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Effects of Exercise on the Amelioration of Fatigue in Cancer Survivors: A Pilot Study

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Authors' contributions

This work was carried out in collaboration between all authors. Author SJS designed the study and wrote the protocol. Under the supervision of authors SJS, DFN and AFC worked with the participants and collected the data. Authors DFN, AFC, SJS and AM presented a portion of the research at the annual meeting of association for psychological science. Author DMC performed the data analysis. Authors DFN and DMC wrote the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Aims: To acquire preliminary information in order to assess the efficacy of a university-based exercise program developed to serve members of the community suffering from symptoms associated with cancer fatigue.

Study Design: The pilot study included 35 adult cancer patients who underwent intensive medical screenings to ensure that the exercise program would be appropriate for them. Each participant was assigned an individual student to guide him or her through specific exercises for 8 successive weeks, meeting 3 times per week. At the end of each week, the participants filled out the Fatigue Symptom Inventory, designed to assess cancer-related fatigue on three dimensions – intensity, duration, and interference with daily life.

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Methodology: Each participant had one student (exercise science or pre-occupational therapy) assigned to work with them and guide them through specific exercises. All exercise routines were specially designed by a registered physical therapist who had conducted all evaluations, had previously designed, and implemented the Exercise Fatigue Program. During the workout, a second measurement of blood pressure and pulse rate was recorded. After the workout was complete, the participants participated in a series of stretching activities. Stretching exercises were followed by a third and final measurement of resting blood pressure and pulse rate.

Results: Evidence was found that, among those who remained in the exercise program experienced less intense and shorter duration fatigue levels and reported lower levels of interference in activities of daily living (ADLs) associated with cancer-related fatigue patients.

Conclusion: Supervised exercise regimens adapted to the needs of individual cancer patients show promise in reducing the symptoms associated with cancer-related fatigue. However, because of the limited sample size and participant attrition, the results reported here should be considered preliminary in nature. Further work using a larger sample size with more systematic consideration of possible confounding variables is required in order to validate the program.

Keywords: Fatigue; cancer; cancer-related fatigue; exercise.

1. INTRODUCTION

Currently the second most common cause of death, cancer has long been among the deadliest and most mysterious diseases known to humanity. In 2014, there was an estimated 1,665,540 new cancer cases diagnosed and, in the United States alone over 500,000 deaths are attributed to cancer each year [1]. Considered globally, more than 60% of deaths attributed to cancer occurred in second- and third-world countries, with an estimated 14.1 million cases diagnosed worldwide in 2012 [1].

One common complaint associated with cancer is cancer-related fatigue (CRF). CRF has been defined as debilitating subjective impression that cancer patients associate with the illness or the treatment [2]. Unfortunately, although various criteria are available (e.g., ICD-10) [3], consensus has not been achieved in developing a universally accepted definition [4]. Currently, the National Comprehensive Cancer Network has provided the most inclusive and instructive definition.

> *Cancer-related fatigue is a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning* [5, p. FT-1].

Often undermining the life of the individual to a point where normal activities are perceived as impossible, it is estimated that as many as 90% of patients actively receiving treatment report CRF [6]. However, due to a lack of common diagnostic criteria, varying application, and complicated by the type and severity of the cancer diagnosis, the estimates reported in the literature are quite variable [7-11]. Nonetheless, many patients report that the symptoms of CRF continue for time periods that continue after active treatment, with one estimate suggesting that as many as 33% of cancer survivors experience CRF 5 years after the completion of cancer treatment [9].

Although pharmacologic interventions of CRF have been explored, the results thus far have not been promising [6,12]. While interventions that include an exercise component during chemotherapy can improve physical capacity [13-17], the specific impact of exercise interventions on the amelioration of CRF remain equivocal [18]. When the treatment of CRF was examined as a central study variable as part of a randomized control trial, some reported significant positive effects on CRF during chemotherapy [15,18-23]. Unfortunately, other reports were not as encouraging [24,25].

Nonetheless, there has been encouraging reports. According to Windsor and colleagues [26], it is quite common for the primary oncologist to acknowledge or effectively manage CRF, even when the patient reports this as their most debilitating problem [27]. Windsor et al. [26] provided information about fatigue and exercise and observed 115 men and 90 women over the course of 8 months. During the measurement period, information on cancer or treatment-related fatigue and the use of exercise while in the facility was collected. The results showed 88.3% of the patients reported exercising during treatment. Further, approximately 3/4ths of the patients found the information helpful and those who were able to exercise during treatment had lower fatigue levels. Such results are consistent with that of others [18,28-30].

Naturally, the word exercise encompasses a variety of activities. In the Merriam-Webster dictionary [31], exercise is defined as the bodily or mental exertion of energy, especially for the sake of training or improvement of health. This activity is usually undertaken so that a person can keep his/her body in healthy physical shape. Sometimes it is used to get the body back into shape following an extended period of time not exerting physical energy. Exercise is not only good for the external organs, but also it is also good for the internal organs. It is essential for holistic health. Fitness training may involve strenuous activities such as interval efforts on stationary bicycles, with an intensity of 85-95% of each patient's maximum heart rate. Such efforts are coordinated around warm-up and cool-down exercises incorporating dynamic stretching actions with different muscle groups as well as coordination training [32,33]. In addition, relaxation training may be incorporated [18].

The present pilot study was designed to examine the idea that correctly using exercise as an effective method of decreasing the symptom of fatigue that cancer patients face, regardless of whether the cancer treatment was on-going or was completed in the past. While a pilot study, the value of the present study is that it took place within a controlled environment. Detailed questions, notes, and doctor's orders were examined before the patient was accepted into the program. On the basis of this information, a registered physical therapist customized the exercise program for each participant to ensure that it would specifically help that particular patient.

In the present study, each potential participant volunteered to join the program and accompanied pilot study, completing a cancer fatigue index to evaluate their level of fatigue at the end of each week. Thus, the primary goal of both the program and the pilot study was to ascertain whether systematic and controlled exercise is useful as an agent of meaningful reductions in fatigue levels of having experienced or currently experiencing cancer treatments. The primary hypothesis was that exercise would decrease the fatigue experienced by the screened participants.

2. MATERIALS AND METHODS

2.1 Participants

The present study included 35 participants, 33 women and 2 men, who volunteered to participate. All individuals currently resided in the greater West Palm Beach, Florida area and were under the care of a local physician. The participants ranged in age from 42 to 82 years old (M = 60.72, SD = 9.41). All participants had previously received information about the exercise fatigue program and the study, either verbally, or by recommendation from their Doctors. The participants were either actively receiving cancer treatments or in a period of post-treatment recovery and/or remission. Inclusion criteria included reported moderate to high levels of fatigue and acute concerns concerning the best exercise strategies following surgery and recovery and/or chemotherapy.

The individuals reported one of nine different types of cancer, with breast cancer as the most common type among the participants (n = 16). Additional cancers included 3 individuals with lymphoma, 1 with endometrial cancer, 1 with ocular melanoma, 1 with primary myelofibrosis, 1 with lymphedema, 1 with sarcoma, 1 with prostate cancer, and 1 diagnosed with lung cancer. Last, some of the individuals in the study reported that their cancer had metastasized to other regions of the body.

2.2 Materials

Offering an athletic training program, Palm Beach Atlantic University's gym includes fitness equipment consistent with those found at a top-level fitness company of rehabilitation facility. Briefly, the equipment used as part of the exercise regimen included a TRUE ES900 treadmill and a TRUE ES700 home elliptical trainer, the latter of which was effective in working out the individual's upper-body, lower-body, and core. Participants had the option of a TRUE ES900 home upright bicycle or a TRUE ES900 home recumbent bicycle Bike (True Fitness Technology, St. Louis, MO). The recumbent Bicycle was useful for participants with less initial strength requiring a backrest. In addition, exercise equipment options included a Nautilus Nitro Plus Seated Dip S5SD, Nova Abduction/Adduction A8AA, The Nova Abdominal/Lower Back S8ABLB, and the Nova Triceps Press (Nautilus, Inc., Vancouver, WA).

Participants were assigned a wide range of exercises to complete, some of which contained the dumbbell weights (Nautilus 2 Tiered Dumbbell Rack F32TDR). Using the weights, the participant performed exercises ranging from bicep curls, tricep curls, and calf raises. Last, Palm Beach Atlantic University also contained an indoor track 1/15 of a mile in length for walking and/or running.

Participant fatigue was assessed using the Fatigue Symptom Inventory (FSI) [35,36]. The FSI, is a self-report measure consisting of 13 items designed to assess CRF. Using the instrument, three scales can be derived measuring the intensity (4 items) of the fatigue experienced by the respondent, the duration (2 items) of the fatigue experienced, and the extent to which the fatigue interferes with the respondent's quality of life (7 items). Some of the items included:

- Rate your level of fatigue on the day you felt most fatigued during the past week.
- Rate your level of fatigue on the day you felt least fatigued during the past week.
- Rate your level of fatigue on the average during the past week.
- Rate your level of fatigue right now.

The items are measured on 11-point scales, with higher values associated with more fatigue, interference, and impairment. For each scale, an average value was calculated for each participant. The protocol was approved by the Palm Beach Atlantic University Institutional Review Board. The training volunteers and researchers treated all participants in accordance with APA ethical standards for the treatment of human participants in research [34].

2.3 Procedure

Before entering the Exercise Fatigue Program, each potential participant was evaluated to assess their ability to complete the program and level of risk associated with the exercise regimen. Following the evaluations, all participants were provided with detailed information on what would take place. Briefly, participants were told that the program would meet for 3 days a week for 8 weeks. In addition, they were given a tour of the university exercise facilities and provided parking spaces located at the entrance to the gymnasium. Additional instructions included were to avoid using the stairs, and to use the elevator to reach the gymnasium. This specific instruction was given to ensure that initial measures of resting blood pressure and pulse were taken under conditions consistent with their typical levels. The participants were instructed that once they entered the gym, they were to sit comfortably for a 5-minute period, followed by the first of three measures of blood pressure and pulse for the exercise session.

Each participant had one student (exercise science or pre-occupational therapy) assigned to work with them one on one and guide them through specific exercises. To ensure the safety of each patient in the program, a registered nurse was present at all times. Exercise routines varied with each tailored to meet the individual needs of the patient. All routines were specially designed by the registered physical therapist who had conducted all evaluations, had previously designed, and implemented the Exercise Fatigue Program. During the workout, a second measurement of blood pressure and pulse rate was recorded. After the workout was complete, the participants participated in a series stretching activities. Stretching exercises were followed by a third and final measurement of resting blood pressure and pulse rate.

At the end of the week, the participants completed the FSI [35,36], which contained 13 questions to provide an assessment of the level of fatigue the individual experienced throughout the week. Statistical analyses involved repeated measures analysis of variance (ANOVAs), with weeks (for the FSI scales) or within-session and weeks (for the blood pressure measures) as within-subjects factors. Post-hoc analyses were performed using t-tests with a Bonferroni correction to control for multiple comparisons. The alpha level for acceptance was set at $P < .05$ and analyses were performed using SPSS (IBM, 2013).

3. RESULTS

Fifteen of the 35 individuals were actively participating in the study at the end of the assessment period (see below) and included in the results reported here. Those who completed the final assessment period were of the same approximate age (M = 61.60, SD = 10.01) as those who were not active on the day of the final assessment (M = 60.07, SD = 9.15).

Scores from the three subscales of the Fatigue Symptom Inventory were derived from the data collected during the course of the exercise program. Due to a number of both health-related and non-health-related reasons, the total number of participants declined across the 8-week period. As a consequence, responses from weeks one through four and week six are considered here. The responses from the three subscales of the Fatigue Symptom Inventory are presented in Fig. 1. Fatigue intensity (panel A) declined significantly across the measurement period, $F(4, 56) = 3.39$, $P = .015$, $\eta_p^2 = .195$. Trend analysis indicated that the data were best fit by a linear model, accounting for significant proportion of the variance in fatigue intensity scores ($\eta_p^2 = .421$, $P = .007$). Nonetheless, pairwise comparisons with Bonferroni correction revealed a significant difference only between weeks 1 and 6.

When data from the interference subscale were considered, a similar pattern emerged (see Fig. 1, panel B). Interference from the effects of fatigue declined significantly over the measurement period, $F(4, 56) = 7.47$, $P < .001$, $\eta_p^2 = .348$. Once again the data were best fit by a linear model, with the model accounting got 53.4% of the variance in fatigue intensity scores ($P = .001$). Pairwise comparisons with Bonferroni correction revealed significant differences between weeks 1 versus weeks 4 and 6. Fatigue intensity was somewhat but significantly lower on week 3 than on week 4 but comparable to week 6.

Consideration of the data from the fatigue duration subscale revealed a significant change as a function of time, $F(4, 56) = 5.58$, $P = .001$, $\eta_p^2 = .285$. However, as seen in Fig. 1, panel C, the trend associated with the data is best accounted for cubic ($\eta_p^2 = .382$, $P = .011$) and quadratic ($\eta_p^2 = .335$, $P = .019$) models. The trend is reflected in a consideration of pairwise comparisons of the weekly means. These comparisons suggested a significant rise in fatigue duration scores between week 1 versus weeks 2 and 3, with a significant decline in fatigue duration found on week 4. Nonetheless, week 6 fatigue duration scores were not significantly different from that on any of the other weeks.

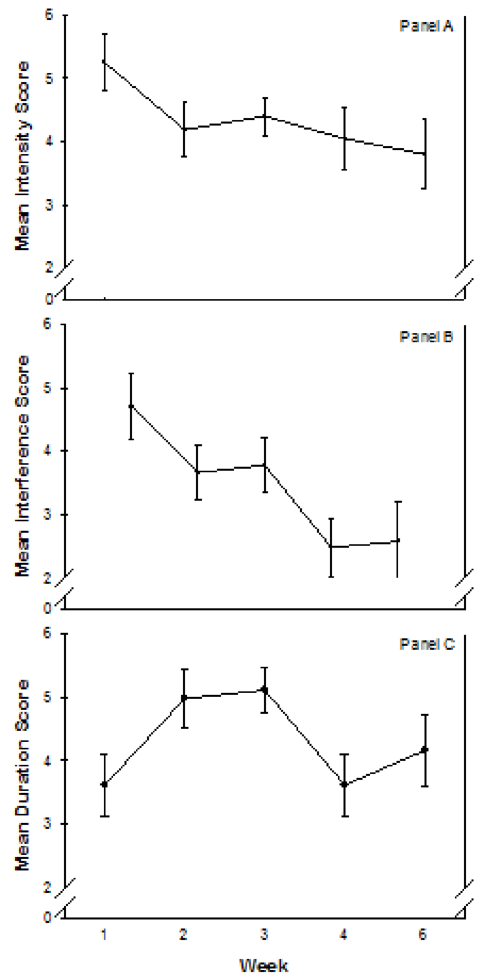

Fig. 1. Mean scores on the three scales of the fatigue symptom inventory (FSI) for weeks 1-4 and 6

Panel A = Fatigue Intensity scale; Panel B = Fatigue Interference scale; Panel C = Fatigue Duration scale. Vertical bars represent ±SEM

In addition to assessment of the fatigue measures described above, a series of cardiac measures was also explored. Once again data from the first four weeks of the program and the sixth week were considered. Because the cardiac measures were taken at three time points at each weekly session, the data was analyzed using two-within ANOVAs. These analyses revealed the following. First, pulse rate differed within each exercise session, $F(2, 28) = 55.74$, $P < .001$, $\eta_p^2 = .799$, a result that was expected and consistent with exercise. However, pulse rate did not change over the course of the exercise program and the week X within-session measures interaction was nonsignificant. Measures of systolic blood pressure revealed main effects of exercise session, $F(4, 56) = 3.82$, $P = .008$, $\eta_p^2 = .214$, within-session measure, $F(4, 56) = 5.81$, $P = .008$, ηp2 = .293, as well as the week X within-session measure interaction, $F(8, 56) = 4.05$, $P = .0003$, $\eta_p^2 = .224$. Multiple comparisons with Bonferroni adjustment of systolic blood pressure revealed that the main effect of change across weeks was nonsignificant (i.e., all Ps > .05) and reflective of somewhat lower systolic blood pressure on weeks two and four and somewhat higher systolic blood pressure on weeks one, three, and five. The within-session measurement of systolic blood pressure indicated significantly higher levels at the second time point, a result that was not surprising since this point is most closely associated with the current state of exertion. Finally, analysis of diastolic blood pressure revealed no main effects or interaction.

Because this study involved a preliminary pre-experimental design, the point-biserial correlations between each subscale at weeks one and four and whether or not the participant finished the 8-week exercise program were calculated. None of the three correlations were close to being significant (smallest P = .51), lending credence to the supposition that factors other than adverse physical effects were related to the likelihood that the participant dropped out.

4. DISCUSSION

The main hypothesis presented in this study was the proposition that directed exercise regimens would lead to a reduction in fatigue among individuals currently undergoing cancer treatments or having done so in the past but still experiencing marked fatigue. While a systematic investigation with better experimental controls is needed, the results provided preliminary evidence that exercise was effective in ameliorating the effects of CRF that interfered with daily activities.

As pointed out by others [27], fatigue is one of the predominant symptoms of cancer treatments. As an unintended side-effect, CRF can severely impact the quality of life of cancer patients. For example, Curt [27] had participants rank categories of symptoms in terms of their effect on daily life. Fatigue was ranked first (60%), followed by nausea (22%), depression (10%), and pain (6%). In addition, such marked fatigue can affect patients economically. When patient fatigue resulting from their cancer treatments undermines their ability to work effectively, the patient is often forced to find other employment options - if they felt well enough to work at all. This is unsurprising in light of reports of a complete lack of energy and severe mental exhaustion [27].

While the present results are encouraging, the conclusions that can be drawn here are preliminary at best. First and foremost, the design was descriptive so no determination of the causal drivers of fatigue reduction are possible. Indeed, subject mortality is worthy of consideration [37]. Although no differences between those completing the program and those who did not were found, there remains concern that such differences were present. In addition, section bias and the fact that most of the participants were female is a concern. Nonetheless, at the pilot testing stage of program development, the descriptive function of this simple time series design has value simply because the exercise program intervention extend over 24 sessions during an 8 week period [38].

In a recent synthesis of the literature using meta-analysis [39] the results indicated that the largest exercise benefits were found among participants with lower baseline cancer fatigue scores and those individuals who strictly followed the exercise regimen. In addition, as the time between cancer treatment completion and the beginning of the exercise program increased, so did the size of the improvement. Collectively, the results of the meta-analysis indicated that exercise regimens have differing effects, with a palliative effect observed among individuals undergoing cancer treatments while post-treatment programs tended to produce recuperative effects [39]. Conversely, there are other reports suggesting that supervised exercise training generally does not improve the post-surgical quality of lung cancer patients (the exception was bodily pain) [40]. Nonetheless, the conclusions offered in the meta-analysis [39] are consistent with other reviews and research [26,41] suggesting that supervised physical activities can facilitate a marked reduction in the symptoms associated with CRF. Further, combinations of resistance and aerobic exercise programs routines should become an integral component of rehabilitation programs for cancer patients [41]. Certainly, there is a need to consider other risk factors that could be affected by the program regimen. Indeed, among these should be a thorough consideration of the cardiovascular health of the participant, including arrhythmias such as atrial fibrillation [42]. Fortunately, appropriate intensity exercise can impact positively both physiological processes, such as increased cardiac functional capacity and ventricular rate control, as well as behavioral processes such as activities of daily living (ADLs) [42].

As noted elsewhere [26], programs developed to promote physical activity may offset reported 5-hydroxytryptamine (serotonin) decreases observed in patients with symptoms of CRF [43]. Since, as a neurotransmitter, serotonin is implicated in a number effects ranging from pain regulation to anxiety levels and mood [44], increasing neural monoamine levels through activity-based programs could promote greater health and psychological well-being.

As part of our Exercise Fatigue Program, in future studies we plan explore the efficacy of the exercise interventions through more specific examination of what types of exercise intensity and frequency are most effective for individuals currently undergoing cancer treatments and those at different post-treatment time points. Further, additional physiological and psychological measures will be included. Finally, through expansion of the program, we hope to obtain a more representative sample in terms of gender, age, and racial considerations. In doing so, we hope to maximize the long-term benefits [26] derived from exercise regimens as a means of combating cancer-fatigue.

5. CONCLUSION

Evidence was found that those who remained in the exercise program experienced less intense and shorter duration fatigue levels and reported lower levels of interference in associated with CRF patients. Supervised exercise regimens adapted to the needs of individual cancer patients show promise in reducing the symptoms associated with CRF. However, the study was based on a small sample size and suffered from considerable participant attrition. In addition, one of the primary dependent measures was the scales of the Fatigue Symptom Inventory, a self-report measure. Self-report measures often suffer from responses biases including social desirability [45]. Therefore, the results reported here should be considered quite preliminary in nature. Further work using a larger sample size with more systematic consideration of possible confounding variables is required in order to validate the efficacy of the program.

CONSENT

The authors declare that written informed consent was obtained from all participants for this study.

ETHICAL APPROVAL

This investigation occurred following approval and under the supervision of the Palm Beach Atlantic University Institutional Review Board. The authors hereby declare that the research has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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