Chapter 18
Exercise and Chronic Fatigue

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Chapter Overview

Fatigue is a symptom that can be experienced by anyone, whether through extended physical or mental activity, sleep deprivation or other environmental and social factors. Typically, fatigue is temporary and can be alleviated by rest or sleep. However, for some people, fatigue is an ever-present symptom that causes considerable distress and negatively impacts quality of life. Fatigue that is pathological, persistent and not resolved by rest can be called chronic fatigue. One of the most striking things about chronic fatigue is that it is common in people with many different diseases and disorders. Even though the underlying causes of fatigue may be different from one disease to the next, there are remarkable similarities in the experience of chronic fatigue. One consequence is that treatments and therapies which reduce fatigue in people with one disease may also be effective in reducing fatigue in people with a completely different disease. Exercise is one such treatment. Perhaps because of the historical (and incorrect) view that fatigue is caused by the depletion of an unspecified physiological source of energy (Hockey, 2013), exercise has long been examined as a possible treatment for chronic fatigue. Interestingly, there is growing evidence that exercise is an effective treatment to reduce chronic fatigue, at least in some cases. In this chapter, we will present the evidence for exercise as a treatment for chronic fatigue in four different patient groups; people living with and beyond cancer, people with multiple sclerosis, people who have had a stroke, and people with myalgic encephalomyelitis/chronic fatigue syndrome. First, it is important to understand what is meant by the word *fatigue*, both in general and in relation to these clinical populations.

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What is Fatigue?

Fatigue is a word familiar to many people; it can be used to describe how a person is feeling ("I'm really fatigued from my flight") or describe an apparent alteration in someone's behaviour, for example, a decline in an athlete's performance ("they are fatigued and making lots of mistakes"). Somewhat surprisingly, despite the ubiquitous use of the word in everyday language, scientists have had a hard time describing what fatigue actually is. Fatigue has been described as either a feeling of tiredness, weariness or exhaustion, a measurable decrement in performance of an activity caused by the prior extended performance of the same activity, or an insufficiency of the muscles or central nervous system to maintain physical or mental performance (Hockey, 2013). Fatigue is also often delineated by its proposed cause and consequence: Fatigue has been described as either mental/cognitive or physical/physiological, can be either central or peripheral, or can be acute or chronic. The term *mental fatigue* is typically used to describe feelings or behaviours which arise from the sustained performance of mentally demanding tasks, whilst *physical fatigue* is used to describe feelings and behaviours which arise from sustained performance in physically demanding tasks. Central fatigue can mean either mental fatigue or fatigue caused by, or which causes, a change in central nervous system function. Peripheral fatigue usually, but not always, refers to fatigue caused by or which causes changes in muscle function. Acute fatigue describes the *temporary* fatigue which arises from sustained task performance and which is alleviated by rest. Almost everyone experiences acute fatigue at one point in their lives, perhaps from studying hard for an exam or from a physically demanding hike.

With all these different definitions and delineations, you might have become fatigued! Thankfully for us, and for the purposes of this book chapter, several attempts have recently been made to provide a unified description of fatigue that, as scientists, we can use to describe, study, and treat fatigue (Kluger et al., 2013; I. Penner & Paul, 2017). Many diseases and disorders have their own definitions of chronic fatigue. We will present some of these for cancer, multiple sclerosis and stroke in sections of this chapter. However, as you will see, there are many common traits in each definition, supporting the proposal that a unified taxonomy can be used to describe fatigue (Kluger et al., 2013). Drawing together these disease-specific definitions, we propose the following definition of chronic fatigue, which is applicable across a range of diseases: *A persistent feeling or perception of weariness, tiredness or exhaustion that is not alleviated by rest, is not proportional to activity levels and is a disabling negative symptom that interferes with daily activities and impairs quality of life*. Importantly, the definition allows us to focus on fatigue as a symptom that is experienced across a range of diseases and disorders. This feeling or perception of fatigue may or may not be accompanied by a measurable decline in physical or mental function and performance, which has been referred to as *performance fatigability* (Kluger et al., 2013).

Prioritizing the Patient Experience

In exercise science, there is a tendency to focus on performance fatigability and use the term fatigue when referring to objective decrements in performance. There is also a tendency to place more value on *objective* measurements (such as a decrease in force during a motor task) rather than *subjective* self-report measures. Using the term fatigue in this way may originate from a focus on the sport or athletic performance. However, using fatigue to mean performance does not always reflect how the general public understands the term fatigue (a feeling of weariness, tiredness or exhaustion). In the case of clinically relevant chronic fatigue, the emphasis on *objective* (or even *actual*) fatigue makes little sense. There are many examples where a measure of fatiguability (such as a decline in muscle force during a sustained submaximal contraction) is deemed to be a more important measure than a patient's self-reported experience of fatigue. However, such objective measures are not inherently superior to a person's experience, and this is particularly important to emphasize in relation to clinical populations with chronic fatigue. A patient does not come to the clinic because they can no longer sustain a submaximal contraction of the forearm muscles. Patients come to the clinic because, for example, they are feeling overwhelming tiredness that is reducing their ability to go about their normal daily activities (e.g., interacting with family and friends, concentrating on completing work tasks, the ability to walk to the shops without causing a huge energy crash) and reducing their quality of life. In fact, most patients would only think something like sustained handgrip force was important if an exercise scientist told them it was. And what would happen if, for example, we improved the ability of the patient to sustain this handgrip force, perhaps by strengthening the forearm muscles used in the task? Would the patient's chronic fatigue then be treated? Of course not. The patient experience, reported to the clinician or scientists, is what matters. Patient-reported outcomes are questionnaires that are used to get a rating of fatigue from the patient and often ask questions about fatigue severity or intensity, and interference with usual activities, and dimensions/manifestations of fatigue (e.g., physical, mental, emotional). Some questionnaires are disease-specific and have been carefully validated (for example, based on clinical features of fatigue in a specific disease, qualitative interviews, and expert clinical consensus). That is, they are highly relevant to the patient. In the sections below, we will be concentrating on the effect of exercise on fatigue measured as a patient-reported outcome in several clinical populations.

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Exercise and Cancer-Related Fatigue

Definition and Description

More than one-third of people will be diagnosed with cancer in their lifetime. Due to improvements in cancer prevention and treatment, more people are now living longer with and beyond cancer. Fatigue can be one of the principal concerns for people with cancer. The most widely accepted definition of cancer-related fatigue (CRF) 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" (Berger et al., 2015, p. 1014). It can be hard to understand CRF if you have not personally experienced it, but compared with fatigue that can be experienced by healthy individuals, CRF is more severe (people with CRF describe it as "overwhelming" and "all-encompassing"), less likely to be relieved by rest, can limit daily activities, and can be debilitating (Scott et al., 2011). CRF is a significant clinical problem that has historically been under-recognized, especially in comparison to other common cancer symptoms such as pain or nausea. The experience of CRF can be highly individual, but there are several common clinical features that have been identified. Alongside significant fatigue and an increased need to rest, these features can include limb heaviness or weakness, problems with short-term memory, unrefreshing or non-restorative sleep, a perceived need to struggle to overcome inactivity, and emotional reactivity (Cella et al., 1998). CRF is assessed as a patient-reported outcome, and for routine screening in clinical practice, individuals are asked to self-report fatigue intensity over the past week on a scale of 0-10 (where 0 = no fatigue and 10 = worst fatigue). A score of ≥4 (where 0–3 = none to mild, 4–6 = moderate, and 7–10 = severe) helps identify fatigue as a problem and should be followed by a comprehensive fatigue assessment (Howell et al., 2013).

Cancer-related fatigue is common during active treatment (the period of weeks or months that a patient is receiving, for example, chemotherapy or radiation therapy), and this can be true for treatment delivered with both curative and palliative intent. Estimates of the prevalence of CRF vary due to differences in the methods used to measures CRF and differences in the specific population being assessed (considering there are many different cancer types and treatment protocols). However, fatigue does tend to worsen with the progression of the disease and can be more severe with multimodality or dose-intense treatment protocols. In the case of curative cancer treatment, fatigue resolves for most people in the weeks after the treatment has been delivered. However, for a sub-set of people, fatigue can become a chronic issue that can continue for years (Jones et al., 2016). This type of chronic CRF (also called post-cancer fatigue) can prevent people from returning to work and is associated with high levels of disability.

Although the mechanisms leading to CRF are not completely understood, it is well accepted that CRF is multidimensional and is influenced by a range of factors, including underlying biological mechanisms (Bower, 2014). Some of the factors that can contribute to CRF are psychosocial, including depression, anxiety, and lack of social support. People with CRF often report a lack of understanding from family, friends or doctors, and a lack of social and medical legitimacy for the symptom (Pertl et al., 2014; Rosman, 2009). CRF can lead to social isolation and disengagement, loss of identity, and feelings of guilt and frustration about fatigue (Corbett et al., 2017; C. Penner et al., 2020). CRF can be difficult to articulate, and there are barriers that prevent people with CRF from communicating with healthcare professionals about their fatigue, including not wanting to complain and a lack of awareness that there are effective treatments for fatigue (Passik et al., 2002). CRF is not trivial and more people now recognize the importance of the patient's experience. Clearly, CRF can have a significant impact on a person's overall quality of life.

The Role of Exercise in Treating Fatigue in People with Cancer-Related Fatigue

All people with cancer should avoid inactivity, be as physically active as current abilities and conditions allow, and return to daily activities as soon as possible following a cancer diagnosis (Cormie et al., 2018). However, for people with CRF, exercise can be considered first-line treatment. The mechanisms for the reductions of fatigue severity with exercise are not well understood but may include physiological factors such as increased cardiorespiratory fitness or reduced inflammation, and psychological factors, including reduced symptoms of depression, anxiety, and increased social support. Some of the evidence that supports exercise as a treatment for CRF is based on systematic reviews and meta-analyses. A systematic review is a methodical search of the literature that aims to summarize the current body of research. A meta-analysis is a statistical analysis that combines the results of multiple studies, often randomized controlled trials, and provides a high level of evidence on the effectiveness of an intervention. There are now several systematic reviews with meta-analyses on the topic of exercise for CRF. In 2020, van Vulpen et al. concluded that the beneficial effects of exercise on fatigue in patients with cancer are consistent across demographic and clinical characteristics. In 2018, Kessels et al. found that exercise has a large effect on CRF in cancer survivors and that aerobic interventions with high adherence have the best result. In 2017, Mustian et al. found that both exercise and psychological interventions are effective for reducing CRF during and after cancer treatment, and they are significantly better than the available pharmaceutical options. In perhaps the most comprehensive review to date, Oberoi et al. (2018) included 170 randomized controlled trials and found that physical activity significantly decreases the severity of fatigue in patients with cancer.

Although there are many studies on exercise for CRF, the body of research is not without limitations. In fact, in a systematic review of systematic reviews with meta-analyses, Kelley & Kelley (2017) concluded that more well-designed randomized controlled trials are needed because the results on exercise for CRF vary and are inconclusive. However, the researchers also noted that because exercise does not seem to make CRF worse and is associated with numerous health benefits, exercise programs that take into consideration the unique needs of cancer patients can be recommended. Another limitation is that some populations are underrepresented as most research is conducted on people diagnosed with breast cancer, whereas other cancer types have been overlooked. Similarly, most research includes interventions that are delivered during chemotherapy or radiation therapy, but there are far fewer studies on exercise for people with chronic CRF or for people with advanced cancer. Finally, the vast majority of studies do not specifically target participants with clinically relevant fatigue (Twomey et al., 2020), and this may contribute to the fact that although the beneficial effect of exercise of CRF is consistently demonstrated, the size of the effect (that is, the amount of improvement in fatigue) is usually only small to moderate.

In 2019, a consensus statement from an international multidisciplinary roundtable presented the most recent exercise guidelines for cancer survivors (Campbell et al., 2019). For some cancer-related health outcomes, there was consensus that the evidence was enough to recommend an exercise prescription based on the FITT principle (Frequency, Intensity, Time and Type). For CRF, the recommendation is to exercise three times per week at a moderate-to-vigorous intensity for 30 min, either as aerobic exercise or aerobic exercise plus resistance training. The FITT prescription provides a useful guideline, but exercise should be tailored to ensure the overall well-being of the individual. There is no "one size fits all" exercise prescription for CRF, and some people can exercise more frequently, for a longer duration or at higher intensities than the recommendations made by Campbell et al. (2019) without adverse effects. In contrast, a subset of people with CRF may experience a worsening of symptoms for multiple days after an exercise bout, and therefore, responses to exercise must be monitored carefully to avoid causing harm (Twomey et al., 2020). Finally, it can be counterintuitive or intimidating to become more physically active when you have CRF, and so support for behaviour change must also be considered alongside any exercise prescription.

Exercise and Fatigue in People with Multiple Sclerosis

Definition and Description

Multiple sclerosis (MS) is an auto-immune disease, primarily affecting the brain and spinal cord. It is estimated that over 2.5 million people worldwide have MS, and MS is a leading cause of adult disability (Compston & Coles, 2008). The exact cause of MS is unknown but likely involves genetic and environmental factors. MS is characterized by the demyelination of axons in the central nervous system.

It is believed that in people with MS, the immune system "attacks'' myelin, the insulating sheath around axons that enables efficient action potential transmission in the central nervous system. Failures in myelin-producing cells have also been indicated as a possible mechanism of MS. The loss of myelin causes dysfunction throughout the central nervous system and can cause problems with motor function (including weakness), sensory, autonomic and visual processes. The disease course of MS can be unpredictable, and the majority (~80%) of people with MS have *relapsing-remitting* MS, meaning they experience periods with few or no symptoms (remission), which can be followed by periods where symptoms flare again (relapse). Eventually, relapsing-remitting MS becomes what is known as *secondary progressive* MS, where symptoms get progressively worse (Compston & Coles, 2008).

Between 50–90% of all people with MS also report problems with fatigue, including adverse effects on activities of daily living, quality of life, and ability to work (Krupp et al., 1988). MS-related fatigue is defined as "a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities"(Multiple Sclerosis Council for Clinical Practice Guidelines, 1998, p. 2). For many people with MS, fatigue is the single most debilitating symptom they experience. Despite its prevalence and impact, the exact causes of fatigue in people with MS are unknown. Fatigue in people with MS can be thought of as either a primary or secondary symptom. Primary fatigue is assumed to be caused directly by the pathophysiology of the disease, such as inflammation, demyelination, and neurodegeneration. Secondary fatigue is thought to arise from associated psychological effects of MS, including sleep loss, depression, and pain. There are at present two primary suspected biological mechanisms for primary fatigue in MS: immune and neuroendocrine dysfunction and lesion-induced changes to brain activation. People with MS can have increased expression of pro-inflammatory cytokines, including interferon-γ and TNF-α. Systemic overexpression of these cytokines has been linked to "sickness-like" behaviours and symptoms, including increased fatigue. Alternatively, or even simultaneously, cortical, subcortical, and white matter lesions caused by successive demyelination and relatively unsuccessful remyelination seen in MS may also cause fatigue. The presence of these lesions may alter the structure and function of neural networks involved in cognition and sensorimotor planning and performance, causing increased feelings of effort and fatigue during physical and mental tasks. Secondary fatigue might be the consequence of other primary symptoms of MS. People with MS often have problems sleeping and increased pain, and these symptoms are linked to the experience of fatigue (Kos et al., 2008).

The Role of Exercise in Treating Fatigue in People with Multiple Sclerosis

Despite being advised for many years not to exercise, exercise and physical therapy are now recommended treatments for people with MS. Some of the proposed benefits of exercise for people with MS include improvements in strength and cardiorespiratory fitness, improved balance, walking performance, and proprioception (Amatya et al., 2017). Exercise is also suggested to be an effective treatment for fatigue in MS. In a 2015 Cochrane systematic review and meta-analysis, Heine et al., (2015) reported a moderate effect of exercise on fatigue in people with MS. There were very few side effects of exercise reported, including very few relapses, suggesting that exercise can be safely used to treat fatigue in people with MS. Compared to usual treatment, endurance exercise, mixed exercise (a mixture of strength and conditioning and endurance exercise), and alternative forms of exercise such as yoga and tai chi were all shown to have a moderate beneficial effect on fatigue. However, as with cancer, the literature in support of exercise as a treatment for fatigue in people with MS has some limitations. In their systematic review, Heine et al., (2015) found significant heterogeneity in the literature. This means that there were many differences in methods, study populations, and outcomes between studies. This makes it harder for us to be able to say with certainty that exercise reduces fatigue. Much more research is required, with careful and large replication of previous effects needed for us to become more confident in these results.

It is perhaps unsurprising, given that the exact causes of fatigue are unknown, that we do not know exactly how exercise alleviates fatigue in people with MS. Nonetheless, several candidate mechanisms have been proposed, and these depend on whether it is primary or secondary fatigue. Exercise has been shown to have positive effects on pro-inflammatory cytokine expression and neuroendocrine regulation, possible causes of primary fatigue in MS. Exercise has also been suggested to be neuroprotective and induce neuroplasticity, meaning it has been shown to protect against brain damage and encourage beneficial changes to the brain, both of which may help alleviate primary fatigue. Proposed mechanisms for the effect of exercise on secondary fatigue include reductions in depression and increased socialization. Perhaps surprisingly, at present, it is not clear whether there is a direct link between physical deconditioning and secondary fatigue. Nonetheless, it is possible that the effects of exercise on cardiorespiratory and muscular function may reduce secondary fatigue in people with MS (Langeskov-Christensen et al., 2017).

There is some evidence that endurance and strength exercise may help alleviate both primary and secondary fatigue in people with MS, and exercise appears to be safe and does not cause a significant relapse. However, despite the growing body of evidence linking increased exercise participation and a range of symptom improvements in people with MS, including fatigue, participation levels remain low. It is estimated that perhaps as few as 20% of people with MS participate in physical activity and activity levels appear to decline as the disease progresses. Many factors may limit participation, from direct physical causes such as increased pain or reduced mobility, psychosocial factors including depression, self-efficacy and social support, and environmental factors such as limited access to suitable facilities (Motl et al., 2017). At present, it is not clear what type of exercise and what dose of exercise is best to treat fatigue in people with MS. More research is required on both the mechanisms of fatigue in people with MS and the pathways by which exercise may impact these mechanisms so that the promise of exercise as medicine for people with MS who report fatigue is realized.

Exercise and Post-Stroke Fatigue

Definition and Description

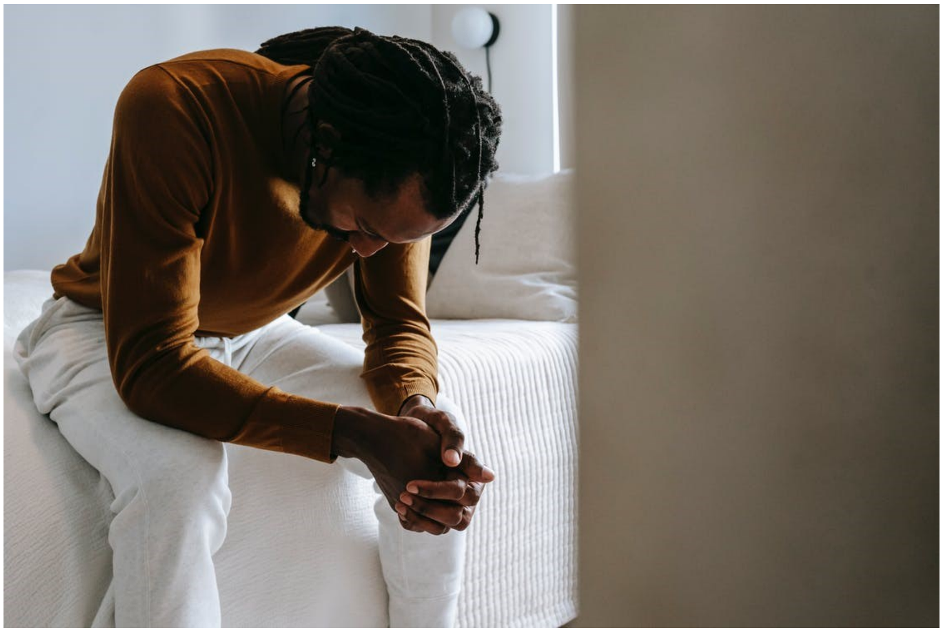
Stroke describes the brain damage caused by either a blockage or rupture of the blood vessels which carry oxygenated blood to the brain. It is estimated that over 30 million people worldwide have survived a stroke, and it is estimated that between 25% and 85% of these people experience post-stroke fatigue (PSF). PSF can reduce the quality of life and negatively impacts activities of daily living for many months and years after stroke, even after successful rehabilitation of motor and cognitive function. The development of strategies and therapies to help reduce and manage fatigue is a priority for people who have had a stroke and has thus become a priority for researchers and clinicians (Ingles et al., 1999).

Though multiple definitions for PSF exist, Lynch and colleagues have described PSF as a period of at least two weeks when an individual who has had a stroke experienced fatigue and a lack of energy, or an increased need to rest nearly every day or every day and this fatigue led to difficulty taking part in everyday activities (Lynch et al., 2007). The causes of PSF are unclear. The majority of people who have had a stroke report feeling fatigued in the weeks afterwards and this is often referred to as "early" PSF. However, not all of these people go on to experience chronic or "late" PSF. Indeed, a small number of people only experience fatigue some months after having a stroke. This suggests that chronic PSF is not a direct consequence of injury to the brain but of the long-term consequences of the stroke on brain structure and function. Whilst the location of the stroke might be related to early PSF, it does not appear to relate to chronic PSF. Several psychosocial and biological mechanisms of chronic PSF have been proposed. A number of studies have shown that chronic PSF is associated with post-stroke depression

(Schepers et al., 2006; Spalletta et al., 2005). There is some evidence that chronic PSF may also be related to pre-stroke depression, though one must be cautious when interpreting these studies because there is a risk of recall bias. PSF is also associated with a locus of control directed at more powerful others, such as clinicians, rather than a high internal locus of control. Possible biological mechanisms include increases pro-inflammatory markers, reduced corticomotor drive, and physical impairment (Doncker et al., 2017).

The Role of Exercise in Treating Post-Stroke Fatigue

Exercise has been proposed as a treatment for chronic PSF. In their 2014 Physical Activity and Exercise Recommendations for Stroke Survivors and 2016 Guidelines for Adult Stroke Rehabilitation and Recovery, the American Stroke Association suggests that exercise may help alleviate PSF (Billinger et al., 2014; Winstein et al., 2016). Stroke patients often do not meet the recommended guidelines for daily activity, and up to 75% of people who have a stroke are characterized as sedentary. However, perhaps surprisingly, there is limited evidence that exercise alleviates PSF. In a small pilot study, Clarke et al. (2012) suggested that a lifestyle education intervention, which included physical exercise education, was effective in reducing PSF. Perhaps surprisingly, at the time of writing, the only direct evidence for the effects of exercise on PSF has been provided from a single randomized controlled trial by Zedlitz and colleagues (Zedlitz et al., 2012). These authors reported that the addition of a graded exercise protocol to a cognitive-behavioural intervention doubled the number of people who reported a clinically relevant reduction in PSF compared to when just the cognitive intervention was applied. The exercise program was delivered so that it was tailored to the participants' individual heart rates, and intensity was increased every two weeks. Although this small study provides some evidence of the effect of exercise on PSF, it has yet to be replicated and does not provide any information about the mechanisms by which PSF might be alleviated. Why, then, is exercise a recommended treatment for PSF? One reason might be that exercise has many positive effects on people with stroke, and thus the prescription of exercise is recommended regardless of its effect on fatigue. However, much more research is needed about the effects of exercise after a stroke so that we can understand the types and volume of exercise required to provide meaningful help to patients in whom fatigue is a burden



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Exercise and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Definition and Description

Exercise has been described as medicine for more than 26 chronic diseases (Pedersen & Saltin, 2015) but can exercise really be considered medicine for everyone with a chronic illness? This section will explore how people with a condition called myalgic encephalomyelitis or chronic fatigue syndrome (ME/CFS) can be affected by even mild levels of exertion. ME/CFS is a complex, debilitating, and long-term illness characterized by chronic fatigue, a substantial reduction in the ability to do usual activities, and other symptoms such as cognitive dysfunction and sleep abnormalities. ME/CFS has been a topic of much debate and controversy, and historically, patients have felt marginalized and have had to struggle to have the legitimacy of ME/CFS recognized (Blease et al., 2017). Many people with ME/CFS have not been diagnosed, partly due to the lack of laboratory or diagnostic tests and a lack of education for healthcare professionals about the condition. People with ME/CFS can struggle to keep a job, go to school or fully participate in their family and social life. One of the main characteristics of ME/CFS is post-exertional malaise, a worsening of symptoms after a physical or mental activity that would not have caused a problem before the illness (Centers for Disease Control and Prevention, 2018). There has been difficulty in defining and measuring post-exertional malaise (Chu et al., 2018; Holtzman et al., 2019), but it can involve exhaustion, cognitive difficulties, and muscle/joint pain that can peak between 24-72 hours after the exertion (Chu et al., 2018; Holtzman et al., 2019). Post-exertional malaise can be unpredictable, disruptive to everyday life (often requiring complete bed rest with little sensory input), and can have a significant impact on emotional well-being (Stussman et al., 2020). Considering this issue of post-exertional malaise, it becomes easier to see that for a minority of people, a blanket recommendation for exercise has the potential to be harmful.

Is Exercise Therapeutic for People with ME/CFS?

The 2011 PACE trial, published in The Lancet (a world-leading, prestigious medical journal), involved a comparison of graded exercise therapy and cognitive behavioural therapy for people with ME/CFS (see White et al., 2011, 2013). The investigators concluded both therapies were moderately effective for ME/CFS and led to "recovery" in over 20% of participants. However, there were several serious criticisms of the trial, including methodological concerns such as outcome switching. This means that during the trial, the researchers lowered their original threshold for recovery (i.e., switched a study outcome), resulting in more participants meeting the criteria for recovery. In general, improvements in self-report measures were not reflected in markers of functional recovery (e.g., the number of days lost from work). Another area of controversy was that the interventions were based on a cognitive behavioural model of ME/CFS, which proposed that rather than ongoing disease processes, ME/CFS is maintained and perpetuated by dysfunctional cognitions and avoidance of activity (see (Geraghty et al., 2019b)). Patients with ME/CFS can benefit from psychological support to help cope with the condition but reject the implication that the disease can be reversed by overcoming illness beliefs (Wilshire et al., 2018). This model is disputed because it suggests that there is no ongoing biological basis for the disease, despite growing evidence to the contrary.

Most patients do not think that graded exercise therapy is appropriate for their needs, and people with more severe ME/CFS report that exercise can have a negative impact (Geraghty et al., 2019a). Because the results of the PACE trial conflicted with a patient's experience of managing their condition, and due to the previously mentioned methodological issues, the researchers were challenged to release the study data for reanalysis by independent scientists. Eventually, the controversy culminated in a UK court tribunal, where the researchers were ordered to share their data. A reanalysis of the data found that if the researchers had used their original criteria for recovery, only 4% of patients who received graded exercise therapy would have met the threshold, compared to 3% of patients who received standard medical care (Wilshire et al., 2018). This is an interesting case to consider because this published research not only distorted the scientific record (i.e. indicated that graded exercise therapy was more beneficial than is likely the case) but was so influential that it directly affected standard treatment recommendations for people with ME/CFS. Some organizations have now removed these recommendations from their guidance for people with ME/CFS, and an updated Cochrane systematic review is underway due to the limited applicability of previous reviews (Larun et al., 2019). Currently, increases in activity are only advised if patients feel they are coping with current activity levels (Bested & Marshall, 2015). Any program involving exercise must be tailored to the individual, with awareness and understanding that worsening of symptoms is possible, and symptoms must be monitored over several days (not only immediately after exercise).

Future Directions: Coronavirus Disease 2019 (COVID-19)

At the time of writing, more than one year since the first outbreak, the coronavirus disease 2019 (COVID-19) pandemic continues worldwide. This contagious and multi-system illness is caused by a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). To date (February 2021), more than 100 million cases have been confirmed worldwide. Alongside fever, cough and shortness of breath, fatigue is one of the acute clinical features of SARS-CoV-2 infection. Clinicians and researchers have focused on the acute phase of COVID-19, but there is now a growing awareness that some patients experience an unexpectedly long and challenging recovery, with ongoing symptoms and complications that can last for months after infection. Researchers, patient groups and those affected by the condition are collectively calling this phenomenon *long COVID* (Brown et al., 2021). Long COVID does not seem to be an issue that is only affecting the minority of people who require hospitalization due to severe respiratory problems. Young and otherwise healthy people who had a mild presentation of symptoms can also experience prolonged symptoms. Patient-led initiatives, such as the Patient-Led Research Team, were the first to conduct surveys to explore health problems after confirmed or suspected SARS-CoV-2 infection (McCorkell et al., 2020). Fatigue, shortness of breath, brain and fog/concentration challenges are just some of the common symptoms, and many respondents who had been physically active before symptom onset had become largely sedentary. Furthermore, reports of fluctuating symptoms that can flair up unpredictably or in response to over-exertion reveal the potential similarities between long COVID and ME/CFS (Komaroff et al., 2021).

The development of chronic fatigue has been observed in survivors of other epidemics (Islam et al., 2020). In earlier coronavirus outbreaks, approximately one-third of survivors of hospitalization or intensive care unit admission had fatigue, reduced quality of life, reduced exercise capacity, and psychological issues including post-traumatic stress disorder, depression and anxiety, even beyond six months after the illness (Ahmed et al., 2020). Although the long-term impact of the SARS-CoV-2 infection is not yet well understood, similar findings are emerging (Halpin et al., 2021). Because COVID-19 is a new disease and research is evolving rapidly, little is known about the mechanisms leading to lingering symptoms or what rehabilitation support is needed. As we have seen in this chapter, exercise can be therapy for conditions where chronic fatigue, inactivity, deconditioning, and mental health concerns are major problems. Looking to the future, helping people manage fatigue, gradually increase activity, regain lost quality of life and return to normal function should be a priority. Improvements in energy levels and breathlessness may be aided by careful tailoring, pacing, prioritization, and modest goal setting (Greenhalgh et al., 2020). There is a potential role for exercise scientists with knowledge of chronic fatigue, working alongside clinicians in the development of such exercise and rehabilitation recommendations for COVID-19 long haulers (Barker-Davies et al., 2020). However, as we have seen in the case of ME/CFS, given the potential for post-exertional malaise, a great deal of caution is required. Future research on responses to exertion and the efficacy of exercise as an intervention must be transparently reported and co-created with the patients (and patient doctors [Alwan et al., 2020]) who have survived not only a global pandemic but one of the major public health crises of our lifetimes.

Conclusion

Fatigue is a symptom common across several diseases and disorders. The etiology of fatigue likely differs between each disease, although often the precise causes are unknown. However, the experience and overall impact of chronic fatigue can be similar across different diseases and conditions. For several clinical populations, exercise is a recommended therapy to improve health and quality of life. There is also some evidence that exercise alleviates chronic fatigue in some diseases. Indeed, even when the evidence base is poor, such as in stroke, exercise may still be recommended due to numerous other benefits to physical and mental health. However, as we have also shown in the case of ME/CFS, extreme caution is required when recommending exercise to people with chronic fatigue. Without knowing the causes of the symptom, it is possible that a therapy that alleviates fatigue in one set of patients may worsen it in another. It is often said that exercise is medicine (Pedersen & Saltin, 2015). For this to be true, then much like a drug, it is vital that we understand the mechanisms of action and the dose of exercise that is safe and beneficial. With these caveats in mind, in certain people, such as those who have been diagnosed with cancer or MS, exercise seems to be an effective and safe method to alleviate fatigue. In these people, a cautious prescription of exercise is likely warranted. Often, specific guidelines for the prescription of exercise in a clinical population have already been developed, and these can help the exercise scientist when designing and implementing an exercise program (Billinger et al., 2014; Campbell et al., 2019; Latimer-Cheung et al., 2013). However, much more research is required before we can fully understand if, how, and why exercise can be used to treat chronic fatigue.

Learning Exercises

1. Read Kluger et al. (2013). Fatigue and fatigability in neurologic illnesses: Proposal for a unified taxonomy (in Further Reading). Write down some examples of the type of statements you might hear from a client or patient when describing their fatigue. Think about whether they are describing their perceptions of fatigue or fatigability. Write down how you might explain to the patient why you need to measure both.

2. Read Campbell et al. (2019). Exercise guidelines for cancer survivors: Consensus statement from international multidisciplinary roundtable (in Further Reading, paying attention to the sections on fatigue). Design a 2-week intervention for a person who has completed their cancer treatment six months ago but still reports feeling fatigued. Write down how you would explain the purpose of the exercise you have prescribed and some considerations for the exerciser, including possible side effects.

3. We have provided four examples of clinical conditions where fatigue is a common symptom. Try searching for two more. Are there any existing recommendations for exercise for people with these conditions? If so, what are the proposed mechanisms by which exercise might help?

Further Reading

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