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## Relaxation and imagery and cognitive-behavioral training reduce pain during cancer treatment: a controlled clinical trial

Karen L. Syrjala<sup>a,b,\*</sup>, Gary W. Donaldson<sup>a</sup>, Martha W. Davis<sup>a</sup>, Michael E. Kippes<sup>a</sup>, John E. Carr<sup>b</sup>

<sup>a</sup> Fred Hutchinson Cancer Research Center, Seattle, WA 98104 (USA) and <sup>b</sup> University of Washington School of Medicine, Department of Psychiatry and Behavioral Sciences, RP-10, Seattle, WA 98195 (USA)

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**Summary** Few controlled clinical trials of psychological interventions for cancer pain relief exist in spite of frequent support for their importance as adjuncts to medical treatment. This study compared oral mucositis pain levels in 4 groups of cancer patients receiving bone marrow transplants (BMT): (1) treatment as usual control, (2) therapist support, (3) relaxation and imagery training, and (4) training in a package of cognitive-behavioral coping skills which included relaxation and imagery. A total of 94 patients completed the study which involved two training sessions prior to treatment and twice a week 'booster' sessions during the first 5 weeks of treatment. Results confirmed our hypothesis that patients who received either relaxation and imagery alone or patients who received the package of cognitive-behavioral coping skills would report less pain than patients in the other 2 groups. The hypothesis that the cognitive-behavioral skills package would have an additive effect beyond relaxation and imagery alone was not confirmed. Average visual analogue scale (VAS) report of pain within the therapist support group was not significantly lower than the control group ( $P = 0.103$ ) nor significantly higher than the training groups. Patient reports of relative helpfulness of the interventions for managing pain and nausea matched the results of VAS reports. From these results, we conclude that relaxation and imagery training reduces cancer treatment-related pain; adding cognitive-behavioral skills to the relaxation with imagery does not, on average, further improve pain relief.

**Key words:** Cancer; Pain; Relaxation; Imagery; Cognitive-behavioral; Hypnosis; Oral mucositis; Bone marrow transplantation

### Introduction

Given the prevalence and magnitude of cancer-related pain, clinical trials of psychological methods are surprisingly scarce. Research studies examining treatments for cancer pain have focused primarily on pharmacologic interventions. As data readily demonstrate, pharmacologic treatment modalities do not completely relieve cancer pain (Bonica 1990; Hill et al. 1990). Cognitive-behavioral interventions have been shown to be effective in reducing persistent pain (Malone and Strube 1988; Turner and Clancy 1988; Turner and Jensen 1993), thus they have been advocated as ad-

adjuncts to the traditional medical management of persistent cancer pain (Cleeland and Tearnan 1986; Cleeland et al. 1986; Jay et al. 1986).

Although there has been considerable interest in the use of psychological interventions for persistent cancer pain management, few controlled clinical trials have examined the efficacy of these techniques. In one of the few controlled studies, Spiegel and Bloom (1983) assigned metastatic breast cancer patients to 1 of 3 conditions: a support group, a support group combined with a self-hypnosis procedure, or a non-treatment control group. Patients assigned to the psychological treatment groups reported significantly less pain than those in the control condition. The lowest pain was reported by patients in the self-hypnosis condition, although pain in this group was not significantly lower than in the support-only group.

\* Corresponding author: Karen Syrjala, Ph.D., Fred Hutchinson Cancer Research Center, FB600, 1124 Columbia St., Seattle, WA 98104, USA. Tel.: (206) 667-4579; FAX: (206) 667-3531.

Syrjala and colleagues (1992a) assigned bone marrow transplantation (BMT) patients expected to have persistent treatment-related pain to 1 of 4 conditions: hypnosis training, cognitive-behavioral coping skills training including relaxation but not imagery or hypnosis, an attention control, or a treatment as usual control. All intervention patients met with a psychologist twice for training before being admitted to the hospital and were then followed as inpatients during the course of oral mucositis pain. Results indicated that patients receiving hypnosis training reported significantly less pain over the 3-week period of mucositis. Patients receiving cognitive-behavioral training without hypnosis reported no significant difference in pain compared to the control groups.

The BMT setting provides an opportunity to examine the use of cancer pain interventions for persistent pain. The medical treatment is fairly standardized and is conducted in a controlled environment, thereby facilitating clinical research. Cancer patients undergoing BMT receive supralethal doses of chemotherapy often followed by supralethal doses of total body irradiation. As a result of this treatment, nausea, vomiting, and oral mucositis pain develop, lasting from several days to several weeks. The resulting mucositis and corresponding pain usually requires parenteral opioid medication and frequently impairs patients' abilities to eat and speak (Chapko et al. 1989, 1991; Hill et al. 1990).

The purpose of the present study was to refine the interventions used in the previous study (Syrjala et al. 1992a), and further examine the effectiveness of cognitive-behavioral techniques and relaxation and imagery (or hypnosis) training in reducing cancer-related pain. We made several modifications to the psychological interventions. We relabeled hypnosis 'relaxation and imagery' to facilitate patient acceptance of this intervention (Hendler and Redd 1986). Techniques identified as relaxation, imagery and hypnosis do not differ empirically (Burish and Redd 1983; Hendler and Redd 1986; Syrjala 1990), and our intervention remained essentially the same. In the cognitive-behavioral training, we reduced the number of skills taught to ease the learning demands on patients and added imagery to the relaxation training component. Finally, instead of the attention control group, we included active psychotherapeutic support, similar to that commonly provided by oncology psychotherapists, without cognitive-behavioral or imagery training. This control group allows a more rigorous test of the additive effects of the cognitive-behavioral interventions versus the non-specific effects of active support. In addition, in the previous study we found that patients undergoing the extreme physical demands of BMT had difficulty tolerating the attention control when it did not involve active support, but merely occupied their time and energy.

In this study, we randomized patients to 1 of 4 conditions: treatment as usual control which emphasized medical interventions for pain, therapist support, relaxation and imagery training, or a package of cognitive-behavioral coping skills which included relaxation and imagery. We hypothesized first that both the relaxation and imagery training and the cognitive-behavioral package would be effective for pain and nausea management. Second, we hypothesized that the cognitive-behavioral package would be most effective (since it provides multiple skills, including relaxation with imagery, that patients can select from to apply toward reducing pain or nausea). Finally, we hypothesized no pain effect for the therapist support because it provided no skills for symptom management.

## Methods

### *Patients*

Patients in the final sample completing the study were 94 men and women undergoing their first BMT at the Fred Hutchinson Cancer Research Center in Seattle. All patients were English speaking, 18 years or older, and diagnosed with leukemia, myelodysplasia, or lymphoma. Patients were excluded from the study if they had pain problems at the time of consenting or were actively practicing imagery on their own. To be included in the final sample, patients had to receive 2 outpatient training sessions (except for the treatment as usual control group) and remain well enough through the 1st month of their transplant to participate in the study interventions and data collection. Demographic and medical data, including diagnostic and preparative regimen characteristics, are listed in Table I. Mean age of the sample completing the study was 36 with a standard deviation of 9.4. No significant group differences occurred in age, gender, education or income.

Sixty-seven additional patients were randomized but did not complete the study. Table II describes the reasons patients did not complete the study. Causes of patient drop-out, including protocol violations and rescinded consent, did not differ significantly across groups.

Patients were randomized to 1 of 4 intervention conditions: (1) treatment as usual control group (TAU); (2) therapist support (TS); (3) relaxation and imagery training (R&I); and (4) cognitive-behavioral skills training including relaxation and imagery (CB). Randomization was stratified for conditioning regimen with or without total body irradiation (TBI) and for gender. Our previous study with this population found a main effect for gender in predicting pain report (Syrjala et al. 1992a). In addition, data have demonstrated that patients receiving TBI have more severe mucositis (Schubert et al. 1992). To reduce the influence of expectation or demand characteristics, patients were not told the content of each intervention group. During consent, they were told the time requirements and general intention of the study. After consent and randomization, they were told the content only for the intervention they received.

### *Procedure*

All procedures were approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center. Following consenting to the study and prior to randomization, all patients completed psychological measures and a background form. Patients were randomly assigned to 1 of the 4 groups. The TS, R&I, and CB patients participated in two 90-min training sessions prior to hospitalization.

These sessions were audiotaped to monitor adherence to treatment guidelines. After in-patient admission, patients assigned to the treatment conditions participated in ten 30-min 'booster' sessions held twice weekly. The 'booster' sessions were designed to reinforce use of the interventions for pain and symptom control. While hospitalized, patients reported daily subjective pain and nausea. On the last day of data collection, patients in the intervention groups completed a post-treatment evaluation questionnaire.

### Therapists

Therapists were 8 Ph.D.-level clinical psychologists experienced in pain management, cognitive-behavioral treatment methods and relaxation and imagery. All received supervised training in applying the study procedures to the BMT patient population. A senior clinical psychologist (J.E.C.) screened each therapist for competence with the techniques prior to the therapist being assigned patients. This senior psychologist then monitored audiotapes of outpatient sessions for each therapist on an ongoing basis. In addition, therapists met for weekly individual and group supervision with the first author (K.L.S.). Therapists followed a detailed treatment manual which specified the content of each intervention session.

### Interventions

All patients received standard pharmacologic interventions for pain, nausea and emesis. Anesthesiologists with the pain service followed all patients to assure standardized medical approaches to pain management.

*Treatment-as-usual control.* This group provided an untreated control group. These patients did not receive cognitive-behavioral training with a psychologist, but staff social workers were available to all patients as needed. Social workers did not provide hypnosis, imagery or interventions related to pain or nausea management.

*Therapist support.* Patients assigned to this condition met with a therapist for equivalent time and session frequency as patients in the CB and R&I groups. Therapists provided general psychotherapeutic support, focusing on affective status, relationships with caregivers, activities the patient was involved in, and preexisting coping skills that patients used on their own. Psychological techniques such as relaxation and imagery, deep breathing, goal-setting, coping skill training, and distraction were not introduced to the patient. Although skills were not taught, patients were provided positive reframing by the therapist (Syrjala 1993) emphasizing what was going well and what the patient had accomplished. Therapists also provided information related to the normal course of pain and nausea and answered questions about medical treatments for these symptoms. Thus active reassurance was provided for symptoms and their treatment.

*Relaxation and imagery training.* Training material was presented through one-to-one interaction, written instruction, audio relaxation tapes and homework practice of the relaxation and imagery. During prehospital training sessions, patients were provided with information regarding the physiological mechanisms of pain and nausea. Patients were instructed in deep breathing followed by progressive muscle relaxation (Bernstein and Borkovec 1973) in the first session and an abbreviated form of autogenic relaxation in the second session (Schultz and Luthe 1969). These were followed by imagery to deepen relaxation using descending a staircase or another counting method of deepening and then imagery of a place the patient chose. References to patient well-being, strength, competence and comfort were included in the imagery. During sessions when patients had pain, images of cold as a form of sensory transformation were included in the imagery. As patients became accustomed to the relaxation and imagery and as they became more ill, with reduced attention span, relaxation inductions were necessarily shortened based on preferences of the patient for entering a relaxed state. Patients were presented with an audiotape of the outpatient relax-

ation training and guided imagery sessions, and instructed to practice these techniques daily. During hospitalization, patients were seen twice a week for 20–40-min sessions. Each week, one session included in vivo relaxation and imagery. Patients were provided additional audiotapes to assist their practice between sessions.

*Cognitive-behavioral coping skills group.* During the 2 prehospital sessions, patients received training in cognitive coping strategies and relaxation techniques. Training material was presented through in vivo instruction, a patient handbook (Syrjala et al. 1992b), audio relaxation tapes, and homework practice of the skills. Patients in-

TABLE I  
DEMOGRAPHIC AND MEDICAL CHARACTERISTICS OF THE FINAL SAMPLE

Age	
Mean (SD)	36.315 (9.430)
Range	18–56
Gender	
Male	53
Female	41
Education	
< High School	7
High School Degree	34
2-Year College Degree	11
4-Year College Degree	30
Graduate Degree	10
Unknown	2
Income	
< \$10,000	4
\$10,000–19,999	7
\$20,000–29,999	13
\$30,000–49,999	36
\$50,000–99,999	20
≥ \$100,000	7
Unknown	7
Diagnostic and preparative regimen characteristics of patients	
Diagnosis	
Acute lymphocytic leukemia (ALL)	8
Acute myelogenous leukemia (AML)	16
Chronic myelogenous leukemia (CML)	51
Non-Hodgkin's lymphoma (NHL)	10
Hodgkin's disease	2
Other	7
Risk <sup>a</sup>	
Low	48
High	46
Preparative chemotherapy and total body irradiation regimen <sup>b</sup>	
Cy + 1200 cGy TBI	39
Cy + 1320 cGy TBI	19
Cy + 1440 cGy TBI	4
Cy + 1575 cGy TBI	10
Bu + Cy + 1200 cGy TBI	5
Bu + Cy	10
VP-16, BCNU, Cy	5
Other	2

<sup>a</sup> Low risk = first remission AML or ALL; chronic phase CML; myelodysplasia. High risk = leukemics in relapse, 2nd or 3rd remission; CML in accelerated phase or blast crisis, all Hodgkin's and NHL.

<sup>b</sup> Cy = cyclophosphamide, 60 mg/kg/day × 2; Bu = busulfan, 2 mg/kg/day × 4; cGy = centigray; TBI = total body irradiation; BCNU = carmustine.

structured in CB were presented the following techniques. (1) *Relaxation and imagery training* was identical to that used in the R&I condition. (2) *Self-statements*: this component was based on the pain control model developed by Turk et al. (1983) which included training in attention redirection and restructuring self-defeating cognitions. Patients were taught to identify helpless or self-defeating thoughts, and to interrupt and change these using prepared, substitute coping thoughts. (3) *Distraction*: patients were instructed in the use of distraction to focus their attention away from noxious physical sensations to other areas of concentration (Turk et al. 1983). The methods used to used to redirect patient's attention included: imagining being in a more pleasant place; focusing on an alternative sensation such as massage or exercise; and focusing on an activity such as music, simple games, or talk with family. (4) *Short-term goals*: patients were assisted in setting and charting a daily goal, such as completing a bath or playing a game and to focus their goals on pleasures, rather than on required medical activities. In addition to short-term goal setting, long-term 'visions', such as going to a favorite place with a special person were also encouraged and incorporated into imagery. Therapists discouraged patients from setting long-term goals that could not be controlled such as date of discharge from the hospital. The 10 inpatient sessions provided patients with an opportunity to problem-solve difficulties in dealing with the stresses of hospitalization and transplant procedures by applying CB techniques. Each week, one session included in vivo relaxation and imagery. Patients were provided additional audiotapes to assist their practice between sessions.

### Measures

**Oral pain VAS.** Daily while hospitalized, until 22 days post-transplant, all patients were asked to rate their oral mucositis pain level in the preceding 24 h by marking a point on a 100 mm line anchored with 'no mouth or throat pain at all' to the 'worst mouth or throat pain possible'. This VAS has been demonstrated to be a reliable and sensitive measure of pain (Syrjala and Chapman 1984). The data collectors were blind to the randomizations of the patients.

**Nausea VAS.** With the same method as the pain VAS, patients completed a nausea VAS daily while hospitalized. The VAS was anchored with 'no nausea at all' and the 'worst nausea possible.'

**Opioid intake.** Opioids were provided i.v. for all patients. Continuous infusion opioids were supplemented with boluses from patient-controlled analgesia (PCA) pumps. Opioid dosing range was set for each patient by anesthesiologists who were blind to patient randomization. All patients were encouraged by the anesthesiologist to use

as much medication as needed to achieve optimal comfort. Opioid medications used for each 24-h period were extracted from each patient's medical chart. These were converted to morphine equivalents using conversion factors reported by Jaffee and Martin (1980) and Stimmel (1983). Because of skew in the distribution of opioid intake, scores were log-transformed.

**Oral Mucositis Index.** Mucositis severity following conditioning for BMT can range from virtually none to severe, requiring intubation to maintain the airway. This measure provides an objective clinical assessment of the type and degree of observable physical change of oral tissues following BMT (Schubert et al. 1992). Research dental assistants assessed oral cavity tissue changes 2 to 3 times per week immediately following the chemotherapy and radiation conditioning period until each patient's mucositis had resolved. Scores can range from 0 to 92. Our research indicates that mucositis severity significantly predicts pain report (Syrjala and Chapko, 1995). These research assistants were blind to the randomization of the patients.

**SCL-90-R.** As part of the pretransplant assessment, patients completed the well-standardized and validated Symptom Checklist 90-Revised (SCL-90-R) (Derogatis 1977), which includes 9 subscales on psychological status such as depression, anxiety, phobic anxiety, somatization and hostility. Each of the 90 items is rated 0 = not at all to 3 = extremely. Because of skew in the distribution, SCL-90-R scores were log-transformed.

**Post-treatment evaluation.** On the last day of data collection in the hospital (either the day of discharge or day 25 after transplant whichever came first) patients in the TS, R&I and CB groups completed this form. Patients were asked "how did your involvement with this program affect your ability to cope with: pain, nausea, stress?" Pain, nausea and stress were rated separately on scales from 0 to 4 where 0 = did not use, 1 = used, not helpful, 2 = used, a little bit helpful, 3 = used, moderately helpful, 4 = used, extremely helpful.

**Background.** Patients were asked to complete a form that included basic background information such as age, education, income, and previous treatment history.

**Risk.** Risk was measured by dividing patients into 2 groups: 'low risk' and 'high risk'. The low-risk group included those patients with chronic myelogenous leukemia in chronic phase, acute myelogenous leukemia and acute lymphocytic leukemias in first remission and myelodysplasias. The high-risk group included all other patients: second remission, relapse, blast crisis or accelerated phase leukemias and all lymphomas. This classification was based on research demonstrating that patients with diagnoses in the low-risk group evidenced higher survival rates than those patients with the other diagnoses (Sullivan and Storb 1990).

TABLE II  
PATIENTS LOST TO THE STUDY (n = 67)

Reasons patients were lost to the study	Study randomization				
	TAU	TS	R&I	CB	Overall
Early medical crisis <sup>a</sup>	5	8	5	8	26
Admitted prior to completing pretransplant protocol	2	2	5	8	17
Protocol violations by patient or medical staff <sup>b</sup>	4	4	4	1	13
Rescinded consent <sup>c</sup>	2	4	3	1	10
Incomplete data	1	0	0	0	1
Total	14	18	17	18	67

<sup>a</sup> Includes toxicities resulting in major cognitive impairment or death.

<sup>b</sup> Includes: extra sessions needed because of patient psychological distress (n = 5); insistence on imagery or cognitive-behavioral interventions by the patient (n = 6); and refusal of at least 1 consecutive week of sessions by the patient (n = 3).

<sup>c</sup> Includes: refusing assessments (n = 7) and refusing further intervention (n = 3).

## Results

### Group differences

To test for pretreatment demographic differences among the 4 groups, we conducted a multivariate analysis of variance (MANOVA) with age, income and education as dependent variables and intervention group as the independent variable. The multivariate effect was not significant ( $P = 0.13$ ). There was a trend for more non-TBI patients to be in the TAU group (TAU = 7 non-TBI; TS = 4; R&I = 2; CB = 2;  $P = 0.15$ ). Since TBI predicts more severe mucositis, intervention tests are, at worst, conservative. There was no significant association between intervention group and gender (chi-squared = 4.36,  $df = 3$ ,  $P = 0.23$ ), or between intervention group and risk (chi-squared = 3.76,  $df = 3$ ,  $P = 0.29$ ). Thus age, income, education, gender and risk were not considered in subsequent analyses.

### Covariates

Since mucositis is the principal determinant of oral pain in this population, we introduced it as the primary covariate in all analyses. Correlations between the oral mucositis index (averaged over the 22-day time period) and the outcomes (similarly averaged) of pain, nausea, and opioid intake were 0.43 ( $P < 0.001$ ), 0.06 ( $P = 0.570$ ), and 0.45 ( $P < 0.001$ ), respectively. The pre-transplant SCL-90-R correlated significantly ( $P < 0.01$ ) with all 3 outcomes, and so was included as a second covariate in all analyses.

### Data aggregation

To facilitate repeated-measures analyses for pain and opioid intake, we aggregated daily VAS data into time periods conformable to the scheduling of mucositis examinations. Time 1 measures were based on the average of daily scores from day 0 through day 5 when pain is generally mild, but increasing in intensity; time 2 measures were averages for days 6–16 reflecting peak pain; time 3 measures were averages for days 17–22 when pain is resolving. Nausea aggregate scores were the same as those for pain, but, in addition, we included a time period from days –10 through –1 before transplant, during conditioning with chemotherapy and irradiation. This is the period of peak nausea and emesis, before mucositis has begun (Chapko et al. 1989). Table III displays means and standard deviations for pain VAS, nausea VAS, opioid intake and the Oral Mucositis Index, indicating the observed univariate sample size for each time period.

### Missing data

The analysis sample comprised 94 randomized patients who completed the study and provided pain data through day 16 post-transplant, the end of the second time period. Of these 94 patients, all but one completed pain and nausea reports through the 3rd time period as well. All patients had data available on opioid use in each time period. Nineteen patients had oral mucositis data missing for at least 1 week, leaving 74 patients with pain and mucositis data on all mea-

TABLE III

UNADJUSTED MEANS AND STANDARD DEVIATIONS (SD) FOR MUCOSITIS SEVERITY, PAIN, OPIOID INTAKE AND NAUSEA BY GROUP AND TIME

	Day –10 to –1			Day 0 to 5			Day 6 to 16			Day 17 to 22		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
<b>Mucositis</b>												
TAU	–	–	–	22	14.94	6.36	23	29.35	9.94	18	22.25	10.71
TS	–	–	–	22	13.06	10.08	24	28.83	10.37	22	19.14	10.98
R&I	–	–	–	20	16.70	6.15	23	31.96	11.24	22	22.45	13.31
CB	–	–	–	21	12.55	6.39	24	28.75	8.28	19	22.80	10.38
<b>Pain</b>												
TAU	23	4.47	6.40	23	31.01	22.22	23	53.78	23.25	22	33.37	24.66
TS	24	4.65	6.55	24	28.14	18.91	24	44.71	23.95	24	22.40	21.47
R&I	23	4.00	8.32	23	24.29	18.49	23	45.56	23.70	23	26.57	24.20
CB	24	4.28	11.22	24	20.44	13.35	24	45.66	16.95	24	19.18	18.99
<b>Log opioid intake</b>												
TAU	23	0.15	0.21	23	0.71	0.56	23	1.49	0.53	23	1.21	0.68
TS	24	0.22	0.32	24	0.59	0.54	24	1.43	0.61	24	1.09	0.81
R&I	23	0.19	0.28	23	0.57	0.61	23	1.38	0.67	23	1.25	0.69
CB	24	0.19	0.29	24	0.37	0.43	24	1.48	0.51	24	1.05	0.76
<b>Nausea</b>												
TAU	23	31.40	14.74	23	26.16	17.33	23	21.41	15.81	22	20.77	16.81
TS	24	26.79	13.46	24	22.88	16.23	24	19.09	12.07	24	18.58	19.44
R&I	23	27.35	14.18	23	21.80	19.34	23	22.23	17.61	23	20.86	19.22
CB	24	29.31	13.30	24	23.17	13.47	24	23.28	13.09	24	21.47	13.98

tures at all time points. In many cases, a target day falling on a weekend resulted in missing data; in other cases the patient was not in the room at the time the research assistant came to do the exam.

With this sample size and number of mucositis observations missing, analyses can depend critically on treatment of missing data. Restricting analyses only to complete cases risks bias (Laird 1988; Louis 1988; Zwinderman 1992), but standard methods for estimating the missing observations pose risks as well. Good predictors of mucositis are not available. Any estimation method would, therefore, provide poor proxies for the missing covariates, and would generally distort variances and degrees of freedom that affect statistical tests (Little and Rubin 1987).

Preliminary analyses indicated that generating an analysis data set by either eliminating incomplete cases or by filling in missing observations with estimates yielded inferences that were sensitive to how the missing observations were eliminated or estimated. Consequently, we elected to base our primary analyses on a method explicitly designed to be robust with respect to missing data patterns. The general rationale for this approach is given by Dawson and Lagakos (1991). This method is valid under broader conditions than complete-case analyses. Specifically, the approach allows different rates of missing data in the treatment groups, provided that the probability of missingness for a given outcome score is constant across groups.

#### Therapist effects

Therapist effects on patient pain report were tested using repeated-measures MANOVA across the 3 aggregate time periods for patients in the 3 active intervention groups. There was a consistent, but not significant, trend for one therapist's patients to report higher pain scores ( $P = 0.145$ ). Since the analysis was not significant, and the therapist's patients were equally distributed across the groups, no adjustments were made in analyses.

#### Inferential analyses

To minimize missing data influences, we summarized statistics for average pain, nausea, opioid intake and mucositis across all time periods, stratified by missing data patterns in the covariate. This resulted in partitioning into 3 data sets defined as: patients having complete data at all 3 time periods, patients missing data in only the 3rd time period, and patients having any other pattern of missing data. Within each stratum, between-group contrasts and standard errors were computed from standard analyses of covariance (ANCOVA), then pooled in a weighted composite according to the inverse of the within-strata squared standard errors (Dawson and Lagakos 1991), which depend on the number of patients in the strata. The

TABLE IV

POOLED REGRESSION ESTIMATES OF GROUP CONTRASTS AND COVARIATE EFFECTS FOR PAIN AND OPIOID INTAKE

	Estimate	SE	Approx. $z$	$P$
VAS pain report adjusted for mucositis severity and distress				
<sup>a</sup> TS- <sup>a</sup> TAU	-7.00	4.29	-1.63	0.1031
<sup>a</sup> R&I- <sup>a</sup> TAU	-11.62	4.44	-2.62	0.0088
<sup>a</sup> CB- <sup>a</sup> TAU	-11.72	4.35	-2.69	0.0071
Mucositis	1.00	0.22	4.55	0.0000
Log(SCL-90-R + 1)	35.00	15.66	2.23	0.0257
Log of opioid intake adjusted for mucositis severity and distress				
<sup>a</sup> TS- <sup>a</sup> TAU	-0.042	0.122	-0.34	0.7339
<sup>a</sup> R&I- <sup>a</sup> TAU	-0.120	0.126	-0.95	0.3421
<sup>a</sup> CB- <sup>a</sup> TAU	-0.128	0.121	-1.06	0.2891
Mucositis	0.025	0.006	4.35	0.0000
Log(SCL-90-R + 1)	1.440	0.420	3.43	0.0006

resulting composite is robust to missing data bias and valid by construction for generalization to new patients meeting study recruitment criteria. As a secondary analysis, we also conducted conventional between- and within-group tests on the stratum with complete data. Thus we have included a 'standard analysis' based on the subset of patients having complete data.

Table IV displays the results of our principal analyses for VAS pain report and opioid intake. Three contrasts were defined among the treatment means of the summary pain variable: R&I vs. TAU, CB vs. TAU and TS vs. TAU. These contrasts were estimated separately for each missing data stratum using standard ANOVA and covariance techniques, then pooled to obtain the reported estimate. Contrasts were adjusted for the effects of the summary oral mucositis index and for pretreatment distress as measured by the log-transformed SCL-90-R scores. To control for the 3 multiple comparisons for each dependent variable, we used a Bonferroni correction, thus contrasts with  $P < 0.0167$  ( $0.05/3$ ) were regarded as significantly different from zero. Covariate coefficients are evaluated at their nominal significance levels (i.e.,  $P < 0.05$  indicates significance).

Table IV indicates that both R&I and CB patients have significantly less pain than patients in the TAU condition. Because the comparison between R&I and CB is of interest, we also tested its significance explicitly. Adjusted for 2 covariates, the estimated R&I-CB contrast is 2.47 (approximate  $z = 0.56$ ,  $P = 0.58$ ). Although the TS group also reports less pain descriptively than the TAU group, this difference is not significant. The pattern of adjusted group effects for opioid intake agrees with the pattern for pain report, but the results are not significant. Figs. 1 and 2 display individual pain scores by treatment group, adjusted for the 2 covariates and identified by missing data stratum.

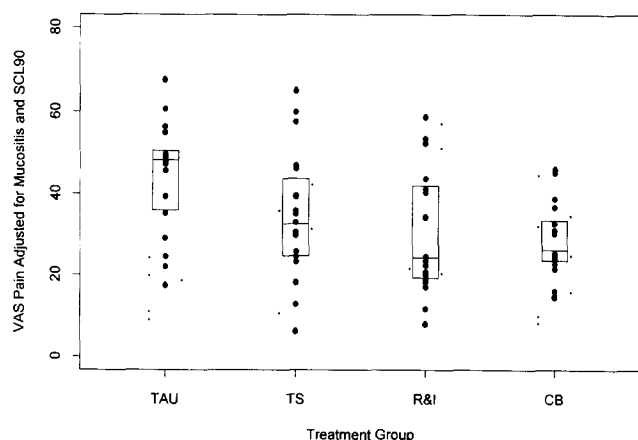


Fig. 1. Box plots representing the distributions of scores for adjusted mean pain across all 3 time periods, within each intervention group, with displayed point sizes proportional to weights based on statistical analyses. All data points are adjusted for mucositis (when available) and SCL-90-R. The large data points in the center of each box represent the pain scores of the patients with complete data. The small data points on the sides represent the pain scores for those patients lacking mucositis data in at least 1 time period. The box length encompasses 50% of the complete data cases, with the median at the line across the box and with the 75th and 25th percentiles at the top and bottom of the box. The possible range for pain on the VAS is 0-100. TAU = treatment as usual; TS = therapist support; R&I = relaxation and imagery training; CB = cognitive-behavioral training.

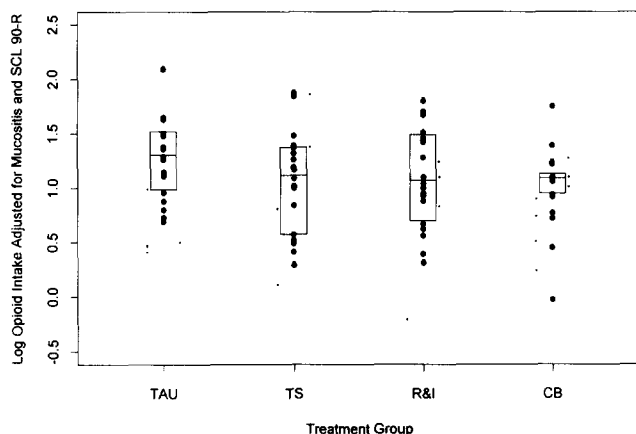


Fig. 2. Box plots representing the distribution of scores for the log-transformations of adjusted mean opioid intake across all 3 time periods, in morphine equivalent units, within each intervention group with displayed point sizes proportional to weights based on statistical analyses. All data points are adjusted for mucositis (when available) and SCL-90-R. The large data points in the center of each box represent the opioid intake for patients with complete data, adjusted for mucositis severity and log-transformation of SCL-90-R. The small data points on the sides represent opioid intake for those patients lacking mucositis data in at least 1 time period. The box length encompasses 50% of the complete data cases, with the median at the line across the box and with the 75th and 25th percentiles at the top and bottom of the box. TAU = treatment as usual; TS = therapist support; R&I = relaxation and imagery training; CB = cognitive-behavioral training.

For the subsample having complete data at all 3 time periods, we conducted conventional ANCOVA to evaluate intervention effects adjusted for overall mucositis severity and baseline SCL-90-R. The hypothesis of equal adjusted overall pain means was rejected ( $P = 0.007$ ), but the adjusted overall opioid intake means did not differ significantly from one another ( $P = 0.250$ ). These tests correspond to the box plots and large data points in Figs. 1 and 2 (i.e., ignoring the small data points belonging to the missing data strata).

For the same subsample, the tests of time period effects, ignoring intervention group, were highly significant ( $P < 0.001$ ) for both pain and opioid intake, with highest outcome scores at the 2nd time period. The intervention-group-by-time period interaction was marginally significant ( $P = 0.03$ , Pillai's criterion) for opioid intake, indicating little or no reduction between time periods 2 and 3 for the R&I group alone. The interaction test for pain was not significant ( $P = 0.780$ , Pillai's criterion).

Similar pooled contrasts and conventional analysis for nausea report indicated no significant differences or trends between groups.

Analyses of the post-treatment evaluation data reflect results from pain and nausea VAS analyses. Comparison of scores to the untreated TAU group is not possible because untreated patients cannot be asked to indicate the extent to which non-treatment helped their coping with pain, nausea or stress. Descriptive results are displayed in Fig. 3. In a planned contrast, the R&I and CB groups together trended toward report of greater perceived helpfulness of their interventions for coping with pain when compared to the TS group ( $P = 0.06$ ). The groups did not differ in reported help-

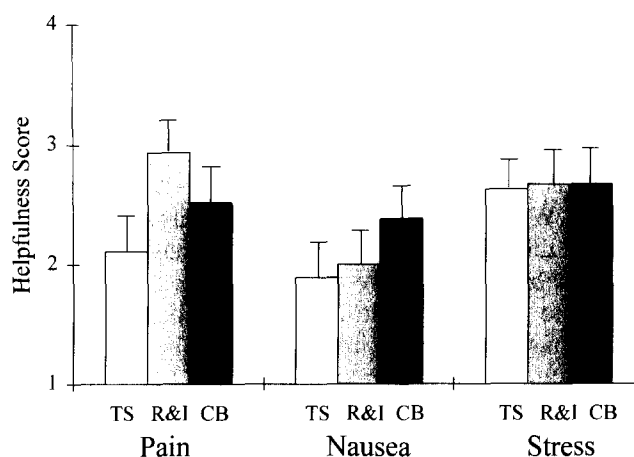


Fig. 3. Bar graph presenting the means and standard errors of patient reported perceived helpfulness of each intervention for coping with pain, nausea and stress. Possible scores range from 0 to 4, with 0 = did not use, 1 = used, not helpful, 2 = used, a little bit helpful, 3 = used, moderately helpful, 4 = used, extremely helpful. TS = therapist support (n = 19); R&I = relaxation and imagery training (n = 18); CB = cognitive-behavioral training (n = 21).

fulness of their interventions for nausea or stress. Patients in the treatment groups overall reported significantly greater perceived efficacy of their interventions for coping with pain ( $t = 3.18$ ,  $P = 0.002$ ) and stress ( $t = 3.63$ ,  $P = 0.001$ ) when compared to perceived efficacy for coping with nausea.

## Discussion

Results confirmed our hypothesis that relaxation and imagery and cognitive-behavioral coping skills training reduce pain in patients undergoing BMT for cancer. The hypothesis that the cognitive-behavioral training would have an additive effect beyond relaxation and imagery alone was not confirmed. The differences in pain report between the training groups and the untreated control group were strengthened when we controlled for severity of oral mucositis and psychological distress. No differences were observed between groups on nausea ratings. The results for pain and nausea were confirmed in analyses of patients' perceptions of helpfulness of the interventions for coping with these symptoms.

Severity of mucositis and level of psychological distress were significant predictors of both pain report and opioid use while distress, but not mucositis, predicted nausea. These results replicate similar findings in our previous clinical trial (Syrjala et al. 1992a). This information may be useful in planning more aggressive treatment of symptoms in those patients with high levels of distress prior to transplant or those predicted to have more severe mucositis (see Schubert et al. 1992).

Interesting questions are raised in considering the differences, both descriptively and statistically between the 4 groups in pain report. Analyses indicate that the cognitive-behavioral skills are not effective over and above the impact of the relaxation and imagery training. Comparing these results with those from our previous study (Syrjala et al. 1992a), we confirm that imagery is a powerful component of persistent pain treatment. Whether called hypnosis or relaxation and imagery, the interventions with imagery have been effective in both studies we have completed, whereas we have no data to confirm the independent efficacy of non-imagery cognitive interventions. These results are consistent with the meta-analysis of Fernandez and Turk (1989), who found imagery to be the most powerful psychological strategy for reducing persistent pain. Results are also consistent with the chronic pain controlled clinical trial of Turner and Jensen (1993) where all 3 treatment groups (relaxation with imagery, cognitive training, and cognitive training + relaxation with imagery) reported similar reductions in pain compared to untreated patients.

In looking at the distribution of average pain scores of individuals in the relaxation with imagery group and the cognitive-behavioral group, and from clinical experience, we believe a select number of patients benefit from the added elements of the cognitive training. In such select cases, the power to demonstrate an effect of this combined intervention would require very large samples or as yet undefined methods for selecting those patients likely to benefit from the addition of cognitive skill training. Alternatively, the addition of distraction, self-statements and goal setting may be more than some patients can competently learn and apply in this short training, even followed by booster sessions. Thus, for some patients, the added skills may only detract from the relaxation and imagery effects while for other patients, who do not respond to relaxation with imagery, there may be a benefit from some of the additional cognitive-behavioral skills. The mean differences between these 2 groups is most supportive of the hypothesis that relaxation with imagery has an effect, with little positive or negative effect from the other cognitive-behavioral skills.

Tests revealed that both relaxation and imagery and cognitive-behavioral training reduce pain, while reported pain within the therapist support group is not significantly lower than the untreated group with this sample size. Yet descriptively and statistically the support group appears to fall between the other treated groups and the untreated group, suggesting some effect of basic support from therapists skilled in dealing with cancer and pain. While monitored audiotapes of the training confirmed that no cognitive-behavioral training was provided, these therapists knew the BMT process and pain management. The reassurance, acknowledgment of accomplishments and normalization about the course of mucositis and medication use, as provided by therapists in the support condition, may have been of some value to some patients. These results replicate the findings of Spiegel and Bloom (1983), comparing no treatment with support or support + hypnosis, who determined that both interventions were more effective than no psychological treatment. Similar to our results, these researchers did not find a significant difference between support-only and support + hypnosis, although the hypnosis group had the lowest pain scores. As noted by Andersen (1992), 'non-specific' effects require further research since they may have significant effects in some cancer patients.

Patient perceptions reflect similar findings on the helpfulness of the various interventions for pain, nausea and stress. From patients' perspectives, interventions were significantly more effective for pain and stress than for nausea. Patients in all groups reported the interventions to be equally helpful for stress and equally not as helpful for nausea. Results for perceived helpfulness of the interventions for pain are in the

same direction of effect as for VAS reports of pain. There was a trend for the relaxation and imagery group and cognitive behavioral group to report greater helpfulness than reported by the therapist support group.

Consistent with our previous clinical trial, no differences were found in opioid intake or nausea between the intervention groups. Opioid intake means followed the same pattern as the pain report means although results did not reach significance. This indicates that the differences in pain report between treatment groups cannot be explained by increases or decreases in use of opioids to relieve pain.

In this context, medication use results are difficult to interpret. Change in medication use was not a target of the interventions. Instead, patients were encouraged to use opioids optimally for their needs. The greatest success of the interventions would be demonstrated by reduced pain report and reduced opioid use. Alternatively, if patients in the intervention groups had reported less pain, but used more medication, we would have considered the study interventions successful in assisting patients with more optimal medication use. With the finding that opioid use does not significantly differ between groups, we cannot rule out the influence of demand characteristic on the self-report of pain. Two factors mitigate against the potential demand to reduce pain report to please the therapist or researcher. Patients were not aware of which intervention they received relative to the other interventions available. Patients also were experiencing mucositis pain for the first time in an unfamiliar environment with very little contact with other patients experiencing mucositis. These factors may have made perceived demand characteristics more difficult to ascertain, still we cannot rule out their possible influence.

Results of this study and our prior study consistently indicate no effect of these interventions on the postchemotherapy and irradiation nausea in transplantation. Several explanations are possible. First, the intensity of the challenge posed by the massive doses of the preparative regimens may pose too great a challenge to newly learned skills. Second, the high doses of anti-emetic agents used to control nausea and emesis are sedating to most patients. This sedation may interfere with the practice of cognitive methodologies. Third, we may have a floor effect of the nausea measure. Since average nausea, with pharmacologic treatment, ranged between 15 and 30 on a 0–100 mm VAS scale, the measure may have inadequate sensitivity to treatment effects.

The consistent effectiveness of these interventions for reducing pain, on average across groups of patients, requires us to define which treatments should be provided with which patients. While the emphasis in testing these interventions with cancer patients and chronic

pain patients has focused on comparing different interventions, in the current cost-conscious, managed health care environment, we need to define which patients benefit from specific interventions. Equally important, we need to identify which patients do well without intervention and therefore can be well managed with medical treatment alone.

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