A Systematic Review of Chronic Fatigue Syndrome: Don't Assume It's Depression

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Objective: Chronic fatigue syndrome (CFS) is characterized by profound, debilitating fatigue and a combination of several other symptoms resulting in substantial reduction in occupational, personal, social, and educational status. CFS is often misdiagnosed as depression. The objective of this study was to evaluate and discuss different etiologies, approaches, and management strategies of CFS and to present ways to differentiate it from the fatigue symptom of depression.

Data Sources: A MEDLINE search was conducted to identify existing information about CFS and depression using the headings *chronic fatigue syndrome* AND *depression*. The alternative terms *major depressive disorder* and *mood disorder* were also searched in conjunction with the term *chronic fatigue syndrome*. Additionally, MEDLINE was searched using the term *chronic fatigue*. All searches were limited to articles published within the last 10 years, in English. A total of 302 articles were identified by these searches. Also, the term *chronic fatigue syndrome* was searched by itself. This search was limited to articles published within the last 5 years, in English, and resulted in an additional 460 articles. Additional publications were identified by manually searching the reference lists of the articles from both searches.

Study Selection and Data Extraction: CFS definitions, etiologies, differential diagnoses (especially depression) and management strategies were extracted, reviewed, and summarized to meet the objectives of this article.

Data Synthesis: CFS is underdiagnosed in more than 80% of the people who have it; at the same time, it is often misdiagnosed as depression. Genetic, immunologic, infectious, metabolic, and neurologic etiologies were suggested to explain CFS. A biopsychosocial model was suggested for evaluating, managing, and differentiating CFS from depression.

Conclusions: Evaluating and managing chronic fatigue is a challenging situation for physicians, as it is a challenging and difficult condition for patients. A biopsychosocial approach in the evaluation and management is recommended. More studies about CFS manifestations, evaluation, and management are needed.

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"She is depressed," her physician wrote when referring Ms. A, a 65-year-old married woman, for a psychiatric consult. "She has been feeling tired for more than a year and described being exhausted most of the time, with headaches, joint pain, and problems with her concentration and memory. Her fatigue is frustrating for her and for her family; she cannot function well even in the morning. She denied being depressed, and does not have any previous mental or medical illnesses. Every lab I checked was normal. I still think that she is hiding her depression and manifesting it with all these somatic complaints."

Prolonged fatigue is defined as self-reported, persistent fatigue of 1 month or longer.[1] Chronic fatigue syndrome (previously known as myalgic encephalomyelitis[2] or neurasthenia[3]) is characterized by profound, debilitating fatigue and a combination of symptoms resulting in substantial reduction in occupational, personal, social, and educational status[1,2,4–7] (see Table 1). Diagnosis of the chronic fatigue syndrome (CFS) can be made only after alternate medical and psychiatric causes of chronic fatiguing illness have been excluded.

At least 1 million Americans have CFS,[1,8] more than have lung cancer or multiple sclerosis; yet more than 80% go undiagnosed. In the primary care setting, the prevalence of CFS ranges from 3% to 20% and from 80% to 90% at the end of life.[9,10] There are no ethnic or racial differences. Previous reports have mentioned a female:male ratio of 1.3:1,[6] but a recent report by the U.S. Centers for Disease Control and Prevention (CDC) showed a female:male ratio of 4:1. It occurs most often in the 40- to 59-year age group and in the geriatric population.[1,9,10]

Although the concept of neurasthenia was introduced in 1869 by George Miller Beard,[3] CFS was defined in 1988 by the CDC, and while more than 3000 research studies have been done in this field, there is still some debate about the existence of this syndrome.[1,11,12] The

Table 1. Chronic Fatigue Syndrome Criteria[a]

1. Unexplained, persistent fatigue that is not due to ongoing exertion, is not substantially relieved by rest, is of new onset (not lifelong), and results in a significant reduction in previous levels of activity

AND

2. Four or more of the following symptoms are present for 6 months or more:
   - Impaired memory or concentration
   - Postexertional malaise (extreme, prolonged exhaustion and exacerbation of symptoms following physical or mental exertion)
   - Unrefreshing sleep
   - Muscle pain
   - Multijoint pain without swelling or redness
   - Headaches of a new type or severity
   - Sore throat that's frequent or recurring
   - Tender cervical or axillary lymph nodes

[a]From the Centers for Disease Control and Prevention.[1]

uncertainty about its existence and the lack of a specific laboratory test or marker to identify it, associated with hesitancy about making a diagnosis without knowing exactly how to treat it, all act as barriers to the diagnosis and treatment of CFS by primary care practitioners and psychiatrists.

Unlike the uncertainty about its existence, there is strong certainty about the impact of CFS. CFS patients, by definition, are functionally impaired and as disabled as patients with multiple sclerosis, heart disease, end-stage renal disease, and similar chronic conditions. The annual economic impact of CFS in the United States is estimated to be $9.1 billion in lost productivity.[1]

DATA SOURCES

A MEDLINE search was conducted to identify existing information about CFS and depression using the headings *chronic fatigue syndrome* AND *depression*. The alternative terms *major depressive disorder* and *mood disorder* were also searched in conjunction with the term *chronic fatigue syndrome*. Additionally, MEDLINE was searched using the term *chronic fatigue*. All searches were limited to articles published within the last 10 years, in English. A total of 302 articles were identified by these searches. Also, the term *chronic fatigue syndrome* was searched by itself. This search was limited to articles published within the last 5 years, in English, and resulted in an additional 460 articles. Additional publications were identified by manually searching the reference lists of the articles from both searches.

FATIGUE ETIOLOGIES

CFS cannot be considered either physical or psychological but instead requires a biopsychosocial approach to the illness. Numerous studies have tried to pinpoint specific etiologies by considering the following fields.

Genetic Etiologies

CFS is sometimes seen in members of the same family,[13,14] but there is no evidence that it is contagious; instead, there may be a familial predisposition or a genetic link. The concordance rate was higher in monozygotic than in dizygotic female twins for chronic fatigue.[15] Hickie et al.[16] evaluated genetic and environmental determinants of prolonged fatigue in a twin study and found 44% (95% CI = 25% to 60%) of the genetic variance for fatigue was not shared by the other forms of psychological distress, and also found that environmental factors made negligible contributions to fatigue. On the other hand, Cho et al.[17] found evidence of a partly genetic influence, but environmental effects continued to be predominant. Clearly, further research is needed to explore these possible relationships.

Immunologic Etiologies

Abnormal natural killer cell cytotoxicity,[18] increase immune activation markers,[19] greater numbers of $CD16^+/CD3^-$ natural killer cells,[20] and the presence of interferon in serum and cerebrospinal fluid in CFS patients[21] have been identified. Staines[22] suggested the loss of immunologic tolerance to vasoactive neuropeptides or their receptors following infection, other events, or de novo as a mechanism.

Infectious Etiologies

Possible infectious etiologies have generated the most interest among CFS researchers. It has been postulated that chronic fatigue is a continuum ranging from cases with chronic viremia on the one hand to instances of frank psychiatric illness on the other.[23] Multiple infectious agents have been linked to CFS, including Borna disease virus,[24,25] parvovirus B19,[26,27] glandular fever,[28] Enterovirus,[29] human herpesviruses 4, 6, and 7,[30–32] infectious mononucleosis,[33] Nipah virus encephalitis,[34] and Q fever.[35]

Infections have not only played important etiologic roles, but also have been considered predictors of better prognoses when compared to noninfectious CFS cases.[36] Human herpesvirus 6 reactivation has been suggested as an objective biomarker for fatigue.[30]

Endocrinology/Metabolism Etiologies

Hypothalamic-pituitary-adrenal (HPA) axis abnormalities have been studied as potential biological tests to diagnose CFS. Studies have shown HPA hypoactivity and higher chronic adrenocorticotropic hormone (ACTH) autoantibody levels as significant pathologic factors in CFS.[37–39] Also reduced area under the ACTH response curve in CFS patients undergoing insulin tolerance test was significantly associated with the duration of CFS symptoms ($r = –0.592$, $p = .005$) and the severity of fatigue symptomatology.[40] Other studies have suggested

upregulation of hypothalamic 5-hydroxytryptamine receptors in patients with postviral fatigue syndrome but not in those with primary depression.[41] However, another study showed no etiologic role for deficiency in central opioids or the HPA axis in the symptoms of CFS.[42] Other biological factors have been investigated and considered as biological markers in CFS, including low magnesium level,[43] low arachidonic acid level, low L-carnitine level,[25] serum dehydroepiandrosterone (DHEA) sulfate deficiency,[44] and impairments of the 2′,5′-oligoadenylate (2–5A) synthetase/RNase L pathway.[45] Other studies showed no role of linoleic acid, eicosatrienoic acid (both $p > .05$),[25] ferritin, vitamin B_{12}, folate, or serum erythropoietin levels.[46]

Mental/Neurologic Etiologies

Psychosocial factors are frequently thought to contribute to fatigue. Rangel et al.[13] found that CFS in childhood and adolescence is associated with higher levels of parental mental distress, emotional involvement, and family illness burden than those observed in association with juvenile rheumatoid arthritis, a chronic pediatric physical illness. Endicott[14] described stressors including earlier mortality age and increased prevalence of cancer, autoimmune disorders, and CFS-like conditions in parents of psychiatric patients with CFS as compared to control groups. Thirty percent of the CFS patients and none of the controls reported dilemmas in the 3 months prior to the CFS onset in one study.[47] History of abuse, particularly during childhood, may play a role in the development and perpetuation of chronic fatigue,[48] and childhood trauma was associated with a 3- to 8-fold increased risk for CFS across different trauma types in one study.[49] Sleep is also an interesting etiologic factor, as many patients with CFS have sleep disorders, and those with sleep disorders showed greater functional impairment independent of their psychiatric disorders.[50–52]

FATIGUE: DON'T ASSUME IT'S DEPRESSION

Fatigue is a part of a wide spectrum of diagnoses ranging from being a symptom in depression, anxiety, seasonal affective disorder,[53] and multiple other diagnoses to being a full syndromal disorder in CFS, yet CFS goes undiagnosed in 80% of cases and is often misdiagnosed as depression. The *Diagnostic and Statistical Manual of Mental Disorders* doesn't list CFS as a diagnosis although *the International Classification of Diseases, 10th Revision*, does.[12] In clinical practice, CFS presentations range from complicated cases associated with a psychotic state resulting in multiple murders in one case report[54] to noncomplicated presentations with multiple psychiatric disorders, primarily depression.[55] It is very important to understand the distinctive features between chronic fatigue and depressive disorder when evaluating a patient with a main complaint of fatigue. A full detailed history accompanied by questionnaire forms can be very helpful to differentiate CFS from major depressive disorder. There is still no specific test that can confidently differentiate between them. Multiple studies have tried to find distinctive factors and they are listed in Table 2.

EVALUATION OF FATIGUE

Diagnosing CFS can be challenging for health care professionals for many reasons; the most important one is finding fatigue in a large number of illnesses and disorders. We reviewed information available about evaluation of chronic fatigue and discuss it in 3 parts: history, exam, and diagnostic tests.

History and Differentials

Because CFS is a diagnosis of exclusion,[1] a full detailed history is considered essential. The history should include a detailed account of the symptoms, the associated disability, the choice of coping strategies, and importantly, the patient's own understanding of his/her illness.[65] Every patient should be carefully evaluated for certain medical, psychiatric, and neurologic diseases that can cause fatigue as the most prominent symptom (Table 3). Two of the important differential diagnoses are depression and fibromyalgia. Although it is difficult to differentiate CFS from fibromyalgia confidently depending on the history or other reported differences of cognitive dysfunction components or clinical pain measures,[66,67] CFS and fibromyalgia commonly co-occur within the concept of central sensitivity syndromes or functional somatic syndromes.[68] This co-occurring increases functional impairment when compared to CFS individuals alone.[69,70] Some of the distinguishing features between CFS and fibromyalgia include evidence for triggering viral infection and lower level of serum acylcarnitine observed in CFS patients, which is lacking in the majority of patients with fibromyalgia;[71] slower information-processing in CFS patients compared to impaired control of attention in fibromyalgia patients;[66] and lacking of the characteristic diffuse soft tissue pain and pain on palpation in at least 11 of 18 paired tender points in CFS patients.

Exam

Every CFS evaluation should include a mental status examination to identify abnormalities in mood, intellectual function, memory, and personality. Particular attention should be directed toward current symptoms of depressive, anxious, self-destructive thoughts and observable signs such as psychomotor retardation.[1] Although there is no definite physical finding, a full and thorough physical examination may be helpful in excluding other conditions. Multiple studies have suggested dysautonomia with greater increase in heart rate together

Table 2. Comparison Between Chronic Fatigue Syndrome (CFS) and Depression Across Different Studies

Domain	CFS	Depression
History	Postexertional malaise[56]	Feeling better after exercise/activities
	Unrefreshing sleep/excessive sleep[56]	Insomnia or excessive sleep
	Fatigue is associated with intense frustration at not functioning well[57]	Fatigue is associated with apathy and anhedonia
	Patients are less likely to interpret symptoms in terms of negative emotional states[58]	Patients are more likely to interpret symptoms in terms of negative emotional states
	Patients attribute their illness to external or somatic experiences[59,60]	Patients may attribute their illness to psychological factors
	More likely to cope with their illness by limiting stress and activity levels[59]	More likely to cope with their illness by increasing their activity levels
	Difficulties in the doctor-patient relationship related to frustration of no diagnosis[61]	Less likely to develop difficulties in the doctor-patient relationship, and most likely related to treatment or comorbid disorders
Physical and mental status examinations	Patients are weaker and they have more pain complaints[62]	Patients are stronger and they have fewer pain complaints
	Sore throat that is frequent or recurring[1]	NA
	Tender cervical or axillary lymph nodes[1]	NA
	CFS patients generally performed worse on cognitive tests than healthy controls, but better than patients with MDD[63]	MDD patients generally performed worse on cognitive tests than healthy controls, and worse than patients with CFS
Diagnostic tests[a]	Low DHEA level[64]	Low DHEA sulfate derivative level
	Sleep studies showed more non-REM sleep disturbances[56]	Sleep studies showed more REM sleep disturbances
	More resting T ($CD3^+/CD25^-$) cells. Fewer $CD20^+/CD5^+$ B cells[20]	Fewer resting T ($CD3^+/CD25^-$) cells. More $CD20^+/CD5^+$ B cells

[a]There is no definite diagnostic test.
Abbreviations: DHEA = dehydroepiandrosterone, MDD = major depressive disorder, NA = not applicable, REM = rapid eye movement.

with a more pronounced systolic blood pressure fall on standing in CFS patients compared to healthy individuals.[46,72] Other studies found no statistically significant differences in either heart rate or galvanic skin resistance both during a normal day and before, during, and after exercise testing.[73]

Tests

The CDC has recommended the following initial screening tests when evaluating patients with CFS: urinalysis, total protein, glucose, C-reactive protein, phosphorus, electrolyte, complete blood count with leukocyte differential, alkaline phosphatase, creatinine, blood urea nitrogen, albumin, antinuclear antibody and rheumatoid factor, globulin, calcium, alanine aminotransferase or aspartate transaminase serum level, and thyroid function tests (thyroid stimulating hormone and free T4).[1] Further tests or referral to specialists may be indicated to confirm or exclude a diagnosis that better explains the fatigue state or to follow up on results of the initial screening tests.

Multiple other studies have tried to find biomarkers or radiological markers for CFS. Erythrocyte sedimentation rate was normal in all 23 CFS patients in one study.[74] Another study found that concentrations of C-reactive protein, β_2-microglobulin, and neopterin were higher in patients with CFS ($p \leq .01$).[75] On the other hand, a study by Swanink et al.[76] found that complete blood cell count, serum chemistry panel, C-reactive protein, and serologic tests were not different in 88 patients with CFS when compared to a control group. A potential role for DHEA in CFS, both therapeutically and as a diagnostic tool, was suggested in one study.[64]

Magnetic resonance imaging studies have been inconsistent, with some of them suggesting larger ventricular volumes.[77–84] Functional magnetic resonance was more promising, as it showed quantitative and qualitative differences in activation of the working memory network,[85] attenuation of the responsiveness to stimuli not directly related to the fatigue-inducing tasks,[86] utilization of more extensive regions of the network associated with the verbal working memory system,[87] impaired functioning and reduced gray-matter volume in the bilateral prefrontal cortex,[88] and inactive ventral anterior cingulate after making an error.[89]

Single-photon emission computed tomography (SPECT) and brain electrical activity mapping scans were promising in one study,[90] and SPECT scans showed more abnormalities than did magnetic resonance scans in one study ($p < .025$).[91] Siessmeier et al.[92] detected abnormalities in 18-fluorodeoxyglucose positron emission tomography in approximately half the CFS patients examined, but found that no specific pattern for CFS could be identified. Positron emission tomography showed an alteration of the serotonergic system in the rostral anterior cingulate

Table 3. Chronic Fatigue Syndrome Differential Diagnoses

Psychiatric/neurological disorders
Depressive disorders
Anxiety disorders
Fibromyalgia
Substance abuse/dependence
Sleep disorders
Infectious diseases
Herpesvirus infections
Lyme disease
Parvovirus B19
Borna disease virus
Glandular fever
Human mononucleosis
Q fever
Enterovirus
Nipah virus encephalitis
Endocrine diseases
Hypothyroidism
Severe obesity
Diabetes mellitus
Immunologic disorders
Lupus
Multiple sclerosis
Temporomandibular joint disorder
Others
Medications
Irritable bowel syndrome
Multiple chemical sensitivity
Gulf War syndrome
Interstitial cystitis

in one study, which was suggested as an etiology.[93] Recently, Puri[94] described the application of proton neurospectroscopy and 31-phosphorus neurospectroscopy in chronic fatigue syndrome. It is essential to mention that evidence to date does not support routine use of the imaging modalities discussed above in evaluating potential CFS patients.

Finally, it is important to remember that a good history is more important than any available test to diagnose CFS and differentiate it from depression. The algorithm shown in Figure 1, which is based on the CDC recommendations and the results of the studies reviewed, is suggested for evaluating chronic fatigue.

MANAGEMENT OF FATIGUE

It is important to manage fatigue in the context of each patient suffering with it. Treatment of CFS, with its various major clinical and functional impacts, should be associated with a "biopsychosocial model" of management. Educating patients about their diagnoses is crucial. Physicians should emphasize distinction among factors that may have predisposed patients to develop, trigger, or perpetuate the illness.[65] Progressive muscular rehabilitation, combined with behavioral and cognitive treatment, and appropriate choice of medications are essential parts of therapy.[8]

We will review the major concepts of CFS management and the evidence behind them.

Supportive and Symptomatic Treatment

Educating patients about CFS and validating their illness experience in addition to establishing a working alliance are the initial steps in the treatment.[1,65] Direct the treatment toward the most problematic symptoms, as prioritized by the patient,[1] and other illness-perpetuating factors.[65] Encourage a well-balanced diet, and discuss with patients their nutritional habits. Advice about preventing over- and under-activity is essential. "Start low and go slow" is the correct advice for activities and exercise, the same as for using medications. Gear activities toward improving function in areas that are of greatest importance in achieving activities of daily living and remain open-minded about alternative therapies (electroacupuncture was helpful in one study[95]) and discuss them with your patients when appropriate.[1] Consider referring or asking for consults and discuss that with patients early in the treatment.

Cognitive Behavioral Therapy

The short-term studies of cognitive behavioral therapy (CBT) in CFS have shown improvement in function and symptom management, especially in conjunction with other treatment modalities and in comparison to relaxation controls.[96–99] Reports about good outcome following CBT ranged from 70%[99] to none or even worsening of the symptoms.[100] CBT was effective in treating symptoms of fatigue, mood, and physical fitness, but no improvement in cognitive function or quality of life was noticed in one study.[101] Other studies showed limited effect on pain and fatigue.[1] When treating CFS patients, the CBT therapist needs to be familiar with CFS, to be aware of the evidence for CFS as a biologically based disorder, and to validate the patient's experience of living with a misunderstood illness.

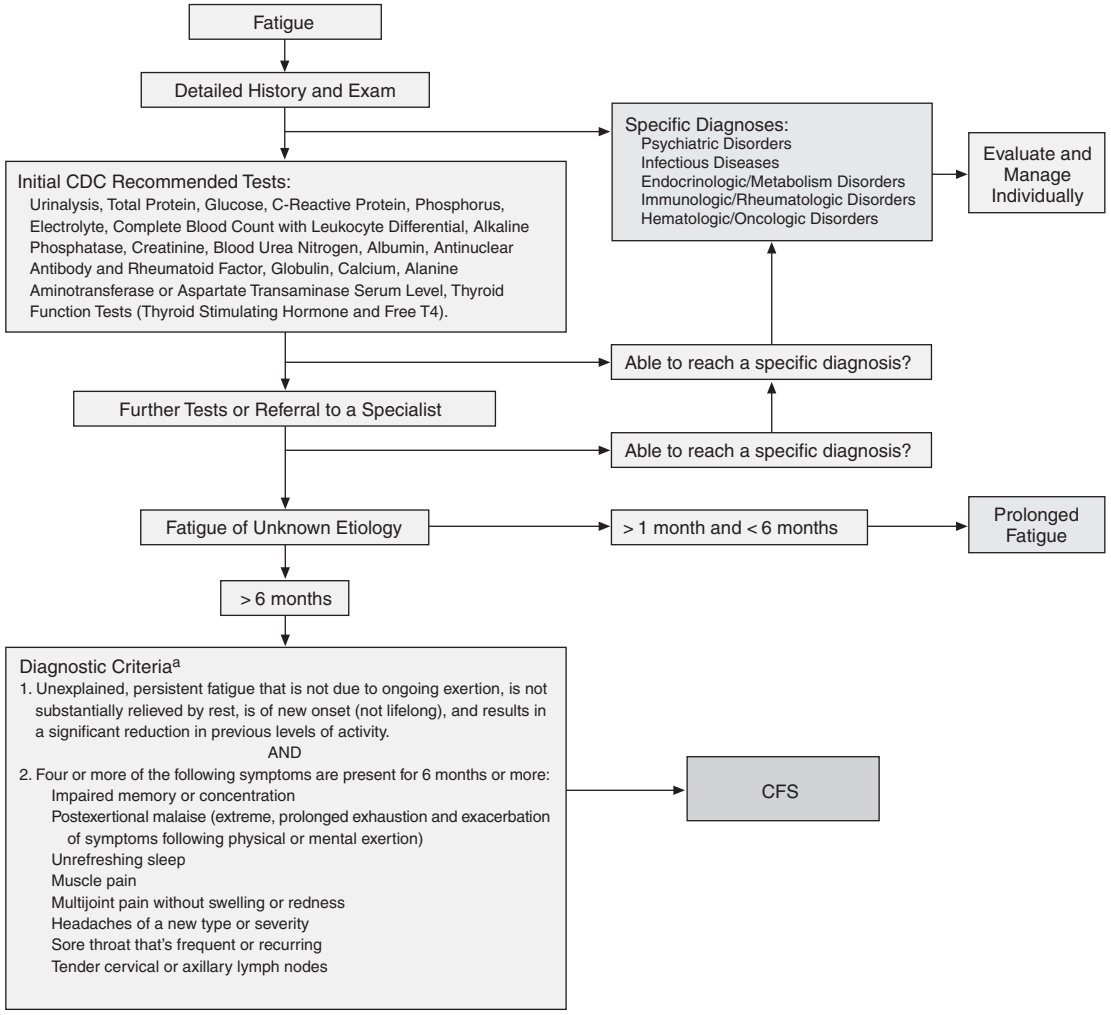
Exercise

CFS patients are very sensitive, and any treatment modality including exercise should start low and advance slowly. All exercises need to be followed by a rest period at a 1:3 ratio (i.e., 10 minutes of exercise: 30 minutes of rest). Review of the studies showed that exercise decreased the psychological stress[102] and improved fatigue, functional capacity, and fitness significantly better than flexibility treatment,[103] especially when associated with mood-enhancing, stress-reducing activities.[104,105]

Pharmacologic Treatment

Multiple studies have evaluated different treatment interventions, including recombinant erythropoietin, psychostimulants, corticosteroids, anti-inflammatory drugs, L-carnitine, and others.[10,106] Antidepressants are the most common medications used in this regard; selegiline had a small but significant therapeutic effect independent of its antidepressant effect.[107] Fluoxetine has been shown to

Figure 1. Algorithm for Evaluating Chronic Fatigue Syndrome (CFS)



[a]Adapted from the Centers for Disease Control and Prevention.[1]
Abbreviation: CDC = Centers for Disease Control and Prevention.

improve overall symptoms and measures of immune function in one study,[108] but failed in randomized, double-blind studies against placebo[109] and graded exercise.[110] Bupropion was effective for treatment of the fatigue and depressive symptoms associated with CFS in 9 fluoxetine-resistant patients[111] and was also helpful in augmenting paroxetine in one case report.[112] Venlafaxine was effective in 2 case reports.[113] Moclobemide up to 600 mg a day for 6 weeks showed significant but small reductions in fatigue, depression, anxiety, and somatic amplification, as well as a modest overall improvement.[114] Duloxetine may have a theoretical therapeutic benefit because of its characteristic of targeting pain. We could not find any study evaluating it in CFS patients. It is essential to mention that evidence to date does not support superiority of one medication over the others.

Other medications have been studied also. Clonidine enhanced both growth hormone ($p = .028$) and cortisol release ($p = .021$) and increased speed in the initial stage of a planning task ($p = .023$) only without affecting hormonal, physiologic, symptomatic, or neuropsychological measures.[115] Low-dose hydrocortisone therapy caused increases in plasma leptin levels, with this biological response being more marked in those CFS subjects who showed a positive therapeutic response to hydrocortisone therapy.[116] Essential fatty acid supplement rich in eicosapentaenoic acid was beneficial in a case report.[117] Carnitine supplementation has been shown to reduce chronic inflammation and oxidative stress in hemodialysis patients and, in cancer patients, reduce fatigue and improve outcome.[118] Treatment with modafinil was not beneficial in patients with CFS in one study.[119]

No therapeutic effects were found for natural killer cell stimulant,[120] low-dose combination therapy of hydrocortisone and fludrocortisone,[121] immunologic and antiviral substances, melatonin, or bright-light phototherapy.[122]

CONCLUSION

Evaluating and managing chronic fatigue is a challenging situation for physicians as it is a challenging and difficult condition for patients. A biopsychosocial approach in the evaluation and management is recommended. More studies about CFS manifestations, evaluation, and management are needed.

Drug names: bupropion (Wellbutrin and others), duloxetine (Cymbalta), clonidine (Catapres, Duraclon, and others), fluoxetine (Prozac and others), hydrocortisone (Cortef, Texacort, and others), modafinil (Provigil), paroxetine (Paxil, Pexeva, and others), selegiline (Eldepryl, Emsam, and others), venlafaxine (Effexor).

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