



CIGNA MEDICAL COVERAGE POLICY

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**Subject Chronic Fatigue Syndrome:
Diagnostic and Treatment
Services**

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Coverage Policy

CIGNA does not cover ANY of the following tests for the diagnostic evaluation of possible or presumed chronic fatigue syndrome (CFS), as each is considered experimental, investigational or unproven when used for this indication (this list may not be all-inclusive):

- viral serologies including Epstein-Barr virus (EBV), enteroviruses, retroviruses, human herpesvirus 6, cytomegalovirus, coxsackie, Candida albicans and Mycoplasma incognita

- immunological tests, including cell profiling tests, cytokine tests (interleukin-1, interleukin-6 or interferon), natural killer (NK) cell assays, quantitative immunoglobulin A (IgA); immunoglobulin G (IgG); and immunoglobulin M (IgM)
- cell marker tests, including CD 25, CD 16, T- and B-cell profiles
- delayed type hypersensitivity assays
- enzyme-linked immunosorbent assay/activated cell test (ELISA/ACT)
- ribonuclease L proteolysis (RNase L) enzymatic activity assay or RNase L protein quantification
- genetic testing
- brain imaging studies, including magnetic resonance imaging (MRI), positron emission tomography (PET), single-photon emission computed tomography (SPECT)
- tilt table testing
- quantitative electroencephalography (QEEG)
- thermography/temperature gradient studies
- neuropsychological testing

CIGNA does not cover ANY of the following services for the treatment of possible or presumed chronic fatigue syndrome (CFS), as each is considered experimental, investigational or unproven for this indication (this list may not be all-inclusive):

- cognitive behavioral therapy (CBT)
- graded exercise therapy (GET)
- antihistamine therapy
- antiviral therapy
- corticosteroid therapy
- essential fatty acid (EFA) therapy
- immunological therapy (e.g., immune globulins, interferon, Ampligen[®])
- nicotinamide adenine dinucleotide (NADH)
- dehydroepiandrosterone (DHEA) therapy
- nutritional counseling
- dietary supplements of vitamins, coenzymes, minerals, essential fatty acids, and extracts
- herbal preparations
- acupuncture
- hyperbaric oxygen therapy

General Background

Chronic fatigue syndrome (CFS), also referred to as Royal Free Disease, Iceland disease, neurasthenia, myalgic encephalomyelitis (ME), chronic fatigue and immune dysfunction syndrome (CFIDS), and post-viral fatigue syndrome, is a heterogeneous disorder characterized by persistent fatigue, myalgias, tender lymph nodes, arthralgias, chills, feverish feelings, postexertional malaise, and multiple other symptoms. Symptoms are persistent for at least six months and result in a substantial reduction in personal, social, educational, and/or occupational activities.

The multiple symptoms of CFS, which are seen in numerous other conditions, make it a difficult condition to diagnose. Therefore, diagnosis is made by exclusion of other conditions, and the treatment is focused on relief of symptoms. Despite extensive research, the etiology of CFS is unknown.

Diagnosis of CFS

There are no diagnostic studies (e.g., laboratory, imaging, psychosomatic or other testing) or physical findings that are specific to the diagnosis of CFS. The Centers for Disease Control and Prevention (CDC, 2010a) recommends that a diagnosis of CFS be considered when the following two criteria are met:

- “have severe chronic fatigue for at least 6 months or longer that is not relieved by rest and not due to medical or psychiatric conditions associated with fatigue as excluded by clinical diagnosis; and

- concurrently have four or more of the following symptoms: self-reported impaired short-term memory or concentration severe enough to cause substantial reduction in previous levels of occupational, educational, social, or personal activities; sore throat that's frequent or recurring; tender cervical or axillary lymph nodes; muscle pain; multijoint pain without swelling or redness; headaches of a new type, pattern or severity; unrefreshing sleep; and postexertional malaise (extreme, prolonged exhaustion and sickness following physical or mental activity) lasting more than 24 hours. The fatigue and impaired memory or concentration must have impaired normal daily activities, along with other symptoms that must have persisted or recurred during 6 or more consecutive months of illness and must not have predated the fatigue.”

Evaluation of the patient may include a detailed medical history, complete physical examination, mental status examination, and a standard series of laboratory studies to identify other possible causes of illness. If test results suggest an alternative explanation for the symptoms, additional tests may be performed to confirm the possibility of another disease. If no underlying etiology is identified, a physician may render a diagnosis of CFS if the symptom criteria are met.

Laboratory testing may include: complete blood count with leukocyte differential, erythrocyte sedimentation rate, alanine aminotransferase (ALT), total protein, albumin, globulin, alkaline phosphatase, calcium, phosphorus, glucose, blood urea nitrogen, electrolytes, creatinine, thyroid-stimulating hormone, transferrin saturation and urinalysis. The routine use of screening tests has no known value.

There are a number of additional diagnostic studies available, but their clinical utility in the diagnosis of CFS is not supported by the published peer-reviewed scientific literature. These studies include:

- viral serologies including Epstein-Barr virus (EBV), enteroviruses, retroviruses, human herpesvirus 6 (HHV-6), cytomegalovirus, coxsackie, Candida albicans and Mycoplasma incognita
- immunological tests, including cell profiling tests, cytokine tests (interleukin-1, interleukin-6 or interferon), natural killer (NK) cell assays, quantitative immunoglobulin A (IgA); immunoglobulin G (IgG); and immunoglobulin M (IgM)
- cell marker tests, including CD 25, CD 16, T- and B-cell profiles
- delayed type hypersensitivity assays
- enzyme linked immuno-sorbent assay/activated cell test (ELISA/ACT)
- ribonuclease L proteolysis (RNase L) enzymatic activity assay or RNase L protein quantification
- genetic testing
- brain imaging studies, including magnetic resonance imaging (MRI), positron emission tomography (PET), single-photon emission computed tomography (SPECT)
- tilt table testing
- quantitative electroencephalography (QEEG)
- thermography/temperature gradient studies
- neuropsychological testing

Literature Review

Laboratory Tests: Laboratory studies are conducted to aid in assessing the presence or absence of disease. Many patients with CFS attribute the onset of their illness to an acute influenza-like infection and therefore the role of viruses as possible causative agents has been studied. Early studies indicating that the Epstein-Barr virus (EBV) was a causative agent in CFS have been refuted. Other viral pathogens such as coxsackie virus, human herpes virus 6, cytomegalovirus, measles and human T-cell lymphotropic virus (HTLV-II), xenotropic murine leukemia virus-related virus (XMRV) have been found to have no consistent or conclusive data to suggest a causative etiology in CFS (CDC, 2010c; Groom, et al., 2010; Hong, et al., 2010; Craig, 2002).

It has been reported that the retrovirus, xenotropic murine leukemia virus-related virus (XMRV), was detected in patients with CFS. However studies using polymerase chain reaction (PCR) to analyze serum of patients samples (n=51–299) with CFS reported that there was no association between XMRV infection and CFS (Groom, et al., 2010; Hong, et al., 2010; Switzer, et al., 2010; van Kuppeveld, et al., 2010).

To evaluate morning salivary cortisol profiles and their association with functional status, Nater et al. (2008) compared the free cortisol concentration in CFS patients (n=75) to healthy controls (n=110). A single morning

salivary sample was collected by all subjects immediately upon waking, and 30 and 60 minutes later. The average salivary cortisol levels across all three times were not significantly different between the groups. However, the mean awakening level was significantly lower in CFS women compared to control women ($p=0.011$), as was the cortisol area under the curve increase ($p=0.020$). The correlation between the cortisol outcomes and CFS-related symptoms measured by questionnaires suggested that there was an association between lower cortisol levels and worse physical fatigue. Cevik et al. (2004) also reported significantly lower cortisol concentrations in CFS premenopausal patients ($n=43$) compared to healthy controls ($n=35$).

Siegel et al. (2006) reported that low natural killer cell activity in CFS patients ($n=41$) was associated with less vigor, more daytime dysfunction and cognitive impairment compared to normal subjects. Following analysis of archived serum samples, Vernon and Reeves (2005) reported that a subset CFS patients ($n=56$) had higher rates of antibodies to microtubule-associated protein 2 ($p=0.03$) and single-stranded DNA ($p=0.04$).

Jones et al. (2005) conducted a study on samples from the Georgia physician surveillance study to detect antibodies against the GB virus-C (GBV-C) in CFS patients. An analysis of 12 CFS patients and 21 control patients revealed no evidence that GBV is associated with CFS.

Kennedy et al. (2004) examined the concentrations of the anti-inflammatory cytokine, transforming growth factor $\beta 1$ (TGF $\beta 1$) in 47 CFS patients compared to 34 matched healthy control subjects. The CFS patients had higher concentrations of active TGF $\beta 1$, higher numbers of apoptotic neutrophils and lower numbers of viable neutrophils than healthy subjects.

Genetic Testing: Zhang et al. (2010) conducted a study ($n=62$) to validate the previous identification of the abnormal expression of 88 genes in patients with CFS. Six patients were diagnosed with CFS secondary to Q fever, and the remaining patients had idiopathic CFS. Clinical and quantitative real time polymerase chain reaction (qPCR) data were analyzed on the 62 patients as well as, 55 CFS patients from a previous study, 14 patients with endogenous depression and 29 healthy donors (control group). Differential expression of all 88 genes was confirmed in CFS patients, and the data were clustered into eight subtypes with distinct differences in Short-Form 36 (SF-36) health survey scores, clinical phenotypes, levels of severity and geographical distribution. Three patients' genotypes did not fit into the subcategories. With the exception of five genes, gene expression in patients with depression was similar to the healthy donors. Antibody testing for Epstein-Barr virus, enterovirus, Coxiella burnetii and parvovirus B19 revealed evidence of subtype-specific relationships for Epstein-Barr and enterovirus. The authors noted that additional studies are needed to validate and develop the findings of this analysis and to determine "what precise sequence of events is involved in the genesis of gene signatures in each subtype."

Brain Imaging Techniques: Imaging studies are proposed for evaluation of the cranial blood flow in CFS patients. Yoshiuchi et al. (2006) utilized xenon-computed tomography to determine if CFS patients ($n=25$) had reduced blood flow. CFS patients with and without Axis I diagnosis had significantly reduced blood flow in the left middle cerebral artery area ($p<0.05$ in both groups), and CFS patients without Axis I diagnosis had statistically significantly lower blood flow to the right middle cerebral artery area ($p<0.05$) suggesting that CFS "patients devoid of psychopathology are the group most at risk of having some of the symptoms of CFS due to brain dysfunction".

Evaluation of cerebral blood flow using single-photon emission computed tomography (SPECT) and Paced Auditory Serial Addition Test (PASAT) (Schmaling, et al., 2003) showed more diffuse blood flow in CFS patients ($n=15$), but no significant differences were seen in performance on the PASAT. Using MRI and voxel-based morphometry (VBM), Okada et al. (2004) compared the gray-matter volume of CFS patients ($n=16$) to healthy controls and reported a significant reduction in gray-matter volume in the bilateral prefrontal cortex in the CFS patients, suggesting that prefrontal hypofunction might reflect a functional deficiency that makes patients susceptible to fatigue.

Tilt Table Testing: Wyller et al. (2007) conducted a head-up tilt test (HUTT) comparing CFS patients ($n=27$) to healthy controls ($n=33$) and reported that during tilt testing, increased heart rate, diastolic blood pressure, mean blood pressure, total peripheral resistance index, and stroke index were greater in the CFS group.

Naschitz et al. (2006) conducted a phase I ($n=15$) and phase II study ($n=30$) to determine if the corrected QT (QTc) interval in CFS patients would differ from controls. The studies demonstrated that the computation of the

QTc in the CFS patients was significantly shorter than in the control groups, supporting the theory that short QTc intervals are features of CFS-related dysautonomia.

Naschitz et al. (2003) conducted HUTT evaluations to determine the reproducibility of hemodynamic instability scores. The study included 40 CFS patients, 73 patients with non-CFS chronic fatigue, 58 patients with syncope, 41 patients with fibromyalgia, 30 patients with generalized anxiety disorder, 50 patients with familial Mediterranean fever (FMF), 28 patients with essential hypertension, and 59 healthy control subjects. Naschitz et al. (2001) compared HUTT responses between 25 patients with CFS, 25 patients with fibromyalgia, 15 patients with generalized anxiety disorder, 20 patients with essential hypertension, and 37 healthy control subjects. Both studies reported a significant difference in the hemodynamic instability scores calculated from blood pressure and heart rate changes in the CFS patients compared to other groups except for those patients with generalized anxiety disorder. In an earlier study, following an evaluation of CFS patients using capnography HUTT (CHUTT), Naschitz et al. (2000) reported that an abnormal CHUTT was not specific to CFS (n=32) compared to healthy controls.

Neuropsychological Testing: Neuropsychological testing uses behavioral measures to assess abilities and skills that relate to brain functioning to help diagnose brain damage or dysfunctions. Comparative prospective studies involving neuropsychological testing of CFS patients were primarily conducted prior to the year 2000. When compared to healthy subjects, the studies reported that CFS patients had a higher percentage of somatization disorder symptoms (Johnson et al., 1996), were more likely to have used psychotropic medication or experienced psychiatric disorder in the past, had a current psychiatric disorder (Wessely, et al., 1996) and had a very high prevalence of generalized anxiety disorder (Fischler, et al., 1997).

Treatment of CFS

Since there is no known cause or cure for CFS, treatment is directed at the relief of symptoms based on the patient's overall medical condition, and modified when indicated based on ongoing assessment of the patient's condition. The management of patients also includes: educating the patient and family in developing effective coping strategies for living with the disease, teaching the patient to manage activity level, and pharmacotherapy (CDC, 2010a; Ferri, 2005; Gantz, 2004).

Other proposed modalities that have not been proven effective for the treatment of CFS include the following:

- cognitive behavioral therapy (CBT)
- graded exercise therapy (GET)
- antihistamine therapy
- antiviral therapy
- corticosteroid therapy
- essential fatty acid (EFA) therapy
- immunological therapy (e.g., immune globulins, interferon, Ampligen®)
- dehydroepiandrosterone (DHEA) therapy
- nutritional counseling
- dietary supplements of vitamins, coenzymes, minerals, essential fatty acids, and extracts (e.g., liver extract, adenosine monophosphate, coenzyme Q-10, germanium, glutathione, iron, magnesium sulfate, melatonin, nicotinamide adenine dinucleotide [NADH], selenium, 1-tryptophan, vitamin B12, and zinc)
- herbal preparations (e.g., comfrey, ephedra, kava, germander, chaparral, bitter orange, licorice root, yohimbe)
- acupuncture
- hyperbaric oxygen therapy

Literature Review

Following a systematic review of 11 nonrandomized articles related to musculoskeletal pain in CFS patients, Meeus et al. (2007) stated that there is a lack of consensus in defining CFS pain and etiology, and there are limited studies on the etiology and treatment of CFS, but chronic pain associated with CFS can be debilitating. A second systematic review of CFS literature by Maquet et al. (2006) agreed that the etiology is unknown, and the biological, physical and psychosocial aspects should be recognized and supported with therapy. Physical activity does not appear harmful and graded exercise is recommended.

Chambers et al. (2006) conducted a systematic review of 70 CFS studies (i.e., 59 randomized controlled trials and 11 non-randomized studies) that met inclusion criteria. Studies including behavioral, immunological, pharmacological and complementary therapies, nutritional supplements, and other miscellaneous interventions were reviewed. Based on findings from randomized trials, the authors concluded that cognitive behavioral therapy and graded exercise therapy “appeared to reduce symptoms and improve function” in patients with CFS. Evidence for the effectiveness of other therapies was inconclusive and, in some cases, adverse effects were reported. The authors noted that although there has been an increase in the size and quality of studies on CFS interventions, there remains a need to define the characteristics of patients who would benefit from specific interventions and to develop clinically relevant outcomes.

Cognitive Behavioral Therapy (CBT) and Graded Exercise Therapy (GET): CBT is a psychological approach that focuses mainly on thoughts and beliefs that may be maintaining CFS symptoms, as opposed to a focus on those that triggered the condition. Planned activity and rest, graded exercise, and a sleep routine may be lifestyle modifications used in conjunction with CBT. GET involves a structured, managed activity program that progresses from low effort aerobic activity, usually walking, and increases to more demanding activities as tolerance improves (Rimes and Chalder, 2005).

White et al. (2011) conducted a multicenter, randomized controlled trial, known as PACE, to compare the effectiveness of specialist medical care (SMC) alone (n=160), SMC with adaptive pacing therapy (APT) (n=160), cognitive behavior therapy (CBT) (n=161) and graded exercise therapy (GET) (n=160). Outcomes were measured by various tools including the Chalder Fatigue Questionnaire, Short Form-36 physical function subscale, Clinical Global Impression scale and Jenkins Scale score. At the 52-week follow-up, compared to SMC alone mean fatigue scores were significantly lower for CBT (p=0.0001) and GET (p=0.0003), but not for APT (p=0.38) and mean physical function scores were significantly higher for CBT (p=0.0068) and GET (p=0.0005), but not for APT (p=0.18). Compared to APT, significantly less fatigue was associated with CBT (p=0.0027) and GET and significantly better physical function scores were reported following CBT (p=0.0002) and GET (p<0.0001). Serious adverse events (i.e., death, hospital admission, increased severe and persistent disability, self-harm, life-threatening, or required an intervention to prevent one of these) were reported in one percent of all groups with the exception of two percent in the CBT group, not statistically significant. Author-noted limitations of the study included a selection bias by the exclusion of subjects unable to attend treatment sessions and the inability to mask clinicians, subjects and research assessors.

In a randomized controlled trial, Chalder et al. (2010) compared the effectiveness of family-focused CBT (n=32) to psycho-education (n=31) in children, ages 11–18 years old, with CFS. Subjects underwent 13 sessions of family-focused CBT or four sessions of psycho-education. Follow-ups occurred at three, six and 12 months. At six months, there were no significant differences between the two groups in improved school attendance (p=0.26), fatigue and social adjustment. Over time, school attendance was higher in the family-focused CBT group. However, at the 12-month follow-up school attendance increased more in the psycho-education group. The drop-out level was higher in the psycho-education group. Child and mother satisfaction were significantly higher in the CBT group (p=0.07 and p=0.15, respectively). Overall, family-focused CBT was as effective as psycho-education. Limitations of the study include the small patient population, short-term follow-up and the number of subjects lost to follow-up (n=13).

Heins et al. (2010) analyzed data from three randomized controlled trials (n=508), that shared an overall positive effect of CBT, to determine if CFS patients experienced a deterioration of symptoms during CBT compared to an improvement in symptoms. Outcomes on the frequency and severity of symptom deterioration in fatigue, pain, functional impairment and psychological distress, as well as self-rated overall symptom change for CBT patients were compared to control group patients. Control group treatment included care as usual, guided support group or wait list. Clinically significant symptom deterioration did not occur more often in CBT-treated patients compared to control group patients except for psychological deterioration (i.e., 77 patients in CBT group vs. 74 patients in control group). Clinically significant deterioration ranged from 2%–12% in the CBT group and 7%–17% in the control groups. Using the Sickness Impact Profile, CBT patients reported significantly less deterioration on self-rated changes, daily observed fatigue and functional impairment compared to control patients. Limitations of the study include a high drop-out rate and possible selection bias in randomized controlled trials reporting positive outcomes of CBT.

Tummers et al. 2010 conducted a randomized controlled trial to compare the effectiveness and efficiency of stepped care (n=84) to care as usual (i.e., 6–12 month wait period) (n=85) for the treatment of CFS patients.

Stepped care involved minimal intervention consisting of CBT-based protocol. Patients received a self-instruction booklet with week-by-week steps for obtaining individual goals (e.g., returning to work). The program took at least 16 weeks or longer at the patient's discretion, and a therapist was available via phone or email for questions every two weeks and as needed. Following minimal intervention or care as usual, all patients were offered CBT. There were no significant differences in fatigue severity, disabilities and physical functioning between the two groups following the interventions. After guided self-instruction, patients (n=36) needed a mean 10.9 CBT sessions, compared to 14.5 sessions in the care as usual group (n=66) ($p<0.01$). Total therapist time was significantly less in the stepped care group compared to care as usual ($p=0.01$). Based on the results of this study, the authors proposed that stepped care is as effective as usual care, more time efficient, and tailored to the individual needs of the patient. Author noted limitations of the study included: the waiting period prior to CBT in the care as usual group; the treatment integrity of guided self-instruction and CBT was not tested; and retrospective calculation of the therapist's time. Other limitations include the small patient population and patients lost to follow-up.

Malouff et al. (2008) conducted a meta-analysis to determine the efficacy of CBT for the treatment of CFS or a similar disorder. The 13 randomized controlled trials that were selected for analyses included subjects with CFS or subjects with chronic mental, physical or mental and physical fatigue (n=1371; specific number of patients with CFS not identified). Patients were randomized to either treatment with a cognitive and/or behavioral emphasis or to a control condition (e.g., being on a waiting list; treatment as usual; treatment not expected to be helpful, such as stretching). Compared to control groups, fatigue levels of CBT patients were significantly lower ($d=0.48$) following intervention. Although all treatments in the study were CBT, the types of treatments varied widely in intensity and therapeutic method. Treatment duration ranged from 0.2 to 16 hours, and the dropout rate ranged from 0–42%. The outcomes varied based upon whether the fatigue was mental ($d=0.20$) or physical ($d=0.81$), and the number of patients not in the clinical range of fatigue varied from 33%–73% at the last recorded follow-up. The authors stated that “there presently appears to be no empirical basis for including cognitive components in treatment of fatigue disorders,” and that all the treatments included prompting of gradual increases in activity making it difficult to determine if the activity added potency to the treatment.

Price et al. (2008) conducted a systematic review of CBT randomized controlled trials in patients with CFS (n=210), age over 16 years. Three studies met inclusion criteria. In two studies, CBT was compared to routine medical care (i.e., clinic attendance, investigation, reassurance and simple advice) or relaxation. In the third study, CBT in combination with placebo injections, purported as immunological therapy, was compared to routine medical care and placebo injections. Follow-up ranged from 3–7 months. In each study, the measure of function was by either self- or observer-rating. The diagnostic criteria for CFS differed between trials, and there was an absence of explicit psychological therapy and other interventions not meeting CBT criteria. Use of antidepressant medication differed between groups. Other limitations included the lack of reported standard deviations in two studies, missing data from one study, and a lack of reported outcomes in employment status. Noting that the outcomes of the studies were modest due to the few relevant trials of high quality, the authors concluded that CBT in adults with CFS:

- improved physical functioning and other relevant outcomes (e.g., mood) compared to standard medical management
- had a modest impact on clinical improvement in physical functioning at the end of treatment
- provided no evidence of the effectiveness of therapy for milder forms of CFS seen frequently in primary care or for more severe cases of CFS who may be unable to attend outpatient clinics
- provided no evidence for CBT use in group situations or in children
- was not more effective than simpler interventions, such as the provision of a program of graded exercise and activity.

In a three-armed randomized controlled cross-over study involving CFS subjects (n=72), Stubhaug et al. (2008) evaluated the effects of 12 weeks of comprehensive CBT (CCBT) (i.e., CBT, body awareness, and exercise) to placebo or mirtazapine (an antidepressant) followed by a 12-week crossover combination therapy of CBT and placebo or mirtazapine. At 12 weeks, significant improvements were seen on the Fatigue Scale ($p=0.01$) and Clinical Global Impression (CGI) scale ($p=0.001$) in the CCBT group compared to the mirtazapine and placebo groups. At 24 weeks, significant improvements were seen in the Fatigue Scale ($p<0.001$) and the CGI scale ($p=0.002$) in patients who received 12 additional weeks of CCBT in combination with mirtazapine, indicating that multimodal interventions had a positive effect on CFS.

O'Dowd et al. (2006) randomly compared the results of CBT (n=25) to education and support (EAS) (n=50) and to standard medical care (SMC) (n=51) for the treatment of CFS. At the six-month follow-up, the CBT patients had significantly higher SF-36 mental health scores, less fatigue, and were able to walk faster than the SMC group, and walked faster and had less fatigue than the EAS group. Twelve months following therapy, increased walking speed in the CBT group was statistically significant. No other significant differences were found across the three arms. Moss-Morris et al. (2005) reported on 49 CFS patients randomized to a 12-week graded exercise program or to standard medical care. At the end of treatment, the exercise group rated themselves as significantly more improved and less fatigued than the control group.

In a systematic review conducted by Rimes and Chalder (2005), three of four randomized controlled trials compared CBT with a control condition and reported improved outcomes with CBT for up to five years in one trial. One trial did not report improved outcomes. CBT appeared effective but did not help all patients. The review also included randomized controlled trials evaluating the effectiveness of GET. Four studies demonstrated a beneficial effect of GET on fatigue and functional work capacity compared to control groups.

In a systematic review of randomized controlled trials, Edmonds et al. (2004) investigated the "relative effectiveness of exercise therapy and control treatments for CFS." Five randomized control trials (n=336) met the diagnostic criteria. The following treatment comparisons were made: 1) exercise therapy versus control (i.e., treatment as usual or relaxation and flexibility); 2) exercise therapy versus pharmacotherapy (i.e., fluoxetine); 3) exercise therapy versus exercise therapy and pharmacotherapy (i.e., fluoxetine); and 4) exercise therapy alone versus exercise therapy and patient education. At 12 weeks' follow-up, the exercise therapy group reported less fatigue and improved physical functioning compared to the control group, but the differences were not significant at 24 weeks. Significant improvements were not seen in depression or fatigue with the use of exercise, patient education and/or fluoxetine.

Other randomized controlled trials reported no significant differences when CFS patients were treated with CBT (Leone, et al., 2006; Huibers, et al., 2004) or educational intervention (Powell, et al., 2004). Ridsdale et al. (2004) reported no significant difference in outcomes when CBT was compared to GET.

Antihistamine, Antiviral and Immunological Therapy: Hypothesizing that CFS may be due to an allergic condition, virus or disease of the immune system, these therapies are proposed as treatment modalities for CFS. Rimes and Chalder (2005) reported in a systematic review of five randomized controlled trials that the effects of immunoglobulin were limited or demonstrated no benefit at all. Two trials using interferon demonstrated benefit, but the methodology was poor. One study reported some positive effects using *Staphylococcus toxoid*. No beneficial outcomes were found with the use of the antihistamine, terfenadine, or with dialyzable leucocyte extract.

Corticosteroid Therapy: Because some CFS patients demonstrate a trend toward hypocortisolism, some sources advocate for the use of corticosteroids for the relief of CFS symptoms. It has been suggested that CFS may be associated with a deficiency of dehydroepiandrosterone (DHEA) and its sulphate (DHEA-S). Cleare et al. (2004) reported on the affect of corticotrophin-releasing hormone on DHEA and DHEA-S levels in 16 CFS patients. Basal levels of DHEA were higher in the study group than in the control group and correlated with higher self-reported CFS disability scores. Basal levels of DHEA-S were not different from controls. The DHEA and DHEAS levels were lower in patients following administration of hydrocortisone treatment with a return to normal levels similar to the control group. This study indicated that DHEA levels are higher in CFS patients.

In a systematic review, Rimes and Chalder (2005) reported that a randomized controlled trial of a low-dose hydrocortisone demonstrated short-term improvement, but the drug had to be discontinued because the benefit rapidly deteriorated. Two randomized controlled trials investigating the use of fludrocortisone resulted in no beneficial outcomes.

Essential Fatty Acids (EFAs): EFAs (i.e., omega-3, omega-6, and omega-9) are fatty acids that are required in the diet (i.e., essential) because they are not synthesized by the body. Low levels of EFAs are thought to contribute to depression and behavioral changes. Some propose that EFA supplements may be beneficial in the treatment of CFS. Vermeulen and Scholte (2004) reported on the effects of acetylcarnitine, propionylcarnitine and a combination of both compounds in an open randomized study with three groups of 30 CFS patients. Attention and concentration improved in all groups; pain complaints did not decrease in any group; and two

weeks after treatment, worsening of fatigue was experienced by 52%, 50% and 37% in the acetylcarnitine, propionylcarnitine and combined groups, respectively.

Nicotinamide Adenine Dinucleotide (NADH): NADH is a coenzyme that boosts the brain's production of serotonin and adenosine triphosphate (ATP). It plays a role in energy production and has been suggested as a treatment option for fatigue. Forsyth et al. (1999) randomized 26 patients with CFS to receive NADH or placebo. Eight patients responded favorably to NADH compared to two placebo patients.

Miscellaneous Therapies: Homeopathic medicine, massage therapy, Chinese herbs, moxibustion, complementary and alternative medicines, acupuncture, hyperbaric oxygen therapy, nutritional counseling, and various medications have also been proposed as treatment alternatives for CFS. The evidence in the published peer-reviewed scientific literature does not support these therapies in the treatment of CFS.

Porter et al. (2010) conducted a systematic review to evaluate the literature on complementary and alternative medicine (CAM) for the treatment of CFS and fibromyalgia. Seventy studies met inclusion criteria. Eight randomized controlled trials and non-randomized comparison studies evaluated manual medicine (focuses on treating and strengthening the musculoskeletal framework by natural hands-on care), massage therapy, mindfulness-based stress reduction, Qigong, traditional Chinese Medicine and osteopathy for the treatment of CFS. Nineteen studies evaluated nonpharmacological supplements including fatty acids, amino acids, liver extract containing folic acid and cyanocobalamin (LEFAC), L-carnitine, coenzyme Q10, ginseng, antioxidant pollen, mushrooms, echinacea, homeopathy, NADH, and magnesium. A total of 86% of studies showed some beneficial effects and 74% reported improvement in symptoms. However, due to the heterogeneity of symptomatology, outcome measures, diagnostic criteria and treatment regimens no definite CAM treatment recommendations for CFS could be made. No treatments were identified as being consistently effective.

Weatherly-Jones et al. (2004) reported on a randomized controlled triple-blind trial of the efficacy of homeopathic treatment for 103 CFS patients compared to placebo. Patients met with a homeopath monthly for six months, and the homeopathic medicines and placebo were identical in appearance and taste. The study found that there was a mean improvement in score for those in the homeopathic group. Differences between treatment and placebo were nonsignificant between groups.

A randomized controlled trial by Blacker et al. (2004) compared the efficacy and tolerability of galantamine hydrobromide (n=89), an acetyl cholinesterase inhibitor, to placebo (n=82) in CFS patients. After 16 weeks of therapy, the trial demonstrated no benefit of galantamine hydrobromide over placebo. Another randomized controlled trial (Randall, et al., 2005) studied the effects of modafinil, a wakefulness-promoting agent, on 14 CFS patients. After twenty days of treatment in each group, the study produced no evidence that modafinil was beneficial in the treatment of these CFS patients.

A systematic review by Rimes and Chalder (2005) included three randomized controlled trials: one evaluated massage therapy; one evaluated homeopathic remedies; and one evaluated osteopathy. Each individual study reported some beneficial effects but, according to the authors, the studies were either of poor quality, small population, or included within group comparison.

McDermott et al. (2006) conducted a placebo-controlled, double-blind randomized controlled trial to assess the effectiveness of BioBran™ MGN-3, a natural killer-cell stimulant, for the treatment of CFS. Seventy-one patients received BioBran orally for eight weeks. Outcomes in 64 patients did not support the use of BioBran for the treatment of CFS.

Professional Societies/Organizations

American College of Radiology (ACR): In their practice guideline on single photon emission computerized tomography (SPECT) (2007), ACR stated that the indications for SPECT for chronic fatigue syndrome have not been "fully characterized."

National Institute for Health and Clinical Excellence (NICE): NICE (United Kingdom) published a 2007 (reaffirmed 2011) guidance document on the management of CFS. The following information was included:

- "The following tests should usually be done: urinalysis for protein, blood and glucose; full blood count; urea and electrolytes; liver function; thyroid function; erythrocyte sedimentation rate or plasma viscosity; C-

reactive protein; random blood glucose; serum creatinine; screening blood tests for gluten sensitivity; serum calcium; creatine kinase; assessment of serum ferritin levels (children and young people only).

- Tests for serum ferritin in adults should not be carried out unless a full blood count and other hematological indices suggest iron deficiency.
- Tests for vitamin B12 deficiency and folate levels should not be carried out unless a full blood count and mean cell volume show a macrocytosis.
- The following tests should not be done routinely to aid diagnosis: the head-up tilt test, auditory brainstem responses, electrodermal conductivity.
- Serological testing should not be carried out unless the history is indicative of an infection. Depending on the history, tests for the following infections may be appropriate: chronic bacterial infections, such as borreliosis; chronic viral infections, such as HIV or hepatitis B or C; acute viral infections, such as infectious mononucleosis (use heterophile antibody tests), latent infections, such as toxoplasmosis, Epstein–Barr virus or cytomegalovirus.
- The following drugs should not be used for the treatment of CFS/ME: monoamine oxidase inhibitors, glucocorticoids (such as hydrocortisone), mineralocorticoids (such as fludrocortisone), dexamphetamine; methylphenidate; thyroxine; antiviral agents.
- There is insufficient evidence for the use of supplements – such as vitamin B12, vitamin C, coenzyme Q10, magnesium, NADH (nicotinamide adenine dinucleotide) or multivitamins and minerals.
- Cognitive behavioural therapy (CBT) and/or graded exercise therapy (GET) should be offered to people with mild or moderate CFS/ME and provided to those who choose these approaches, because currently these are the interventions for which there is the clearest research evidence of benefit.
- The evidence shows that immunoglobulin therapy is not of benefit. There is insufficient evidence of benefit of other immunological therapies.”
- Studies that examined essential fatty acid supplements were conflicting, with one good-quality randomized controlled trial reporting no improvements and one slightly larger controlled trial conducted in patients with postviral syndrome reporting an overall beneficial effect.

Royal Australian College of Physicians (RACP): The RACP guidelines (Working Group of RACP, 2002) on CFS stated that the following diagnostic studies are not indicated in the diagnosis of CFS: Epstein-Barr virus, enteroviruses, tests of immunity, urinary protein metabolite screening, neuroimaging (e.g., MRI and radionuclide studies), autoantibody assays and serum creatinine kinase. They noted that “any claim that a particular treatment can ‘cure’ most people with CFS should be regarded with a high degree of skepticism” because CFS occurs in a heterogeneous population and all CFS patients are not going to respond uniformly. With regard to management of the patient, RACP stated that consistent evidence shows that no single pharmacologic therapy has been shown to be effective, and CBT and GET may be effective for some CFS patients. Consensus of opinion of respected authorities stated that physical and intellectual activities should be “paced” and that antidepressant drugs may provide symptomatic relief to this population.

Royal College of Pediatric and Child Health (RCPCH): In an evidence-based guideline on the management of CFS in patients up to age 18 years, the RCPCH (2004) stated that there are no “accepted diagnostic criteria” for CFS in patients age 18 years and under. They recommended that the diagnosis be based “primarily on the impact of the condition on the patient” regardless of duration of symptoms. They further stated that the literature does not identify a single approach to the treatment of CFS that is applicable to all patients. Management of CFS for children and young adults should include activity management, advice, symptomatic treatment and ongoing evaluation of progress.

Summary

Chronic fatigue syndrome (CFS) is a complex condition and difficult to diagnose. The published peer-reviewed scientific studies indicate that there are no specific laboratory tests, radiological studies, psychological tests or other diagnostic studies that can be used to definitively diagnose CFS.

Evidence in the published peer-reviewed scientific literature does not support specific treatment for CFS. Although some CFS patients may derive positive outcomes and improvement of symptoms through a structured exercise program, such as graded exercise therapy (GET) or cognitive behavioral therapy (CBT), the studies are inconclusive and show mixed results. The scientific studies do not support the use of other various treatment options for CFS.

Coding/Billing Information

Experimental/Investigational/Unproven/Not Covered when used to report testing or treatment for chronic fatigue syndrome:

Note: This list of codes may not be all-inclusive.

CPT* Codes	Description
70551	Magnetic resonance (eg, proton) imaging, brain (including brain stem); without contrast material
70552	Magnetic resonance (eg, proton) imaging, brain (including brain stem); with contrast material(s)
70553	Magnetic resonance (eg, proton) imaging, brain (including brain stem); without contrast material, followed by contrast material(s) and further sequences
70554	Magnetic resonance imaging, brain, functional MRI; including test selection and administration of repetitive body part movement and/or visual stimulation, not requiring physician or psychologist administration
70555	Magnetic resonance imaging, brain, functional MRI; requiring physician or psychologist administration of entire neurofunctional testing
78600	Brain imaging, less than 4 static views;
78601	Brain imaging, less than 4 static views; with vascular flow
78605	Brain imaging, minimum 4 static views;
78606	Brain imaging, minimum 4 static views; with vascular flow
78607	Brain imaging, tomographic (SPECT)
78608	Brain imaging, positron emission tomography (PET); metabolic evaluation
78609	Brain imaging, positron emission tomography (PET); perfusion evaluation
78610	Brain imaging, vascular flow only
82784	Gammaglobulin (immunoglobulin); IgA, IgD, IgG, IgM, each
83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified
83890	Molecular diagnostics; molecular isolation or extraction, each nucleic acid type (ie, DNA or RNA)
83891	Molecular diagnostics; isolation or extraction of highly purified nucleic acid, each nucleic acid type (ie, DNA or RNA)
83892	Molecular diagnostics; enzymatic digestion, each enzyme treatment
83893	Molecular diagnostics; dot/slot blot production, each nucleic acid preparation
83894	Molecular diagnostics; separation by gel electrophoresis (eg, agarose, polyacrylamide), each nucleic acid preparation
83896	Molecular diagnostics; nucleic acid probe, each
83897	Molecular diagnostics; nucleic acid transfer (eg, Southern, Northern), each nucleic acid preparation
83898	Molecular diagnostics; amplification, target, each nucleic acid sequence
83900	Molecular diagnostics; amplification, target, multiplex, first 2 nucleic acid sequences
83901	Molecular diagnostics; amplification, target, multiplex, each additional nucleic acid sequence beyond 2 (List separately in addition to code for primary procedure)
83902	Molecular diagnostics; reverse transcription
83903	Molecular diagnostics; mutation scanning, by physical properties (eg, single strand conformational polymorphisms [SSCP], heteroduplex, denaturing gradient gel electrophoresis [DGGE], RNA'ase A), single segment, each
83904	Molecular diagnostics; mutation identification by sequencing, single segment, each segment
83905	Molecular diagnostics; mutation identification by allele specific transcription, single segment, each segment
83906	Molecular diagnostics; mutation identification by allele specific translation, single segment, each segment

83907	Molecular diagnostics; lysis of cells prior to nucleic acid extraction (eg, stool specimens, paraffin embedded tissue), each specimen
83908	Molecular diagnostics; amplification, signal, each nucleic acid sequence
83909	Molecular diagnostics; separation and identification by high resolution technique (eg, capillary electrophoresis), each nucleic acid preparation
83912	Molecular diagnostics; interpretation and report
84311	Spectrophotometry, analyte not elsewhere specified
86001	Allergen specific IgG quantitative or semiquantitative, each allergen
86003	Allergen specific IgE; quantitative or semiquantitative, each allergen
86005	Allergen specific IgE; qualitative, multiallergen screen (dipstick, paddle, or disk)
86318	Immunoassay for infectious agent antibody, qualitative or semiquantitative, single step method (eg, reagent strip)
86355	B cells, total count
86357	Natural killer (NK) cells, total count
86359	T cells; total count
86360	T cells; absolute CD4 and CD8 count, including ratio
86361	T cells; absolute CD4 count
86628	Antibody, candida
86658	Antibody; enterovirus (eg, coxsackie, echo, polio)
86663	Antibody; Epstein-Barr (EB) virus, early antigen (EA)
86664	Antibody; Epstein-Barr (EB) virus, nuclear antigen (EBNA)
86665	Antibody; Epstein-Barr (EB) virus, viral capsid (VCA)
86694	Antibody; herpes simplex, non-specific type test
86701	Antibody; HIV-1
86702	Antibody; HIV-2
86703	Antibody; HIV-1 and HIV-2, single assay
86738	Antibody; mycoplasma
86790	Virus, not elsewhere specified
87252	Virus isolation; tissue culture inoculation, observation, and presumptive identification by cytopathic effect
87253	Virus isolation; tissue culture, additional studies or definitive identification (eg, hemabsorption, neutralization, immunofluorescence stain), each isolate
87254	Virus isolation; centrifuge enhanced (shell vial) technique, includes identification with immunofluorescence stain, each virus
87255	Virus isolation; including identification by non-immunologic method, other than by cytopathic effect (eg, virus specific enzymatic activity)
87480	Infectious agent detection by nucleic acid (DNA or RNA); Candida species, direct probe technique
87481	Infectious agent detection by nucleic acid (DNA or RNA); Candida species, amplified probe technique
87482	Infectious agent detection by nucleic acid (DNA or RNA); Candida species, quantification
87495	Infectious agent detection by nucleic acid (DNA or RNA); cytomegalovirus, direct probe technique
87496	Infectious agent detection by nucleic acid (DNA or RNA); cytomegalovirus, amplified probe technique
87497	Infectious agent detection by nucleic acid (DNA or RNA); cytomegalovirus, quantification
87498	Infectious agent detection by nucleic acid (DNA or RNA); enterovirus, amplified probe technique
87531	Infectious agent detection by nucleic acid (DNA or RNA); Herpes virus-6, direct probe technique
87532	Infectious agent detection by nucleic acid (DNA or RNA); Herpes virus-6, amplified probe technique
87533	Infectious agent detection by nucleic acid (DNA or RNA); Herpes virus-6, quantification
87797	Infectious agent detection by nucleic acid (DNA or RNA), not otherwise specified; direct probe technique, each organism
87798	Infectious agent detection by nucleic acid (DNA or RNA), not otherwise specified;

	amplified probe technique, each organism
87799	Infectious agent detection by nucleic acid (DNA or RNA), not otherwise specified; quantification, each organism
87800	Infectious agent detection by nucleic acid (DNA or RNA), multiple organisms; direct probe(s) technique
87801	Infectious agent detection by nucleic acid (DNA or RNA), multiple organisms; amplified probe(s) technique
90471	Immunization administration (includes percutaneous, intradermal, subcutaneous, or intramuscular injections); 1 vaccine (single or combination vaccine/toxoid)
90472	Immunization administration (includes percutaneous, intradermal, subcutaneous, or intramuscular injections); each additional vaccine (single or combination vaccine/toxoid) (List separately in addition to code for primary procedure)
93660	Evaluation of cardiovascular function with tilt table evaluation, with continuous ECG monitoring and intermittent blood pressure monitoring, with or without pharmacological intervention
93740	Temperature gradient studies
95120	Professional services for allergen immunotherapy in prescribing physicians office or institution, including provision of allergenic extract; single injection
95125	Professional services for allergen immunotherapy in prescribing physicians office or institution, including provision of allergenic extract; 2 or more injections
95957	Digital analysis of electroencephalogram (EEG) (eg, for epileptic spike analysis)
95961	Functional cortical and subcortical mapping by stimulation and/or recording of electrodes on brain surface, or of depth electrodes, to provoke seizures or identify vital brain structures; initial hour of physician attendance
95962	Functional cortical and subcortical mapping by stimulation and/or recording of electrodes on brain surface, or of depth electrodes, to provoke seizures or identify vital brain structures; each additional hour of physician attendance (List separately in addition to code for primary procedure)
96116	Neurobehavioral status exam (clinical assessment of thinking, reasoning and judgment, eg, acquired knowledge, attention, language, memory, planning and problem solving, and visual spatial abilities), per hour of the psychologist's or physician's time, both face-to-face time with the patient and time interpreting test results and preparing the report
96118	Neuropsychological testing (eg, Halstead-Reitan Neuropsychological Battery, Wechsler Memory Scales and Wisconsin Card Sorting Test), per hour of the psychologist's or physician's time, both face-to-face time administering tests to the patient and time interpreting these test results and preparing the report
96119	Neuropsychological testing (eg, Halstead-Reitan Neuropsychological Battery, Wechsler Memory Scales and Wisconsin Card Sorting Test), with qualified health care professional interpretation and report, administered by technician, per hour of technician time, face-to-face
96120	Neuropsychological testing (eg, Wisconsin Card Sorting Test), administered by a computer, with qualified health care professional interpretation and report
97110	Therapeutic procedure, 1 or more areas, each 15 minutes; therapeutic exercises to develop strength and endurance, range of motion and flexibility
97532	Development of cognitive skills to improve attention, memory, problem solving (includes compensatory training), direct (one-on-one) patient contact by the provider, each 15 minutes
97802	Medical nutrition therapy; initial assessment and intervention, individual, face-to-face with the patient, each 15 minutes
97803	Medical nutrition therapy; re-assessment and intervention, individual, face-to-face with the patient, each 15 minutes
97810	Acupuncture, 1 or more needles; without electrical stimulation, initial 15 minutes of personal one-on-one contact with the patient
97811	Acupuncture, 1 or more needles; without electrical stimulation, each additional 15 minutes of personal one-on-one contact with the patient, with re-insertion of needle(s) (List separately in addition to code for primary procedure)
97813	Acupuncture, 1 or more needles; with electrical stimulation, initial 15 minutes of personal

	one-on-one contact with the patient
97814	Acupuncture, 1 or more needles; with electrical stimulation, each additional 15 minutes of personal one-on-one contact with the patient, with re-insertion of needle(s) (List separately in addition to code for primary procedure)
99183	Physician attendance and supervision of hyperbaric oxygen therapy, per session

HCPCS Codes	Description
C1300	Hyperbaric oxygen under pressure, full body chamber, per 30 minute interval
G0270	Medical nutrition therapy; reassessment and subsequent intervention(s) following second referral in same year for change in diagnosis, medical condition or treatment regimen (including additional hours needed for renal disease), individual, face-to-face with the patient, each 15 minutes
S8040	Topographic brain mapping
S9470	Nutritional counseling, dietitian visit

ICD-9-CM Diagnosis Codes	Description
780.71	Chronic fatigue syndrome

*Current Procedural Terminology (CPT®) © 2010 American Medical Association: Chicago, IL.

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	07/15/2008	0102	Chronic Fatigue Syndrome: Diagnostic and Treatment Services

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