


PAPER

A randomized control trial of stress management for caregivers of stem cell transplant patients: Effect on patient quality of life and caregiver distress

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Abstract

Background: Psychological interventions reduce caregiver distress (CG-distress). Less distress in caregivers may contribute to improved patient quality of life (QoL), but empirical evidence is lacking. Will a caregiver stress management intervention improve patient QoL?

Methods: In this replication study, we randomized 155 allogeneic hematopoietic stem cell transplant (Allo-HSCT) patients and caregivers to PsychoEducation, Paced Respiration, and Relaxation (PEPRR) or enhanced treatment as usual (eTAU). We provided PEPRR over 3 months following transplant. Functional Assessment of Cancer Therapy–Bone Marrow Transplant (FACT-BMT) evaluated patient QoL, and CG-distress was based on depressive, anxious, and stress symptoms. Hierarchical linear models tested intervention, time, and interactions as fixed effects with participant as random effects.

Results: Patients whose caregivers received PEPRR did not differ on FACT-BMT between baseline and 6 months (mean = +3.74; 95% CI, -3.54 to 11.02) compared with patients of caregivers in eTAU (mean = +3.16; 95% CI, -2.88 to 9.20) even though CG-distress was decreased by PEPRR (mean = -0.23; 95% CI, -0.448 to -0.010) compared with those receiving eTAU (mean = +0.27; 95% CI, 0.033-0.504) at 6 months.

Conclusions: PEPRR reduced CG-distress without affecting their patient's FACT-BMT score. The FACT-BMT may not have distinguished unique psychological changes associated with their caregiver receiving PEPRR.

KEYWORDS

anxiety, caregiver, depression, quality of life, stem cell transplant, stress management, and stress, cancer, oncology

1 | BACKGROUND

Sixty-six million Americans cared for an ill person in 2015, reflecting a 49% increase in caregivers since 2008 of which 3.9 million cared for cancer patients.¹ Caregiver numbers continue to rise while caregivers rarely obtain psychological support for themselves² despite reporting high levels of stress.³ Caregiving for hematopoietic stem cell transplant (HSCT) patients is particularly challenging. An HSCT is an aggressive treatment for hematological malignancies and other conditions.⁴ Following ablation of the patient's marrow, hematopoietic stem cells are infused into the patient's peripheral blood to regenerate the patient's marrow. Transplanted stem cells come from either patient (autologous or Auto) or closely matched donor (allogeneic or Allo). HSCT patients require close supervision and care that can be challenging⁵ particularly for untrained family caregivers. Allogeneic hematopoietic stem cell transplants (Allo-HSCTs) increased by 1.9-fold in the past decade.⁶ In the transplant programs on which we focus, Allo-HSCT patients require close caregiver support for at least 100 days posttransplant,⁷ but patients may remain dependent for longer durations, representing an additional caregiver challenge. Informal caregiver contributions include monitoring a complex medication regimen, responding to emergent problems, and attending multiple medical appointments, while maintaining an aseptic home environment. For 100 days following transplant, Allo-HSCT patients and caregivers are encouraged to remain within a 30-minute transportation radius of the transplant facility to allow rapid specialized responses by trained staff not always present at nontransplant facilities. Allo-HSCT caregivers provide considerable "supportive care" for their patient at a cost of substantial distress.^{5,8} Caregiver education in providing supportive care for their patients may improve both patient and caregiver quality of life (QoL).

Despite distress experienced by HSCT caregivers, they have not been recipients of stress management interventions until recently.⁹ Indirect impacts of caregiver intervention on patients' QoL have been suggested.¹⁰ We previously modified a cognitive behavioral stress management program¹¹ designed for medically ill patients to address distress of Allo-HSCT caregivers.^{12,13} In brief, PsychoEducation, Paced Respiration, and Relaxation (PEPRR) consists of eight manualized one-on-one sessions devoted to specific stress management topics. Based in cognitive behavioral therapy, the goal was to have caregivers develop and apply stress management skills including problem solving, identifying cognitive distortions, applying relaxation techniques, using social support, and establishing appropriate goals. In our first trial, PEPRR compared with treatment as usual (TAU) was associated with reduced perceived stress as a primary outcome (effect size [ES] = 0.39) with reduced secondary outcomes of depression (ES = 0.46) and anxiety (ES = 0.66).¹³ However, in the prior work, we did not measure patient QoL nor the impact of intervening on to reduce caregiver distress (CG-distress) on patient QoL.

Patient and caregiver psychological status are interrelated across many domains. For example, we noted CG-distress in the peritransplant period was associated with patient QoL.¹⁴ In that analysis, patient physical functioning was a primary contributor to CG-distress after accounting for interdependence of caregiver and patient distress.

Only limited interventions have been directed toward Allo-HSCT caregivers. Education in *practical aspects* of caregiving (meal preparation, nursing/welfare care, or symptom management) improves caregiver and patient QoL.¹⁵ Also a nonrandomized problem-solving program including both Allo-HSCT patients and their caregiver was effective in reducing CG-distress and increasing self-efficacy.⁹ Reduced CG-distress may act via improvement in caregiver physical and psychological availability for their patient. There is some support for this since increasing caregiver time with HSCT patients increases survival. The presence of a steady in-hospital caregiver (a caregiver who spent ≥ 7 h/d for ≥ 5 d/wk with the patient during hospitalization) was associated with improved patient outcome, accounting for 44% of the variance in patient survival after controlling for medical factors.¹⁶ Follow-up work found survival 4 years later was 42% for patients with an in-hospital caregiver compared with 25% without an in-hospital caregiver.¹⁷ Yet evidence is limited for the overarching hypothesis of the present replication trial: *Mitigating psychological distress of Allo-HSCT caregivers through stress management training will improve quality of life (QoL) in patients.*

Allo-HSCT patients are not often capable of receiving psychoeducational interventions because of side effects of HSCT.¹⁸ Thus, our focus was on supporting caregivers, specifically hypothesizing that lower distress in caregivers associated with PEPRR would lead to improved patient QoL (patient primary outcome) measured by the Functional Assessment of Cancer Therapy–Bone Marrow Transplant (FACT-BMT).¹⁹ Our primary caregiver outcome, CG-distress, was based on a composite measure of depression, anxiety, and stress we previously developed on the basis of principal component analysis (PCA).^{5,13} In this replication study, we hypothesized patients whose caregivers received PEPRR would have increased QoL compared with patients whose caregivers receive enhanced treatment as usual (eTAU) and that caregivers receiving PEPRR will have reduced distress compared with eTAU.

2 | METHODS

2.1 | Trial design

This was a 1:1 randomized control trial (RCT) with intent-to-treat analysis. Allo-HSCT patients and their caregivers were randomized by permuted block to either PEPRR or TAU with a separate randomization allocation for each site to ensure equivalency. Randomization assignment was placed in sealed envelopes and assigned only after completion of baseline questionnaires. The Colorado Multiple Institutional Review Board approved the study, which was registered at www.ClinicalTrials.gov (NCT02037568).

2.2 | Participants

Between 1 March 2014 and 4 November 2016, we approached all Allo-HSCT patient and his or her primary caregiver at the only regional Allo-HSCT sites, a community-based transplant program (n = 98) and a

university-based cancer center ($n = 61$). Participants were approached during pretransplant screening, and the study was explained to both patient and caregiver. If interested, they were consented. Eligibility criteria included Allo-HSCT patient and his or her primary caregiver *both* agreeing to participate, spoke and read English, telephone access, and 18 years or older. In addition, caregiver eligibility criteria included willingness to use a smartphone and, if randomized to PEPRR, willingness to participate in intervention sessions. Exclusion criteria included uncontrolled psychiatric disorder in the patient or caregiver in the past 18 months unrelated to patient illness as well as caregiver alcohol consumption greater than two drinks per day. We defined caregivers as the individual in the patient's life who was primarily responsible for care posttransplant, emotionally invested in the patient, and responsible for major decisions regarding care. Dyads received monetary reimbursement for participation.

2.3 | Intervention

Three master's level social workers (interventionists) provided PEPRR for eight, 60-minute sessions during the 100-day posttransplant period. Each caregiver maintained the same interventionist. The intervention took place during a time of distress for Allo-HSCT caregivers.^{5,8} PEPRR incorporated aspects of cellular technology²⁰ not applied in our prior trial¹³ and also added two optional booster sessions. We provided video chat when caregivers could not attend one-on-one sessions. We offered smartphones and data plans at no cost for six caregivers without smartphones. The first session began 17.4 days (95% CI, 10.3-24.5) after transplant with delays related mostly to caregiver availability. Sessions generally occurred weekly for the first four weeks and then every other week for remaining sessions.

PEPRR was developed from a stress management intervention for medically ill patients¹¹ and modified for delivery to caregivers.^{12,13} Caregivers randomized to PEPRR received a workbook. Content specific sessions, described in detail elsewhere,¹² included in order the following: (1) introduction to stress management and the biofeedback device; (2) stress and the mind-body connection; (3) cognitions and stress; (4) coping strategies; (5) strategies for maintaining energy and stamina; (6) coping with uncertainty; (7) managing changing relationships; and (8) getting the support you need. Two additional open-ended booster sessions⁹ and ¹⁰ were available if requested by the caregiver. Each session began with a check-in to address new or emerging problem(s) providing flexibility for interventionists to address unique needs. Intervention fidelity was determined from video recordings. Three clinicians (B.B., K.K., and T.S.) randomly reviewed 15% of all videos for adherence to a five- to seven-item checklist/session. Coverage of the checklist was 100% across interventionists for over 100 sessions. A biofeedback device, *emWave2™* (Heartmath, Inc), was provided to caregivers assigned to PEPRR for relaxation exercises outside of session to provide biofeedback of vagal activity (a sign of relaxation).²¹

As an attention control, caregivers randomized to eTAU received, via email, all sections from the workbook provided with PEPRR.

Sections were sent weekly the first month then biweekly for the next two months in the same order in which sessions were presented one-on-one for PEPRR. Check-in calls after each mailing to eTAU ensured receipt of the materials.

2.4 | Outcomes

Patients and caregivers completed questionnaires via a Health Information Portability and Accountability Act (HIPAA) compliant website using REDCap²² or paper format when requested (less than 25%). Meta-analyses have indicated equivalences between paper and electronic formats.²³ Patients and caregivers were asked to complete questionnaires before randomization assignment (baseline) and 1.5, 3, and 6 months following transplant. Final questionnaires were completed 6.4 months (95% CI, 6.2-6.7) and 6.4 months (95% CI, 6.2-6.6) following transplant for patients and caregivers, respectively. The present analysis used full-scale scores and focused on primary and secondary outcomes as registered at www.ClinicalTrials.gov.

2.4.1 | Demographic variables

We obtained demographic information from patients and caregivers including age, sex, race/ethnicity, patient diagnosis, income, education level, patient/caregiver relationship, time of transplant, health behavior information (diet, exercise, nutrition, smoking, etc), medications, and employment status.

2.4.2 | Patient chart review

Information related to transplant was abstracted from patients' medical charts.

Patients completed a QoL questionnaire at baseline and 1.5, 3, and 6 months posttransplant as their primary outcome.

2.4.3 | Functional Assessment of Cancer Therapy–Bone Marrow Transplant

FACT-BMT¹⁹ consists of the FACT-G (FACT-General)²⁴ and the BMT scale¹⁹ to assess QoL related to HSCT anchored to the past 7 days. The FACT-G (27 items) and the BMT component (10 items) were rated on a Likert scale from 0 (not at all) to 4 (very much). Summed scores range from 0 to 148 with higher scores reflecting better QoL.²⁵ Cronbach alpha for the FACT-BMT was 0.87 across assessments.

Caregivers completed the following questionnaires at baseline and 1.5, 3, and 6 months posttransplant as primary and secondary outcomes.

2.4.4 | Center for Epidemiologic Studies–Depression

Center for Epidemiologic Studies–Depression (CES-D) consists of 20 items with total scores ranging from 0 to 60. Higher scores reflect greater depressive symptomology. Test-retest validity ranges from 0.51 to 0.67 over 2 to 8 weeks with an internal validity of 0.85 for a

normal population.²⁶ Scores of 16 and above reflect depressive symptomatology. Cronbach alpha was 0.83 across assessments.

2.4.5 | State-Trait Anxiety Inventory

State-Trait Anxiety Inventory (STAI)²⁷ is a 40-item scale that asked subjects to rate how they feel "right now" (state measure; STAI-S). Internal consistency ranges from 0.89 to 0.92, and test-retest correlations range from 0.73 to 0.86. The scale has been used in both patient and caregiver populations.²⁸ Total score ranges from 20 to 80 with a score of 36 reflecting the population norm for this scale. Higher scores reflect greater anxiety. Cronbach alpha was 0.95 across assessments.

2.4.6 | Perceived Stress Scale

Perceived Stress Scale (PSS) is a 14-item measure of the degree to which participants feel their lives are unpredictable, uncontrollable, and overwhelming during the past month on a 5-point Likert scale²⁹ with good reliability and validity with normative data available. Total score ranges from 0 to 56 with a score of 19 reflecting the population norm. Higher scores reflect greater perceived stress. Cronbach alpha was 0.89 across assessments.

2.4.7 | CG-distress

A PCA extracted the first principal component (CG-distress) from caregiver summary scores from the CES-D, STAI, and PSS. A similar approach combining several psychological measures into a composite score was used previously.⁵ CG-distress has a mean of 0.0 and standard deviation (SD) of 1.0. Higher scores reflect greater distress.

2.4.8 | Caregiver reaction assessment

Caregiver reaction assessment (CRA)³⁰ is a widely used measure of caregiver burden³¹ that includes 24 items scored on a 5-point Likert scale covering domains of self-esteem, family support, finances, schedule, and health. It has excellent test-retest reliability of 0.9 and responsiveness to change of 0.81.³⁰ Total scores range from 5 to 25 with a higher score representing greater caregiver burden. Cronbach alpha was 0.73 across assessments.

2.5 | Analysis

Analyses were completed with SPSS v24.0 (IBM Corporation, Armonk, New York) and SAS v9.4 (SAS Institute INC, Cary, North Carolina) software. All comparisons utilized two-tailed, 0.05 significance levels. Baseline differences in demographic and outcome variables for patients and caregivers in PEPRR and eTAU and between sites were assessed by independent t tests, Fisher exact test, chi-square, Mann-Whitney U test, or Kruskal-Wallis test as appropriate.

Primary and secondary patient and caregiver outcomes were analyzed separately in the intent-to-treat sample by mixed model analyses

of covariance (ANCOVAs) providing group estimates at each month with fixed effects of intervention (PEPRR and eTAU), month (baseline and months 1.5, 3, and 6), site and their interactions and random effect of participant (patient or caregiver, depending on outcome). We removed nonsignificant interactions successively, beginning with most nonsignificant highest-order interactions (group by site by month). The final model for each outcome included group, site, month, and the group by site interaction as well as any significant higher-order interactions. For caregiver outcomes, caregiver age was also included because older age is associated with reduced distress in caregivers.^{5,13} Specified secondary caregiver outcomes included the separate scores from the PCA (depression, anxiety, and stress) as well as caregiver burden.

To provide some protection for multiple comparisons, differences between intervention groups in change from baseline to 6 months were tested only if the omnibus test of the global null hypothesis (ie, means for each group by month combination were equal) was rejected. ESs were calculated as (MeTAU - MPEPRR)/SD, where MeTAU and MPEPRR represent estimated mean change (baseline-6 mo) for eTAU and PEPRR, respectively; SD was computed as the square root of the average of estimated variances at each of the four time points.

To allow adequate (>85%) statistical power to detect medium ESs on CG-distress and to provide power to detect smaller ESs corresponding to hypothesized indirect influences of caregivers' participation in PEPRR on patient FACT-BMT, we initially targeted 112 dyads per group or 224 total dyads. Unfortunately, we were unable to meet recruitment goals within the time allotted by the funding agency. This reduced recruitment to 155 total patient/caregiver dyads. A sample size of 155 patient/caregiver pairs provided 80% to 95% power to detect ESs in the range of 0.23 to 0.30.

The first author (M.L.L.), statistician (S.K.M.-G.), and data manager (C.N.) remained unaware of group assignment until the blind was broken.

3 | RESULTS

3.1 | Participant characteristics

Allo-HSCT patient/caregiver dyads (n = 407) were approached at both sites, of these 331 met eligibility criteria. Of those eligible, 159 consented to participate (47.5%). Dyads were ineligible for the following reasons: (1) did not receive an allogeneic HSCT (28.9%), (2) was not the primary caregiver for the transplant patient (35.5%), (3) could not read or speak English (15.8%), (4) alcohol consumption exceeded two drinks per day (1.3%), (5) were under 18 years of age (2.6%), (6) had a history of an uncontrolled psychiatric illness unrelated to their experience as caregiver within past 18 months (2.6%), or (7) other (18.4%). A CONSORT diagram is available as Figure S1. Intent-to-treat analyses included all randomized participants after removing four screen failures, where one patient did not receive transplant and three patients could not participate because their

caregiver did not consent. Reasons for attrition were related to patient disease progression/death as well as the caregiver feeling overwhelmed. Comparisons of baseline characteristics of caregiver and patients who completed and those who dropped out revealed no differences.

Average patient age was 53.3 years, 64.5% male, predominately Caucasian (80.0%), with a college or higher education (47.7%), a diagnosis of leukemia (60.6%) for which the HSCT was required, and mean diagnosis occurred 19.7 months prior to transplant. Patient baseline demographics are given in Table S1 and for caregivers in Table S2. Caregivers were 54.1 years of age and predominately female (80.0%), Caucasian (83.2%), and many college graduates or above (47.7%). A minority of caregivers were employed full- or part-time while caregiving (39.3%). Initiating care affected employment status such that caregivers employed full-time prior to transplant declined from 41.3% to 20.6% afterwards. Percentage employed part-time did not change significantly (17.4% before the transplant to 18.7% after the transplant). Groups did not differ on primary and secondary psychological outcomes at baseline (see Table 1) or demographics (Tables S1 and S2) signifying adequate randomization. The most frequent reasons for refusal to consent came from caregivers indicating they were either too busy or overwhelmed with the transplant process. "Not interested" occurred on occasion.

3.2 | Primary outcomes

FACT-BMT was not influenced by their caregiver's participation in PEPRR (PEPRR M = 101.8; 95% CI, 94.2-109.4 vs eTAU M = 101.5; 95% CI, 96.2-106.8; group × month interaction: $F_{3,82.3} = 0.11, 0.96$). FACT-BMT did not differ by site but increased (improvement) following a decline at 1.5 months (PEPRR M = 95.8; 95% CI, 90.3-101.2 and

eTAU M = 95.7; 95% CI, 90.4-100.90) with a significant main effect of month ($F_{3,82.3} = 3.47, 0.02$; see Figure 1 and Table 2 for FACT-BMT model estimates).

As predicted, the composite CG-distress score, declined (improved) over time in PEPRR compared with eTAU, evidenced by a significant group by month interaction ($F_{3,95.4} = 4.28, 0.007$) with estimated ES = 0.51 for the change from baseline to 6 months (Table 2) (PEPRR M = -0.20; 95% CI, -0.47 to 0.07 and eTAU M = 0.14; 95% CI, -0.11 to 0.39). The composite CG-distress score was lower in PEPRR compared with eTAU at 6 months (see Figure 2) indicating intervention efficacy.

3.3 | Secondary outcomes

We assessed individual caregiver psychological components contributing to composite CG-distress score to evaluate the separate impact of PEPRR on each variable alone in addition to caregiver burden (CRA) (see Table 2). Depression (CES-D) showed a significant group by month interaction ($F_{3,98.3} = 2.66, 0.05$) with a significant difference between groups in the change from baseline to 6 months ($t_{104} = 2.78, 0.006, ES = 0.61$). The interaction only approached significance for anxiety (STAI) ($F_{3,98} = 2.42, 0.07$) and perceived stress (PSS) ($F_{3,97} = 2.31, 0.08$). However, the change from baseline to 6 months for STAI was significant ($t_{98.2} = 2.52, 0.013, ES = 0.44$) and approached significance for PSS ($t_{102} = 1.93, 0.06$).

Caregiver burden (CRA) was unaffected by participation in PEPRR and did not change from baseline to 6 months for either group.

For caregiver covariates, there was a significant effect of age on CG-distress (0.02). Younger caregivers had higher scores on the CES-D (0.01), STAI (0.04), PSS (0.02) but not on total CRA. None of the outcomes showed significant differences between sites.

TABLE 1 Means (95% CIs) for primary and secondary outcomes at baseline with group comparisons

Characteristics ^a	Mean (95% CI)		Significance ^b
	eTAU (n = 80)	PEPRR (n = 75)	
Primary outcomes			
Caregiver distress score	-0.07 (-0.29 to 0.14)	0.08 (-0.18 to 0.33)	0.36
Patient FACT-BMT total	97.6 (93.3-102.5)	98.4 (94.0-102.8)	0.81
Secondary outcomes			
Caregiver: CES-D	19.9 (18.4-21.5)	20.7 (19.2-22.2)	0.51
Caregiver: STAI	39.5 (36.9-42.1)	41.7 (38.3-45.0)	0.32
Caregiver: PSS	24.3 (22.4-26.2)	25.7 (23.6-27.8)	0.31
Caregiver: CRA total	10.5 (10.0-11.0)	10.4 (9.8-11.1)	0.89

Abbreviations: CES-D, Center for Epidemiologic Studies-Depression; CRA, caregiver reaction assessment; eTAU, enhanced treatment as usual; FACT-BMT, Functional Assessment of Cancer Therapy-Bone Marrow Transplant; PSS, Perceived Stress Scale; STAI, State-Trait Anxiety Inventory.

^aInformation was not available for eTAU for the following variables: caregiver distress (n = 8), FACT-BMT total (n = 13), CES-D (n = 5), STAI (n = 5), PSS (n = 8), and CRA (n = 6). Information was not available for PEPRR for the following variables: caregiver distress (n = 6), FACT-BMT total (n = 7), CES-D (n = 2), STAI (n = 3), PSS (n = 5), and CRA (n = 3).

^bSignificance from independent t test.

Patient FACT-BMT

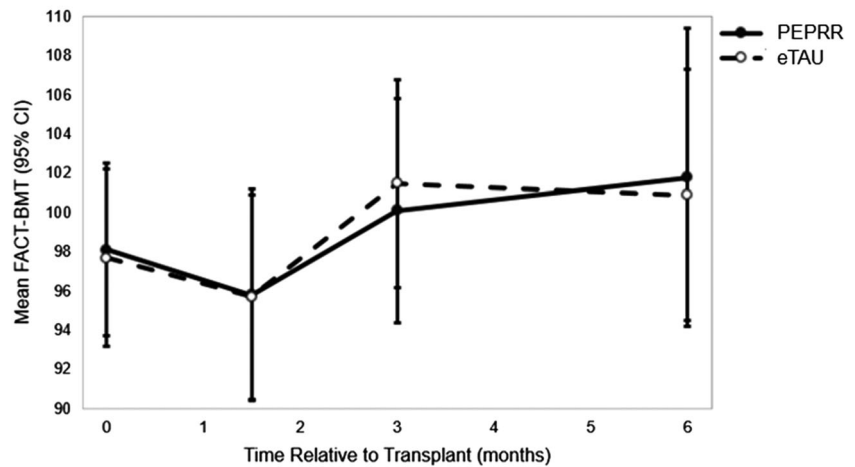
[$F_{(3, 82.3)} = 0.11$; $p=0.96$, $ES=.03$]

FIGURE 1 Patient Functional Assessment of Cancer Therapy–Bone Marrow Transplant (FACT-BMT) over time as a function of group randomization. PsychoEducation, Paced Respiration, and Relaxation (PEPRR) is represented by the solid line and filled symbols. Enhanced treatment as usual (eTAU) is represented by the broken line and open symbols. Error bars enclose 95% CI

4 | DISCUSSION

We began with a pervasive “clinical impression” that patients do better with less distressed caregivers. One assumption is that less distressed caregivers provide more effective emotional support and medical care to patients and thus improve their QoL. A clinical trial ideally selects a single focused primary outcome on which to base efficacy of a trial.³² We selected patient FACT-BMT and CG-distress as primary outcomes. We previously established the combining of psychological measures to create a composite CG-distress score⁵ and found herein that this metric declined in the PEPRR group compared with eTAU replicating our prior trial.¹³ However, the present study failed to find improved patient QoL on the basis of the FACT-BMT despite reduced CG-distress. Using a hybrid approach that combined one-on-one interventions with video chat/telephone chat sessions did not reduce efficacy of PEPRR on CG-distress. These changes were acceptable to caregivers. Although some studies³³ fail to find efficacy for cognitive behavioral therapy interventions similar to PEPRR for cancer caregivers, the present study replicated efficacy in reducing CG-distress across two different transplant programs (academic and community) as well as three interventionists but without an impact on patient's FACT-BMT.

4.1 | Limitations

The present study had several limitations. Lack of support for our primary outcome may reflect our QoL measure (FACT-BMT). Albeit with widespread use,^{19,34} the FACT-BMT focuses on somatic symptoms (nausea, pain, skin and bowel symptoms, etc). It does not directly document psychological status and may oversimplify a complex outcome. We presented only hypotheses registered at ClinicalTrials.gov. The FACT-BMT was our primary patient outcome. Consequently, completion of other psychological questionnaires was deemed more burdensome and less important. Consequentially,

these exploratory measures were not emphasized. Further, we did not collect detailed information regarding the caregiver-patient relationship (duration, quality, or presence of additional caregivers). Failure to support our primary hypothesis may simply reflect the absence of a relationship, our choice of QoL instrument, or inadequate power to detect a change due to its indirect effect. The study was powered on the basis of the impact of PEPRR on caregiver outcomes not those of the patient. PEPRR was efficacious mitigating CG-distress. Despite the use of multilevel modeling to maximize use of every participant regardless of missing data, attrition was greater than expected and represents a significant limitation. Future studies will apply engagement approaches³⁵ to enhance participants' intrinsic motivation by focusing on their own story and their worth to the study and society. Future exploratory analyses including the patients' psychological outcomes will be focused on in follow-up reports.

Another limitation was our inability to recruit a diverse population of caregivers. Despite a large Latino population in Colorado, we have not translated the intervention to Spanish. English is the predominate form of communication in our transplant programs by patients and caregivers. Only a small number of participants identified as Latino (8%), which may relate to the overall underrepresentation of minorities among HSCT patients.³⁶ Another limitation is the restriction to HSCT patients and their caregivers, which we are presently addressing for other cancer diagnoses.

These observations inform best practices for stem cell transplant clinics as far as caregiver wellbeing. The number of stem cell transplants has increased nationally from 16 660 in 2010 to 19 862 in 2015 or about 19%.⁶ The central role of caregivers in HSCTs and its stressful nature⁵ suggests the need for efficacious psychological support to sustain caregivers.¹² A limitation for provision of PEPRR within a transplant clinic is additional staff. Time required to implement PEPRR in a clinic setting is 60 to 75 min per session and 15 to 30 min for record keeping or roughly 90 to 100 min per patient per session.

TABLE 2 Estimates and test results from mixed model analyses of covariance for primary and secondary outcomes and composite scores

Outcome	Intervention		Mean (95% CI)		Mean (95% CI)		Mean (95% CI)		Model Tests		Model Tests		Baseline-6 Mo	
	Group	Baseline	Month 1.5	Month 3	Month 6	Main Effects	Interaction	Group Comparison; Effect Size (ES) ^a						
Primary outcomes														
Caregiver distress score ^b	PEPRR	0.07 (-0.16 to 0.30)	-0.06 (-0.31 to 0.19)	0.00 (-0.27 to 0.28)	-0.20 (-0.47 to 0.07)	Group: $F_{1,140} = 0.27$; 0.60	Group * Month: $t_{101} = -3.07$; 0.003							
	eTAU	-0.09 (-0.31 to 0.14)	0.02 (-0.22 to 0.26)	0.05 (-0.21 to 0.32)	0.14 (-0.11 to 0.39)	Month: $F_{3,93.9} = 1.61$; 0.19	$F_{3,95.4} = 4.28$; ES = -0.51							
Patient FACT-BMT total	PEPRR	98.1 (93.6-102.5)	95.8 (90.3-101.2)	100.1 (94.5-105.8)	101.8 (94.2-109.4)	Group: $F_{1,133} = 0.00$; 1.00	Group * Month: $t_{72.5} = 0.12$; 0.902							
	eTAU	97.7 (93.3-102.2)	95.7 (90.4-100.9)	101.5 (96.2-106.8)	100.9 (94.5-107.3)	Month: $F_{3,82.3} = 3.47$; 0.02	$F_{3,82.3} = 0.11$; ES = 0.03							
Secondary outcomes														
Caregiver: CES-D	PEPRR	20.5 (19.0-22.0)	18.3 (16.9-19.7)	17.8 (16.0-19.7)	18.0 (16.0-20.0)	Group: $F_{1,139} = 2.99$; 0.09	Group * Month: $t_{104} = -2.78$; 0.006							
	eTAU	20.0 (18.5-21.4)	19.6 (18.3-21.0)	20.0 (18.3-21.7)	21.3 (19.4-23.2)	Month: $F_{3,98.3} = 2.03$; 0.11	$F_{3,98.3} = 2.66$; ES = -0.61							
Caregiver: STAI	PEPRR	41.6 (38.6-44.6)	39.6 (36.5-42.6)	39.3 (35.8-42.8)	35.7 (32.2-39.2)	Group: $F_{1,144} = 0.00$; 1.0	Group * Month: $t_{98.2} = -2.53$; 0.013							
	eTAU	39.6 (36.7-42.5)	38.4 (35.4-41.3)	39.2 (35.9-42.6)	39.1 (35.8-42.4)	Month: $F_{3,98.1} = 3.71$; 0.01	$F_{3,98} = 2.42$; ES = -0.44							
Caregiver: PSS	PEPRR	25.5 (23.5-27.4)	22.9 (21.1-24.8)	22.4 (20.1-24.6)	20.5 (18.3-22.7)	Group: $F_{1,139} = 0.03$; 0.86	Group * Month: $t_{102} = -1.93$; 0.06							
	eTAU	24.2 (22.3-26.1)	23.0 (21.2-24.8)	21.3 (19.2-23.5)	21.9 (19.9-24.0)	Month: $F_{3,97.5} = 9.03$; $P < 0.0001$	$F_{3,97.4} = 2.31$; ES = -0.35							
Caregiver: CRA total	PEPRR	10.3 (9.7-10.9)	10.9 (10.3-11.6)	10.9 (10.2-11.7)	10.5 (9.6-11.3)	Group: $F_{1,142} = 0.00$; 0.95	Group * Month: $t_{81.8} = 0.10$; 0.92							
	eTAU	10.4 (9.9-11.0)	10.8 (10.1-11.4)	10.8 (10.0-11.5)	10.5 (9.7-11.4)	Month: $F_{3,91.7} = 2.93$; 0.04	$F_{3,91.6} = 0.25$; ES = 0.02							

Abbreviations: CES-D, Center for Epidemiologic Studies-Depression; CRA, Caregiver Reaction Assessment; PSS, Perceived Stress Scale; STAI-State, State-Trait Anxiety Inventory-State.

^aChange (baseline-6 mo) post hoc t test group comparison and corresponding estimated ES when Group * Month interaction was significant (or 7 df test).

^bComponents of caregiver distress score include CES-D, STAI, and PSS.

Caregiver Distress

[$F_{(3, 95.4)} = 4.28, p = 0.007, ES = .51$]

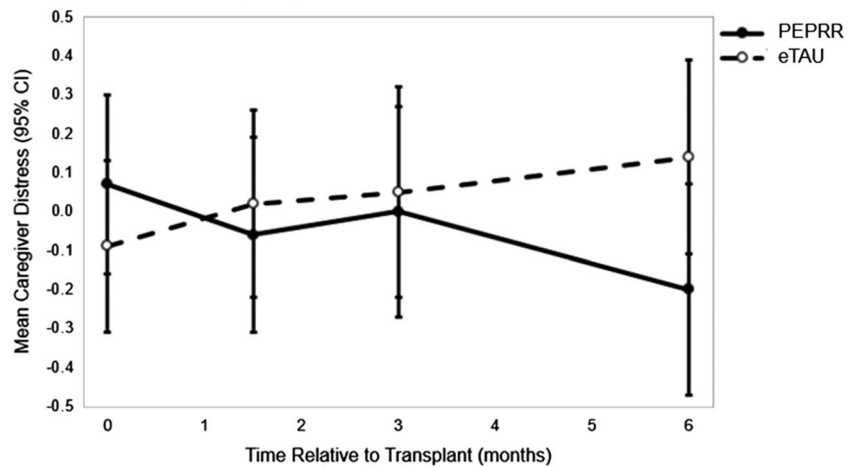


FIGURE 2 Caregiver distress over time as a function of group randomization. PsychoEducation, Paced Respiration, and Relaxation (PEPRR) is represented by the solid line and filled symbols. Enhanced treatment as usual (eTAU) is represented by the broken line and open symbols. Error bars enclose 95% CI

4.2 | Recommendation for future studies

To expand the reach of PEPRR, we hope to implement PEPRR for other cancer caregivers such as breast, lung, or colorectal disease. Additionally, PEPRR for noncancer caregivers (Alzheimer, stroke recovery, or cardiovascular disease patients) needs exploration. These caregivers are also highly distressed with a more prolonged caregiving responsibility compared with HSCT caregivers for whom the challenges tend to begin around transplant.³⁷ We predict similar efficacy, and this will be the focus of future studies that will include both symptom burden scales³⁸ as well as assessing patient satisfaction with care received and patient, caregiver, and family relationships.³⁴ Questionnaires addressing quality and amount of care from the principal caregiver will better inform caregiver science.

Cancer centers increasingly offer some psychosocial services for patients and families while actual use of any psychosocial support services by Allo-HSCT caregivers is quite low.³⁹ There are no published approaches, to our knowledge, for facilitating utilization of caregiver support services. A consistent frustration of caregivers in this study was lack of time to care for themselves. In response, we developed a web-based version of PEPRR⁴⁰ that provides essential elements of PEPRR lasting 7 to 12 minutes. This approach was well received.⁴⁰ If efficacious, it allows for wider dissemination of PEPRR to those unable to participate in the one-on-one approach.

Patient survival is a question for investigation. In our previous study¹³ and the present study, there appears to be no differences in survival at 6 to 12 months posttransplant based on randomization, but this is limited to dyads who remained in the study at those times. Study sites maintain registries of Allo-HSCTs and include posttransplant data collected yearly including transplant outcomes (graft-versus-host disease [GvHD] and relapse) and cause of death. These electronic medical records can provide important insights into meaningful patient outcomes like other work.^{16,17}

5 | SUMMARY

Provision of PEPRR failed to influence patient's QoL based on the FACT-BMT despite reduced CG-distress. Teaching stress management tools to caregivers remain important for reducing CG-distress and may ultimately influence patients in ways not measured by the present study. Following Allo-HSCT patients over a longer time may provide important insights into long-term benefits of caregiver interventions. This project confirmed efficacy of PEPRR for caregivers of Allo-HSCT patients, which may extend to caregivers of other cancer types. This project advances caregiver science by replicating an evidence-based intervention after adding new technology. Unpacking the active component(s) of PEPRR and making it more accessible remain important future goals.

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CONFLICT OF INTEREST

The authors report no conflict of interest.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

- Family Caregiver Alliance. Selected caregiver statistics updated 2015. <https://www.caregiver.org/selected-caregiver-statistics>
- Wolff JL, Spillman BC, Freedman VA, Kasper JD. A national profile of family and unpaid caregivers who assist older adults with health care activities. *JAMA Intern Med.* 2016;176(3):372.
- Kessler ER, Moss A, Eckhardt SG, et al. Distress among caregivers of phase I trial participants: a cross-sectional study. *Support Care Cancer.* 2014;22(12):3331-3340.
- Blazar BR, Murphy WJ, Abedi M. Advances in graft-versus-host disease biology and therapy. *Nat Rev Immunol.* 2012;12(6):443-458.
- Simoneau TL, Mikulich-Gilbertson SK, Natvig C, et al. Elevated peri-transplant distress in caregivers of allogeneic blood or marrow transplant patients. *Psychooncology.* 2013;22(9):2064-2070.
- U. S. Department of Health and Human Services, Health Resources and Services Administration. https://bloodcell.transplant.hrsa.gov/research/transplant_data/transplant_activity_report/index.html#summary
- Sabo B, McLeod D, Couban S. The experience of caring for a spouse undergoing hematopoietic stem cell transplantation: opening Pandora's box. *Cancer Nurs.* 2013;36(1):29-40.
- Beattie S, Lebel S. The experience of caregivers of hematological cancer patients undergoing a hematopoietic stem cell transplant: a comprehensive literature review. *Psychooncology.* 2011;20(11):1137-1150.
- Bevans M, Wehrlen L, Castro K, et al. A problem-solving education intervention in caregivers and patients during allogeneic hematopoietic stem cell transplantation. *J Health Psychol.* 2014;19(5):602-617.
- Applebaum AJ, Bevans M, Son T, et al. A scoping review of caregiver burden during allogeneic HSCT: lessons learned and future directions. *Bone Marrow Transplant.* 2016;51(11):1416-1422.
- Antoni MH, Lehman JM, Kilbourn KM, et al. Cognitive-behavioral stress management intervention decreases the prevalence of depression and enhances benefit finding among women under treatment for early-stage breast cancer. [see comment]. *Health Psychol.* 2001;20(1):20-32.
- Simoneau TL, Kilbourn K, Spradley J, Laudenslager ML. An evidence-based stress management intervention for allogeneic hematopoietic stem cell transplant caregivers: development, feasibility and acceptability. *Support Care Cancer.* 2017;10:10.
- Laudenslager ML, Simoneau TL, Kilbourn K, et al. A randomized control trial of a psychosocial intervention for caregivers of allogeneic hematopoietic stem cell transplant patients: effects on distress. *Bone Marrow Transplant.* 2015;50(8):1110-1118.
- Sannes TS, Simoneau TL, Mikulich-Gilbertson SK, et al. Distress and quality of life in patient and caregiver dyads facing stem cell transplant: identifying overlap and unique contributions. *Support Care Cancer.* 2019;27(6):2329-2337.
- Belgacem B, Auclair C, Fedor M-C, et al. A caregiver educational program improves quality of life and burden for cancer patients and their caregivers: a randomised clinical trial. *Eur J Oncol Nurs.* 2013;17(6):870-876.
- Foster LW, McLellan LJ, Rybicki LA, Sassano DA, Hsu A, Bolwell BJ. Survival of patients who have undergone allogeneic bone marrow transplantation: the relative importance of in-hospital lay care-partner support. *J Psychosoc Oncol.* 2004;22(2):1-20.
- Foster LW, McLellan L, Rybicki L, Dabney J, Copelan E, Bolwell B. Validating the positive impact of in-hospital lay care-partner support on patient survival in allogeneic BMT: a prospective study. *Bone Marrow Transplant.* 2013;48(5):671-677.
- Grulke N, Albani C, Bailer H. Quality of life in patients before and after haematopoietic stem cell transplantation measured with the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Core Questionnaire QLQ-C30. *Bone Marrow Transplant.* 2012;47(4):473-482.
- McQuellon RP, Russell GB, Cella DF, et al. Quality of life measurement in bone marrow transplantation: development of the Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT) scale. *Bone Marrow Transplant.* 1997;19(4):357-368.
- Miller G. The smartphone psychology manifesto. *Perspect Psychol Sci.* 2012;7(3):221-237.
- Sarabia-Cobo CM. Heart coherence: a new tool in the management of stress on professionals and family caregivers of patients with dementia. *Appl Psychophysiol Biofeedback.* 2015;40(2):75-83.
- Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform.* 2009;42(2):377-381.
- Gwaltney CJ, Shields AL, Shiffman S. Equivalence of electronic and paper-and-pencil administration of patient-reported outcome measures: a meta-analytic review. *Value Health.* 2008;11(2):322-333.
- 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(3):570-579.
- Shaw BE, Lee SJ, Horowitz MM, Wood WA, Rizzo JD, Flynn KE. Can we agree on patient-reported outcome measures for assessing hematopoietic cell transplantation patients? A study from the CIBMTR and BMT CTN. *Bone Marrow Transplant.* 2016;51(9):1173-1179.
- Radloff LS. The CESD scale: a self report depression scale for research in the general population. *Appl Psychol Measur.* 1977;1(3):385-401.
- Spielberger CD, Gorsuch RL, Lushene R, Vagg PR, Jacobs GA. *Manual for the State-Trait Anxiety Inventory.* Palo Alto: Consulting Psychologists Press; 1983.
- Raveis VH, Karus D, Pretter S. Correlates of anxiety among adult daughter caregivers to a parent with cancer. *J Psychosoc Oncol.* 1999;17(3-4):1-26.
- Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav.* 1983;24(4):385-396.
- Given CW, Given B, Stommel C, Collins C, King S, Franklin S. The caregiver reaction assessment (CRA) for caregivers to persons with chronic physical and mental impairments. *Res Nurs Health.* 1992;15:271-283.
- Deeken JF, Taylor KL, Mangan P, Yabroff KR, Ingham JM. Care for the caregivers: a review of self-report instruments developed to measure the burden, needs, and quality of life of informal caregivers. *J Pain Symptom Manage.* 2003;26(4):922-953.
- Stanley K. Design of randomized controlled trials. *Circulation.* 2007;115(9):1164-1169.

33. O'Toole MS, Zachariae R, Renna ME, Mennin DS, Applebaum A. Cognitive behavioral therapies for informal caregivers of patients with cancer and cancer survivors: a systematic review and meta-analysis. *Psychooncology*. 2017;26(4):428-437.
34. El-Jawahri AR, Traeger LN, Kuzmuk K, et al. Quality of life and mood of patients and family caregivers during hospitalization for hematopoietic stem cell transplantation. *Cancer*. 2015;121(6):951-959.
35. Grote NK, Swartz HA, Zuckoff A. Enhancing interpersonal psychotherapy for mothers and expectant mothers on low incomes: adaptations and additions. *J Contemp Psychother*. 2008;38(1):23-33.
36. Majhail NS, Nayyar S, Santibanez MEB, Murphy EA, Denzen EM. Racial disparities in hematopoietic cell transplantation in the United States. *Bone Marrow Transplant*. 2012;47(11):1385-1390.
37. Laudenslager ML. "Anatomy of an Illness": control from a caregiver's perspective. *Brain Behav Immun*. 2014;36:1-8.
38. Manne SL, Ostroff JS, Norton TR, Fox K, Grana G, Goldstein L. Cancer-specific self-efficacy and psychosocial and functional adaptation to early stage breast cancer. *Ann Behav Med*. 2006;31(2):145-154.
39. Ouseph R, Croy C, Natvig C, Simoneau T, Laudenslager ML. Decreased mental health care utilization following a psychosocial intervention in caregivers of hematopoietic stem cell transplant patients. *Ment Illn*. 2014;6(1):5120.
40. Pensak NA, Joshi T, Simoneau T, et al. Development of a web-based intervention for addressing distress in caregivers of patients receiving stem cell transplants: formative evaluation with qualitative interviews and focus groups. *J Med Internet Res*. 2017;6(6):e120.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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