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Patient-reported changes in hot flash-related interference and quality of life after venlafaxine in breast cancer patients receiving tamoxifen: a prospective single-arm secondary analysis

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Abstract

Purpose

Hot flashes during tamoxifen (TAM) therapy can compromise quality of life (QOL) and adherence. We evaluated whether venlafaxine treatment was associated with changes in hot flash-related daily interference and QOL in breast cancer patients with TAM-associated hot flashes.

Methods

In this prospective single-arm trial, women receiving TAM with moderate-to-severe hot flashes received venlafaxine for 4 weeks. Patient-reported outcomes (PROs) were assessed at baseline and Week 4 using the Hot Flash-Related Daily Interference Scale (HFRDIS), EORTC QLQ-C30, Hospital Anxiety and Depression Scale (HADS), and Pittsburgh Sleep Quality Index (PSQI). This prespecified secondary analysis evaluated PRO endpoints that were collected as part of the HOFLA-V protocol and included preplanned exploratory subgroup analyses by baseline symptom severity. Changes were evaluated with the Wilcoxon signed-rank test; Hodges-Lehmann estimates were calculated for QLQ-C30 domains. All analyses were exploratory and no adjustment for multiplicity was applied.

Results

Seventeen patients completed the 4-week treatment and were included in the analysis. HFRDIS total scores decreased significantly (median 25 to 14; P = 0.004), indicating reduced interference of hot flashes with daily activities. In exploratory QLQ-C30 analyses, emotional functioning, cognitive functioning, social functioning, and global health status/QOL improved, while fatigue decreased. HADS-Anxiety and HADS-Depression scores decreased in exploratory analyses, whereas PSQI scores did not change significantly. Exploratory subgroup analyses suggested larger numerical improvements among patients with greater baseline symptom burden, but these findings were descriptive because of the small sample sizes.

Conclusion

Venlafaxine treatment was associated with reduced hot flash-related interference and favorable changes in several patient-reported QOL domains in breast cancer patients receiving TAM. These findings are exploratory and should be confirmed in controlled studies. Integrating systematic PRO monitoring into routine care may inform timely supportive interventions to optimize endocrine therapy tolerability and adherence.

Trial registration

Japan Registry of Clinical Trials (jRCT), jRCTs031220435, registered on 4 November 2022.

Introduction

Adjuvant endocrine therapy for hormone receptor-positive breast cancer reduces the risk of recurrence; however, treatment-related adverse events remain an important clinical challenge. Hot flashes are particularly common among patients receiving tamoxifen (TAM), especially in premenopausal women and in those receiving concomitant ovarian suppression. Adverse events associated with endocrine therapy are diverse and it has been noted that physician-based assessments alone may not fully capture patient burden. Therefore, to manage hot flashes, among other symptoms, it is essential to incorporate quality of life (QOL) assessments based on patient-reported outcomes (PROs) [1] since recent studies using PROs suggest that hot flashes are associated with decreased adherence to endocrine therapy [1]. Furthermore, a longitudinal study of postmenopausal women receiving adjuvant endocrine therapy for breast cancer reported that patients with higher symptom burdens, including vasomotor symptoms such as hot flashes and psychological symptoms, demonstrated significantly lower endocrine therapy adherence. In that study, each additional vasomotor symptom was associated with an approximately 2-percentage-point reduction in adherence [2]. In addition, breast cancer survivors experiencing severe hot flashes have been shown to report significantly greater mood disturbances and negative effects compared to those with no or mild symptoms. They also experience greater impairment in daily activities, including sleep quality, concentration, and sexual function, resulting in significantly poorer overall QOL [3]. Taken together, these findings suggest that, in order to support adherence to adjuvant endocrine therapy for breast cancer, therapeutic efficacy must be paired with appropriate management of treatment-related adverse events to maintain or improve QOL.

Venlafaxine, a serotonin-norepinephrine reuptake inhibitor (SNRI), is a strongly recommended non-hormonal pharmacologic treatment for hot flashes [4]. Previous studies in Western populations have demonstrated that venlafaxine is effective in reducing vasomotor symptoms in both menopausal women and breast cancer survivors experiencing treatment-related hot flashes [5, 6]. In addition to improving vasomotor symptoms, the pharmacological properties of venlafaxine as an SNRI suggest potential benefits for psychological symptoms, such as anxiety and depression, as well as for sleep disturbances. Indeed, previous studies have suggested that venlafaxine may improve these symptoms alongside reductions in hot flashes [6, 7]. Although several studies have reported associations between improvement in hot flashes and QOL [5, 6, 8], relatively few have comprehensively evaluated related outcomes (e.g., psychological symptoms and sleep disturbances). Furthermore, among patients receiving concomitant luteinizing hormone-releasing hormone agonists (LHRHa), abrupt endocrine changes may exacerbate menopausal-like symptoms, including hot flashes [9]. Despite these clinical challenges, prospective studies evaluating the impact of hot flash treatment on QOL in premenopausal breast cancer patients remain limited, especially those focusing on Asian populations. Moreover, while treatment effects for hot flashes have traditionally been evaluated using PROs that capture symptom frequency and severity (plus impacts on QOL and daily functioning), the selection and weighting of these outcome measures vary across studies. Consequently, the extent to which improvements in hot flash

symptoms translate into broader benefits for patient daily lives and psychological well-being remains incompletely understood.

The primary analysis of the HOFLA-V study demonstrated that venlafaxine reduced hot flash scores and did not show clinically meaningful effects on TAM or active metabolite concentrations. The present report represents a prespecified secondary analysis of that prospective interventional clinical trial and focuses on patient-centered outcomes. Specifically, we evaluated whether venlafaxine treatment was associated with changes in hot flash-related daily interference, health-related QOL, psychological symptoms, and sleep quality in breast cancer patients experiencing endocrine therapy-related hot flashes. Notably, the study population included a substantial proportion of premenopausal patients receiving concomitant LHRHa.

Methods

Trial design

The present study represents a prespecified secondary analysis of the HOFLA-V study focusing on PROs related to hot flash interference and QOL. The trial design and methodology of the HOFLA-V study have been described in detail in our previous report presenting the primary analysis of this study [10]. Briefly, this was a prospective single-arm study evaluating the effect of venlafaxine on TAM-associated hot flashes. The primary analysis focused on hot flash score reduction, pharmacokinetic safety, CYP2D6-related venlafaxine exposure, and adverse events. The present analysis extends those findings by evaluating PRO endpoints collected at baseline and Week 4. The trial was conducted between November 2022 and June 2025 at the University of Tsukuba Hospital in Japan and was registered in the Japan Registry of Clinical Trials (jRCTs031220435) on 4 November 2022. The study was conducted in accordance with the Declaration of Helsinki and written, informed consent was obtained from all participants.

Inclusion criteria

Briefly, eligible patients were adult women with hormone receptor-positive primary breast cancer (Stage I-IIIC) who were receiving adjuvant TAM therapy after surgery and experiencing troublesome hot flashes (≥ 14 episodes per week). Patients aged between 18 and 60 years with an Eastern Cooperative Oncology Group performance status of 0–1 were eligible. Concomitant use of an LHRHa was permitted but not required.

Exclusion criteria

Patients were excluded if they had a current or prior diagnosis of major depressive disorder or depression, were receiving treatment for thyroid disease, or had severe renal dysfunction (estimated

glomerular filtration rate < 15 mL/min/1.73 m² or ongoing dialysis) or severe hepatic impairment (serum bilirubin ≥ 2.0 mg/dL, or AST or ALT > 100 U/L). Patients using medications known to interact with venlafaxine or TAM metabolism, including selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors other than the investigational drug, strong or moderate CYP2D6 inhibitors, CYP3A inhibitors or inducers, gabapentinoids, or monoamine oxidase inhibitors, were also excluded. A known hypersensitivity to venlafaxine was an additional exclusion criterion.

Intervention and follow-up

Briefly, baseline assessments were performed prior to treatment initiation, followed by a 4-week venlafaxine administration period and a post-treatment follow-up.

Baseline

Before starting venlafaxine, each participant completed a daily hot flash diary for one week to establish baseline symptom frequency and severity. Patient-reported outcome measures were also obtained at baseline.

Week 1–4

Clinical evaluations by study physicians were conducted at Week 2 (± 3 days) and at the end of the treatment period (Week 4 ± 3 days). At these visits, hot flash symptoms and adverse events were assessed, and dose escalation to 75 mg once daily was permitted from Week 2 onward if symptom control was insufficient and the participant requested it. Adverse events were also monitored weekly using patient-completed hot flash diaries throughout the treatment period. Patient-reported outcome measures were reassessed at the end of Week 4 (± 3 days).

Outcomes

The outcomes for this secondary analysis were changes in PROs from baseline to Week 4. The following validated instruments were used: the Hot Flash-Related Daily Interference Scale (HFRDIS) [11], the EORTC core quality of life questionnaire (QLQ-C30) [12, 13], the Hospital Anxiety and Depression Scale (HADS) [14], and the Pittsburgh Sleep Quality Index (PSQI) [15]. These PRO assessments were specified in the HOFLA-V protocol before completion of the present analysis. Validated Japanese versions of all questionnaires were used. These instruments were selected to comprehensively assess the impact of endocrine therapy-associated hot flashes on daily functioning, overall quality of life, psychological status, and sleep quality.

Adverse events were monitored throughout the treatment period and evaluated according to the Common Terminology Criteria for Adverse Events version 5.0, as described in the primary report [10].

Analysis

No formal sample size calculation was performed specifically for the present PRO analysis, because it was conducted as a prespecified secondary analysis of the parent HOFLA-V study. The parent study enrolled 20 participants, and the present analysis evaluated PRO endpoints collected within that prospective interventional protocol.

The present study represents a prespecified secondary analysis of the HOFLA-V study focusing on PROs related to hot flash interference and quality of life. Changes from baseline to the end of Week 4 were evaluated using the HFRDIS, the QLQ-C30, the HADS, and the PSQI. Changes were defined as absolute differences between Week 4 and baseline values. For the QLQ-C30, scores were interpreted in accordance with the EORTC scoring manual, whereby higher scores indicate better global health status or functioning for the global health status/QoL and functioning scales, but greater symptom burden for symptom scales. Changes from baseline were calculated and presented according to these scale-specific definitions and the direction of change was explicitly described for each domain.

The full analysis set included all participants who received at least one dose of venlafaxine and had baseline patient-reported outcome data. Analyses were performed using available paired data without additional exclusions for missing values.

Because outcome variables were not normally distributed and demonstrated skewness and/or floor effects, paired comparisons between baseline and Week 4 were performed using nonparametric methods, primarily the Wilcoxon signed-rank test. For QLQ-C30 outcomes, the magnitude of change was additionally summarized using the Hodges-Lehmann estimator, with corresponding 95% confidence intervals, to complement statistical testing by providing an estimate of effect size. For HADS and PSQI, which were considered exploratory secondary outcomes, changes from baseline to Week 4 were evaluated in the overall cohort using the Wilcoxon signed-rank test.

In addition, preplanned exploratory subgroup analyses stratified by baseline symptom severity were conducted. For HADS, participants were categorized based on predefined and widely used cutoff values (HADS-A or HADS-D ≥ 8), and results in these subgroups were summarized descriptively without formal statistical testing due to the small sample size. For PSQI, an exploratory analysis restricted to participants with poor sleep quality at baseline (PSQI > 5) was performed using the Wilcoxon signed-rank test.

All analyses were performed using R software (version 4.5.0). All statistical tests were two-tailed and a $P < 0.05$ was considered statistically significant for exploratory purposes. No adjustment for multiplicity was applied because all analyses were secondary and exploratory; therefore, P values should be interpreted as descriptive rather than confirmatory. Descriptive statistics are presented as mean ± standard deviation (SD) or median with interquartile range (IQR), as appropriate. Figures depict data distributions and individual-level changes using box-and-whisker plots with participant-level data points and, where appropriate, individual trajectory plots.

Results

A total of 20 participants were enrolled in the study. Of these, three participants were excluded from the present analysis: two discontinued the study during Week 1 and one was later deemed ineligible after completion of treatment. Accordingly, patient-reported outcome analyses were conducted in the 17 participants who completed the 4-week treatment period and had evaluable paired data. The full analysis set included all participants who received at least one dose of venlafaxine and had baseline patient-reported outcome data. Analyses were performed using available paired data without imputation for missing values. Baseline characteristics of the study population were described in detail in the primary analysis [10].

Hot flash related daily interference scale (HFRDIS)

Hot flash-related daily interference, as assessed by the HFRDIS, was significantly reduced after 4 weeks of venlafaxine treatment. The HFRDIS total score decreased from baseline to Week 4 (baseline: mean 29.9, SD 15.5, median 25.0, IQR 21.0 to 39.0; Week 4: mean 17.0, SD 14.0, median 14.0, IQR 9.0 to 20.0), and the within-participant reduction was statistically significant (P = 0.004). Individual patient trajectories demonstrated consistent improvement, with most participants showing lower HFRDIS scores at Week 4 compared with baseline (Fig. 1).

EORTC core quality-of-life questionnaire (QLQ-C30)

Changes in health-related quality of life were evaluated using the QLQ-C30. In exploratory analyses, improvements from baseline to Week 4 were observed in fatigue, emotional functioning, cognitive functioning, social functioning, and global health status/QoL. The magnitude of change was estimated using the Hodges-Lehmann estimator, with median changes and corresponding 95% confidence intervals summarized in Table 1.

Table 1
Changes in the QLQ-C30 domain scores from Baseline to Week 4

Domain	Baseline Median [IQR]	Week 4 Median [IQR]	P value (Wilcoxon, Paired)	HL Estimate (95% CI)	Effect Size r
Functioning Domains					
Physical Functioning	100 [93–100]	100 [93–100]	0.072	7.0 (CI not estimable)	0.82
Role Functioning	100 [83–100]	100 [83–100]	0.089	17.0 (17.0 to 17.0)	0.82
Emotional Functioning	83 [67–92]	100 [83–100]	0.004	24.5 (12.5 to 37.5)	0.87
Cognitive Functioning	67 [67–100]	100 [83–100]	0.008	24.5 (16.5 to 33.0)	0.87
Social Functioning	100 [83–100]	100 [100–100]	0.033	25.0 (0.5 to 33.5)	0.80
Global Health Status/QOL	67 [50–83]	75 [67–83]	0.023	20.5 (4.0 to 33.0)	0.68
Symptom Domains					
Fatigue	33 [22–44]	22 [11–33]	0.006	-17.0 (-23.0 to -11.0)	0.78
Nausea and Vomiting	0 [0–0]	0 [0–0]	1.00	0.0 (0.0 to 0.0)	0.00
Pain	0 [0–33]	0 [0–17]	0.05	-24.5 (-41.5 to 0.0)	0.73
Dyspnea	0 [0–33]	0 [0–0]	0.089	-33.0 (-33.0 to -33.0)	0.82
Insomnia	33 [0–67]	33 [0–33]	0.107	-34.0 (-67.0 to -0.5)	0.50
Appetite Loss	0 [0–0]	0 [0–0]	0.773	5.7(33.0 to 33.0)	-0.15
Constipation	33 [0–33]	33 [33–67]	0.069	33.0 (-0.5 to 50.0)	-0.59
Diarrhea	12 [0–33]	6 [0–0]	0.371	-50.0 (-50.0 to -50.0)	0.63
Financial Difficulties	0 [0–33]	0 [0–0]	0.089	-33.0 (-33.0 to -33.0)	0.82

Scores were calculated according to the QLQ-C30 scoring manual (0-100 scale). For functioning scales and global health status/QoL, higher scores indicate better functioning or quality of life, whereas, for symptom scales, higher scores indicate greater symptom burden. Values are presented as median [interquartile range].The Hodges-Lehmann estimator was used to estimate the median change from baseline with 95% confidence intervals. For Physical functioning, the 95% CI was not estimable due to a high number of ties (no change in 13/17 pairs).

Hospital anxiety and depression scale (HADS)

HADS-Anxiety scores decreased from baseline to Week 4 (baseline: mean 5.1, SD 4.3, median 4.0, IQR 2.0 to 6.0; Week 4: mean 2.8, SD 2.1, median 3.0, IQR 2.0 to 4.0), with an exploratory within-participant P value of 0.009. HADS-Depression scores also decreased from baseline to Week 4 (baseline: mean 5.0, SD 3.3, median 5.0, IQR 3.0 to 5.0; Week 4: mean 3.6, SD 2.7, median 3.0, IQR 1.0 to 5.0; exploratory P = 0.012) (Fig. 2). These findings should be interpreted cautiously given the small sample size and lack of multiplicity adjustment.

Individual paired plots demonstrated substantial inter-individual variability in changes in HADS scores, with larger numerical improvements observed among participants with higher baseline scores.

Pittsburgh sleep quality index (PSQI)

PSQI global scores showed a modest numerical decrease from baseline to Week 4 (baseline: mean 8.5, SD 3.2, median 8.0, IQR 7.0 to 11.0; Week 4: mean 7.8, SD 3.4, median 8.0, IQR 5.0 to 9.0); however, the within-participant change did not reach statistical significance (P = 0.283). Visualization of paired individual trajectories demonstrated substantial inter-individual variability in PSQI changes (Fig. 3).

Subgroup analysis

Exploratory subgroup analyses were conducted according to baseline symptom severity, as prespecified in the study protocol. Given the exploratory design and the small sample sizes in most subgroups, results are summarized descriptively.

Among participants with elevated anxiety symptoms at baseline (HADS-Anxiety ≥ 8, n = 3), all individuals showed a reduction in HADS-Anxiety scores from baseline to Week 4 (baseline mean 13.0, Week 4 mean 5.0; mean change − 8.0). Similarly, among those with elevated depressive symptoms at baseline (HADS-Depression ≥ 8, n = 2), HADS-Depression scores decreased over the study period (baseline mean 12.5, Week 4 mean 8.5; mean change − 4.0). Due to the very small number of participants, no formal statistical testing was performed and these findings should be interpreted cautiously. Individual scores are presented in Table 2.

Table 2
Individual HADS scores in participants with elevated baseline symptoms (HADS ≥ 8)

Subgroup	Patient	Baseline	Week 4	Change
HADS-Anxiety ≥ 8	A1	16	8	-8
	A2	10	3	-7
	A3	13	4	-9
HADS-Depression ≥ 8	D1	15	9	-6
	D2	10	8	-2

In an exploratory analysis restricted to participants with poor sleep quality at baseline (PSQI > 5, n = 13), PSQI global scores showed a modest decrease from baseline to Week 4.

Discussion

In this prespecified secondary analysis of a prospective single-arm trial, four weeks of venlafaxine treatment was associated with reduced hot flash-related interference with daily life, as assessed by HFRDIS. Exploratory improvements were also observed in several domains of the QLQ-C30, including emotional functioning, cognitive functioning, social functioning, global health status/QOL, and fatigue. Psychological and sleep-related outcomes showed more heterogeneous responses, with exploratory reductions in HADS scores but no significant change in PSQI global scores. The primary analysis of the HOFLA-V study established the reduction in hot flash scores and pharmacokinetic safety; the present analysis adds patient-centered information by examining whether symptom improvement was accompanied by changes in daily-life interference and QOL. Previous studies evaluating venlafaxine for hot flashes associated with adjuvant endocrine therapy in breast cancer have primarily assessed treatment effects using the frequency and severity of hot flashes recorded in patient diaries [6, 8]. In contrast, relatively few studies have directly evaluated the impact of hot flashes on daily life and quality of life using PROs. In the present study, hot flash-related interference with daily activities was assessed using HFRDIS [11]. In addition, by incorporating the QLQ-C30, we were able to comprehensively examine how symptom burden is reflected in important domains of quality of life.

The improvement in HFRDIS observed in this study was consistent with previous reports, even considering differences in study populations and treatment duration [7]. In the interpretation of QLQ-C30 scores, a change of approximately 10 points is generally considered a benchmark for minimal clinically important difference (MCID) in breast cancer patients [16–18]. In the domains that showed statistically significant differences in this study, the magnitude of change based on the Hodges-Lehmann estimates substantially exceeded this threshold, suggesting clinically meaningful improvements. Moreover, even in domains that did not reach statistical significance, some showed improvements exceeding 10 points. Given the exploratory nature of this small single-arm study, these findings require further confirmation;

however, they suggest that improvements in hot flash symptoms may extend to multiple aspects of QOL. Although there are very few studies directly comparable to ours, these results indicate that alleviation of hot flash symptoms may translate into reduced interference with daily life and highlight the clinical relevance of supportive care interventions targeting symptom burden associated with endocrine therapy. Hot flashes and QOL impairment related to endocrine therapy remain important unmet clinical needs. In the present study, PRO-based assessments were implemented in a relatively simple manner and were able to capture changes in symptoms over a short period. These findings support the importance of using PROs to identify symptoms early and to consider timely supportive care interventions.

In contrast, outcomes related to psychological status and sleep showed more variable responses. Exploratory reductions were observed in both HADS-Anxiety and HADS-Depression scores, whereas PSQI global scores did not change significantly and individual trajectories varied considerably. Although hot flashes have been reported to be associated with anxiety and sleep disturbances [3, 19, 20], these symptoms are known to be influenced by multiple factors, including psychological background and lifestyle factors [8]. The findings of the present study should therefore be interpreted cautiously with regard to effects on psychological and sleep-related outcomes. Rather than indicating a generalized benefit in these domains, the results may be better viewed as exploratory findings that highlight the value of using PROs to broadly assess symptom burden.

This study has several limitations. First, this was a single-center, prospective single-arm exploratory study with a limited sample size. The present secondary analysis included 17 patients who completed the treatment and the statistical power may therefore have been insufficient to detect smaller effects. Second, the observation period was relatively short at four weeks and different results might have been observed with longer intervention or follow-up, particularly for outcomes related to psychological symptoms and sleep quality. Third, because this was a single-arm study without a control group, the observed changes may have been influenced by placebo effects or regression to the mean and caution is warranted when interpreting treatment effects. Fourth, multiple PRO domains were evaluated without multiplicity adjustment; therefore, P values should be interpreted descriptively and the findings should not be considered confirmatory. Nevertheless, improvements were observed across several patient-centered measures and the direction of effect was generally concordant. These findings provide supportive, hypothesis-generating evidence that venlafaxine may alleviate symptom burden associated with endocrine therapy-related hot flashes.

In summary, by using questionnaires capable of evaluating the impact of symptoms on daily life and quality of life, this study captured the burden associated with hot flashes from the patient perspective and provided findings that complement the primary HOFLA-V report. Although constrained by the single-arm design, small sample size, short follow-up, and lack of multiplicity adjustment, favorable changes were observed across several PROs. The study population included a substantial proportion of premenopausal breast cancer patients receiving concomitant LHRHa, a population for whom evidence regarding supportive care interventions for hot flashes remains limited [9, 21]. These findings contribute to a better understanding of how endocrine therapy-related hot flashes affect the daily life quality of

patients and support further evaluation of PRO-guided supportive care. Future studies, including randomized, controlled trials and investigations with longer intervention and follow-up periods, are warranted. In addition, combining pharmacologic treatment with sleep-focused interventions, such as sleep hygiene education or behavioral therapy, and conducting larger studies (inclusive of younger patient cohorts) may help to further clarify supportive care strategies for managing hot flashes associated with endocrine therapy.

Declarations

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Competing interests

The authors declare that they have no competing interests.

Author contributions

H.B. conceived the study, and R.S. designed the protocol. R.S., H.B., R.K., T.M., A.S., M.O., S.H., and A.I.-M. were responsible for patient enrollment and clinical management. R.I. and K.S. conducted statistical analyses. All authors reviewed and approved the final version of the manuscript.

Ethics approval

This study was performed in accordance with the principles of the Declaration of Helsinki and was approved by the Certified Review Board of the University of Tsukuba (CRB21-015).

Consent to participate

Written informed consent was obtained from all participants.

Consent to publish

Not applicable.

Data availability statements

The datasets generated and/or analyzed during the current study are not publicly available due to privacy and ethical restrictions but are available from the corresponding author on reasonable request.

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Figures

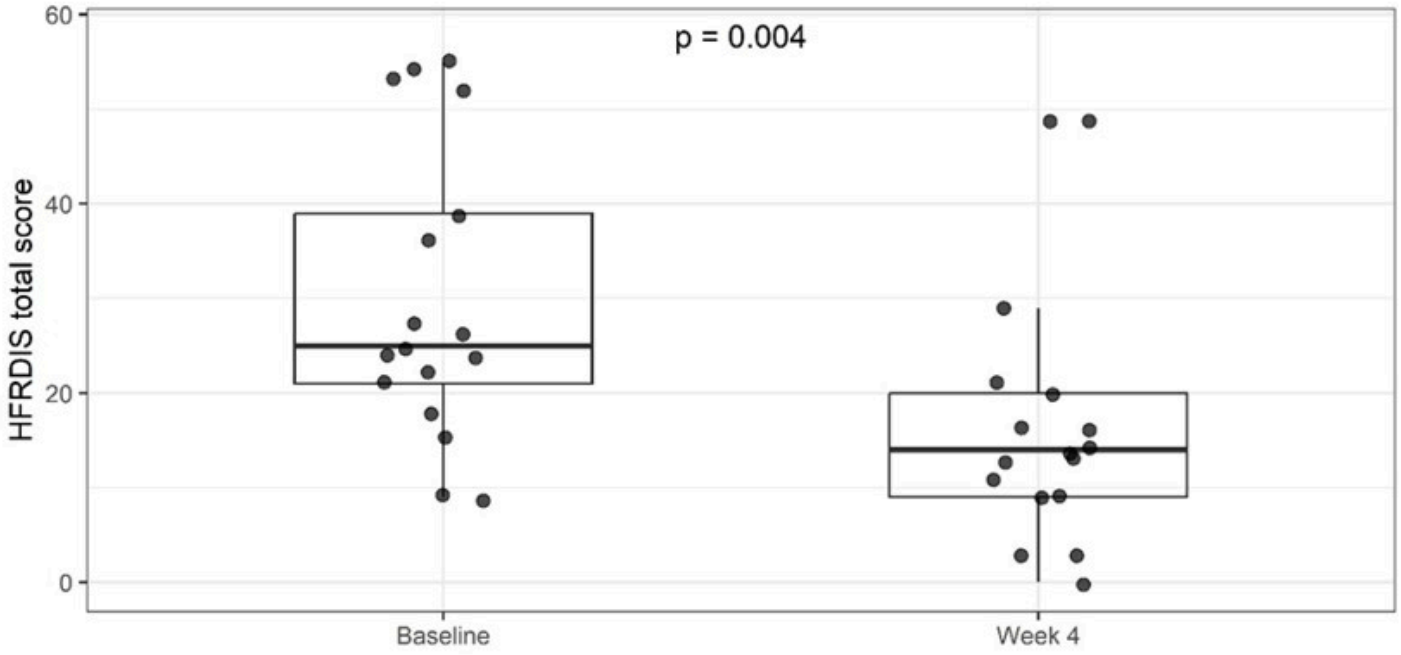


Figure 1

Changes in hot flash-related daily interference from Baseline to Week 4. Boxplots show Hot Flash Related Daily Interference Scale (HFRDIS) total scores at Baseline and Week 4. Boxes indicate the interquartile range (IQR), horizontal lines indicate the median, and individual dots represent participant-level data. Differences between time points were assessed using the Wilcoxon signed-rank test

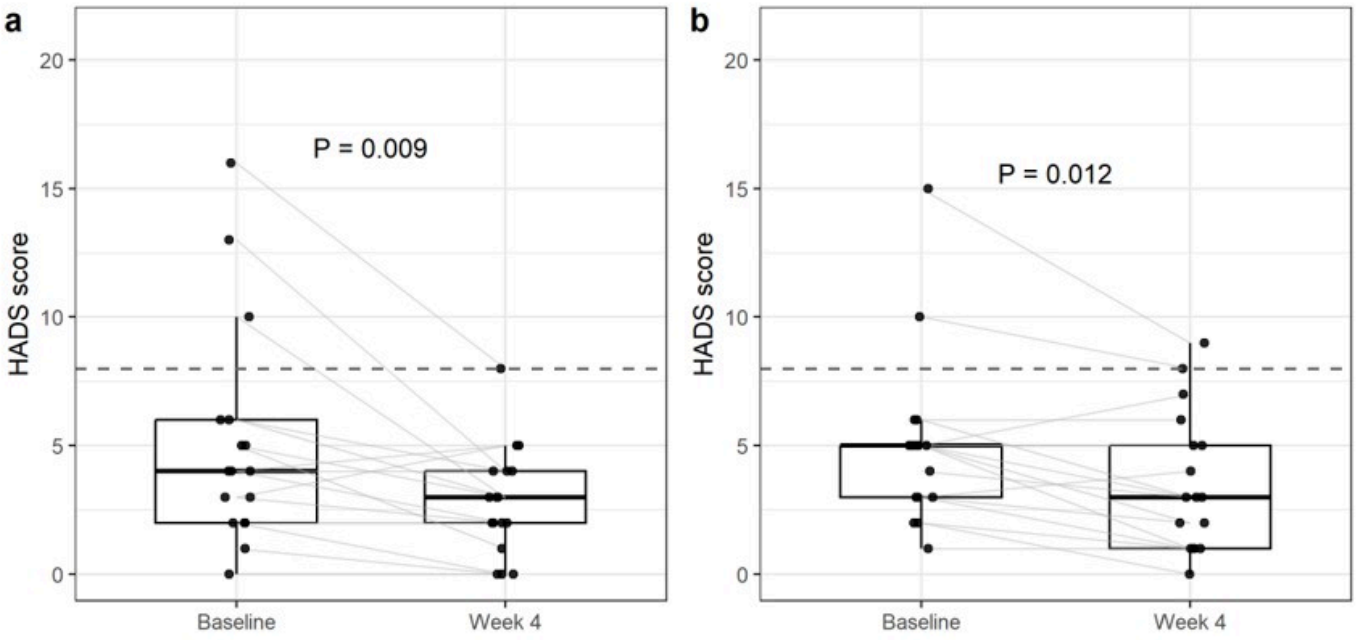


Figure 2

Changes in anxiety and depressive symptoms from Baseline to Week 4. (a) HADS-Anxiety scores and (b) HADS-Depression scores at Baseline and Week 4. Boxplots show the median and interquartile range (IQR), and individual participant trajectories are displayed as paired lines connecting Baseline and Week 4 values. The dashed horizontal line indicates the commonly used HADS cutoff score (≥8), suggestive of clinically relevant anxiety or depressive symptoms. Differences between time points were assessed using the Wilcoxon signed-rank test

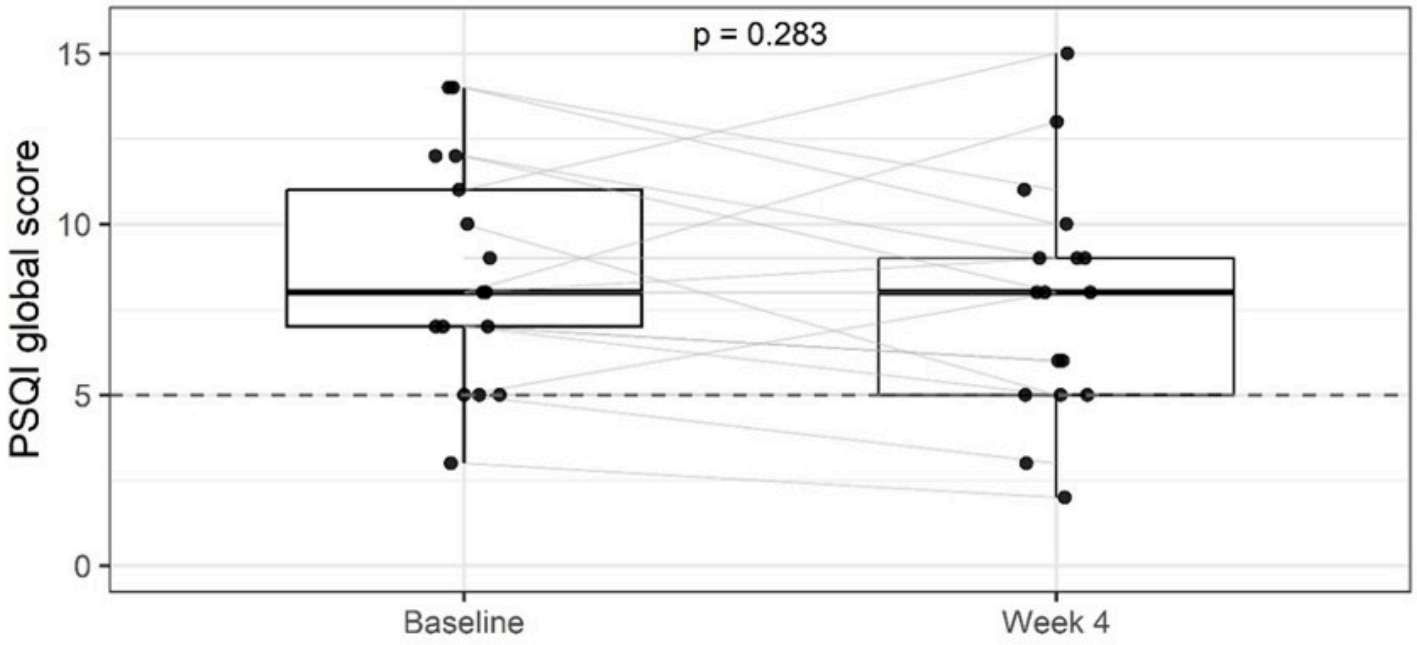


Figure 3

Changes in sleep quality from Baseline to Week 4. Boxplots show Pittsburgh Sleep Quality Index (PSQI) global scores at Baseline and Week 4. Boxes indicate the interquartile range (IQR) and horizontal lines indicate the median. Individual participant trajectories are displayed as paired lines connecting Baseline and Week 4 values. The dashed horizontal line indicates the commonly used PSQI cutoff score (>5), suggestive of poor sleep quality. Differences between time points were assessed using the Wilcoxon signed-rank test