pharmaceutical intervention. CBT-I is well established and considered the "gold standard" for the treatment of chronic insomnia by the American College of Physicians and the American Academy of Sleep Medicine[24,25]. Despite this, up to 40% of patients withdraw from treatment prior to completion[26,27]. Poor adherence and retention present significant barriers for utility in clinical care, because premature dropout can lead to increases in perceived burden, worsening of psychiatric symptoms, and reduced motivation to receive further treatment[28]. In addition, access to CBT-I is limited due to a lack of qualified providers and the uneven geographical distribution of CBT-I clinics in the USA, and therefore, is underutilized and limited in pragmatic appeal[29–31].

Pharmaceutical intervention is the most common treatment for insomnia[32]. Drugs for the treatment of insomnia are sedative-hypnotic pharmacological agents, which often include benzodiazepines, Z-drugs (non-benzodiazepines), barbiturates, and antihistamines[21]. A meta-analysis of randomized controlled trials for the use of benzodiazepine for the treatment of insomnia showed that compared to placebo, benzodiazepines decreased sleep latency and increased sleep duration. However, benzodiazepines have been associated with many reports of adverse effects including dizziness and cognitive impairment[33]. Paltiel and colleagues have shown the use of tranquilizers and sleeping pills among cancer patients is associated with a poorer quality of life[34]. These treatments are not intended for long-term use due to the increased risk of severe adverse effects (e.g. depression, cancer, mortality), physiological and psychological dependence, and drug-induced withdrawal insomnia[35,36]. Other studies have shown persistent sedative-hypnotic use in breast cancer patients can increase the risk drug dependence[37]. These drawbacks to the use of common sedative-hypnotic drugs raises significant concerns about the associated risks for patients suffering from cancer[34,35,37]. This is especially a significant concern in women with breast cancer as insomnia treatments can be complicated by other factors, including adjuvant therapy[21,38].

To address pressing unmet health needs as described above, we designed this open-label clinical trial to evaluate the feasibility, safety, and efficacy of transcutaneous auricular vagus nerve stimulation (taVNS) for the treatment of insomnia in a sample of breast cancer patients. Studies over the last couple decades have shown that taVNS modulates ascending arousal pathways acting upon the locus coeruleus (LC) and norepinephrine (NE) neurotransmitter system, which play well-established roles in mood and cognition[39–41], as well as sleep onset and rapid eye movement (REM) sleep regulation[42,43]. Other studies have shown that taVNS also modulates descending vagal pathways activating the cholinergic anti-inflammatory pathway (CAIP) to reduce inflammation[44]. Several clinical trials have shown that taVNS is safe and effective for the treatment of insomnia[45–48], depression[49–52], and inflammation[53–55]. However, taVNS has not been evaluated for treatment of insomnia in breast cancer patients. In this open-label trial, we used bilateral, taVNS hydrogel earbud electrodes targeting fibers of the auricular branch of the vagus nerve (ABVN), which line the walls of the external acoustic meatus (EAM)[56]. Below we describe the safety, feasibility, tolerability and clinical impacts of two weeks, nightly taVNS treatment on insomnia, sleep quality, and mental health outcomes in breast cancer patients.

Results

We had an 83.3% study completion rate of participants who were consented and enrolled in the study (Fig. 1). One subject dropped from the study due to contracting a sinus infection during baseline and another subject dropped due to an inability to make appointments due to chemotherapy. Two subjects had difficulty completing the study due to their living arrangements. Of the 20 female trial participants completing this study 50% (n = 10) were diagnosed with stage 1 breast cancer, 40% (n = 8) with stage 2, 10% (n = 2) with stage 3, and 0% (n = 0) with stage 4. Participants had an average age of 58.55 ± 1.93 (95% CI 54.5–62.6) with an average BMI of 28.41 ± 2.23 (95% CI 23.7–33.1). In our study sample, 75% (n = 15) of the participants were Caucasian, 20% (n = 4) were Black/African American, and 5% (n = 1) were Hispanic/Latino. We found 85% (n = 17) were prescribed some type of hormone therapy and reported worsening of sleep difficulties because of hormone therapy. In addition, 30% (n = 6) participants reported difficulties adhering to hormone therapy treatment due to adverse side effects including sleep disruption, fatigue, mood disorders. All participants had ongoing, self-reported sleep difficulties, poor sleep quality, and complaints of insomnia indicated by the Insomnia Severity Index (ISI). The CONSORT study diagram in Fig. 1a. Following baseline data collection, trial participants were treated nightly for two weeks (14 days) using bilateral, taVNS conductive hydrogel earbud electrodes targeting ABVN fibers lining the EAM of the external ear (Fig. 1b). The taVNS treatment was self-administered, at-home, by participants for 15 min each night within 30 min of going to bed.

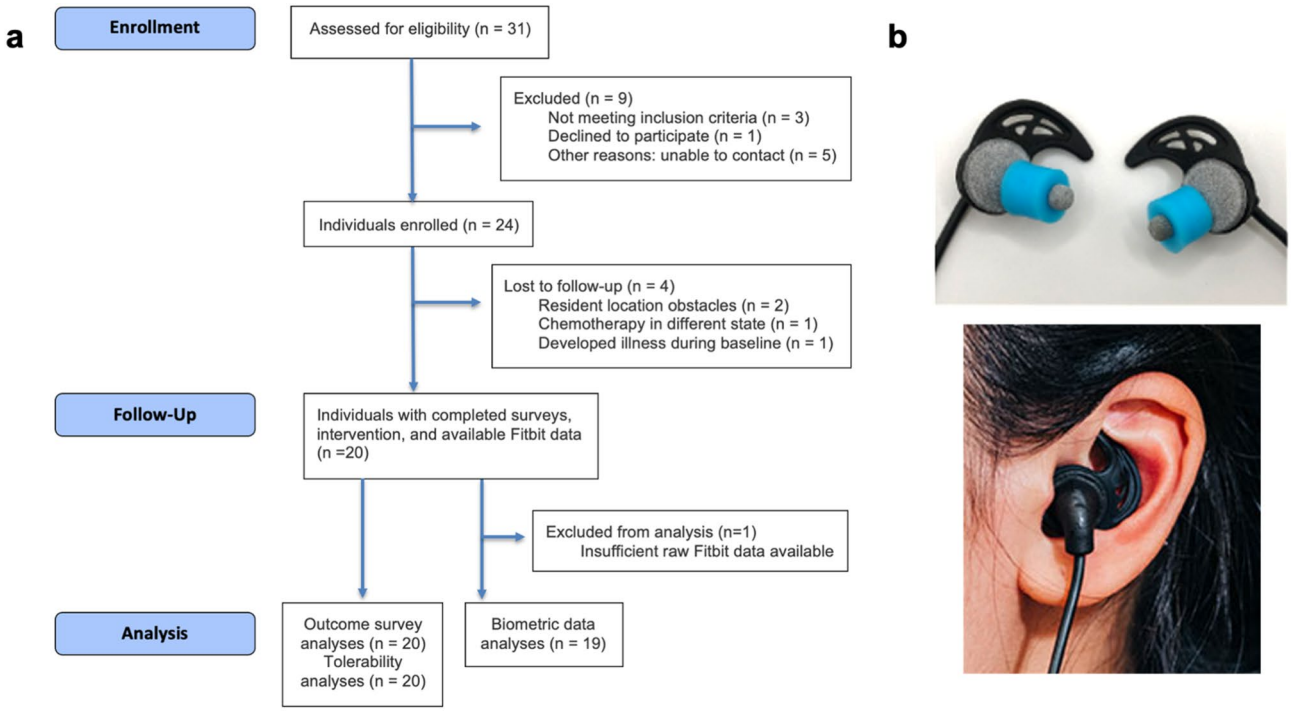


Fig. 1. Approach to trial and transcutaneous auricular vagus nerve stimulation. **a**, A CONSORT diagram for the trial is illustrated. **b**, Bilateral hydrogel earbud electrodes for delivering transcutaneous auricular vagus nerve stimulation to the external acoustic meatus are shown.

Transcutaneous auricular vagus nerve stimulation reduces insomnia severity

Baseline ISI scores of 16.65 ± 0.93 (95% CI 14.70–18.60) and Pittsburgh Sleep Quality Index (PSQI) scores of 11.2 ± 0.80 (95% CI 9.52–12.87) indicate the breast cancer patients began treatment with moderate to severe insomnia and poor sleep quality. Two weeks of nightly taVNS produced very strong evidence for a significant ($t(19) = 4.55$, $p = 0.0002$, $BF_{10} = 137.26$) reduction in ISI scores to 12.35 ± 1.13 (95% CI 9.98–14.72; Fig. 2a). Treatment with taVNS also produced very strong evidence for a significant ($t(19) = 4.50$, $p = 0.0002$, $BF_{10} = 125.05$) improvement in PSQI scores to 8.35 ± 0.76 (95% CI 6.76–9.94; Fig. 2a). The 4.30-point reduction in ISI and 2.85-point reduction in PSQI scores produced by taVNS approach previously reported Minimal Clinically Important Difference (MCID) scores of 6 for ISI and 3 for PSQI scores[57,58] (Fig. 2b). These data provide strong preliminary evidence that taVNS can improve subjective insomnia scores and sleep quality in breast cancer patients.

Nightly vagus nerve stimulation improves sleep quality and heart rate variability biometrics

Nightly actigraphy and heart rate photoplethysmography biometrics were used to objectively quantify sleep onset latency, the number of nightly awakenings, and sleep efficiency. Repeated measures analysis of variance (ANOVA) on weekly averaged biometric data showed taVNS produced a significant reduction in sleep latency during treatment weeks compared to baseline ($F(2,34) = 19.62$, $p = 2.5 \times 10^{-6}$; Fig. 3a). Post-hoc comparisons produced very strong evidence for a significant ($t(17) = 4.78$, $p = 0.0005$, $BF_{10} = 173.48$) reduction in sleep latency within one week of taVNS treatment (Fig. 3b and Table 1). A significant reduction in sleep latency was also evident in the second week of taVNS treatment (Fig. 3b and Table 1). Repeated measures ANOVA also revealed there was a significant improvement in sleep efficiency from baseline through taVNS treatment weeks ($F(2,36) = 12.70$, $p = 9.7 \times 10^{-5}$; Fig. 3a). Further improvements in sleep quality were observed by a significant reduction in the number of nightly awakenings from baseline compared to treatment weeks ($F(2,36) = 6.04$, $p = 0.005$; Fig. 3a). Results from post-hoc comparisons across the two taVNS treatment weeks compared to baseline are summarized in Table 1 and illustrated in Fig. 3b.

Measures of heart rate variability (HRV) quantified as the root mean square of successive differences (RMSSD) were also acquired using nightly heart rate photoplethysmography during sleep throughout the study. A repeated measures ANOVA of weekly RMSSD showed taVNS significantly increased HRV compared to baseline measures ($F(2,34) = 6.37$, $p = 0.004$; Fig. 3a). Post-hoc comparisons of each treatment week against baseline revealed moderate evidence for a significant ($t(17) = 2.86$, $p = 0.03$, $BF_{10} = 4.89$) increase in HRV RMSSD during the first week taVNS treatment compared to baseline (Fig. 3b and Table 1). The effects of taVNS on HRV RMSSD during week 2 of treatment were increased from baseline. While this timepoint measure failed to reach significant thresholds by conventional alpha-thresholds, the Bayes Factor revealed evidence for a weak effect (($t(17) = 2.37$, $p = 0.09$, $BF_{10} = 2.15$; Fig. 3b and Table 1). Collectively these data provide moderate to strong

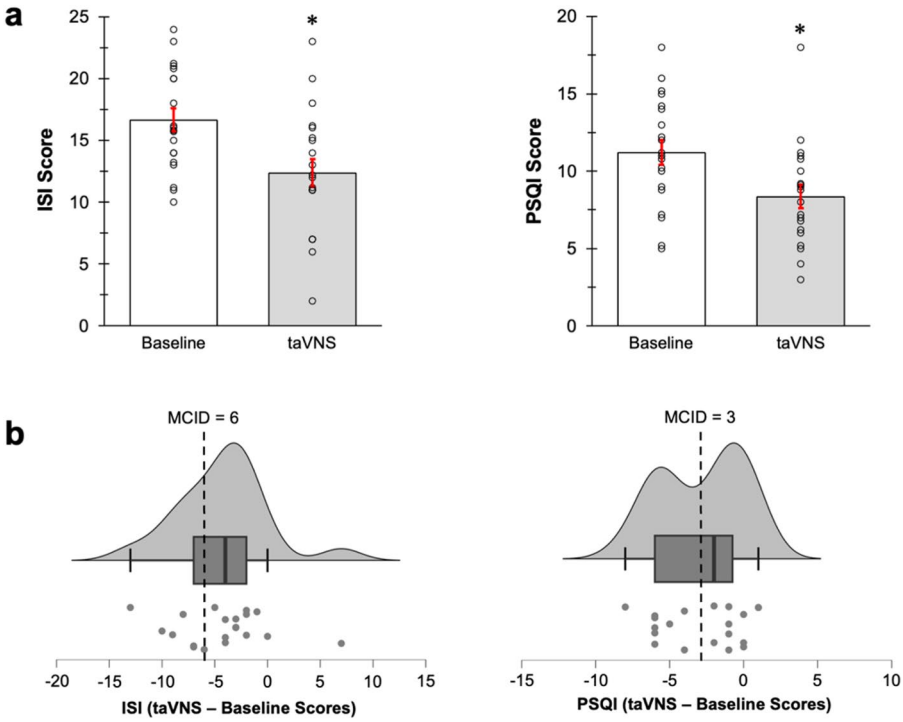


Fig. 2. Insomnia severity and sleep quality scores. **a**, Histograms illustrate mean (vertical bars ± SEM, red error bars) and individual scores (small circles) for the Insomnia Severity Index (ISI; left) and Pittsburg Sleep Quality Index (PSQI; right) at baseline and after two weeks of nightly transcutaneous auricular vagus nerve stimulation (taVNS). The results illustrate taVNS produced a significant reduction in both ISI and PSQI scores compared to baseline. **b**, Plots illustrate the sample distributions, mean, and 95% credible intervals for difference scores in the ISI (left) and PSQI (right) between taVNS and baseline. A Minimal Clinically Important Difference (MCID) score of 6 for the ISI and 3 for the PSQI is illustrated on the difference plot by a dashed line. An asterisk indicates $p < 0.001$.

evidence that nightly taVNS can significantly improve actigraphy and photoplethysmography-based biometrics of sleep quality within the first week of treatment.

Nightly vagus nerve stimulation reduces fatigue and depression

We acquired anxiety outcome measures using the Patient-Reported Outcome Measures Information System (PROMIS) anxiety form and the Generalized Anxiety Disorder-7 (GAD-7) scale. Other outcomes for depression scores were measured using the Patient Health Questionnaire-9 (PHQ-9) and fatigue was assessed using the Cancer Fatigue Scale (CFS). There were no significant differences ($t(19) = 1.51$, $p = 0.15$, $BF_{10} = 0.61$) in GAD-7 scores between baseline (7.05 ± 1.48; 95% CI 3.96–10.14) and post-treatment (6.00 ± 1.41; 95% CI 3.05–8.95; Fig. 4). We observed taVNS produced a slight, but non-significant ($t(19) = 1.82$, $p = 0.08$, $BF_{10} = 0.94$) reduction in PROMIS anxiety scores from baseline (58.63 ± 2.16; 95% CI 54.11–63.15) to post-treatment (56.45 ± 1.83; 95% CI 52.63–60.26; Fig. 4).

We found moderate evidence that two weeks of nightly taVNS significantly reduced ($t(19) = 2.81$, $p = 0.01$, $BF_{10} = 4.89$) PHQ-9 depression scores by 26% (baseline: 8.25 ± 1.41, 95% CI 5.31–11.19; taVNS: 6.1 ± 1.32, 95% CI 3.33–8.87; Fig. 4.). Reflecting a consequence on daily function, we found very strong evidence that two weeks of nightly taVNS significantly reduced ($t(19) = 4.52$, $p = 0.0002$, BF10 = 134.90) cancer related fatigue by 27% (baseline: 23.95 ± 3.03, 95% CI 17.59–30.31; taVNS: 17.55 ± 3.05, 95% CI 11.16–23.94; Fig. 4.). Collectively these data provide strong preliminary evidence that taVNS can improve depression and fatigue in patients with breast cancer by improving their sleep quality.

Tolerability of transcutaneous auricular vagus nerve stimulation in breast cancer patients

No serious adverse events or adverse effects were reported during the use of bilateral taVNS earbud electrodes inserted into the external acoustic meatus. Two subjects reported mild discomfort while wearing the taVNS device, but this was resolved with proper fitting earbuds. No pain, warmth, or pressure was reported (Fig. 5). Sixty percent (n = 12) reported experiencing the sensation of tingling during stimulation (Fig. 5). These subjects reported the sensations were present on the external ear during stimulus onset only and that the sensation was very mild (n = 10) or mild (n = 2). Two subjects reported minimal anxiety or emotional discomfort during use, but this dissipated after the first two days of device use. Two subjects reported itching during taVNS in a few treatment sessions. All subjects found taVNS delivered through the bilateral taVNS hydrogel earbud electrodes

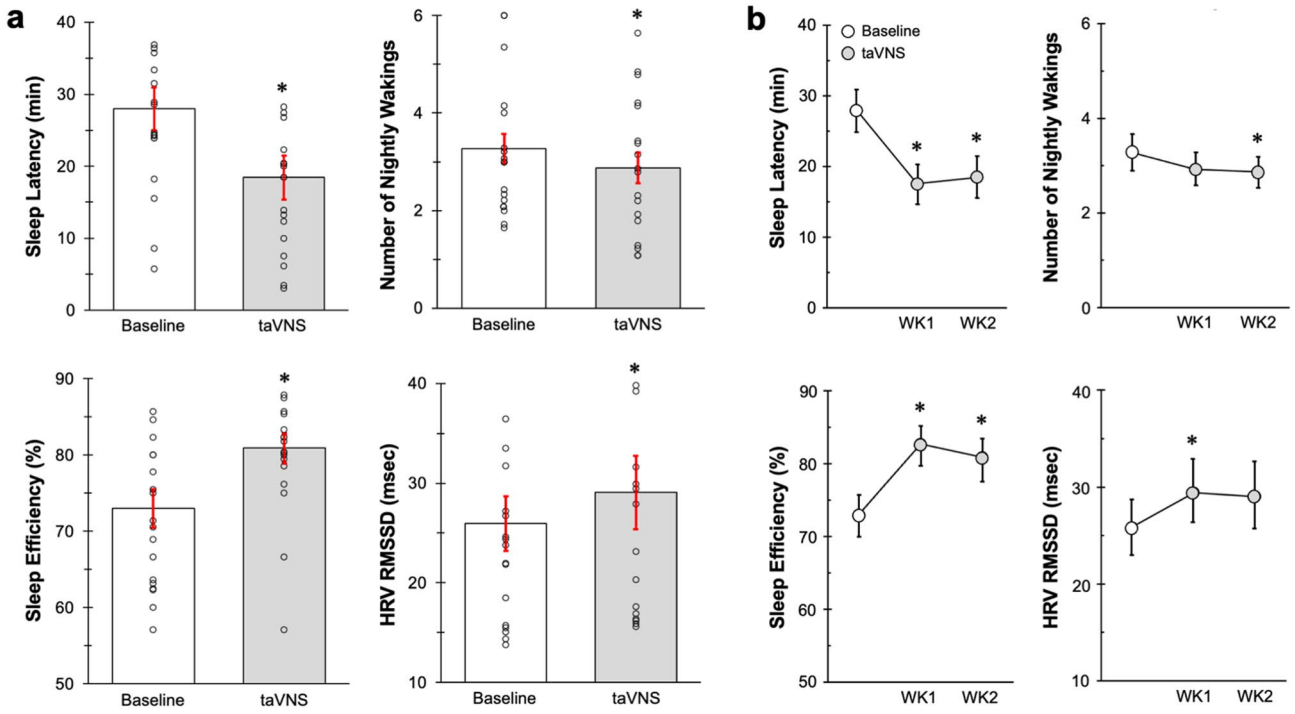


Fig. 3. Biometrics of sleep quality. **a**, Histograms illustrate mean (vertical bars) and individual data (small circles) for sleep latency, number of nightly awakenings, sleep efficiency, and heart rate variability (HRV) root mean square of successive differences (RMSSD) for baseline and two-weeks of nightly treatment with transcutaneous auricular vagus nerve stimulation (taVNS). **b**, Line plots illustrate the mean sleep latency, number of nightly awakenings, sleep efficiency, and HRV RMSD across treatment week (WK) showing the temporal evolution of taVNS effects on biometric measures of sleep quality analyzed by repeated measures ANOVA and Bonferroni's procedure for post-hoc comparisons. All data shown are mean ± SEM (red and black error bars). An asterisk indicates $p < 0.05$.

	Baseline		Transcutaneous auricular vagus nerve stimulation				Week 1 versus baseline		Week 2 versus Baseline	
Outcome measure	Baseline	95% CI	Week 1	95% CI	Week 2	95% CI	*p*-value	BF_{10}	*p*-value	BF_{10}
Sleep latency (min)	27.99	21.70–34.30	17.54	11.27–23.82	18.45	11.97–24.92	0.0005	173.48	0.001	68.48
Sleep efficiency (%)	72.99	67.76–78.23	82.71	79.22–86.20	80.91	76.81–85.02	0.003	38.15	0.02	6.85
Nightly wakings	3.27	2.64–3.91	2.92	2.23–3.61	2.87	2.21–3.54	0.06	2.99	0.04	4.50
HRV RMSSD (msec)	25.87	19.74–32.00	29.42	21.51–37.32	29.02	20.85–37.18	0.03	4.90	0.09	2.15

Table 1. Influence of taVNS on sleep biometrics across treatment weeks.

was tolerable (n = 6) or very tolerable (n = 14; Fig. 5). Collectively our observations indicate that bilateral taVNS is safe, tolerable, and feasible for treatment of insomnia in breast cancer patients.

Discussion

Despite the high prevalence of sleep disturbances in breast cancer survivors, fewer than 50% of survivorship programs at National Cancer Institute–designated comprehensive cancer centers routinely screen for sleep disorders[59,60]. This diagnostic gap may contribute to the under-treatment of insomnia in this population, emphasizing the critical need for accessible, low-burden interventions that can be implemented even in the absence of formal sleep disorder diagnoses. We investigated the therapeutic effects of taVNS by delivering pulsed (30 Hz) electrical currents (< 4 mA) to fibers of the ABVN lining the external acoustic meatus (EAM). Stimulation of ABVN has been shown to activate structures along the vagal afferent pathway in humans, and thus, has gained attention for its safe ability to modulate autonomic nervous system activity, inflammation, and brain regions implicated in sleep–wake arousal[56,61–65]. Consistent with previous trials in other populations[45–48], we found that nightly taVNS across two weeks significantly reduced insomnia severity and improved sleep quality as indicated by ISI and PSQI scores respectively (Fig. 2). These observations were supported by quantitative biometric outcomes showing taVNS significantly improved sleep quality (Fig. 3. and Table 1). Below we discuss possible underlying mechanisms of action and the implications of these observations.

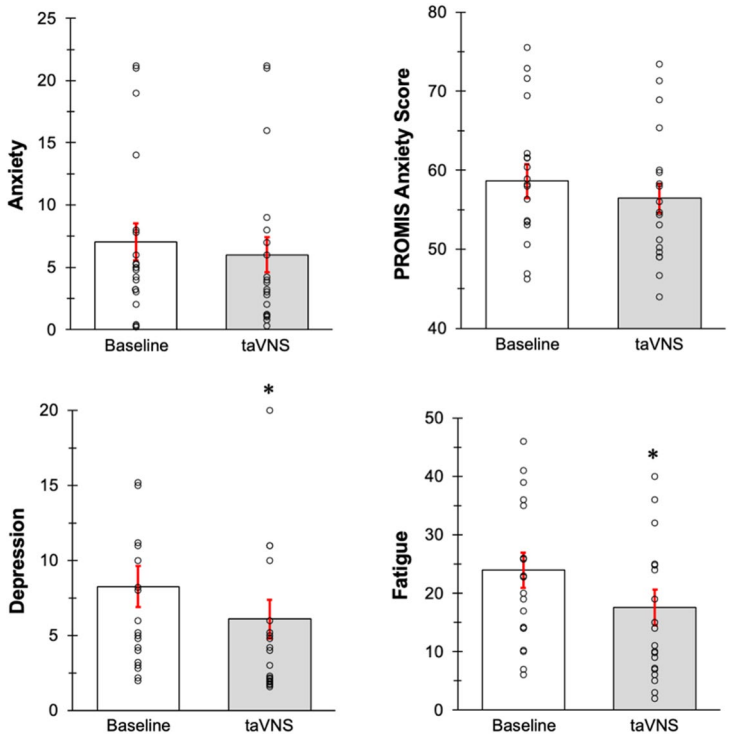


Fig. 4. Mental health and fatigue outcomes. Histograms illustrate the mean (vertical bars) and individual scores (small circles) for the Generalized Anxiety Disorder 7 (GAD-7), Patient-Reported Outcome Measures Information System (PROMIS), Patient Health Questionnaire-9 (PHQ-9), and the Cancer Fatigue Scale (CFS) at baseline and following two weeks of nightly transcutaneous auricular vagus nerve stimulation (taVNS) treatment. The data illustrate that taVNS produced a significant reduction in PHQ-9 depression scores and CFS fatigue scores. All data shown are mean ± SEM (red error bars). An asterisk indicates $p < 0.05$.

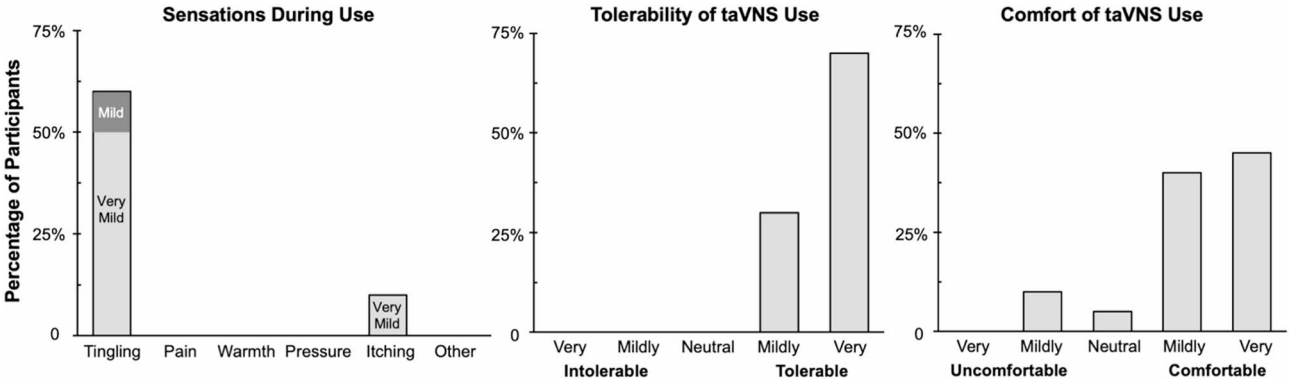


Fig. 5. Tolerability and comfort of taVNS. Histograms illustrate the percentage of trial participants experiencing different types of sensations during transcutaneous auricular vagus nerve stimulation (taVNS) treatment (left). Histograms also illustrate the level of tolerability ranging from very intolerable to very tolerable (middle) and comfort ranging from very uncomfortable to very comfortable (right) of bilateral taVNS using conductive hydrogel earbud electrodes placed in the external acoustic meatus.

Using actigraphy and heart rate photoplethysmography (PPG) measures, we observed very strong evidence that taVNS produced a significant decrease in sleep onset latency (Fig. 3 and Table 1). Interestingly, stimulation of the vagus nerve and vago-aortic nerves has been shown to induce rapid sleep onset and REM modulation measured by neurophysiological recordings in cats[66–68]. It has been well-established through neuroimaging and neurophysiological studies that taVNS acts in part by modulating locus coeruleus—norepinephrine (LC-NE) system activity[69–72]. This seems at first to be somewhat paradoxical given that historically, the LC-NE system has been implicated in alertness and high levels of arousal characterized by the canonical fight-or-flight nervous system. More recent observations and advances in scientific knowledge show the LC-NE system is intimately

involved in regulating a broader range of brain functions and processes including autonomic activity, mood, attention, memory, sensory processing, and sleep/wake cycles[40,43,73–75].

An examination of noradrenergic (NE) receptor subtypes and actions helps to elucidate how stimulation of LC-NE by taVNS may facilitate sleep onset. Pharmacological studies investigating the influence of α2-adrenergic receptor agonists, like clonidine, on sleep–wake cycles have shown LC-NE activity can induce sedative states in rats by acting locally in a negative feedback manner[76,77]. We have previously suggested that trigeminal vagal modulation using transcutaneous pulsed currents can produce outcomes that resemble clonidine-like action and α2-adrenergic activation[78]. Clonidine can enhance sleep duration[79] and quality[80], as well as produce sedative like effects[81]. Clonidine activates α2-adrenergic receptors to inhibit tonic activity of LC neurons without suppressing phasic activity[82,83]. The well-characterized firing patterns of the LC and its regulation of NE release are closely linked to sleep–wake cycles and arousal states[40,73,84]. The LC functions as a metronome of arousal and consciousness, integrating neuromodulatory inputs to regulate cortical state through noradrenergic tone[84]. Positron emission tomography imaging in pigs has indeed shown that vagus nerve stimulation increases the activation of α2-adrenergic receptors[85]. These observations and outcomes are consistent with the hypothesis that taVNS may produce effects partially mediated by α2-adrenergic receptors to reduce sympathetic activity and promote sleep onset. Conversely, modulating LC-NE activity by taVNS may amplify or perturb β-adrenergic signaling, which has also shown to be implicated in sleep regulation[86,87]. Future studies conducted across a range of taVNS doses (intensity levels and durations) should be combined with imaging, polysomnography, and pharmacology to further delineate and validate mechanisms of action.

We observed two weeks of taVNS produced a significant increase in HRV measured by RMSSD calculated from heart rate PPG data acquired during sleep (Fig. 3 and Table 1). HRV is a well-established marker of autonomic function, reflecting the dynamic balance between sympathetic and parasympathetic nervous system activity[88–90]. Numerous studies have demonstrated that higher HRV is associated with reduced sympathetic arousal, increased vagal tone, and greater physiological resilience to stress[91,92]. In contrast, low HRV has been linked to poor health and low sleep quality, underscoring the reciprocal relationship between sleep and autonomic nervous system function[93,94]. It has been shown that taVNS can improve HRV metrics, reflecting enhanced autonomic regulation[91,95–97]. High vagal activity, as indexed by elevated HRV, has been associated with improved prognosis and increased survival across multiple cancer types, including breast cancer, due to vagal-mediated decreased inflammation[98].

Caution should be taken when interpreting the effects of taVNS on HRV in this study for several reasons. First, our open-label feasibility study lacked a placebo treatment group for comparisons. Second, we measured HRV was derived from PPG sensors rather than electrocardiography (ECG). Although the Fitbit RMSSD estimates during sleep have been validated against ECG, PPG is more susceptible to motion artifacts, and the Fitbit signal processing algorithms are proprietary, limiting transparency and replicability. While consumer grade wearables are useful for collecting remote or at-home data, these devices tend to lack the calibrated precision required for making robust clinical inferences. Future studies should incorporate more controlled physiological monitoring for example using electrode-based ECG measurements with respiratory tracking to more precisely dissociate autonomic and stimulation effects. Third, as a pilot study the sample size was modest and may not generalize to broader populations. Replication with larger, more diverse cohorts is needed to confirm these findings. Reliable measures of ECG activity should be used to examine the temporal and frequency domain effects of taVNS on HRV in patients with breast cancer. This would be a particularly prudent approach especially since cancer patients including those with breast cancer can suffer from dysautonomia [99,100]. It is not known and our study does not provide any conclusionary evidence whether taVNS may adversely influence HRV or cardiac function in this patient population. In general, the increases in HRV we observed in response to taVNS seem to reflect an improved healthy state, but further investigations are required to fully understand whether these changes may harm or benefit patients with breast cancer.

Our observations indicate a benefit of taVNS for improving insomnia include a significant reduction in cancer-related fatigue (Fig. 4), which is a chief complaint of women with breast cancer. In our feasibility study, participants only suffered from mild anxiety symptoms at baseline. Following taVNS treatment we observed a slight reduction in anxiety scores. Although this effect did not reach significance thresholds using frenquetist methods, Bayesian analyses supported strong evidence for a reduction in anxiety scores following taVNS treatment (Fig. 4). We observed significantly reduced mild depression scores following taVNS treatment (Fig. 4). As mentioned, the participants in this study did not suffer from generalized anxiety disorder (GAD) or major depressive disorder (MDD) and only reported mild anxiety and depressive symptoms at baseline. Thus, we cannot determine whether taVNS may produce mental health improvements in breast cancer patients suffering from GAD or MDD. Randomized controlled studies in participants suffering from moderate to severe anxiety or depression are required to determine whether taVNS can clinically improve GAD or MDD. This possibility warrants further investigation given that taVNS has been shown to elicit antidepressant effects in patients with treatment-resistant depression and major depressive disorder[49–52].

Inflammation might also serve as a vulnerability factor, in which subsequent exposure to sleep disturbance triggers increase in depressive symptoms. Sleep disruption elevates sympathetic activity [101–103], which in turn triggers inflammation and increasing cytokine levels of IL-6 and TNF, which are linked to depression[17,20]. Inflammation, in turn, can further impair sleep[104]. Given the critical role of the vagus nerve in modulating inflammatory reflexes, emerging evidence suggests that VNS may exert antidepressant effects by reducing proinflammatory cytokines and promoting anti-inflammatory responses[105]. Chronic inflammation is a key contributor to sleep disturbances, fatigue, and diminished quality of life in breast cancer survivors[7,106]. Vagus nerve stimulation activates the cholinergic anti-inflammatory pathway (CAIP), which has been shown to suppress systemic inflammation by reducing pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6[44,107]. Elevation of these cytokines has been associated with disrupted sleep architecture and increased fatigue in cancer

populations[7,106], as well as with tumor progression, metastasis, and poorer prognosis[108,109]. Previous research has demonstrated taVNS can reduce circulating levels of pro-inflammatory cytokines in clinical and preclinical models of systemic inflammation[53,55,110]. More specifically, recent human studies have shown that taVNS can reduce pro-inflammatory cytokine levels and inflammation due to sepsis[55] and subarachnoid hemorrhage[53] within four days of treatment while producing significant clinical benefits within seven days. More acute models of lipopolysaccharide-induced inflammation in mice have shown that taVNS can produce significant decreases in pro-inflammatory cytokine production within two hours of administration[111]. These and other studies indicate taVNS warrants further investigation as an acute approach to reducing cancer-related inflammation and its downstream effects on sleep, fatigue, HRV, and quality of life in breast cancer patients[112,113].

Perhaps one of the most difficult aspects of evaluating potential bioelectronic therapies relates to the calculation or estimation of effective dose. Numerous factors affect sensory thresholds including electrode surface area, electrode coupling method, electrode location, electrical impedance, current pulse characteristics, electrical charge, and baseline arousal[56]. These and other psychophysiological variables can bias the outcome and effects on autonomic nervous system activity[92] leading to challenges when estimating the taVNS effective dose for a particular application. It has been shown that even sub-perceptual levels of taVNS can produce significant activation sufficient to induce cortical activation[114]. In this study, we maintained consistency across other methods by asking patients to set current intensities at or just above sensory thresholds at a level where they are comfortable. The current intensities used in our study are consistent with those reported by many other studies in the literature[64]. Future investigations may start to address gaps in our understanding of effective taVNS dose by developing dose response curves across sub-perceptual (~ 2 mA) and perceptual levels (~ 2–4 mA) of current intensity.

It has been reported across the literature that taVNS is a low-risk procedure and is well-tolerated across populations ranging from premature infants[115] to older adults[64]. A review of 177 studies and 6322 subjects found that current taVNS methods are safe and tolerable[64]. As anticipated from these reports, all participants in this study found the taVNS to be tolerable or very tolerable (Fig. 5). When appropriate stimulation intensity is used, taVNS has a favorable safety profile even when repeated over a long period of time [64,116,117]. Future investigations are required to explore the long-term safety and tolerability of taVNS specifically in patients diagnosed with cancer. This will be a particularly important issue to address since many cancer patients including breast cancer patients suffer from peripheral neuropathies[118–120] that may influence the safety and tolerability of taVNS in this population.

In summary, two weeks of nightly taVNS delivered bilaterally through hydrogel earbud electrodes produced clinically meaningful reductions in insomnia severity (Fig. 2), reduced sleep onset latency, improved sleep efficiency (Fig. 3 and Table 1), and decreased cancer-related fatigue (Fig. 4). The improvements in sleep quality were accompanied by a decrease in mild depression scores (Fig. 4) and increase in nightly HRV (Fig. 3 and Table 1). Importantly, we observed no adverse events in this study. Participants reported taVNS was comfortable and well-tolerated highlighting the feasibility of integrating this approach into routine breast cancer care. Due to the small size and open-label nature of this feasibility study, it is difficult to draw conclusions regarding the generalizability of our observations to larger populations. Multi-site, randomized, placebo-controlled trials with longer study periods are required to fully evaluate the durability of the taVNS effects, as well as to investigate optimal dosing parameters. Mechanistic studies may focus on the interplay between α2-adrenergic signaling, inflammation, sleep–wake regulation, and depression. Because hydrogel earbud electrodes are comfortable, easy to use, and have a familiar form factor, they offer a high degree of scalability and interoperability within oncology rehabilitation and palliative care frameworks[56]. Larger dose finding studies using placebo controls should combine at-home polysomnography (EEG), clinical-grade actigraphy, ECG, and decentralized clinical trial approaches with implementation science to further navigate the clinical translation of taVNS for improving the sleep, mood, and health of breast cancer patients.

Methods

This pilot study was conducted to evaluate the tolerability, feasibility, and preliminary efficacy of at-home use of bilateral taVNS over a two-week intervention period as a treatment for insomnia in women with breast cancer. The study was approved by the University of Alabama at Birmingham Institutional Review Board for Human Use (IRB-300010460; ClinicalTrials.gov NCT06006299, Registered 08/21/2023) and conducted in accordance with institutional policies, local legislation, and federal requirements. All participants provided their written informed consent prior to experimentation.

Participants

Patient enrollment is delineated using CONSORT 2010 guidelines (Fig. 1). We recruited 31 women for study participation and determined through a screening interview performed prior to the study that 24 were to be allocated for intervention. Of those 24 subjects, 20 were eligible and participated in the study.

Participants were eligible if they were (1) At least 18 years of age; (2) Diagnosed with stage I-IV breast cancer; (3) Reported difficulty initiating sleep, maintaining sleep, or having frequent awakenings for at least three nights per week for a duration of at least three months; (4) Have a minimum Insomnia Severity Index (ISI) score > 8; and (5) Reported beginning or worsening of sleep disturbance with the diagnosis of cancer or while having cancer.

Participants were excluded if they (1) Used sleep medication; (2) Have a history of severe mental illness; (3) Have an implanted medical device of any type; (4) Have a history of seizures; (5) Have peripheral neuropathy, including temporal mandibular disorders and Bell's Palsy; (6) Have vasovagal syncope; (7) Have moderate to severe cognitive impairment (Montreal Cognitive Assessment score < 16/30); and (8) Have less than 6 months to live as determined by a physician.

Study procedures

Participants received 14 consecutive days of bilateral taVNS for 15 min each night within 30 min of going to bed. The at-home, self-administered taVNS treatment was delivered through conductive hydrogel earbud electrodes (BRAIN Buds; IST, LLC, Birmingham, Alabama, USA) positioned in the external acoustic meatus (EAM) of both external ears[56]. The stimulus controller (Vagus.net, London, United Kingdom) was modified to deliver taVNS through the earbud electrodes using a biphasic, square wave having pulse widths of 250 microseconds and an interphase gap of 50 microseconds delivered at a pulse frequency of 30 Hz. The maximum output current was 4 mA and treatment intensities ranged from 1.5 to 4 mA.

Subjects were instructed to set the stimulation intensity to a level at or just above their perceived sensory thresholds and to ensure sensations remained effective yet comfortable. The sensory/perceptual threshold for electrical stimulation is defined in this study as the minimum intensity of electrical current required to perceive a sensation, such as tingling or prickling on the skin. This psychophysical sensory threshold represented the point at which detectable conscious perception of the stimulus became present. Participant sensory thresholds were established in person by the study investigator during the device training portion using a simple step-up approach where device stimulation began at 0.5 mA and increased. We note that none of the subjects reached perceptual thresholds < 1.5 mA and 9/20 subjects reached a peak intensity of 4 mA before experiencing perceptual thresholds.

Outcome measures

Behavioral and psychological assessments were implemented at two timepoints: pre-intervention baseline and post-intervention following two consecutive weeks (14 days) of nightly taVNS treatment. Participants were instructed to self-report their sleep daily using the Consensus Sleep Diary throughout the study and self-report taVNS tolerability daily during the intervention period. Primary outcomes measures of sleep quality were assessed by the Pittsburgh Sleep Quality Index (PSQI)[121] and insomnia symptoms were assessed by the Insomnia Severity Index (ISI)[122]. Additional primary outcomes included actigraphy and heart rate photoplethysmography measurements of sleep quality obtained using Fitbit Charge 5 devices (Google, Inc., Mountain View, CA, USA). Fitbit devices were assigned to participants to be worn daily and nightly throughout the study. Participants were instructed to activate sleep modes on their Fitbit devices manually each night before bed to disable the screen and mute notifications throughout the night. This served to minimize potential sleep disruptions due to wearing the device. Sleep onset, sleep efficiency, number of awakenings, and HRV (RMSSD) during sleep were measured as primary outcomes from Fitbit data. The RMSSD HRV measures are calculated as an average across nights as measured during sleep using proprietary Fitbit algorithms. Sleep onset and efficiency, as well as number of awakenings were calculated as averages across the baseline and treatment periods.

Secondary outcomes related to sleep disturbances were measured using the Patient Reported Outcome Measurement Information Systems (PROMIS®)[123] Anxiety survey and the Generalized Anxiety Disorder 7-item (GAD-7)[124] for anxiety. We also used the Patient Health Questionnaire 9 (PHQ-9) item depression scale to quantify secondary outcomes related to mood symptoms[125]. Finally, the Cancer Fatigue Scale (CFS) was used to measure the severity and impact of fatigue experienced by cancer patients[126].

Statistical analysis

REDCap was used to develop and manage project tools and outcomes (REDCap, RRID:SCR_003445). Data were collected through REDCap and stored for analysis. The R Project for Statistical Computing (R Project for Statistical Computing, RRID:SCR_001905) and JASP (JASP, RRID:SCR_015823) were used for statistical computing and data graphing. Bayesian and students paired samples t-test were conducted using JASP on baseline and post-treatment ISI, PSQI, CFS, PHQ-9, GAD-7, and PROMIS scores. Difference scores for the ISI and PSQI were calculated by subtracting the post-treatment scores from baseline scores and are illustrated in Fig. 2B. The *t* statistics, *p*-values, 95% CI levels, and Bayes Factor (BF_{10}) are reported in the results. Figure 2 illustrates ISI and PSQI scores and Fig. 4 illustrates CFS, PHQ-9, GAD-7, and PROMIS data.

Repeated measures analysis of variance (ANOVA) was used to analyze biometric sleep outcomes from Fitbit data (sleep latency, sleep efficiency, number of wakings, and HRV RMSSD) on a weekly averaged basis. Post-hoc comparisons were performed using Bonferroni's procedure for multiple comparisons in addition to Bayesian repeated measures ANOVA approaches using JASP. Post-hoc comparisons were made for taVNS treatment weeks 1 and 2 versus baseline. Biometric data illustrated in Tabel 1 and Fig. 3a illustrates the two-week averaged data while Fig. 3b shows the weekly data. The resulting F and t statistics, p-values, 95% CI levels, and BF_{10} values are reported in the results. A p-value < 0.05 was considered significant. Data reported in the results and shown in histograms are the mean ± the standard error of the mean (SEM) unless otherwise stated. Histograms in Figs. 2, 3, and 4 also illustrate individual data.

Data availability

Data are available upon reasonable request by contacting the corresponding author WJT. Upon approval unidentified data may be made available. All experiments and implementation details are described thoroughly in the Methods section so they can be independently replicated.

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References

1. Howell, D. et al. Sleep disturbance in adults with cancer: A systematic review of evidence for best practices in assessment and management for clinical practice. *Ann. Oncol.* **25**, 791–800. https://doi.org/10.1093/annonc/mdt506 (2014).
2. Nissen, E. R. et al. Interventions for insomnia in cancer patients and survivors—A comprehensive systematic review and meta-analysis. *JNCI Cancer Spectrum* **8**, pkae041. https://doi.org/10.1093/jncics/pkae041 (2024).
3. Kwak, A., Jacobs, J., Haggett, D., Jimenez, R. & Peppercorn, J. Evaluation and management of insomnia in women with breast cancer. *Breast Cancer Res Treat* **181**, 269–277. https://doi.org/10.1007/s10549-020-05635-0 (2020).
4. Davidson, J. R., MacLean, A. W., Brundage, M. D. & Schulze, K. Sleep disturbance in cancer patients. *Soc. Sci. Med.* **54**, 1309–1321. https://doi.org/10.1016/S0277-9536(01)00043-0 (2002).
5. Palesh, O. et al. Actigraphy-measured sleep disruption as a predictor of survival among women with advanced breast cancer. *Sleep* **37**, 837–842. https://doi.org/10.5665/sleep.3642 (2014).
6. Byar, K. L., Berger, A. M., Bakken, S. L. & Cetak, M. A. Impact of adjuvant breast cancer chemotherapy on fatigue, other symptoms, and quality of life. *Oncol. Nurs. Forum* **33**, E18–E26. https://doi.org/10.1188/06.ONF.E18-E26 (2006).
7. Irwin, M. R. Depression and insomnia in cancer: Prevalence, risk factors, and effects on cancer outcomes. *Curr. Psychiatry Rep.* **15**, 404. https://doi.org/10.1007/s11920-013-0404-1 (2013).
8. Desai, K. et al. Prevalence and risk factors for insomnia among breast cancer patients on aromatase inhibitors. *Support Care Cancer* **21**, 43–51. https://doi.org/10.1007/s00520-012-1490-z (2013).
9. Costa, A. R. et al. Impact of breast cancer treatments on sleep disturbances—A systematic review. *The Breast* **23**, 697–709. https://doi.org/10.1016/j.breast.2014.09.003 (2014).
10. Spiegel, D. & Giese-Davis, J. Depression and cancer: Mechanisms and disease progression. *Biol. Psychiat.* **54**, 269–282. https://doi.org/10.1016/S0006-3223(03)00566-3 (2003).
11. Reich, M., Lesur, A. & Perdrizet-Chevallier, C. Depression, quality of life and breast cancer: A review of the literature. *Breast Cancer Res. Treat.* **110**, 9–17. https://doi.org/10.1007/s10549-007-9706-5 (2008).
12. Giese-Davis, J. et al. Depression and stress reactivity in metastatic breast cancer. *Psychosom. Med.* **68**, 675–683. https://doi.org/10.1097/01.psy.0000238216.88515.e5 (2006).
13. Wang, X. et al. Prognostic value of depression and anxiety on breast cancer recurrence and mortality: A systematic review and meta-analysis of 282,203 patients. *Mol. Psychiatry* **25**, 3186–3197. https://doi.org/10.1038/s41380-020-00865-6 (2020).
14. Watson, M., Haviland, J., Greer, S., Davidson, J. & Bliss, J. Influence of psychological response on survival in breast cancer: A population-based cohort study. *The Lancet* **354**, 1331–1336. https://doi.org/10.1016/S0140-6736(98)11392-2 (1999).
15. Lei, F. et al. Influence of depression on breast cancer treatment and survival: A Kentucky population-based study. *Cancer* **129**, 1821–1835. https://doi.org/10.1002/cncr.34676 (2023).
16. Ibrar, M., Peddie, N., Agnew, S., Diserholt, A. & Fleming, L. Breast cancer survivors' lived experience of adjuvant hormone therapy: A thematic analysis of medication side effects and their impact on adherence. *Front. Psychol.* **13**, 861198. https://doi.org/10.3389/fpsyg.2022.861198 (2022).
17. Besedovsky, L., Lange, T. & Haack, M. The sleep-immune crosstalk in health and disease. *Physiol. Rev.* **99**, 1325–1380. https://doi.org/10.1152/physrev.00010.2018 (2019).
18. Dzierzewski, J. M., Donovan, E. K., Kay, D. B., Sannes, T. S. & Bradbrook, K. E. Sleep inconsistency and markers of inflammation. *Front. Neurol.* **11**, 1042. https://doi.org/10.3389/fneur.2020.01042 (2020).
19. Irwin, M. R., Olmstead, R. & Carroll, J. E. Sleep disturbance, sleep duration, and inflammation: A systematic review and meta-analysis of cohort studies and experimental sleep deprivation. *Biol. Psychiat.* **80**, 40–52. https://doi.org/10.1016/j.biopsych.2015.05.014 (2016).
20. Yang, Y. et al. Relationship between sleep and serum inflammatory factors in patients with major depressive disorder. *Psychiatry Res.* **329**, 115528. https://doi.org/10.1016/j.psychres.2023.115528 (2023).
21. Fiorentino, L., Rissling, M., Liu, L. & Ancoli-Israel, S. The symptom cluster of sleep, fatigue and depressive symptoms in breast cancer patients: Severity of the problem and treatment options. *Drug Discov. Today Dis. Model.* **8**, 167–173. https://doi.org/10.1016/j.ddmod.2011.05.001 (2011).
22. Tong, H.-H. et al. The association between sleep disturbance and proinflammatory markers in patients with cancer: A meta-analysis. *Cancer Nurs.* **46**, E91–E98. https://doi.org/10.1097/NCC.0000000000001055 (2023).
23. Fiorentino, L. & Ancoli-Israel, S. Insomnia and its treatment in women with breast cancer. *Sleep Med. Rev.* **10**, 419–429. https://doi.org/10.1016/j.smrv.2006.03.005 (2006).
24. Edinger, J. D. et al. Behavioral and psychological treatments for chronic insomnia disorder in adults: An American Academy of Sleep Medicine clinical practice guideline. *J. Clin. Sleep Med.* **17**, 255–262. https://doi.org/10.5664/jcsm.8986 (2021).
25. Qaseem, A. et al. Management of chronic insomnia disorder in adults: A clinical practice guideline from the american college of physicians. *Ann. Intern Med.* **165**, 125–133. https://doi.org/10.7326/M15-2175 (2016).
26. Ong, J. C., Kuo, T. F. & Manber, R. Who is at risk for dropout from group cognitive-behavior therapy for insomnia?. *J. Psychosom. Res.* **64**, 419–425. https://doi.org/10.1016/j.jpsychores.2007.10.009 (2008).
27. Koffel, E. & Wisdom, J. Why do patients drop-out from cognitive behavioral therapy for insomnia (CBT-I)? A qualitative interview study. *Sleep* **42**, A157–A158. https://doi.org/10.1093/sleep/zsz067.387 (2019).
28. Yeung, W.-F., Chung, K.-F., Ho, F.Y.-Y. & Ho, L.-M. Predictors of dropout from internet-based self-help cognitive behavioral therapy for insomnia. *Behav. Res. Ther.* **73**, 19–24. https://doi.org/10.1016/j.brat.2015.07.008 (2015).
29. Cheng, W. H., Teo, R. H., Cheng, L. J., Lau, Y. & Lau, S. T. Global prevalence of sleep disturbances among breast cancer survivors: A systematic review with meta-analysis. *Sleep Health* **9**, 704–716. https://doi.org/10.1016/j.sleh.2023.04.004 (2023).
30. Cheung, J. M. Y., Jarrin, D. C., Ballot, O., Bharwani, A. A. & Morin, C. M. A systematic review of cognitive behavioral therapy for insomnia implemented in primary care and community settings. *Sleep Med. Rev.* **44**, 23–36. https://doi.org/10.1016/j.smrv.2018.11.001 (2019).
31. Thomas, A. et al. Where are the Behavioral Sleep Medicine Providers and Where are They Needed? A Geographic Assessment. *Behav. Sleep Med.* **14**, 687–698. https://doi.org/10.1080/15402002.2016.1173551 (2016).
32. Clarke, K., Orlov, N. & Soong, C. Treatment of chronic insomnia in adults. *Can. Fam. Phys.* **70**, 176–178. https://doi.org/10.46747/cfp.7003176 (2024).
33. Holbrook, A. M., Crowther, R., Lotter, A., Cheng, C. & King, D. Meta-analysis of benzodiazepine use in the treatment of insomnia. *CMAJ* **162**, 225–233 (2000).
34. Paltiel, O. et al. Use of tranquilizers and sleeping pills among cancer patients is associated with a poorer quality of life. *Qual. Life Res.* **13**, 1699–1706. https://doi.org/10.1007/s11136-004-8745-1 (2004).
35. Grassi, L. et al. Insomnia in adult patients with cancer: ESMO Clinical Practice Guideline. *ESMO Open* **8**, 102047. https://doi.org/10.1016/j.esmoop.2023.102047 (2023).
36. Chang, W. P. & Lin, C. C. Use of opioid analgesics or sleeping medication and survival of cancer patients. *Eur. J. Oncol. Nurs.* **19**, 199–206. https://doi.org/10.1016/j.ejon.2014.11.007 (2015).
37. Cogan, J. C. et al. New and persistent sedative-hypnotic use after adjuvant chemotherapy for breast cancer. *JNCI J. Natl. Cancer Inst.* **114**, 1698–1705. https://doi.org/10.1093/jnci/djac170 (2022).
38. Oneschuk, D. & Bruera, E. The 'dark side' of adjuvant analgesic drugs. *Progress Palliative Care* **5**, 5–13. https://doi.org/10.1080/09699260.1997.11746767 (1997).

39. Ross, J. A. & Van Bockstaele, E. J. The locus coeruleus- norepinephrine system in stress and arousal: Unraveling historical, current, and future perspectives. *Front. Psychiatry* https://doi.org/10.3389/fpsyt.2020.601519 (2021).
40. Poe, G. R. et al. Locus coeruleus: A new look at the blue spot. *Nat. Rev. Neurosci.* **21**, 644–659. https://doi.org/10.1038/s41583-020-0360-9 (2020).
41. Schwarz, L. A. & Luo, L. Organization of the locus coeruleus-norepinephrine system. *Curr. Biol.* **25**, R1051–R1056. https://doi.org/10.1016/j.cub.2015.09.039 (2015).
42. Jones, B. E. Arousal and sleep circuits. *Neuropsychopharmacology* **45**, 6–20. https://doi.org/10.1038/s41386-019-0444-2 (2020).
43. Osorio-Forero, A., Cherrad, N., Banterle, L., Fernandez, L. M. J. & Lüthi, A. When the locus coeruleus speaks up in sleep: Recent insights. *Emerg. Perspect. Int. J. Mol. Sci.* https://doi.org/10.3390/ijms23095028 (2022).
44. Kelly, M. J., Breathnach, C., Tracey, K. J. & Donnelly, S. C. Manipulation of the inflammatory reflex as a therapeutic strategy. *Cell Rep. Med.* **3**, 100696. https://doi.org/10.1016/j.xcrm.2022.100696 (2022).
45. He, J.-K. et al. Transcutaneous auricular vagus nerve stimulation modulates the prefrontal cortex in chronic insomnia patients: fMRI study in the first session. *Front. Neurol.* **13**, 827749. https://doi.org/10.3389/fneur.2022.827749 (2022).
46. Jiao, Y. et al. Effect of transcutaneous vagus nerve stimulation at auricular concha for insomnia: A randomized clinical trial. *Evid. Based Complement. Altern. Med. eCAM* **2020**, 6049891. https://doi.org/10.1155/2020/6049891 (2020).
47. Zhang, L. et al. Transcutaneous vagus nerve stimulation for insomnia in people living in places or cities with high altitudes: A randomized controlled trial. *Brain Sci.* **13**, 985. https://doi.org/10.3390/brainsci13070985 (2023).
48. Zhang, S. et al. Transcutaneous auricular vagus nerve stimulation for chronic insomnia disorder: A randomized clinical trial. *JAMA Netw. Open* **7**, e2451217–e2451217. https://doi.org/10.1001/jamanetworkopen.2024.51217 (2024).
49. Ma, S.-N., Liu, X.-H. & Cai, W.-S. Preventive noninvasive vagal nerve stimulation reduces insufficient sleep-induced depression by improving the autonomic nervous system. *Biomed. Pharmacother.* **173**, 116344. https://doi.org/10.1016/j.biopha.2024.116344 (2024).
50. Kong, J., Fang, J., Park, J., Li, S. & Rong, P. Treating depression with transcutaneous auricular vagus nerve stimulation: State of the art and future perspectives. *Front. Psych.* **9**, 20. https://doi.org/10.3389/fpsyt.2018.00020 (2018).
51. Evensen, K., Jørgensen, M. B., Sabers, A. & Martiny, K. Transcutaneous vagal nerve stimulation in treatment-resistant depression: A feasibility study. *Neuromodul. J. Int. Neuromodul. Soc.* **25**, 443–449. https://doi.org/10.1111/ner.13366 (2022).
52. Li, S. et al. Comparative effectiveness of transcutaneous auricular vagus nerve stimulation vs citalopram for major depressive disorder: A randomized trial. *Neuromodul. Technol. Neural Interface* **25**, 450–460. https://doi.org/10.1016/j.neurom.2021.10.021 (2022).
53. Huguenard, A. L. et al. Auricular vagus nerve stimulation for mitigation of inflammation and vasospasm in subarachnoid hemorrhage: A single-institution randomized controlled trial. *J. Neurosurg.* **142**, 1720–1731. https://doi.org/10.3171/2024.10.Jns241643 (2025).
54. van Beekum, C. J. et al. Transcutaneous vagal nerve simulation to reduce a systemic inflammatory response syndrome and the associated intestinal failure: Study protocol of a prospective, two-armed, sham-controlled, double-blinded trial in healthy subjects (the NeuroSIRS-Study). *Int. J. Colorectal Dis.* **37**, 259–270. https://doi.org/10.1007/s00384-021-04034-1 (2022).
55. Wu, Z. et al. Transcutaneous auricular vagus nerve stimulation reduces cytokine production in sepsis: An open double-blind, sham-controlled, pilot study. *Brain Stimul.* **16**, 507–514. https://doi.org/10.1016/j.brs.2023.02.008 (2023).
56. Tyler, W. J. Auricular bioelectronic devices for health, medicine, and human-computer interfaces. *Front. Electron.* **6**, 1503425. https://doi.org/10.3389/felec.2025.1503425 (2025).
57. Qin, Z. et al. The gap between statistical and clinical significance: Time to pay attention to clinical relevance in patient-reported outcome measures of insomnia. *BMC Med. Res. Methodol.* **24**, 177. https://doi.org/10.1186/s12874-024-02297-0 (2024).
58. Yang, M., Morin, C. M., Schaefer, K. & Wallenstein, G. V. Interpreting score differences in the Insomnia Severity Index: Using health-related outcomes to define the minimally important difference. *Curr. Med. Res. Opin.* **25**, 2487–2494. https://doi.org/10.1185/03007990903167415 (2009).
59. Zhou, E. S., Partridge, A. H., Syrjala, K. L., Michaud, A. L. & Recklitis, C. J. Evaluation and treatment of insomnia in adult cancer survivorship programs. *J. Cancer Surviv.* **11**, 74–79. https://doi.org/10.1007/s11764-016-0564-1 (2017).
60. Zhou, E. S., Recklitis, C. J. & Partridge, A. H. When cancer centers snooze, patients lose: It is time to make insomnia a priority for survivors. *JCO Oncol. Pract.* **20**, 169–172. https://doi.org/10.1200/OP.23.00540 (2023).
61. Butt, M. F., Albusoda, A., Farmer, A. D. & Aziz, Q. The anatomical basis for transcutaneous auricular vagus nerve stimulation. *J. Anat.* **236**, 588–611. https://doi.org/10.1111/joa.13122 (2020).
62. Chen, Y., Lu, X. & Hu, L. Transcutaneous Auricular Vagus Nerve Stimulation Facilitates Cortical Arousal and Alertness. *International Journal of Environmental Research and Public Health* **20** (2023).
63. Croft, J. R. et al. Transcutaneous auricular vagus nerve stimulation: efficacy, applications, and challenges in mood disorders and autonomic regulation—A narrative review. *Military Med.* https://doi.org/10.1093/milmed/usaf063 (2025).
64. Kim, A. Y. et al. Safety of transcutaneous auricular vagus nerve stimulation (taVNS): A systematic review and meta-analysis. *Sci Rep* **12**, 22055. https://doi.org/10.1038/s41598-022-25864-1 (2022).
65. Le Roy, B. et al. Evaluation of taVNS for extreme environments: An exploration study of health benefits and stress operationality. *Front. Neurol.* https://doi.org/10.3389/fneur.2023.1286919 (2023).
66. Puizillout, J. J. & Foutz, A. S. Characteristics of the experimental reflex sleep induced by vago-aortic nerve stimulation. *Electroencephalogr. Clin. Neurophysiol.* **42**, 552–563. https://doi.org/10.1016/0013-4694(77)90219-X (1977).
67. Puizillout, J. J. & Foutz, A. S. Vago-aortic nerves stimulation and REM sleep: evidence for a REM-triggering and a REM-maintenance factor. *Brain Res.* **111**, 181–184. https://doi.org/10.1016/0006-8993(76)91060-x (1976).
68. Valdés-Cruz, A. et al. Chronic stimulation of the cat vagus nerve: Effect on sleep and behavior. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **26**, 113–118. https://doi.org/10.1016/S0278-5846(01)00228-7 (2002).
69. Frangos, E., Ellrich, J. & Komisaruk, B. R. Non-invasive access to the vagus nerve central projections via electrical stimulation of the external ear: fMRI evidence in humans. *Brain Stimul.* **8**, 624–636. https://doi.org/10.1016/j.brs.2014.11.018 (2015).
70. Urbin, M. A. et al. Electrical stimulation of the external ear acutely activates noradrenergic mechanisms in humans. *Brain Stimul.* **14**, 990–1001. https://doi.org/10.1016/j.brs.2021.06.002 (2021).
71. Phillips, I. et al. Three hundred hertz transcutaneous auricular vagus nerve stimulation (taVNS) impacts pupil size non-linearly as a function of intensity. *Psychophysiology* **62**, e70011. https://doi.org/10.1111/psyp.70011 (2025).
72. Sharon, O., Fahoum, F. & Nir, Y. Transcutaneous vagus nerve stimulation in humans induces pupil dilation and attenuates alpha oscillations. *J. Neurosci. Off. J. Soc. Neurosci.* **41**, 320–330. https://doi.org/10.1523/JNEUROSCI.1361-20.2020 (2021).
73. Aston-Jones, G., Rajkowski, J. & Cohen, J. Role of locus coeruleus in attention and behavioral flexibility. *Biol. Psychiat.* **46**, 1309–1320. https://doi.org/10.1016/S0006-3223(99)00140-7 (1999).
74. Reyes, B. A. S. The locus coeruleus: Anatomy, physiology, and stress-related neuropsychiatric disorders. *Eur J Neurosci* **61**, e70111. https://doi.org/10.1111/ejn.70111 (2025).
75. Van Egroo, M., Koshmanova, E., Vandewalle, G. & Jacobs, H. I. L. Importance of the locus coeruleus-norepinephrine system in sleep-wake regulation: Implications for aging and Alzheimer's disease. *Sleep Med. Rev.* **62**, 101592. https://doi.org/10.1016/j.smrv.2022.101592 (2022).
76. Correa-Sales, C., Rabin, B. C. & Maze, M. A hypnotic response to dexmedetomidine, an α2 agonist, is mediated in the locus coerüleus in rats. *Anesthesiology* **76**, 948–952. https://doi.org/10.1097/00000542-199206000-00013 (1992).

77. De Sarro, G. B., Ascioti, C., Froio, F., Libri, V. & Nisticò, G. Evidence that locus coeruleus is the site where clonidine and drugs acting at α1- and α2-adrenoceptors affect sleep and arousal mechanisms. *Br. J. Pharmacol.* **90**, 675–685. https://doi.org/10.1111/j.1476-5381.1987.tb11220.x (1987).
78. Tyler, W. J. et al. Transdermal neuromodulation of noradrenergic activity suppresses psychophysiological and biochemical stress responses in humans. *Sci. Rep.* **5**, 13865. https://doi.org/10.1038/srep13865 (2015).
79. Autret, A., Minz, M., Beillevaire, T., Cathala, H. P. & Schmitt, H. Effect of clonidine on sleep patterns in man. *Eur. J. Clin. Pharmacol.* **12**, 319–322. https://doi.org/10.1007/bf00562444 (1977).
80. Jang, Y. J. et al. Effectiveness of clonidine in child and adolescent sleep disorders. *Psychiatry Investig.* **19**, 738–747. https://doi.org/10.30773/pi.2022.0117 (2022).
81. Jamadarkhana, S. & Gopal, S. Clonidine in adults as a sedative agent in the intensive care unit. *J. Anaesthesiol. Clin. Pharmacol.* **26**, 439–445 (2010).
82. Saunler, C. F. et al. Activation of brain noradrenergic neurons during recovery from halothane anesthesia: Persistence of phasic activation after clonidine. *Anesthesiology* **79**, 1072–1082. https://doi.org/10.1097/00000542-199311000-00026 (1993).
83. Svensson, T. H., Bunney, B. S. & Aghajanian, G. K. Inhibition of both noradrenergic and serotonergic neurons in brain by the α-adrenergic agonist clonidine. *Brain Res.* **92**, 291–306. https://doi.org/10.1016/0006-8993(75)90276-0 (1975).
84. Aston-Jones, G. & Cohen, J. D. An integrative theory of locus coeruleus-norepinephrine function: Adaptive gain and optimal performance. *Annu. Rev. Neurosci.* **28**, 403–450. https://doi.org/10.1146/annurev.neuro.28.061604.135709 (2005).
85. Landau, A. M. et al. Acute vagal nerve stimulation lowers & #x3b1;2 adrenoceptor availability: Possible mechanism of therapeutic action. *Brain Stimul. Basic Transl. Clin. Res. Neuromod.* **8**, 702–707. https://doi.org/10.1016/j.brs.2015.02.003 (2015).
86. Hilakivi, I. The role of β- and α-adrenoceptors in the regulation of the stages of the sleep-waking cycle in the cat. *Brain Res.* **277**, 109–118. https://doi.org/10.1016/0006-8993(83)90912-5 (1983).
87. Shi, G. et al. A rare mutation of β(1)-adrenergic receptor affects sleep/wake behaviors. *Neuron* **103**, 1044-1055.e1047. https://doi.org/10.1016/j.neuron.2019.07.026 (2019).
88. Thayer, J. F. & Lane, R. D. Claude Bernard and the heart–brain connection: Further elaboration of a model of neurovisceral integration. *Neurosci. Biobehav. Rev.* **33**, 81–88. https://doi.org/10.1016/j.neubiorev.2008.08.004 (2009).
89. Billman, G. E. Heart rate variability ? A historical perspective. *Front. Physiol.* https://doi.org/10.3389/fphys.2011.00086 (2011).
90. Reyes Del Paso, G. A., Langewitz, W., Mulder, L. J. M., Van Roon, A. & Duschek, S. The utility of low frequency heart rate variability as an index of sympathetic cardiac tone: A review with emphasis on a reanalysis of previous studies. *Psychophysiology* **50**, 477–487. https://doi.org/10.1111/psyp.12027 (2013).
91. Clancy, J. A. et al. Non-invasive vagus nerve stimulation in healthy humans reduces sympathetic nerve activity. *Brain Stimul.* **7**, 871–877. https://doi.org/10.1016/j.brs.2014.07.031 (2014).
92. Lopez Blanco, C. & Tyler, W. J. The vagus nerve: A cornerstone for mental health and performance optimization in recreation and elite sports. *Front. Psychol.* https://doi.org/10.3389/fpsyg.2025.1639866 (2025).
93. Rajendra Acharya, U., Paul Joseph, K., Kannathal, N. & Lim, S. Heart rate variability: A review. *Med. Biol. Eng. Comput.* **44**, 1031–1051. https://doi.org/10.1007/s11517-006-0119-0 (2006).
94. Sajjadieh, A. et al. The association of sleep duration and quality with heart rate variability and blood pressure. *Tanaffos* **19**, 135–143 (2020).
95. Goldstein, D. S., Bentho, O., Park, M.-Y. & Sharabi, Y. Low-frequency power of heart rate variability is not a measure of cardiac sympathetic tone but may be a measure of modulation of cardiac autonomic outflows by baroreflexes: Low-frequency power of heart rate variability. *Exp. Physiol.* **96**, 1255–1261. https://doi.org/10.1113/expphysiol.2010.056259 (2011).
96. Geng, D., Liu, X., Wang, Y. & Wang, J. The effect of transcutaneous auricular vagus nerve stimulation on HRV in healthy young people. *PLoS ONE* **17**, e0263833. https://doi.org/10.1371/journal.pone.0263833 (2022).
97. Machetanz, K., Berelidze, L., Guggenberger, R. & Gharabaghi, A. Brain-heart interaction during transcutaneous auricular vagus nerve stimulation. *Front. Neurosci.* **15**, 632697. https://doi.org/10.3389/fnins.2021.632697 (2021).
98. Abdullahi, A., Wong, T. W. L. & Ng, S. S. M. Putative role of non-invasive vagus nerve stimulation in cancer pathology and immunotherapy: Can this be a hidden treasure, especially for the elderly?. *Cancer Med.* **12**, 19081–19090. https://doi.org/10.1002/cam4.6466 (2023).
99. Stone, C. A., Kenny, R. A., Nolan, B. & Lawlor, P. G. Autonomic dysfunction in patients with advanced cancer; prevalence, clinical correlates and challenges in assessment. *BMC Palliat Care* **11**, 3. https://doi.org/10.1186/1472-684x-11-3 (2012).
100. Geraldes, V. et al. Cardiovascular dysautonomia in patients with breast cancer. *Open Cardiovasc. Med. J.* https://doi.org/10.2174/18741924-v16-e2206271 (2022).
101. Zhong, X. et al. Increased sympathetic and decreased parasympathetic cardiovascular modulation in normal humans with acute sleep deprivation. *J. Appl. Physiol.* **98**, 2024–2032. https://doi.org/10.1152/japplphysiol.00620.2004 (2005).
102. McEwen, B. S. Sleep deprivation as a neurobiologic and physiologic stressor: Allostasis and allostatic load. *Metabolism* **55**, S20–S23. https://doi.org/10.1016/j.metabol.2006.07.008 (2006).
103. Chouchou, F. et al. Sympathetic overactivity due to sleep fragmentation is associated with elevated diurnal systolic blood pressure in healthy elderly subjects: The PROOF-SYNAPSE study. *Eur. Heart J.* **34**, 2122–2131. https://doi.org/10.1093/eurheartj/eht208 (2013).
104. Fang, H., Tu, S., Sheng, J. & Shao, A. Depression in sleep disturbance: A review on a bidirectional relationship, mechanisms and treatment. *J. Cell Mol. Med.* **23**, 2324–2332. https://doi.org/10.1111/jcmm.14170 (2019).
105. Carreno, F. R. & Frazer, A. Vagal nerve stimulation for treatment-resistant depression. *Neurotherapeutics* **14**, 716–727. https://doi.org/10.1007/s13311-017-0537-8 (2017).
106. Miller, A. H., Ancoli-Israel, S., Bower, J. E., Capuron, L. & Irwin, M. R. Neuroendocrine-immune mechanisms of behavioral comorbidities in patients with cancer. *J. Clin. Oncol.* **26**, 971–982. https://doi.org/10.1200/JCO.2007.10.7805 (2008).
107. Koopman, F. A. et al. Vagus nerve stimulation inhibits cytokine production and attenuates disease severity in rheumatoid arthritis. *Proc. Natl. Acad. Sci. U.S.A.* **113**, 8284–8289. https://doi.org/10.1073/pnas.1605635113 (2016).
108. Mantovani, A., Allavena, P., Sica, A. & Balkwill, F. Cancer-related inflammation. *Nature* **454**, 436–444. https://doi.org/10.1038/nature07205 (2008).
109. Grivennikov, S. I., Greten, F. R. & Karin, M. Immunity, Inflammation, and cancer. *Cell* **140**, 883–899. https://doi.org/10.1016/j.cell.2010.01.025 (2010).
110. Salama, M., Akan, A. & Mueller, M. R. Transcutaneous stimulation of auricular branch of the vagus nerve attenuates the acute inflammatory response after lung lobectomy. *World J. Surg.* **44**, 3167–3174. https://doi.org/10.1007/s00268-020-05543-w (2020).
111. Go, Y.-Y., Ju, W.-M., Lee, C.-M., Chae, S.-W. & Song, J.-J. Different transcutaneous auricular vagus nerve stimulation parameters modulate the anti-inflammatory effects on lipopolysaccharide-induced acute inflammation in mice. *Biomedicines* **10**, 247 (2022).
112. Bretherton, B. et al. Effects of transcutaneous vagus nerve stimulation in individuals aged 55 years or above: Potential benefits of daily stimulation. *Aging* **11**, 4836–4857. https://doi.org/10.18632/aging.102074 (2019).
113. Gidron, Y., De Couck, M. & De Greve, J. If you have an active vagus nerve, cancer stage may no longer be important. *J. Biol. Regul. Homeost. Agents* **28**, 195–201 (2014).
114. Mao, Y. et al. Effects of sub-threshold transcutaneous auricular vagus nerve stimulation on cingulate cortex and insula resting-state functional connectivity. *Front. Hum. Neurosci.* **16**, 862443. https://doi.org/10.3389/fnhum.2022.862443 (2022).
115. Badran, B. W. et al. Transcutaneous auricular vagus nerve stimulation-paired rehabilitation for oromotor feeding problems in newborns: An open-label pilot study. *Front. Hum. Neurosci.* **14**, 77. https://doi.org/10.3389/fnhum.2020.00077 (2020).

116. Badran, B. W. et al. Short trains of transcutaneous auricular vagus nerve stimulation (taVNS) have parameter-specific effects on heart rate. *Brain Stimul.* **11**, 699–708. https://doi.org/10.1016/j.brs.2018.04.004 (2018).
117. Badran, B. W. et al. Laboratory administration of transcutaneous auricular vagus nerve stimulation (taVNS): Technique, targeting, and considerations. *J. Visual. Exp. JoVE* https://doi.org/10.3791/58984 (2019).
118. Bandos, H. et al. Long-term peripheral neuropathy in breast cancer patients treated with adjuvant chemotherapy: NRG oncology/NSABP B-30. *JNCI J. Natl. Cancer Inst.* **110**, djx162. https://doi.org/10.1093/jnci/djx162 (2018).
119. Godiveau, M., Jahanmohan, J. P., Abrial, C. & Durando, X. Chemotherapy-induced peripheral neuropathy in patients with breast cancer treated with taxanes (Review). *Oncol. Lett.* **30**, 508. https://doi.org/10.3892/ol.2025.15254 (2025).
120. Fallon, M. T. Neuropathic pain in cancer. *BJA Br. J. Anaes.* **111**, 105–111. https://doi.org/10.1093/bja/aet208 (2013).
121. Buysse, D. J., Reynolds, C. F. 3rd., Monk, T. H., Berman, S. R. & Kupfer, D. J. The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. *Psychiatry Res.* **28**, 193–213. https://doi.org/10.1016/0165-1781(89)90047-4 (1989).
122. Morin, C. M., Belleville, G., Bélanger, L. & Ivers, H. The Insomnia Severity Index: Psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep* **34**, 601–608. https://doi.org/10.1093/sleep/34.5.601 (2011).
123. Cella, D. et al. The Patient-Reported Outcomes Measurement Information System (PROMIS): Progress of an NIH Roadmap cooperative group during its first two years. *Med. Care* **45**, S3-s11. https://doi.org/10.1097/01.mlr.0000258615.42478.55 (2007).
124. Spitzer, R. L., Kroenke, K., Williams, J. B. & Löwe, B. A brief measure for assessing generalized anxiety disorder: The GAD-7. *Arch. Intern. Med.* **166**, 1092–1097. https://doi.org/10.1001/archinte.166.10.1092 (2006).
125. Kroenke, K., Spitzer, R. L. & Williams, J. B. The PHQ-9: Validity of a brief depression severity measure. *J. Gen. Intern. Med.* **16**, 606–613. https://doi.org/10.1046/j.1525-1497.2001.016009606.x (2001).
126. Okuyama, T. et al. Development and validation of the cancer fatigue scale: A brief, three-dimensional, self-rating scale for assessment of fatigue in cancer patients. *J. Pain Symptom Manage.* **19**, 5–14. https://doi.org/10.1016/S0885-3924(99)00138-4 (2000).

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Author contributions

WJT, MD, and AE conceived and designed the study. MD and AE conducted the study and acquired data. WJT, MD, and AE analyzed the data, interpreted the observations, and wrote the manuscript.

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Declarations

Competing interests

WJT is a co-founder of IST, LLC and an inventor and co-inventor on neuromodulation methods and devices for treating various disorders. All other authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Additional information

Correspondence and requests for materials should be addressed to W.J.T.

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