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Systematic Review and Meta-Analysis of Psychological and Activity-Based Interventions for Cancer-Related Fatigue

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Abstract

Context—Fatigue is among the most common and distressing symptoms experienced by cancer patients.

Objective—This systematic review and meta-analysis evaluates the efficacy of psychological and activity-based interventions against cancer-related fatigue in cancer patients.

Data Sources—MEDLINE, PsycINFO, and CINAHL.

Study Selection—Randomized controlled trials of psychological and activity-based interventions involving adult cancer patients in which fatigue was an outcome were reviewed.

Extraction—Forty-one trials were reviewed and 30 were included in a meta-analysis.

Data Synthesis—Fifty percent of psychological trials and 44% of activity-based trials rated fair or better in quality yielded significant findings favoring the intervention condition. Meta-analysis yielded an overall effect size of 0.09 (95% CI = .02 – .16) favoring nonpharmacological conditions. Further analysis indicated that effect sizes were significant for psychological interventions (d_w = .10, 95% CI = .02–.18) but not activity-based interventions (d_w = .05, 95% CI = −.08 – .19).

Conclusions—Findings provide limited support for use of nonpharmacological interventions to manage cancer-related fatigue. The lack of research with heightened fatigue as an eligibility criterion is a notable weakness of the existing evidence base.

Keywords

fatigue; cancer; psychological interventions; activity-based interventions; randomized controlled trials

Cancer-related fatigue has been defined as “a persistent subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning” (Mock et al., 2000). Studies suggest it is among the most common symptoms experienced by cancer patients with advanced disease and those being treated with radiotherapy and chemotherapy (Ahlberg, Ekman, Gaston-Johansson, & Mock, 2003). Furthermore, fatigue does not appear to be limited to the active treatment period. Many individuals with no clinical evidence of disease continue to experience fatigue for months or even years following treatment completion (Servaes, Verhagen, & Bleijenberg, 2002). The clinical significance of fatigue has been examined primarily in terms

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*References marked with an asterisk indicate studies included in the meta-analysis.

of its impact on quality of life. Among patients treated with chemotherapy or radiotherapy, more than one third perceived that fatigue interfered with their ability to work, relationships with others, and physical and emotional well-being (Vogelzang et al., 1997).

Mechanisms involved in the development and persistence of cancer-related fatigue are only partially understood. Available evidence suggests that fatigue can occur as a consequence of metabolic changes associated with the underlying disease as well those induced by cancer treatments (Stasi, Abriani, Beccaglia, Terzoli, & Amadori, 2003). In addition, fatigue can occur as a concomitant of other common symptoms experienced by cancer patients (e.g., nausea, and pain; Stasi et al., 2003). A growing body of research also suggests that cognitive and behavioral factors may contribute to exacerbation and persistence of fatigue (Stasi et al., 2003). With regard to behavioral factors, attention has focused on the role of physical activity. Preliminary evidence suggests that cancer patients who reduce their physical activity may experience a worsening and perpetuation of fatigue due to reductions in cardiorespiratory fitness or muscle weakening (Ahlberg et al., 2003). With regard to cognitive factors, several studies have shown that the tendency to catastrophize (i.e., have negative expectations regarding one's ability to cope with fatigue) is associated with worse fatigue (Broeckel, Jacobsen, Horton, Balducci, & Lyman, 1998; Donovan, Small, Andrykowski, Munster, & Jacobsen, 2007; Jacobsen, Andrykowski, & Thors, 2004; Jacobsen, Azzarello, & Hann, 1999).

Research bearing on the management of fatigue can be divided into studies that have evaluated pharmacological or nonpharmacological approaches. In drawing this distinction, we note the lack of any studies that have formally evaluated a combination of pharmacological and nonpharmacological approaches. The current review focuses on the body of scientific evidence regarding the efficacy of nonpharmacological approaches for the management of cancer-related fatigue. As described below, previous reviews suggest this literature can be divided into activity-based interventions and psychological interventions. Activity-based interventions include professionally supervised programs and unsupervised (i.e., home-based) programs designed to promote exercise activity. Psychological interventions represent a more heterogeneous set of approaches that can include cognitive– behavioral therapy, supportive therapy, supportive-expressive therapy, and psychoeducation.

To date, there has been one systematic review (Lawrence, Kupelnick, Miller, Devine, & Lau, 2004) and no meta-analysis encompassing both psychological and activity-based interventions for people with cancer. The previous review, which included studies published through 2001, sought to identify all English language articles that dealt with the assessment, occurrence, and treatment of fatigue in cancer patients. With regard to treatment studies, the search identified 10 randomized controlled trials (RCTs) assessing the efficacy of interventions for cancer-related fatigue. Although specific search items used were not described, the results of our search (described below) suggest they may have been too narrow to result in identification of all relevant studies. This earlier review identified four principal methodological concerns with the existing treatment literature. First, reporting of the basic design elements was found to be inconsistent across studies. Second, studies typically evaluated numerous endpoints without identifying those that were of primary interest and without identifying effect sizes that would be considered clinically important. Third, because endpoints were typically not defined prospectively, sample sizes in these studies were viewed as having been chosen arbitrarily. Fourth, the patient populations in several trials were quite heterogeneous with regard to cancer types and treatments. This heterogeneity was considered responsible for much of the observed variance in fatigue in these trials. With regard to the efficacy of nonpharmacological interventions, the authors concluded that the results of two trials suggested exercise (Dimeo, Stieglitz, Novelli-Fischer, Fetscher, & Keul, 1999; Mock et al., 1997) might be helpful in reducing or preventing cancer-related fatigue.

The objective of this review is to provide a systematic evaluation of the efficacy of nonpharmacological interventions on fatigue in people with cancer. Toward this end, we sought to identify all RCTs of activity-based and psychological interventions conducted with adults with cancer in which fatigue was assessed as an outcome and to evaluate the efficacy of these interventions against fatigue using qualitative and quantitative methods. As part of the review, we also evaluated the methodological quality of these trials.

Method

Search Strategy

Identification of appropriate RCTs began with electronic searches of English language journal articles in PsycINFO (1967–November 2005), MEDLINE (1966 –November 2005), and CINAHL (1982–November 2005). The search terms used were the following: neoplasms AND cognitive therapy OR counseling OR mind-body and relaxation techniques OR patient education OR psychotherapy OR self-help groups OR group psychotherapy OR anxiety management OR behavior therapy OR hypnosis OR relaxation therapy OR client education OR support groups OR self-help techniques OR exercise movement techniques OR exercise. Reference lists from publications retrieved and from relevant systematic reviews and meta-analyses (Knols, Aaronson, Uebelhart, Fransen, & Aufdemkampe, 2005; Lawrence et al., 2004; Newell, Sanson-Fisher, & Savolainen, 2002; Schmitz et al., 2005; Stricker, Drake, Hoyer, & Mock, 2004) were also examined to identify RCTs. In addition, requests for information about relevant RCTs were posted on several electronic mailing lists likely to be viewed by behavioral oncology researchers.

Selection Strategy

Five inclusion criteria were applied to studies retrieved. First, each study must have described a controlled comparison that included a no treatment or placebo condition. Second, one of the experimental conditions in the study must have been a psychological or activity-based intervention. Third, study participants must have been adults diagnosed with cancer. Fourth, one of the study outcomes must have been fatigue, or the related constructs of vitality or vigor, assessed using a self-report measure. Fifth, the results reported must have included statistical significance testing of differences between an intervention condition and a control condition.

Review Strategy

Information about methods and results was abstracted for each study that met inclusion criteria. Abstraction of results focused on comparisons between the control condition and the intervention condition(s). Specifically, we tabulated the number of comparisons that were performed for each outcome variable at each follow-up assessment and the number of these comparisons reported to be statistically significant in favor of the intervention condition. Information was also abstracted for purposes of assessing methodological quality using criteria set forth by the Cochrane Collaboration (Mulrow & Oxman, 1997) and adapted from those used in a systematic review of psychological therapies for people with cancer (Newell et al., 2002). Appendix 1 lists the 10 quality indicators and the criteria used for each rating. Consistent with prior use of similar criteria (Newell et al., 2002), each indicator was evaluated as having been entirely fulfilled (3 points), mostly fulfilled (2 points), mostly not fulfilled (1 point), not at all fulfilled (0 points), or as providing insufficient information for adequate assessment (0 points). A study was considered good if it earned a score greater than 20 points, fair if it scored between 11 and 20 points, and poor if it scored less than 11 points out of a total of 30 possible points.

Statistical Analysis

Meta-analytic procedures were based on those outlined by Hedges and Olkin (1985). From the results reported or provided upon request by one of the publication authors, an effect-size estimate (*g*) was first calculated to indicate the difference between the control and intervention groups divided by the pooled standard deviation. The information used to generate *g* values was based upon group differences at the final measurement point for the control and intervention groups. To pool results across studies, the effect size (*d*) was computed (i.e., the standardized difference between the control and intervention groups weighted by the sample sizes of the individual studies).

In addition to describing the differences between the control and intervention groups, we examined several moderating characteristics that could potentially impact the magnitude of the observed treatment effects. Normally, a statistically significant chi-square homogeneity statistic (Q_W) would trigger a search for potential moderators. However, this statistic suffers from low statistical power when the number of studies to be included is small (Takkouche, Cadarso-Suarez, & Spiegelman, 1999). Therefore, we identified a priori a number of characteristics to stratify studies along. Specifically, we compared efficacy for psychological and activity-based interventions and compared efficacy based on whether fatigue or vigor was measured as an outcome. In addition, we compared intervention efficacy based on patient characteristics and intervention modality characteristics suggested by qualitative review of study findings (see below). The Q_B statistic was used to evaluate the significance of differences in effect sizes based on study stratification variables.

Results

Search Results and Organization of Selected Studies

Based on application of the search and selection strategies, 41 publications were identified for review. Twenty-four publications were categorized as psychological intervention studies (Badger et al., 2005; Barsevick et al., 2003; Boesen et al., 2005; Bordeleau et al., 2003; de Wit et al., 1997; Decker, Cline-Elsen, & Gallagher, 1992; Edelman, Bell, & Kidman, 1999; Fawzy et al., 1990; Forester, Kornfeld, & Fleiss, 1985; Gaston-Johansson et al., 2000; Goodwin et al., 2001; Hack et al., 2003; Jacobsen et al., 2002; Oyama, Kaneda, Katsumata, Akechi, & Ohsuga, 2000; Rawl et al., 2002; Sandgren & McCaul, 2003; Sandgren, McCaul, King, O'Donnell, & Foreman, 2000; Speca, Carlson, Goodey, & Angen, 2000; Spiegel, Bloom, & Yalom, 1981; Telch & Telch, 1986; Vos, Garssen, Visser, Duivenvoorden, & de Haes, 2004; Wenzel, Robinson, & Blake, 1995; Williams & Schreier, 2004; Wydra, 2001) and 17 were categorized as activity-based intervention studies (Burnham & Wilcox, 2002; Campbell, Mutrie, White, McGuire, & Kearney, 2005; Coleman et al., 2003; Courneya, Friedenreich, Quinney et al., 2003; Courneya, Friedenreich, Sela et al., 2003; Courneya, Mackey et al., 2003; Drouin et al., 2005; Headley, Ownby, & John, 2004; McKenzie & Kalda, 2003; Mock et al., 1994, 1997; Mock et al., 2005; Pinto, Clark, Maruyama, & Feder, 2003; Segal et al., 2001; Segal et al., 2003; Thorsen et al., 2005; Windsor, Nicol, & Potter, 2004). All 17 activity-based intervention studies focused on evaluation of exercise programs; included in this category is the only study identified that evaluated a combination of exercise and psychotherapy (Mock et al., 1994). As described below, the psychological intervention studies evaluated a more heterogeneous set of interventions.

Characteristics of the Psychological Intervention Studies

Demographic and clinical characteristics of participants in the 24 psychological intervention studies are described in Appendix 2. Eleven studies (46%) were of breast cancer patients only, ten (42%) were of patients with more than one type of cancer, two (8%) were of melanoma patients only, and one (4%) was of gynecologic cancer patients only. With regard to disease

severity, eight (33%) included only patients with nonmetatstatic disease and four (17%) included only patients with metastatic disease. The 12 remaining studies (50%) either did not specify metastatic status or were not restricted in terms of metastatic status. Thirteen studies (54%) included patients undergoing or about to start cancer treatment (e.g., chemotherapy and/or radiotherapy), ten (42%) included patients either on or off treatment, and one (4%) included only patients who had completed treatment. Twelve studies (50%) included only women; among the remaining studies, the representation of men ranged from 15% to 51% (median = 34%).

Design characteristics of the psychological intervention studies are also described in Appendix 2. The total sample size for each study ranged from 30 to 627 (median = 109). Twenty-two studies (92%) employed no intervention control conditions in which participants did not receive the intervention of interest or may have received it following completion of follow-up assessments. The two remaining studies (8%) used conditions that attempted to control for the amount of attention participants in the intervention condition received. A total of 27 interventions were evaluated in these 24 studies. Ten of the interventions (37%) were delivered using a group format. Eleven interventions (41%) were cognitive–behavioral forms of therapy, three (11%) were educational programs, three (11%) were supportive-expressive group therapy, and three (11%) were supportive forms of therapy. The seven other interventions (26%) were evaluated in only one study. Four studies (17%) assessed outcomes at a single assessment shortly after intervention; the 20 remaining studies (83%) all assessed outcomes at longer intervals or on multiple occasions after intervention. Fatigue and vigor were the outcomes assessed in eleven studies (46%), fatigue was the only outcome assessed in ten studies (42%), and vitality was the only outcome assessed in three studies (12%). Fatigue, vigor, or vitality was identified as a primary outcome in five publications (21%). In none of the publications was a specified baseline level of fatigue, vigor, or vitality used as a study eligibility criterion.

Quality of the Psychological Intervention Studies

The summary quality score for each psychological intervention study appears in Appendix 2, and the percentage of psychological intervention studies performing at each level of quality on each indicator appears in Appendix 1. Methodological quality was rated good for one study (4%), fair for seventeen studies (71%), and poor for six studies (25%). Areas where criteria for a quality indicator were not at all fulfilled or could not be evaluated for the majority of psychological intervention studies were the following: random selection of patients, acceptable adherence to the intervention, analysis by intention to treat, and outcome assessed by blinded personnel.

Findings of the Psychological Intervention Studies

Ten of 24 publications (42%) yielded at least one finding significant at $p \leq .05$ favoring the intervention condition. Among publications rated fair or better in quality, 9 of 18 (50%) yielded at least one finding significant at $p \leq .05$ favoring the intervention condition. Average quality ratings were similar for publications that did and did not yield significant findings ($M = 14.40$ and $M = 12.86$, respectively). Cancer type and intervention modality appeared to differentiate studies with and without significant results. Relative to control conditions, 18% of studies that enrolled only breast cancer patients yielded significant results compared to 54% of studies that enrolled other types of patients. Relative to control conditions, 60% of group-based interventions yielded significant findings compared to 36% of individual-based interventions.

Characteristics of the Activity-Based Intervention Studies

Demographic and clinical characteristics of participants in the 17 activity-based intervention studies are described in Appendix 3. Ten studies (59%) were of breast cancer patients only,

three (17%) were of patients with more than one type of cancer, two (12%) were of prostate cancer patients only, one (6%) was of multiple myeloma patients only, and one (6%) was of colorectal cancer patients only. With regard to disease severity, 10 studies (50%) included only patients with nonmetastatic disease and one (6%) included only patients with metastatic disease; the six remaining studies (35%) either did not specify metastatic status or were not restricted in terms of metastatic status. Eleven studies (65%) included patients undergoing or about to start cancer treatment (e.g., chemotherapy and/or radiotherapy), five (29%) included only patients who had completed treatment, and one (6%) included patients either on or off treatment. Ten studies (59%) included only women and two studies (12%) included only men; among the remaining studies, the representation of men ranged from 14% to 58% (median = 32%).

Design characteristics of the activity-based intervention studies are also described in Appendix 3. The total sample size for each activity-based intervention study ranged from 14 to 155 (median = 50). Sixteen studies (4%) employed no intervention control conditions in which participants did not receive an activity-based intervention or may have received it following completion of follow-up assessments. The one remaining study (6%) used a placebo stretching control condition. A total of 18 interventions were evaluated in the 17 studies reviewed. Eleven of these interventions (61%) were home-based programs and seven (39%) were supervised programs. Thirteen studies (76%) assessed outcomes during the intervention and/or at an assessment shortly after intervention; the four remaining studies (24%) all assessed outcomes at longer intervals following intervention. Fatigue was the only outcome assessed in 13 studies (76%). Vitality was the only outcome assessed in two studies (12%); fatigue and vigor were the outcomes assessed in two studies (12%). Fatigue, vitality, or vigor was identified as a primary outcome in nine studies (53%). In none of the publications was a specified level of fatigue, vigor, or vitality used as an eligibility criterion.

Quality of the Activity-Based Intervention Studies

The summary quality score for each activity-based intervention study appears in Appendix 3, and the percentage of activity-based intervention studies performing at each level of quality on each indicator appears in Appendix 1. Methodological quality was rated good for two studies (12%), fair for fourteen studies (82%), and poor for one study (6%). Areas where criteria for a quality indicator were not at all fulfilled or could not be evaluated for the majority of activity-based intervention studies were: random selection of patients, analysis by intention to treat, and outcome assessed by blinded personnel.

Findings of the Activity-Based Intervention Studies

Seven of 17 publications (41%) yielded at least one finding significant at $p \leq .05$ favoring the intervention condition. Among publications rated fair or better in quality, 7 of 16 (44%) yielded at least one finding significant at $p \leq .05$ favoring the intervention condition. Average quality ratings were similar for publications that did and did not yield significant findings ($M = 16.71$ and $M = 16.50$, respectively). Cancer type and intervention modality appeared to differentiate studies with and without significant results. Relative to control conditions, 50% of studies that enrolled only breast cancer patients yielded significant results compared to 29% of studies that enrolled other types of patients. Relative to control conditions, 55% of home-based programs yielded significant results compared to 29% of supervised programs.

Meta-Analytic Findings

Of the 41 studies selected for review, 19 provided sufficient published statistical information to be included in the meta-analysis and information provided in response to written requests allowed an additional 11 studies to be included. Results for these 30 studies were first pooled to determine the combined effect size for psychological and activity-based interventions. As

shown in Table 1, a statistically significant effect of intervention was present in the combined analysis. We then categorized studies into those that evaluated a psychological intervention or an activity-based intervention. The results indicated that the effect size for psychological interventions, but not activity-based interventions, was statistically significant.

Studies that evaluated psychological interventions were then partitioned into those that measured fatigue or vigor as an outcome. Results indicated that psychological interventions showed a statistically significant effect for fatigue but not vigor. Focusing on fatigue as an outcome, results indicated that a statistically significant intervention effect was not present for breast cancer samples, but was present for samples not limited to breast cancer. Results also indicated that the effect for group-based but not individual interventions was significant. Among comparisons for vigor, neither cancer type nor intervention modality resulted in any significant intervention effects. For the activity-based interventions, there were no differences in effect sizes as a function of cancer type or intervention modality.

All effect sizes found to be statistically significant were small in magnitude (Cohen, 1988). Further, even when analysis of moderating variables revealed effect sizes that were qualitatively different (i.e., one was statistically significant and the other was not) none of the Q_B statistics were statistically significant. This pattern suggests caution when interpreting differences in the pattern of significant results based on type of intervention, patient characteristics, and intervention modality characteristics.

Discussion

This review represents the largest and most comprehensive exploration to date of RCTs of nonpharmacological interventions for cancer-related fatigue. In contrast to a previous review that identified only 10 RCTs (Lawrence et al., 2004), we identified 24 studies of psychological interventions and 17 studies of activity-based interventions. Nevertheless, the current review is not without its limitations. The possibility remains that some potentially relevant studies were not identified despite the use of multiple search strategies. Even with this limitation, the review yielded important information about the characteristics, quality, and efficacy of studies investigating psychological and activity-based interventions for cancer-related fatigue.

Information abstracted about patient characteristics demonstrates both the strengths and weaknesses of existing research. Close to a majority of studies were conducted on women with breast cancer, indicating the depth of research on the most common cancer among U.S. women. On the other hand, very few studies were conducted on men with prostate cancer, the most common cancer among U.S. men, or individuals with lung or colorectal cancer, the second and third most common cancers among U.S. men and women. We also found that less than 10% of studies focused on patients whose disease had metastasized. Evidence indicating that more severe disease is associated with worse fatigue (Hwang, Chang, Rue, & Kasimis, 2003; Stone, Richards, A'hern, & Hardy, 2000) suggests that many current interventions have not been evaluated in patients for whom disease burden is a likely cause of their fatigue. In addition, fewer than 15% of studies were conducted only on patients experiencing fatigue in the post-treatment period (i.e., following completion of chemotherapy or radiotherapy) and just one of these studies evaluated a psychological intervention. In contrast to predictable relationships between receipt of chemotherapy or radiotherapy and changes in fatigue (Donovan et al., 2004), the factors contributing to fatigue during the posttreatment period are not as well defined, suggesting the need to carefully evaluate intervention efficacy in each treatment period separately.

Information abstracted about intervention characteristics indicated that the psychological interventions were very heterogeneous. With the exception of three studies that evaluated

weekly supportive-expressive group psychotherapy, there were numerous differences in the number and content of sessions and the mode of intervention delivery (i.e., telephone or in-person), even among just those studies evaluating cognitive– behavioral interventions. Consequently, the replicability of results for most of these interventions remains unknown. Activity-based interventions all involved exercise recommendations; however, 39% were conducted in supervised settings while 61% were home-based. Although details were not included in this review, there were also numerous differences across these studies in the type (e.g., aerobic or resistance), mode (e.g., walking or cycle ergometer) and intensity of exercise evaluated. Thus, replicability of results for specific exercise regimens is also an issue for many activity-based interventions. Other methodological information abstracted indicated that fatigue, vigor, or vitality were more likely to have been identified as a primary outcome in activity-based studies (53%) than in psychological studies (21%). This feature suggests that the activity-based interventions were better designed to evaluate fatigue, assuming other aspects of study design (e.g., statistical power and Type I error) were consistent with the identification of fatigue as a primary outcome.

A notable methodological feature that characterized all the studies reviewed was the absence of eligibility criteria related to current level of fatigue. As a result, the possibility exists that many participants were experiencing little or no fatigue at the time of recruitment, thus limiting the ability of the study designs to detect intervention effects. In addition to improving the power to detect effects, limiting eligibility to patients experiencing heightened fatigue would provide a test of intervention strategies more consistent with how they are being used or would be used in clinical practice.

The system used to evaluate methodological quality indicated that few psychological or activity-based intervention studies met the criterion for either “good” or “poor” with most studies earning a “fair” rating. Among the more common methodological limitations were nonrandom or nonconsecutive recruitment of participants, absence of intent-to-treat analyses, and administration of outcome measures by personnel not blinded to intervention assignment. Activity-based studies were more likely to report acceptable intervention adherence and provide detailed loss to follow-up information, while psychological studies were more likely to report monitoring interventionists’ protocol adherence. With increasing numbers of journals adopting reporting standards such as the Consolidated Standards of Reporting Trials (CONSORT) (Moher, Schulz, & Altman, 2001), it seems likely that methodological quality and its documentation will improve over time.

Meta-analysis showed a small but significant intervention effect that, upon further analysis, reflected a significant effect size for psychological but not activity-based interventions. Among the psychological studies, there was evidence that intervention was more likely to decrease fatigue than increase vigor. This pattern suggests a difference in efficacy based on whether patients were rating negative or positive perceptions of energy and is consistent with other evidence indicating that fatigue and vigor are distinct constructs (Christensen & Piper-Terry, 2004). The lack of sufficient numbers of activity-based intervention trials assessing vigor precluded a similar comparison among these studies.

Subsequent comparisons guided by the qualitative review indicated that psychological interventions yield significant effect sizes for group-based interventions and for studies in which the sample was not limited to breast cancer patients. Although marked heterogeneity in content among psychological interventions limits the conclusions that can be drawn, findings suggest that characteristics differentiating group-based interventions from individual interventions may facilitate management of fatigue. One possibility is the greater opportunity for downward social comparison that exists in a group format. Similar to the impact on emotional distress (VanderZee et al., 1996), individuals may benefit from group-based

interventions, in part, by perceiving that their problems with fatigue are not as severe as those of others. Heterogeneity in content also obscures the relationship of disease type to intervention efficacy. This finding may primarily reflect gender differences in that samples limited and not limited to breast cancer patients also differ in their representation of male and female participants. The absence of any studies limited to male participants among the psychological studies reviewed precludes any comparison of efficacy based on gender.

We are aware of only three previous meta-analytic findings about the effects of psychological or activity-based interventions on cancer-related fatigue. Analysis of two RCTs of relaxation training interventions yielded an effect size (d_w) of .24 (Luebbert, Dahme, & Hasenbring, 2001). Given the limited scope and number of publications reviewed, comparison with our findings must be considered with caution. With regard to activity-based interventions, one publication (Conn, Hafdahl, Porock, McDaniel, & Nielsen, 2006) reported an effect size (d) of .11 based on six studies that included nonrandomized trials. A second publication (Schmitz et al., 2005), which also included nonrandomized trials, reported effect sizes (d_w) separately for fatigue/tiredness based on whether the intervention was conducted during the active treatment or posttreatment period. Effect sizes were .13 for six on-treatment studies and .16 for five posttreatment studies. Comparison with the present study suggests that effect sizes are reduced when more recent studies are added and meta-analysis is limited to RCTs.

The results of this review provide limited support for the clinical use of nonpharmacological interventions to prevent or relieve cancer-related fatigue. As noted previously, evidence of efficacy is stronger for psychological interventions than for activity-based interventions. The current recommendation is based on evidence compiled primarily from women with breast cancer, patients with nonmetastatic disease, and patients undergoing active treatment. Future research should expand the evidence base to include more patients with other forms of cancer, more patients with metastatic disease, and more patients who have completed active treatment. Evidence is also lacking for patients experiencing heightened fatigue. This situation reflects the fact that none of the studies reviewed used level of fatigue as an eligibility criterion, an issue that also needs to be addressed in future research. As a result, it is unclear whether interventions found to be effective are preventing fatigue (e.g., among patients about to undergo chemotherapy) or are relieving fatigue once it has developed. The studies reviewed also do not provide evidence that would assist clinicians in treatment selection. That is, there have been no direct comparisons of activity-based and psychological interventions that might indicate the superiority of one approach over the other or identify moderators of intervention efficacy that might be used to match patients to a particular treatment.

In addition to addressing these issues, future research should examine mechanisms suggested by previous research and theory that may underlie intervention efficacy. Understanding why interventions work could lead to refinement and enhancement of current intervention strategies and greater knowledge about factors that cause and contribute to cancer-related fatigue. Biological, cognitive, and behavioral mechanisms all merit investigation. With regard to biological mechanisms, there is preliminary evidence that improvements in cardiopulmonary function mediate the beneficial effects of exercise training on fatigue in cancer survivors (Courneya, Mackey et al., 2003). Evidence that persistent fatigue is associated with increased cytokine production in some cancer survivors (Bower, Ganz, Aziz, & Fahey, 2002; Collado-Hidalgo, Bower, Ganz, Cole, & Irwin, 2006) should also encourage study of the immune effects of current intervention strategies. With regard to cognitive and behavioral mechanisms, we have already described evidence indicating that catastrophic coping and physical inactivity are contributing factors to cancer-related fatigue. In addition to studying whether these variables mediate intervention efficacy, it may be useful to examine whether an intervention strategy that targets both cognitive and behavioral mechanisms (e.g., a combined stress management

and exercise training intervention) is more effective than a strategy that targets only one mechanism (e.g., exercise training alone).

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Table 1

Effect Sizes for Psychological and Activity-Based Intervention Studies

Intervention/outcome	Number of studies	Control (*n*)	Intervention (*n*)	Effect size (d_w)	95% CI	Q_W	Q_B
All interventions/all outcomes	30	1616	1827	.09*	.02–.16	41.60	
Intervention type							88
Psychological	18	1232	1378	.10*	.02–.18	30.20*	
Activity	12	384	449	.05	−.08–.19	11.03	
Psychological/fatigue	18	1232	1378	.09*	.02–.17	30.49*	
Cancer type							.51
Breast cancer	10	670	827	.07	−.03–.17	13.24	
Other	8	562	552	.13*	.01–.25	16.24*	
Intervention modality							.73
Group	9	368	473	.15*	.01–.28	17.23	
Individual	9	864	906	.07	−.02–.17	12.53	
Psychological/vigor	11	682	744	.06	−.04–.17	23.10*	
Cancer type							1.89
Breast	6	483	559	.02	−.11–.14	1.99	
Other	5	199	186	.18	−.02–.39	19.23*	
Intervention modality							2.05
Group	7	264	281	.16	−.01–.33	18.34*	
Individual	4	418	464	.00	−.13–.14	2.72	
Activity/fatigue	10	336	401	.08	−.07–.23	9.19	
Cancer type							.13
Breast	4	100	109	.12	−.15–.30	9.61	
Other	6	236	292	.06	−.11–.24	8.46	
Intervention modality							.56
Home-based	6	223	271	.04	−.14–.22	7.55	
Supervised	4	113	130	.16	−.09–.41	1.09	

* $p < .05$;

** $p < .01$;

*** $p < .001$.