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The Therapeutic Effects of Exercise on Fatigue

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Chapter 14

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Introduction

Fatigue has been identified as the most distressing and prevalent cancer-related symptom in a variety of cancer populations. Incidence of cancer-related fatigue ranges from 40% to 100%, depending on cancer diagnoses, treatment modalities, and disease stages (Berger 1998; Fu *et al.* 2002; Hickok *et al.* 1996; Hinds *et al.* 1999; Schag *et al.* 1994; Porock *et al.* 2000; Winningham *et al.* 1994). People with cancer describe their fatigue experience as being different from the fatigue that healthy people experience. Cancer-related fatigue has usually been described as being more intense, severe, chronic, debilitating, distressing, and less likely to be relieved by rest (Andrykowski *et al.* 1998; Fu *et al.* 2002; Glaus *et al.* 1996; Porock *et al.* 2000; Schwartz 1998). Unlike cancer-related fatigue, acute fatigue in healthy people is usually an expected tiredness with rapid onset and short duration. Acute fatigue in healthy people serves as a protective function that signals people to take a rest to restore energy. Generally, a good night's sleep or a few hours of rest will restore a healthy individual to a normal level of functioning. However, cancer-related fatigue often imposes a persistent or relapsing, unpleasant, distressing, and debilitating sensation on individuals with cancer. For many patients, cancer-related fatigue is a common and significant contributor to decreased quality of life (Aistars 1987). It exerts a great impact on an individual's sense of well-being and usual functioning, including daily performance, activities of daily living, relationships with family and friends, and compliance with treatment (Glaus 1993; Pickard-Holley 1991).

Despite the prevalence of fatigue in individuals with cancer and the extent to which it can interfere with daily activities, intervention research designed to prevent or ameliorate fatigue has only begun to emerge. Rest is still the most frequently recommended intervention in practice (Nail *et al.* 1991; Ream and Richardson 1996). However, it is now accepted in the research community that rest alone is generally not effective in returning the cancer patient with chronic fatigue to their previous level of functioning (Winningham 1991). Unnecessary bedrest and prolonged sedentariness can contribute significantly to the development of fatigue and weakness that may result in rapid and potentially irreversible losses in energy and functioning.

Since the mid 1980s exercise has been recognized as a promising strategy for managing and ameliorating fatigue in individuals with cancer and other chronic illness. Research suggests that physical exercise is an effective strategy for reducing cancer-related fatigue, by maintaining or restoring functional capacity, improving depression and anxiety, as well as enhancing quality of life in individuals with cancer (Dimeo *et al.* 1997; MacVicar *et al.* 1989; Mock *et al.* 1997; Porock *et al.* 2000).

Winningham's psychobiological entropy model (Winningham 1992) provides a theoretical framework for exercise as an intervention for managing cancer-related fatigue. This model seeks to link activity, fatigue, symptoms, and functional status, and is based on the clinical observation that individuals who become less active as a result of disease- and/or treatment-related symptoms lose energizing metabolic resources. According to the model, fatigue fulfils a unique and substantial role in the origin of disability that sets it apart from other symptoms. Decreased physical activity, regardless of the cause, leads to decreased energetic capacity (measured in terms of respiratory oxygen uptake or its correlate, calories consumed) for activity. This, in turn, is responsible for increasing fatigue, further decreasing activity, and, subsequently resulting in functional disability.

Five propositions are derived from Winningham's model:

- Too much as well as too little rest contributes to feelings of fatigue.
- Too little as well as too much activity contributes to feelings of fatigue.
- A balance between activity and rest promotes restoration; an imbalance promotes deterioration.
- Any symptom that contributes to decreased activity will lead to increased fatigue and decreased functional status.
- Any intervention providing relief of a symptom that contributes to decreased activity may also serve to mitigate fatigue, and promote functioning, providing that intervention does not have a sedating or catabolic effect.

The physiological effects of exercise

Defining exercise

Exercise can be defined as episodic performance of repetitive bodily movements produced by skeletal muscles that requires energy expenditure. In the healthy population, exercise with a duration of 30–45 min for each episode and a frequency of at least three times a week is advocated in order to produce cardiovascular benefits. Cancer-related fatigue is characterized by a persistent, intense, and chronic sense of tiredness and exhaustion that interferes with usual functioning. Therefore the duration, intensity, and frequency of exercise aimed at managing and ameliorating cancer-related fatigue is expected to be different from that of the healthy population. To help us understand the physiological effects of exercise in populations of cancer patients a review of the physiological effects of exercise in the healthy population is outlined in Table 14.1.

Table 14.1 Phases of exercise in a healthy population

Phases of exercise	Physical and chemical response of human body to the severity and duration
Phase I: the phosphagenic energy phase	The preexisting stores of high-energy compounds (such as adenosine triphosphate (ATP) and phosphocreatine (PCr)) can be depleted within a few seconds under maximal exercise effort The high-energy compounds can be rapidly replenished in the aerobic energy phase
Phase II: the aerobic energy phase	The process of oxidative phosphorylation is the important mechanism for rapid repletion of the high-energy compounds During oxidative phosphorylation, glycogen, serum glucose, and serum fatty acids are denatured to acetyl coenzyme A and fed into the citric acid cycle, with the ultimate production of carbondioxide (CO_2) and water (H_2O) The process of oxidative phosphorylation leads to either the energy being stored as ATP and PCr or energy release as heat. It can provide the needed energy as long as the level of the activity remains less than 70% of the maximum rate of ATP breakdown The aerobic metabolism cannot always cope in time, especially with heavy exercise workload
Phase III: the anaerobic phase	An alternative energy-producing mechanism to prevent individuals from energy depletion Pyruvic acid is formed from glycogen and transformed into lactic acid (lactate), this process is not economic and only yields enough energy to form 2 moles of ATP, comparing to 38 moles of ATP via the aerobic phase Lactic acid accumulation leads to a continuous fall in blood pH, thus an individual has to stop the exhausting exercise More depletion of oxygen may result from the process in which oxygen is needed to reconvert the lactic acid into pyruvic acid in the liver and muscles Individuals may experience soreness or even pain in the muscle for up to several days following the specific exercise activity The more oxygen that can be delivered for the oxidative phosphorylation, the less will be the need to rely on anaerobic metabolism

Individual maximal oxygen uptake

The amount of oxygen carried and delivered to contracting muscle is called the maximal oxygen uptake ($VO_{2\,max}$) or maximum aerobic power. Maximum aerobic power refers to the highest oxygen uptake attained during physical work (activity or exercise), breathing air at sea level (Astrand 1973). $VO_{2\,max}$ has become the 'gold standard' for measuring an individual's capacity to supply energy aerobically during physical activity and exercise (Glaser 1997). It is directly related to the functional capacities of the cardiovascular, pulmonary, and muscular systems. The higher an individual's $VO_{2\,max}$, the greater is the physiological reserve and the lower will be the relative stress experienced for performing certain given activities. In addition, a high correlation exists between cardiac output and oxygen uptake; thus measurement of oxygen uptake not only reveals the capacity to yield aerobic energy, but also the load on the heart (Astrand 1973).

Training effects

It is common knowledge that after a period of training exercise becomes easier and progressively greater loads can be tolerated. This training effect results from physical and chemical changes which occur as muscle contracts, and implies an increased $VO_{2\,max}$ resulting from increased oxygen delivery due to the increased cardiac output, and by more efficient use of oxygen via contracting muscle cells (Morris 1975). Training not only improves left ventricular performance leading to increased cardiac output, but also enhances elimination of lactate by trained muscles, resulting in lower blood lactate levels (Morris 1975). Consequently, increased cardiac output and efficient elimination of lactate results in an increase in maximum aerobic power. As oxygen uptake reaches maximal levels the cardiac output and stroke volume are also maximal. A further increase in work intensity is possible because of an anaerobic energy yield, but the cardiac output and stroke volume may be somewhat reduced. Certainly the work becomes very exhausting and straining (Astrand 1973).

Physical activity

Physical activity is defined as bodily movement produced by skeletal muscles that require energy expenditure (NIH Consensus Development Panel on Physical Activity and Cardiovascular Health 1996). Physical activity ranges from repeated work periods from a few seconds' duration up to hours of continuous work, creating a major load on the oxygen-transporting organs, and thereby inducing a training effect. The total amount of physical activity may be as important as episodic exercise in producing important outcomes relating to health and well-being (King 1994; O'Neill and Reid 1991). Increasing physical activity in people with cancer may be an effective intervention for reducing fatigue, promoting functional independence, and physical functioning. The rationale for increasing physical activity in people with cancer is:

- The training effect of physical activity that forms part of everyday functioning may be more effective in relieving fatigue and improving physical functioning than episodic exercise.
- Physical activity can be carried at any time and in any setting (home, street, gym), an encouraging factor for individuals affected by cancer to engage in activities they enjoy and tolerate.
- Unlimited types and durations of physical activity permit individuals with cancer to perform physical activities according to their preference, thus reducing the possibility of boredom.

Beneficial effects of exercise in individuals with cancer

The benefits of exercise are the same for people with cancer as for healthy people. Research on the impact of exercise and physical activity on cancer-related fatigue has been undertaken with patients receiving, or those who have completed, treatment.

Most intervention studies have been conducted with patients undergoing treatment for breast cancer and/or receiving bone marrow transplantation (MacVicar and Winningham 1986; Mock *et al.* 1994, 1997; Schwartz 2000). All of these studies used different types of aerobic exercise: a walking programme (Mock *et al.* 1994, 1997, 1998), cycling (Dimeo *et al.* 1997), patients' own choices of type and time of exercise (Schwartz 2000). In a study conducted by Porock *et al.* (2000), a range of physical activity was prescribed to people with advanced cancer. For example, an individual might walk for 5 min, perform arm exercises with a resisted rubber band in a chair, march on the spot in the kitchen, or dance to favourite music. The duration of exercise regimes in these studies varied from 6 weeks for patients undergoing radiation to 6 months for breast cancer patients undergoing chemotherapy and bone marrow transplantation, respectively. Some of the exercise regimes in the studies were under supervision in a laboratory whilst others were home-based. All of the studies demonstrated that exercise significantly reduces fatigue in patients undergoing cancer treatment. Specific benefits that have been evaluated with cancer patients are summarized in Table 14.2.

Fatigue is recognized as a significant correlate of impaired functional activity among patients receiving radiation and chemotherapy treatment (Irvine *et al.* 1994). Moreover, research indicates an inverse relationship between levels of physical activity and fatigue (Mock *et al.* 1994, 1997; Porock *et al.* 2000). Although the mechanism of how exercise reduces fatigue and increases energy remains unclear, research shows that exercise, particularly aerobic exercise, may be beneficial in relieving fatigue and

Table 14.2 Summary of the research on the benefits of exercise in patients with cancer

Benefit	Study findings	Reference
Relieves fatigue and enhances energy	Studies in women with breast cancer, bone marrow transplantation, and people with metastatic cancer all benefited in terms of perception of fatigue and feelings of enhanced energy. None of these studies were able to isolate the mechanism(s) by which fatigue was relieved	Berger (1998), Dimeo *et al.* (1998), MacVicar *et al.* (1989), Winningham (1996), Mock *et al.* (1997), Porock *et al.* (2000), Schwartz (1998)
Improves physical functioning	Exercise helps to break the cycle of deconditioning	Mock *et al.* (1994, 1997), Porock *et al.* (2000)
Improves mood	Exercise is associated with elevated levels of beta-endorphins and increased brain serotonin levels after acute exercise	Artal and Sherman (1998), Chaouloff (1997)
Weight control	Women receiving adjuvant chemotherapy for breast cancer who did not exercise gained an average of 3.2 kg, while those in the exercise group maintained their pretreatment weight	Schwartz (2000)

enhancing energy. Two hypotheses have been proposed:

- The training effect of aerobic exercise increases cardiac output and thus oxygen perfusion, as long as the individual sustains physical activity (Astrand 1973).
- Exercise induces increased levels of beta-endorphins and their euphoric effect elicits the perception that one is less fatigued (Kennedy and Newton 1997).

In addition to extreme muscular deconditioning related to cancer disease and treatment modalities, cancer-related fatigue is worsened by prolonged rest and inactivity, contributing to muscular catabolism. As a result patients need a higher degree of effort to carry out normal activities. A consequence of this is a persistent and self-perpetuating condition of diminished activity caused by easy fatigability for many weeks and even months post-treatment (Dimeo *et al.* 1997; Winningham 1992). Aerobic exercise may reduce fatigue and improve physical functioning by breaking the cycle of lack of exercise, impaired functioning, and easy fatigability.

The psychological effects of exercise

Cancer diagnosis, treatment, and uncertainty of reoccurrence is a chronic and dynamic process that exerts a great deal of emotional stress on individuals with cancer. Depression may be a co-morbid and disabling syndrome that elicits anxiety, sadness, and fatigue. It is difficult to differentiate whether fatigue causes depression or vice versa. Both fatigue and depression are strong predictors of quality of life in cancer patients (Hopwood and Stephens 2000) and depression is more likely than fatigue to cause emotional distress in family caregivers. Thus, it is important to manage depression not only for the comfort of the patient, but also in order to reduce distress in the family.

Psychological effects of exercise on depression

The psychological effects of exercise refer to what individuals feel psychologically and emotionally when the human body exercises. Currently, most psychopharmacological agents relieve depression by restoring a balance between neuroreceptors and neurotransmitters. Antidepressant medications, including the selective serotonin re-uptake inhibitors (SSRIs), are believed to ameliorate depression by increasing the availability of neurotransmitters at receptor sites (Artal and Sherman 1998). The biological mechanism of exercise in reducing depression still needs clarification. However, there is a body of evidence to suggest that exercise may exert antidepressant effects by influencing the metabolism and availability of central neurotransmitters (Artal and Sherman 1998), and by increasing levels of brain serotonin (Chaouloff 1997). Despite evidence that exercise leads to increased levels of beta-endorphins, it is questionable whether this increase is sufficient to reduce depression (Artal and Sherman 1998). The action of elevated levels of beta-endorphins remains unclear, but its ability to induce euphoria and thus reduce the perception of pain might exert an antidepressant effect by changing the perception of depression.

Research on the psychological effects of exercise in individuals with cancer is limited. Nevertheless, the results of existing studies have demonstrated that exercise does benefit individuals with cancer both psychologically and emotionally, including increased self-concept, improved self-esteem, increased self-control, feeling of decreased depression and anxiety, as well as overall improved quality of life (Courneya and Friedenreich 1997, 1999; Mock *et al.* 1997; Winningham *et al.* 1994). The psychological mechanism of exercise may play the most important role in reducing depression and anxiety by bringing about positive changes in mood states, changes shown to occur in young and older healthy adults and in a variety of patients (Table 14.3).

In one study assessing the effectiveness of an aerobic exercise programme in older patients with depression (Blumenthal *et al.* 1999), aerobic capacity was found to have statistically significant correlation with improved depression. The authors suggested that improved aerobic capacity might account for at least part of the reduction in depression.

Table 14.3 Summary of the research on the psychological effects of exercise

Psychological effects of exercise	Populations	Types of exercise	References
Reduces tension, anger and depression, enhances feelings of vigour	Healthy male and female	Aerobic dance	Kennedy and Newton (1997)
Enhances positive emotions and reduces negative emotions; reduces anxiety	Healthy undergraduate students	Pedalling a stationary bicycle (bicycle ergometer)	Petruzzello *et al.* (1997)
Reduces clinical signs and symptoms of depression	Male and female older patients (aged 50–77 years) with diagnosis of depression	Walking or jogging	Blumenthal *et al.* (1999)
Decreases tension/anxiety, reduces depression/dejection, enhances feelings of vigour	Breast cancer patients	Walking	MacVicar and Winningham (1986)
Reduces anxiety	Stage I or II breast cancer survivors	Pedalling a stationary bicycle (bicycle ergometer)	Blanchard *et al.* (2001)
Enhances sense of well-being, improves self-efficacy in controlling pain and fatigue, reduces depression	Fibromyalgia patients	Walking/jogging/side-stepping/arm exercise against water resistance in a warm therapeutic pool	Gowans *et al.* (1999)

Porock *et al.* (2000) hypothesized that improvement of any aspect of physical, social, and mental well-being will be reflected in an overall improvement in reported quality of life.

Forms of exercise

Theoretically exercise type, intensity, frequency, and duration, are vital in producing effective psychological effects. Activities that are aerobic, non-competitive, predictable, and rhythmical, such as walking, cycling, swimming, aerobic dancing, running (Barabasz 1991; Berger and Owen 1983; Blumenthal *et al.* 1999; Kennedy and Newton 1997; McMurdo and Burnett 1992; Courneya and Friedenreich 1997, 1999; MacVicar and Winningham 1986; Mock *et al.* 1997; Porock *et al.* 2000; Winningham *et al.* 1994), have been shown to produce psychological benefit (Kennedy and Newton 1997).

The intensity of exercise is measured by the amount of exertion. For healthy adults, both high- and low-intensity exercise are thought to lead to positive changes in mood and have positive psychological impact (Kennedy and Newton 1997). However, in an early study comparing high- and low-intensity exercise by Steptoe and Cox (1988), only subjects who exercised at low-intensity demonstrated positive mood change. Research on the intensity of exercise in people with cancer shows that a low to moderate intensity of exercise produces both physical and psychological effects on reducing fatigue, depression, and anxiety (Courneya and Friedenreich 1999; MacVicar and Winningham 1986; Mock *et al.* 1997; Porock *et al.* 2000; Winningham *et al.* 1994).

The duration of exercise refers to both the time for which each episode of exercise lasts and the time frame (usually weeks, months, or years) in which the exercise behaviour lasts. The majority of studies examining aspects of psychological well-being using exercise sessions of at least 20 min duration have obtained positive results on psychological measures (Kennedy and Newton 1997). Blumenthal *et al.* (1999) found that exercise was equally as effective as medication after 16 weeks of an aerobic exercise programme in older patients diagnosed with depression. Most studies employing exercise with a duration from 6 weeks to 6 months in people with cancer have revealed findings of positive psychological changes, such as decreased depression and anxiety, reduced fatigue, increased self-esteem, increased sense of self-control, as well as improved overall well-being and quality of life (Mock *et al.* 1994, 1997, 1998; Dimeo *et al.* 1997, 1999).

Implications for practice and research

More in-depth research still needs to be conducted on the physiological and psychological effects and mechanisms of exercise on fatigue. Nevertheless, the existing literature has revealed that exercise and physical activity are vital aspects of fatigue management at a physical and psychological level. Exercise and physical activity should be encouraged whatever the level of capability the patient or cancer survivor may have, from bed/chair exercises through to fitness training.

Implications for practice

Fatigue assessment and prescriptions for managing fatigue should be a vital aspect of care for cancer patients and survivors during treatment and follow-up care. Exercise and physical activity should be considered as an important fatigue management strategy. Prescription of exercise or physical activities should consider individual health status, exercise type, intensity, duration, frequency, and progression. Table 14.4 lists suggested considerations when prescribing exercise and physical activities (Winningham 1999).

It should be noted that exercise and physical activity are one of several possible interventional strategies for managing fatigue. The multidimensionality of cancer-related

Table 14.4 Prescriptions of physical exercise and activity

Prescription	Rationale/explanation
Status of the individual	Exercise should be tailored to age, gender, condition, risk factors, disease, and treatment
Type of exercise	Should encourage rhythmic, repetitive movement of large muscle groups such as walking, swimming, cycling, dancing, or stretching. Walking and cycling are the most appropriate because they are safe and easily tolerated by cancer patients and survivors. Exercise should be modified based on treatment modalities and disease progression
Intensity of exercise	Low to moderate exercise should be encouraged depending on patient's current fitness level and treatment modalities. Exercise or physical activities should never be so hard that the person is out of breath. Winningham's (1991) half rule of thumb can be an excellent reference, especially for individuals with cancer who are under active treatment and evident disease progression. The half rule of thumb involves finding out how much activity the patient can comfortably tolerate and then instructing them to begin with half that much several times daily, with rest periods between. Instead of a single type, a variety of exercise or physical activities should be prescribed
Frequency of exercise	For moderate exercise or activity (walking or cycling), three to five times per week is sufficient. For low-intensity and shorter-duration exercise and physical activities (stretching or marching in the room), a few minutes two or three times a day is beneficial
Duration of exercise	For cancer survivors and patients with stable conditions, 20–30 min of continuous exercise should be encouraged. For patients who are undergoing treatment and evident disease progression, 3–5 min short exercise bouts with rest intervals are preferable
Progression of exercise	Cancer patients and survivors should be instructed to increase exercise intensity until they meet the frequency and duration prescribed. Long-term exercise from months to a lifetime should be encouraged. A general rule of thumb is starting with what the person can do comfortably and working up very gradually from there

fatigue needs an integrative approach. Exercise and physical activity should be integrated with other fatigue management strategies, including modifying dietary needs, relieving other symptoms, practicing progressive muscle relaxation, and assessing/meeting emotional and spiritual needs. Cognitive therapy focusing on increasing individuals' self-efficacy can be an effective motivational intervention to encourage individuals with cancer to participate in exercise and physical activity (Haas 2000). It can be assumed that an integrative approach to fatigue management will improve the ability of cancer patients and survivors to manage their fatigue.

Implications for research

Although fatigue has been studied from the point of view of many health-related disciplines, its nature and characteristics are not well recognized or widely accepted (Aaronson *et al.* 1999; Ream and Richardson 1996; Tiesinga *et al.* 1996). The effectiveness of each individual intervention has not been rigorously researched. Future study should focus on establishing intensity, frequency, duration, and progression of exercise or physical activities for each intervention as well as its effectiveness. Determining the optimal exercise prescription for cancer patients and survivors for various treatment modalities and at various disease stages is an important focus for future research.

Using a cognitive approach to motivating individuals with cancer to participate in exercise or physical activities is an important direction for future research. Cognitive intervention focusing on increasing individuals' self-efficacy beliefs holds promise in motivating individuals to engage in exercise or physical activity. Self-efficacy belief, a component of social cognitive theory, has been found to be the strongest predictor of exercise behaviour among diverse populations (Conn 1997; Bandura 1997; King *et al.* 1992). Self-efficacy beliefs are personal assessments of one's ability to successfully perform a given behaviour (Bandura 1989, 1997). Research using self-efficacy in cancer patients has focused on disease prevention and early detection behaviours (Lev 1997). To date, no research has been conducted to establish the relationship between self-efficacy beliefs and the motivation of individuals with cancer to participate in exercise or physical activity. In addition, addressing self-efficacy may enhance smoking cessation, adoption of a healthy diet, and relaxation techniques (Haas 2000).

Fatigue is a multidimensional phenomenon and its management necessitates an integrative approach (Fu *et al.* 2001, 2002; Porock 1999). To date, there is still a lack of a systematic and integrative programme for fatigue management. Future fatigue research should focus on providing systematic and integrative management programmes based on strategies of energy conservation, effective energy use, and energy restoration (Piper *et al.* 1989). Such a systematic and integrative programme should encompass a variety of interventions, such as planned rest/sleep periods during the day, scheduled aerobic exercise and progressive muscle relaxation, provision of an adequate diet, and assessing/meeting emotional and spiritual needs. As future research documents the effectiveness of intervention programmes in managing fatigue, the quality of life in patients with metastatic disease will be improved.

Conclusion

Fatigue is a complex, subjective symptom that is very prevalent at all stages of the cancer trajectory. Although for many years fatigue was a hidden and ignored symptom of cancer and its treatment, recent focus and research efforts have provided a scientific basis for understanding fatigue, its impact, and management; a foundation that is acknowledged and used by all the health professions. Despite incomplete understanding of the mechanisms of fatigue, several research-based interventions have been tested with encouraging results. Exercise should be encouraged. Careful assessment and treatment of depression needs to be pursued in conjunction with exercise in managing fatigue.

Fatigue is one of a constellation of symptoms that can adversely affect individuals with cancer and their families. It is not an easy symptom to manage; nevertheless its complexity requires the listening empathic ear of health providers to ensure that whatever the outcome, the patient and family feel they have had the best of care possible.

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