A randomized control trial of a psychosocial intervention for caregivers of allogeneic hematopoietic stem cell transplant patients: Effects on distress

Mark L. Laudenslager, PhD.[1], **Teri L. Simoneau, PhD.**[1], **Kristin Kilbourn, PhD.**[2], **Crystal Natvig, BS.**[1], **Sam Philips, BS.**[1], **Janet Spradley, MSW.**[3,4], **Patrick Benitez, BS.**[1], **Peter McSweeney, MB Ch.B.**[3,4], and **Susan K. Mikulich-Gilbertson, PhD.**[1]

[1] University of Colorado Denver Anschutz Medical Campus Department of Psychiatry Aurora Colorado, 80045

[2] Univerity of Colorado Denver Department of Psychology Denver, Colorado, 80217

[3] Presbyterian/St. Luke's Medical Center Denver, CO 80218

Corresponding Author: Mark L. Laudenslager, PhD University of Colorado Denver Anschutz Medical Campus Department of Psychiatry 12700 E. 17th Ave Mail Stop C268-09 Aurora Colorado, 80045 Phone 303-724-9276 Mark.Laudenslager@ucdenver.edu.

4Colorado Blood Cancer Institute Denver, CO 80218

Abstract

Caregivers of patients receiving allogeneic hematopoietic stem cell transplants (Allo-HSCT) serve a pivotal role in patient care but experience high stress, anxiety, and depression as a result. We theorized that a stress management adapted for Allo-HSCT caregivers would reduce distress compared to treatment as usual (TAU). From 267 consecutive caregivers of Allo-HSCT patients approached, 148 (mean=53.5 years, 75.7% female) were randomized to either psychosocial intervention (n=74) or TAU (n=74). Eight 1-on-1 stress management sessions delivered across the 100 day post-transplant period focused on understanding stress, changing role(s) as caregiver, cognitive behavioral stress management, pacing respiration, and identifying social support. Primary outcomes included perceived stress (psychological) and salivary cortisol awakening response (CAR) (physiological). Randomized groups were not statistically different at baseline. Mixed models analysis of covariance (intent-to-treat) showed that intervention was associated with significantly lower caregiver stress 3 months post-transplant (Mean=20.0, CI_{95}=17.9-22.0) compared to TAU (Mean=23.0, CI_{95}=21.0-25.0) with an effect size (ES) of 0.39 (p=0.039). Secondary psychological outcomes, including depression and anxiety, were significantly reduced with ESs of 0.46 and 0.66 respectively. Caregiver CAR did not differ from non-caregiving controls at baseline and was unchanged by intervention. Despite significant caregiving burden, this psychosocial intervention significantly mitigated distress in Allo-HSCT caregivers.

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (Allo-HSCT) is increasingly used for hematological malignancies[1]. Allo-HSCT can be far more demanding than other cancer treatments for patients and families[2]. Recipients require a fulltime caregiver 24/7 for the first 100 days post-transplant or longer. Post-transplant, caregivers must monitor the recipient for numerous complications such as graft versus host disease while providing social and practical support, e.g., transportation[3]. Programs often require that patients remain near the treating hospital thus requiring relocation so emergent issues can be managed by staff trained in Allo-HSCT. Multiple challenges take place while caregivers must additionally balance personal responsibilities (job and other family members). Thus allo-HSCT caregivers experience uncontrollable stressors associated with increased depression and anxiety including a decline of their loved-one's health, separation from their social support and uncertainty about patient prognoses[3, 4].

Depression and anxiety are strikingly elevated in both cancer patients and their caregivers[5] as well as Allo-HSCT caregviers[3]. Allo-HSCT caregivers request help in meeting their patient needs, navigating care transitions, and finding social and emotional support[6]. The Surgeon General provided a prescription for caregivers of reducing stress, attending to depression and anxiety, identifying sources of support, maintaining physical health, and receiving education regarding patient illness[7]. In addition to psychological toll of caregiving, there may be hidden biologic costs to caring for cancer patients[8] similar to those reported in other caregiver populations[9, 10]. Although decrements in cancer

caregiver well-being have been reported(11), physiological consequences in Allo-HSCT caregivers have not been reported.

Psychosocial interventions targeting distress of cancer caregivers are needed(12), yet there are relatively few(13) and trials of these intervention suffer from methodological problems(14). The present randomized clinical trial (RCT) tested a psychosocial intervention for Allo-HSCT caregiver's unique needs that addressed the Surgeon General's recommendations(7). We modified an efficacious cognitive-behavioral stress management intervention for cancer *patients* to meet the unique needs of Allo-HSCT *caregivers* based on clinical experience, stakeholder input, and a transactional stress and coping model(15, 16). We added a supplementary means for the participants to create a brief relaxing respite though the use of a biofeedback device approved for blood pressure reduction that paces and slows respiration (17) which we felt would facilitate relaxation. As the primary _behavioral_ outcome, stress was assessed via the Perceived Stress Scale (PSS)(18) due to the scale measuring a sense of control. As the primary _physiological_ outcome, the cortisol awakening response (CAR) represents the change, typically a rise, in salivary cortisol between awakening and 30 min later and is tied to anticipation of the upcoming day's activities, high demands the preceding day, or depression(19, 20). CAR is reduced in depression(20, 21) as well as in caregivers(22) and is negatively associated with the PSS(23). We hypothesized that the intervention would mitigate distress in caregivers such that at the three-month intervention completion point, caregivers randomized to stress management would have 1) reduced PSS, 2) increased CAR, 3) a decline in secondary psychological outcomes (e.g., anxiety and depression) and 4) reduced markers of immune disturbance in comparison to those randomized to TAU.

METHODS

Eligibility Criteria

Caregivers and their patients were recruited consecutively between 11/2008 and 4/2012 during pre-transplant screening of _all_ Allo-HSCT patients (n= 267) and their caregivers at a single site (Presbyterian St. Luke's Medical Center, Denver, CO). Caregiver inclusion criteria included caring for an Allo-HSCT patient at least 50% of the time during the first 100 days post-transplant, able to speak/read English, 18 years or older, and with telephone access; their patients must have received an Allo-HSCT, able to speak/read English, and 18 years or older. Exclusion criteria included history of psychiatric illness (based on caregiver report) in the past 18 months (_unrelated_ to patient illness) or diagnosis of medical condition or medications that might affect biomarkers. Caregivers and patients provided informed consent approved by the Colorado Multiple Institutional Review Board. Collecting demographics or information from those refusing consent was not permitted. Thirty-two non-caregiving controls were recruited from the university community to provide a comparison group for the biomarkers which did not have widely accepted norms (See Supplemental Information for description).

Study Design

Consented participants (n=148 caregivers) were randomized with intent-to-treat by permuted block design to either PsychoEducation, Paced Respiration and Relaxation (PEPRR) or treatment as usual (TAU) as indicated in the CONSORT diagram(24) in Figure 1(also see additional comments in Footnote). The biostatistician (SKM-G) developed the randomization allocation which was available only to the site coordinator (TLS).

Intervention

PEPRR consisted of eight semi-structured 1-on-1 sessions with a master's level social worker beginning 16 ± 10 days (Mean $\pm$ SD) post-transplant (transplantation day set as 0). Sessions were based on an intervention for cancer _patients_ (16) which we modified to address Allo-HSCT _caregiver_ specific needs. PEPRR utilized a Transactional Model of Stress and Coping, which predicts that those able to handle and adapt to the challenges of caregiving using tools taught in the program will show lower levels of stress(16). This approach has been the basis for numerous effective interventions and shown to improve coping and adaptation to stressful life events(25).

Sessions began on average 2 weeks post-transplant and continued weekly to complete all sessions before the three month assessment. Sessions lasted 60-75 min, were manualized, and followed the same order with some flexibility in content as needed. To minimize caregiver burden, all sessions took place at the hospital when caregivers were visiting with their patients during hospitalization or at the clinic during times when caregivers brought patients to appointments.

Sessions included in order: 1) program overview, instructions for biofeedback device (see below), and introduction to stress management, 2) impact of stress on physical and emotional health, 3) how thoughts and emotions lead to stress, 4) coping skills training, 5) management of fatigue, sleep, and other health behaviors, 6) addressing lack of control, uncertainty, and fear, 7) improving partner communication strategies and adapting to changing role(s), and 8) effective utilization of social support. A workbook including session topics was provided for use during sessions with homework recommended but not assessed. Interventionist fidelity (>90%) to the manual was randomly checked by video for 20% of sessions. Details of this intervention are the subject of a subsequent report.

Caregivers randomized to PEPRR also received a biofeedback device, RESPeRATE® (InterCure, Fort Luc, NJ), with established efficacy for reducing hypertension(17). The RESPeRATE® entrained respiration to specific tones which increased in duration to slow and deepen respiration. Caregivers were asked to use this device for 15 min at least 4-5 times/week to facilitate relaxation. The device recorded participant's use and this data was uploaded to address adherence. Of the research participants randomized to PEPRR, only 12 caregivers (16%) showed consistent (weekly) use for the device throughout the intervention phase with overall usage by others declining by the third week after beginning PEPRR. Adherence and satisfaction with this device was mixed and will be reported elsewhere.

All caregivers were encouraged to avail themselves of programs at the transplant clinic including individual counseling, support groups and education classes. These voluntary

programs focused on caregiving stress, taking care of oneself, identifying important community resources, and specific problems raised by participants. Support in navigating the complex HSCT program (e.g., arranging local housing following patient hospital discharge, insurance, diet restrictions, etc.) was also available. Programs were free of charge to anyone who wanted assistance (family and/or caregivers) and were attended at least one time by 16.1% of the TAU group and 7.2% of the PEPRR group during the 100 day post-transplant period. TAU caregivers received follow up calls from research staff to sustain study retention, set up return appointments, and encourage questionnaire completion.

Psychological Outcomes

Questionnaires were completed prior to study randomization and patient transplant (M=-1 day relative to transplant which was treated as day zero, SD=10) reflecting Baseline, and at Month 1 (M=37 days post-transplant, SD=10) and Month 3 (M=93 days post-transplant, SD=14). The Month 1 assessment was typically completed after 1-2 intervention sessions and the Month 3 assessment always occurred after completion of the full program. Instruments were anchored to the preceding month and included the primary psychological outcome, the 14 item Perceived Stress Scale (PSS)(18), a validated self-report of control over stress which we have shown to be elevated in Allo-HSCT caregivers(3) and other caregivers(26). Secondary psychological outcomes included depression (Center for Epidemiological Studies Depression scale, CESD score)(27) and state anxiety (State-Trait Anxiety Inventory, STAI score)(28) which show significant elevation in cancer patients and caregivers(5)(5). The Caregiver Reaction Assessment (CRA)(29) assessed post-transplant changes in burden. Total mood disturbance (Profile of Mood States, POMS-TMD)(30), sleep (Pittsburgh Sleep Quality Inventory, PSQI)(31), mental and physical health (Short Form Health Survey Version 2, SF-36 summary scales)(32), and trauma (Impact of Events Scale, IES)(33) were evaluated. All instruments have excellent validity and reliability. Of caregivers enrolled at baseline and those remaining at 1 and 3 month collection times, 99, 93, and 90% returned their questionnaires respectively. Since the focus was on caregivers and to minimize burden, patients completed *only* demographic questionnaires and SF-36 at times corresponding to caregivers.

A caregiver composite distress score (CG-Distress) was created by principal component analysis (PCA) on 5 affective variables (PSS, POMS-TMD, CESD, STAI, and IES) at each time and a composite measure of caregiver physical "well-being" (CG-Well-being) summed standardized scores of CG-Distress, PSQI, CRA, and SF-36 Physical score as described elsewhere(3).

Physiological Outcomes

The cortisol awakening response (CAR)(19) was the primary physiological outcome. A comprehensive panel of physiological markers (Supplemental Information) reflecting neuroendocrine status (diurnal salivary cortisol and DHEA) and immune parameters (natural cytotoxicity and inflammation) were collected as secondary physiological outcomes from caregivers at the time of questionnaire completion.

Statistical analysis

To allow sufficient (90%) statistical power based on existing literature (36)(34) to detect small to medium effect sizes (ES), 170 pairs of caregivers and their corresponding patients were initially targeted. Funding cut-backs lowered this to 148 caregivers with their corresponding patients, which still provided power to detect ESs greater than 0.27, after allowing for planned attrition. Intent-to-treat analyses (including all randomized participants after removing one screen failure) used SPSS version 20.0 (IBM Corporation) and SAS version 9.3 (SAS Institute, Inc.) software. Baseline differences between PEPRR and TAU caregivers and patients on demographic and other key variables were assessed by chi-square and independent t-tests or nonparametric Mann-Whitney U and Fisher's Exact tests when data distributions were non-normal. Patient' and caregiver age was compared by paired t-test between TAU and PEPRR. Analyses of Variance (ANOVAs) compared biomarker levels at baseline among PEPRR and TAU caregivers and non-caregiving controls. Patterns of missing data were evaluated with chi-square tests comparing PEPRR and TAU groups at each time.

Caregiver outcomes were analyzed by mixed models analyses of covariance (ANCOVA) using Satterthwaite approximation for degrees of freedom providing group estimates at each month with fixed effects of intervention (PEPRR, TAU), month (Baseline, Month1 and Month 3), and their interaction while co-varying for caregiver age because older age is associated with greater resilience in response to challenge(35). Repeated measures were assumed to have unstructured covariance(36). To provide some protection for multiple comparisons(37), group effects were tested at month 3 *only if* the omnibus test of the global null hypothesis (i.e. means for each group by month combination were equal) was rejected. Effect Sizes (ESs) at month 3 were calculated as (MTAU - MPEPRR)/SD, where MTAU and MPEPRR represents adjusted means of TAU and PEPRR respectively at month 3 for outcomes and standard deviation (SD) was computed as the square root of estimated variance of each outcome at Month 3. Comparisons utilized a two-tailed, 0.05 significance level. Outcomes collected at 6 and 12 months are not included here but are an ongoing secondary analysis.

RESULTS

Sample Characteristics

Neither caregiver nor patient characteristics differed by randomization group. Tests evaluating continuous outcomes indicated variances were similar between groups. Caregivers averaged 53.5 years (range 21-80) and were predominately female (75.7%)/ Caucasian (89.9%) consistent with caregiver demographics(38). During this recruiting period, the percentage of all males presenting for Allo-HSCT at this clinic was 65.3% and thus the consented sample was representative of this clinic's patients. Fully employed caregivers declined from 48% pre-transplant to 23.7% post-transplant. Complete details are provided in Table 1.

Half of patients (54.1%) were diagnosed with leukemia. Patients' illness demographics were similar across groups (Table 1) with one exception; time to neutrophil engraftment [absolute

neutrophil count >500/microliter for three consecutive days(39)] was 2.5 days earlier for TAU compared to PEPRR (p=.04). Since engraftment and first intervention session occurred around the same day (+16 days), this was unlikely related to group assignment. During the 100 days post-transplant, a total of 11 patients died representing 6 in TAU and 5 in PEPRR. Although encouraged to continue completing questionnaires and the intervention, only two caregivers from PEPRR returned questionnaires while none completed the intervention. However all available caregiver data is included in the intent to treat design.

Prior to randomization, perceived stress (PSS) exceeded population norms of 19.2 for this age range(40). Scores on the CESD for individual caregivers approached and occasionally exceeded published depression cutoffs of 16 (27)(Table 2). Scores greater than 16 triggered a clinical follow up by staff regardless of group assignment (Table 2). Elevated anxiety and poor sleep based on national norms were also noted in caregivers prior to intervention. There was no difference between groups at baseline in psychological measures based on randomization as indicated in Table 2.

Efficacy Outcomes

Chi-square tests confirmed no differences between groups in the pattern of missing data. Of 148 participants, 18.9% and 17.9% were missing data respectively on primary psychological and physiological outcomes across months. Caregivers typically found the intervention acceptable with 70% completing all eight sessions. Reasons for drop-out included inadequate time (n=10), patient becoming gravely ill (n=2), or patient death (n=11) and did not differ by group. Table 3 presents model estimates (Mean, 95% CI) by month for PEPRR and TAU for primary and secondary psychological outcomes based on ANCOVAs of outcomes by group, month, and interaction. Caregiver age was a significant covariate (p's<. 05); younger caregivers reported greater distress as predicted(35). All main effects and interaction test results are reported in Table 3 regardless of significance as well as post hoc comparisons and estimated ESs for the three month comparisons *only when interactions were significant*.

A *reliable pattern of reduced distress* at month three across psychological measures was noted for participants receiving PEPRR (Table 3). Figure 2 shows model predictions for the primary outcome, PSS. At three months post-transplant, PEPRR caregivers were significantly lower than TAU for PSS [$t_{(117)}$=2.09; p=0.039] with an ES of 0.39 which declined below population norms at three months whereas PSS in TAU *increased*. Similarly anxiety and depression were significantly lower in PEPRR compared to TAU with ESs of 0.66 and 0.46, respectively. This overall pattern held for total mood disturbance (POMS-TMD) as well as the composite distress score. Graphic model predictions with confidence intervals for anxiety (Figure 3) and depression (Figure 4) are provided. Consistency across multiple psychological domains supports that PEPRR is efficacious in mitigating distress in spite of increasing caregiver burden (CRA) reflecting rising demand post-transplant.

Unlike reports of other caregiver populations(9, 10), caregivers' biomarkers at baseline did not differ from non-caregiving controls (Supplemental Information Table A). CAR and other caregivers' biomarkers did not change as a function of intervention nor with regard to time (Supplemental Table B). Consequently, detailed descriptions of methods, analysis, and

results of primary and secondary physiological outcomes are provided as Supplementary Information.

DISCUSSION

Allo-HSCT caregivers are highly distressed during the transplant process. The present observations are significant because they indicate that distress commonly reported in caregivers(3, 41) can be mitigated by a semi-structured psychosocial intervention tailored to meet the needs of Allo-HSCT caregivers. Comparable reductions in distress have also been reported for Alzheimer's patient caregivers receiving a similar intervention(42).

Visual inspection suggests a trend for a decline in caregiver distress in both groups one month post-transplant (Table 3) during patient hospitalization. At discharge 2-5 weeks post-transplant, Allo-HSCT caregivers assume full burden of care. Increasing caregiver burden (see CRA, Table 3) post-transplant indicated the realities of an Allo-HSCT, e.g., uncertainties, sudden changes in patient's physical condition, and most of all increased caregiver demands following discharge. Despite rising caregiver burden, the ability to attenuate key psychological markers through eight sessions of stress management training is significant in this challenging situation.

Reduced distress in caregivers are consistent with patient populations receiving a similar intervention. For example, breast cancer patients receiving this intervention showed reduced depression(25). Although HIV+ males receiving a similar intervention revealed changes in plasma cortisol and DHEA(43), the present study noted no changes. This difference may be due to the physiological disruption present in HIV+ participants unlike the present caregivers (see Supplemental Information) in spite of significant psychological distress. Caregiver's self-reported physical health score also remained close to population norms (32) throughout the first 100 days (see Table 3) suggesting participants were relatively healthy.

A lack of physiological disruption as measured by the CAR and other secondary biomarkers differs from reports of physiological disturbance in caregivers of other patient populations(8-10). This was unanticipated in light of signficant psychological distress. Reasons for this discrepancy may include duration of Allo-HSCT caregiving, patient prognosis, and/or a bias to select only healthy caregivers for Allo-HSCT patients. Interestingly, duration of caregiving is rarely reported in caregiver research but when reported it often exceeds four years(4). For the present group, the average time since cancer diagnosis, and importantly not necessarily caregiving per se, was 26 months, full caregiving responsibilities may not begin until the patient is discharged from the hospital following transplant. It is likely the impact of the cancer diagnosis and/or caregiving stress on physiological functioning is not measurable in during the current timeframe. Longitudinal studies of these caregivers are needed to address this question more fully and are presently underway.

Secondly, Allo-HSCT is a relatively efficacious treatment option(1) with up to 70% long term survival compared to the experiences of caring for progressive decline in cognitively impaired persons(44). Thus shorter caregiving duration and better prognosis for Allo-HSCT

patients may have contributed to the lack of differences in biomarkers in Allo-HSCT caregivers compared to other caregiver groups. Longer term caregiving represents a chronic stressor affecting allostatic load wherein regulation of the hypothalamic pituitary adrenal (HPA) axis and other stress responsive systems are disrupted(45).

Poor sleep is associated with increased inflammation (46). However self-reported caregiver sleep(31) and inflammatory markers were not affected by PEPRR which was also unrelated to the caregiver's symptom experience in the immediate post-transplant period. That is, the composite physical well-being score from the SF36 was stable and within population norms(32). We have observed a similar pattern of good physical health in caregivers of Phase 1 trial cancers patients in the presence of considerable psychological distress(41). Medically healthy caregivers are necessary given the rigor of the Allo-HSCT procedure. Caregivers undergo significant prescreening before approval raising a potential selection bias against disrupted physiological regulation.

The median 100 day cost for Allo-HSCT is $203,206 (USD) covering all aspects of the treatment(47). Caregiver intervention delivered by a social worker represented about 12-14 care hours. Mean pay for a master's level social worker is approximately $24.28/hr (May, 2011, United States Bureau of Labor Statistics), representing less than $350. The biofeedback devices cost less than $150 bringing the cost of this intervention to $500. An allogeneic transplant is impossible without a caregiver 24/7. This comes at a cost to the caregiver in terms of mental health consequences as well as lost wages. Similar coping training for Alzheimer's caregivers was cost neutral and associated with improved caregiver quality of life(48).The burden of caregiving for a loved one with cancer clearly points to a need for a cost-benefit analysis of providing cancer caregiver intervention(s) as part of the standard of care for families experiencing an Allo-HSCT. A future cost effectiveness analysis of the present approach is definitely warranted.

Several limitations were present. First the demographics of this particular clinic limited the diversity of caregivers creating a relatively homogenous group as well as a relatively small sample size. Second, there was a single interventionist. Third, we did not address differences in the caregiver-patient dyadic relationships. Fourth, we did not assess patient quality of life based on commonly accepted approaches. Finally, caregiver's personal health and well-being may affect the quality of support caregivers provide their patients in significant and poorly understood ways which we did not assess. These limitations are targets of a multisite trial currently underway utilizing this intervention.

In summary in spite of increasing caregiver burden post-transplant, PEPRR proved to be efficacious in mitigating the corresponding psychological 4distress in Allo-HSCT caregivers. Recuing distress has the potential benefit of improving caregiver well-being and thus may permit the caregiver to be more effective in fulfilling their caregiver task(s).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

References

1. Li HW, Sykes M. Emerging concepts in haematopoietic cell transplantation. Nature Rev Immunol. 2012; 12(6):403–16. [PubMed: 22627859]

2. Bevans M, Sternberg EM. Caregiving burden, stress, and health effects among family caregivers of adult cancer patients. Jama. 2012; 307(4):398–403. [PubMed: 22274687]

3. Simoneau TL, Mikulich-Gilbertson SK, Natvig C, Kilbourn K, Spradley J, Grzywa-Cobb R, et al. Elevated peri-transplant distress in caregivers of allogeneic blood or marrow transplant patients. Psychooncology. 2013; 22(9):2064–70. [PubMed: 23440998]

4. Laudenslager ML. "Anatomy of an Illness": control from a caregiver's perspective. Brain Behav Immun. 2014; 36:1–8. [PubMed: 24012646]

5. Mitchell AJ, Ferguson DW, Gill J, Paul J, Symonds P. Depression and anxiety in long-term cancer survivors compared with spouses and healthy controls: a systematic review and meta-analysis. The Lancet Oncology. 2013; 14(8):721–32. [PubMed: 23759376]

6. Tsigaroppoulos T, Mazaris E, Chatzidarellis E, Skolarikos A, Varkarakis I, Deliveliotis C. Problems faced by relatives caring for cancer patients at home. Int J Nurs Pract. 2009; 15(1):1–6. [PubMed: 19187163]

7. Ulrich B. Caring for the caregivers. Nephrology Nursing Journal. 2007; 33(2):129. [PubMed: 16613410]

8. Rohleder N, Marin TJ, Ma R, Miller GE, Rohleder N, Marin TJ, et al. Biologic cost of caring for a cancer patient: dysregulation of pro- and anti-inflammatory signaling pathways. J Clin Oncol. 2009; 27(18):2909–15. [PubMed: 19433690]

9. Kiecolt-Glaser JK, Preacher KJ, MacCallum RC, Atkinson C, Malarkey WB, Glaser R. Chronic stress and age-related increases in the proinflammatory cytokine IL-6. Proc Natl Acad Sci U S A. 2003; 100(15):9090–5. [PubMed: 12840146]

10. von Kanel R, Dimsdale JE, Mills PJ, Ancoli-Israel S, Patterson TL, Mausbach BT, et al. Effect of Alzheimer caregiving stress and age on frailty markers interleukin-6, C-reactive protein, and D-dimer. J Gerontol A Biol Sci Med Sci. 2006; 61(9):963–9. [PubMed: 16960028]

11. Braun M, Mikulincer M, Rydall A, Walsh A, Rodin G. Hidden morbidity in cancer: spouse caregivers. J Clin Oncol. 2007; 25(30):4829–34. [PubMed: 17947732]

12. Northouse LL, Katapodi MC, Schafenacker AM, Weiss D. The impact of caregiving on the psychological well-being of family caregivers and cancer patients. Semin Oncol Nurs. 2012; 28(4):236–45. [PubMed: 23107181]

13. Gillick MR. THe critical role of caregivers in achieving patient-centered carethe critical role of caregivers in achieving patient-centered careviewpoint. Jama. 2013:1–2.

14. Northouse L, Williams A-L, Given B, McCorkle R. Psychosocial care for family caregivers of patients with cancer. J Clin Oncol. 2012; 30(11):1227–34. [PubMed: 22412124]

15. Antoni MH, Lutgendorf SK, Blomberg B, Carver CS, Lechner S, Diaz A, et al. Cognitive-behavioral stress management reverses anxiety-related leukocyte transcriptional dynamics. Biol Psychiatry. 2012; 71(4):366–72. [PubMed: 22088795]

16. Antoni MH, Lechner S, Diaz A, Vargas S, Holley H, Phillips K, et al. Cognitive behavioral stress management effects on psychosocial and physiological adaptation in women undergoing treatment for breast cancer. Brain Behav Immun. 2009; 23(5):580–91. [PubMed: 18835434]

17. Gavish B. Device-guided breathing in the home setting: technology, performance and clinical outcomes. Biol Psychol. 2010; 84(1):150–6. [PubMed: 20193729]

18. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. Journal of Health & Social Behavior. 1983; 24(4):385–96. [PubMed: 6668417]

19. Clow A, Hucklebridge F, Stalder T, Evans P, Thorn L. The cortisol awakening response: more than a measure of HPA axis function. Neurosci Biobehav Rev. 2010; 35(1):97–103. [PubMed: 20026350]

20. Saban KL, Mathews HL, Bryant FB, O'Brien TE, Janusek LW. Depressive symptoms and diurnal salivary cortisol patterns among female caregivers of stroke survivors. Biol Res Nurs. 2012; 14(4): 396–404. [PubMed: 22531368]

21. Huber TJ, Issa K, Schik G, Wolf OT. The cortisol awakening response is blunted in psychotherapy inpatients suffering from depression. Psychoneuroendocrinology. 2006; 31(7):900–4. [PubMed: 16707227]

22. de Vugt ME, Nicolson NA, Aalten P, Lousberg R, Jolle J, Verhey FRJ. Behavioral problems in dementia patients and salivary cortisol patterns in caregivers. J Neuropsychiatry Clin Neurosci. 2005; 17(2):201–7. [PubMed: 15939974]

23. Wahbeh H, Kishiyama SS, Zajdel D, Oken BS. Salivary cortisol awakening response in mild Alzheimer disease, caregivers, and noncaregivers. Alzheimer Dis Assoc Disord. 2008; 22(2):181–3. [PubMed: 18525292]

24. Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG, et al. CONSORT for reporting randomised trials in journal and conference abstracts. Lancet. 2008; 371(9609):281–3. [PubMed: 18221781]

25. Antoni MH, Lechner SC, Kazi A, Wimberly SR, Sifre T, Urcuyo KR, et al. How stress management improves quality of life after treatment for breast cancer. Journal of Consulting & Clinical Psychology. 2006; 74(6):1143–52. [PubMed: 17154743]

26. Ostwald SK, Bernal MP, Cron SG, Godwin KM. Stress experienced by stroke survivors and spousal caregivers during the first year after discharge from inpatient rehabilitation. Topics in Stroke Rehabilitation. 2009; 16(2):93–104. [PubMed: 19581196]

27. Radloff LS. The CESD Scale: A self report depression scale for research in the general population. Applied Psycholoigcal Measurement. 1977; 1:385–401.

28. Spielberger, CD.; Gorsuch, RL.; Lushene, R.; Vagg, PR.; Jacobs, GA. Manual for the State-Trait Anxiety Inventory. Consulting Psychologists Press; Palo Alto: 1983.

29. Given CW, Given B, Stommel C, Collins C, King S, Franklin S. The caregiver reaction assessment (CRA) for caregivers to persons wth chronic physical and mental impairments. Research in Nursing and Health. 1992; 15:271–83. [PubMed: 1386680]

30. McNair, DM.; Lorr, M.; Droppleman, LO. EITS Manual for the profile of moods states. Educational Testing Service; San Diego CA: 1971. p. 23

31. Buysse DJ, Reynolds CF 3rd, Monk TH, Bergman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Research. 1989; 28:193–213. [PubMed: 2748771]

32. Ware, JE.; Kosinski, M.; Dewey, JE. How to Score Version 2 of the SF-36 Health Survey. Quality Metric Incorporated; Lincoln, RI: 2000. p. 281

33. Horowitz M, Wilner N, Alverez W. Impact of event scale: a measure of subjective stress. Psychosom Med. 1979; 41:209–18. [PubMed: 472086]

34. Gemmill R, Cooke L, Williams AC, Grant M. Informal caregivers of hematopoietic cell transplant patients: a review and recommendations for interventions and research. Cancer Nurs. 2011; 34(6):E13–21. [PubMed: 21242762]

35. Charles ST. Strength and vulnerability integration: a model of emotional well-being across adulthood. Psychol Bull. 2010; 136(6):1068–91. [PubMed: 21038939]

36. Brown, H.; Prescott, R. Applied Mixed Models in Medicine. John B. Wiley & Sons; New York, NY: 1999.

37. D'Agostino RB, Heeren TC. Multiple comparisons in over-the-counter drug clinical trials with both positive and placebo controls. Stat Med. 1991; 10(1):1–6. discussion 7-31. [PubMed: 2006348]

38. Vlachantoni A. The demographic characteristics and economic activity patterns of carers over 50: evidence from the English Longitudinal Study of Ageing. Popul Trends. 2010; (141):51–73. [PubMed: 20927029]

39. Hoffman, R.; Benz, E.; Silberstein, L.; Heslop, H.; Weitz, J.; Anastazi, J. Hematology: Basic Principles and Practice. 6 ed.. Saunders; Philadelphia: 2013.

40. Cohen, S.; Williamson, G. Perceived stress in a probability sample of the United States.. In: Spacapan, S.; SE, O., editors. The social psychology of health. Sage; Newbarry Park, CA: 1988.

41. Kessler ER, Moss A, Eckhardt SG, Laudenslager ML, Kilbourn K, Mauss IB, et al. Distress among caregivers of phase I trial participants: a cross-sectional study. Support Care Cancer. 2014; 22(12): 3331–40. [PubMed: 25120010]

42. Livingston G, Barber J, Rapaport P, Knapp M, Griffin M, King D, et al. Clinical effectiveness of a manual based coping strategy programme (START, STrAtegies for RelaTives) in promoting the mental health of carers of family members with dementia: pragmatic randomised controlled trial. Bmj. 2013; 347:f6276. [PubMed: 24162942]

43. Cruess DG, Antoni MH, Kumar M, Ironson G, McCabe P, Fernandez JB, et al. Cognitive-behavioral stress management buffers decreases in dehydroepiandrosterone sulfate (DHEA-S) and increases in the cortisol/DHEA-S ratio and reduces mood disturbance and perceived stress among HIV-seropositive men. Psychoneuroendocrinology. 1999; 24(5):537–49. [PubMed: 10378240]

44. Lopez OL, Schwam E, Cummings J, Gauthier S, Jones R, Wilkinson D, et al. Predicting cognitive decline in Alzheimer's disease: an integrated analysis. Alzheimer's dement. 2010; 6(6):431–9. [PubMed: 21044773]

45. McEwen B, Lasley EN. Allostatic load: when protection gives way to damage. Adv Mind Body Med. 2003; 19(1):28–33. [PubMed: 12825411]

46. Irwin MB, Wang M, Ribiero D, Cho HJ, Olmstead R, Breen EC, et al. Sleep loss activates cellular inflammatory signaling. Biol Psychiatry. 2008; 64:538–40. [PubMed: 18561896]

47. Majhail NS, Mau LW, Denzen EM, Arneson TJ. Costs of autologous and allogeneic hematopoietic cell transplantation in the United States: a study using a large national private claims database. Bone Marrow Transplant. 2013; 48(2):294–300. [PubMed: 22773126]

48. Knapp M, King D, Romeo R, Schehl B, Barber J, Griffin M, et al. Cost effectiveness of a manual based coping strategy programme in promoting the mental health of family carers of people with dementia (the START (STrAtegies for RelaTives) study): a pragmatic randomised controlled trial. Bmj. 2013; 347:f6342. [PubMed: 24162943]
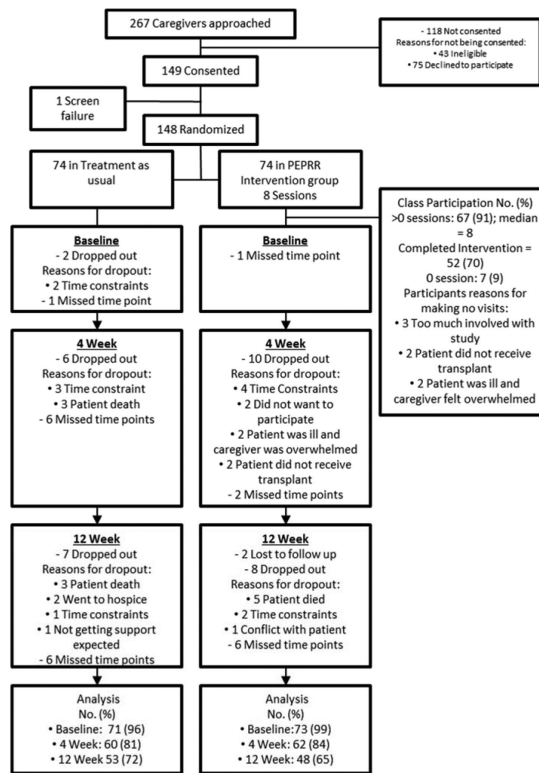
Figure 1.
CONSORT diagram (24) representing subject flow and attrition through the study. From 267 patient-caregiver pairs approached, 149 were consented and 148 were randomized. Reasons for dropout are indicated as well as numbers available for analysis. See Footnote.
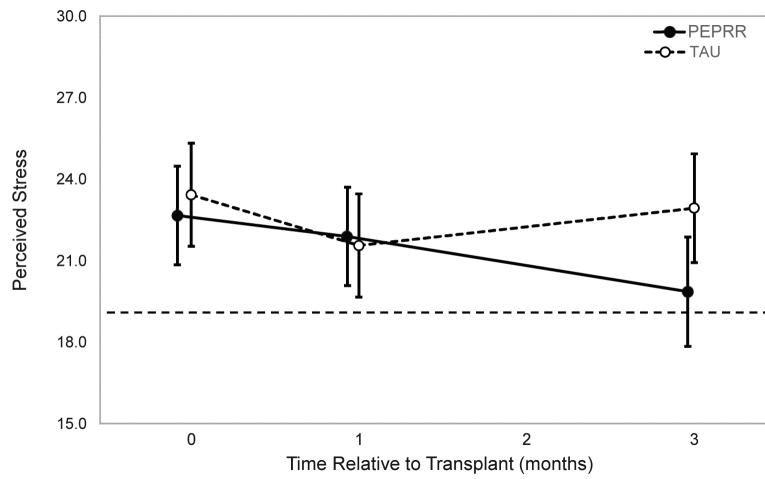
Figure 2.
Primary psychological outcome of Perceived Stress Score (PSS) (18). Model predictions at Baseline and months 1 and 3 post-transplant for treatment as usual (TAU) [open symbols, broken line] and the intervention, Psychoeducation, Paced Respiration, and Relaxation (PEPRR), [filled symbols, solid line] with 95% CI at each collection time are shown. The horizontal broken line indicates the population mean in a healthy comparably aged population (40).
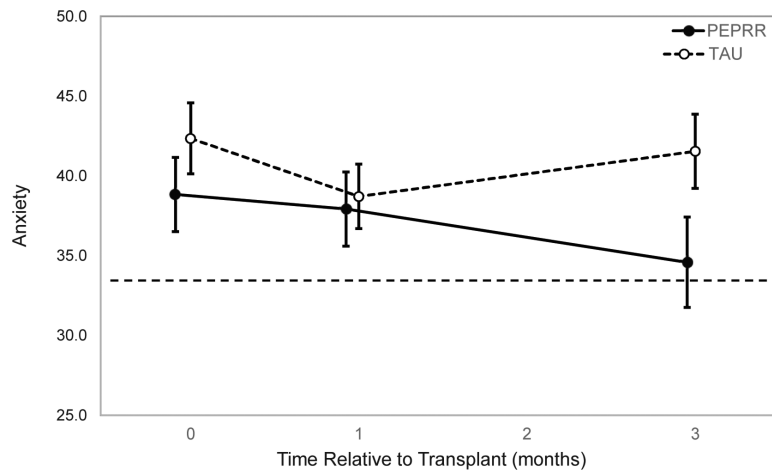
Figure 3.
Secondary psychological outcome of anxiety based on the Spielberger State Anxiety Score (28). Model predictions at Baseline and months 1 and 3 post-transplant for treatment as usual (TAU) [open symbols, broken line] and the intervention, Psychoeducation, Paced Respiration, and Relaxation (PEPRR), [filled symbols, solid line] with 95% CI at each collection time are shown for this secondary psychological outcome. The horizontal broken line indicates the population mean in a healthy comparably aged population (28).
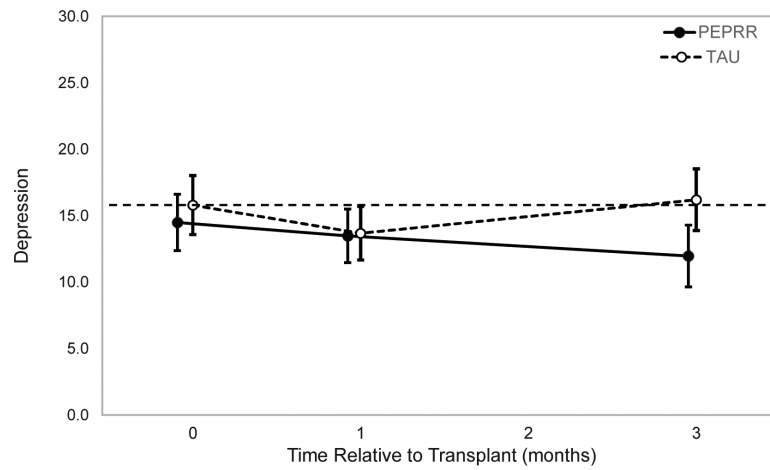
Figure 4.
Secondary psychological outcome of depression based on the CESD (27). Model predictions at Baseline and months 1 and 3 post-transplant for treatment as usual (TAU) [open symbols, broken line] and the intervention, Psychoeducation, Paced Respiration, and Relaxation (PEPRR), [filled symbols, solid line] with 95% CI at each collection time are shown for this secondary psychological outcome. The horizontal broken line indicates the clinical cut off score for depression risk (27).

Table 1

Baseline Characteristics of Caregivers and Patients

Characteristics	OVERALL (n = 148)	TAU (n = 74)	PEPRR (n = 74)	Significance[d]
			Caregivers[b]	
Age, mean (CI), y	53.5 (51.5, 55.5)	54.8 (51.9, 57.7)	52.2 (49.4, 55.1)	p=0.21
Sex, n (%)				
Female	112 (75.7)	56 (75.7)	56 (75.7)	
Male	35 (23.6)	17 (23.0)	18 (24.3)	p=0.88
Ethnicity, n (%)				
Caucasian	133 (89.9)	68 (91.9)	65 (87.8)	
Other	12 (8.2)	4 (5.5)	8 (10.9)	p=0.24
Education, n (%)				
College or above	117 (79.1)	57 (77.0)	60 (81.1)	p=0.52
Annual income $, n (%)				
< 25,000	24 (16.2)	13 (17.6)	11 (14.9)	
25,000-44,999	29 (19.6)	15 (20.3)	14 (18.9)	
45,000-64,999	26 (17.6)	11 (14.9)	15 (20.3)	
> 65,000	60 (40.5)	31 (41.9)	29 (39.2)	p=0.83
Relationship, n (%)				
Spouse/partner	103 (69.6)	46 (62.2)	57 (77.0)	
Parent	27 (18.2)	19 (25.7)	8 (10.8)	
Other	16 (10.8)	8 (10.8)	8 (10.8)	p=0.06
Employment Status, n (%)				
Before Caregiving				
Full-time	71 (48.0)	35 (47.3)	36 (48.6)	
Part-time	24 (16.2)	11 (14.9)	13 (17.6)	
Unemployed	15 (10.1)	8 (10.8)	7 (9.5)	
On leave	3 (2.0)	1 (1.4)	2 (2.7)	
Retired	29 (19.6)	16 (21.6)	13 (17.6)	p=0.93
During Caregiving				
Full-time	35 (23.6)	16 (21.6)	19 (25.7)	
Part-time	17 (11.5)	7 (9.5)	10 (13.5)	
Unemployed	22 (14.9)	14 (18.9)	8 (10.8)	
On leave	36 (24.3)	17 (23.0)	19 (25.7)	
Retired	30 (20.3)	15 (20.3)	15 (20.3)	p=0.64
			Patients[c]	
Age, mean (CI), y	49.5 (47.4, 51.6)	48.0 (44.8, 51.2)	51.1 (48.2, 53.9)	p=0.15
Sex, n (%)				
Female	47 (31.8)	27 (36.5)	20 (27.0)	
Male	97 (65.5)	46 (62.2)	51 (68.9)	p=0.26
Ethnicity, n (%)				

Characteristics	OVERALL (n = 148)	TAU (n = 74)	PEPRR (n = 74)	Significance[d]
Caucasian	116 (78.4)	59 (79.7)	57 (77.0)	
Other	9 (6.1)	3 (4.1)	6 (8.1)	p=0.49[e]
Education, n (%)				
College or above	93 (62.8)	49 (66.2)	44 (59.5)	p=0.33
Annual income $, n (%)				
< 25,000	31 (20.9)	17 (23.0)	14 (18.9)	
25,000-44,999	25 (16.9)	12 (16.2)	13 (17.6)	
45,000-64,999	22 (14.9)	13 (17.6)	9 (12.2)	
> 65,000	46 (31.1)	20 (27.0)	26 (35.1)	p=0.61
Patient Diagnosis[a], n (%)				
Leukemia	80 (54.1)	40 (54.1)	40 (54.1)	
Lymphoma	25 (16.9)	14 (18.9)	11 (14.9)	
MDS/MPS	26 (17.6)	12 (16.2)	14 (18.9)	
Other (MM, SAA)	15 (10.1)	7 (9.5)	8 (10.8)	p=0.90
Duration of Illness, mean (CI), m	25.9 (20.1, 31.8)	28.8 (19.5, 38.1)	23.2 (15.8, 30.5)	p=0.80[f]
Transplant conditioning intensity, n (%)				
Myeloablative	71 (39.4)	36 (48.6)	35 (47.3)	
Non-myeloablative	24 (13.3)	10 (13.5)	14 (18.9)	
Reduce intensity	47 (26.1)	26 (35.1)	21 (28.4)	p=0.55
Time To Engraftment, mean (CI), d	16.0 (14.9, 17.1)	14.8 (13.3, 16.4)	17.3 (15.7, 18.8)	p=0.04[f]

[a] Abbreviations: MDS, myelodysplastic syndrome; MPS, myeloproliferative syndrome; MM, multiple myeloma; SAA, severe aplastic anemia.

[b] Caregiver information was not available for TAU for the following variables: age (n = 1), sex (n = 1), ethnicity (n = 2), education (n = 2), annual income (n = 4), relationship (n = 1) employment status before caregivng (n = 3) and after caregivng (n = 5). PEPRR for the following variables: ethnicity (n = 1), education (n = 2), annual income (n = 5), relationship (n = 1) employment status before caregiving (n = 3) and after caregivng (n = 3).

[c] Patient information was not available for TAU for the following variables: age (n = 1), sex (n = 1), ethnicity (n = 12), education (n = 9), annual income (n = 12), patient diagnosis (n = 1), duration of illness (n = 3), transplant conditioning intensity (n = 2) and time to engraftment (n = 17). PEPRR for the following variables: age (n = 2), sex (n = 3), ethnicity (n = 11), education (n = 9), annual income (n = 12), patient diagnosis (n = 1), duration of illness (n = 1), transplant conditioning intensity (n = 4) and time to engraftment (n = 19).

[d] Significance based on independent t-test or Pearson's Chi-square test as appropriate.

[e] Significance based on Fisher's Exact Test.

[f] Significance based on Mann Whitney U Test.

Table 2

Baseline Assessment Means and 95% CIs for Caregivers

Characteristics[a]	Mean (95% CI)[b]			Significance[c]
	OVERALL (n = 148)	TAU (n = 74)	PEPRR (n = 74)	
PRIMARY OUTCOME				
PSS	23.11 (21.71, 24.51)	23.11 (21.00, 25.23)	23.10(21.21, 24.99)	p=0.99
SECONDARY OUTCOMES				
CESD	15.22 (13.62, 16.82)	15.52 (13.19, 17.85)	14.93(12.69, 17.18)	p=0.72
STAI-STATE	40.60 (38.84, 42.37)	42.08 (39.40, 44.77)	39.16(36.85, 41.48)	p=0.10
POMS-TMD	63.53 (57.62, 69.44)	64.90 (56.30, 73.50)	61.65 (53.30, 70.00)	p=0.59
CRA	10.27 (9.91, 10.62)	10.31 (9.77, 10.84)	10.23 (9.75, 10.71)	p=0.84
PSQI	11.28 (10.81, 11.76)	11.10 (10.44, 11.76)	11.47 (10.77, 12.16)	p=0.45
SF-36: Mental Summary Score	43.94 (41.98, 45.89)	42.98 (39.97, 45.99)	44.90 (42.35, 47.44)	p=0.33
SF-36: Physical Summary Score	54.34 (52.97, 55.70)	53.67 (51.66, 55.68)	55.00(53.11, 56.89)	p=0.34
IES	30.65 (29.28, 32.03)	31.39 (29.49, 33.28)	29.94 (27.93, 31.96)	p=0.30
COMPOSITE SCORES				
CG-Distress	0.00 (−.17, .17)	0.06 (−.20, .31)	−0.05 (−.28, .18)	p=0.52
CG-Wellbeing	0.01 (−.48, .50)	0.09 (−.61, .78)	−0.06 (−.76, .65)	p=0.77

[a] Abbreviations: PSS, Perceived Stress Scale; CESD, Center for Epidemiologic Studies Depression; STAI-State, State-Trait Anxiety Inventory-State; POMS-TMD, Profile of Mood States-Total Mood Disturbance; CRA, Caregiver Reaction Assessment; PSQI, Pittsburgh Sleep Quality Index; SF-36, Short Form Health Survey; IES, Impact of Events Scale; CG-Distress, Caregiver Distress Composite Score; CG-Wellbeing, Caregiver Wellbeing Composite Score.

[b] Information was not available for TAU for the following variables: PSS (n = 4), CESD (n = 5), STAI-STATE (n = 3), POMS-TMD (n = 4), CRA (n = 5), PSQI (n = 3), SF-36: Mental Summary Score (n = 4), SF-36: Physical Summary Score (n = 4), IES (n = 4), CG-Distress (n = 8), CG-Wellbeing (n = 10), Information was not available for PEPRR for the following variables: PSS (n = 2), CESD (n = 2), STAI-STATE (n = 1), POMS-TMD (n = 1), CRA (n = 1), PSQI (n = 1), SF-36: Mental Summary Score (n = 4), SF-36: Physical Summary Score (n = 4), IES (n = 2), CG-Distress (n = 4), CG-Wellbeing (n = 6).

[c] Significance based on independent t-test

Table 3

Estimates and Test Results from Mixed Model Analyses of Covariance for Primary and Secondary Psychological Outcomes and Composite Scores

Outcome[a]	Intervention Group	Mean (95% CI) Baseline	Mean (95% CI) Month 1	Mean (95% CI) Month 3	Model Tests: Main Effects	Model Tests: Interaction	Month 3 Group Comparison Effect Size[b]
PRIMARY OUTCOME							
PSS	**PEPRR**	22.7 (20.9, 24.6)	22.0 (20.1, 23.8)	20.0 (17.9, 22.0)	Group: $F_{1,141}=0.92$; p =0.34	**Group*Month: $F_{2,112}=$ 4.08; p =0.020**	$t_{117}=2.09$; p=0.039
	TAU	23.5 (21.6, 25.3)	21.6 (19.7, 23.5)	23.0 (21.0, 25.0)	Month: $F_{2,112}=3.43$; p =0.036		ES = 0.39
SECONDARY OUTCOMES							
CESD	**PEPRR**	14.6 (12.5, 16.8)	13.6 (11.6, 15.5)	12.1 (9.8, 14.5)	Group: $F_{1,142}=2.11$; p=0.15	**Group*Month: $F_{2,116}=$ 3.66; p =0.029**	$t_{117}=2.46$; p=0.016
	TAU	15.9 (13.7, 18.1)	13.8 (11.8, 15.8)	16.3 (14.0, 18.6)	Month: $F_{2,116}=2.54$; p=0.083		ES=0.46
STAI-State	**PEPRR**	38.9 (36.6, 41.3)	38.0 (35.7, 40.4)	34.7 (31.9, 37.5)	Group: $F_{1,137}=6.33$; p=0.013	**Group*Month: $F_{2,115}=$ 6.10; p =0.003**	$t_{109}=3.42$; p=0.0009
	TAU	42.4 (40.0, 44.8)	38.8 (36.4, 41.2)	41.6 (38.8, 44.4)	Month: $F_{2,115}=4.60$; p=0.012		ES=0.66
POMS-TMD	**PEPRR**	61.0 (53.2, 68.9)	59.4 (51.8, 67.0)	53.0 (44.8, 61.2)	Group: $F_{1,142}=1.31$; p =0.25	**Group*Month: $F_{2,116}=$ 4.62; p =0.012**	$t_{114}=2.09$; p=0.039
	TAU	66.8 (58.9, 74.8)	58.0 (50.2, 65.7)	65.2 (57.1, 73.3)	Month: $F_{2,116}=2.95$; p =0.56		ES =0.39
CRA	**PEPRR**	10.2 (9.7, 10.6)	10.8 (10.3, 11.4)	10.6 (9.9, 11.2)	Group: $F_{1,145}=0.27$; p =0.60	Group*Month: $F_{2,110}=0.92$; p =0.40	-
	TAU	10.4 (9.9, 10.8)	10.8 (10.2, 11.4)	10.9 (10.3, 11.5)	Month: $F_{2,110}=8.19$; p=0.0005		
PSQI	**PEPRR**	11.4 (10.8, 12.1)	11.2 (10.6, 11.9)	11.0 (10.3, 11.7)	Group: $F_{1,137}=0.01$; p =0.92	Group*Month: $F_{2,110}=0.83$; p =0.44	-
	TAU	11.1 (10.4, 11.7)	11.2 (10.6, 11.9)	11.2 (10.5, 11.9)	Month: $F_{2,110}=0.25$; p =0.78		
SF36-Mental	**PEPRR**	45.1 (42.6, 47.7)	45.7 (42.9, 48.4)	47.0 (43.9, 50.0)	Group: $F_{1,138}=2.62$; p =0.11	Group*Month: $F_{2,116}=0.29$; p =0.75	-
	TAU	42.7 (40.1, 45.3)	43.8 (41.0, 46.6)	43.5 (40.6, 46.4)	Month: $F_{2116}=0.72$; p =0.49		
SF36-Physical	**PEPRR**	54.7 (52.8, 56.6)	52.9 (50.6, 55.2)	54.0 (51.8, 56.1)	Group: $F_{1,136}=0.00$; p =0.98	Group*Month: $F_{2,109}=181$; p =0.17	-
	TAU	53.8 (51.9, 55.7)	54.0 (51.7, 56.3)	53.7 (51.6, 55.8)	Month: $F_{2,109}=1.04$; p =0.36		
IES	**PEPRR**	29.8 (27.9, 31.7)	29.1 (27.1, 31.1)	28.4 (26.1, 30.8)	Group: $F_{1,138}=2.01$; p =0.16	Group*Month: $F_{2,116}=0.03$; p =0.97	-
	TAU	31.4 (29.5, 33.3)	31.0 (29.0, 33.0)	30.3 (28.0, 32.6)	Month: $F_{2,116}=1.19$; p =0.31		
COMPOSITE SCORES							
CG-Distress	**PEPRR**	−0.11 (−0.33, 0.11)	−0.09 (−0.32, 0.15)	−0.22 (−0.48, 0.05)	Group: $F_{1,139}=2.55$; p =0.11	**Group*Month: $F_{2,109}=$ 4.02; p =0.021**	$t_{114}=2.39$; p=0.019
	TAU	0.12 (−0.11, 0.34)	−0.03 (−0.28, 0.21)	0.23 (−0.03, 0.49)	Month: $F_{2,109}=0.77$; p =0.46		ES=0.45

Outcome [a]	Intervention Group	Mean (95% CI) Baseline	Mean (95% CI) Month 1	Mean (95% CI) Month 3	Model Tests: Main Effects	Model Tests: Interaction	Month 3 Group [b] Comparison Effect Size
CG-Wellbeing	PEPRR	−0.13 (−0.79, 0.52)	−0.20 (−0.86, 0.45)	−0.31 (−1.03, 0.39)	Group: $F_{1,132}=0.74$; p =0.39	Group*Month: $F_{2,102}=2.69$; p =0.073	
	TAU	0.18 (−0.48, 0.85)	−0.17 (−0.83, 0.49)	0.45 (−0.25, 1.16)	Month: $F_{2,102}=1.80$; p =0.17		

[a] Abbreviations: PSS, Perceived Stress Scale; CESD, Center for Epidemiologic Studies Depression; STAI-State, State-Trait Anxiety Inventory-State; POMS-TMD, Profile of Mood States-Total Mood Disturbance; CRA, Caregiver Reaction Assessment; PSQI, Pittsburgh Sleep Quality Index; SF-36, Short Form Health Survey; IES, Impact of Events Scale; CG-Distress, Caregiver Distress Composite Score; CG-Wellbeing, Caregiver Wellbeing Composite Score.

[b] Month 3 group post hoc t-test comparison and corresponding estimated effect size (ES) when Group*Month interaction was significant.