Chronic Fatigue Syndrome

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.

I. Aetna considers the following as medically necessary exclusionary tests to be used for the evaluation of members suspected of having chronic fatigue syndrome (CFS) as recommended by the National Institutes of Health. The selection of studies depends on the specific characteristics of a given case:

A. Anti-nuclear antibodies (ANA)
B. Blood and serum chemistries (blood urea nitrogen, calcium, creatinine, glucose, serum electrolytes)
C. Complete blood count (CBC) with differential cell count
D. Erythrocyte sedimentation rate (ESR)
E. HIV serology
F. Immunoglobulin levels (in patients with documented recurrent bacterial infections)
G. Liver function tests (chemistries)
H. Lyme serology (when endemic)
I. MRI of head (to rule out multiple sclerosis)
J. Polysomnography (to rule out sleep disorder)
K. Rheumatoid factor (RF)
L. Serum cortisol
M. TB skin test
N. Thyroid function tests (thyroid hormone [T3 or T4] uptake or thyroid hormone binding ratio [THBR], thyroid stimulating hormone [TSH])

O. Urinalysis

Optional tests to be used when clinically indicated.

II. Aetna considers the following laboratory tests and procedures experimental and investigational for the diagnosis or treatment of members with CFS. The peer-reviewed medical literature does not support their value in the diagnosis or treatment of individuals with CFS:

A. Adrenocorticotrophic hormone (ACTH) stimulation test
B. Blood and cerebrospinal fluid cytokines assays
C. ELISA/ACT testing
D. Evaluation of enteric dysbiosis (abnormal microbial ecology)
E. Evaluation of premature telomere attrition (accelerated aging)
F. Functional elevation of NK cells
G. Gene expression profiling
H. Measurements of delayed hypersensitivity
I. Production and response to cytokines
J. Quantification of B and T cell subsets
K. Quantification of natural killer (NK) cells
L. RNAse L enzymatic activity assay or RNase L protein quantification
M. Serological tests for Candida albicans
N. Serum 2-5A synthetase activity
O. T cell response to mitogenic stimulation
P. Unstimulated salivary cortisol activity
Q. Viral serologies including but not limited to:

1. Coxsackie virus serology
2. Enterovirus serology
3. Herpes virus serologies (e.g., cytomegalovirus, Epstein Barr virus, human herpes virus-6)
4. Retrovirus serologies (except HIV)

R. Acupuncture and moxibustion
S. Anakinra
T. Anti-viral agents (e.g., acyclovir, famciclovir)
U. Body awareness interventions
V. Breathing re-training
W. Clonidine
X. Dexamphetamine
Y. Distant healing
Z. Duloxetine
AA. Galantamine
AB. Gastro-intestinal flora altering therapy
AC. Glucocorticoids
AD. Graded exercise therapy
AE. Intramuscular immunoglobulin injections
AF. Intravenous immunoglobulin (IVIG)
AG. Melatonin
AH. Methylphenidate
AI. Mineralocorticoids
AJ. Monoamine oxidase inhibitors (e.g., isocarboxazid, moclobemide, nialamide, phenelzine, rasagiline, selegiline, and tranylcypromine)
AK. Ondansetron
AL. Probiotics
AM. Repetitive transcranial magnetic stimulation
AN. Rintatolimod
AO. Rituximab
AP. Thyroxine
AQ. Vitamin injections (e.g., vitamin C, thiamine, B-complex vitamins)

III. Aetna considers tilt table testing experimental and investigational for identifying members with CFS or for evaluating treatment effectiveness of this condition because its effectiveness for these indications has not been established. (See CPB 0299 - Tilt Table Testing (../200_299/0299.html)).

IV. Aetna considers measurements of muscle blood flow (e.g., by Doppler ultrasound), muscle metabolism (e.g., by magnetic resonance spectroscopy) and muscle oxygen saturation and blood volume (e.g., by near-infrared spectroscopy) experimental and investigational for identifying members
with CFS because their clinical values have not been established.

V. Aetna considers the following imaging studies experimental and investigational for CFS because they do not confirm or exclude the diagnosis of CFS and, according to available literature, should not be routinely performed for this indication:

A. Magnetic resonance imaging (MRI) scans (except MRI of the head where signs and symptoms suggest multiple sclerosis).
B. Radionuclide scans (such as single-photon emission computed tomography (SPECT) and positron emission tomography (PET)).

VI. Aetna considers measurements of plasma brain natriuretic peptide levels for guidance of targeted therapy of CFS experimental and investigational because the effectiveness of this approach has not been established.

Note: Based on the position of the Centers for Disease Control and Prevention (CDC), the following guidelines should be used for the evaluation and study of CFS.

A thorough medical history, physical examination, mental status examination, and laboratory tests must be conducted to identify underlying or contributing conditions that require treatment. Diagnosis or classification can not be made without such an evaluation. Clinically evaluated, unexplained chronic fatigue cases can be classified as CFS if the member meets both of the following criteria:

I. Clinically evaluated, unexplained persistent or relapsing chronic fatigue that is of new or definite onset (i.e., not lifelong), is not the result of ongoing exertion, is not substantially alleviated by rest, and results in substantial reduction in previous levels of occupational, educational, social, or personal activities; and

II. The concurrent occurrence of 4 or more of the following symptoms: substantial impairment in short-term memory or concentration; sore throat; tender lymph nodes; muscle pain, multi-joint pain without swelling or redness; headaches of a new type, pattern, or severity; non-refreshing
sleep; and post-exertional malaise lasting more than 24 hours. These symptoms must have persisted or recurred during 6 or more consecutive months of illness and must not have predated the fatigue.

**Conditions that exclude a diagnosis of CFS**

I. Alcohol or other substance abuse, occurring within 2 years of the onset of chronic fatigue and any time afterwards. Severe obesity as defined by a body mass index [BMI = weight in kilograms divided by (height in meters)$^2$] equal to or greater than 45. [Note: BMI values vary considerably among different age groups and populations. No “normal” or “average” range of values can be suggested in a fashion that is meaningful. The range of 45 or greater was selected because it clearly falls within the range of severe obesity]. Any active medical condition that may explain the presence of chronic fatigue, such as untreated hypothyroidism, sleep apnea and narcolepsy, and iatrogenic conditions such as side effects of medication.

II. Any active medical condition that may explain the presence of chronic fatigue, such as untreated hypothyroidism, sleep apnea and narcolepsy, and iatrogenic conditions such as side effects of medication.

III. Any past or current diagnosis of a major depressive disorder with psychotic or melancholic features; bipolar affective disorders; schizophrenia of any subtype; delusional disorders of any subtype; dementia of any subtype; anorexia nervosa; or bulimia nervosa.

IV. Some diagnosable illnesses may relapse or may not have completely resolved during treatment. If the persistence of such a condition could explain the presence of chronic fatigue, and if it can not be clearly established that the original condition has completely resolved with treatment, then such members should not be classified as having CFS. Examples of illnesses that can present such a picture include some types of malignancies and chronic cases of hepatitis B or C virus infection.

Any unexplained abnormality detected on examination or other testing that strongly suggests an exclusionary condition must be resolved before attempting further classification.
Conditions that do not exclude a diagnosis of CFS

I. Any condition defined primarily by symptoms that can not be confirmed by diagnostic laboratory tests, including fibromyalgia, anxiety disorders, somatoform disorders, non-psychotic or melancholic depression, neurasthenia, and multiple chemical sensitivity disorder.

II. Any condition under specific treatment sufficient to alleviate all symptoms related to that condition and for which the adequacy of treatment has been documented. Such conditions include hypothyroidism for which the adequacy of replacement hormone has been verified by normal thyroid-stimulating hormone levels, or asthma in which the adequacy of treatment as been determined by pulmonary function and other testing.

III. Any condition, such as Lyme disease or syphilis that was treated with definitive therapy before development of chronic symptoms.

IV. Any isolated and unexplained physical examination finding, or laboratory or imaging test abnormality that is insufficient to strongly suggest the existence of an exclusionary condition. Such conditions include an elevated anti-nuclear antibody titer that is inadequate, without additional laboratory or clinical evidence, to strongly support a diagnosis of a discrete connective tissue disorder.

A note on the use of laboratory tests in the diagnosis of CFS:

According to the CDC, a minimum battery of laboratory screening tests should be performed. Routinely performing other screening tests for all individuals has no known value. However, further tests may be indicated on an individual basis to confirm or exclude another diagnosis, such as multiple sclerosis. In these cases, additional tests should be done according to accepted clinical standards.

The use of test to diagnose CFS (as opposed to excluding other diagnostic possibilities) should be done only in the setting of protocol-based research. The fact that such tests are investigational and do not aid in diagnosis or management should be explained to the individual.
In clinical practice, no tests can be recommended for the specific purpose of diagnosing CFS. Tests should be directed toward confirming or excluding other possible clinical conditions. Examples of specific tests that do not confirm or exclude the diagnosis of CFS include serologic tests for Epstein-Barr virus, enteroviruses, retroviruses, human herpes virus 6, and Candida albicans; tests of immunologic function, including cell population and function studies; and imaging studies, including magnetic resonance imaging scans and radionuclide (such as single-photon emission computed tomography and positron emission tomography).

Background

Chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis, is a clinically defined condition characterized by severe, persistent, disabling fatigue and a combination of symptoms that prominently feature self-reported impairments in concentration and short-term memory, sleep disturbances, and musculoskeletal pain. Diagnosis of CFS can be made only after alternative medical and psychiatric causes of chronic fatiguing illnesses have been excluded. No definitive diagnostic tests for this condition have been validated in scientific studies. Because CFS is clinically non-specific and lacks an identifiable cause or diagnostic test, it remains a diagnosis of exclusion.

In the revised definition, a consensus viewpoint from many of the leading CFS researchers and clinicians (including input from patient group representatives), CFS is treated as a subset of chronic fatigue, a broader category defined as unexplained fatigue of greater than or equal to 6-month's duration. Chronic fatigue in turn, is treated as a subset of prolonged fatigue, which is defined as fatigue lasting 1 or more months. The expectation is that scientists will devise epidemiologic studies of populations with prolonged fatigue and chronic fatigue, and search within those populations for illness patterns consistent with CFS.

In addition to a thorough history and physical examination, recommended procedures for evaluating patients suspected of having CFS include a mental status examination to identify abnormalities in mood, intellectual function, memory and personality. Evidence of psychiatric, neurologic or cognitive disorder requires that an appropriate psychiatric, psychological, or neurological evaluation be done.
Laboratory tests include a complete blood count with differential cell count, an
erthrocyte sedimentation rate, a chemistry profile including liver function tests,
thyroid function test (either a thyroid panel or thyroid stimulating hormone), anti-
nuclear antibodies, and urinalysis. Additional tests, if indicated, include rheumatoid
factor, immune globulin levels, tuberculin skin test, Lyme disease serology (if
patient lives in an endemic area), HIV serology, MRI of the head (if indicated to rule
out multiple sclerosis), and polysomnography (if indicated to rule out a sleep
disorder).

The following tests do not confirm or exclude the diagnosis of CFS: serologic tests
for Epstein-Barr virus, retroviruses (except HIV), human herpes virus 6,
enteroviruses and Candida albicans; and tests of immunologic function, including
cell population and function studies.

Immunologic abnormalities in patients with suspected CFS is an active area of
research into the pathogenesis of CFS. However, the published literature is
inadequate to determine the sensitivity, specificity, and positive and negative
predictive values of these tests. Most of the research has compared the
immunologic function of patients with CFS with healthy normal controls, so that it is
impossible to know whether the subtle immunologic abnormalities seen are specific
to CFS or could be seen in other patients with a wide variety of illnesses with
overlapping symptoms.

Although it was originally thought that CFS was related to a viral etiology, more
recent studies have failed to find any predictable association between CFS and any
particular virus.

A National Institutes of Health consensus conference recommended a list of
exclusionary laboratory tests that were considered appropriate for the work-up of a
patient with suspected CFS. Since that time, there have been investigations into the
immune function of patients with CFS, such as quantitative studies of natural killer
cells, B and T cell subsets, and the production of cytokines, such as interferons and
interleukin-2. Assessments of these immunologic parameters have produced
conflicting results, in part related to varying methodologies used, the heterogeneity
of patients who are tested at different points in their disease, and the dynamic
nature of the immune system that makes assessment of single tests difficult. While
assessments of levels of IgG subsets have shown a decrease in IgG1 and IgG3,
the studies were performed on small numbers of patients with undefined control
groups or only healthy controls. Therefore, it is not unexpected that the published data fail to indicate the sensitivity, specificity, positive and negative predictive value of the above immunologic tests. While immune function may provide a fertile path for research, its use in the clinical diagnosis and management of CFS is still investigational.

McCully et al (2004) examined if CFS is associated with reduced blood flow and muscle oxidative metabolism. Muscle blood flow was measured in the femoral artery with Doppler ultrasound after exercise. Muscle metabolism was measured in the medial gastrocnemius muscle with (31)P-magnetic resonance spectroscopy. Muscle oxygen saturation and blood volume were measured using near-infrared spectroscopy. The authors concluded that CFS patients showed evidence of reduced hyperemic flow and reduced oxygen delivery but no evidence that this impaired muscle metabolism. Thus, CFS patients might have altered control of blood flow, but this is unlikely to influence muscle metabolism. In addition, abnormalities in muscle metabolism do not appear to be responsible for the CFS symptoms.

Ribonuclease L (RNase L) is a protein induced by interferon that may affect certain anti-viral and anti-tumor effects observed when interferon is induced. Once activated, RNase L is thought to cleave viral DNA and triggering removal of the infected cell by inducing apoptosis. It has been posited that, in the immune cells of CFS patients, RNase L is cleaved by proteases; the resultant RNase L fragments have been posited to increase RNase L enzymatic activity and cleave cellular RNA at an accelerated rate, and also bind to and disrupt normal cellular ion flow. In this way, the RNase L fragments are thought to account for some of the physiological symptoms of CFS. Tests have been developed to quantify RNase L protein fragments (RNase L protein assay (RNAP), R.E.D. Laboratories, Reno, NV)) and to measure abnormal RNase L activity (RNase L activity assay (RNAA)). Although there is evidence that RNase L fragments are increased in a subset of patients with CFS, it has not been demonstrated that measurement of RNase L fragments or enzymatic activity is useful for either the diagnosis or management of persons with CFS.

Kawai and Rokutan (2007) noted that CFS is a complex disease and has no laboratory biomarkers, which makes diagnosis of CFS difficult. Several research groups challenged to identify genes specific for CFS; however, there are no overlaps between studies. The U.S. Centers for Disease Control and Prevention
reported remarkable gene expression profiles of a large scale cohort study (n = 227). Reported genes were mostly different from the previously reported genes, again featuring the complexity of CFS. Separately, these investigators identified 9 genes that were significantly and differentially expressed between CFS patients and healthy subjects using an original microarray.

Fostel and colleagues (2006) stated that CFS is a complex syndrome that can not simply be associated with changes in individual laboratory tests or expression levels of individual genes. No clear association with gene expression and individual symptom domains was found. However, analysis of such multi-faceted datasets is likely to be an important means to elucidate the pathogenesis of CFS.

Wang et al (2008) reviewed studies on the treatment of CFS with acupuncture and moxibustion in China. All studies concluded the treatments were effective, with response rates ranging from 79 % to 100 %. However, the qualities of the studies were generally poor, and none of them used a randomized controlled trial design. The common acupoints/sites used in the treatment of CFS, which may reflect the collective experience of acupuncturists in China based on Traditional Chinese Medicine theories can be used to evaluate the effectiveness of acupuncture for the treatment of CFS in future studies using more scientifically rigorous study designs.

In a pilot study, Nijs et al (2008) examined (i) the point prevalence of asynchronous breathing in patients with CFS; (ii) if CFS patients with an asynchronous breathing pattern present with diminished lung function in comparison with CFS patients with a synchronous breathing pattern; and (iii) if 1 session of breathing re-training in CFS patients with an asynchronous breathing pattern is able to improve lung function. A total of 20 patients fulfilling the diagnostic criteria for CFS were recruited for participation in a pilot controlled clinical trial with repeated measures. Patients presenting with an asynchronous breathing pattern were given 20 to 30 mins of breathing re-training. Patients presenting with a synchronous breathing pattern entered the control group and received no intervention. Of the 20 enrolled patients with CFS, 15 presented with a synchronous breathing pattern and the remaining 5 patients (25 %) exhibited an asynchronous breathing pattern. Baseline comparison revealed no group differences in demographic features, symptom severity, respiratory muscle strength, or pulmonary function testing data (spirometry). In comparison to no treatment, the session of breathing re-training resulted in an acute (immediately post-intervention) decrease in respiratory rate (p < 0.001) and an increase in tidal
volume ($p < 0.001$). No other respiratory variables responded to the session of breathing re-training. The authors concluded that these findings provided preliminary evidence supportive of an asynchronous breathing pattern in a subgroup of CFS patients, and breathing re-training might be useful for improving tidal volume and respiratory rate in CFS patients presenting with an asynchronous breathing motion.

In a randomized controlled partially blinded study, Walach and colleagues (2008) examined the effectiveness of distant healing (a form of spiritual healing) for patients with CFS. These researchers randomized 409 patients from 14 private practices for environmental medicine in Germany and Austria in a $2 \times 2$ factorial design to immediate versus deferred (waiting for 6 months) distant healing. Half the patients were blinded and half knew their treatment allocation. Patients were treated for 6 months and allocated to groups of 3 healers from a pool of 462 healers in 21 European countries with different healing traditions. Change in Mental Health Component Summary (MHCS) score (SF-36) was the primary outcome and Physical Health Component Summary score (PHCS) the secondary outcome. This trial population had very low quality of life and symptom scores at entry. There were no differences over 6 months in post-treatment MHCS scores between the treated and untreated groups. There was a non-significant outcome ($p = 0.11$) for healing with PHCS (1.11; 95% confidence interval [CI]: -0.255 to 2.473 at 6 months) and a significant effect ($p = 0.027$) for blinding; patients who were unblinded became worse during the trial (-1.544; 95% CI: -2.913 to -0.176). These investigators found no relevant interaction for blinding among treated patients in MHCS and PHCS. Expectation of treatment and duration of CFS added significantly to the model. The authors concluded that in patients with CFS, distant healing appears to have no statistically significant effect on mental and physical health, but the expectation of improvement did improve outcome.

VanNess et al (2010) examined the effects of an exercise challenge on CFS symptoms from a patient perspective. This study included 25 female CFS patients and 23 age-matched sedentary controls. All participants underwent a maximal cardio-pulmonary exercise test. Subjects completed a health and well-being survey (SF-36) 7 days post-exercise. Subjects also provided, approximately 7 days after testing, written answers to open-ended questions pertaining to physical and cognitive responses to the test and length of recovery. Data on SF-36 were compared using multi-variate analyses. Written questionnaire responses were used to determine recovery time as well as number and type of symptoms.
experienced. Written questionnaires revealed that within 24 hours of the test, 85% of controls indicated full recovery, in contrast to 0% CFS patients. The remaining 15% of controls recovered within 48 hours of the test. In contrast, only 1 CFS patient recovered within 48 hours. Symptoms reported after the exercise test included fatigue, light-headedness, muscular/joint pain, cognitive dysfunction, headache, nausea, physical weakness, trembling/instability, insomnia, and sore throat/glands. A significant multi-variate effect for the SF-36 responses (p < 0.001) indicated lower functioning among the CFS patients, which was most pronounced for items measuring physiological function. The authors concluded that these findings suggest that post-exertional malaise is both a real and an incapacitating condition for women with CFS and that their responses to exercise are distinctively different from those of sedentary controls.

Porter et al (2010) systematically reviewed the current literature related to alternative and complementary treatments for myalgic encephalomyelitis/CFS and fibromyalgia. It should be stressed that the treatments evaluated in this review do not reflect the clinical approach used by most practitioners to treat these illnesses, which include a mix of natural and unconventionally used medications and natural hormones tailored to each individual case. However, nearly all clinical research has focused on the utility of single complementary and alternative medicine interventions, and thus is the primary focus of this review. Several databases (e.g., PubMed, MEDLINE, PsychInfo) were systematically searched for randomized and non-randomized controlled trials of alternative treatments and non-pharmacological supplements. Included studies were checked for references and several experts were contacted for referred articles. Two leading subspecialty journals were also searched by hand. Data were then extracted from included studies and quality assessments were conducted using the Jadad scale. Upon completion of the literature search and the exclusion of studies not meeting criterion, a total of 70 controlled clinical trials were included in the review. Sixty of the 70 studies found at least one positive effect of the intervention (86%), and 52 studies also found improvement in an illness-specific symptom (74%). The methodological quality of reporting was generally poor. The authors concluded that several types of alternative medicine have some potential for future clinical research. However, due to methodological inconsistencies across studies and the small body of evidence, no firm conclusions can be made at this time. Regarding alternative treatments, acupuncture and several types of meditative practice show the most promise for future scientific investigation. Likewise, magnesium,
l-carnitine, and S-adenosylmethionine are non-pharmacological supplements with the most potential for further research. Individualized treatment plans that involve several pharmacological agents and natural remedies appear promising as well.

Sanchez-Barcelo et al (2010) noted that the efficacy of melatonin has been assessed as a treatment of aging and depression, blood diseases, CFS, cardiovascular diseases, diabetes, fibromyalgia, gastrointestinal tract diseases, infectious diseases, neurological diseases, ocular diseases, rheumatoid arthritis, as well as sleep disturbances. Melatonin has been also used as a complementary treatment in anesthesia, hemodialysis, in vitro fertilization and neonatal care. The conclusion of the current review is that the use of melatonin as an adjuvant therapy seems to be well-founded for arterial hypertension, diabetes, glaucoma, irritable bowel syndrome, macular degeneration, protection of the gastric mucosa, side effects of chemotherapy and radiation in cancer patients or hemodialysis in patients with renal insufficiency and, especially, for sleep disorders of circadian etiology (e.g., jet-lag, delayed sleep phase syndrome, sleep deterioration associated with aging) as well as in those related with neurological degenerative diseases (e.g., Alzheimer) or Smith-Magenis syndrome. The utility of melatonin in anesthetic procedures has also been confirmed. More clinical studies are needed to clarify whether, as the preliminary data suggest, melatonin is useful for treatment of CFS, fibromyalgia, infectious diseases, neoplasias or neonatal care.

In a randomized, placebo-controlled, double-blind trial, The and colleagues (2010) examined the effect of ondansetron, a 5-HT(3) receptor antagonist, on fatigue severity and functional impairment in adult patients with CFS. A total of 67 adult patients who fulfilled the CDC criteria for CFS and who were free from current psychiatric co-morbidity participated in the clinical trial. Participants received either ondansetron 16 mg per day or placebo for 10 weeks. The primary outcome variables were fatigue severity (Checklist Individual Strength fatigue severity subscale [CIS-fatigue]) and functional impairment (Sickness Impact Profile-8 [SIP-8]). The effect of ondansetron was assessed by analysis of co-variance. Data were analyzed on an intention-to-treat basis. Thirty-three patients were allocated to the ondansetron condition, 34 to the placebo condition. The 2 groups were well-matched in terms of age, sex, fatigue severity, functional impairment, and CDC symptoms. Analysis of co-variance showed no significant differences between the ondansetron- and placebo-treated groups during the 10-week treatment period in
fatigue severity and functional impairment. The authors concluded that these findings demonstrated no benefit of ondansetron compared to placebo in the treatment of CFS.

Alraek et al (2011) performed a systematic review of randomized controlled trials (RCTs) of complementary and alternative medicines (CAM) treatments in patients with CFS/myalgic encephalomyelitis (ME) was undertaken to summarize the existing evidence from RCTs of CAM treatments in this patient population. A total of 17 data sources were searched up to August 13, 2011. All RCTs of any type of CAM therapy used for treating CFS were included, with the exception of acupuncture and complex herbal medicines; studies were included regardless of blinding. Controlled clinical trials, uncontrolled observational studies, and case studies were excluded. A total of 26 RCTs, which included 3,273 participants, met the inclusion criteria. The CAM therapy from the RCTs included the following: mind-body medicine, distant healing, massage, tuina and tai chi, homeopathy, ginseng, and dietary supplementation. Studies of qigong, massage and tuina were demonstrated to have positive effects, whereas distant healing failed to do so. Compared with placebo, homeopathy also had insufficient evidence of symptom improvement in CFS. Seventeen studies tested supplements for CFS. Most of the supplements failed to show beneficial effects for CFS, with the exception of NADH and magnesium. The authors concluded that the results of this systematic review provided limited evidence for the effectiveness of CAM therapy in relieving symptoms of CFS. However, the authors were not able to draw firm conclusions concerning CAM therapy for CFS due to the limited number of RCTs for each therapy, the small sample size of each study and the high risk of bias in these trials. They stated that further rigorous RCTs that focus on promising CAM therapies are warranted.

An UpToDate review on “Clinical features and diagnosis of chronic fatigue syndrome” (Gluckman, 2013a) states that “The United States Centers for Disease Control and Prevention and the International Chronic Fatigue Syndrome Study Group published guidelines in 1994 regarding the standard evaluation in a patient suspected of having CFS. Patients with CFS must have clinically evaluated, unexplained, persistent, or relapsing fatigue plus four or more specifically defined associated symptoms. After a thorough history and physical examination, the patient is asked to keep temperature and weight records and limited laboratory testing is performed including: (i) complete blood count with differential count, (ii) erythrocyte sedimentation rate, (iii) chemistry screen, (iv) thyroid stimulating
hormone level, and (v) other tests when clinically indicated. Expensive immunologic tests and serologies are not useful. We do not routinely perform serologies for EBV, CMV, or Lyme disease, or test for antinuclear antibodies. In the setting of low pretest probability, any positive test is likely to be a false positive result, which may complicate the evaluation.

An UpToDate review on “Treatment of chronic fatigue syndrome” (Gluckman, 2013b) states that “A number of medications and special diets have been evaluated in patients with CFS, but none has proved successful. Among the modalities that have been tried are immune serum globulin, rituximab, acyclovir, galantamine, fluoxetine and other antidepressants, methylphenidate and modafinil (stimulants), glucocorticoids, amantadine, doxycycline, magnesium, evening primrose oil, vitamin B12, Ampligen, essential fatty acids, bovine or porcine liver extract, dialyzable leukocyte extract, cimetidine, ranitidine, interferons, exclusion diets, BioBran MGN-3 (a natural killer cell stimulant), and removal of dental fillings”.

Knight et al (2013) noted that a range of interventions have been used for the management of CFS/ME in children and adolescents. Currently, debate exists as to the effectiveness of these different management strategies. These researchers synthesized and critically appraised the literature on interventions for pediatric CFS/ME. CINAHL, PsycINFO and Medline databases were searched to retrieve relevant studies of intervention outcomes in children and/or adolescents diagnosed with CFS/ME. Two reviewers independently selected articles and appraised the quality on the basis of predefined criteria. A total of 24 articles based on 21 studies met the inclusion criteria. Methodological design and quality were variable. The majority assessed behavioral interventions (10 multi-disciplinary rehabilitation; 9 psychological interventions; 1 exercise intervention; 1 immunological intervention). There was marked heterogeneity in participant and intervention characteristics, and outcome measures used across studies. The strongest evidence was for cognitive behavioral therapy (CBT)-based interventions, with weaker evidence for multi-disciplinary rehabilitation. Limited information exists on the maintenance of intervention effects. The authors concluded that evidence for the effectiveness of interventions for children and adolescents with CFS/ME is still emerging. Methodological inadequacies and inconsistent approaches limit interpretation of findings. Moreover, they stated that there is some evidence that children and adolescents with CFS/ME benefit from particular interventions; however, there remain gaps in the current evidence base.
Powell et al. (2013) stated that the hypothalamic-pituitary-adrenal (HPA) axis is a psycho-neuroendocrine regulator of the stress response and immune system, and dysfunctions have been associated with outcomes in several physical health conditions. Its end product, cortisol, is relevant to fatigue due to its role in energy metabolism. These investigators examined the relationship between different markers of unstimulated salivary cortisol activity in everyday life in CFS and fatigue assessed in other clinical and general populations. Search terms for the review related to salivary cortisol assessments, everyday life contexts, and fatigue. All eligible studies (n = 19) were reviewed narratively in terms of associations between fatigue and assessed cortisol markers, including the cortisol awakening response (CAR), circadian profile (CP) output, and diurnal cortisol slope (DCS). Subset meta-analyses were conducted of case-control CFS studies examining group differences in 3 cortisol outcomes: (i) CAR output; (ii) CAR increase; and (iii) CP output. Meta-analyses revealed an attenuation of the CAR increase within CFS compared to controls (d = -0.34) but no statistically significant differences between groups for other markers. In the narrative review, total cortisol output (CAR or CP) was rarely associated with fatigue in any population; CAR increase and DCS were most relevant. The authors concluded that outcomes reflecting within-day change in cortisol levels (CAR increase; DCS) may be the most relevant to fatigue experience, and future research in this area should report at least one such marker. Moreover, they stated that results should be considered with caution due to heterogeneity in 1 meta-analysis and the small number of studies.

Furthermore, an UpToDate review on “Clinical features and diagnosis of chronic fatigue syndrome” (Gluckman, 2014a) does not mention the use of salivary cortisol assessments as a diagnostic tool.

Sulheim et al. (2014) explored the pathophysiology of CFS and assessed clonidine hydrochloride pharmacotherapy in adolescents with CFS by using a hypothesis that patients with CFS have enhanced sympathetic activity and that sympatho-inhibition by clonidine would improve symptoms and function. Participants were enrolled from a single referral center recruiting nationwide in Norway. A referred sample of 176 adolescents with CFS was assessed for eligibility; 120 were included (34 males and 86 females; mean age of 15.4 years). A volunteer sample of 68 healthy adolescents serving as controls was included (22 males and 46 females; mean age of 15.1 years). The CSF patients and healthy controls were assessed cross-sectionally at baseline. Thereafter, patients with CFS were randomized 1:1 to treatment with low-dose clonidine or placebo for 9 weeks and monitored for 30
weeks; double-blinding was provided. Data were collected from March 2010 until October 2012 as part of the Norwegian Study of Chronic Fatigue Syndrome in Adolescents: Pathophysiology and Intervention Trial. Clonidine hydrochloride capsules (25 µg or 50 µg twice-daily) versus placebo capsules for 9 weeks. Main outcome measure was number of steps per day. At baseline, patients with CFS had a lower number of steps per day (p < 0.001), digit span backward score (p=0.002), and urinary cortisol to creatinine ratio (p = 0.001), and a higher fatigue score (p < 0.001), heart rate responsiveness (p = 0.02), plasma norepinephrine level (p < 0.001), and serum C-reactive protein concentration (p = 0.04) compared with healthy controls. There were no significant differences regarding blood microbiology evaluation. During intervention, the clonidine group had a lower number of steps per day (mean difference, -637 steps; p = 0.07), lower plasma norepinephrine level (mean difference, -42 pg/ml; p = 0.01), and lower serum C-reactive protein concentration (mean ratio, 0.69; p = 0.02) compared with the CFS placebo group. The authors concluded that adolescent CFS is associated with enhanced sympathetic nervous activity, low-grade systemic inflammation, attenuated HPA axis function, cognitive impairment, and large activity reduction, but not with common microorganisms. Low-dose clonidine attenuated sympathetic outflow and systemic inflammation in CFS but has a concomitant negative effect on physical activity; thus, sympathetic and inflammatory enhancement may be compensatory mechanisms. They stated that low-dose clonidine is not clinically useful in CFS.

Also, an UpToDate review on “Treatment of chronic fatigue syndrome” (Gluckman, 2014b) does not mention the use of clonidine as a therapeutic option.

The National Institute for Health and Clinical Excellence’s guideline on “Chronic fatigue syndrome/myalgicencephalomyelitis (or encephalopathy): Diagnosis and management of CFS/ME in adults and children” (NICE, 2007) stated that the following drugs should not be used for the treatment of CFS/ME:

- Anti-viral agents
- Dexamphetamine
- Glucocorticoids (such as hydrocortisone)
- Methylphenidate
- Mineralocorticoids (such as fludrocortisone)
- Monoamine oxidase inhibitors
- Thyroxine
In a 12-week, randomized, double-blind study, Arnold et al (2015) compared duloxetine 60 to 120 mg/day (n = 30) with placebo (n = 30) for safety and effectiveness in the treatment of patients with CFS. The primary outcome measure was the Multidimensional Fatigue Inventory general fatigue subscale (range of 4 to 20, with higher scores indicating greater fatigue). Secondary measures were the remaining Multidimensional Fatigue Inventory subscales, Brief Pain Inventory, Medical Outcomes Study Short Form-36, Hospital Anxiety and Depression Scale, Centers for Disease Control and Prevention Symptom Inventory, Patient Global Impression of Improvement, and Clinical Global Impression of Severity. The primary analysis of efficacy for continuous variables was a longitudinal analysis of the intent-to-treat sample, with treatment-by-time interaction as the measure of effect. The improvement in the Multidimensional Fatigue Inventory general fatigue scores for the duloxetine group was not significantly greater than for the placebo group (p = 0.23; estimated difference between groups at week 12 = -1.0 [95 % CI: -2.8 to 0.7]). The duloxetine group was significantly superior to the placebo group on the Multidimensional Fatigue Inventory mental fatigue score, Brief Pain Inventory average pain severity and interference scores, Short Form-36 bodily pain domain, and Clinical Global Impression of Severity score. Duloxetine was generally well-tolerated. The authors concluded that the primary efficacy measure of general fatigue did not significantly improve with duloxetine when compared with placebo. They stated that significant improvement in secondary measures of mental fatigue, pain, and global measure of severity suggested that duloxetine may be effective for some CFS symptom domains, but larger controlled trials are needed to confirm these results.

Courtois et al (2015) stated that patients with long-lasting pain problems often complain of lack of confidence and trust in their body. Through physical experiences and reflections they can develop a more positive body- and self-experience. Body awareness has been suggested as an approach for treating patients with chronic pain and other psychosomatic conditions. These investigators evaluated the effectiveness of body awareness interventions (BAI) in fibromyalgia (FM) and CFS. Two independent readers conducted a search on Medline, Cochrane Central, PsycINFO, Web of knowledge, PEDro and Cinahl for RCTs. They identified and screened 7.107 records of which 29 articles met the inclusion criteria. Overall, there is evidence that BAI has positive effects on the Fibromyalgia Impact Questionnaire (FIQ) (standardized mean difference [SMD] -5.55; CI: -8.71 to -2.40), pain (SMD -0.39, CI: -0.75 to -0.02), depression (SMD -0.23, CI: -0.39 to -0.06), anxiety (SMD -0.23, CI: -0.44 to -0.02) and Health Related Quality of Life. 
(HRQoL) (SMD 0.62, CI: 0.35 to 0.90) when compared with control conditions. The overall heterogeneity is very strong for FIQ (I(2) 92 %) and pain (I(2) 97 %), which cannot be explained by differences in control condition or type of BAI (hands-on/hands-off). The overall heterogeneity for anxiety, depression and HRQoL ranges from low to moderate (I(2) 0 % to 37 %). The authors concluded that body awareness seems to play an important role in anxiety, depression and HRQoL. Moreover, they stated that interpretations have to be done carefully since the lack of high quality studies.

Blundell et al (2015) stated that there has been much interest in the role of the immune system in the pathophysiology of CFS, as CFS may develop following an infection and cytokines are known to induce acute sickness behavior, with similar symptoms to CFS. Using the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-analyses) guidelines, a search was conducted on PubMed, Web of Science, Embase and PsycINFO, for CFS related-terms in combination with cytokine-related terms. Cases had to meet established criteria for CFS and be compared with healthy controls. Papers retrieved were assessed for both inclusionary criteria and quality. A total of 38 papers met the inclusionary criteria. The quality of the studies varied; 77 serum or plasma cytokines were measured without immune stimulation. Cases of CFS had significantly elevated concentrations of transforming growth factor-beta (TGF-β) in 5 out of 8 (63 %) studies. No other cytokines were present in abnormal concentrations in the majority of studies, although insufficient data were available for some cytokines. Following physical exercise there were no differences in circulating cytokine levels between cases and controls and exercise made no difference to already elevated TGF-β concentrations. The authors concluded that the finding of elevated TGF-β concentration, at biologically relevant levels, needs further exploration, but circulating cytokines do not seem to explain the core characteristic of post-exertional fatigue.

Experimental and Investigational Therapies

An UpToDate review on “Treatment of systemic exertion intolerance disease (chronic fatigue syndrome)” (Gluckman, 2016) states that “Galantamine is a centrally acting acetylcholinesterase inhibitor that has been used to treat Alzheimer disease. In the largest and best designed randomized, double-blind, controlled trial that has been performed for the treatment of CFS/SEID, 434 patients at multiple centers were randomly assigned to one of four doses of galantamine or placebo.
At 16 weeks, there was no benefit from galantamine in the primary end point (improvement in the Clinical Global Impression Scale) or in any secondary end points. Intramuscular immunoglobulin injections appeared to be beneficial in one small controlled trial. However, this finding is in contrast to the more general experience. Controlled trials of intravenous immune globulin yielded conflicting and unimpressive results with a high incidence of adverse effects. There were no differences in B cell levels between patients in the rituximab group who achieved a response compared with those who did not achieve a response. Though intriguing, these findings are too preliminary to support the use of rituximab, a drug that can cause immunosuppression and serious complications. This study needs to be repeated with a larger number of patients .... Rintatolimod is an investigational immune modulator and antiviral drug that has been approved for the treatment of CFS/SEID in Canada and Europe. It improved measures of exercise performance in two randomized trials; however, the clinical implications were unclear. Treatment with this drug should be considered experimental until more studies have been done".

Rekeland and colleagues (2018) noted that previous phase-II clinical trials indicated benefit from B-cell depletion using rituximab in patients with CFS/ME. The association between rituximab serum concentrations and the effect and clinical relevance of anti-drug antibodies (ADAs) against rituximab in CFS/ME is unknown. In an open-label, phase-II clinical trial, these researchers retrospectively measured rituximab concentrations and ADAs in serum samples from patients with maintenance rituximab treatment (KTS-2-2010) to examine possible associations with clinical improvement and clinical and biochemical data. Patients with CFS/ME meeting the Canadian criteria received rituximab (500 mg/m2) infusions: 2 infusions 2 weeks apart (induction), followed by maintenance treatment at 3, 6, 10, and 15 months. The measured rituximab concentrations and ADAs in serum samples included 23 of 28 patients from the trial. There were no significant differences in mean serum rituximab concentrations between 14 patients experiencing clinical improvement versus 9 patients with no improvement. Female patients had higher mean serum rituximab concentrations than male patients at 3 months (p = 0.05). There was a significant negative correlation between B-cell numbers in peripheral blood at baseline and rituximab serum concentration at 3 months (r = -0.47; p = 0.03). None of the patients had ADAs at any time-point. The authors concluded that clinical improvement of patients with CFS/ME in the KTS-2-2010 trial was not related to rituximab serum concentrations or ADAs. These researchers stated that
this finding was also in line with a recent randomized trial examining the efficacy of rituximab in CFS/ME; rituximab concentrations and ADAs still offer supplemental information when interpreting the results of these trials.

Drug Therapies

Collatz and colleagues (2016) noted that the pathogenesis of CFS/ME is complex and remains poorly understood. Evidence regarding the use of drug therapies in CFS/ME is currently limited and conflicting. These researchers evaluated the existing evidence on the effectiveness of drug therapies and examined if any can be recommended for patients with CFS/ME. Medline, Embase, and PubMed databases were searched from the start of their records to March 2016 to identify relevant studies; RCTs focusing solely on drug therapy to alleviate and/or eliminate CFS symptoms were included in the review. Any trials that considered graded exercise therapy, CBT, adaptive pacing, or any other non-pharmaceutical treatment plans were excluded. The inclusion criteria were examined to ensure that study participants met specific CFS/ME diagnostic criteria. Study size, intervention, and end point outcome domains were summarized. A total of 1,039 studies were identified with the search terms; 26 studies met all the criteria and were considered suitable for review; 3 different diagnostic criteria were identified: (i) the Holmes criteria, (ii) International Consensus Criteria, and (iii) the Fukuda criteria. Primary outcomes were identified as fatigue, pain, mood, neurocognitive dysfunction and sleep quality, symptom severity, functional status, and well-being or overall health status; 20 pharmaceutical classes were trialed; 10 medications were shown to be slightly to moderately effective in their respective study groups (p < 0.05). The authors concluded that these findings indicated that no universal pharmaceutical treatment can be recommended. The unknown etiology of CFS/ME, and complications arising from its heterogeneous nature, contributed to the lack of clear evidence for pharmaceutical interventions. However, patients report using a large number and variety of medications. This finding highlighted the need for trials with clearly defined CFS/ME cohorts. Trials based on more specific criteria such as the International Consensus Criteria are recommended to identify specific subgroups of patients in whom treatments may be beneficial.

Adrenocorticotrophic Hormone (ACTH) Stimulation Test
Bearn et al (1995) noted that chronic fatigue syndrome (CFS) is a disorder characterized by severe physical and mental fatigue and fatigability of central rather than peripheral origin. These researchers hypothesized that CFS is mediated by changes in hypothalamo-pituitary function and so measured the adrenocorticotrophic hormone (ACTH), cortisol, growth hormone (GH), and prolactin responses to insulin-induced hypoglycemia, and the ACTH, cortisol, and prolactin responses to serotoninergic stimulation with dexfenfluramine in non-depressed CFS patients and normal controls. These investigators have shown attenuated prolactin responses to hypoglycemia in CFS. There was also a greater ACTH response and higher peak ACTH concentrations (36.44 +/- 4.45 versus 25.60 +/- 2.78 pg/ml), whereas cortisol responses did not differ, findings that were compatible with impaired adrenal cortical function. The authors concluded that the findings of this study provided evidence for both pituitary and adrenal cortical impairment in CFS; they stated that further studies are needed to both confirm and determine more precisely their neurobiological basis so that rational treatments can be evolved.

Scott et al (1998) stated that hypo-functioning of the pituitary-adrenal axis has been suggested as the pathophysiological basis for CFS. Blunted ACTH responses but normal cortisol responses to exogenous corticotropin-releasing hormone (CRH), the main regulator of this axis, have been previously demonstrated in CFS patients, some of whom had a co-morbid psychiatric disorder. These researchers re-examined CRH activation of this axis in CFS patients free from concurrent psychiatric illness. A sample of 14 patients with CDC-diagnosed CFS were compared with 14 healthy volunteers. ACTH and cortisol responses were measured following the administration of 100 ug ovine CRH. Basal ACTH and cortisol values did not differ between the 2 groups. The release of ACTH was significantly attenuated in the CFS group (p < 0.005), as was the release of cortisol (p < 0.05). The blunted response of ACTH to exogenous CRH stimulation may be due to an abnormality in CRH levels with a resultant alteration in pituitary CRH receptor sensitivity, or it may reflect a dysregulation of vasopressin or other factors involved in HPA regulation. The authors concluded that a diminished output of neurotrophic ACTH, causing a reduced adrenocortical secretory reserve, inadequately compensated for by adrenoceptor up-regulation, may explain the reduced cortisol production demonstrated in this study. This was a small study (n = 14); its findings need to be validated by well-designed studies.
De Becker et al (1999) noted that previous studies have demonstrated concentrating neuroendocrinological disturbances in CFS patients, concentrating in particular on low cortisol levels and a hypothalamic deficiency. In order to investigate the dynamic response of the adrenal glands, these investigators measured dehydroepiandrosterone (DHEA) in serum after ACTH stimulation during 60 minutes in 22 CFS-patients and 14 healthy controls. These researchers found normal basal DHEA levels, but a blunted serum DHEA response curve to i.v. ACTH injection. This observation added to the large amount of evidence of endocrinological abnormalities in CFS. The authors concluded that relative glucocorticoid deficiency might contribute to the overall clinical picture in CFS, and could explain some of the immunological disturbances observed in this syndrome. Again, this was a small study (n = 22); its findings need to be validated by well-designed studies.

Scott et al (2000) stated that abnormalities of the production of DHEA, the adrenal androgen, have been linked with disorders such as obesity and psychological disorders such as major depression; ACTH is the primary stimulant of DHEA, and cortisol, from the adrenal. These researchers examined the DHEA and DHEA/cortisol response to the novel low-dose ACTH test in healthy subjects and a cohort with CFS: this test is useful in assessing subtle irregularities of pituitary-adrenal activity. A total of 19 CFS subjects (diagnosed by CDC criteria) and 10 healthy subjects were examined. These investigators demonstrated that 1 ug ACTH significantly elevated DHEA levels, with no difference in output between CFS and healthy subjects. The DHEA/cortisol ratio decreased in response to ACTH stimulation in healthy subjects but not in the CFS cohort. The authors suggested this divergence of response between the 2 groups represented an imbalance in the relative synthetic pathways of the CFS group which, if present chronically and if comparable to daily stressors, may manifest itself as an inappropriate response to stress. This difference may be important in either the genesis or propagation of the syndrome.

Zarkovic et al (2003) stated that CFS is defined as constellation of the prolonged fatigue and several somatic symptoms, in the absence of organic or severe psychiatric disease. However, this is an operational definition and conclusive biomedical explanation remains elusive. Similarities between the signs and symptoms of CFS and adrenal insufficiency prompted the research of the hypothalamo-pituitary-adrenal axis (HPA) derangement in the pathogenesis of the CFS. Early studies showed mild glucocorticoid deficiency, probably of central origin
that was compensated by enhanced adrenal sensitivity to ACTH. Further studies showed reduced ACTH response to vasopressin infusion. The response to CRH was either blunted or unchanged. Cortisol response to insulin induced hypoglycemia was same as in the control subjects while ACTH response was reported to be same or enhanced. However, results of direct stimulation of the adrenal cortex using ACTH were conflicting. Cortisol and DHEA responses were found to be the same or reduced compared to control subjects. Scott et al found that maximal cortisol increment from baseline is significantly lower in CFS subjects. The same group also found small adrenal glands in some CFS subjects. These varied and inconsistent results could be explained by the heterogeneous study population due to multi-factorial causes of the disease and by methodological differences. These researchers evaluated cortisol response to low-dose (1 ug) ACTH using previously validated methodology. They compared cortisol response in the CFS subjects with the response in control and in subjects with suppressed HPA axis due to prolonged corticosteroid use. Cortisol responses were analyzed in 3 subject groups: (i) control (C), (ii) secondary adrenal insufficiency (AI), and (iii) CFS. The C group consisted of 39 subjects, AI group of 22, and CFS group of 9 subjects. Low-dose ACTH test was started at 0800 h with the i.v. injection of 1 ug ACTH. Blood samples for cortisol determination were taken from the i.v. cannula at 0, 15, 30, and 60 min. Data were presented as mean +/- standard error (SE). Statistical analysis was done using ANOVA with the Games-Howell post-hoc test to determine group differences. ACTH dose per kg or per square meter of body surface was not different between the groups. Baseline cortisol was not different between the groups. However, cortisol concentrations after 15 and 30 minutes were significantly higher in the C group than in the AI group. Cortisol concentration in the CFS group was not significantly different from any other group. Cortisol increment at 15 and 30 minutes from basal value was significantly higher in C group than in other 2 groups. However, there was no significant difference in cortisol increment between the AI and CFS groups at any time of the test. On the contrary, maximal cortisol increment was not different between CFS and other 2 groups, although it was significantly higher in C group than in the AI group. Maximal cortisol response to the ACTH stimulation and area under the cortisol response curve was significantly larger in C group compared to AI group, but there was no difference between CFS and other two groups. Several previous studies assessed cortisol response to ACTH stimulation. Hudson and Cleare analyzed cortisol response to 1 ug ACTH in CFS and control subjects. They compared maximum cortisol attained during the test, maximum cortisol increment, and area under the cortisol response curve. There was no difference between the groups in
any of the analyzed parameters. However, the authors commented that responses were generally low. On the contrary Scott et al found that cortisol increment at 30 min was significantly lower in the CFS than in the control group. Taking into account of these researchers’ data it appeared that the differences found in previous studies papers were caused by the methodological differences. These investigators have shown that cortisol increment at 15 and 30 min was significantly lower in CFS group than in C group. Nevertheless, maximum cortisol attained during the test, maximum cortisol increment, and area under the cortisol response curve were not different between the C and CFS groups. This was in agreement with the authors’ previous findings that cortisol increment at 15 minutes had the best diagnostic value of all parameters obtained during of low-dose ACTH test. However, there was no difference between CFS and AI group in any of the parameters, although AI group had significantly lower cortisol concentrations at 15 and 30 minutes, maximal cortisol response, area under the cortisol curve, maximal cortisol increment, and maximal cortisol change velocity than C group. Consequently, reduced adrenal responsiveness to ACTH existed in CFS. The authors concluded that regarding the adrenal response to ACTH stimulation, CFS subjects presented heterogeneous group. In some subjects cortisol response was preserved, while in the others it was similar to one found in secondary adrenal insufficiency.

Cleare et al (2011) found that ACTH responses to hCRH and the hypothalamic challenges IST and d-fenfluramine did not differ between CFS subjects and healthy controls. This indicated that central response mechanisms in the HPA axis are intact in CFS. The finding of reduced UFC output, and the finding of reduced adrenal responses to these challenges when pituitary responses were controlled for, together with other findings of reduced adrenal gland output in other studies suggested an alternative hypothesis of adrenal gland dysfunction in CFS. The authors concluded that these findings suggested that future studies should focus on adrenal gland, rather than hypothalamic or pituitary, function in CFS.

Furthermore, an UpToDate review on “Clinical features and diagnosis of systemic exertion intolerance disease (chronic fatigue syndrome)” (Gluckman, 2017) does not mention ACTH/adrenocorticotropic hormone stimulation as a diagnostic test.

**Repetitive Transcranial Magnetic Stimulation**
In a case-series study, Kakuda and colleagues (2016) applied facilitatory high-frequency repetitive transcranial magnetic stimulation (rTMS) to the dorsolateral prefrontal cortex (DLPFC) of 7 CFS patients over 3 days; 5 patients completed the 3-day protocol without any adverse events (AEs). For the other 2 patients, these researchers had to reduce the stimulation intensity in response to mild AEs. In most of the patients, treatment resulted in an improvement of fatigue symptoms. The authors concluded that high-frequency rTMS applied over the DLPFC can therefore be a potentially useful therapy for CFS patients. They stated that further large-scale studies are needed to confirm the therapeutic benefits of high-frequency rTMS, determine the optimal cortical target area and find the optimal duration and intensity of treatment for CFS.

This study had several drawbacks: (i) this was a case-series, pilot study with only a small number of patients (n = 7) that lacked a control group. Comparative studies, such as randomized controlled design studies that include a large number of patients, are needed to confirm the efficacy of rTMS in CFS patients, (ii) although all patients met the inclusion criteria for rTMS application, they were a heterogeneous group based on the wide variability of age, duration of illness and severity of the fatigue symptoms. The identification of the clinical factors that correlate with the effectiveness of rTMS can help in the selection of patients who will best benefit from the treatment, (iii) although it is difficult to stimulate deep brain lesions using the currently available technology, the stimulation of other brain areas with functional or structural abnormalities in CFS, such as the cingulate cortex and brainstem, may produce a better clinical improvement, and (iv) for 1 left-handed patient, these researchers applied high-frequency rTMS to the right hemisphere unlike the other 6 patients. The appropriateness of this therapeutic strategy of rTMS depending on whether patients were right-handed or left-handed should be also confirmed.

**Circulating Cytokine Profiling**

Moneghetti and colleagues (2018) stated that CFS/ME is a heterogeneous syndrome in which patients often experience severe fatigue and malaise following exertion. Immune and cardiovascular dysfunction have been postulated to play a role in the pathophysiology. These researchers examined if cytokine profiling or cardiovascular testing following exercise would differentiate patients with CFS/NE. A total of 24 CFS/ME patients were matched to 24 sedentary controls and underwent cardiovascular and circulating immune profiling. Cardiovascular
analysis included echocardiography, cardiopulmonary exercise and endothelial function testing. Cytokine and growth factor profiles were analyzed using a 51-plex Luminex bead kit at baseline and 18 hours following exercise. Cardiac structure and exercise capacity were similar between groups. Sparse partial least square discriminant analyses of cytokine profiles 18 hours post-exercise offered the most reliable discrimination between CFS/ME and controls ($\kappa = 0.62 (0.34, 0.84)$). The most discriminatory cytokines post-exercise were CD40L, platelet activator inhibitor, interleukin 1-β, interferon-α and CXCL1. The authors concluded that cytokine profiling following exercise may help differentiate patients with CFS/ME from sedentary controls. Moreover, they stated that replicating these findings and examining profiling using a 2-day protocol will be important steps for future research.

The authors stated that this study had several drawbacks. First, although these patients were carefully selected and matched with sedentary controls, the sample size was small ($n = 24$ for the CFS/ME group) with a small but statistically significant difference in BMI between groups. There was however, no difference in the number of participants, overweight or obese by this classification. In an effort to avoid false discovery rates, these researchers also conducted careful adjustment of multiple measures. The fact that exercise was able to reveal similar factors of the larger resting study of Hornig et al increased confidence in these findings. Despite no exercise validation cohort, the fact that several factors discussed emerged in both patients with CFS/ME as well as sedentary controls also brought more confidence in the results. Luminex assays were also known not to have a good signal to noise ratio for interleukin (IL)-6, however, these findings appeared consistent with contemporary studies. Finally, the author selected a sub-group of patients with CFS/ME, with severe post-exercise fatigue to ensure a more specific phenotype.

**Evaluation of Premature Telomere Attrition (Accelerated Aging)**

Rajeevan and colleagues (2018) noted that CFS (also known as ME) is a severely debilitating condition of unknown etiology. The symptoms and risk factors of CFS/ME share features of accelerated aging implicated in several diseases. Using telomere length as a marker, this study was performed to test the hypothesis that CFS/ME is associated with accelerated aging. Participant ($n = 639$) data came from the follow-up time-point of the Georgia CFS surveillance study. Using the 1994 CFS Research Case Definition with questionnaire-based subscale thresholds
for fatigue, function, and symptoms, participants were classified into 4 illness groups: CFS if all criteria were met (n = 64), CFS-X if CFS with exclusionary conditions (n = 77), ISF (insufficient symptoms/fatigue) if only some criteria were met regardless of exclusionary conditions (n = 302), and NF (non-fatigued) if no criteria and no exclusionary conditions (n = 196). Relative telomere length (T/S ratio) was measured using DNA from whole blood and real-time PCR. General linear models were used to estimate the association of illness groups or T/S ratio with demographics, biological measures and co-variates with significance set at p < 0.05. The mean T/S ratio differed significantly by illness group (p = 0.0017); the T/S ratios in CFS (0.90 ± 0.03) and ISF (0.94 ± 0.02) were each significantly lower than in NF (1.06 ± 0.04). Differences in T/S ratio by illness groups remained significant after adjustment for covariates of age, sex, BMI, waist-hip ratio, post-exertional malaise and education attainment. Telomere length was shorter by 635, 254, and 424 base pairs in CFS, CFS-X and ISF, respectively, compared to NF. This shorter telomere length translated to roughly 10.1 to 20.5, 4.0 to 8.2 and 6.6 to 13.7 years of additional aging in CFS, CFS-X and ISF compared to NF respectively. Furthermore, stratified analyses based on age and sex demonstrated that the association of CFS/ME with short telomeres was largely moderated by female subjects of less than 45 years of age. The authors concluded that this study found a significant association of CFS/ME with premature telomere attrition that was largely moderated by female subjects of less than 45 years of age. They stated that these findings indicated that CFS/ME could be included in the list of conditions associated with accelerated aging; further work is needed to evaluate the functional significance of accelerated aging in CFS/ME.

Anakinra

In a randomized, placebo-controlled trial, Roerink and associates (2017) examined the effect of subcutaneous anakinra versus placebo on fatigue severity in female patients with CFS. Patients, providers, and researchers were blinded to treatment assignment. A total of 50 women aged 18 to 59 years with CFS and severe fatigue leading to functional impairment were included in this study. Participants were randomly assigned to daily subcutaneous anakinra, 100 mg (n = 25), or placebo (n = 25) for 4 weeks and were followed for an additional 20 weeks after treatment (n = 50). The primary outcome was fatigue severity, measured by the Checklist Individual Strength subscale (CIS-fatigue) at 4 weeks. Secondary outcomes were level of impairment, physical and social functioning, psychological distress, and pain severity at 4 and 24 weeks. At 4 weeks, 8 % (2 of 25) of anakinra recipients
and 20 % (5 of 25) of placebo recipients reached a fatigue level within the range reported by healthy persons. There were no clinically important or statistically significant differences between groups in CIS-fatigue score at 4 weeks (MD, 1.5 points [95 % CI: -4.1 to 7.2 points]) or the end of follow-up. No statistically significant between-group differences were seen for any secondary outcome at 4 weeks or the end of follow-up. One patient in the anakinra group discontinued treatment because of an adverse event (AE). Patients in the anakinra group had more injection site reactions (68 % [17 of 25] versus 4 % [1 of 25]). The authors concluded that peripheral IL-1 inhibition using anakinra for 4 weeks did not result in a clinically significant reduction in fatigue severity in women with CFS and severe fatigue.

Probiotics for Chronic Fatigue Syndrome

Corbitt and colleagues (2018) stated that gastro-intestinal (GI) symptoms and irritable bowel (IB) symptoms have been associated with CFS/ ME. These investigators performed a systematic review of these symptoms in CFS/ME, along with any evidence for probiotics as treatment. PubMed, Scopus, Medline (EBSCOHost) and Embase databases were searched to source relevant studies for CFS/ME. The review included any studies examining GI symptoms, irritable bowel syndrome (IBS) and/or probiotic use. Studies were required to report criteria for CFS/ME and study design, intervention and outcome measures. Quality assessment was also completed to summarize the level of evidence available. A total of 3,381 publications were returned using the search terms. A total of 25 studies were included in the review; RCTs were the predominant study type (n = 24). Most of the studies identified examined the effect of probiotic supplementation on the improvement of IB symptoms in IBS patients, or IB symptoms in CFS/ME patients, as well as some other significant secondary outcomes (e.g., quality of life [QOL], other GI symptoms, psychological symptoms). The level of evidence identified for the use of probiotics in IBS was excellent in quality; however, the evidence available for the use of probiotic interventions in CFS/ME was poor and limited. The authors concluded that there is currently insufficient evidence for the use of probiotics in CFS/ME patients, despite probiotic interventions being useful in IBS. The studies pertaining to probiotic interventions in CFS/ME patients were limited and of poor quality overall; standardization of protocols and methodology in these studies is needed.
Roman and associates (2018) noted that evidence suggested that the gut microbiota might play an important role in fibromyalgia syndrome (FMS) and CFS. These investigators reviewed the reported effect of probiotic treatments in patients diagnosed with FMS or CFS. They performed a systematic review using 14 databases (PubMed, Cochrane Library, Scopus, PsycINFO, and others) in February 2016 to search for RCTs and pilot studies of CFS or FMS patient, published in the past 10 years (from 2006 to 2016). The Jadad scale was used to evaluate the quality of the clinical trials considered; 2 studies (n = 83) met the inclusion criteria, which were performed in CFS patients and both studies were considered as a “high range of quality score”. The administration of Lactobacillus casei strain Shirota in CFS patients, over the course of 8 weeks, reduced anxiety scores. Likewise, this probiotic changed the fecal composition following 8 weeks of treatment. Additionally, the treatment with Bifidobacterium infantis 35624 in CFS patients, during the same period, reduced inflammatory biomarkers. The authors concluded that the evidence on the usefulness of probiotics in CFS and FMS patients remains limited. The studied strains of probiotics have demonstrated a significant effect on modulating the anxiety and inflammatory processes in CFS patients. However, these researchers stated that more experimental research, focusing mainly on the symptoms of the pathologies studied, is needed.

Measurements of Plasma Brain Natriuretic Peptide Levels for Guidance of Targeted Therapy of CFS

In a case-control study, Tomas and colleagues (2017) examined levels of the brain natriuretic peptide (BNP) and their association with the cardiac abnormalities recently identified in CFS. Cardiac magnetic resonance examinations were performed using 3T Philips Intera Achieva scanner in CFS patients and sedentary controls matched for age and sex; BNP was also measured by using an enzyme immunoassay in plasma from 42 patients with CFS and 10 controls. BNP levels were significantly higher in the CFS cohort compared with the matched controls (p = 0.013). When these researchers compared cardiac volumes (end-diastolic and end-systolic) between those with high BNP levels (BNP greater than 400 pg/ml) and low BNP (less than 400 pg/ml), there were significantly lower cardiac volumes in those with the higher BNP levels in both end-systolic and end-diastolic volumes (p = 0.05). There were no relationships between fatigue severity, length of disease and BNP levels (p = 0.2) suggesting that these findings were unlikely to be related to deconditioning. The authors concluded that the findings of this study confirmed an association between reduced cardiac volumes and BNP in CFS; lack of
relationship between length of disease suggested that findings were not secondary to deconditioning. They stated that further studies are needed to examine the utility of blood BNP to act as a stratification paradigm in CFS that directs targeted treatments.

**Evaluation of Enteric Dysbiosis (Abnormal Microbial Ecology) / Gastro-Intestinal Flora Altering Therapy**

Du Preez and colleagues (2018) CFS or myalgic encephalomyelitis (CFS/ME) is an illness characterized by profound and pervasive fatigue in addition to a heterogeneous constellation of symptoms. The etiology of this condition remains unknown; however, it has been previously suggested that enteric dysbiosis is implicated in the pathogenesis of CFS/ME. These researchers examined the evidence for the presence of abnormal microbial ecology in CFS/ME in comparison to healthy controls, with one exception being probiotic-supplemented CFS/ME patients, and whether the composition of the microbiome plays a role in symptom causation. Embase, Medline (via EBSCOhost), PubMed and Scopus were systematically searched from 1994 to March 2018. All studies that investigated the gut microbiome composition of CFS/ME patients were initially included before the application of specific exclusion criteria. The association between these findings and patient-centered outcomes (fatigue, QOL, GI symptoms, psychological wellbeing) were also reported. A total of 7 studies that met the inclusion criteria were included in the review. The microbiome composition of CFS/ME patients was compared with healthy controls, with the exception of 1 study that compared to probiotic-supplemented CFS/ME patients. Differences were reported in each study; however, only 3 were considered statistically significant, and the findings across all studies were inconsistent. The quality of the studies included in this review scored between poor (less than 54 %), fair (54 to 72 %) and good (94 to 100 %) using the Downs and Black checklist. The authors concluded that there is currently insufficient evidence for enteric dysbiosis playing a significant role in the pathogenic mechanism of CFS/ME. Recommendations for future research in this field included the use of consistent criteria for the diagnosis of CFS/ME, reduction of confounding variables by controlling factors that influence microbiome composition before sample collection and including more severe cases of CFS/ME. Furthermore, these researchers stated that based on currently available data presented in this systematic review, the effectivity of GI flora altering therapy in the treatment of CFS/ME is yet to be confirmed.
Blood and Cerebrospinal Fluid Cytokines Assays

Groven and associates (2018) noted that reports regarding the status of the immune system in patients with CFS/ME have been inconclusive. These researchers approached this question by comparing a strictly defined group of CFS/ME out-patients to healthy controls, and thereafter studied cytokines in subgroups with various psychiatric symptoms. A total of 20 patients diagnosed with CFS/ME according to the Fukuda criteria and 20 age- and sex-matched healthy controls were enrolled in the study. Plasma was analyzed by ELISA for levels of the cytokines tumor necrosis factor-alpha (TNF-α), IL-4, IL-6 and IL-10. Subjects also answered questionnaires regarding health in general, and psychiatric symptoms in detail. Increased plasma levels of TNF-α in CFS/ME patients almost reached significance compared to healthy controls (p = 0.056). When studying the CFS/ME and control groups separately, there was a significant correlation between TNF-α and the Hospital Anxiety and Depression Scale (HADS) depressive symptoms in controls only, not in the CFS/ME group. A correlation between IL-10 and psychoticism was found in both groups, whereas the correlation for somatization was observed only in the CFS/ME group. When looking at the total population, there was a significant correlation between TNF-α and both the HADS depressive symptoms and the SCL-90-R cluster somatization. Furthermore, there was a significant association between IL-10 and the SCL-90-R cluster somatization when analyzing the cohort (patients and controls together). The authors concluded that these findings indicated that immune activity in CFS/ME patients deviated from that of healthy controls, which implied potential pathomechanisms and possible therapeutic approaches to CFS/ME. These investigators stated that more comprehensive studies should be performed on defined CFS/ME subgroups.

VanElzakker and colleagues (2019) stated that CFS/ME is the label given to a syndrome that could entail long-term flu-like symptoms, profound fatigue, trouble concentrating, and autonomic problems, all of which worsen after exertion. It is unclear how many individuals with this diagnosis are suffering from the same condition or have the same underlying pathophysiology, and the discovery of biomarkers would be clarifying. The name "myalgic encephalomyelitis" essentially means "muscle pain related to central nervous system inflammation" and many efforts to find diagnostic biomarkers have focused on one or more aspects of neuro-inflammation, from periphery to brain. As the field uncovers the relationship between the symptoms of this condition and neuro-inflammation, attention must be paid to the biological mechanisms of neuro-inflammation and issues with its
potential measurement. These researchers focused on 3 methods used to study putative neuro-inflammation in CFS/ME: First, positron emission tomography (PET) neuroimaging using translocator protein (TSPO) binding radio-ligand. Secondly, magnetic resonance spectroscopy (MRS) neuroimaging, and lastly assays of cytokines circulating in blood and cerebrospinal fluid (CSF). PET scanning using TSPO-binding radio-ligand is a promising option for studies of neuro-inflammation. However, methodological difficulties that exist both in this particular technique and across the CFS/ME neuroimaging literature must be addressed for any results to be interpretable. These investigators argued that the vast majority of CFS/ME neuroimaging has failed to use optimal techniques for studying brain-stem, despite its probable centrality to any neuro-inflammatory causes or autonomic effects; MRS was discussed as a less informative but more widely available, less invasive, and less expensive option for imaging neuro-inflammation, and existing studies using MRS neuroimaging were reviewed. Studies seeking to find a peripheral circulating cytokine "profile" for CFS/ME were reviewed, with attention paid to the biological and methodological reasons for lack of replication among these studies. The authors argued that both the biological mechanisms of cytokines and the innumerable sources of potential variance in their measurement made it unlikely that a consistent and replicable diagnostic cytokine profile will ever be discovered.

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CPT codes covered if selection criteria are met:</td>
</tr>
<tr>
<td>70551 -</td>
<td>70553 Magnetic resonance (e.g., proton) imaging, brain (including brain stem)</td>
</tr>
<tr>
<td>70554 -</td>
<td>70555 Magnetic resonance imaging, brain, functional MRI</td>
</tr>
<tr>
<td>80047</td>
<td>Basic metabolic panel (Calcium, ionized)</td>
</tr>
<tr>
<td>80048</td>
<td>Basic metabolic panel (Calcium, total)</td>
</tr>
<tr>
<td>80050</td>
<td>General health panel</td>
</tr>
<tr>
<td>80051</td>
<td>Electrolyte panel</td>
</tr>
<tr>
<td>80076</td>
<td>Hepatic function panel</td>
</tr>
<tr>
<td>81000 -</td>
<td>81099 Urinalysis</td>
</tr>
</tbody>
</table>

http://www.aetna.com/cpb/medical/data/300_399/0369.html 06/27/2019
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>84443</td>
<td>Thyroid stimulating hormone (TSH)</td>
</tr>
<tr>
<td>84479</td>
<td>Thyroid hormone (T3 or T4) uptake or thyroid hormone binding ratio (THBR)</td>
</tr>
<tr>
<td>85025</td>
<td>Blood count; complete (CBC), automated (Hgb, Hct, RBC, WBC and platelet count)</td>
</tr>
<tr>
<td>85027</td>
<td>complete (CBC), automated (Hgb, Hct, RBC, WBC and platelet count)</td>
</tr>
<tr>
<td>85651</td>
<td>Sedimentation rate, erythrocyte; non-automated</td>
</tr>
<tr>
<td>85652</td>
<td>automated</td>
</tr>
<tr>
<td>86038</td>
<td>Antinuclear antibodies (ANA)</td>
</tr>
<tr>
<td>86430</td>
<td>Rheumatoid factor; qualitative</td>
</tr>
<tr>
<td>86580</td>
<td>Skin test; tuberculosis, intradermal</td>
</tr>
<tr>
<td>86617</td>
<td>Borrelia burgdorferi (Lyme disease) confirmatory test (e.g., Western Blot or Immunoblot)</td>
</tr>
<tr>
<td>86618</td>
<td>Borrelia burgdorferi (Lyme disease)</td>
</tr>
<tr>
<td>95782</td>
<td>Polysomnography; younger than 6 years, sleep staging with 4 or more additional parameters of sleep, attended by a technologist</td>
</tr>
<tr>
<td>95783</td>
<td>younger than 6 years, sleep staging with 4 or more additional parameters of sleep, with initiation of continuous positive airway pressure therapy or bi-level ventilation, attended by a technologist</td>
</tr>
<tr>
<td>95808 - 95811</td>
<td>Polysomnography</td>
</tr>
</tbody>
</table>

CPT codes not covered for indications listed in the CPB:
Evaluation of premature telomere attrition, Unstimulated salivary cortisol activity, Blood and cerebrospinal fluid cytokines assays, Evaluation of enteric dysbiosis (abnormal microbial ecology), Gastro-intestinal flora altering therapy:
No specific code

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>72195 - 72197</td>
<td>Magnetic resonance (e.g., proton) imaging, pelvis; without contrast material(s), with contrast material(s), or without contrast material(s), followed by contrast material(s) and further sequences</td>
</tr>
<tr>
<td>73218 - 73223</td>
<td>Magnetic resonance (e.g., proton) imaging, upper extremity, other than joint; without contrast material(s), with contrast material(s), or without contrast material(s), followed by contrast material(s) and further sequences</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>------------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>73718 - 73723</td>
<td>Magnetic resonance (e.g., proton) imaging, lower extremity, other than joint; without contrast material(s), with contrast material(s), or without contrast material(s), followed by contrast material(s) and further sequences</td>
</tr>
<tr>
<td>74181 - 74183</td>
<td>Magnetic resonance (e.g., proton) imaging, abdomen; without contrast material(s), with contrast material(s), or without contrast material(s), followed by contrast material(s) and further sequences</td>
</tr>
<tr>
<td>76390</td>
<td>Magnetic resonance spectroscopy</td>
</tr>
<tr>
<td>78320</td>
<td>Bone and/or joint imaging; tomographic (SPECT)</td>
</tr>
<tr>
<td>78607</td>
<td>Brain imaging, tomographic (SPECT)</td>
</tr>
<tr>
<td>78608</td>
<td>Brain imaging, positron emission tomography (PET); metabolic evaluation</td>
</tr>
<tr>
<td>78609</td>
<td>perfusion evaluation</td>
</tr>
<tr>
<td>78647</td>
<td>Cerebrospinal fluid flow, imaging (not including introduction of material); tomographic (SPECT)</td>
</tr>
<tr>
<td>78807</td>
<td>Radiopharmaceutical localization of inflammatory process; tomographic (SPECT)</td>
</tr>
<tr>
<td>80400</td>
<td>ACTH stimulation panel; for adrenal insufficiency this panel must include the following: Cortisol (82533 x 2)</td>
</tr>
<tr>
<td>83880</td>
<td>Natriuretic peptide</td>
</tr>
<tr>
<td>86355</td>
<td>B cells, total count</td>
</tr>
<tr>
<td>86357</td>
<td>Natural killer (NK) cells, total count</td>
</tr>
<tr>
<td>86359</td>
<td>T cells; total count</td>
</tr>
<tr>
<td>86360</td>
<td>absolute CD4 and CD8 count, including ratio</td>
</tr>
<tr>
<td>86361</td>
<td>absolute CD4 count</td>
</tr>
<tr>
<td>86628</td>
<td>Antibody; Candida</td>
</tr>
<tr>
<td>86644</td>
<td>cytomegalovirus (CMV)</td>
</tr>
<tr>
<td>86645</td>
<td>cytomegalovirus (CMV), IgM</td>
</tr>
<tr>
<td>86658</td>
<td>enterovirus (e.g., coxackie, echo, polio)</td>
</tr>
<tr>
<td>86663</td>
<td>Epstein-Barr (EB) virus, early antigen (EA)</td>
</tr>
<tr>
<td>86664</td>
<td>Epstein-Barr (EB) virus, nuclear antigen (EBNA)</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
</tbody>
</table>
|---------|---------------------------------------------------------------- Evepstein-Barr (EB) virus, viral capsid (VCA) 86665 | 86695 | herpes simplex, type 1 86696 | herpes simplex, type 2 87480 | Candida species, direct probe technique 87482 | Candida species, quantification 90867 | Therapeutic repetitive transcranial magnetic stimulation (TMS) treatment; initial, including cortical mapping, motor threshold determination, delivery and management 90868 | Therapeutic repetitive transcranial magnetic stimulation (TMS) treatment; subsequent delivery and management, per session 90869 | Therapeutic repetitive transcranial magnetic stimulation (TMS) treatment; subsequent motor threshold re-determination with delivery and management 93660 | Evaluation of cardiovascular function with tilt table evaluation, with continuous ECG monitoring and intermittent blood pressure monitoring, with or without pharmacological intervention 93922 | Limited bilateral noninvasive physiologic of upper or lower extremity arteries, (eg, for lower extremity: ankle/brachial indices at distal posterior tibial and anterior tibial/dorsalis pedis arteries plus bidirectional, Doppler waveform recording and analysis at 1-2 levels, or ankle/brachial indices at distal posterior tibial and anterior tibial/dorsalis pedis arteries plus volume plethysmography at 1-2 levels, or ankle/brachial indices at distal posterior tibial and anterior tibial/dorsalis pedis arteries with transcutaneous oxygen tension measurements at 1-2 levels)
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>93923</td>
<td>Complete bilateral noninvasive physiologic studies of upper or lower extremity arteries, 3 or more levels (eg, for lower extremity: ankle/brachial indices at distal posterior tibial and anterior tibial/dorsalis pedis arteries plus segmental blood pressure measurements with bidirectional Doppler waveform recording and analysis, at 3 or more levels, or ankle/brachial indices at distal posterior tibial and anterior tibial/dorsalis pedis arteries plus segmental volume plethysmography at 3 or more levels, or ankle/brachial indices at distal posterior tibial and anterior tibial/dorsalis pedis arteries plus segmental transcutaneous oxygen tension measurements at 3 or more level(s), or single level study with provocative functional maneuvers (eg, measurements with postural provocative tests, or measurements with reactive hyperemia))</td>
</tr>
<tr>
<td>93924</td>
<td>Noninvasive physiologic studies of lower extremity arteries, at rest and following treadmill stress testing, (ie, bidirectional Doppler waveform or volume plethysmography recording and analysis at rest with ankle/brachial indices immediately after and at timed intervals following performance of a standardized protocol on a motorized treadmill plus recording of time of onset of claudication or other symptoms, maximal walking, and time to recover), complete bilateral study</td>
</tr>
<tr>
<td>93965</td>
<td>Noninvasive physiologic studies of extremity veins, complete bilateral study (e.g., Doppler waveform analysis with responses to compression and other maneuvers, phleborheography, impedance plethysmography)</td>
</tr>
<tr>
<td>97810</td>
<td>Acupuncture, 1 or more needles; without electrical stimulation, initial 15 minutes of personal one-on-one contact with the patient</td>
</tr>
<tr>
<td>97811</td>
<td>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)</td>
</tr>
<tr>
<td>97813</td>
<td>Acupuncture, 1 or more needles; with electrical stimulation, initial 15 minutes of personal one-on-one contact with the patient</td>
</tr>
<tr>
<td>97814</td>
<td>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)</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>--------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>98960</td>
<td>Education and training for patient self-management by a qualified, nonphysician health care professional using a standardized curriculum, face-to-face with the patient (could include caregiver/family) each 30 minutes; individual patient</td>
</tr>
<tr>
<td>98961</td>
<td>2-4 patients</td>
</tr>
<tr>
<td>98962</td>
<td>5-8 patients</td>
</tr>
</tbody>
</table>

Other CPT codes related to the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>96365</td>
<td>Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour</td>
</tr>
<tr>
<td>96366</td>
<td>Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); each additional hour (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>96367</td>
<td>Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); additional sequential infusion, up to 1 hour (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>96368</td>
<td>Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); concurrent infusion (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>96373</td>
<td>Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); intra-arterial</td>
</tr>
<tr>
<td>96374</td>
<td>Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); intravenous push, single or initial substance/drug</td>
</tr>
<tr>
<td>96375</td>
<td>Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); each additional sequential intravenous push of a new substance/drug provided in a facility (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>96376</td>
<td>Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); each additional sequential intravenous push of the same substance/drug provided in a facility (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>96379</td>
<td>Unlisted therapeutic, prophylactic or diagnostic intravenous or intra-arterial injection or infusion</td>
</tr>
</tbody>
</table>

HCPCS codes not covered for indications listed in the CPB:

- Anakinra, probiotics - no specific code:
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C9723</td>
<td>Dynamic infrared blood perfusion imaging (DIRI)</td>
</tr>
<tr>
<td>G0237</td>
<td>Therapeutic procedures to increase strength or endurance of respiratory muscles (i.e. breathing retraining), face to face, one on one, each 15 minutes (includes monitoring)</td>
</tr>
<tr>
<td>J0133</td>
<td>Injection, acyclovir, 5 mg</td>
</tr>
<tr>
<td>J0702</td>
<td>Injection, betamethasone acetate 3 mg and betamethasone sodium phosphate 3 mg</td>
</tr>
<tr>
<td>J0735</td>
<td>Injection, clonidine hydrochloride (HCL), 1 mg</td>
</tr>
<tr>
<td>J0833</td>
<td>Injection, cosyntropin, not otherwise specified, 0.25 mg</td>
</tr>
<tr>
<td>J0834</td>
<td>Injection, cosyntropin (Cortrosyn), 0.25 mg</td>
</tr>
<tr>
<td>J1020</td>
<td>Injection, methylprednisolone acetate, 20 mg</td>
</tr>
<tr>
<td>J1030</td>
<td>Injection, methylprednisolone acetate, 40 mg</td>
</tr>
<tr>
<td>J1040</td>
<td>Injection, methylprednisolone acetate, 80 mg</td>
</tr>
<tr>
<td>J1094</td>
<td>Injection, dexamethasone acetate, 1 mg</td>
</tr>
<tr>
<td>J1100</td>
<td>Injection, dexamethasone sodium phosphate, 1 mg</td>
</tr>
<tr>
<td>J1459</td>
<td>Injection, immune globulin,(Privigen), intravenous, non-lyophilized (e.g, liquid), 500 mg</td>
</tr>
<tr>
<td>J1460</td>
<td>Injection, gamma globulin, intramuscular, 1 cc</td>
</tr>
<tr>
<td>J1556</td>
<td>Injection, immune globulin, (Bivigam), 500 mg</td>
</tr>
<tr>
<td>J1557</td>
<td>Injection, immune globulin, (gammaplex), intravenous, non-lyophilized (e.g., liquid), 500 mg</td>
</tr>
<tr>
<td>J1559</td>
<td>Injection, immune globulin (hizentra), 100 mg</td>
</tr>
<tr>
<td>J1560</td>
<td>Injection, gamma globulin, intramuscular, over 10 cc</td>
</tr>
<tr>
<td>J1561</td>
<td>Injection, immune globulin, (Gamunex-c/Gammaked), nonlyophilized (e.g. liquid), 500 mg</td>
</tr>
<tr>
<td>J1566</td>
<td>Injection, immune globulin, intravenous, lyophilized (e.g., powder), not otherwise specified, 500 mg (Carimune, Gammagard S/D, Polygam)</td>
</tr>
<tr>
<td>J1568</td>
<td>Injection, immune globulin, (Octagam), intravenous, non-lyophilized (e.g., liquid), 500 mg</td>
</tr>
<tr>
<td>J1569</td>
<td>Injection, immune globulin, (Gammagard liquid), nonlyophilized, (e.g. liquid), 500 mg</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>-------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>J1572</td>
<td>Injection, immune globulin, (flebogamma/flebogamma DIF), intravenous, non-lyophilized (e.g., liquid), 500 mg</td>
</tr>
<tr>
<td>J1575</td>
<td>Injection, immune globulin/hyaluronidase, (hyqvia), 100 mg immunoglobulin</td>
</tr>
<tr>
<td>J1599</td>
<td>Injection, immune globulin, intravenous, non-lyophilized (eg, liquid), not otherwise specified, 500 mg</td>
</tr>
<tr>
<td>J1700</td>
<td>Injection, dexamethasone sodium phosphate, 1 mg</td>
</tr>
<tr>
<td>J1710</td>
<td>Injection, hydrocortisone sodium phosphate, up to 50 mg</td>
</tr>
<tr>
<td>J1720</td>
<td>Injection, hydrocortisone sodium succinate, up to 100 mg</td>
</tr>
<tr>
<td>J2405</td>
<td>Injection, ondansetron hydrochloride, per 1 mg</td>
</tr>
<tr>
<td>J2650</td>
<td>Injection, prednisolone acetate, up to 1 ml</td>
</tr>
<tr>
<td>J2920</td>
<td>Injection, methylprednisolone sodium succinate, up to 40 mg</td>
</tr>
<tr>
<td>J2930</td>
<td>Injection, methylprednisolone sodium succinate, up to 125 mg</td>
</tr>
<tr>
<td>J3300</td>
<td>Injection, triamcinolone acetonide, preservative free, 1 mg</td>
</tr>
<tr>
<td>J3301</td>
<td>Injection, triamcinolone acetonide, not otherwise specified, 10 mg</td>
</tr>
<tr>
<td>J3302</td>
<td>Injection, triamcinolone diacetate, per 5 mg</td>
</tr>
<tr>
<td>J3303</td>
<td>Injection, triamcinolone hexacetonide, per 5 mg</td>
</tr>
<tr>
<td>J7509</td>
<td>Methylprednisolone, oral, per 4 mg</td>
</tr>
<tr>
<td>J7510</td>
<td>Prednisolone, oral, per 5 mg</td>
</tr>
<tr>
<td>J7512</td>
<td>Prednisone, immediate release or delayed release, oral, 1 mg</td>
</tr>
<tr>
<td>J8540</td>
<td>Dexamethasone, oral, 0.25 mg</td>
</tr>
<tr>
<td>J9312</td>
<td>Injection, rituximab, 10 mg</td>
</tr>
<tr>
<td>Q0162</td>
<td>Ondansetron 1 mg, oral, FDA approved prescription antiemetic, for use as a complete therapeutic substitute for an IV antiemetic at the time of chemotherapy treatment, not to exceed a 48 hour dosage regimen</td>
</tr>
<tr>
<td>S0119</td>
<td>Ondansetron, oral, 4 mg (for circumstances falling under the Medicare statute, use HCPCS Q code)</td>
</tr>
</tbody>
</table>

ICD-10 codes covered if selection criteria are met:

- **R53.82**: Chronic fatigue, unspecified
- **R53.81, R53.83**: Other malaise and fatigue
The above policy is based on the following references:


25. Bagnall A, Whiting P, Wright K, Sowden AJ. The effectiveness of interventions used in the treatment/management of chronic fatigue syndrome and/or myalgic encephalomyelitis in adults and children. York,


53. Gluckman SJ. Clinical features and diagnosis of chronic fatigue syndrome. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed February 2013a; January 2014a.

54. Gluckman SJ. Treatment of chronic fatigue syndrome. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed February 2013b; January 2014b.


AETNA BETTER HEALTH® OF PENNSYLVANIA

Amendment to
Aetna Clinical Policy Bulletin Number: 0369 Chronic Fatigue Syndrome

There are no amendments for Medicaid.

www.aetnabetterhealth.com/pennsylvania  revised 06/19/2019