Clinical Benefits of Exercise and Psychological Interventions in Patients with Cancer-Related Fatigue


Study Overview

Objective. To compare the effect of 4 commonly recommended treatments for cancer-related fatigue (CRF): exercise, psychological, combined exercise and psychological, and pharmaceutical.

Design. Meta-analysis.

Study selection. The authors searched electronic databases (PubMed, PsycINFO, CINAHL, EMBASE and Cochrane Library) for randomized controlled trials published on or before 31 May 2016 that tested exercise, psychological treatment, exercise plus psychological, and pharmaceutical intervention and used CRF severity as a study outcome. Other inclusion criteria included randomized controlled study design, age > 18 with cancer, and CRF assessment independent of cancer treatment. Studies that included use of erythropoietin drugs as the pharmacological intervention, alternative physical modalities (eg, yoga, tai chi) as the exercise therapy, and reduced energy, vitality, or vigor as the fatigue outcome were excluded. Article review was performed independently by 3 reviewers. Independent third-party reviewers resolved all discrepancies. The methodologic quality of the selected studies were evaluated using the previously validated Physiotherapy Evidence-Based Database (PEDro) scale. This scale ranks studies numerically from 0–12 with 12 being the highest quality. Exercise interventions were defined as aerobic, anaerobic, or both based on the provided description in the original published article. Similarly, psychological interventions were categorized as cognitive behavioral, psychoeducational, or eclectic based on the original study.

Main outcome measure. Severity of CRF.

Results. The authors identified 17,033 potential studies during the screening period. After applying exclusion criteria, 351 articles were selected for full review. Of the selected articles, 113 studies were included and analyzed in this meta-analysis. Fourteen articles had more than 1 intervention arm, which resulted in a total of 127 effect sizes: 69 evaluated exercise, 34 evaluated psychological intervention, 10 evaluated the combination of exercise and psychological interventions, and 14 evaluated pharmaceutical intervention. The pooled analysis of all 113 studies yielded a sample size of 11,525 participants. Of these, 78% were female and 22% were male. The
majority of included studies were conducted on a cohort of women with breast cancer (~47%). 44% of the studies enrolled patients with nonmetastatic cancer while only 10% enrolled patients with metastatic disease.

Pharmaceutical interventions included the use of paroxetine hydrochloride (n = 2 studies), modafinil or armodafinil (4), methylphenidate or dexamphetamine (5), dexamphetamine (1) and methylprednisolone (1). Exercise studies used aerobic modes (36), anaerobic modes (13), and a combination of aerobic and anaerobic modes (20). Psychological interventions included cognitive behavioral therapy (19), psychoeducational methods (14), and a combination of psychotherapeutic methods (1). There were 10 studies that assessed the combination of combined exercise plus psychological interventions.

The authors found a significant improvement in CRF across all included studies. The studies that used exercise as their intervention had the greatest improvement in CRF (P < 0.001). Psychological interventions also yielded significant improvements in CRF (P < 0.001). When combined, exercise and psychological interventions also showed significant improvement of CRF (P < 0.001). On the other hand, pharmaceutical interventions yielded a much smaller albeit significant improvement in CRF (P = 0.05). Comparison across all interventions types showed that pharmaceutical interventions yielded the least improvement in CRF.

Further analysis of independent variables showed that the greatest effect was seen in patients with early stage, nonmetastatic disease who had completed their primary treatment. Group-based and in-person intervention methods were found to be more effective than individual interventions. Of the psychological interventions used, cognitive behavioral therapy was the most effective. This intervention was particularly effective in those who had early stage disease who had completed their primary treatment. Type of cancer, patient age, and exercise modality were not associated with treatment effectiveness.

Conclusion. The results of this study suggest that exercise with or without psychological interventions are effective at reducing CRF with greater improvement than with pharmaceutical interventions.

Commentary

Fatigue has been recognized as one of the most common symptoms associated with cancer and CRF. Some authors have estimated the prevalence of CRF may vary from 60% to 90% [1]. Moreover, the type of anticancer therapy appears to impact the severity of CRF. For example, patients receiving chemotherapy have reported CRF more commonly than those undergoing radiation therapy [1]. It is vital that the treating oncologist as well as the primary care provider be able to recognize CRF early in the treatment course and intervene in order to improve quality of life in this patient population.

According to the authors, this study is one of the first and most comprehensive attempts to examine the influence of various interventions on CRF. The results of this meta-analysis suggest that exercise (both aerobic and anaerobic), psychological therapy, or the combination of exercise and psychological therapy are more effective means to improve CRF compared with pharmacologic interventions. Notably, these results may suggest that specific interventions may be more effective depending on where the patient is in their treatment course. For example, the effect of exercise seemed greatest for patients who were receiving their primary treatment while the addition of psychological interventions may be best reserved for those who have completed their primary therapy. In addition, the greatest effect seemed to be seen in patients who had early stage disease following completion of definitive therapy.

Numerous authors have sought to assess the impact of various interventions on CRF; however, such studies have had small sample sizes and were often limited to a certain group of patients (eg, breast cancer). Despite these limitations, numerous trials have demonstrated improved fatigue, decreased emotional distress, and improved sleep and better quality of life with exercise [2–4]. This study corroborates the effects of exercise noted previously and further supports evidence that pharmacological therapy offers limited clinical benefit in the management of CRF.

There are some noteworthy limitations to the current meta-analysis. Most of the studies included in this analysis were among patients with breast cancer or patients who had completed primary therapy for breast cancer. Furthermore, the severity of fatigue was not quantified in many of the included trials. This analysis excluded pharmaceutical interventions that evaluated the use of an erythropoietin-stimulating agents (ESAs). ESAs have been widely studied in cancer patients and are currently recommended for patients with a hemoglobin less than 10 g/dL due to chemotherapy who being treated for a nonhematologic malignancy and have no
other treatable cause of anemia. Numerous randomized trials have shown decreased red blood cell transfusion with the use of ESAs; however, the impact on CRF has been difficult to correlate. A meta-analysis by Cella and colleagues failed to demonstrated an improvement in fatigue-related symptoms with the use of ESAs in cancer patients [5]. In general, the use of ESAs is controversial in patients who are receiving myelosuppressive therapy for curative intent. This is largely related to the associated thromboembolic risks as well as data suggesting higher mortality rates. Finally, this analysis included patients with primarily non-metastatic disease and the effect of such interventions on patients with advance cancer requires further analysis.

Applications for Clinical Practice
CRF remains a common problem encountered in clinical practice. The treating oncologist and primary care provider must be astute at recognizing and promptly intervening in order to improve quality of life in patients with cancer. This study and prior trials continue to demonstrate the clinical benefits of exercise and psychological interventions in improving quality of life measures in this patient population and these interventions should be recommended. Pharmacologic therapies continue to offer little in the management of CRF and should be reserved for those who fail other intervention strategies.

Such an approach is reinforced by the NCCN guidelines, which recommend nonpharmacologic interventions such as physical activity, psychosocial interventions, and nutrition counseling as front-line therapy (category 1) while reserving psychostimulants for those who do not derive benefit from these interventions [6].

—Daniel Isaac, DO, MS

References
VA-based primary care, which uses the patient-centered medical home model [2].

**Intervention.** The intensive outpatient care group received care from a multidisciplinary team comprising a nurse practitioner, physician, social worker, and recreational therapist. The enhanced care included comprehensive patient assessment, identification and tracking of patients’ health-related goals and priorities, assessment of physical function, cognitive function, social support, medical adherence and level of patient activation, and care management for medical and social needs. Frequent contacts using telephone lines and in-person visits as needed, weekly team discussions of high-acuity patients, and coordination of care with VA and non-VA clinicians also occurred. Additionally, the program offered interventions to support patients’ and caregivers’ quality of life, such as recreation therapy.

**Main outcome measures.** The main outcome measures were health care costs and utilization. Total health care costs included inpatient, outpatient, and fee-basis care provided outside the VA. Utilization measures included hospitalization frequency, hospital length of stay, and number of outpatient and emergency room visits. The study team examined cost and utilization patterns during the 16 months prior to initiation of the program (baseline period) and the 17 months after initiation of the program (follow-up period). The study also evaluated patient care experience in the intensive care group via survey at baseline and at 6 months after enrollment. The survey included items from the Patient Satisfaction questionnaire, the Patient Activation Measures tool, and questions about satisfaction with the intensive care program and the likelihood to recommend the program to others.

**Main results.** Of the 150 patients assigned to the intervention, 140 patients were included in the analysis after excluding those who were ineligible or died before the intervention began; there were 405 in the usual care group. Among the 140 patients, 96 engaged in the program and 60 completed the follow-up survey. The average patient age was 66 years and over 90% were male, with the majority living in an urban area. The average number of chronic conditions was approximately 10, and about two-thirds had a mental health diagnosis. In the follow-up period, patients in the intensive outpatient care group had a higher number of outpatient primary care visits (average of 21.8 visits [SD 17.4]) compared with the usual care group (average of 7.4 visits [SD 7.5]). The number of acute medical or surgical hospitalizations in the follow-up period was similar between the 2 groups, as was the number of emergency room visits. There were also no significant differences on other inpatient or outpatient health care utilization measures. The intensive outpatient care program was not associated with reduced costs of care when compared with usual care. For measurements on patient experience, the majority of patients who completed the survey (92%) indicated that they would recommend the program to others and 70% indicated that they were extremely satisfied with the program’s medical care.

**Conclusions.** Intensive outpatient care for high-need patients in this VA setting was not associated with a decrease in acute health care utilization or reduced costs. Patients in the intensive outpatient care program indicated that they were satisfied with the program and would recommend the program to others.

**Commentary**

Management of high-risk, high-cost patients continues to be a challenge for the health care system. High-users account for a disproportionate amount of health care costs. It would seem reasonable that attending to these patients’ complex needs by providing lower-cost supplemental primary care services early would reduce the need for more expensive care (eg, hospitalization) downstream.

In this study, researchers examined the impact of an intensive outpatient care program targeting high-need veterans on health care utilization and costs. Although patients liked the program, the results demonstrated no reduction in either acute care utilization, including inpatient hospitalization or emergency room visits, or costs. The findings are consistent with a number of prior studies that have demonstrated limited impact of care coordination programs on cost and utilization [3] albeit demonstrating impact on other clinically relevant outcomes, including patient experience.

The study authors proposed a few factors that may have contributed to this finding. One was that a longer follow-up period may be needed to demonstrate improved outcomes. Another was that there may be a mismatch between the patients’ needs and the services
offered by the program. In addition, the intensive outpatient services may have uncovered unmet needs that led to appropriate care, which could increase costs. The role of these factors might be examined using process measures, or with ongoing collection of administrative data, perhaps in a future study.

In interpreting this study, it is important to point out certain differences between this study and the typical randomized clinical trial. In this study, patients were not enrolled in a clinical trial at the time of the intensive outpatient care program—it was considered a quality improvement initiative at the time when the program was started. Thus, the study subjects may be different from the subjects likely to be included in a randomized clinical trial, where subjects must agree to participate in research in order to be part of the study. The patients in this study therefore likely resemble the patient population in a clinical setting rather than in a research study setting.

The other difference is that in addition to examining the impact of the intervention, the study tests the targeting strategy of the intervention—in this case, targeting patients with high need using algorithms already embedded in the VA. This strategy contrasts with a number of outpatient collaborative care interventions [4,5] that target specific medical conditions. While targeting high-utilizers makes sense from an economic point of view, such a group may be more diverse and have more diverse needs than a study population with a condition-specific profile, eg, patients with chronic disease and depression [4]. Two thirds of the study population had a mental health diagnosis, but the team did not include specific mental health personnel or care protocols for mental health management.

Because of its design as a quality improvement project, the study suffers from a number of shortcomings that may threaten its internal validity, namely, the low follow-up rate, the lack of a comparison group for some outcomes, and perhaps, less assurance that participants were treated equally except for the study intervention.

Applications for Clinical Practice
The study adds to the current literature on interventions for improving care and reducing costs for patients with high health care needs. As health care costs continue to escalate, implementing strategies to improve efficiency continues to be a priority. The intensive outpatient care program may not be the solution for curbing costs for the study population at this time; perhaps follow-up studies that assess its impact on other relevant clinical outcomes with longer follow-up may tell a different story.

—William W. Hung, MD, MPH

References
What PCP-Related Factors Contribute to Successful Weight Loss Among Positive Deviant Low-Income African-American Women?


Study Overview

Objective. To evaluate factors related to interactions with primary care physicians (PCPs) that may contribute to successful weight loss and maintenance among low-income, African-American women.

Design. Mixed methods, positive deviance framework.

Setting and participants. Participants were African-American women aged 18–64 years from an urban university-based family medicine practice who received Medicaid, resided in Philadelphia, and had a body mass index (BMI) of $\geq 30$kg/m². From among these, “positive deviant” cases were identified as patients with EMR-confirmed weight loss of at least 10% of patient’s maximum weight between 2007–2012 and maintenance of this loss for at least 6 months. Controls were defined as patients who had not lost a significant amount of weight during this time period. Patients were excluded if they were an amputee or wheelchair-bound; had bariatric surgery, severe illness during weight loss, EMR-documented unintended weight loss, pregnancy at time of weight loss, a psychiatric disorder or were taking antipsychotic medication; had an intellectual disability; or could not give consent to participate.

Main outcomes measures. PCP- and patient-reported weight variables were collected through the EMR (documentation of dietary counseling by PCP, documentation of a weight-related problem, diagnosis of overweight, obesity, or morbid obesity on the problem list), surveys (additional predictors of positive deviant membership, including patient-reported weight-related diagnosis or discussion of weight with PCP or health professional), and interviews. Logistic regression was used to determine whether a priori-identified EMR and survey variables could predict positive deviant group membership, adjusting for demographic variables significantly associated with the outcome of interest or hypothesized to be confounders of the associations between predictors and outcomes (results were adjusted for age in the EMR analysis and for employment status and education level in the survey analysis). Once thematic saturation was reached, interviews were analyzed by a 4-member coding panel using a modified approach to grounded theory to identify themes.

Main results. For the EMR analysis, data from 161 positive deviant cases and 602 controls were analyzed. For the survey analysis, data from 35 positive deviant cases and 36 controls matched for age and maximum BMI were analyzed. For in-depth interviews, thematic saturation was reached after collecting data from 20 positive deviant participants. In the EMR analyses, documentation of dietary counseling and a weight-related diagnosis were significant predictors of positive deviant membership after adjusting for age ($P < 0.001$ and $P = 0.011$, respectively). However, documentation of obesity on the problem list was predictive of control group membership ($P = 0.032$). In the survey analysis, neither patient-reported weight-related diagnosis nor discussion of weight with a medical provider were predictors of positive deviant membership ($P = 0.890$ and $P = 0.373$, respectively).

In the qualitative analysis of interviews with positive deviant participants, 5 themes emerged: (1) framing the problem of obesity in the context of other health problems provided motivation; (2) having a full discussion around weight management was important; (3) an ongoing conversation and relationship was valuable; (4) celebrating small successes was beneficial for ongoing motivation; and (5) advice was helpful but self-motivation was required in order to make a change.

Conclusions. PCP counseling may be an important factor in promoting weight loss in low-income, African-American women, a population at high risk for obesity. Patients may benefit from their PCPs drawing connec-
tions between obesity and weight-related medical conditions and enhancing intrinsic motivation for weight loss.

Commentary

The increasing prevalence and clinical consequences of having obesity are well-documented, with low-income minorities disproportionately burdened by this condition [1,2]. The United States Preventive Services Task Force (USPTF) recommends that all patients be screened for obesity and offered intensive lifestyle counseling [3], yet evidence-based guidelines for best approaches to incorporate this into practice are few and unclear, and even fewer are specific to high-risk patient populations [4–9].

This study adds to the literature by using a positive deviance approach to identify PCP-related factors that predict successful weight loss among low-income African-American women. This approach has rarely been used in the obesity literature. In a few childhood obesity studies, this approach was used to identify motivations used by child “positive outliers” to improve their BMI [10], characterize variations of feeding and activity practices by parents of healthy children normally at high risk for obesity [11], and explore successful health and BMI reduction strategies used among positive outlier families [12]. Positive deviance has also been used to characterize and change nutritional behavior and understand successful weight-control practices among adults [13–15]. One study has suggested that studying “positive deviant” physicians that regularly provide weight counseling may help to provide practice methods to increase these practices in the primary care settings [16].

Thus, the study approach in using a positive deviance framework is an important and unique strength. Additionally, the authors used a mixed-methods approach, analyzing EMR, survey, and interview data to assess PCP- and patient-reported weight-related factors that predict successful weight loss. As the authors describe, their results confirm findings from previous studies looking at counseling preferences among ethnic minority women and PCP attitudes and practices related to weight management.

They acknowledge important limitations of their study design, primarily the generalizability of findings only to urban, low-income, African-American women, the small sample size in the survey analysis, and the use of EMR data to collect data on PCP counseling (as opposed to interviews, for example). It important to also acknowledge that this study was conducted at a family medicine practice, and physician behavior and practices likely do not generalize to other PCPs and specialists. Additionally, while their intention was to use a positive deviance framework, conducting interviews among a subset of their control cases may have provided useful information regarding negative or ineffective PCP interactions regarding weight loss and management.

Applications for Clinical Practice

As the authors emphasize, the outcomes of this study are especially relevant for PCPs and other health practitioners, as the identified themes can help guide weight counseling that incorporates patient preferences and promotes successful weight loss. Importantly, these findings underscore that the role of the physician is important in promoting weight loss, yet it does not require in-depth knowledge and training in evidence-based weight loss strategies. While dietary counseling is still helpful, patients with successful weight loss value the supportive relationship with their physician, their physician drawing connections between obesity and weight-related medical conditions, and their physician enhancing intrinsic motivations for weight loss.

—Katrina F. Mateo, MPH

References

8. Osolinski G, Jiwa M, McManus A. Weight management practices and evidence for weight loss through primary care: