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Effects of a Problem-Solving Intervention (COPE) on Quality of Life for Patients with Advanced Cancer on Clinical Trials and their Caregivers: Simultaneous Care Educational Intervention (SCEI): Linking Palliation and Clinical Trials

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Abstract

Context: Patients on investigational clinical trials and their caregivers experience poor quality of life (QOL), which declines as the disease progresses.
Objective: To examine the effect of a standardized cognitive–behavioral problem-solving educational intervention on the QOL of patients enrolled on investigational clinical trials and their caregivers.
Design: Prospective, multi-institution, randomized trial. QOL was measured repeatedly over 6 months.
Participants: Patients were simultaneously enrolled onto phase 1, 2, or 3 Institutional Review Board (IRB)-approved cancer clinical trials.
Intervention: Intervention arm dyads participated in three conjoint educational sessions during the first month, learning the COPE problem solving model. Nonintervention arm dyads received usual care.
Outcome Measures: Global QOL was measured by the City of Hope Quality of Life Instruments for Patients or Caregivers; problem solving skills were measured by the Social Problem Solving Inventory-Revised.
Results: The results are reported using the CONSORT statement. The analytic data set included 476 dyads including 1596 patient data points and 1576 care giver data points. Patient QOL showed no significant difference in the rate of change between the intervention and usual care arms ($p = 0.70$). Caregiver QOL scores in the intervention arm declined, but at less than half the rate in the control arm ($p = 0.02$).
Conclusions: The COPE intervention enabled the average caregiver to come much closer to stable QOL over the 6-month follow-up. Future studies should enroll subjects much earlier in the cancer illness trajectory, a common patient/caregiver theme. The maximum effect was seen in caregivers who completed the 6-month follow-up, suggesting that the impact may increase over time.

Introduction

Patients with advanced cancer and their families experience significant distress in four domains: physical,[1,2] psychological, social, and spiritual.[3–5] These domains are often summarized by the term "quality of life." High levels of distress are associated with increased health care utilization.[6] Quality of life (QOL) and reduction of distress are recognized as important goals of cancer care.[7–9] A systematic review emphasized the need for increased research to yield evidence-based strategies to guide end-of-life care.[10]

The detrimental effects of cancer extend to the patient's family and friends and may be particularly burdensome for primary caregivers. Psychological distress is well documented in patients with a wide variety of cancer types, stages and sites as well as in their caregivers.[11–19] Patients' perception of distress may reflect problems in multiple domains.[20,21] Patients with cancer report that quality of life may be related

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to treatment as well as psychosocial factors such as external stress and perceived support.[22,23]

Several barriers have been identified that impair efforts to improve the quality of life of patients with advanced cancer on investigational clinical trials and their caregivers: (1) patients and their physicians often focus on disease-directed investigational or ad hoc therapy, utilizing palliative care late in the disease trajectory or never[24,25]; (2) patients and families have widely variable problem-solving skills and face diverse emotional and situational challenges[26]; (3) QOL assessment and/or intervention is not universally integrated into practice or clinical research.[10]

Patients, families, and some health professionals experience cognitive dissonance when treatment focuses only on disease-directed therapy for cancer that is refractory to curative treatment while minimal attention is devoted to palliative care.[24] Models integrating palliative care with disease-directed therapy reduce this cognitive dissonance.[27,28] Houts and colleagues[29] have described a cognitive/behavioral problem solving approach summarized by the acronym COPE (Creativity, Optimism, Planning and Expert information). A trial of the COPE intervention reported improvement in symptom management in the hospice setting.

We initiated a multisite randomized controlled trial of COPE, "Simultaneous Care Educational Intervention (SCEI): Linking Palliation and Clinical Trials." Global QOL was the primary end point of the study. We measured problem-solving abilities as a secondary end point.

Study Design, Patient Population, and Statistics

Health educators were trained by an expert in the COPE model (M.L.). Sessions were videotaped and reviewed with the expert and educators between sites to increase intersite consistency of the intervention. Adults with relapsed, refractory, or recurrent solid tumors or lymphoma enrolled onto phase 1 or 2, or phase 3 trials that compared therapy for advanced cancer were eligible. These patients are among the sickest and most distressed cancer patients; clinical trial participation usually follows depleting conventional therapies or because few effective therapies exist for a given diagnosis. Advanced disease carries a higher symptom burden for patients and greater distress for caregivers. Although each of the participating cancer centers had a unique roster of eligible trials, the criteria for a qualifying phase 1, 2, or 3 clinical trial were the same across institutions. The eligible patient pool was stable (refractory, recurrent or metastatic disease) despite the variety of clinical trials; patients who went off their clinical trial continued to have advanced illness with high symptom burden, and were continued on the SCEI study.

Exclusion criteria included patients: receiving concomitant chemotherapy and radiation; on adjuvant phase III studies; with hematopoietic malignancies; with primary brain tumors; not fluent in English; less than 18 years of age or lacking a willing caregiver.

Patients designated one caregiver as their coparticipant. "Caregiver" was defined as an adult regularly involved with the patient and their care. Patients and caregivers signed informed consent to participate in SCEI. Participation stopped with the death of the patient, when a patient or caregiver requested or at the completion of study follow-up (6 months).

SCEI was presented as a complementary study to the therapeutic clinical trial, which acted as the standardized threshold for entry onto SCEI. Randomization assignments to SCEI or the control group were generated by the biostatistics office, using a three-to-one weighted randomization scheme, blocked by site. Randomization only occurred after consents were signed; the operations office was contacted to procure a unique patient identifier and determine intervention/control assignment.

Intervention

Intervention arm dyads received a copy of *The Home Care Guide for Cancer*.[30] Each book chapter addresses a problem known to affect patients with cancer including physical symptoms (pain or nausea), psychological symptoms (anxiety or depression), or issues related to resources or relationships, including communicating with one's health care team or getting support or services from family, friends, and community organizations. Each chapter follows the same problem-solving formula.

Each educational session included the trained educator, the patient, and their designated caregiver. The first educational session was conducted up to 7 days prior to or on the day the patient started their investigational clinical trial. The first session focused on becoming familiar with the guide and the COPE problem-solving model, using COPE to address a patient or caregiver-identified problem. The two additional conjoint instructional sessions were conducted within the first 30 days, reinforcing this learning by focusing on two additional patient or caregiver-identified problems. Dyads could use one of the problems in the book's chapters, or identify another problem and apply the model. In either event, the instructors facilitated this process of using the Guide and the COPE model, being careful not to solve the problem for them. Following each session, the educator documented the problem and recorded process notes.

Outcome measures

The primary measurement tools were the City of Hope (COH) Quality of Life (QOL) Instruments for Patients or Caregivers[31] and the Social Problem Solving Inventory-Revised.[32,33]

Patients and caregivers completed baseline psychometric evaluation and demographic information. Follow-up data collection was scheduled at 30, 60, 90, 120, and 180 days after randomization. The patient and caregiver were asked to complete the instruments independently.

The COH QOL Instrument (Cancer Patient/Cancer Survivor Version) is a 41-item ordinal scale that measures global QOL and four subdomains: physical, psychological, social, and spiritual well-being.[34] The Family Version is a 37-item ordinal instrument that measures the QOL of a family member caring for a patient with cancer, adapted from the patient QOL tool, revised, and tested with 219 family caregivers of patients with cancer.[35]

The SPSI-R is a 52-item multidimensional measure of social problem-solving ability derived from a factor analysis of the original theory-driven Social Problem-Solving Inventory.[32,36,37] In addition to a total score, it consists of five scales that measure two constructive dimensions (Positive Problem Orientation, Rational Problem Solving) and three

dysfunctional dimensions (Negative Problem Orientation, Impulsivity/Carelessness Style, Avoidance Style). Tables for age standardization are included in the scoring manual. The SPSI-R has strong internal consistency, test-retest reliability and strong structural, concurrent, predictive, convergent, and discriminant validity.[32]

Data were verified at entry and at analysis, and audited for accuracy and Institutional Review Board (IRB) compliance. Summary scores for instruments and subscales were calculated according to the instructions for each instrument. Quality of life scores were rescaled from 0 (minimum possible) to 100 (maximum possible) to allow direct comparison of patients and caregivers.

This study was approved by the IRB at UC Davis and underwent IRB review at all collaborative sites.

Statistical analysis

We summarized baseline patient and caregiver data with univariate descriptive measures, using frequency tables for categorical variables and mean, standard deviation and percentiles for quantitative data. We compared the usual care group to SCEI patients and caregivers to ensure that randomization produced similar groups. All participants with at least one assessment were included in outcome analysis, using intent-to-treat criteria. We compared baseline QOL and problem solving scores for those who completed at least one follow-up with those who completed only baseline, to assess the effects of early attrition. To compare longitudinal change in outcome measures, we used random effects regression models,[32] which differ from standard repeated measures analysis of variance (ANOVA), allowing the inclusion of participants with incomplete data.

The primary analysis fitted a linear trend over time for the usual care group (rate of change per month in QOL or problem solving) and tested whether there was an effect of the intervention to increase or decrease the rate of change (interaction between treatment and rate of change, comparison of slopes). To adjust for differences in baseline levels, we included a random effect for baseline score but not for rate of change, as the person-to-person variation in rate of change was not found to exceed the variation expected based on within-person variation. A secondary approach allowed for a post intervention difference that was constant over the follow-up period, rather than increasing with time since baseline. Each model was validated using residual diagnostics. Secondary analyses examined subscales of QOL and of problem solving. Additional analyses explored the effect of possible

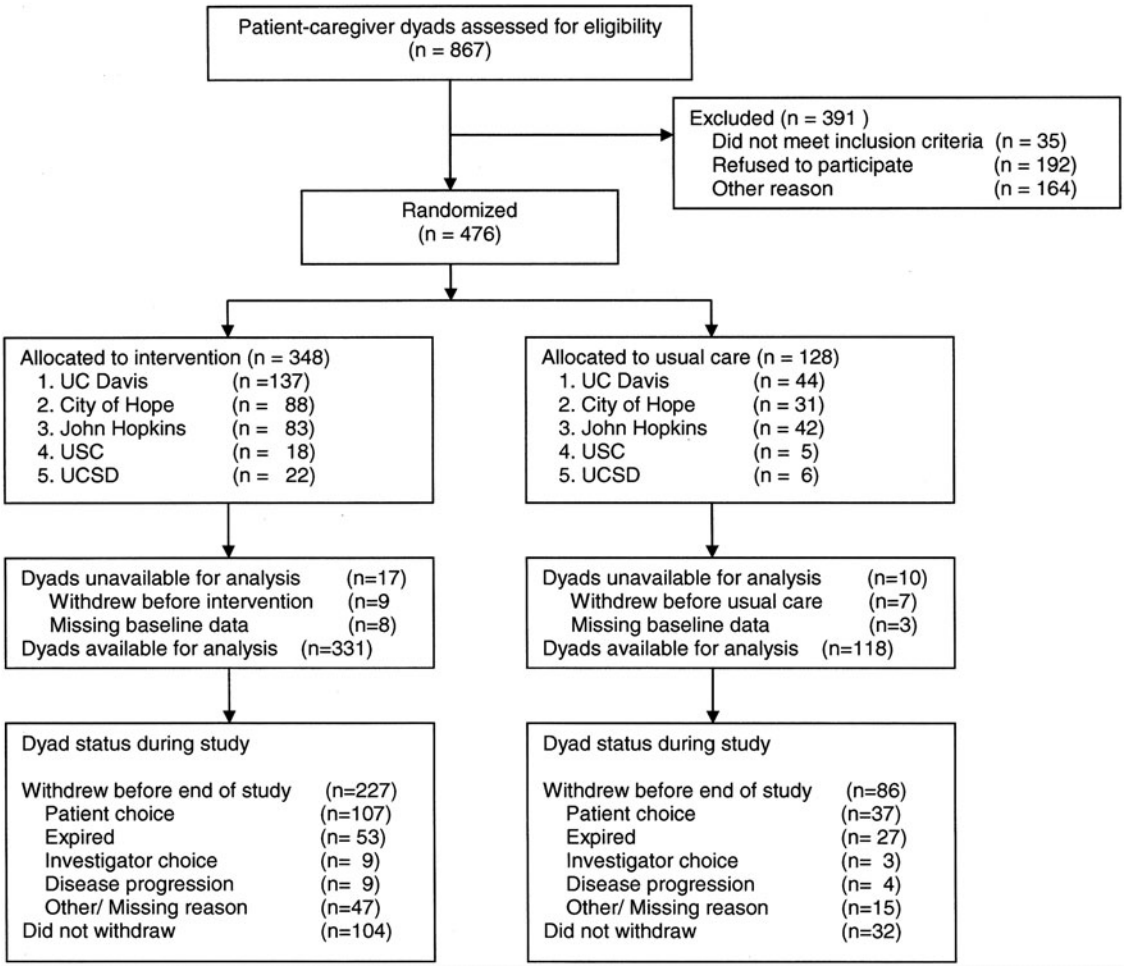

FIG. 1. Study flow diagram. Numbers in individual analyses may differ because dyads with data available for analysis may not have had data on both patient and caregiver, or on both quality of life and problem-solving scales.

predictors such as age, relationship of caregiver, and gender. All hypothesis tests were two-sided at level 0.05, and all analyses were carried out using R[38] and SAS/STAT® software.[39]

Initial sample size calculations were designed to have 80% power to detect a standardized difference between the SCEI group and controls of 0.22 standard deviations. We expected to enroll 1152 patients over a 4-year period, and assumed that 80% would complete at least one follow-up. With our actual accrual and drop-out before first follow-up, our power to detect a 0.22 effect size was between 0.48 and 0.51 for patients and caregivers, and to detect an effect size of 0.35 exceeded 80% for both groups.

A data safety monitoring committee (DSMC) met regularly over the 5 years of the study. Only one investigator, the statistician (Dr. Beckett) viewed the interim data with the DSMC.

Results

Accrual and demographics

Accrual of patient/caregiver dyads began in February 2003 and was ended by the DSMC on October 1, 2007. The results are reported using the CONSORT statement [40] (Fig. 1). Of 476 patient–caregiver dyads randomized to treatment (55% of screened dyads), 94% (449 dyads) had at least one participant complete an assessment, allowing inclusion in the primary outcome analysis. Thus 444 patients contributed a total of 1596 data time points (mean 3.6 data points per person); 165 patients completed data through the 6-month visit follow-up. Data were available on 446 caregivers with a total of 1576 observations (mean 3.5 data points per person; 162 caregivers completed the 6-month visit). The primary reasons for failure to complete the entire follow-up period were patient or caregiver withdrawal of consent (30% of usual care, 31% in SCEI) and death (21% of usual care, 15% in SCEI).

Patient (Table 1) and caregiver (Table 2) demographics are shown along with tumor type. (Table 3).

Table 1. Demographics

n = 441 Dyads *Intervention 324 (73.5%)* *Control 117 (26.5%)*	*Patients*		*Caregivers*	
	Number	*Percentage*	*Number*	*Percentage*
Gender				
Male	196	44%	302	68%
Female	243	55%	131	31%
Mean age	61.5 years		61.4 years	
Race/ethnicity				
African American	20	5%	23	6%
Asian/Pacific Islander	29	7%	32	8%
Caucasian/ Other	381	88%	338	85%
Native American/ Indigenous	3	1%	5	1%
Hispanic (any race)	41	9%	31	8%
Education				
(K–12)	155	35%	142	32%
College	170	39%	209	47%
Graduate School	105	24%	82	19%
Unknown	11	2%	8	2%
Household income?				
<10K / year	32	7%		
10–50 K	188	41%		
50–80 K	83	18%		
>80 K	104	29%		
Missing data	35	8%		

Table 2. Caregiver Characteristics

Relationship to patient	*Number*	*Percentage*
Spouse	308	70%%
Child	71	16%
Parent	12	3%
Unrelated	18	4%
Other	24	5%
Employment status	*Number*	*Percentage*
Working full or part time	117	49%
Retired	136	31%
Not working at all	79	20%
Hours of care per day/week	*Number*	*Percentage*
1 hour	133	31%
2–4 hours	105	24%
5–9 hours	57	13%
10–14 hours	29	7%
15–20 hours	14	3%
>20 hours	90	21%
Born in the United States	*Number*	*Percentage*
Yes	350	80%
No	83	19%

Baseline psychometric results

Baseline quality of life and problem solving skills were similar in the two study arms (Table 4). Mean QOL levels were about 8 percentage points higher for patients who had at least one follow-up than for those who did not complete any follow-ups ($p < 0.001$, analysis of variance), but did not differ significantly for caregivers. The QOL scores were slightly higher for patients than for their caregivers ($p = 0.04$) but varied widely on a standardized 0–100 point scale, with one quarter of patient scores above 75% and one quarter below 50%, with some extreme scores below 25% for patients and 30% for caregivers. Baseline problem solving skills did not differ for patients and caregivers, and were comparable to the general population.[33]

Table 3. Cancer by Site

Gastrointestinal	120	28%
Genito-urinary	113	27%
Thoracic	88	21%
Breast	41	10%
Gynecologic	28	7%
Sarcoma	6	1%
Melanoma	5	1%
Other	24	6%

Table 4. Baseline Quality of Life (on 0–100 scale) and Problem-Solving Skills

Outcome measure	Mean score (SD)		p value for difference	
	Usual care	SCEI intervention	Usual care vs SCEI	Patients vs. caregivers
QOL (0–100 scale)				
Patients	64.4 (15.6)	61.7 (15.2)	$p = 0.11$	
Caregivers	61.1 (13.5)	62.6 (13.8)	$p = 0.33$	$p = 0.04$ (usual care and SCEI combined)
Problem solving				
Patients	106.2 (15.5)	104.4 (13.7)	$p = 0.37$	
Caregivers	104.9 (13.6)	106.8 (13.5)	$p = 0.65$	$p = 0.14$ (usual care and SCEI combined)

SD, standard deviation; SCEI, Simultaneous Care Educational Intervention.

Results of primary outcome analysis

QOL analysis. In random effects regression models, patients showed a modest but significant decline in overall QOL (based on estimated slope) of about half a percentage point per month on the 0–100 percent QOL scale ($p < 0.001$, Table 5), corresponding to approximately a 5-point (0.2 standard deviation [SD]) drop in QOL over 6 months compared to the mean level at baseline. There was no significant difference in the rate of change between the intervention and the usual care arms ($p = 0.70$).

Caregivers also showed a significant decline in overall QOL, with scores that declined almost one point per month in the usual care arm ($p < 0.001$, Table 5). This would correspond to a drop of approximately 8.5% (0.4 SD) of baseline mean level over the six-month follow-up period. Caregiver QOL scores in the intervention arm also declined, but at less than half the rate of the control arm, a statistically significant difference ($p = 0.02$) with a predicted decline from baseline QOL of only 3.6 points at 6 months. Secondary analysis assuming a one-time impact on QOL rather than a difference in rate of decline showed a difference but did not find it statistically significant, suggesting that the impact may increase over time as our primary model proposed. Secondary analyses did not find evidence of outcome differences between centers, or of violation of the assumptions of normality of the residuals.

SPSI-R problem solving. Patients showed a decline in problem solving skills of about half a point per month ($p = 0.01$, Table 5). Caregivers did not show any significant changes in problem solving skills over the course of the study in either the usual care or intervention arms (Table 5).

Secondary end points

QOL subdomains. Subscale analysis for the patients showed significant declines in the psychological and social

Table 5. Estimates of Effects of SCEI Intervention on Quality of Life and Problem-Solving Skills Based on Random Effects Models Assuming Constant Change per Month that May Differ Between Treatment Groups (primary hypothesis)

Outcome measure	Model-based estimate	Standard error	p value: for parameter = 0
Quality of life (0–100 scale)			
Patients			
Baseline level	63.4	0.70	<0.001
Change per month in QOL, usual care group	−0.53	0.23	0.02
Effect of SCEI on change/mo[a]	−0.10	0.27	0.70
Caregivers			
Baseline level	61.7	0.64	<0.001
Change per month in QOL, usual care group	−0.87	0.19	<0.001
Effect of SCEI on change/mo[a]	0.50	0.22	0.02
Problem-solving skills			
Patients			
Baseline level	104.6	0.69	<0.001
Change per month in problem solving, usual care	−0.53	0.21	0.01
Effect of SCEI on change/mo[a]	−0.04	0.24	0.86
Caregivers			
Baseline level	106.5	0.65	<0.001
Change per month in problem solving, usual care	−0.23	0.21	0.28
Effect of SCEI on change/mo[a]	−0.30	0.24	0.21

Models allow for different baseline levels and length of follow-up.

[a]Estimates of difference between rate of change per month under usual care and rate of change under SCEI intervention. Positive values indicate higher (more favorable) levels for the SCEI intervention, with slower decline in the outcome, while negative values indicate faster decline in the outcome compared to usual care.

SCEI, Simultaneous Care Educational Intervention; QOL, quality of life.

Table 6. Estimates of Effects of SCEI Intervention on Quality of Life Subscales Based on Random Effects Models Assuming Constant Change per Month that May Differ between Treatment Groups (primary hypothesis)

Outcome: quality of life subscales	*Model-based estimate*	*Standard error*	p *value: for parameter = 0*
Psychological			
Change per month, patients, usual care group	−0.27	0.08	0.001
Effect of SCEI on patient change[a]	0.02	0.09	0.82
Change/mo, caregivers, usual care	−0.79	0.37	0.03
Effect of SCEI on caregiver change[a]	0.59	0.42	0.16
Social			
Change/mo, patients, usual care	−0.15	0.06	0.01
Effect of SCEI on patient change[a]	−0.02	0.07	0.81
Change/mo, caregivers, usual care	−1.30	0.24	<0.001
Effect of SCEI on caregiver change[a]	0.46	0.27	0.09
Physical			
Change/mo. patients, usual care	−0.04	0.10	0.72
Effect of SCEI on patient change	−0.00	0.11	0.97
Change/mo. caregivers, usual care	−0.23	0.16	0.14
Effect of SCEI on caregiver change[a]	0.09	0.18	0.61
Spiritual			
Change/mo, patients, usual care	−0.05	0.08	0.54
Effect of SCEI on patient change[a]	−0.06	0.09	0.47
Change/mo, caregivers, usual care	−0.91	0.18	<0.001
Effect of SCEI on caregiver change[a]	0.76	0.21	<0.001

Models allow for different baseline levels and length of follow-up.
[a]Estimates of difference between rate of change per month under usual care and rate of change under SCEI intervention. Positive values indicates (more favorable) levels for the SCEI intervention, with slower decline in the outcome, while negative values indicate faster decline in the outcome compared to usual care.
SCEI, Simultaneous Care Educational Intervention.

Table 7. Estimates of Effects of SCEI Intervention on SPSI-R Subscale Measures During Follow-Up, Based on Random Effects Models Assuming Constant Change per Month that may Differ between Treatment Groups (primary hypothesis)

Outcome: problem solving subscales	*Parameter estimate*	*Standard error*	p *value: for parameter = 0*
Positive approaches			
Change/mo, patients, usual care	−0.79	0.30	0.009
Intervention effect on patient change[a]	−0.09	0.34	0.80
Change/mo, caregivers, usual care	−0.45	0.30	0.13
Intervention effect on caregiver change[a]	−0.47	0.24	0.17
Rational approaches			
Change/mo, patients, usual care	−0.68	0.27	0.01
Intervention effect on patient change[a]	0.05	0.31	0.88
Change/mo, caregivers, usual care	−0.56	0.27	0.04
Intervention effect on caregiver change[a]	−0.30	0.31	0.33
Avoidance			
Change/mo, patients, usual care	0.41	0.21	0.053
Intervention effect on patient change[b]	−0.07	0.24	0.77
Change/mo, caregivers, usual care	0.02	0.21	0.91
Intervention effect on caregiver change[b]	0.38	0.24	0.12
Impulsivity			
Change/mo, patients, usual care	0.17	0.22	0.44
Intervention effect on patient change[b]	0.09	0.25	0.72
Change/mo, caregivers, usual care	0.37	0.22	0.09
Intervention effect on caregiver change[b]	−0.31	0.25	0.22
Negative approaches			
Change/mo, patients, usual care	−0.08	0.21	0.72
Intervention effect on patient change[b]	0.10	0.24	0.68
Change/mo, caregivers, usual care	−0.31	0.21	0.14
Intervention effect on caregiver change[b]	0.12	0.24	0.62

Models allow for different baseline levels and length of follow-up.
[a]Positive values indicate higher (more favorable) levels for the SCEI intervention.
[b]Positive values indicate less favorable levels (more dysfunctional problem solving) for the SCEI intervention.
SCEI, Simultaneous Care Educational Intervention; SPSI-R, Social Problem Solving Inventory-Revised.

domains but no significant changes in physical or spiritual domains (Table 6). There were no differences between the intervention and the usual care arms.

Subscale analysis for the caregivers showed significant decline in psychological, social, and spiritual domains, with declines of about a point per month in each area, but no change in physical well-being (Table 6). The decline of almost a point per month for spiritual well-being in the usual care group ($p < 0.001$) was nearly completely canceled out in the SCEI group ($p < 0.001$). Psychological well-being declined approximately 0.8 points per month in the usual care group ($p = 0.03$), compared to a decline of 0.2 points per month in the SCEI group ($p = 0.16$). Social well-being declined over a point per month in the usual care group ($p < 0.001$); SCEI participants scored about one third higher, with a trend for significance ($p = 0.09$). In secondary models hypothesizing a one-time effect of the SCEI intervention rather than a continuous gain over time, the caregivers in the SCEI group showed significant impact for psychological, social, and spiritual QOL.

Problem-solving subscales

In patients, positive and rational problem solving approaches decreased and avoidance approaches showed a trend for increasing over time ($p = 0.009$, 0.01, 0.053, respectively, Table 7). Caregivers showed a decrease in rational problem solving skills ($p = 0.04$, Table 7). There were no significant differences between arms, suggesting that the relatively better psychosocial QOL trajectories for caregivers in the COPE intervention arm are likely not a direct result of improved problem solving skills.

Discussion

This trial showed a moderately statistically significant impact of the COPE intervention on QOL for caregivers, but not for patients. The impact would correspond to about a one-point overall improvement on the measurement scale on most of the psycho-social questions during a 6-month follow-up, which translates into almost no decline in QOL rather than a significant decline in QOL over 6 months. An intervention that responds to the caregiver addresses the reduced confidence in caregiver ability to manage the illness and the perception of decreased support as cancer progresses.[41]

Is the statistically significant finding clinically significant? One proposal is that clinical significance be equal to ½ SD or more of effect size.[42] Our effect size is a decrease of about 0.3 SD (relative to baseline variation) in the 6-month decline in overall QOL for caregivers, with somewhat larger effects in the psychosocial subdomains, consistent with a moderately clinically significant impact. The PROMIS investigators[43] are working toward a consensus view on clinical significance in QOL trials.

Poorer problem solving of emotional and situational challenges by patients and family members is associated with diminished QOL.[44] Certainly the increased and highly complex burdens that caregivers report[20,45,46] and the risks to caregivers[47–50] underscore the importance of this group as a target.[51] A different dosing of the problem solving intervention or an additional intervention may be necessary for the patients with more dysfunctional problem-solving styles.[52]

The limitations of this study include slower than anticipated accrual, turnover in trainers that might affect the educational intervention, limited enrollment of ethnic minorities, and the English language requirements.

The impact of COPE in our study increased over time, reinforcing our view that introducing COPE at initial diagnosis has the potential to increase the benefit of the intervention,[23] especially before the presence of highly distressing physical symptoms.[53,54]

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Author Disclosure Statement

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