

## Management of Chronic Fatigue in Primary Care

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### Abstract

**Introduction:** Chronic fatigue syndrome (CFS) is considered to be one of the widespread problems around the world. It is approximated that more than two million American patients have Chronic fatigue syndrome, of which many have not been even diagnosed.

**Aim of Work:** In this review, we will discuss the most recent evidence regarding chronic fatigue syndrome.

**Methodology:** We did a systematic search for management of chronic fatigue syndrome using PubMed search engine and Google Scholar search engine. All relevant studies were retrieved and discussed. We only included full articles.

**Conclusions:** Chronic fatigue syndrome is generally characterized by the presence of debilitating fatigue that is usually not relieved following rest and is linked to the presence of physical clinical manifestations. The Centers for Disease Control and Prevention criteria for chronic fatigue syndrome include the presence of severe fatigue lasting longer than 6 months, as well as the presence of at least 4 of the following physical clinical manifestations: post-exertional malaise; unrefreshing sleep; impaired memory or concentration; muscle pain; polyarthralgia; sore throat; tender lymph nodes; or new headaches.

**Keywords:** Chronic Fatigue Syndrome; Management; Fatigue Self-Management; Unexplained Chronic Fatigue; Chronic Fatigue Syndrome; Cognitive Behavior Therapy; Primary Care; Nurse-Delivered Intervention

### Introduction

Chronic fatigue syndrome (CFS) is considered to be one of the widespread problems around the world. It is approximated that more than two million American patients have Chronic fatigue syndrome, of which many have not been even diagnosed [1]. Generally, females are two times more likely than males to develop Chronic fatigue syndrome [1] and it is more frequent in individuals who are older than forty years [1,2]. Until now, there is not any detected racial or educational predisposition [2].

Chronic fatigue syndrome is usually mentally and emotionally exhausting, and individuals with a diagnosis of Chronic fatigue syndrome are two times less likely to be employed as individuals with fatigue who do not meet formal criteria for Chronic fatigue syndrome [3]. In the year 2002, the approximated yearly cost of lost productivity was more than nine billion dollars in the US alone [4]. Moreover, individuals with Chronic fatigue syndrome are significantly more likely to demonstrate subjective functional impairment when compared to those without chronic fatigue.

In this review, we will discuss the most recent evidence regarding chronic fatigue syndrome.

### Methodology

We did a systematic search for management of chronic fatigue syndrome using PubMed search engine (<http://www.ncbi.nlm.nih.gov/>) and Google Scholar search engine (<https://scholar.google.com>). All relevant studies were retrieved and discussed. We only included full articles.

The terms used in the search were: chronic fatigue syndrome, management, Fatigue self-management; unexplained chronic fatigue; chronic fatigue syndrome; cognitive behavior therapy; primary care; nurse-delivered intervention.

### Diagnosis

Chronic fatigue syndrome is considered to be a clinical diagnosis that could be only made when other possible etiologies and causes of chronic fatigue have all been ruled out. Specific diagnostic criteria to be used for Chronic fatigue syndrome were introduced by the Centers for Disease Control and Prevention in the year 1988. At which, it was hypothesized that viral organisms were the main cause of developing Chronic fatigue syndrome; thus, the criteria focused mainly on the presence of physical clinical manifestations. To parallel the World Health Organization's classification of Chronic fatigue syndrome as a neurological medical condition, the Oxford criteria were later developed in the year 1991. These Oxford criteria focuses on mental fatigue more than putting focus on physical clinical manifestations. The CDC's criteria were later reviewed in the year 1994 to widen the definition of Chronic fatigue syndrome, and currently, are the most commonly used diagnostic criteria for the diagnosis of Chronic fatigue syndrome [4].

The generally applied approach to deal with an individual with suspected Chronic fatigue syndrome must start with taking a proper medical history and perform a complete physical examination, with putting emphasis on detecting the most annoying clinical manifestations along with the presence of any red flag clinical manifestations which might suggest the presence of a more serious underlying etiology according to the National Institute for Health and Clinical Excellence (NICE) guidelines [5]. Patients with suspected Chronic fatigue syndrome should also have a thorough mental status assessment, that includes complete assessment for the presence of depression, which is estimated to be present in up to forty-seven percent of patients with Chronic fatigue syndrome [3]. Despite that the differential diagnosis for individuals who present with signs and symptoms chronic fatigue is wide, it is estimated that about thirty percent of them will be found to meet the criteria for diagnose Chronic fatigue syndrome [3]. No laboratory investigations could be used to diagnose Chronic fatigue syndrome; but on the other hand, they are still usually done to exclude the presence of other etiologies that can explain the fatigue and would preclude confirming the diagnosis of Chronic fatigue syndrome. The CDC and NICE advise performing at least a minimal set of laboratory investigations for any individual who is presenting with signs and symptoms of chronic fatigue [5].

The CDC have recommended performing an initial assessment of patients who present with symptoms of chronic fatigue with the following laboratory investigations: urinalysis; full blood count; complete metabolic panel; and measurement of phosphorus concentrations, thyroid-stimulating hormone concentrations, and C-RP concentrations. Similarly, NICE guidelines have also recommended the use of immunoglobulin A endomysial antibodies concentrations to screen for the presence of celiac disease, and if indicated by past history or complete physical examination, urine screening for drugs, testing of rheumatoid factor, and testing for antinuclear antibody concentrations [5]. Viral titers are generally not recommended to be performed routinely except for cases where the patient's medical history is indicative of the presence of an infectious process, as viral titers usually fail to confirm the diagnosis of chronic fatigue syndrome or rule it out.

### Etiology

The real underlying cause of Chronic fatigue syndrome is still unclear and is more likely to be a complex one. It still remains an area of debate as to whether there is a single responsible etiology for Chronic fatigue syndrome; there actually might be several poorly understood subgroups of the condition, or there might be several predisposing factors that could interact with each another to produce Chronic fatigue syndrome. These complex predisposing factors, along with the presence of numerous psychiatric comorbidities of Chronic fatigue syndrome, have resulted in some researchers questioning whether any organic cause exists at all in the etiology of Chronic fatigue syndrome. Current research that is performed on Chronic fatigue syndrome focuses mainly on auto-immune etiologies and the adrenal systems, along with genetics, the biopsychosocial model, sleep patterns and nutritional factors.

### Immune system

As many clinical manifestations of viral infections and Chronic fatigue syndrome can significantly overlap, some clinicians have hypothesized that Chronic fatigue syndrome may have a post-infectious cause. One common hypothesis is that Chronic fatigue syndrome can be caused by a chronic infection with Epstein-Barr virus; on the other hand, there is not solid evidence that proves any correlation between specific viruses and Chronic fatigue syndrome.

### Genetics

More solid evidence has been pointing to areas of genetic predisposition in individuals who have Chronic fatigue syndrome. A previous study has demonstrated the presence of a variation in the expression of certain genes in patients who have Chronic fatigue syndrome following exercise that play an important role in the metabolism and immune system responses [6]. Another published study has demonstrated the presence of a correlation between specific genetic mutations, Chronic fatigue syndrome, and certain viral infections that have been associated with Chronic fatigue syndrome [7].

### Biopsychosocial model

Chronic fatigue syndrome is usually linked to depression, the fact that has led many clinicians to hypothesize that Chronic fatigue syndrome is a purely somatic medical condition. Evidence that supports this conclusion is absent, however. Solid evidence proposed that the presence of a history of a childhood trauma can significantly elevate the risk of developing Chronic fatigue syndrome by as high as six folds. Some individuals might assume that a past history of childhood trauma can reduce resiliency levels, but there is evidence that suggests that it might also actually play an organic factor by leading to an increase in the risk of adrenal glands dysfunctions [8]. It is essential to keep in mind that the social support systems for individuals with Chronic fatigue syndrome tend to be less reliable than for those who are healthier [9]. Management of Chronic fatigue syndrome is usually less likely to be successful in individuals who have poor social adjustment [10].

### Adrenal system

Hypo-cortisolism state has been noticed in individuals with Chronic fatigue syndrome; a previous study concluded that cortisol concentrations in patients who have Chronic fatigue syndrome were about five mcg per dL (137.94 nmol per L) lower than the concentrations

in individuals who do not have Chronic fatigue syndrome [11]. This is likely to be secondary to dysfunctional adrenal cortex responsiveness to adrenocorticotrophic hormones and not due to hypothalamo-pituitary impairments [12]. It is still unclear, however, if these dysfunctions are caused by the underlying presence of an infection, genetic predisposition, past history of childhood trauma, other unknown factors, or some combination of all of these together.

### Sleep and nutrition

There is a significant correlation between delayed dim light melatonin onset and Chronic fatigue syndrome, indicating that delayed circadian rhythm may have a contribution to Chronic fatigue syndrome [13]. Despite that melatonin is available as an over the counter medication to be used for delayed dim light melatonin onset in the US, there is no solid evidence that there is real improvement in patients with Chronic fatigue syndrome with melatonin [14].

One study has demonstrated that individuals who have Chronic fatigue syndrome show lower ratios of omega-3 to omega-6 unsaturated fatty acids and lower zinc concentrations when compared to healthy individuals [15]. On the other hand, studies of the use of nutritional supplementation in individuals who have Chronic fatigue syndrome have failed to demonstrate any benefits [16].

### Treatment

Family clinicians must emphasize initially on the management of clinical manifestations that are usual comorbidities associated with Chronic fatigue syndrome. These include the presence of sleep disturbances, depression, and pain. Any comorbidities which are detected must be sufficiently treated [5]. Patients with Chronic fatigue must be encouraged to have rest periods and relax as necessary, and to practice the application of different relaxation techniques. Although there is no solid evidence proving that these relaxation modalities are actually effective, they are not likely to be harmful and might help indeed [5].

There is significant evidence for two treatment modalities for Chronic fatigue syndrome. These are cognitive behavior therapy and graded exercise treatment. There is less solid evidence regarding the benefits of pharmacological treatment for Chronic fatigue syndrome in patients who do not manifest with comorbid depression or anxiety disorders.

### Cognitive behavior therapy

Trained psychotherapists who provide cognitive behavior therapy focus on the role of thinking and its influence on how individuals act and feel. They could aid individuals with Chronic fatigue syndrome recognize how their fears of activity result in behaviors that could potentially lead them to feel worse, more fatigued, and disabled. In fact, a large randomized controlled trial in adults with Chronic fatigue syndrome confirmed that cognitive behavioral therapy can have positive effects on fatigue, work and social adjustment, depression, anxiety, and post-exertional malaise. Most subjects in this study considered themselves as “much” or “very much” improved following finishing the study [17].

A Cochrane systematic review that was published in 2008 also supported the use of cognitive behavioral therapy in patients who have Chronic fatigue syndrome [18]. Multiple other studies have demonstrated similar outcomes [19], including in adolescents with Chronic fatigue syndrome [20]. In addition, a previous study concluded less absences from school and better improvements in fatigue levels and overall physical activities among adolescents who were being treated with Internet-based cognitive behavioral therapy [21]. Cognitive behavioral therapy has been well studied in group settings [22] and in the form of self-guided tutoring [23], with debatable efficacy. As a result of this, it is advised that cognitive behavioral therapy be individualized on a case basis to maximize potential benefits [5]. Disadvantages of cognitive behavioral therapy include the continuous need for experts' consultations, considerations of time, and potentially high costs. There is not enough data to propose that cognitive behavioral therapy provided by trained family clinicians is worse or better than cognitive behavioral therapy provided by expert psychotherapists.

### Exercise

Graded exercise treatment involves the use of a program that includes a steady increase in levels of physical activity hoping of increasing physical functions. A previous randomized trial demonstrated that graded exercise treatment can be as effective as cognitive behavioral therapy for the treatment of chronic fatigue and the other aspects of functional impairments that were mentioned previously, except for depression [17]. Subjects who participated in this study were educated to increase gradually the duration of their physical exercise over the course of fifty-two weeks to reach a final target of thirty minutes of mild exercising for at least five days every week, taking into consideration not to exceed the target heart rate to prevent cases of over-exertion. Most patients with chronic fatigue syndrome preferred to walk as a physical exercise. Once this target was reached, patients worked with their supervising expert physio-therapists every month to elevate aerobic exercise intensity.

Multiple other studies have concluded consistent outcomes [24]. There is some evidence that the benefits of graded exercise treatment are not significantly associated with increased physical exercise capacity, recommending that the efficacy of graded exercise treatment, like cognitive behavioral therapy, have more to do with reducing manifestations-focusing behavior in persons with chronic fatigue syndrome [25]. Impediments to graded exercise treatment include considerations of time and concerns for patients whose exercise will worsen their conditions.

### Other nonpharmacologic treatments

A previous study has demonstrated that an educational intervention that is known as pragmatic rehabilitation provided by specially trained nurses improves fatigue in individuals who have chronic fatigue syndrome; on the other hand, these improvements did not continue for longer than seventy weeks. The interventions included education about chronic fatigue syndrome, that was followed by a negotiated therapeutic plan of gradually increasing physical activity [26]. Despite that pragmatic rehabilitation is appealing as it prevents the requirement for experts' consultations, more solid evidence is still required before determining its potential efficacy.

Despite showing positive results with cognitive behavioral therapy and graded exercise treatment, these effects are often moderate and rarely cause complete resolution of chronic fatigue syndrome. Patients who show signs of poor social adjustment, a strong belief in the presence of an organic etiology for their fatigue, or any sort of sickness benefit (like the presence of financial incentive) tend to have worse responses to treatments [27]. In contrast to many other medical and psychological conditions, being member in a chronic fatigue syndrome support group was linked to significantly worse outcomes [27].

Other potential therapies that did not improve chronic fatigue syndrome clinical manifestations in clinical trials include homeo-pathic therapies and multivitamins [28].

### Pharmacologic therapy

Several pharmacologic agents for use in patients with chronic fatigue syndrome have shown disappointing results when tested clinical trials, with relatively weak effects of questionable clinical significance or no evidence of efficacy at all. There is no solid evidence to support the use of antiviral pharmacological agents, hydrocortisone drugs, or fludrocortisone; only small or poorly designed trials exist [29].

A previous study demonstrated some clinical improvements in patients with chronic fatigue syndrome following treatment with staphylococcus toxoid; the authors hypothesized that provided treatment stimulated the hypoactive immune systems of individuals with chronic fatigue syndrome and later led to improvements in their fatigue. On the other hand, the treatment required to be continued to avoid relapse of clinical manifestations. Staphylococcus toxoid is not generally available and could not now be administered as a routine therapy for patients who suffer from chronic fatigue syndrome [30].

Other possible treatment modalities that did not lead to improvements in patients who have chronic fatigue syndrome clinical manifestations in clinical trials include methylphenidate [31], melatonin, citalopram [32] and galantamine [33]. More research is still required to clarify the cause of chronic fatigue syndrome to better target potential treatment modalities.

## Conclusions

Chronic fatigue syndrome is generally characterized by the presence of debilitating fatigue that is usually not relieved following rest and is linked to the presence of physical clinical manifestations. The Centers for Disease Control and Prevention criteria for chronic fatigue syndrome include the presence of severe fatigue lasting longer than 6 months, as well as the presence of at least 4 of the following physical clinical manifestations: post-exertional malaise; unrefreshing sleep; impaired memory or concentration; muscle pain; polyarthralgia; sore throat; tender lymph nodes; or new headaches. Chronic fatigue syndrome is considered to be a clinical diagnosis that could be only made when other potential diagnoses have been already excluded. The etiology of chronic fatigue syndrome is still unclear, and is likely to be complex, and might involve dysfunction of the immune or adrenal systems, a correlation with certain genetic markers, or a history of childhood trauma. Individuals who have with chronic fatigue syndrome must be assessed for concurrent depression, pain, and sleep disturbances. Treatment modalities include the application of cognitive behavior therapy and graded exercise treatment, both of which have been demonstrated to moderately improve fatigue levels, work and social adjustment, anxiety, and post-exertional malaise. No pharmacologic agents or alternative medicine therapies have been proven to be effective.

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