Physical Activity and Dexamethasone for Cancer-Related Fatigue: A Preliminary Placebo-Controlled, Randomized, Double-Blind Trial

Sriram Yennurajalingam, MD, MS[1]; Vicente Valero, MD[2]; Brandon G. Smalgo, MD[3]; Michael J. Overman, MD[3]; Aravind Dasari, MD[3]; Robert A. Wolff, MD[3]; Kanwal Pratap Singh Raghav, MBBS, MD[3]; Carlos H. Barcenas, MD[2]; Naifa L. Busaidy, MD[4]; Bryan Fellman, MS[5]; Karen Basen-Engquist, PhD, MPH[6]; Kenneth R. Hess, PhD[5,†]; Debasish Tripathy, MD[2]; and Eduardo Bruera, MD[1]

Abstract

Background: Physical activity (PA) and dexamethasone (Dex) when used independently have modest benefits for cancer-related fatigue (CRF) in patients with advanced cancer. In this study we aimed to determine the feasibility (adherence, safety, and satisfaction) of combining PA with Dex versus PA with placebo (PBO) for CRF, and to explore the effects of PA+Dex and PA+PBO on CRF. **Patients and Methods:** In this phase II, randomized, double-blind controlled trial, eligible patients had advanced cancer and a CRF score of ≥4 on the Edmonton Symptom Assessment Scale (ESAS) for fatigue (0–10 scale). Patients were randomized to standardized PA for 4 weeks with either 4 mg of Dex (PA+Dex arm) or PBO (PA+PBO arm) twice daily for the first 7 days. Changes in Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) scores from baseline to days 8 and 29 were assessed. Other outcomes included change in quality-of-life scores. **Results:** A total of 64 (89%) patients were evaluable. Adherence rates for study medication, resistance exercise, and aerobic exercise were 91% and 92% ($P=.15$), 83% and 70.6% ($P=.35$), and 82.9% and 78.3% ($P=.73$), respectively, in the PA+Dex and PA+PBO arms. The satisfaction rates for the PA+Dex and PA+PBO arms were 98% and 79%, respectively. Median (IQR) changes in FACIT-F scores at days 8 and 29 from baseline were 9 (2 to 16; $P<.001$) and 5.75 (0 to 12.5; $P=.015$) for the PA+Dex arm, respectively, and 3.5 (−2.1 to 10; $P=.054$) and 6.5 (2.5 to 15.5; $P=.006$) for the PA+PBO arm, respectively. We found a significant treatment effect in the PA+Dex arm using exploratory linear mixed model analysis, with treatment showing an improvement of 5.63 units for FACIT-F scores (95% CI, 1.74–9.52; $P=.005$). We found significant improvement in Functional Assessment of Cancer Therapy-General (FACT-G), Patient-Reported Outcomes Measurement Information System-Fatigue Short Form 7a (PROMIS-Fatigue SF-7a), and Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF) totals on days 8 and 29 in the PA+Dex arm. There was no significant difference in grade ≥3 adverse events between the arms ($P=.36$). **Conclusions:** Our study found that the use of combination PA+Dex and PA+PBO for CRF was feasible and associated with high rates of satisfaction, adherence to medication and PA intervention, and tolerability. CRF improvement with PA+Dex was clinically significant at days 8 and 29. Further larger studies are justified.

ClinicalTrials.gov identifier: NCT03583255

J Natl Compr Canc Netw 2025;23(1):e247071
doi:10.6004/jnccn.2024.7071

Background

Cancer-related fatigue (CRF) is the most common cancer-related symptom and is defined as a "distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning."[1] CRF is more frequent, persistent, and severe in patients with advanced cancer than in those with early cancer or in posttreatment survivors.[2,3] In patients with advanced cancer, CRF negatively affects quality of life, interferes with daily activity, has potentially devastating social and economic consequences, and affects the patient's ability to receive palliative cancer therapy.[2,4–7] Although the population of patients with advanced cancer continues to increase, effective treatments for CRF in these patients remain elusive.[3,8,9] Established therapies for CRF, such as physical activity (PA), have demonstrated only modest efficacy,[10–14] and results from pharmaceutical agents for CRF have been mixed.[13,15,16] Recent studies suggest that the most efficient strategies may involve combining existing treatments—both pharmacologic and nonpharmacologic—that have shown promise in order to target the multifactorial causes of CRF in patients with advanced cancer. Previous studies from our group[16,17] and others,[17–23] as well as recently updated ASCO,[24] NCCN,[25] and ESMO guidelines,[13] suggest that corticosteroids can improve CRF and related symptoms in patients with advanced cancer. NCCN and ESMO advise short-term use of corticosteroids for CRF in patients with advanced cancer.[13] Prior research by our team found that dexamethasone (Dex) was safe and efficacious in patients with advanced cancer[26] but, like PA, it had only small to modest effects, largely due to the multifactorial nature of fatigue.[13,14,26–28] In a recent pilot study, we found that the combination of PA with Dex was feasible, and appeared to be effective for the treatment of CRF.[29] The improvement in CRF may be related to the synergistic effect due to the augmentation of the CRF-alleviating effects of PA by Dex. This may be through

Supplementary material is published online at https://doi.org/10.6004/jnccn.2024.7071

[1]Division of Cancer, Department of Palliative Care, Rehabilitation, and Integrative Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; [3]Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; [4]Department of Endocrine Neoplasia and Hormonal Disorders, The University of Texas MD Anderson Cancer Center, Houston, TX; [5]Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX; and [6]Department of Behavioral Science, The University of Texas MD Anderson Cancer Center, Houston, TX.

[†]Deceased.

improvements in inflammation, fitness, and psychological distress,[30–34] or may be due to the effects Dex has on different factors that contribute to CRF, such as cancer symptoms like anorexia, nausea, pain, and mood changes.[35,36] Further studies are needed to characterize the mechanism through which this combination therapy improves CRF. Therefore, in this phase II study, we aimed to determine the feasibility (adherence, safety, and satisfaction) of PA+Dex and PA+PBO (placebo) for CRF, and to explore the effects of PA+Dex and PA+PBO on CRF as assessed by change in Functional Assessment of Chronic Illness Therapy–fatigue (FACIT-F) score; fatigue dimensions and quality of life at days 8 and 29 using the Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF); Patient-Reported Outcomes Measurement Information System-Fatigue Short Form 7a (PROMIS-Fatigue SF-7a); Edmonton Symptom Assessment Scale (ESAS) and its symptom distress scores; Hospital Anxiety and Depression Scale (HADS); Pittsburgh Sleep Quality Index (PSQI); Godin Leisure-Time Exercise Questionnaire (GLTEQ); and Functional Assessment of Cancer Therapy-General (FACT-G).

Patients and Methods

The MD Anderson Cancer Center (MDACC) Institutional Review Board approved the study protocol, and all participants signed an informed consent (see Appendix in the supplemental materials, available online with this article). The study was activated for patient accrual on June 29, 2018, and was closed to new patient accrual on January 4, 2023. We reported study findings using the EQUATOR Reporting guidelines.

Participants

Patients were enrolled from the outpatient oncology and supportive care clinics at MDACC. Eligibility criteria included (1) diagnosis of advanced cancer with average intensity of fatigue of ≥4 on the ESAS fatigue item (ESAS-Fatigue; scale, 0–10)[37] in the previous 24 hours, (2) presence of fatigue for at least 2 weeks, (3) normal cognition as assessed by a Memorial Delirium Assessment Scale (MDAS) score of ≤13 (range, 0–30),[38] (4) no evidence of significant anxiety or depression as determined by a HADS[39] total score of <21, (5) hemoglobin level ≥8 g/L within 1 week of enrollment, (6) life expectancy of at least 4 months, (7) no severe cardiac disease (New York Heart Association functional class III or IV), (8) no regular participation in moderate- or vigorous-intensity physical activity for ≥30 minutes at least 5 times a week or in strength training for ≥2 days, (9) no history of falls in the past 30 days, (10) no infections and absolute neutrophil count ≥1,000 cells/mm^3 within 1 week of enrollment in the study, and/or (11) no uncontrolled diabetes mellitus or surgery within 2 weeks prior to study enrollment.

Interventions

A total of 92 eligible patients were randomized equally between the 2 treatment arms. All patients enrolled in the study received standardized PA intervention for 4 weeks and were randomly assigned to receive either 4 mg of oral Dex or matching PBO twice a day, administered at 8 AM and 2 PM every day for the first 7 days. Patients and all members of the research team except the investigational pharmacist and statistician were blinded to the study medication assignment throughout the study.

We used the same PA regimen as in our previous study of PA+Dex,[29] which showed that PA was safe and feasible. The PA prescription included a graded resistance exercise program and a walking regimen. We used resistance tubes as our mode of providing resistance exercises. These tubes were color-coded to indicate their specific resistance level (light, moderate, or hard). Prescribed resistance exercises targeted major muscle groups: squats (modified to sit-to-stand if needed), chest press, biceps curls, seated back row, seated leg extension using body weight, standing leg extension using body weight, and standing hip extension. The prescription was to complete 2 sets of 12 repetitions of all exercises. The resistance exercise sessions were to be completed 3 days per week, allowing at least 48 hours between each session. Participants also engaged in a walking program in which they were asked to walk a minimum of 5 days a week for at least 30 minutes.

At the first study visit, the research nurse met with each participant to evaluate their current strength and aerobic fitness level and supervised the assigned exercises. The resistance exercise sessions were designed so that the participants began with a lighter resistance and progressed to heavier resistance once a level had been mastered. Likewise, because the level of aerobic fitness varied among participants, the intensity and duration of the walking program was established based on the initial assessment of the participant's current aerobic fitness level using a 6-minute walk test. Patients were given pedometers to self-monitor adherence to the walking prescription. Participants received a weekly check-in call from the trained research nurse to assess their progress, address barriers, and adjust the difficulty of the resistance exercises and walking program. The assessment included the percentage of completion of the prescribed resistance exercise, specific resistance level (light, moderate, hard), and completion of prescribed walking exercise and duration.

We assessed satisfaction with the combination treatment program (resistance and walking exercise with study medication) using a single-item, 5-point, fully word-anchored balanced bipolar scale. The options to assess satisfaction were "completely dissatisfied," somewhat dissatisfied," "neither satisfied nor dissatisfied," "somewhat satisfied," and "satisfied." Tolerability to the study interventions was assessed through monitoring adverse events (AEs), in accordance with NCI's CTCAE version 4.03 (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_4.03.xlsx).

Outcome Measures

Patients' demographic data, including age, sex, race/ethnicity, cancer diagnosis, and treatment history were recorded at the time of randomization. A research nurse supervised the patients' completion of the FACT-G and its fatigue scale (FACIT-F),[40] ESAS,[41] PROMIS-Fatigue SF-7a,[42,43] MFSI-SF,[44] HADS, PSQI, and GLTEQ at baseline, day 8, day 29, and 1 month post study.

The FACT-G is a well-validated quality-of-life instrument widely used for the assessment of CRF in clinical trials. It consists of 27 general quality-of-life questions divided into 4 domains (physical, social, emotional, and functional), with scores based on a scale of 0 (not at all) to 4 (very much).

Our primary outcome measure was the FACIT-F subscale, a highly validated tool that our team and others have used in multiple fatigue treatment trials.[45–49] In addition, our goal in this study was to determine the sensitivity to change in fatigue-related symptoms using the MFSI-SF, PROMIS-Fatigue SF-7a, and ESAS fatigue item that might be of interest for future CRF research.

The FACIT-F is a 13-item subscale of the FACT-G that allows patients to rate the intensity of their fatigue and its related symptoms.[50] The calculated scoring varies from 0 to 52, with a lower score indicating a more severe fatigue level. Test-retest reliability coefficients for the fatigue subscale are 0.84 to 0.90. This scale has also demonstrated strong internal consistency ($\alpha = 0.93–0.95$). In previous studies, a 3-point improvement in FACIT-F scores was considered a minimally important clinical difference.[40,41]

PROMIS-Fatigue SF-7a was used to measure both the experience of fatigue and its interference in patients' daily activities over the past week. This questionnaire consists of 7 items with response options on a 5-point Likert scale, ranging from 1 (never) to 5 (always).[42,43] A higher score indicates greater fatigue. A 3- to 5-point improvement is considered a minimally important clinical difference.[33]

The MFSI-SF is a 30-item scale used to assess the multidimensional nature of fatigue.[44] The MFSI-SF is validated with a Cronbach α of 0.83 to 0.92.[51] Responses are selected using 5-point scale, ranging from 0 (not at all) to 4 (extremely). The MFSI-SF total score is calculated by summing the general, emotional, physical, and mental fatigue subscales scores and subtracting the vigor subscale score. A higher score indicates a higher level of fatigue.

The ESAS is validated scale ranging from 0 to 10 used to assess 10 symptoms commonly experienced by patients with cancer during the previous 24 hours: pain, fatigue, nausea, depression, anxiety, drowsiness, dyspnea, anorexia, sleep, and feelings of well-being.[41,37,52,53] For the purpose of post hoc analysis,[37,54,55] we categorized the ESAS as follows: ESAS physical distress score—sum of pain, shortness of breath, appetite, nausea, fatigue, and drowsiness scores; and ESAS psychological distress score—sum of anxiety and depression scores. The ESAS total is the sum of all ESAS items.

The HADS is a 14-item questionnaire used to measure anxiety and depression. The HADS has been validated and is widely used in medically ill patients.[56]

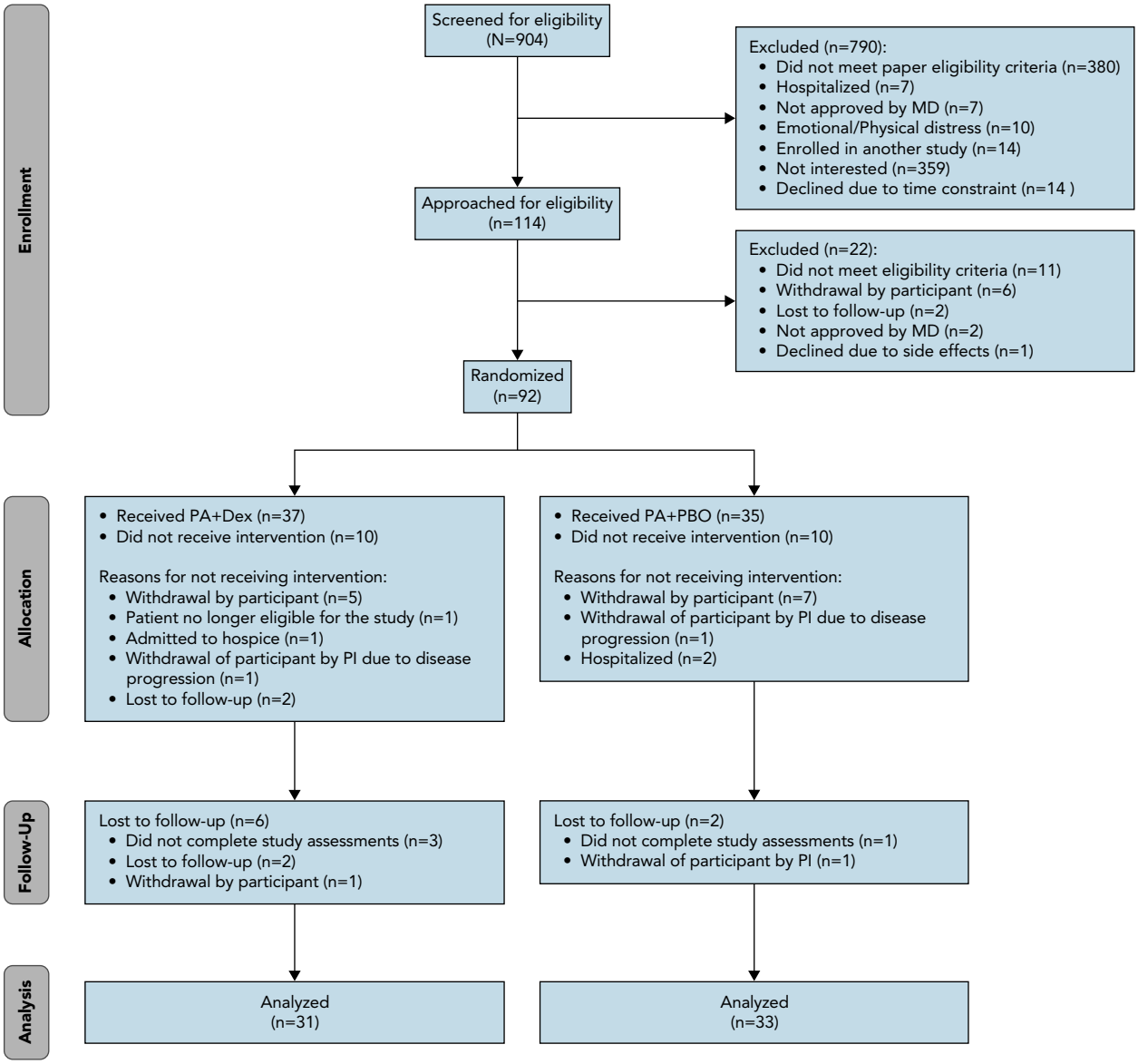

Figure 1. CONSORT diagram.
Abbreviations: Dex, dexamethasone; PA, physical activity; PBO, placebo; PI, principal investigator.

The PSQI is a 19-item validated questionnaire that was to measure sleep quality over the past month.[21,22] For this study, the PSQI was assessed as a measure of tolerability.

The GLTEQ was used to measure frequency and intensity of exercise over the past week. The questionnaire evaluates the number of times one engages in mild, moderate, or strenuous leisure time physical activities of at least 15 minutes in a week.

Statistical Analysis

Descriptive summary statistics were provided using median and IQRs for continuous variables and frequency and percentages for categorical variables. Feasibility was assessed based on satisfaction with, adherence to, and tolerability of study interventions. We estimated the proportion of patients completing the intervention, the adherence rate, and the proportion of patients with a satisfaction rating of "somewhat satisfied" or "completely satisfied." Adherence was defined as reported consumption of 75% of pills prescribed; 65% of walking exercise prescribed; and 65% of resistance exercise prescribed. PA+Dex was deemed feasible if the adherence rate to its daily use during the 4-week intervention was ≥75% and if >75% of patients reported being "somewhat satisfied" or "completely satisfied" with PA+Dex. The chi-square test was used to compare patient characteristics and the Wilcoxon rank sum test was used to assess change from baseline in FACIT-F, PROMIS-Fatigue SF-7a, FACT-G, ESAS-Fatigue item, MFSI-SF, ESAS Total, ESAS Physical Distress, ESAS Psychological Distress, HADS, PSQI, and GLTEQ scores. Exploratory linear mixed models were conducted to test whether there was a treatment effect on fatigue outcomes.

Sample Size Calculation

Our prior data[16] showed that oral Dex at 4 mg twice daily resulted in clinically relevant or robust improvement of CRF (FACIT-F scores) in 33% of patients. In the present study, a change in FACIT-F scores was assessed in the PA+Dex and PA+PBO arms. To obtain a reliable estimate of clinically relevant improvement at day 8, we estimated that 35 subjects were needed in each group, with a total sample size of 70. If the robust response proportions were 0.33 or 0.60, the half-widths of the 95% confidence intervals would be 0.16. Due to the preliminary nature of this study, no intent-to-treat analysis was conducted, and multiple testing was not considered. AEs were described descriptively, with frequencies by relation and grade. Fisher exact tests were used to compare maximum grade and severe AEs (SAEs; defined as grade ≥3) reported between groups. A P value of ≤.05 was considered statistically significant. All statistical analyses were performed using Stata/MP, version 17.0 (StataCorp LLC).

Results

Figure 1 shows the details of patient enrollment, follow-up, and analysis. Of the 92 randomized patients, 72 received the study intervention, and 64 (89%) of these were evaluable. Reasons for not receiving study interventions after randomization included withdrawal of consent (n=12), ineligibility (n=6), and loss to follow-up (n=2). Of the 72 evaluable patients, 8 were lost in follow-up after the start of intervention for the following reasons: failure to complete the study assessments (n=4), loss to follow-up (n=2), withdrawal of consent (n=1), and withdrawal from the study by the principal investigator for nonadherence to protocol (n=1).

We found no significant differences in baseline characteristics between patients who were randomized and completed the study intervention and those who did not complete the study (see Table S1). Table 1 shows patient demographics and clinical characteristics at baseline. There was no difference in baseline characteristics between patients in the PA+Dex and PA+PBO arms except for race/ethnicity and FACT-G physical well-being scores.

A total of 91% and 92% of patients in the PA+Dex and PA+PBO arms, respectively, were adherent to study medication (P=.15). Patients in the PA+Dex and PA+PBO arms completed 83% and 70.6% of prescribed resistance exercises,

Table 1. Patient Demographics and Clinical Characteristics at Baseline

	PA+Dex Arm (n=47)	PA+PBO Arm (n=45)	*P* Value[a]
Characteristic	**n (%)**	**n (%)**	
Age, median (range), y	56 (31–77)	59 (25–87)	.94
Sex			.55
Female	32 (68.09)	28 (62.22)	
Male	15 (31.91)	17 (37.78)	
Race/Ethnicity			**.02**
White	35 (78)	19 (62)	
Hispanic	4 (9)	15 (10)	
Black	4 (9)	9 (7)	
Asian/Other	2 (4.4)	0 (0)	
Cancer diagnosis			.37
Breast	18 (40)	9 (21)	
Lung	5 (11)	5 (11.6)	
Gastrointestinal	16 (36)	21 (49)	
Genitourinary	4 (8.9)	2 (4.7)	
Gynecologic	1 (2)	2 (5)	
Cancer treatment[b]			.44
Chemotherapy	31 (66)	30 (66.7)	
Radiation	8 (17)	12 (26.7)	
Hormone therapy	7 (14.9)	4 (8.9)	
Targeted therapy	17 (25.5)	14 (31.1)	
Assessment	**Median (IQR)**	**Median (IQR)**	
FACIT-F	29 (23–39)	26 (19–28.5)	.07
FACT-G	75.5 (61–86.3)	75.33 (65–90)	.80
FACT-G SWB	20.5 (17.5–26)	24.5 (20–28)	.45
FACT-G PWB	20.5 (16–22)	16.5 (11–22)	**.005**
FACT-G EWB	18 (15–20)	19 (15–22)	.63
FACT-G FWB	17.5 (14–20)	18 (12–23)	.94
HADS Anxiety	5 (3–11)	4 (2–6)	.42
HADS Depression	5 (2–8)	4.5 (2.5–7.5)	.99
ESAS Fatigue	6 (3–6)	5 (4–8)	.86
ESAS Physical Distress	15 (10–22)	21 (15–26)	.11
ESAS Psychological Distress	4 (2–10)	2 (0–5)	.50
PSQI total	10 (6–13)	10.5 (5.5–13)	.39
PROMIS-Fatigue SF-7a	20.5 (18–24)	21.5 (19–25)	.45
MFSI-SF total	22.5 (7.5–30.5)	18 (3–29)	.38

Abbreviations: Dex, dexamethasone; ESAS, Edmonton Symptom Assessment Scale; EWB, Emotional Well-Being; FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; FACT-G, Functional Assessment of Cancer Therapy-General; FWB, Functional Well-Being; HADS, Hospital Anxiety and Depression Scale; MFSI-SF, Multidimensional Fatigue Symptom Inventory-Short Form; PA, physical activity; PBO, placebo; PROMIS-Fatigue SF-7a, Patient-Reported Outcomes Measurement Information System-Fatigue Short Form 7a; PSQI, Pittsburgh Sleep Quality Index; PWB, Physical Well-Being; SWB, Social Well-Being.
[a] P value estimated using chi-square/Fisher exact test for categorical variables and Wilcoxon rank sum test for continuous variables. Bold indicates statistically significant values (P≤.05).
[b] Patients received >1 treatment.

respectively (P=.35), and 82.9% and 78.3% of prescribed aerobic exercises, respectively (P=.73). The satisfaction rate for combination treatment was 98% in the PA+Dex arm and 79% in the PA+PBO arm.

Table 2 shows the changes from baseline in fatigue scores at days 8 and 29 in the PA+Dex and PA+PBO arms. The median (IQR) change for FACIT-F, as well as effect size (ES) and P value, at day 8 and day 29 was 9 (2 to 16; ES, −3.49; P<.001) and 5.75 (0 to 12.5; ES, −2.43; P=.015), respectively, in the PA+Dex arm, and 3.5 (−2.1 to 10; ES, −1.93; P=.054) and 6.5 (2.5 to 15.5; ES, −2.72; P=.006), respectively, in the PA+PBO arm.

Exploratory linear mixed model (LMM) analysis showed significant treatment effect of the PA+Dex arm, with treatment showing an improvement of 5.63 units (95% CI, 1.74 to 9.52; P=.005) for FACIT-F scores and −4.09 units (95% CI, −7.04 to −1.15; P=.006) for PROMIS-Fatigue SF-7a.

Table 3 shows changes from baseline in fatigue-related symptom scores at days 8 and 29 in both arms.

Table 4 shows the frequency of SAEs in the PA+Dex and PA+PBO arms. There was no significant difference in SAEs between the 2 arms (P=.36). All SAEs were unrelated to study treatment except for one that was possibly related to the PA+Dex arm (insomnia, grade 3).

Discussion

In this study, we found that combined therapy with PA+Dex or PA+PBO was associated with high satisfaction rates, adherence to study medications, and tolerability. Combination PA+Dex resulted in a clinically meaningful improvement in CRF (>3 points on FACIT-F). We observed a sustained improvement in CRF and fatigue-related outcomes for up to 3 weeks compared with baseline after discontinuation of Dex, suggesting that possible priming effects of Dex helped sustain PA. We found a significant treatment effect of combination PA+Dex in the improvement of CRF scores.

In addition to improvement of fatigue, we observed an overall improvement in quality of life (FACT-G) in the PA+Dex arm, and it appeared this may have been driven by an improvement of the physical dimension of FACT-G without significant effects on the other dimensions of FACT-G. These results were similar to those of our previous studies using Dex and PA+Dex.[26,29] Furthermore, these results may suggest a possible impact of combination PA+Dex more on the peripheral rather than the central causes,[57] such as reduction of inflammatory components of CRF.[58,59] However, more research is necessary.[26]

The overall symptom burden as assessed by ESAS improved significantly in the PA+Dex arm by day 8 and remained improved by day 29 (Table 3).[16] Dex has been known to significantly improve several cancer-related symptoms, including anorexia, nausea, and pain, as well as overall feelings of well-being, that contribute to the symptom distress.[16] In our study, the improvement in symptom distress may be attributed to improvement of cancer-related symptoms, such as anorexia, fatigue, nausea, and pain.

In our previous study using 2 different doses (8 mg/d and 16 mg/d) of Dex in combination with PA,[29] we found significant improvement of CRF scores at days 8 and 29 in both arms. However, there was no difference in improvement of CRF between the 2 different doses of Dex in this study. Therefore, in this study we chose a lower dose for safety reasons and decided to randomize patients to either Dex with PA or PBO with PA. Results of our study demonstrated high satisfaction rates and rates of adherence to study medication and PA that were comparable to those of our previous study.[29] Our results also suggest that the higher dose of Dex did not appear to have any impact on adherence. In comparison with studies of PA alone in advanced cancer,[60,61] the addition of Dex seems to have a potentially beneficial effect on adherence, and additional research is warranted. In prior studies by our group, we found that PBO has a beneficial effect in improving CRF, and this might have helped adherence to PA in the PA+PBO arm of our study.[62,63] We found a significant treatment effect of PA+Dex in the improvement of CRF. This result was not surprising, as we found similar benefit using a similar dose of Dex with PA in our prior study using combination therapy.[29] These results are consistent with prior fatigue treatment trials using medication or PA interventions.[8,64,65] These findings justify a well-powered multicenter phase III comparative study using a factorial design to ascertain whether the improvement was due

Table 2. Changes in Fatigue Scores at Days 8 and 29 From Baseline[a]

Main Outcome	PA+Dex Arm				PA+PBO Arm			
Day 8 From Baseline	Baseline Median (IQR)	Day 8 Median (IQR)	Change Score Median (IQR)	*P* Value[b]	Baseline Median (IQR)	Day 8 Median (IQR)	Change Score Median (IQR)	*P* Value[b]
FACIT-F	29 (23 to 39)	43 (27 to 47)	9 (2 to 16)	**<.001**	26 (19 to 28.5)	28.5 (21.9 to 37.5)	3.5 (−2.1 to 10)	.054
ESAS Fatigue	6 (3 to 6)	3 (1 to 5)	−2 (−3 to 0)	**.001**	5 (4 to 8)	5 (3 to 7)	0 (−2 to 1)	.23
PROMIS-Fatigue SF-7a	56.4 (53.7 to 62)	50 (43.9 to 55.1)	−7.9 (−12 to 0)	**.003**	58.5 (55.1 to 63.4)	56.4 (50.8 to 62)	−1.4 (−8.3 to 4.2)	.09
MFSI-SF total	22.5 (7.5 to 30.5)	6 (−4 to 19)	−8 (−16 to 1)	**.023**	18 (3 to 29)	15 (1 to 27)	−3.5 (−9 to 3)	.26
Main Outcome	**PA+Dex Arm**				**PA+PBO Arm**			
Day 29 From Baseline	**Baseline Median (IQR)**	**Day 29 Median (IQR)**	**Change Score Median (IQR)**	***P* Value[b]**	**Baseline Median (IQR)**	**Day 29 Median (IQR)**	**Change Score Median (IQR)**	***P* Value[b]**
FACIT-F	29 (23 to 39)	39.5 (29.5 to 45.5)	5.75 (0 to 12.5)	**.015**	26 (19 to 28.5)	34 (26 to 42)	6.5 (2.5 to 15.5)	**.006**
ESAS Fatigue	6 (3 to 6)	4 (2 to 6)	−1 (−2 to 0)	**.015**	5 (4 to 8)	4.5 (2 to 6.5)	0 (−4 to 1)	.07
PROMIS-Fatigue SF-7a	56.4 (53.7 to 62)	51.45 (45.8 to 56.4)	−5.45 (−8.8 to 0)	**.005**	58.5 (55.1 to 63.4)	54.4 (48.4 to 62)	−4.25 (−9.8 to 1.7)	.14
MFSI-SF total	22.5 (7.5 to 30.5)	7.5 (−3 to 16.5)	−11 (−21 to 4)	**.007**	18 (3 to 29)	13 (−2 to 34)	−7.5 (−16 to 3)	.094

Abbreviations: Dex, dexamethasone; ESAS, Edmonton Symptom Assessment Scale; FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; MFSI-SF, Multidimensional Fatigue Symptom Inventory-Short Form; PA, physical activity; PBO, placebo; PROMIS-Fatigue SF-7a, Patient-Reported Outcomes Measurement Information System-Fatigue Short Form 7a.

[a]Number of patients included in this analysis differs from the total study patients analyzed (Figure 1) due to differences in questionnaire completion.

[b]Wilcoxon rank sum test was used to estimate *P* value. Bold indicates statistically significant *P* value (P≤.05).

Table 3. Changes in Fatigue-Related Symptoms at Days 8 and 29 From Baseline[a]

	PA+Dex Arm				PA+PBO Arm			
Day 8 From Baseline	**Baseline Median (IQR)**	**Day 8 Median (IQR)**	**Change Score Median (IQR)**	***P* Value[b]**	**Baseline Median (IQR)**	**Day 8 Median (IQR)**	**Change Score Median (IQR)**	***P* Value[b]**
FACT-G	75.5 (61 to 86.3)	82.5 (68 to 92)	5.5 (−0.8 to 12)	**.017**	75.33 (65 to 90)	83 (68 to 88)	2.17 (−3.83 to 10)	.14
FACT-G PWB	20.5 (16 to 22)	23.7 (21 to 25.7)	3 (0 to 5)	**.001**	16.5 (11 to 22)	16 (14 to 23)	2 (−1 to 3)	**.049**
FACT-G SWB	20.5 (17.5 to 26)	23.2 (19.8 to 27)	1.08 (−1 to 3.3)	.085	24.5 (20 to 28)	25 (22.2 to 27)	0 (−1 to 2.3)	.42
FACT-G EWB	18 (15 to 20)	19 (14 to 21)	0 (−1 to 3)	.298	19 (15 to 22)	20 (18 to 22)	0 (−1 to 2)	.33
FACT-G FWB	17.5 (14 to 20)	19 (14 to 22)	0.5 (−3 to 4)	.32	18 (12 to 23)	18 (13 to 21)	0 (−4 to 3)	.66
Total ESAS	30 (19 to 42)	20 (15 to 32)	−7 (−14 to 0)	**.007**	34.5 (26 to 40)	28.5 (19 to 36)	−2 (−10 to 0)	**.034**
ESAS Physical Distress	15 (10 to 22)	9 (7 to 16)	−5 (−9 to 3)	**.004**	21 (15 to 26)	17.5 (11.5 to 27)	−0.5 (7 to 3)	.38
ESAS Psychological Distress	4 (2 to 10)	3 (0 to 6)	0 (−3 to 0)	**.025**	2 (0 to 5)	1.5 (0 to 4)	0 (−2 to 0)	.085
MFSI-SF General	12 (8 to 15)	6 (4 to 11)	−3 (−6 to −1)	**.002**	12 (10 to 15)	11 (7 to 14)	−2 (−5 to 2)	**.044**
MFSI-SF Physical	5 (3 to 9)	2 (0 to 8)	−1.5 (−4 to 1.5)	.098	5 (3 to 10)	6 (3 to 10)	0 (−2 to 2)	.96
MFSI-SF Emotional	6 (2 to 9)	4 (1 to 9)	0 (−3.5 to 2)	.66	3 (1 to 7)	3 (1.5 to 6)	−1 (−2 to 2)	.39
MFSI-SF Mental	4 (2 to 10)	3 (1 to 6)	−1 (−2 to 0)	.10	4 (2 to 9)	4 (3 to 9)	0 (−1 to 1)	.43
MFSI-SF Vigor	10 (6.5 to 13)	12 (6 to 16)	1 (−1 to 5)	.16	11 (8 to 15)	10 (−3 to 14.5)	−1 (−3 to 3)	.79
HADS Anxiety	5 (3 to 11)	4 (2 to 9)	0 (−3 to 1)	.36	4 (2 to 6)	4 (1 to 6.5)	−1 (−2 to 1)	.29
HADS Depression	5 (2 to 8)	4 (2 to 8)	0 (−2 to 2)	.65	4.5 (2.5 to 7.5)	5 (3 to 8)	0 (−1 to 1.5)	.5
GLTEQ	20 (3 to 29)	34 (12 to 62)	3 (0 to 32)	**.01**	15 (6 to 24)	26 (12 to 46)	10 (0 to 28)	**.002**
	PA+Dex Arm				**PA+PBO Arm**			
Day 29 From Baseline	**Baseline Median (IQR)**	**Day 29 Median (IQR)**	**Change Score Median (IQR)**	***P* Value[b]**	**Baseline Median (IQR)**	**Day 29 Median (IQR)**	**Change Score Median (IQR)**	***P* Value[b]**
FACT-G	75.5 (61 to 86.3)	83 (78 to 8,91)	6.97 (3 to 10.5)	**.001**	75.33 (65 to 90)	78 (73 to 89)	3.09 (−3.75 to 10)	.094
FACT-G PWB	20.5 (16 to 22)	24 (20 to 25)	2 (1 to 4)	**.002**	16.5 (11 to 22)	19 (14 to 23)	0 (−1 to 3)	.15
FACT-G SWB	20.5 (17.5 to 26)	23.8 (20 to 26)	1.2 (−1 to 3)	.19	24.5 (20 to 28)	26 (22 to 28)	0 (0 to 1.6)	**.045**
FACT-G EWB	18 (15 to 20)	18 (15 to 23)	1 (0 to 3)	**.021**	19 (15 to 22)	19 (16 to 22)	0 (−1.5 to 1)	.94
FACT-G FWB	17.5 (14 to 20)	18 (15 to 23)	2 (0 to 3)	**.012**	18 (12 to 23)	19 (13 to 21)	−0.5 (−3.25 to 3.5)	.83
ESAS Total	30 (19 to 42)	22 (13 to 28)	−4 (−14 to 0)	**.049**	34.5 (26 to 40)	24 (10 to 39.5)	−6 (−22 to 4)	**.015**
ESAS Physical Distress	15 (10 to 22)	11 (6 to 18)	−2.5 (−5 to 1)	.063	21 (15 to 26)	16 (5.5 to 24)	−1 (−15 to 3)	.071
ESAS Psychological Distress	4 (2 to 10)	2.5 (0 to 5)	−1 (−4 to 0)	**.005**	2 (0 to 5)	1 (0 to 4.5)	0 (−3 to 0)	.083
MFSI-SF General	12 (8 to 15)	6.5 (4 to 9)	−3.00 (−4.5 to −0.5)	**.009**	12 (10 to 15)	12 (10 to 15)	−4 (−7 to 0)	**.007**
MFSI-SF Physical	5 (3 to 9)	3 (1 to 6)	−2 (−3 to 0.5)	**.015**	5 (3 to 10)	6 (3 to 9)	0 (−2 to 1)	.49
MFSI-SF Emotional	6 (2 to 9)	4 (1 to 5)	−2 (−5 to 1)	**.045**	3 (1 to 7)	5 (1 to 7)	0 (−3 to 2)	.72
MFSI-SF Mental	4 (2 to 10)	4 (2 to 7)	−1 (−4 to 0)	.12	4 (2 to 9)	5 (2 to 8)	−1 (−3 to 1)	.18
MFSI-SF Vigor	10 (6.5 to 13)	12 (9 to 17)	2 (−1 to 4)	.082	11 (8 to 15)	12 (8 to 16)	0 (−3 to 3)	.87
PSQI Total	10 (6 to 13)	8 (5.5 to 11)	−1 (−3 to 1)	.15	10.5 (5.5 to 13)	8 (5 to 10.5)	−1 (−4 to 1)	.11
HADS Anxiety	5 (3 to 11)	4.5 (2 to 7)	−2 (−3 to 1)	**.024**	4 (2 to 6)	4 (2 to 8)	0 (−1 to 1)	.71
HADS Depression	5 (2 to 8)	4 (2 to 8)	−0.5 (−2 to 0)	.13	4.5 (2.5 to 7.5)	3 (2 to 7)	0 (−1.5 to 0.5)	.12
GLTEQ	20 (3 to 29)	31 (0 to 56)	7 (−5 to 25)	.083	15 (6 to 24)	26 (6 to 47)	7.5 (−6 to 30)	**.028**

Abbreviations: Dex, dexamethasone; ESAS, Edmonton Symptom Assessment Scale; EWB, Emotional Well-Being; FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; FACT-G, Functional Assessment of Cancer Therapy-General; FWB, Functional Well-Being; GLTEQ, Godin Leisure-Time Exercise Questionnaire; HADS, Hospital Anxiety and Depression Scale; MFSI-SF, Multidimensional Fatigue Symptom Inventory-Short Form; PA, physical activity; PBO, placebo; PSQI, Pittsburgh Sleep Quality Index; PWB, Physical Well-Being; SWB, Social Well-Being.

[a]Number of patients included in this analysis differs from the total study patients analyzed (Figure 1) due to differences in questionnaire completion.

[b]Wilcoxon rank sum test was used to estimate *P* value. Bold indicates statistically significant *P* value ($P \leq .05$).

to the combination or to the individual intervention, and also whether treatment with Dex impacted adherence to PA intervention and whether levels of adherence were associated with CRF outcomes.

There are challenges with the use of corticosteroids and PA for managing CRF in patients with advanced cancer, including the AEs associated with corticosteroids, especially long-term use, and the need to avoid their use during immunotherapy.[8,35] There are also challenges with adherence to exercise in patients with advanced cancer. Our current study, which used a short course of dexamethasone with a standardized exercise regimen, provided preliminary data on adherence, efficacy, and safety. We also found that sleep quality (PSQI) scores were not significantly different between groups (Table 3). Further studies are needed to assess whether the levels of adherence to study interventions are associated with change in the study outcomes.

Our study has several limitations. Due to the COVID-19 pandemic, we were unable to reach the expected sample size of 70 evaluable patients (only 64 patients were evaluable), and therefore results of the primary outcome should be interpreted cautiously. Results of the secondary outcomes should also be interpreted cautiously, because the study was not powered to detect the differences between the 2 arms regarding secondary outcomes, and further well-powered studies using a randomized controlled design are needed. In this study, we did not document the barriers associated with the interventions during the weekly check-in calls by the study nurse, and further studies are needed to assess potential barriers to adherence and whether adherence was associated with outcomes in patients using the combination therapy. Unlike in our previous study of combination PA+Dex, objective evidence of adherence to PA could not be assessed.[29] Further studies are needed to investigate the optimal methods

Table 4. Serious Adverse Events

SAE[a,b]	Total (n=13)	PA+Dex Arm (n=6)	PA+PBO Arm (n=7)
Abdominal pain	1	1	0
Dizziness	1	1	0
Fatigue	2	1	1
Insomnia	3	1	2
Depression	1	1	0
Shortness of breath	1	1	0
Confusion	1	0	1
Death, NOS	1	0	1
Hypoglycemia	1	0	1
Hyponatremia	1	0	1

Abbreviations: Dex, dexamethasone; NOS, not otherwise specified; PA, physical activity; PBO, placebo; SAE, serious adverse event.
[a]Fisher exact test. Adverse events were graded based on NCI's CTCAE version 4.03. SAEs were defined as grade ≥3 adverse events.
[b]No significant difference in SAEs was reported between groups (P=.36).

for remote self-monitoring of resistance and walking exercise when using the combination therapy of PA+Dex to improve CRF outcomes. However, our study found high satisfaction rates, adherence to study medications, and tolerability. Similar to the findings in our prior studies using Dex, we also found no worsening of poor sleep quality scores due to the use of Dex intervention (Table 3).[26,29] Another potential limitation of the study is the presence of a PBO in the PA+PBO arm, given that we now have data suggesting that PBO per se can result in improvement of CRF, which would therefore impact the comparison between treatment arms; this should be addressed in future studies.[62,63] In previous studies, our group found significant symptomatic improvement, including CRF reduction, using Dex as well as PBO,[8,62] and therefore it is not clear whether the benefits of Dex may have had an impact on the ability of the participants to recognize that they were on an active treatment arm; this should be investigated in future research studies. Lastly, in this study we were unable to assess the differences in satisfaction rates for PA+Dex versus PA+PBO (98% vs 79%) attributable to specific intervention components, and therefore further studies are needed.

Conclusions

Our study found that the use of combination therapies with PA+Dex and PA+PBO for CRF were associated with high rates of satisfaction; adherence to study medication, resistance exercise, and aerobic (walking) exercise; and tolerability. Results of the secondary outcomes of this study suggest that the CRF improvement with PA+Dex was clinically significant at days 8 and 29, and the improvement was sustained 3 weeks after discontinuation of Dex. Further larger studies are justified.

Acknowledgments

The authors sincerely thank the National Institutes of Health for grant support and Debra L. Barton, Penny Stanton, Carolina Diaz Hernandez, Irma Lopez-Quinones, Hilda P. Torres, Paul Chavez, Melissa Gaffney, Jennifer C. Ellefson, Zhanni Lu, Premjit Roy, Aline Rozman Moraes, and Janet L. Williams for patient accrual and data support.

Submitted April 24, 2024; final revision received July 24, 2024; accepted for publication September 6, 2024. Published online January 7, 2025.

Author contributions: *Concept & design:* Yennurajalingam, Bruera. *Acquisition, analysis, or interpretation of data:* Valero, Smalgo, Overman, Dasari, Wolff, Raghav, Barcenas, Busaidy, Fellman, Basen-Engquist, Hess, Tripathy, Bruera, Stanton, Lu. *Statistical analysis:* Yennurajalingam, Fellman. *Administrative, technical, or material support:* Yennurajalingam, Bruera. *Supervision:* Yennurajalingam, Bruera. *Writing—original draft:* Yennurajalingam, Fellman, Bruera. *Writing—review & editing:* Yennurajalingam, Fellman, Bruera.
Disclosures: Dr. Yennurajalingam has disclosed receiving grant/research support from Pfizer. The remaining authors have disclosed that they have not received any financial consideration from any person or organization to support the preparation, analysis, results, or discussion of this article.
Funding: This work was supported by funding from the National Institute of Nursing Research (NIH 1R21NR016737-01A1; S. Yennurajalingam).
Supplementary material: Supplementary material associated with this article is available online at https://doi.org/10.6004/jnccn.2024.7071. The supplementary material has been supplied by the author(s) and appears in its originally submitted form. It has not been edited or vetted by *JNCCN*. All contents and opinions are solely those of the author. Any comments or questions related to the supplementary materials should be directed to the corresponding author.
Correspondence: Sriram Yennurajalingam, MD, MS, Division of Cancer, Department of Palliative Care, Rehabilitation, and Integrative Medicine, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 1414, Houston, TX 77030. Email: syennu@mdanderson.org

References

1. Berger AM, Mooney K, Alvarez-Perez A, et al. Cancer-related fatigue, version 2.2015. J Natl Compr Canc Netw 2015;13:1012–1039.
2. Bower JE. Cancer-related fatigue–mechanisms, risk factors, and treatments. Nat Rev Clin Oncol 2014;11:597–609.
3. Stone P, Candelmi DE, Kandola K, et al. Management of fatigue in patients with advanced cancer. Curr Treat Options Oncol 2023;24:93–107.
4. Charalambous A, Kouta C. Cancer related fatigue and quality of life in patients with advanced prostate cancer undergoing chemotherapy. Biomed Res Int 2016;2016:3989286.
5. Hofman M, Ryan JL, Figueroa-Moseley CD, et al. Cancer-related fatigue: the scale of the problem. Oncologist 2007;12(Suppl 1):4–10.
6. Butt Z, Rosenbloom SK, Abernethy AP, et al. Fatigue is the most important symptom for advanced cancer patients who have had chemotherapy. J Natl Compr Canc Netw 2008;6:448–455.
7. Cella D, Peterman A, Passik S, et al. Progress toward guidelines for the management of fatigue. Oncology (Williston Park) 1998;12:369–377.
8. Yennurajalingam S, Lu Z, Rozman De Moraes A, et al. Meta-analysis of pharmacological, nutraceutical and phytopharmaceutical interventions for the treatment of cancer related fatigue. Cancers (Basel) 2022;15:91.
9. Henson LA, Maddocks M, Evans C, et al. Palliative care and the management of common distressing symptoms in advanced cancer: pain, breathlessness, nausea and vomiting, and fatigue. J Clin Oncol 2020;38:905–914.
10. Peddle-McIntyre CJ, Singh F, Thomas R, et al. Exercise training for advanced lung cancer. Cochrane Database Syst Rev 2017;2017:CD012685.
11. Nadler MB, Desnoyers A, Langelier DM, Amir E. The effect of exercise on quality of life, fatigue, physical function, and safety in advanced solid tumor cancers: a meta-analysis of randomized control trials. J Pain Symptom Manage 2019;58:899–908.e7.
12. Dittus KL, Gramling RE, Ades PA. Exercise interventions for individuals with advanced cancer: a systematic review. Prev Med 2017;104:124–132.
13. Fabi A, Bhargava R, Fatigoni S, et al. Cancer-related fatigue: ESMO clinical practice guidelines for diagnosis and treatment. Ann Oncol 2020;31:713–723.
14. Toohey K, Chapman M, Rushby AM, et al. The effects of physical exercise in the palliative care phase for people with advanced cancer: a systematic review with meta-analysis. J Cancer Surviv 2023;17:399–415.
15. Peuckmann-Post V, Elsner F, Krumm N, et al. Pharmacological treatments for fatigue associated with palliative care. Cochrane Database Syst Rev 2010;10:CD006788.
16. Yennurajalingam S, Bruera E. Review of clinical trials of pharmacologic interventions for cancer-related fatigue: focus on psychostimulants and steroids. Cancer J 2014;20:319–324.
17. Bruera E, Roca E, Cedaro L, et al. Action of oral methylprednisolone in terminal cancer patients: a prospective randomized double-blind study. Cancer Treat Rep 1985;69:751–754.

18. Peuckmann V, Elsner F, Krumm N, et al. Pharmacological treatments for fatigue associated with palliative care. Cochrane Database Syst Rev 2010: CD006788.
19. Mercadante S, Fulfaro F, Casuccio A. The use of corticosteroids in home palliative care. Support Care Cancer 2001;9:386–389.
20. Loprinzi CL, Kugler JW, Sloan JA, et al. Randomized comparison of megestrol acetate versus dexamethasone versus fluoxymesterone for the treatment of cancer anorexia/cachexia. J Clin Oncol 1999;17:3299–3306.
21. Hanks GW, Trueman T, Twycross RG. Corticosteroids in terminal cancer–a prospective analysis of current practice. Postgrad Med J 1983;59: 702–706.
22. Metz CA, Robustelli Della Cuna G, Pellegrini A, Piazzi M. Effect of methylprednisolone sodium succinate on quality of life in preterminal cancer patients: a placebo-controlled, multicenter study. Eur J Cancer Clin Oncol 1989;25:1817–1821.
23. Moertel CG, Schutt AJ, Reitemeier RJ, Hahn RG. Corticosteroid therapy of preterminal gastrointestinal cancer. Cancer 1974;33:1607–1609.
24. Bower JE, Lacchetti C, Alici Y, et al. Management of fatigue in adult survivors of cancer: ASCO–Society for Integrative Oncology guideline update. J Clin Oncol 2024;42:2456–2487.
25. Jankowski C, Carpenter KM, Aranha O, et al. Clinical Practice Guidelines in Oncology: Cancer-Related Fatigue. Version 2.2024. Accessed October 10, 2024. To view the most recent version, visit https://www.nccn.org
26. Yennurajalingam S, Frisbee-Hume S, Palmer JL, et al. Reduction of cancer-related fatigue with dexamethasone: a double-blind, randomized, placebo-controlled trial in patients with advanced cancer. J Clin Oncol 2013;31:3076–3082.
27. Rodríguez-Cañamero S, Cobo-Cuenca AI, Carmona-Torres JM, et al. Impact of physical exercise in advanced-stage cancer patients: systematic review and meta-analysis. Cancer Med 2022;11:3714–3727.
28. Mustian KM, Alfano CM, Heckler C, et al. Comparison of pharmaceutical, psychological, and exercise treatments for cancer-related fatigue: a meta-analysis. JAMA Oncol 2017;3:961–968.
29. Yennurajalingam S, Valero V, Lu Z, et al. Combination therapy of physical activity and dexamethasone for cancer-related fatigue: a phase II randomized double-blind controlled trial. J Natl Compr Canc Netw 2021;20: 235–243.
30. Kalter J, Kampshoff CS, Chinapaw MJM, et al. Mediators of exercise effects on HRQoL in cancer survivors after chemotherapy. Med Sci Sports Exerc 2016;48:1859–1865.
31. Mast IH, Bongers CCWG, Gootjes E, et al. Exercise mechanisms to reduce fatigue in cancer survivors. Med Sci Sports Exerc 2023;55(Suppl 9): 970. Abstract 2842.
32. Mast IH, Bongers CCWG, Gootjes EC, et al. Potential mechanisms underlying the effect of walking exercise on cancer-related fatigue in cancer survivors. J Cancer Surviv. Published online January 31, 2024. doi.org/10.1007/s11764-024-01537-y
33. Hiensch AE, Mijwel S, Bargiela D, et al. Inflammation mediates exercise effects on fatigue in patients with breast cancer. Med Sci Sports Exerc 2021;53:496–504.
34. Juvet LK, Thune I, Elvsaas I, et al. The effect of exercise on fatigue and physical functioning in breast cancer patients during and after treatment and at 6 months follow-up: a meta-analysis. Breast 2017;33:166–177.
35. Yennurajalingam S, Bruera E. Do patients benefit from a trial of corticosteroids at the end of life? Curr Treat Options Oncol 2022;23:796–805.
36. Yennurajalingam S, Williams JL, Chisholm G, Bruera E. Effects of dexamethasone and placebo on symptom clusters in advanced cancer patients: a preliminary report. Oncologist 2016;21:384–390.
37. Bruera E, Kuehn N, Miller MJ, et al. The Edmonton Symptom Assessment System (ESAS): a simple method for the assessment of palliative care patients. J Palliat Care 1991;7:6–9.
38. Breitbart W, Rosenfeld B, Roth A, et al. The Memorial Delirium Assessment Scale. J Pain Symptom Manage 1997;13:128–137.
39. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand 1983;67:361–370.
40. Cella D, Eton DT, Lai JS, et al. Combining anchor and distribution-based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy (FACT) anemia and fatigue scales. J Pain Symptom Manage 2002;24:547–561.
41. Hwang SS, Chang VT, Rue M, Kasimis B. Multidimensional independent predictors of cancer-related fatigue. J Pain Symptom Manage 2003;26: 604–614.
42. Yost KJ, Eton DT, Garcia SF, Cella D. Minimally important differences were estimated for six Patient-Reported Outcomes Measurement Information System-Cancer scales in advanced-stage cancer patients. J Clin Epidemiol 2011;64:507–516.
43. Cella D, Riley W, Stone A, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005–2008. J Clin Epidemiol 2010;63:1179–1194.
44. Stein KD, Jacobsen PB, Blanchard CM, Thors C. Further validation of the Multidimensional Fatigue Symptom Inventory-Short Form. J Pain Symptom Manage 2004;27:14–23.
45. Minton O, Richardson A, Sharpe M, et al. A systematic review and meta-analysis of the pharmacological treatment of cancer-related fatigue. J Natl Cancer Inst 2008;100:1155–1166.
46. Yennurajalingam S, Frisbee-Hume S, Delgado-Guay MO, et al. Dexamethasone (DM) for cancer-related fatigue: a double-blinded, randomized, placebo-controlled trial. J Clin Oncol 2012;30(Suppl 15):Abstract 9002.
47. Bruera E, El Osta B, Valero V, et al. Donepezil for cancer fatigue: a double-blind, randomized, placebo-controlled trial. J Clin Oncol 2007;25: 3475–3481.
48. Bruera E, Driver L, Barnes EA, et al. Patient-controlled methylphenidate for the management of fatigue in patients with advanced cancer: a preliminary report. J Clin Oncol 2003;21:4439–4443.
49. Bruera E, Valero V, Driver L, et al. Patient-controlled methylphenidate for cancer fatigue: a double-blind, randomized, placebo-controlled trial. J Clin Oncol 2006;24:2073–2078.
50. Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol 1993;11:570–579.
51. Donovan KA, Stein KD, Lee M, et al. Systematic review of the multidimensional fatigue symptom inventory-short form. Support Care Cancer 2015; 23:191–212.
52. Carvajal A, Centeno C, Watson R, Bruera E. A comprehensive study of psychometric properties of the Edmonton Symptom Assessment System (ESAS) in Spanish advanced cancer patients. Eur J Cancer 2011; 47:1863–1872.
53. Chang VT, Hwang SS, Feuerman M. Validation of the Edmonton Symptom Assessment Scale. Cancer 2000;88:2164–2171.
54. Cheung WY, Barmala N, Zarinehbaf S, et al. The association of physical and psychological symptom burden with time to death among palliative cancer outpatients. J Pain Symptom Manage 2009;37: 297–304.
55. Richardson LA, Jones GW. A review of the reliability and validity of the Edmonton Symptom Assessment System. Curr Oncol 2009;16:55.
56. Johnston M, Pollard B, Hennessey P. Construct validation of the hospital anxiety and depression scale with clinical populations. J Psychosom Res 2000;48:579–584.
57. Yavuzsen T, Davis MP, Ranganathan VK, et al. Cancer-related fatigue: central or peripheral? J Pain Symptom Manage 2009;38:587–596.
58. Bower JE, Lamkin DM. Inflammation and cancer-related fatigue: mechanisms, contributing factors, and treatment implications. Brain Behav Immun 2013;30(Suppl):S48–57.
59. Saligan LN, Olson K, Filler K, et al. The biology of cancer-related fatigue: a review of the literature. Support Care Cancer 2015;23:2461–2478.
60. Oldervoll LM, Loge JH, Lydersen S, et al. Physical exercise for cancer patients with advanced disease: a randomized controlled trial. Oncologist 2011;16:1649–1657.
61. Ormel HL, van der Schoot GGF, Sluiter WJ, et al. Predictors of adherence to exercise interventions during and after cancer treatment: a systematic review. Psychooncology 2018;27:713–724.
62. Yennurajalingam S, Azhar A, Lu Z, et al. Open-label placebo for the treatment of cancer-related fatigue in patients with advanced cancer: a randomized controlled trial. Oncologist 2022;27:1081–1089.
63. Hoenemeyer TW, Kaptchuk TJ, Mehta TS, Fontaine KR. Open-label placebo treatment for cancer-related fatigue: a randomized-controlled clinical trial. Sci Rep 2018;8:2784.
64. Greer JA, Amoyal N, Nisotel L, et al. A systematic review of adherence to oral antineoplastic therapies. Oncologist 2016;21:354–376.
65. Scott JM, Iyengar NM, Nilsen TS, et al. Feasibility, safety, and efficacy of aerobic training in pretreated patients with metastatic breast cancer: a randomized controlled trial. Cancer 2018;124:2552–2560.