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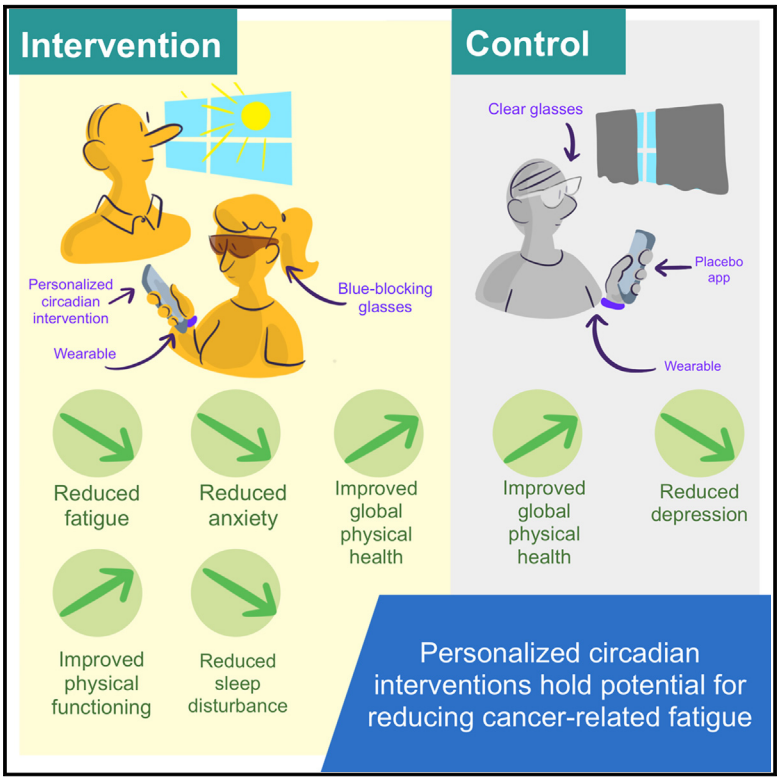
A circadian and app-based personalized lighting intervention for the reduction of cancer-related fatigue

Graphical abstract



Highlights

- We develop a lighting intervention based on wearable-measured circadian rhythms
- Fatigue T-scores do not significantly differ between intervention and control at week 11
- T-scores significantly decrease in intervention, with a significant treatment effect
- Daily fatigue, anxiety, sleep, and physical function improve in the intervention

Authors

Caleb Mayer, Olivia Walch, Walter Dempsey, ..., Muneesh Tewari, Daniel B. Forger, Sung Won Choi

Correspondence

sungchoi@med.umich.edu

In brief

Mayer et al. test the effects of a personalized circadian lighting intervention for the reduction of cancer-related fatigue, developed through wearable data and a mobile application. While fatigue T-scores at study end do not differ between intervention and control, several fatigue and health metrics improve within the intervention arm.

Mayer et al., 2025, Cell Reports Medicine 6, 102001
March 18, 2025
https://doi.org/10.1016/j.xcrm.2025.102001

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A circadian and app-based personalized lighting intervention for the reduction of cancer-related fatigue

Caleb Mayer,[1,2] Olivia Walch,[3,4] Walter Dempsey,[5,6,7] Kevin Hannay,[1,3] Caroline Clingan,[8] Zoe Bowen,[8] Michelle Rozwadowski,[8] Zachery R. Reichert,[9,10] N. Lynn Henry,[9,10] Joshi J. Alumkal,[9,10] Muneesh Tewari,[9,10,11,12] Daniel B. Forger,[1,13,14] and Sung Won Choi[8,10,15,*]

[1]Department of Mathematics, University of Michigan, Ann Arbor, MI 48109, USA
[2]Department of Genetics, Stanford University, Stanford, CA 94305, USA
[3]Arcascope, Arlington, VA 22203, USA
[4]Department of Neurology, University of Michigan, Ann Arbor, MI 48109, USA
[5]Department of Biostatistics, University of Michigan, Ann Arbor, MI 48109, USA
[6]Institute for Social Research, University of Michigan, Ann Arbor, MI 48109, USA
[7]Center for Methodologies for Adapting and Personalizing Prevention, Treatment, and Recovery Services for SUD and HIV (MAPS Center), University of Michigan, Ann Arbor, MI 48109, USA
[8]Department of Pediatrics, University of Michigan, Ann Arbor, MI 48109, USA
[9]Department of Internal Medicine, University of Michigan, Ann Arbor, MI 48109, USA
[10]Rogel Cancer Center, University of Michigan, Ann Arbor, MI 48109, USA
[11]Department of Biomedical Engineering, University of Michigan, Ann Arbor, MI 48109, USA
[12]Center for Computational Medicine and Bioinformatics, University of Michigan, Ann Arbor, MI 48109, USA
[13]Department of Computational Medicine and Bioinformatics, University of Michigan, Ann Arbor, MI 48109, USA
[14]Michigan Institute for Data Science, University of Michigan, Ann Arbor, MI 48109, USA
[15]Lead contact
*Correspondence: sungchoi@med.umich.edu
https://doi.org/10.1016/j.xcrm.2025.102001

SUMMARY

Lighting interventions can mitigate fatigue by promoting circadian rhythmicity. We test whether individualized, wearable-based lighting interventions delivered via a mobile app reduce cancer-related fatigue in a randomized controlled trial with 138 breast cancer, prostate cancer, and hematopoietic stem cell transplant patients. Participants are randomized to tailored lighting intervention or control. The primary endpoint is PROMIS fatigue 4a at trial end, with secondary endpoints including change in daily fatigue, sleep, anxiety, depression, physical function, and overall health. Fatigue T-scores at week 11 do not differ between groups but decrease significantly from week 1 to week 11 (3.07 points, $p = 0.001$) in the intervention group, with a significant final-week treatment effect ($p = 0.014$). Daily fatigue, anxiety, sleep disturbance, and physical function improve within intervention. Further studies are needed to see if these results generalize in broader cancer care. The trial is registered at ClinicalTrials.gov (trial registration number: NCT04827446).

INTRODUCTION

Fatigue is a common symptom for individuals with cancer, with heightened fatigue levels arising during treatment and after remission. This can be a challenging and debilitating condition, impacting quality of life and impairing the ability to complete activities associated with daily living, such as cleaning, preparing food, and socializing.[1–3] Factors that contribute to these heightened fatigue levels include the direct impact of cancer, side effects of treatment, and psychological repercussions of the disease. While the specific mechanisms that generate cancer-related fatigue have yet to be fully understood, they likely involve disruptions to the circadian rhythm.[4,5]

Circadian rhythms are endogenously generated, approximately 24-h signals that affect a range of physiological processes. The core circadian pacemaker in the suprachiasmatic nucleus (SCN) synchronizes peripheral clocks throughout the body and becomes entrained to the environment via lighting and other external information. Disruption to the circadian system can lead to detrimental health outcomes; for example, misalignment between circadian and environmental timing has been associated with sleep disruption, metabolic issues, and mood disorders.[6,7] Furthermore, disturbances to the circadian system have been implicated in relation to cancer-related fatigue and quality of life in cancer patients.[8,9] Fatigue and circadian disruption worsened over six chemotherapy sessions in female breast cancer patients.[8] Additionally, lower levels of activity and increased nighttime awakenings have been associated with heightened cancer-related fatigue.[9] Blunted circadian amplitude and alterations to the mesor, as measured from

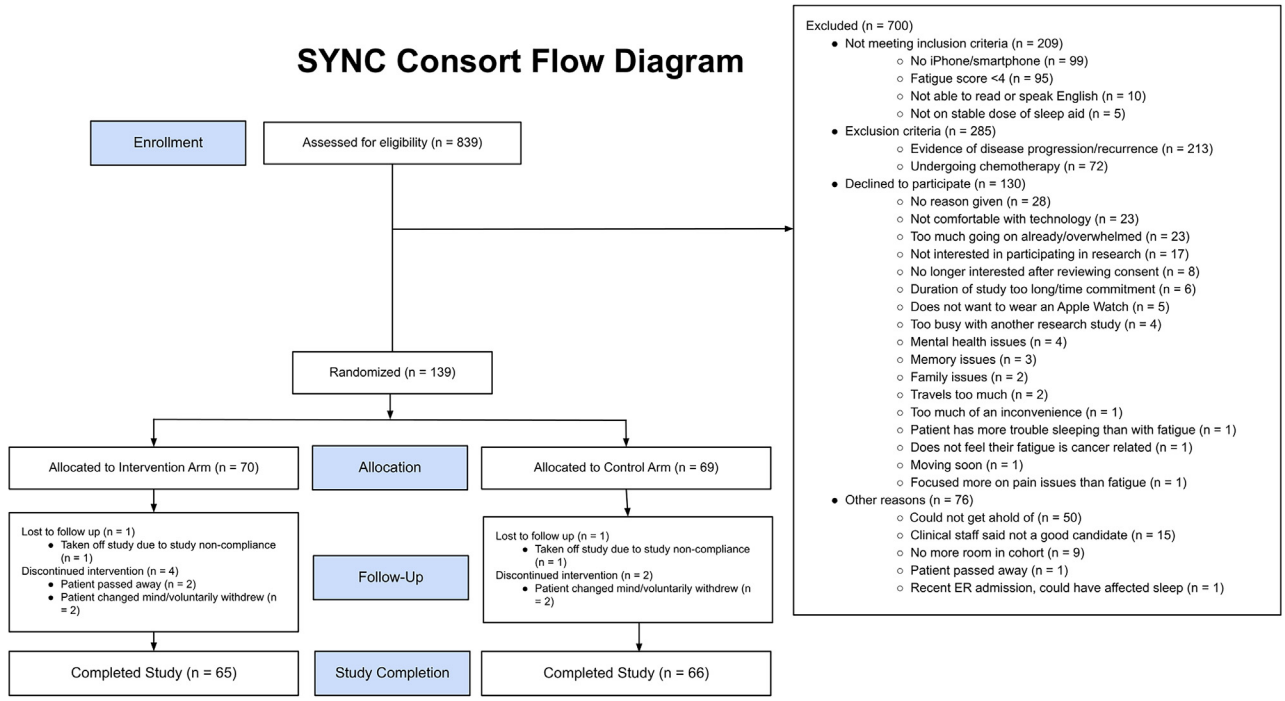

Figure 1. CONSORT flow diagram showing the study recruitment and reasons for exclusion

Completing the study was defined as submitting some amount of survey data, not voluntarily withdrawing, and not being removed by research staff.

activity patterns, were linked to increased fatigue in a cohort of breast cancer patients.[10]

Lighting interventions are a promising, low-cost, and low-burden tool to mitigate disturbances to the circadian clock and promote strong rhythmicity in cancer populations. A preliminary study has shown that 30 min of morning bright white light (BWL)—but not dim red light (DRL)—was associated with a reduction of fatigue in cancer patients from several populations.[11] Similarly, exposure to BWL has been connected to robust circadian rhythmicity in women undergoing chemotherapy for breast cancer[12] and has been shown to prevent worsening of fatigue during chemotherapy.[13] In a population of patients with cancer-related fatigue, bright light exposure in the morning was associated with improvements in sleep quality and efficiency.[14]

While these studies demonstrate the impact of lighting interventions for cancer patients, this previous work provided one-size-fits-all interventions. Lighting instructions given at a fixed time in the morning or after wake do not account for interindividual differences in circadian timing, a timing system, which shows significant interindividual variability and can be quite different from sleep-derived metrics.[15,16] Accounting for these personal differences may be particularly relevant in populations with disrupted rhythms, like cancer patients.[17,18] Previous work has shown that circadian phase, amplitude, and other physiological metrics can be accurately and efficiently determined from mathematical models applied to consumer-grade wearable data.[16,19,20] Indeed, our group has developed algorithms for phase and amplitude prediction from wearable measurements and shown that these predictions largely align with findings from controlled laboratory settings.[16,19,20] The development of these models and algorithms enables personalized lighting interventions based on the circadian rhythm of an individual, as predicted by the models applied to the wearable data.

On the basis of these observations, we conducted a randomized controlled trial (RCT) of an app-based and circadian-rhythm-informed lighting intervention on self-reported fatigue. Here, we report the findings from the prospective RCT in three cancer populations (breast, prostate, and hematopoietic cell transplant [HCT]). We hypothesized that the personalized and circadian-informed lighting interventions would reduce self-reported fatigue in cancer patients on stable systemic therapy, as assessed by the primary outcome of weekly Patient-Reported Outcomes Measurement Information System (PROMIS) 4-item fatigue and the secondary outcome of daily fatigue at the end of the study.

RESULTS

Change from baseline in daily and weekly fatigue

Figure 1 shows the study recruitment overview and reasons for exclusion, and Table 1 displays the baseline demographic and characteristic information. The weekly fatigue T-scores, including missing data and without imputation, were considered. The intervention group completed 62/65 (95.38%) of the weekly fatigue surveys at week 1 and 54/65 (83.08%) at week 11, while the control group completed 62/66 (93.94%) at week 1 and 59/66 (89.39%) at week 11; see Table S2 for further information on the amount of missingness by time point. Similarly, available

Table 1. Baseline demographic and characteristic information by arm and cancer population

	Intervention (Int)				Control (Con)				
	Breast	Prostate	HSCT	Total Int	Breast	Prostate	HSCT	Total Con	Total
Count	23	21	21	65	23	21	22	66	131
Mean (range) age, years	52.09 (33–72)	70.24 (50–87)	54.95 (19–74)	58.88 (19–87)	57.00 (41–74)	67.24 (51–76)	53.91 (25–73)	59.23 (25–76)	59.05 (19–87)
Gender									
Female	23	0	12	35	23	0	12	35	70
Male	0	21	9	30	0	21	10	31	61
Race									
Asian	1	0	0	1	0	1	0	1	2
Black	1	0	1	2	1	1	3	5	7
White	21	20	19	60	21	19	19	59	119
Other/ unknown	0	1	1	2	1	0	0	1	3
Ethnicity									
Hispanic or Latinx	1	1	2	4	0	0	0	0	4
Non-Hispanic or Latinx	22	20	18	60	22	21	21	64	124
Unknown	0	0	1	1	1	0	1	2	3
Sleep aids									
Yes	5	8	7	20	9	8	9	26	46
No	18	13	14	45	14	13	13	40	85
Alcohol (number of alcoholic beverages consumed in past week)									
0 drinks	16	10	14	40	10	7	10	27	67
1–2 drinks	6	5	4	15	10	6	8	24	39
3–6 drinks	1	4	3	8	2	5	4	11	19
7–12 drinks	0	1	0	1	0	2	0	2	3
>12 drinks	0	1	0	1	1	1	0	2	3

Age, gender, race, and ethnicity were collected at baseline, and sleep aid and alcohol usage were extracted from the first available weekly survey (see STAR Methods: data analysis: further details for a full list of the possible sleep aids). Number of participants (of the specific cancer population) is shown.

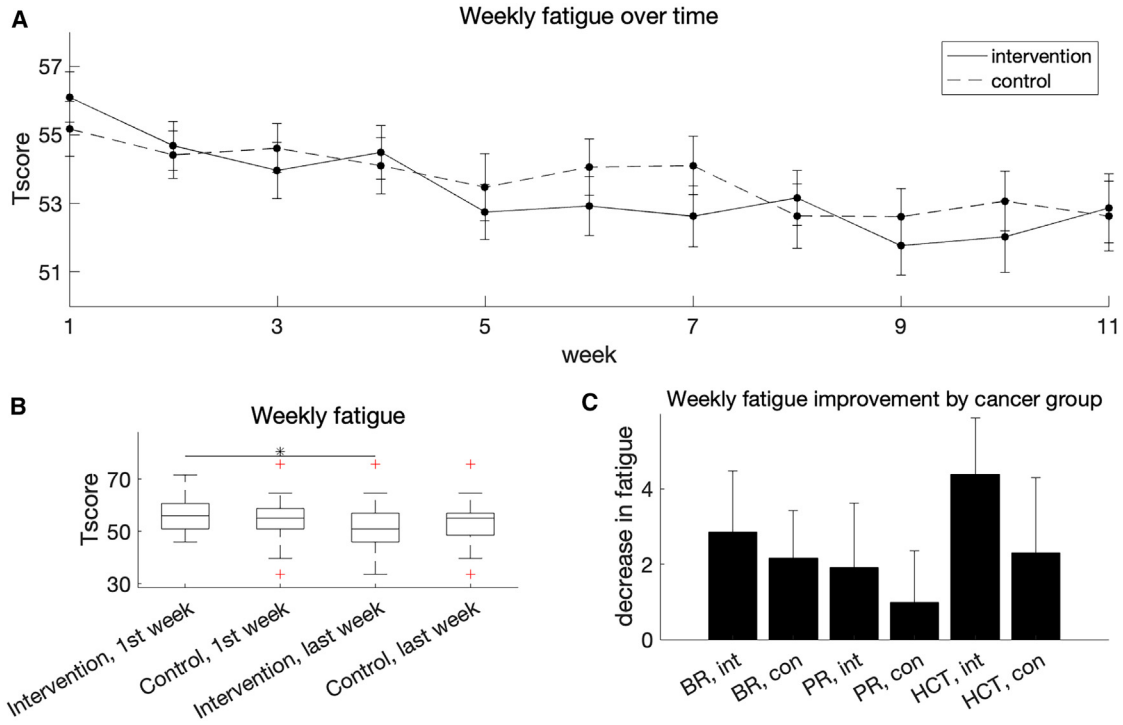

Figure 2. Weekly 4-item fatigue survey results

(A) Mean weekly fatigue T-scores from week 1 to week 11. The control group is shown as a dashed line, and the intervention group as a solid line. Data are represented as mean, and bars denote the standard error of the mean (SEM).

(B) Mean weekly fatigue T-scores, with results from the first week in the first two boxplots and the last (11th) week in the final two boxplots. Statistically significant differences (p value < 0.05) are denoted with a line and *. The median in each boxplot is denoted with a horizontal line, the edges in the box signify the 25th and 75th percentiles, and outliers are red plus signs.

(C) Mean change in weekly fatigue from week 1 to week 11, divided by cancer population (BR, breast cancer; PR, prostate cancer; and HCT, hematopoietic cell transplant) and intervention (int) vs. control (con). Data are represented as mean, and bars denote the SEM.

daily surveys were first averaged by study participant and then by week in this analysis. Using two-tailed t tests, the intervention and control groups did not have significantly different weekly fatigue T-scores in the first week (p value = 0.41) or week 11 (p value = 0.88). The weekly fatigue T-scores decreased from 56.10 (SD = 5.94) to 52.86 (SD = 8.13) for the intervention group from week 1 to week 11 of the trial, a decrease of 3.23 T-score points (p value = 0.015) (Figures 2A and 2B). For the control group, the weekly fatigue T-scores decreased from 55.17 (SD = 6.50) to 52.63 (SD = 8.23) from week 1 to week 11 of the trial, a decrease of 2.54 (p value = 0.062). We divided the change in fatigue by cancer population (Figures 2C and S2A–S2C). Weekly fatigue in the breast cancer population decreased by 2.85 (55.03–52.18) for intervention and by 2.16 (56.08–53.92) for control, that in the prostate cancer population decreased by 1.91 (57.14–55.23) for intervention and 0.99 (55.63–54.63) for control, and that in the HCT population decreased by 4.39 (55.60–51.21) for intervention and 2.31 (52.73–50.43) for control. For daily fatigue, the intervention group decreased by 0.34 from 1.53 (SD = 0.51) to 1.18 (SD = 0.68) from week 1 to week 12 of the trial, while the control group decreased by 0.19 from 1.57 (SD = 0.56) to 1.38 (SD = 0.61) (Figure 3). The groups were not significantly different at the start (p value = 0.66, two-tailed t test) or end (p value = 0.09) of trial, but the intervention group had a significantly lower fatigue at week 12 than at week 1 (p value = 0.002) while the control group did not (p value = 0.07).

Overall, the intervention and control did not significantly differ in daily or weekly fatigue at the end of the trial. However, the intervention group had significantly lower daily and weekly fatigue at the end of the trial than at the beginning of the trial.

Effects of lighting treatment on fatigue through GEEs

Generalized estimating equations (GEEs) were utilized to assess treatment effects over time with the imputed data, adjusting for pre-trial fatigue, age, and gender (see STAR Methods). We observed a significant effect of treatment, pre-trial fatigue, time, treatment by age interaction, and treatment by gender interaction (p values < 0.05) on the weekly fatigue response (Table S3). The estimate of the treatment effect at the final time was −1.7097, with a robust SE of 0.6965 and a robust z of −2.4546. The robust metrics yielded a p value of 0.014 for the treatment effect at the final time (see STAR Methods: Primary GEE model details), demonstrating a significant treatment effect.

Pre- and post-trial PROMIS measures

We restricted the analysis of the pre- and post-PROMIS measures to the complete case scenario of 116 individuals (61 from the intervention group and 55 from the control group)

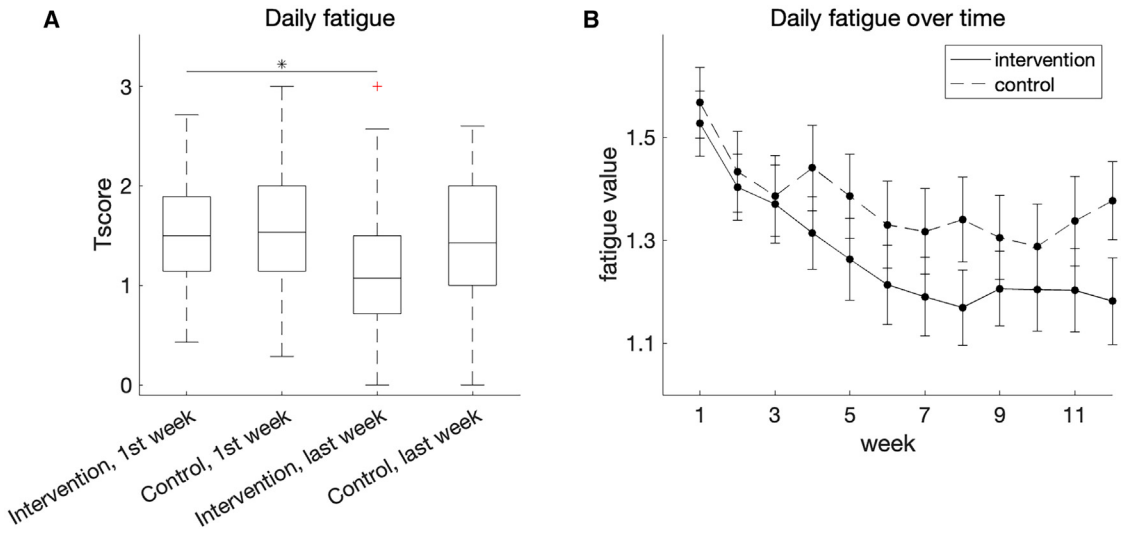

Figure 3. Daily 1-item fatigue survey

Responses options are "Not at all fatigued" (converted to 0), "A little bit fatigued" (converted to 1), "Somewhat fatigued" (converted to 2), and "Very fatigued" (converted to 3).

(A) Daily fatigue for the intervention and control groups, considering surveys from the first week in the first two boxplots and the final (12th) week in the last two boxplots. Statistically significant differences (p value < 0.05, t test) are denoted with a line and *. The median in each boxplot is denoted with a horizontal line, the edges in the box signify the 25th and 75th percentiles, and outliers are given by red plus signs.

(B) Mean daily fatigue value from the first to last week of the study, where the daily surveys were first binned weekly by individual. The control group is shown as a dashed line, and the intervention group as a solid line. Data are represented as mean, and bars denote the SEM.

who completed both a pre- and a post-trial survey. For sleep disturbance, there was no significant difference between the intervention and control groups in post-trial T-scores (p value = 0.86). Intervention had significantly lower post-trial sleep disturbance than pre-trial (decrease of 4.13 T-score points, p value < 0.0001, t test), while control did not (decrease of 1.60, p value = 0.057). The intervention and control groups did not have significantly different anxiety T-scores at post-trial (p value = 0.72). Intervention displayed significantly lower anxiety post-trial than pre-trial (decrease of 2.63, p value = 0.015), while control did not (decrease of 1.25, p value = 0.22). The depression T-scores did not significantly differ between intervention and control at post-trial (p value = 0.47), and they did not differ significantly within intervention from pre- to post-trial (decrease of 1.68, p value = 0.067), although they did within control (decrease of 2.45, p value = 0.0041). For physical function, there were no significant differences between the groups at post-trial (p value = 0.26), but the intervention group significantly increased (by 1.38, p value = 0.017) while control did not (increase of 1.49, p value = 0.079). For the physical health component of global health, there were no significant differences between the groups at post-trial (p value = 0.23), but intervention (increase of 1.34, p value = 0.034) and control (increase of 1.71, p value = 0.018) increased significantly from pre- to post-trial. For global mental health, there were no significant differences between intervention and control at post-trial and no significant changes over time within either arm (Figure 4; Table S1).

Overall, the intervention group significantly decreased in anxiety and sleep disturbance and significantly increased in global physical health and physical function from pre- to post-trial. The control group significantly decreased in depression and significantly improved in global physical health.

Basic mobile app and smartwatch metrics

We examined the lighting recommendation task completion data from the Sync mobile app, based on the participant recording in the study app if they completed a particular lighting recommendation. Participants often did not record if they had completed a lighting task: the percentage of non-control tasks marked as completed ranged from 0% to 64.93% (mean = 20.65%, SD = 10.68%). However, we note that a lack of marking a survey as complete does not mean that the recommendation was not followed. Furthermore, individuals still marked many lighting recommendation tasks as complete: an average of 171.30 (SD = 91.61) non-control tasks were completed per individual. Of these tasks, an average of 37.20 corresponded to exposure to darkness, 35.06 to dim light, 60.52 to moderate light, 8.01 to bright light, and 30.52 to very bright light over the 84-day study. Individuals also did not only complete these tasks at the beginning of the study: 65.33 (SD = 23.26) unique dates exist for task completion per individual (over the 84-day study), demonstrating an overall level of engagement with the app throughout the intervention period.

We studied the simple wearable metrics of total daily steps and average daily heart rate over the 84 days of the study. In terms of missing data for these daily wearable metrics, step recordings were present on 96.45% (10,613/11,004) of the days between day 1 and day 84 for each study participant. Similarly, heart rate recordings were present on 88.88% (9,780/11,004) of the days in the specified range. Taking daily average

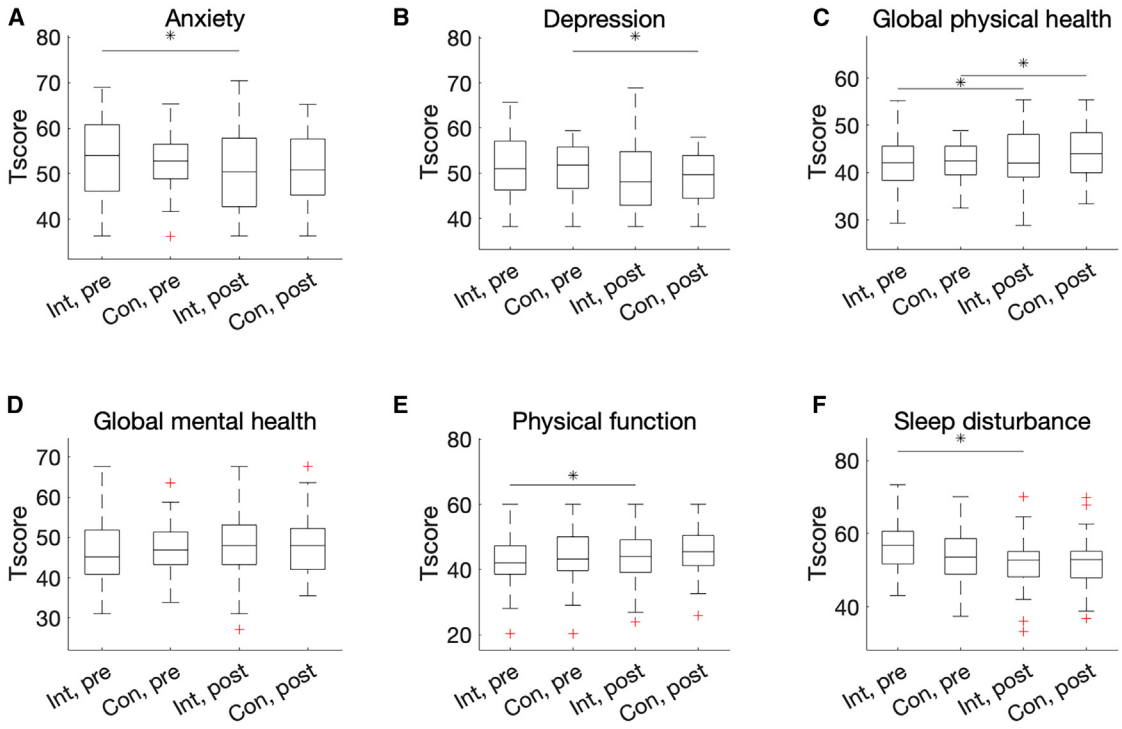

Figure 4. PROMIS pre- and post-trial surveys, by intervention and control groups

Data are shown using boxplots for (A) anxiety, (B) depression, (C) global physical health, (D) global mental health, (E) physical function, and (F) sleep disturbance. Statistically significant differences ($p < 0.05$) are denoted with a line and *. The median in each boxplot is denoted with a horizontal line, the edges in the box signify the 25th and 75th percentiles, and outliers are given by red plus signs.

steps by week, the first week corresponded to 5,492.1 (SD = 3,481.8) steps for the intervention group and 6,196.0 (SD = 3,566.5) steps for the control group. These daily step distributions during the first week were not significantly different between intervention and control (p value = 0.26, two-sample t test). At the final week of the study, the mean daily steps were 5,469.8 (SD = 3,486.0) steps and 6,189.4 (SD = 3,305.9) steps for the intervention and control groups, respectively. These were also not significantly different (p value = 0.24, two-sample t test), and the difference within the intervention and control groups from first to last week was not significant (p value = 0.99 for intervention, p value = 0.64 for control, paired t test). For the mean daily heart rate, the first-week values are 81.83 (SD = 8.54) for the intervention group and 81.65 (SD = 10.76) for the control group, and the final-week mean heart rates are 80.86 (SD = 11.39) for intervention and 80.22 (SD = 12.14) for control. There were again no significant differences between intervention and control at the initial or final week, and the mean heart rate values were not significantly different from the initial to final week within the groups.

DISCUSSION

We have investigated the effects of lighting interventions on cancer-related fatigue in a sizable cohort of patients from three cancer populations (breast, prostate, and HCT). This study leveraged a mobile application providing personalized lighting interventions based on the patient's circadian status, hence supporting an individualized and low-cost interventional framework. The intervention was determined from mathematical models and sensor-derived wearable data, making it a non-invasive and relatively simple data collection process. The intervention was successfully carried out over the 12-week study duration in high-fatigue risk cancer populations, with the mobile Sync app facilitating ease of recommendation delivery.

We are encouraged by the findings, specifically the significant decrease in both daily and weekly fatigue in the intervention group (Figures 2 and 3) and the significant final time effect of treatment on weekly fatigue. There were differences in fatigue levels and dynamics depending on the survey type: for example, the average weekly fatigue at week 1 was slightly higher in the intervention group, while the average daily fatigue at week 1 was slightly higher in the control group. However, this difference was small and not statistically significant, and there were overall correlations between daily and weekly fatigue (e.g., Figure S4). Daily fatigue decreased statistically significantly in this population, and reductions in fatigue were consistently larger in magnitude for the intervention group than the control across the assessments. The average daily fatigue was lower in the intervention group for all weeks of the study, and, while the average weekly fatigue started higher in intervention, it generally became lower for the middle and later weeks. This provides evidence that targeted circadian lighting interventions can affect the fatigue levels patients experience.

The finding of a clearer difference between intervention and control in daily as opposed to weekly fatigue at the end of the study could be explained by a few factors. It is possible that fatigue fluctuates on a daily or even hourly basis[21] (e.g., see time of day variation in daily fatigue in Figure S3), so the weekly surveys could have failed to capture shorter timescale effects in fatigue in response to treatment (although we do expect treatment effects to persist over longer time spans). The simple, 1-item measure likely more reliably estimates fatigue for the current state, whereas the 4-item fatigue inquires about the respondent's past seven days, inducing the variable of recall bias. The absence of a baseline PROMIS fatigue score for the weekly survey could have obscured changes in weekly fatigue, as the first weekly survey was inadvertently administered only after completion of the first week. Alternatively, the 4-item PROMIS fatigue survey may have captured additional aspects of fatigue than the daily survey. Indeed, future work is needed to clarify the components of fatigue that these interventions truly impact. Fatigue is a complex phenomenon that itself displays circadian variability,[22] so the timing of survey administration may impact the results. Other more objective metrics, such as reaction time performance, may be needed to assess fatigue throughout the day. Further studies collecting objective measures may help resolve the variations in the results depending on the daily, weekly, or before/after surveys.

Complex relationships and interactions exist between fatigue, the circadian system, and light exposure. For example, mouse studies have found that light at night impacts behaviors related to mood via activation of the clock gene *Per1*,[23] and fatigue has been negatively correlated with light exposure during chemotherapy in breast cancer patients.[24] Notably, a recently published study did not find a significant difference in the change in PROMIS fatigue T-score from baseline following bright light therapy, although sleep quality, depression, and quality of life improved.[25] This previous study provided light at either morning or night depending on chronotype, however, and thus utilized a non-traditional variety of light therapy. Another recent study comparing BWL and DRL in HCT survivors did not find a significant effect of BWL over DRL for overall cognitive performance or fatigue.[26] It is possible that both light conditions generated therapeutic effects, however, due to the lack of a no-light control condition. Additional work is needed to untangle the effects of these interventions on fatigue as measured at different time intervals.

It is possible that the long duration of the study reduced the differences between the intervention and control groups, potentially due to reductions in compliance over time, yet the daily fatigue score plateau suggests a stability rather than regression. The amount of missing weekly surveys increased in the final weeks of the study (Table S2), suggesting a reduction in app-related compliance. Additionally, simply providing an Apple Watch may have motivated fatigue-reducing behaviors in both the control and intervention group. A recent systematic review concluded that activity tracking through wearables yields improvements in activity and fitness, with step counts rising by roughly 1,800 steps per day.[27] Increased activity levels may therefore contribute to the fatigue reduction observed in both groups, although the lack of a baseline activity level in our study makes this difficult to quantify. Additionally, weekly fatigue improved similarly for breast cancer patients in the intervention and control arms.

We further assessed the effects of treatment and demographic covariates on weekly fatigue using a GEE-based analysis, which yielded a significant final time treatment effect. This provides evidence that, when adjusting for other factors such as age, gender, and pre-trial fatigue, the lighting intervention had an impact on end-of-study fatigue even as measured by the weekly surveys.

The secondary outcomes of the full pre- and post-trial PROMIS surveys did not show significant differences between intervention and control at the end of the study, although anxiety and sleep disturbance significantly decreased in the intervention group, depression decreased in the control group, physical health increased in both, and physical function increased in intervention. The sleep disturbance results align with previous work that found potential for lighting interventions improving sleep quality metrics.[25,28] This targeted mobile intervention may provide a low-cost therapeutic approach for decreasing sleep disturbances, likely through the promotion of robust circadian rhythmicity over time. However, the lack of a significant difference between the final sleep disturbance metrics for intervention and controls brings into question the magnitude and clinical significance of these improvements. Future work focusing on concrete wearable-derived circadian and sleep changes in this population could be valuable. In particular, determining the effects of the intervention on various wearable metrics (heart rate parameters; derived circadian features) could be key future research.

Overall, this study examined the impact of a personalized and circadian-based lighting intervention on the fatigue levels of three cancer populations. While we generally observed lower final-time-point fatigue in the intervention group, the significance and clinical import of these findings vary by the type of measure. This study was made possible by leveraging wearable technology to collect data non-invasively and applying mathematical algorithms (e.g., a limit cycle oscillator model[29]) to base lighting interventions on each individual's circadian patterns. Importantly, this work paves the way for development and testing of app-based lighting interventions in broader cancer populations.

Limitations of the study

We acknowledge that our study has several limitations. The extent to which the user actually followed the lighting recommendations remains largely unknown; while individuals could mark in the mobile app whether they completed a specific task or not, the accuracy, large amount of missingness, and lack of information about if they completed the task at the appropriate time made analysis of these data challenging. We analyzed the available light-related task completion data and determined that, while a large percentage of the tasks for the intervention group were not marked as completed, intervention individuals still completed a sizable amount of tasks over the study. In particular, over 170 non-control tasks were marked as completed on average per individual, over an average of more than 65 unique days per individual (see results: basic mobile app and smartwatch metrics). However, the lack of higher-quality compliance data or a research-grade device to measure light levels objectively remains a limitation of this study. Therefore, the

amount that the light exposure of the individual actually changed remains unclear. More direct assessments of light levels and compliance with lighting recommendations could be valuable in the future, although such devices may still be prone to issues with inaccurate measurements (e.g., due to long sleeves covering the wrist sensor), lack of adequate wear time, and light at the wrist not perfectly reflecting ocular light exposure. Actigraphy may also systematically underreport illuminance levels.[16,30] Another potential limitation is that we did not directly measure diet, stress, sleep, and physical inactivity (which may be risk factors for fatigue) at baseline. However, PROMIS anxiety, depression, and sleep disturbance surveys capture key aspects of psychological and sleep-related risk factors for fatigue and did not differ at baseline between intervention and control (see Figure 4). Furthermore, daily activity levels measured by the Apple Watch during the first week were not significantly different between intervention and control (Results: Basic mobile app and smartwatch metrics). The lack of recording of an initial (week 0) weekly fatigue survey also makes the determination of changes from baseline in the subsequent weekly fatigue difficult. Due to technical limitations, we only enrolled individuals with an iPhone, which may have introduced bias into the patient population.

The impact of treatment-related adverse events on cancer-related fatigue was not directly considered in this study. However, we attempted to minimize effects of active treatments on the participants' fatigue (e.g., recruiting breast cancer patients who have completed chemotherapy and radiation therapy at least three months prior to enrollment and not enrolling participants with planned changes in systemic therapy that would impact fatigue levels; see STAR Methods). Since treatment and treatment-related adverse events can significantly impact fatigue,[31] future work is needed to specifically examine these effects during a lighting intervention. Further, the population was largely white and non-Latinx and recruited from a single institution (Table 1). Future research that recruits a more diverse cohort from multiple locations may be valuable. Finally, the inclusion of a heterogeneous cohort drawn from three different cancer populations serves as both a strength and limitation of this study. The specific mechanistic determinants of cancer-related fatigue may differ widely across these populations. For example, duration of endocrine therapy has been associated with cancer-related fatigue in breast cancer patients.[32] Androgen deprivation therapy may also contribute to heightened fatigue in prostate cancer patients.[33,34] Varying mechanisms and contributors for fatigue, including baseline depression, higher chemotherapy-related toxicity, and low hemoglobin level, have also been found in HCT patients.[35] Indeed, cancer-related fatigue is a multi-faceted phenomenon, characterized by both a range of mechanisms and varying subjective experiences. While this study has examined the effects of a circadian lighting intervention, future work is needed to parse out these interconnections and specific mechanisms across different cancer populations. Future studies with larger sample sizes, objective measures of light exposure, and complete baseline metrics are key to clarify the impact of the intervention. Adjusting for covariates such as baseline fatigue and cancer type is critical for providing contextual relevance as well as understanding the robustness of the findings.

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled as possible by the lead contact, Sung Won Choi (sungchoi@med.umich.edu).

Materials availability

This study did not generate new physical materials or reagents.

Data and code availability

- The data from this study are not publicly available due to patient privacy concerns. Data reported in this study will be shared when possible by the lead contact upon request. The requestor must describe the objectives of the research project for which the data will be used. Data access will be considered for research purposes and non-commercial use only. In order to ensure patient privacy, access to personally identifiable information or sensitive clinical information will not be provided, and requests for data access must rigorously adhere to the consent agreements established with study participants. The protocol will be deposited in the Deep Blue Data repository upon publication and will be made available from the lead contact upon request.
- All code used in this study has been made available via the publicly available repository (https://github.com/mayercl/SYNC-Survey). All original code has been deposited at Zenodo at https://doi.org/10.5281/zenodo.14659558 and is publicly available as of the date of publication.
- Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

ACKNOWLEDGMENTS

We thank the clinical research coordinators (Zoe Bowen, Michelle Rozwadowski, Caroline Clingan, Stephanie Kozar, and Jennifer Wolfgang) for assisting in regulatory work, enrollment, and clinical data extraction. We also thank the other clinicians who accrued patients for this study.

We thank National Institutes of Health (NIH) SBIR R43CA236557 for support. The work was also supported in part by the Edith S. Briskin and Shirley K. Schafer Endowed Research Professorship (S.W.C). C.M. is grateful for support from an NIH Training Grant (2T32AR007422-41).

AUTHOR CONTRIBUTIONS

Conceptualization: O.W., K.H., N.L.H., J.J.A., M.T., D.B.F., and S.W.C. Methodology: C.M., O.W., W.D., and D.B.F. Investigation: C.M., O.W., K.H., and D.B.F. Data curation: C.M., O.W., K.H., C.C., Z.B., and M.R. Visualization: C.M., O.W., Z.B., and M.R. Supervision: O.W., N.L.H., J.J.A., M.T., D.B.F., and S.W.C. Project administration: C.M., O.W., C.C., Z.B., M.R., Z.R.R., N.L.H., J.J.A., M.T., D.B.F., and S.W.C. Writing – original draft: C.M. and O.W. Writing – review and editing: C.M., O.W., W.D., K.H., C.C., Z.B., M.R., Z.R.R., N.L.H., J.J.A., M.T., D.B.F., and S.W.C. All authors agreed to submit the manuscript, read and approved the final draft, and take full responsibility of its content, including the accuracy of the data and the fidelity of the trial to the registered protocol and its statistical analysis. C.M. and O.W. had unrestricted access to all data.

DECLARATION OF INTERESTS

O.W. has given talks at Unilever events and received honorariums/travel expenses; she has also done consulting for Gideon Health. She is the CEO of Arcascope, a company that makes circadian rhythm software. D.B.F. is the CSO of Arcascope. D.B.F. and the University of Michigan are part owners of Arcascope. N.L.H. has received institutional support for the conduct of a clinical trial (Blue Note Therapeutics), receives royalties from UpToDate, and has consulted for AstraZeneca and Myovant Sciences. Z.R.R. has received institutional support from AstraZeneca and consulted for AstraZeneca and Johnson and Johnson.

STAR★METHODS

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SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.xcrm.2025.102001.

Received: March 20, 2024
Revised: September 22, 2024
Accepted: February 12, 2025
Published: March 7, 2025

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
Processed daily wearable metrics	This paper	Upon request
Daily surveys	This paper	Upon request
Weekly surveys	This paper	Upon request
Pre/post surveys	This paper	Upon request
Software and algorithms		
MATLAB	The Mathworks Inc.	https://www.mathworks.com/
R	R Foundation for Statistical Computing, Vienna, Austria	https://www.r-project.org/
Data formatting and non-imputed analysis	This paper	https://github.com/mayercl/SYNC-Survey, Zenodo at https://doi.org/10.5281/zenodo.14659558
GEE and imputed analysis	This paper	https://github.com/mayercl/SYNC-Survey, Zenodo at https://doi.org/10.5281/zenodo.14659558

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

This randomized controlled study enrolled 138 cancer outpatients from the University of Michigan Health System between August 2021 and March 2023. Approval was received from the institutional review board (University of Michigan Medical School IRB), and investigators obtained written informed consent from each individual.

Patients were recruited by screening upcoming clinic schedules and subsequently recruiting potentially eligible patients at clinic visits, in addition to posting a call for volunteers on the University of Michigan Health Research website. Eligibility criteria included being at least 18 years old, able to use an iPhone and application, English speaking, and reporting at least moderate baseline fatigue (score of at least 4/10, where 10 denotes extreme tiredness). Participants had been diagnosed with one of three cancers (breast, prostate, or hematological malignancies requiring hematopoietic cell transplant [HCT]). Participants with stage 1–3 breast cancer must have completed chemotherapy and radiation therapy, if given, at least three months prior to enrollment, and concomitant endocrine therapy and/or anti-HER2 therapy was permitted. Participants with prostate cancer were receiving androgen-deprivation therapy, and concomitant anti-androgen therapy was permitted. Participants with hematologic malignancies who had undergone HCT were also enrolled. No planned changes in systemic therapy that would impact fatigue were planned. Concomitant sleep aid usage was permitted if used for the four weeks prior to randomization. Patients who work the night shift were excluded.

Of the 138 participants enrolled, half (n = 69) were randomly assigned to the control arm and half to the intervention (n = 69). Of the enrolled individuals, 131 (n = 65 intervention, n = 66 control) completed the study and were included in the analyses (Figure 1). The mean age of the study population was 59.1 years (SD = 13.26) and a range of 19–87 years (Table 1). The majority were female (n = 70, 53.4%), White (n = 119, 90.8%), and non-Hispanic or Latinx (n = 124, 94.7%). Gender data were collected using the Epic electronic health record (Verona, WI), extracted by members of the study team. There were no significant differences between the intervention and control groups in terms of age, gender, race, or ethnicity (p-values >0.05, two-sample t-test).

Participants were randomized 1:1 to the study intervention or the control intervention (23 from each cancer population in each arm) and completed protocol-directed activities over 12 weeks. The three cancer populations (breast, prostate, and HCT) were randomized separately, so that there were the same number of intervention and control participants in each population. We did not use a specific block size or otherwise stratify by demographic characteristics. The randomization was determined via a random shuffle function, implemented in Python. No harms occurred as part of this study.

METHOD DETAILS

Participants randomized to the intervention arm were provided with blue light-blocking glasses and personalized recommendations (delivered via the mobile Sync application developed for this study) designed to impact the circadian clock (Figure S1). The intervention group received recommendations such as ‘‘Seek bright light’’ and a time window over which to perform the recommendation, e.g., ‘‘7:30-8:30 a.m.’’. The particular recommendation and time were personalized based on circadian metrics derived from the individual’s wearable data.[16,19,20] Specifically, wearable data were passed through a limit cycle oscillator model of the human circadian clock to arrive at a prediction of circadian phase. This phase prediction, along with the user’s stated preferred wake time, was then

used to construct a daily personalized schedule which aimed to both 1) phase shift the user (advance or delay) to better align their clock with their goals, and 2) boost the amplitude of their circadian rhythms with a light pulse near the peak of the amplitude response curve.[16,19,29] The control arm received clear (non-light blocking) glasses and a sham app that delivered lighting intervention recommendations designed to have minimal impact on the circadian clock; e.g., instructions to wear clear glasses in the mid-afternoon.

All participants received an Apple iOS Watch device, which recorded the wearable data used to determine the recommendations. Participants were instructed to download the Sync or sham app to their smartphone device, free of charge and publically available through the App Store. Within the Sync or sham application, participants could mark that they had or had not completed a given recommendation. Participants were able to keep the Apple Watch after completing the study and were provided with iPhones, if needed. For more details, see STAR Methods: Development and testing of the mobile study app. The research coordinators instructed participants on how to use the Sync or sham app and the watch and to wear it continuously, except for when charging.

The primary outcome was PROMIS Fatigue 4a Short Form (SF) at the end of trial, compared between arms. As we did not have a PROMIS 4-item Fatigue weekly measurement for week 0, we were unable to calculate a change from baseline through this measure alone. We assessed this outcome by looking at differences in fatigue between the intervention and control group at the final week (week 11), and the treatment effect on fatigue at week 11 while controlling (through generalized estimating equations) for baseline fatigue with the 1-item Fatigue question (*"In the past 7 days, how would you rate your fatigue on average?"*) taken from the pre-trial PROMIS Global Health survey. Secondary outcomes included the final week's daily fatigue compared between arms, and change in PROMIS sleep disturbance, anxiety, depression, physical function, and global health (mental and physical); see: STAR Methods: *Data analysis: further details*.

Participants were asked to complete patient-reported outcome (PRO) measures electronically using the app throughout study participation. Every day at noon, participants were given the 1-item question "How fatigued are you?," with response options "Not at all fatigued", "A little bit fatigued", "Somewhat fatigued", and "Very fatigued." These daily responses (referred to as daily fatigue) were translated to a 0–3 scale, with higher values corresponding to more fatigue. Once a week (and with a recall period of one week), participants were prompted to complete a 4-item PROMIS Fatigue 4a Short Form (SF) (referred to as weekly fatigue), an app experience questionnaire, and a sleep aid usage survey. Before starting study participation and after 12 weeks, participants were prompted to complete the PROMIS Sleep Disturbance-SF 8b, the PROMIS Anxiety-SF 7a, the PROMIS Depression-SF 8a, the PROMIS Physical Function-SF 8b, and the PROMIS Global Health v1.2.[36–38] For all measures, higher scores indicate more of the named construct; more detail on the PROMIS surveys are provided in the *PROMIS measures* subsection below. Research coordinators monitored participant adherence to study procedures and provided twice weekly reminders to wear and sync the Apple Watch and complete surveys to participants who were non-adherent.

PROMIS MEASURES

PROMIS Fatigue[36,38]: This measure assesses self-reported symptoms of fatigue, ranging from mild subjective feelings of tiredness to overwhelming exhaustion that may decrease one's ability to perform activities of daily living. Fatigue instruments are available for adults (ages 18+; 4-item fixed length scale) and are scored on a T metric (with a mean of 50 and standard deviation of 10 as provided by the instrument developers for the general population). Higher scores indicate more fatigue.

PROMIS Sleep Disturbance[36,38]: This measure assesses self-reported perceptions of sleep quality, sleep depth, and restoration associated with sleep. This includes perceived difficulties and concerns with getting to sleep or staying asleep, as well as perceptions of the adequacy of and satisfaction with sleep. Sleep disturbance instruments are available for adults (ages 18+; 8-item fixed length scale) and are scored on a T metric (with a mean of 50 and standard deviation of 10). Higher scores indicate more sleep disturbance.

PROMIS Anxiety[36,38]: This measure assesses self-reported feelings of fear, anxiety, and hyperarousal. Anxiety instruments are available for adults (ages 18+; 7-item fixed length scale) and are scored on a T metric (with a mean of 50 and standard deviation of 10). Higher scores indicate more anxiety.

PROMIS Depression[36,38]: This measure assesses self-reported feelings of sadness and worthlessness. Depression instruments are available for adults (ages 18+; 8-item fixed length scale) and are scored on a T metric (with a mean of 50 and standard deviation of 10). Higher scores indicate more depression.

PROMIS Global Health[36,38]: This measure assesses self-reported physical, mental, and social health using 10-items. The adult Global Health measure produces two scores: Physical Health and Mental Health. Items include global ratings of five primary domains (physical function, fatigue, pain, emotional distress, and social health) as well as perceptions of general health that cut across domains. Global items allow respondents to weigh different aspects of health to arrive at a "bottom-line" indicator of health. Resulting scores are on a T-metric (with a mean of 50 and standard deviation of 10). Higher scores indicate more of the concept being measured (i.e., a higher score indicates a higher level of health).

DATA ANALYSIS: FURTHER DETAILS

T-scores for the PROs were computed via the HealthMeasures website and scoring service (www.Healthmeasures.net), comparing adult respondents (age >18 years) with the default calibration sample. For the weekly 4-item fatigue questionnaire, T-scores were

manually calculated based on the scoring guidelines. The T-scores reported correspond to higher values in the particular measurement.

To analyze the daily and weekly PRO data, the dataset was cleaned, pre-processed, and formatted. For the majority of these PROs, a date key recorded the date that the survey corresponded with and timestamp for when the PRO was submitted. To deal with multiple submissions or potential duplicate surveys, all PROs that corresponded with a specific date key (or submitted on a certain date, if the key was not available) were averaged. The first day of the study was designated as the date on which the baseline PRO (pre-study) was completed, or the date of the first daily survey submission if the baseline PRO was not available. This timestamp was used to align the subsequent daily and weekly PROs. Weekly PROs were administered after every week of the trial starting with Week 1 and ending with Week 11, and daily surveys were given during every week of the trial from Week 1 to Week 12. Sleep aid and alcohol usage information were collected in the weekly PROs. Sleep aid usage allowed users to select multiple options from a list of sleep aids (Ambien, Ambien CR (zolpidem tartrate), Dalmane (flurazepam hydrochloride), Halcion (triazolam), Lunesta (eszopiclone), Prosom (estazolam), Restoril (temazepam), Silenor (doxepin), Sonata (zelplon), Desyrel (trazodone), Belsomra (suvorexant), Antihistamines, Melatonin, Alcohol, and Other), while alcohol usage instructed individuals to select an approximate number of drinks consumed in the last week (see Table 1).

When imputing the data for the GEE analysis, we performed the MICE analysis on the weekly fatigue scores and the pre/post fatigue scores based on the weekly fatigue survey responses, age, gender, cancer population, and pre/post-trial fatigue. Daily fatigue scores were imputed based on the daily fatigue alone, and the longer multiple-item PROMIS pre/post-trial surveys were imputed based on the PROMIS pre/post-trial surveys alone. The imputation was performed separately for the intervention and control groups in each case.

For the analysis of the imputed datasets, we compared the fatigue scores between the intervention and control groups at the beginning and end of the trial. Specifically, we compared the daily or weekly fatigue values during the last week of the trial for the intervention and control groups, and additionally compared the daily or weekly fatigue values during the first week of the trial for intervention and control groups, and the change in daily or weekly fatigue from the first to last week for each group individually. To determine significance across the multiple imputations, we pooled the results using Rubin's rules and the Wald test.

DEVELOPMENT AND TESTING OF THE MOBILE STUDY APP

Preliminary testing and hardware selection

An early version of the Sync app was tested for usability with a small group of cancer patients. The initial setup paired the app with a smart light bulb and blue-blocking glasses. Although most patients found the blue-blocking glasses relatively easy to use, the smart light bulb was often deemed confusing and burdensome to set up. Our previous work also demonstrated that the use of 10,000 lux lamps was problematic from a compliance perspective. Therefore, we resolved that the only lighting hardware to be used in conjunction with the Sync app would be the blue-blocking glasses for the intervention group and clear glasses for the control group. Natural sunlight was recommended as the primary source of bright light, and patients were advised to sit near a window or go outside whenever feasible during periods when bright light was recommended.

App design and user interface

Sync's design and user interface were developed based on comprehensive interviews with patients and stakeholders. These interviews underscored the importance of creating an app that was straightforward to use and included adjustable text to facilitate readability.

Lighting recommendations and circadian goals

The app provided lighting recommendations, divided into four categories: very bright, bright, dim, and full darkness. Exposure to very bright light was set to 30 min each day, providing a pulse of light. Bright and dim light had no restrictions, while darkness was confined to the duration of the predicted sleep period. User testing indicated that darkness was assumed to imply that the user should sleep. Hence, if the model predicted a person should be in darkness but they were awake, the app instructed the user to dim the lights and don the blue-blocking glasses, if possible.

The cornerstone of Sync's recommendation system was tying the lighting recommendations to specific circadian goals: phase advancing, phase delaying, and amplitude boosting. We excluded the possibility of amplitude suppressing from this study, given that we hypothesized most cancer-related fatigue patients would exhibit lower, rather than higher, circadian amplitudes.

Onboarding and daily updates

During the onboarding process, users were asked about their desired wake-up time. Depending on this input, the app provided schedules that were either phase advancing, phase delaying, or neither, if their sleep was already well-aligned with their goal wake-up time. For instance, a user who consistently woke up at 5:00 a.m. but aimed to sleep until 7:00 a.m. would be guided to wear the blue-blocking glasses in the morning; this is a phase delaying schedule.

All users were given schedules aiming to achieve the amplitude-boosting goal, aligning with receiving a light pulse near the maximum of the amplitude response curve. The real-time wearable data from the users was monitored continuously, and the

app's recommendations were updated daily, always targeting an amplitude-boosting goal and a phase advance or delay goal if applicable. Someone who traveled but normally was content with their wake up time may have seen transient phase advancing or delaying recommendations. Similarly, someone who successfully phase shifted themselves to a new sleep schedule would stop seeing the phase advancing or delaying recommendations, as they had synced to their goal wake up time, but would continue to see amplitude-boosting recommendations.

Recommendations and predictions

Recommendations made by the app were based on daily predictions of each user's dim light melatonin onset (DLMO), a critical marker for establishing an individual's phase and amplitude response curves. We generated these DLMO predictions using wearable data and our previously published techniques.[16,29] Additionally, we employed the two-process model of the human circadian clock to predict sleep and wake times.[39]

Additional features

The app also offered additional information for promoting healthy sleep and other informational purposes. This included the timing of the wake maintenance zone, cessation times for caffeine intake before sleep, and the expected timing of peak physical performance due to the circadian clock. These timings were calculated either as constant offsets from the predicted DLMO or as constant offsets from predicted sleep onset.

The Sync app allowed users to manually update their recommendations if they significantly deviated from the recommended schedule. As a result, recommendations for the second half of the day might substantially vary if the user had not followed the earlier recommendations.

QUANTIFICATION AND STATISTICAL ANALYSIS

The statistical analysis plan was prepared prior to collecting and analyzing the data. The sample size was determined via a power calculation based on the minimally important clinically meaningful change, having a power of 0.80 (assuming an error rate of 0.05) to detect an effect of half the standard deviation between the intervention and control arms and considered a medium effect size for clinical trials.

We utilized generalized estimating equations (GEEs), an approach that fits a marginal model to the data and has particular utility for longitudinal data analysis.[40] For this analysis only, we performed an imputation analysis on the daily and weekly fatigue PRO data using the multiple imputation by chained equations (*mice*) package in R (version 4.3.1),[41] through which five imputed datasets were constructed. The statistical results were then combined across the datasets following Rubin's rules to pool the mean effect estimates and standard errors (accounting for within imputation variance and between imputation variance).[42] The primary GEE model was

$$f_w \sim treatment + age + gender + f_{pre} + time$$

$$+ treatment \cdot (age + gender + f_{pre} + time)$$

where f_w was the imputed weekly fatigue (PROMIS Fatigue 4a SF), *treatment* denoted intervention or control, and f_{pre} was pre-trial fatigue. The *treatment* value was coded as 0 for control and 1 for intervention, *age* was the age in years at the start of the trial, *gender* was coded as 0 for Female, 1 for Male, and 2 for Other, and *time* was the week (1–11) of the specific survey. All values were mean-centered (i.e., subtracting the mean of each variable from each observation of the given variable) for the GEE. Variations on the GEE model (accounting for nonlinear treatment effects or the cancer population covariate) were analyzed in STAR Methods: *Other GEE models*. The GEE analysis was conducted in R (version 4.3.1) using the *gee* package (v4.13-29). Visualizations and other analyses were conducted in MATLAB R2023a.

Primary GEE model details

Results from Table S3 were determined from the primary GEE model provided in the main text. The coefficients below were used to compute the final time treatment effect. To extract this treatment effect at the final time, the overall treatment effect was combined with the interaction effect between treatment and time, evaluated at the final time point. Given the regression coefficient of treatment β_{treat} and the regression coefficient of treatment x time $\beta_{treat\ x\ time}$, then the estimate of the treatment effect at the final time was $(\beta_{treat} + t_{final} \cdot \beta_{treat\ x\ time}) = -1.7097$

(where $t_{final} = 5$ due to mean-centering; see Table S3). The SE at the final time point was

$$SE_{final} = Var\left(\sqrt{(\beta_{treat} + t_{final} \cdot \beta_{treat\ x\ time})}\right)$$

$$= \sqrt{Var(\beta_{treat}) + t_{final}^2 \cdot Var(\beta_{treat\ x\ time}) + 2 \cdot t_{final} \cdot Cov(\beta_{treat}, \beta_{treat\ x\ time})}$$

So the naive SE at the final time point was $\sqrt{0.3431^2+5^2\cdot0.1076^2+2\cdot5\cdot1.42\times10^{-19}} = 0.6374$, the naive z was -2.6822, the robust SE (calculated in the same fashion as the naive SE above) was 0.6965, and the robust z was -2.4546; this yielded a p-value of 0.014, as given in the main text.

Other GEE models

The specific cancer population (breast, prostate, or HCT) to which the patient belongs can also be considered as a covariate in the GEE analysis. The equation corresponding to this approach is

$$f_w \sim treatment + age + gender + f_{pre} + time + population$$

$$+ treatment \cdot (age + gender + f_{pre} + time + population)$$

We present the results from adding this factor to the GEE in Table S4 below. Including this covariate yielded significant (p-value <0.05) effects for treatment, gender, pre-fatigue, time, population, treatment by age interaction, and treatment by gender interaction (Table S4). At the final time point, the treatment effect from this model is given by

$$(\beta_{treat} + t_{final} \cdot \beta_{treat\ x\ time}) = -0.9474 + 5 \cdot (-0.1549) = -1.7221,$$

and the robust SE is given by

$$SE_{final} = \sqrt{Var(\beta_{treat}) + t_{final}^2 \cdot Var(\beta_{treat\ x\ time}) + 2 \cdot t_{final} \cdot Cov(\beta_{treat}, \beta_{treat\ x\ time})}$$

$= \sqrt{0.3404^2+5^2\cdot0.1065^2+2\cdot5\cdot0.0077} = 0.6898$. The robust z is -2.4964, giving a final time point p-value of 0.0125.

While the previous generalized estimating equations approach considered linear effects of treatment over time, it is possible that the individuals responded to the treatment in a nonlinear manner over the course of the 12 weeks of the study. To account for this, we applied a similar GEE method, with the response remaining the weekly survey fatigue scores, but now including additional flexibility in the time effects by adding a linear spline with knots at each month (i.e., at weeks 4 and 8). The equation corresponding model equation here is

$$f_w \sim treatment + age + gender + f_{pre} + time + month1 + month2$$

$$+ treatment \cdot (age + gender + f_{pre} + time + month1 + month2)$$

where *month2* denotes a time effect of month 1 and month 2. This approach yielded significant (p-value <0.05) effects for the pre-trial fatigue score, the treatment by age interaction, and the treatment by gender interaction (Table S5).

ADDITIONAL RESOURCES

This trial was registered with ClinicalTrials.gov, NCT04827446.