

International Encyclopedia of Rehabilitation

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Myalgic encephalomyelitis / chronic fatigue syndrome: Rehabilitation through activity management, stress management and exercise therapy

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Introduction

In the name ‘Chronic Fatigue Syndrome’ (CFS), ‘chronic’ refers to the long duration of the illness; ‘fatigue’ indicates the presence of persistent or relapsing debilitating fatigue, and ‘syndrome’ is used to indicate that the illness encompasses a combination of signs and symptoms which are indicative of a particular disease. From our current understanding of CFS pathophysiology and psychopathology, it is concluded that CFS represents the combination of both physiologic and psychological impairments (van Middendorp et al. 2001). It is becoming increasingly apparent that CFS is not an appropriate name for this severely underestimated illness. Indeed, fatigue is not at all disease-specific, and in many cases it is not the most debilitating symptom either. Myalgic encephalomyelitis (ME) is frequently advocated by patient support groups, but given the lack of evidence in support of central nervous system inflammation it is not an appropriate alternative. In the present manuscript we will use ME/CFS to acknowledge the lack of an appropriate name.

ME/CFS patients experience a wide variety of symptoms, including musculoskeletal pain, fatigue, impairments in short-term memory, sore throat, tender lymph nodes, sleep disturbances, headache, and post-exertional malaise. In general, rehabilitation of ME/CFS patients aims at reducing the level of fatigue and associated symptoms; to increase the level of activity; and to improve quality of life (Reid et al. 2000). Although the goals for rehabilitation

in people with ME/CFS seem to be straightforward, rehabilitation practice is not. Many experienced clinicians struggle to implement basic rehabilitation principles when treating people with ME/CFS. Therefore, the present manuscript aims at providing basic information required to apply rehabilitation to ME/CFS sufferers. Firstly, we will briefly discuss the diagnostic criteria for ME/CFS. In the second part of the manuscript, the reader is provided with a summary of the main characteristics of ME/CFS pathophysiology. We will focus on those issues that are of prime importance to rehabilitation in those with ME/CFS (e.g. malfunctioning of the body defense system, the exhausted stress response system as well as psychological issues). We will use our current understanding of the illness to provide guidelines for applying rehabilitation to those with ME/CFS. Treatment options like exercise therapy and activity (self-)management will be introduced in the context of ME/CFS. Finally, we will discuss the fact that rehabilitation should not be regarded as a cure for ME/CFS. Instead rehabilitation should replenish medical treatments and should aim at optimizing the circumstances for a successful medical treatment outcome.

Diagnosis of ME/CFS

ME/CFS is mainly a diagnosis of exclusion: fatigue cannot be explained by the presence of other evident medical or psychiatric illness. Hence, a thorough medical history, physical examination, mental status examination, and laboratory tests must be conducted to identify underlying or contributing conditions that require treatment. Diagnosis or classification cannot be made without such an evaluation (Fukuda et al. 1994). In addition, clinically evaluated, unexplained chronic fatigue can be classified as ME/CFS if the patient meets both the following criteria:

1. Clinically evaluated, unexplained persistent or relapsing chronic fatigue that is of new or definite onset (i.e., not lifelong), is not the result of ongoing exertion, is not substantially alleviated by rest, and results in substantial reduction in previous levels of occupational, educational, social, or personal activities.
2. The concurrent occurrence of four or more of the following symptoms: substantial impairment in short-term memory or concentration; sore throat; tender lymph nodes; muscle pain; multi-joint pain without swelling or redness; headaches of a new type, pattern, or severity; unrefreshing sleep; and post-exertional malaise lasting more than 24 hours. These symptoms must have persisted or recurred during 6 or more consecutive months of illness and must not have predated the fatigue.

The above criteria are those advocated by the Centre for Disease Control and Prevention. Over the years, many other sets of diagnostic criteria have been proposed, but none of them were able to replace the 1994 Fukuda et al. criteria. Up to now, these criteria represent the gold standard for diagnosing ME/CFS. The prevalence of ME/CFS in the Netherlands is estimated to be between 30 000 to 40 000 patients (Gezondheidsraad 2005). Incidence estimates of ME/CFS vary from 3 in 1000 (Klimas 1998) to 1% (Clauw and Chrousos 1997).

Understanding this underestimated disorder in order to define appropriate rehabilitation goals

Malfunctioning of the body defense system

Of all the biological systems studied in ME/CFS, the immune system and the hypothalamic-pituitary-adrenal (HPA) axis (explained in section 3.2) have generated the most promising

results. Many immune abnormalities have been identified in people with ME/CFS, but the majority of them were not characteristic of the illness. Rather, they were present in a subset of the ME/CFS population. For example, natural killer cells appear to be malfunctioning in a subset of people with ME/CFS. Natural killer cells serve as one of the primary defense mechanisms in the human body. Some patients with ME/CFS display decreased activity and/or number of natural killer cells (Siegel et al. 2006). In addition, evidence in support of intracellular immune abnormalities is cumulating (reviewed in Nijs & Frémont 2008). These intracellular immune abnormalities imply increased immune cell apoptosis ('programmed cell death') and decreased antiviral capacity of immune cells in people with ME/CFS. For comprehensive reviews of the scientific literature on the body defense system of people with ME/CFS, the reader is referred to Gerrity et al. (2004) and Natelson et al. (2002).

For rehabilitation purposes, it is important to realize that at least an important subgroup of people with ME/CFS display malfunctioning of their body defense system. Given the fact that physical activity and exercise is able to increase the competitiveness of our body defense system (Mackinnon 1999), rehabilitation specialists might view this as another reason for applying exercise therapy to people with ME/CFS. However, caution is required: ME/CFS patients respond to a (sub)maximal exercise challenge with acute changes in the body defense system (Sorensen et al. 2003, Whistler et al. 2005). Vigorous exercise, as well as inappropriate intensities of submaximal exercise, can result in increased oxidative stress and subsequent increased fatigue and musculoskeletal pain (post-exertional malaise) in people with ME/CFS (Figure 1) (Jammes et al. 2005). These are important observations that rehabilitation specialists need to keep in mind when designing and implementing exercise programs for ME/CFS sufferers.

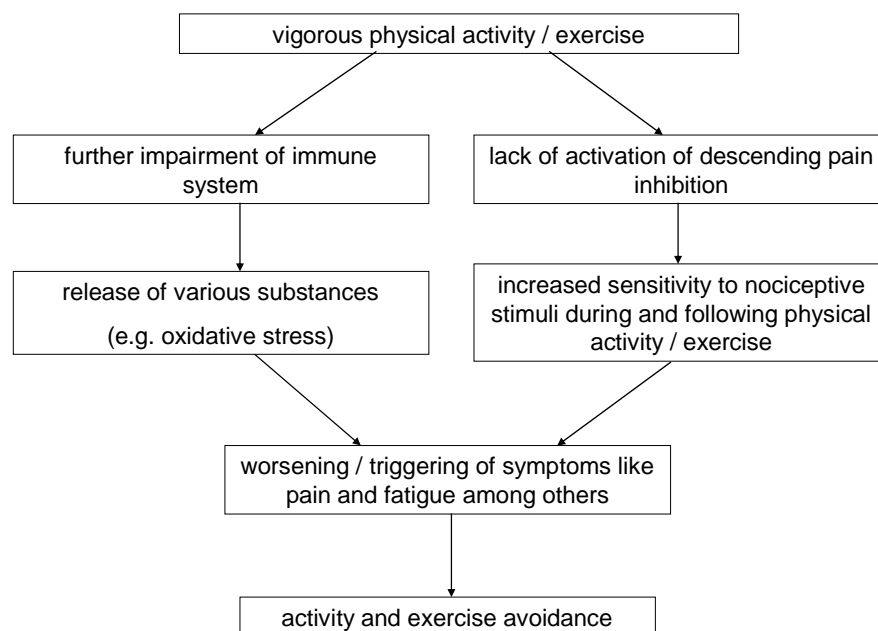


Figure 1: The physiology of post-exertional malaise in people with ME/CFS.

Exhausted stress response system

Everyday, people are exposed to a variety of psychological, emotional and physical stressors. The capacity of the human body to cope with these stressors is challenged by Western society. The human body has two major stress response systems: the sympathetic branch of the

autonomic nervous system for acute stress responses and the hypothalamus-pituitary-adrenal (HPA) axis for prolonged stress responses. There is increasing evidence for malfunctioning of both stress response systems in people with ME/CFS. Altered autonomic nervous system reactivity has been shown repeatedly in people with ME/CFS (De Becker et al. 1998, Winkler et al. 2004, Newton et al. 2007a, 2007b, 2009). Addressing the HPA-axis, people with ME/CFS produce insufficient cortisol in response to stressors (Cleare 2004, Van den Eede et al. 2007, Van Houdenhove et al. 2009). Recent data from gene studies support the presence of a blunted HPA-axis responsiveness and connects malfunctioning of the body defense system to neuroendocrine impairments (Fuite et al. 2008). This might imply a neurobiological 'switch' from hyper(re)activity to hypo(re)activity of the stress system, based on functional or even structural receptor changes, and followed by a cascade of disturbances in neurotransmitter functions, immunological and central pain processing mechanisms (Van Houdenhove & Egle 2004, Fries et al. 2005). Taken together, both major stress response systems appear to be exhausted as a consequence of chronic activation. Hence, rehabilitation specialists should aim at increasing the capacity of the body of people with ME/CFS to cope with everyday's stressors.

Hypersensitivity of the central nervous system

Chronic fatigue has been arbitrarily put forward as the primary symptom of ME/CFS. However, pain and fatigue are equally disabling to ME/CFS sufferers, and up to 75 % of ME/CFS patients experience chronic widespread pain (Nishikai et al. 2001). From a systematic literature review it was concluded that little is known about the nature or treatment of pain in patients with ME/CFS (Meeus et al. 2007). Since then, a number of studies have provided evidence in support of altered central pain processing at rest and during exercise (Meeus et al. 2008, Meeus 2008).

Central sensitization is defined as “an augmentation of responsiveness of central pain-signaling neurons to input from low-threshold mechanoreceptors” (Meyer et al. 1995). It implies that central pain processing pathways localized in the spinal cord and the brain sensitize. Central sensitization encompasses altered sensory processing in the brain (Staud et al. 2007), malfunctioning of descending pain inhibitory mechanisms (Meeus et al. 2008), increased activity of pain facilitatory pathways, temporal summation of second pain or wind-up (Staud et al. 2007, Meeus & Nijs 2007), and long-term potentiation of neuronal synapses in the anterior cingulate cortex (Zhuo 2007). Too vigorous exercise will further impair central pain processing and hence will aggravate central sensitization (Staud et al. 2005) (Figure 1). Comprehensive reviews on the pathophysiology of central sensitization are available (e.g. Vierck 2006, Yunus 2007, Nielsen & Henriksson 2007). The outcome of the processes involved in central sensitization is an increased responsiveness to a variety of stimuli including mechanical pressure, chemical substances, light, sound, cold, heat, electrical stimuli, etc. The process of central sensitization as typically seen in people with ME/CFS has important implications for applying exercise therapy and other conservative interventions to people with ME/CFS (see below).

Psychological issues

As explained above, too vigorous exercise or physical activity frequently triggers post-exertional malaise in people with ME/CFS. Hence, it seems natural for ME/CFS patients to develop fear of movement (Figure 1). Kinesiophobia, a specific kind of fear-avoidance behavior, is defined as “an excessive, irrational, and debilitating fear of physical movement and activity resulting from a feeling of vulnerability to painful injury or reinjury” (Kori et al. 1990). Kinesiophobia has been reported to be a common feature of patients with ME/CFS

(Nijs et al. 2004a & b, Silver et al. 2002), and evidence supportive of its clinical importance to ME/CFS patients has been provided (Nijs et al. 2004a, Silver et al. 2002). Others interpreted the lack of a difference in physical activity in anticipation of an exercise test, both on the day of and the day before the test, as a lack of ‘exercise phobia’ in ME/CFS patients without a comorbid psychiatric disorder (Gallagher et al. 2005). Still, from the available literature data it has been concluded that kinesiophobia has its place in ME/CFS psychopathology.

A body of literature describing the psychology of ME/CFS is available, making it difficult to summarize it for rehabilitation purposes. Psychological factors are known to perpetuate the illness and hence are crucial to all kinds of treatment approaches, including rehabilitation strategies. Catastrophic thoughts, hypervigilance, acceptance (Van Damme et al. 2006), somatization (Johnson et al. 1996), a poor sense of control over symptoms, maladaptive illness perceptions, and social processes can all have a negative impact on rehabilitation in those with ME/CFS. Catastrophic thoughts concern interpretations of pain in terms of relevance and potential danger. In ME/CFS, pain catastrophizing is strongly related to physiological variables of exercise performance (Nijs et al. 2008b). Those patients catastrophizing the consequences of pain, showed the lowest exercise capacity. Hypervigilance refers to a strong focus on bodily sensations and is likely to imply a strong focus on post-exertional symptoms. Not all patients with ME/CFS accept the fact that they are seriously ill and need to change their lifestyle accordingly, suggesting that these patients are unlikely to comply with rehabilitation programs unless acceptance is thoroughly addressed in the first stage of the program.

In the next section, we will use our current understanding of ME/CFS for providing guidelines for designing a comprehensive rehabilitation program.

Rehabilitation content

Education

Firstly, it should be made clear to all people with ME/CFS entering a rehabilitation program that ME/CFS is a serious illness that cannot be cured by conservative strategies (see below: 5. Discussion). Secondly, clinicians applying rehabilitation strategies to people with ME/CFS should be aware of the variety of potential obstacles for a successful rehabilitation outcome. Understanding of this underestimated disorder is required to detect the obstacles during the initial assessment of the patient. For example, initiating the rehabilitation program with exercise therapy is unlikely to be beneficial in case of over-exertion during daily activities and a consequent fluctuating health status. Likewise, those patients presenting with inappropriate illness beliefs, catastrophic thoughts, or the inability to accept the fact that they are seriously ill, will most likely not adhere to rehabilitation programs *unless* these issues are addressed during the initial treatment phase. That is why education is so important at the initial treatment stage.

The content and focus of the education can be diverse and should be client-centered. Intensive education about the neurophysiology of chronic widespread pain is beneficial to those patients with ME/CFS having chronic widespread pain and central sensitization, and is able to improve catastrophic thoughts and coping strategies (Meeus 2008). Other patients with ME/CFS consult a rehabilitation specialist for initiating a graded exercise program, but at the same time they over-exert during daily activities and report a highly fluctuating health status. These type of patients require in-depth education about the nature of post-exertional malaise in ME/CFS (Figure 1). The latter type of education is a prerequisite for teaching pacing self-

management strategies. Others require insight into the perpetuating factors of their illness. Examples of perpetuating factors are an inability to cope with everyday stressors or fear of movement in relation to an inactive lifestyle. Intense education and in-depth discussion about these issues in a one-on-one session is required to motivate the client to actively participate in all aspects of the rehabilitation program.

In general, the first stage of rehabilitation for people with ME/CFS consists of a set of individually-tailored strategies aiming at stabilizing the client's health status (Figure 2). In case of successful completion of stage 1, the patient can enter the grading phase, consisting of either graded activity or graded exercise therapy (or a combination of both strategies).

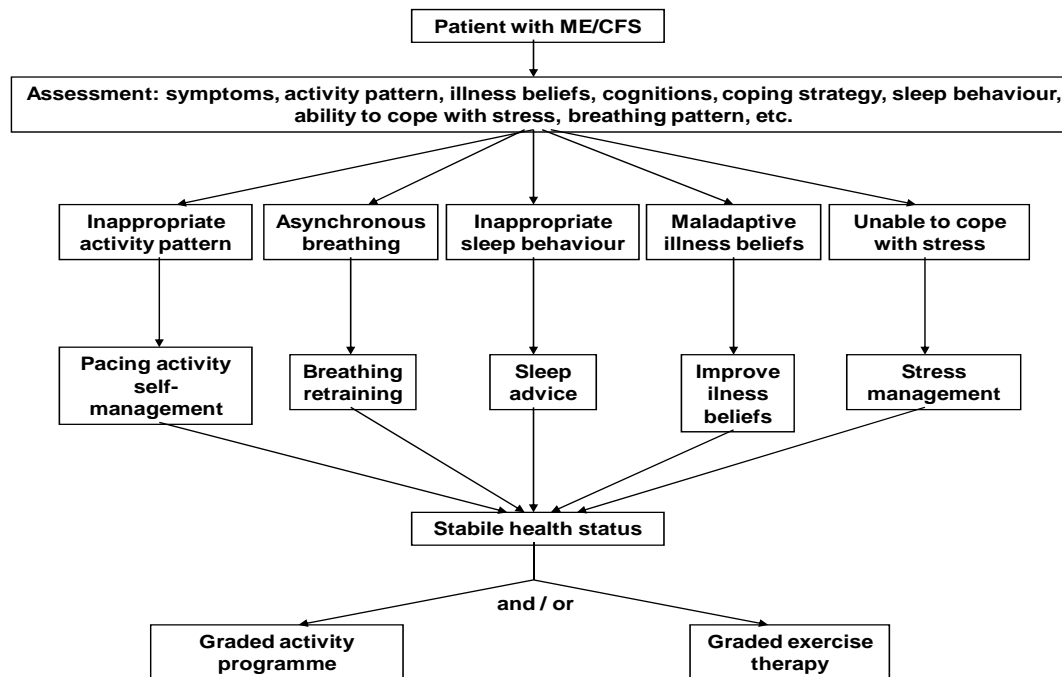


Figure 2: Clinical reasoning process in people with ME/CFS.

Stress management

Given the exhausted stress response system in people with ME/CFS (explained above), it seems warranted to try to increase the ability of the patient to cope with everyday's stressors. Rehabilitation can offer a variety of stress management techniques (e.g. deep breathing, guided imagery or visualization, progressive muscle relaxation, meditation, etc.) to patients with ME/CFS. The rehabilitation specialist can teach the patient to apply stress management techniques. Biofeedback is often helpful. The patient should be able to apply the stress management technique(s) in anticipation of, during, or in the aftermath of a stressful situation effectively. Although we are unaware of evidence in support of stress management techniques as a sole treatment for ME/CFS, it is generally included in comprehensive rehabilitation programs and cognitive behavior therapy programs (see below 4.6).

Breathing retraining targeting hyperventilation

People with ME/CFS often complain of hyperventilation and shortness of breath during exercise. Scientific research addressing the respiratory system in ME/CFS patients has revealed a high prevalence of rhinitis symptoms (Baraniuk et al. 1998), decreased lung function (De Lorenzo et al. 1996), bronchial hyperresponsiveness (Nijs et al. 2003), respiratory infections (Auger et al. 1994), a decreased peak oxygen uptake during exercise

performance testing (De Becker et al. 2000), and an increased prevalence of hyperventilation (59%) compared to healthy controls (22%) (Bazelmans et al. 1997). Hyperventilation is not a causal factor for ME/CFS, but is likely to be a perpetuating factor for some patients, especially those having difficulties with acceptance (Bogaerts et al. 2007).

A proper action of respiratory muscles, including the diaphragm, and consequent synchronous breathing motion is considered essential for optimal ventilation (Cahalin et al. 2002). An asynchronous breathing motion, characterized by a diminished or paradoxical action of the diaphragm, is frequently seen in cases with ME/CFS (McCully et al. 1996, Sisto 1995) and might account for the hyperventilation, decreased lung function, shortness of breath during exercise, delayed recovery from exercise and increased symptoms following exercise as typically seen in these patients.

In a study of 20 patients with ME/CFS, 5 patients (25%) presented with an asynchronous breathing pattern (Nijs et al. 2008b). In comparison to no treatment, one 30' session of breathing retraining resulted in an acute (immediately post-intervention) decrease in respiratory rate ($p < 0.001$) and an increase in tidal volume ($p < 0.001$) (Nijs et al. 2008b). In addition to aiming at improved breathing and lung function, breathing retraining may be useful in diminishing symptoms of hyperventilation, or can take part of a stress management program (diverting the focus away from the stressor to the breathing pattern as a relaxation technique – see above 4.2). Further study is required to examine whether breathing retraining has its place in a comprehensive rehabilitation program for people with ME/CFS.

Activity (self-)management: pacing or graded activity or both?

Activity self-management for people with ME/CFS involves encouraging the patients to pace their activities and respect their physical and mental limitations (Shephard 2001, Paradaens et al. 2006). This self-management strategy has been termed 'pacing' and involves encouraging the patient to achieve an appropriate balance between activity and rest in order to avoid exacerbating symptoms (Nijs et al. 2008a). Pacing self-management requires the patient to set realistic activity/exercise goals on a daily basis (Shephard 2001) and to regularly monitor and manipulated exercise/activity in terms of intensity, duration and rest periods in order to avoid possible over-exertion, which can result in worsening symptoms. Pacing takes into account the considerable fluctuations in symptom severity (Shephard 2001) and delayed recovery from exercise (Paul et al. 1999) that typically occurs in patients with ME/CFS. In addition, it accounts for the process of central sensitization. Pacing self-management techniques encourage a behavioral change and at the same time acknowledge the physical aspects of the illness. Practical guidelines for the use of pacing self-management within a comprehensive rehabilitation program for people with ME/CFS are presented elsewhere (Nijs et al. 2008a).

Although a firm theoretical rationale for the use of pacing self-management is available (Nijs et al. 2008a), the scientific evidence is scarce. One uncontrolled study reported positive outcome from 3 one-on-one sessions of pacing self-management (Nijs et al. 2009), and another study reported that those people with ME/CFS who are able to stay within their 'energy envelope' show significant improvements (Jason et al. 2009).

Pacing self-management aims at stabilizing the patient's health status. After the initial stabilization phase, a grading phase is initiated and comprises of graded activity or graded exercise therapy (figure 1). During the grading phase, the same pacing principles are applied to grade both daily activities as well as exercise levels. When determining an appropriate

exercise level, a formal, regulated exercise regime that is gentle, graded, flexible and manageable according to each individual's capabilities is required. Support for this type of 'grading' for people with ME/CFS comes from an observational study (Coutts et al. 2001) and a well-designed randomized controlled clinical trial, which reported that paced and individually-tailored graded exercise was superior to relaxation and flexibility training in patients with ME/CFS (Wallman et al. 2004). The use of graded exercise therapy for people with ME/CFS will be further discussed below (section 4.5).

Applying exercise therapy: careful with post-exertional malaise

Benefits associated with graded exercise were first demonstrated in a 12-week randomized, controlled trial by Fulcher and White (1997) that compared the efficacy of graded exercise to flexibility exercises in ME/CFS participants. Since then, a number of studies have examined the effectiveness of graded exercise therapy for ME/CFS (e.g. Weardon et al. 1998, Powell et al. 2001). According to the Cochrane Library, graded exercise therapy is effective in the short term for treating ME/CFS patients (Edmonds et al. 2004). However, it should be acknowledged that graded exercise therapy is not suitable per se for *all* people with ME/CFS *at any stage* of their illness. Rather, graded exercise therapy can be one component of an overall rehabilitation approach to ME/CFS.

The majority of exercise therapy trials in people with ME/CFS used a time-contingent approach. Although the outcomes from those studies were positive, a time-contingent approach somewhat contradicts our current understanding of post-exertional malaise as typically experienced by people with ME/CFS (Figure 1). Introduction of exercise that is beyond a participant's capacity may not only promote a relapse, but can also result in feelings of demoralization and pain, thus reinforcing avoidance behavior (Figure 1). Therefore, Wallman et al. (2004) introduced the pacing approach into graded exercise therapy for people with ME/CFS. They designed a graded exercise program that is flexible, realistic and manageable according to each individual's needs and abilities. The program schedules rest periods in conjunction with the exercise periods, as this can help in establishing a manageable routine that can assist in promoting a sense of control over one's life (Pheby 1997, Sharpe et al. 1997). Contrary to the time-contingent approach to exercise as typically is advocated in cognitive behaviorally-guided exercise therapy, Wallman and colleagues (2004) showed that a symptom-contingent approach to graded exercise therapy can be equally effective to people with ME/CFS. Detailed guidelines for the application of this type of flexible graded exercise therapy in people with ME/CFS are presented elsewhere (Wallman et al. 2005).

Cognitive behavioral therapy

Apart from graded exercise therapy, another type of conservative treatment has proven its benefits for people with ME/CFS: cognitive behavioral therapy is effective in the short term for reducing fatigue and improving functioning in ME/CFS patients (Price et al. 2008, Prins et al. 2001). Even full recovery has been reported in some cases (Knoop et al. 2007). Cognitive behavioral therapy focuses on a variety of perpetuating factors (e.g. illness perceptions, coping, acceptance, etc.) rather than searching for etiological factors. By doing so, cognitive behavioral therapists aim at increasing and optimizing patients' functioning. Cognitive behavioral programs for people with ME/CFS combine a variety of treatment options, some of which are explained above (e.g. education, time-contingent activity management, time-contingent graded exercise therapy, stress management, sleep advice, goal setting, etc.).

Discussion: Rehabilitation is not a cure for ME/CFS

When explaining to people with ME/CFS that rehabilitation is not a cure for ME/CFS, it should be explained that conservative strategies will address perpetuating factors of ME/CFS, and hence lead to increased functioning rather than full recovery. Rehabilitation cannot replace medical treatments targeting the biology (and in some cases the co-morbid psychiatry) of the illness. Rather, rehabilitation should replenish medical treatments and should aim at optimizing the circumstances for a successful medical treatment outcome. However, contrary to the increasing body of evidence in support of rehabilitation strategies for people with ME/CFS, little progress has been made regarding medical treatments for people with ME/CFS. At current, not a single pharmacological strategy has proven to be beneficial to people with ME/CFS.

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