

REPORT

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Lay summary

Fatigue or feeling tired is a common symptom associated with many illnesses and even normal conditions. When the symptoms are severe and long-last, it could be caused by many diseases. However judging from the symptoms and history that you presented, the most likely scenario is chronic fatigue syndrome. There are certain overlapping between depression and chronic fatigue syndrome. The causes for both are not well understood. Therefore the available treatments may not be always effective. To help you to manage your situation, we provide you with a broad understanding about the conditions of fatigue and depression in general. Among the many possibilities is hypothyroidism. We have provided a description about this condition. We also provide you with more detailed information about chronic fatigue syndrome. An extensive research on recent literature of this disease found no breakthrough in therapy for this condition. A recent scientific A review article on this condition is also provided that summarizes the latest knowledge about this disease. To address your question about trying out anti-depression drugs, we also included a general description about these drugs. Depression could be a part of chronic fatigue syndrome and you may have both. We suggest that you read the information carefully and go over the information with your doctors. Always consult your physicians before taking any actions about your condition. We hope that the research we performed and information we provided are helpful to you and your health care professionals in understanding and managing your unique medical problem. Please read the nodes listed at the end of this report to have a balanced and realistic understanding of the information in this report.

Your question

I am a 34 years old male, overall in good physical health.

For years I have been feeling depressed and tired. Treatment of Prozac and psychiatric consultation showed no signs of improvement. I was told that this is probably not a depression.

I wake up in the morning very, very tired. There are days (it can go for weeks) that I feel that I did not wake up at all. I can fall asleep at any given moment if given few minutes of quiet. I look tired, and I feel very tired. It comes and goes. Few weeks really bad, then few weeks just bad, then week or two O.K. and then again old routine. It is more or less that way for the last 15 years. Symptoms become so severe that I was not able to work for last year. I am an electrical engineer. I feel that my depressed state could be caused by constant feeling of being physically and mentally tired. All blood tests, over years looked O.K. I have no known severe allergies or asthma. Physical exercise makes me dizzy and red faced. The most characteristic symptom is been very tired in the morning and thru the rest of the day. I can sleep 12 hours and then some. It almost never feels "fresh". My questions: 1. Could f this still be depression, or something else. 2. Can I try myself some anti-depressant drugs, just to verify if this is not a depression? Which ones and what doses?

About Fatigue

What is fatigue?

Fatigue is a condition of tiredness or weakness that is physical, mental, or both.

How does it occur?

Lots of people, especially older people, complain of feeling tired "for no reason." In fact, there is always a reason.

Fatigue may be caused by:

- illness
- certain medicines
- too much physical activity
- poor physical condition
- not getting enough exercise
- not getting enough sleep
- overweight
- drinking too much alcohol
- not eating enough of the right things
- emotional states such as stress, anxiety, boredom, depression, and grief
- psychological problems.

What are the symptoms?

Symptoms include:

- weakness
- tiredness
- indifference
- lack of energy.

How is it diagnosed?

Your health care provider will review your symptoms. He or she may ask about your daily routine, work habits, and home life. You may have a physical exam and basic blood tests to rule out diseases that may cause fatigue (such as diabetes, hypothyroidism, heart disease, lung disease, and anemia).

If you have a history of emotional stress or recurrent anxiety or depression, your fatigue may be caused by psychological problems.

How is it treated?

Treatment depends on the cause. If fatigue is a symptom of another condition or disease, that condition or disease will be treated. If the cause is emotional or psychological, your health care provider may refer you to a mental health professional for counseling or medication.

How long do the effects last?

The effects will last as long as the cause of the symptoms exists.

How can I take care of myself?

- First, get a medical checkup. Tiredness can signal a serious medical problem.
- Follow your health care provider's advice if you have a medical problem.
- Get enough rest and sleep.
- Eat a well-balanced diet. Consider eating smaller meals but eating more often to maintain a higher energy level.
- Lose excess weight if necessary.
- Avoid caffeine, alcohol, and drugs not prescribed by your provider.
- If you smoke, quit.
- Stay fit. Walk or exercise regularly 3 or 4 times a week, for at least 30 minutes.
- See a mental health professional if you have emotional problems.
- Learn to express your feelings.
- Learn to relieve stress.

- Make changes in your daily routine to allow more free time to enjoy things you like to do.
- Meet new people.
- Develop new interests, take up a new hobby or creative project.

About depression - Dysthymic Disorder

When depression lingers

What is dysthymic disorder?

Dysthymic disorder, or dysthymia, is a type of depression that lasts for at least 2 years. Some people suffer from dysthymia for years. The depression is usually mild or moderate, rather than severe. Most people with dysthymia can't tell for sure when they first became depressed.

Symptoms of dysthymic disorder include a poor appetite or overeating, difficulty sleeping or sleeping too much, low energy, fatigue and feelings of hopelessness. But people with dysthymic disorder may have periods of normal mood that last up to 2 months. Family members and friends may not even know that their loved one is depressed. Even though this type of depression is mild, it may make it difficult for a person to function at home, school or work.

When does dysthymic disorder begin?

Dysthymia can begin in childhood or in adulthood. Like most types of depression, it appears to be more common in women. No one knows why depression is more common in women.

How common is dysthymic disorder?

Dysthymic disorder is a fairly common type of depression. Up to 3% of people have dysthymia. From 5 to 15% of patients in a family doctor's office have dysthymia.

What causes dysthymic disorder?

No one knows for sure what causes dysthymia. There may be some changes in the brain that involve a chemical called serotonin. Personality problems, medical problems and chronic life stress may also play a role.

How is dysthymic disorder diagnosed?

If you think you have dysthymia, discuss your concerns with your doctor. Your doctor will ask you questions to find out if you have depression and to identify the type of depression you have. Your doctor may ask you questions about your health and your symptoms, such as how well you're sleeping, if you feel tired all of the time, if you have trouble concentrating. Your doctor will also consider medical reasons that may cause you to feel depressed, such as problems with your thyroid or a medicine you may be taking.

What is the treatment for dysthymic disorder?

Dysthymic disorder can be treated with an antidepressant medicine. This type of drug relieves depression. Antidepressants are commonly prescribed, and they are safe. They do not create an artificial "high," and they are not addicting.

If you are given an antidepressant, it may take a number of weeks or even several months before you and your doctor know whether the drug is helping you. It is important for you to take the medicine as it is prescribed. If the antidepressant drug helps you feel better, you may need to take this medicine for several years. In other words, continue to take the antidepressant drug even though you begin to feel better. If you stop taking the medicine, you may get depressed again.

Will I have to see a psychiatrist?

You will probably not have to see a psychiatrist or psychotherapist unless the medication is not working or you have problems taking the drugs that are usually prescribed for depression. Sometimes, in addition to taking an antidepressant medicine, patients are referred for psychotherapy to help them deal with specific problems. This type of therapy can be very helpful for some people. In general, the treatment of dysthymic disorder is specifically planned for each person.

What can I do to help myself feel better?

Talking to your doctor about how you're feeling and getting treatment for the dysthymic disorder are the first steps to feeling better. Other ways to make yourself feel better are:

- Get involved in activities that make you feel good or make you feel like you've accomplished something. For example, go to a movie, take a drive on a pleasant day, go to a ball game or work in the garden.
- Eat well-balanced, healthy meals.
- Don't use drugs or alcohol. Both can make depression worse.
- Exercise as much as you can. Exercising 3 times a week for 30 minutes to 1 hour is a good goal. Exercise can help lift your mood.

Medicine for depression

What are antidepressants?

Antidepressants are medicines used to help people who have depression. Most people with depression get better with treatment that includes these medicines.

How do antidepressants work?

Antidepressants work by slowing the removal of certain chemicals from the brain. These chemicals are called neurotransmitters. Neurotransmitters are needed for normal brain function. Antidepressants help people with depression by making these natural chemicals more available to the brain.

How long will I have to take an antidepressant?

Antidepressants are typically taken for several months. In some cases, however, patients and their doctors may decide that antidepressants are needed for a longer time.

Do antidepressants have side effects?

Like most medicines, antidepressant drugs can cause side effects. Not all people get these side effects. Any side effects you have will depend on the medicine your doctor has chosen for you. Your doctor will talk to you about your medicine.

What are the different kinds of antidepressants?

There are many different kinds of antidepressants, including:

- Tricyclic antidepressants (tricyclics)
- Selective serotonin reuptake inhibitors (SSRIs)
- Others

Antidepressants work well and are well tolerated. However, like all medicines, they can cause side effects. With time, many side effects will lessen or go away. If they don't, your doctor may change how much you're taking or give you a different medicine. Make sure you tell your doctor if you are bothered by side effects. Don't stop taking your medicine unless your doctor tells you.

Tricyclics

The tricyclics have been used to treat depression for a long time. They include amitriptyline (brand name: Elavil), desipramine (brand name: Norpramin), imipramine (brand name: Tofranil) and nortriptyline (brand name: Pamelor). Common side effects caused by these medicines include dry mouth, blurred vision, constipation, difficulty urinating, worsening of glaucoma, impaired thinking and tiredness. These antidepressants can also affect a person's blood pressure and heart rate.

SSRIs

SSRIs are a newer group of antidepressants and include drugs such as fluoxetine (brand name: Prozac), paroxetine (brand name: Paxil) and sertraline (brand name: Zoloft). These medicines tend to have fewer side effects than the tricyclics. Some of the side effects that can be caused by SSRIs include decreased appetite, nausea, nervousness, insomnia, headache, and sexual problems. People taking fluoxetine might also have a feeling of being unable to sit still. People taking paroxetine might have a dry mouth and feel tired. People taking sertraline might have runny stools and diarrhea.

Other antidepressants

Other types of antidepressants can also be prescribed for people with depression. Some of them are listed here with their possible side effects.

The most common side effects in people taking venlafaxine (brand name: Effexor) include nausea and loss of appetite, anxiety and nervousness, headache, insomnia and tiredness. Dry mouth, constipation, weight loss, sexual problems, increased blood pressure, increased heart rate and increased cholesterol levels can also occur.

Nefazodone (brand name: Serzone) can give people headaches, blurred vision, dizziness, nausea, constipation, dry mouth and tiredness.

There are newer antidepressants such as bupropion (brand name: Wellbutrin), mirtazapine (brand name: Remeron), and trazodone (brand name: Desyrel). Bupropion can cause agitation, insomnia, headache and nausea. Mirtazapine can cause sedation, increased appetite, weight gain, dizziness, dry mouth and constipation. The most common side effects of trazodone are sedation and nausea.

Will antidepressants affect my other medicines?

Antidepressants can have an effect on many other medicines. If you're going to take an antidepressant, tell your doctor all the other medicines you take, including over-the-counter medicines. Ask your doctor and pharmacist if any of your other medicines can cause problems when combined with an antidepressant.

Hypothyroidism

What is hypothyroidism?

Hypothyroidism happens when the thyroid gland does not make enough thyroid hormone. Having too little of this hormone causes many symptoms. If you have any of these symptoms, tell your health care provider.

You may:

- Feel tired all the time.
- Have weak muscles.
- Be constipated.
- Gain weight.
- Have heavy or long monthly periods.

You may have other problems:

- You may not be able to tolerate cold.
- Your hair may be coarse, dry, or gray at a young age.
- Your skin may become thick and dry, or your face or tongue may thicken.
- Your eyelids may be swollen.
- Your voice may deepen or grow hoarse.

Still other problems include:

- Slowed heart rate.
- Depression.
- Loss of interest in sex.
- Loss of hearing.
- Numb and tingling hands.

When this disease is not treated, these problems can happen:

- Mental problems.
- Difficulty breathing.
- Loss of consciousness or even a coma.
- Swelling of the thyroid gland (which is called a goiter).
- Not being able to keep a normal body temperature.

How does it happen?

Hypothyroidism most often happens:

- If you have a disease that causes your thyroid gland to swell.
- If your thyroid gland has been exposed to radiation treatment.

How do I know if I have hypothyroidism?

You will have blood tests to measure the hormones your body makes.

How is it treated?

If you have hypothyroidism, your health care provider will prescribe thyroid hormone tablets. This will take the place of what your body would normally make.

- After you take the hormone tablets for about a week, you will feel better.
- You will have another blood test to make sure you are taking enough hormone.
- After a few months, you should have no signs of the disease.
- Most likely, you will need to take your tablets every day for the rest of your life.

Taking your hormone tablets is a safe, simple, and inexpensive way to keep healthy. It's important to:

- Take your tablets every day.
- Get your thyroid hormone level checked when your health care provider suggests.
- Keep your follow-up appointments.

Chronic Fatigue Syndrome

What is chronic fatigue syndrome?

Chronic fatigue syndrome (CFS) is a complex of possibly related symptoms that may have several causes. The syndrome is not well understood. The main symptom is overwhelming fatigue that lasts for at least 6 months and interferes with daily living.

Most people with CFS are middle-class, 20- to 40-year-old adults. The syndrome seems to especially affect young, well-educated women. However, men and women of all ages can have CFS.

How does it occur?

The cause of chronic fatigue syndrome is not known. We do know that the following conditions may cause some of the symptoms:

- depression
- anxiety
- stress
- allergies
- infections such as Epstein-Barr virus, infectious mononucleosis, Lyme disease, and AIDS
- problems with the body's immune system
- tumors

- rheumatic diseases
- certain disorders of the nervous system
- anemia
- hormone problems, such as with the thyroid and pituitary glands and with diabetes

Medications, such as drugs used to treat anxiety, depression, and hypertension (high blood pressure), may cause symptoms of chronic fatigue.

What are the symptoms?

Physical symptoms of CFS may include:

- overwhelming exhaustion, fatigue, or weakness that lasts longer than 6 months
- mild fever
- sore throat
- chills and night sweats
- swollen or tender lymph nodes
- muscle weakness, aches, and pain
- headache
- joint aches and pain
- allergic reactions
- weight gain or loss
- skin rash
- difficulty being physically active
- dizziness or lightheadedness.

Psychological symptoms of CFS may include:

- confusion
- memory loss
- sleep disturbances
- anxiety
- irritability
- difficulty concentrating
- apathy and depression
- personality changes
- mood swings
- reduced sex drive.

How is it diagnosed?

Many illnesses cause symptoms similar to those of CFS. Your health care provider will try to rule out other illnesses and possible causes of your fatigue by asking about your symptoms and giving you a complete physical exam. If you have been having fevers but

don't have one when you see your provider, you may be asked to record your temperature at home several times a day.

You may have a number of tests, such as urine and blood tests, to check for infections, immune or metabolic diseases, hormone problems, anemia, and tumors.

If your provider cannot find a cause for your fatigue, you may be diagnosed with chronic fatigue syndrome.

How is it treated?

If your health care provider diagnoses an illness or other cause for your fatigue, treatment of the problem will relieve the fatigue. If you have chronic fatigue syndrome, there is currently no known cure. However, two types of treatment can be helpful:

- a special exercise program
- behavior therapy.

The exercise program starts slowly and easily. You increase the amount of exercise very gradually with the goals of increasing your muscle strength and energy. Behavior therapy should focus on the positive (what you **are** able to do) and help you feel more optimistic as your muscle strength and energy improve.

Your health care provider may prescribe medicine for symptoms such as headache and muscle pain. Antidepressant medicines may help lessen your fatigue and improve your ability to function. Treatment for depression often helps relieve painful symptoms.

How long will the effects last?

Chronic fatigue syndrome is not well understood or easily treated. You may continue to have the symptoms for months or years. Usually, the symptoms are most severe during the first year. Most people with CFS feel much better within 2 years.

How can I take care of myself?

- Rest as much as possible while you and your health care provider try to treat the illness.
- Follow the treatment prescribed by your health care provider, including recommendations for exercise and counseling.
- To keep yourself as healthy as possible, make other lifestyle changes such as:
 - o Stop smoking.
 - o Eat balanced, nutritious meals. Drink 6 to 8 glasses of water daily. Drink less coffee and alcohol.
 - o Learn to pace yourself to avoid fatigue. Prioritize your activities each day. Do the most important ones in the morning when your energy level may

be higher. It doesn't matter if everything doesn't get done in 1 day. Ask for help at home and at work when the load is too great to handle. Take frequent rest breaks during the day to relax or walk around.

- Engage in recreational activities at least once or twice a week.
 - Join local support groups. Talking with others who have similar problems can really help.
 - Develop and maintain an attitude that things will work out.
- If nothing helps, you may wish to get a second medical opinion.

What can be done to help prevent fatigue?

Keep yourself as healthy as possible. See your health care provider if you have any unusual or persistent body changes or symptoms. This will allow your provider to identify and treat any underlying health problems early and help prevent your fatigue from becoming worse.

Recent discoveries (a reviewing article)

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Chronic Fatigue Syndrome: Evaluation and Treatment

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Severe fatigue is a common complaint among patients. Often, the fatigue is transient or can be attributed to a definable organic illness. Some patients present with persistent and disabling fatigue, but show no abnormalities on physical examination or screening laboratory tests. In these cases, the diagnosis of chronic fatigue syndrome (CFS) should be considered. CFS is characterized by debilitating fatigue with associated myalgias, tender lymph nodes, arthralgias, chills, feverish feelings, and postexertional malaise. Diagnosis of CFS is primarily by exclusion with no definitive laboratory test or physical findings. Medical research continues to examine the many possible etiologic agents for CFS (infectious, immunologic, neurologic, and psychiatric), but the answer remains elusive. It is known that CFS is a heterogeneous disorder possibly involving an interaction of biologic systems. Similarities with fibromyalgia exist and concomitant illnesses include irritable bowel syndrome, depression, and headaches. Therefore, treatment of CFS may be variable and should be tailored to each patient. Therapy should include exercise, diet, good sleep hygiene, antidepressants, and other medications, depending on the patient's presentation. (Am Fam Physician 2002;65:1083-90,1095. Copyright© 2002 American Academy of Family Physicians.)

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*A patient information handout on **chronic fatigue syndrome**, written by the authors of this article, is provided on page 1095.*

Chronic fatigue syndrome (CFS), also referred to as chronic fatigue immune deficiency syndrome, is a disabling illness characterized by persistent fatigue accompanied by rheumatologic, cognitive, and infectious-appearing symptoms. Despite intense medical research, there is no known cause for CFS, but it appears to be a heterogeneous disorder which affects multiple systems, including hormonal, neurologic, and immunologic. Because there are no specific diagnostic tests or physical findings for CFS, diagnosis requires knowledge of possible symptoms and a method of exclusion. CFS is likely a spectrum of illnesses sharing a common pathogenesis with varying degrees of fatigue and associated symptoms. Other disorders, such as fibromyalgia, have overlapping symptoms with CFS, suggesting that both diseases may share common physiologic abnormalities.

*The Centers for Disease Control and Prevention's criteria for diagnosis of **chronic fatigue syndrome** require the patient to present with severe fatigue lasting at least six consecutive months, have no definable organic disease, and experience associated physical symptoms.*

Chronic fatigue syndrome affects both genders, all racial, ethnic, and socioeconomic populations, and can begin as early as five years of age.^{[1] [2]} Although previous reports showed a predominance of CFS in well-educated, white females between 20 and 50 years of age, these findings may be skewed by study populations that were selected from patients who sought medical care for the disorder.^{[1] [2]} Furthermore, the diagnostic ambiguity surrounding CFS invariably leads to imprecise and inconsistent epidemiologic statistics.

Clinical Presentation

The Centers for Disease Control and Prevention's criteria for diagnosis of CFS (*Table 1 (Table Not Available)*)^[3] require patients to present with severe fatigue lasting for at least six consecutive months, have no definable organic disease, and experience associated physical symptoms. Because fatigue is a common symptom in many diseases, a wide differential diagnosis (*Table 2 (Table Not Available)*)^[3] needs to be excluded. A complete history should be taken and a physical examination should be performed on all patients to exclude secondary fatigue caused by psychiatric illness, substance abuse, or medical conditions that are known to cause persistent fatigue (*Figure 1*).^{[3] [4] [5] [6]} Laboratory tests should be limited to complete blood cell counts and tests specific for the patient's symptoms. For example, serologic and neurologic analyses for Lyme disease or multiple sclerosis need only be conducted if the patient presents with appropriate symptoms.

TABLE 1 -- Current CDC Criteria for Diagnosis of Chronic Fatigue Syndrome
(Not Available)
<i>Adapted with permission from Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann Intern Med 1994;121:953-9.</i>

TABLE 2 -- Differential Diagnosis for Chronic Fatigue Syndrome
(Not Available)
<i>Adapted with permission from Cho WK, Stollerman GH. Chronic fatigue syndrome. Hosp Pract (Off Ed) 1992;27:221-4, 227-30, 233-6.</i>

(The actual figure is presented at the end of this document) **Figure 1.** Algorithm for the evaluation of a patient for chronic fatigue syndrome. (CFS =chronicfatigue syndrome; CBC = complete blood cell count; ESR erythrocytesedimentationrate; ALT = alanine aminotransferase; BUN = blood urea nitrogen; Ca = cancer; PO₄ = phosphate radical; TSH = thyrotropin-stimulating

hormone; UA = urinalysis; HIV = human immunodeficiency virus; ANA = antinuclear antibodies; PPD = purified protein derivative) Information from references 3^[3] 4^[4] 5^[5] through 6^[6].

Etiology

INFECTIOUS

Many patients with CFS attribute the onset of their illness to an acute influenza-like infection, and, subsequently, the role of viruses as possible causative agents for CFS has been intensively studied. In particular, an early study^[2] reported that patients with CFS presented with symptoms similar to acute infectious mononucleosis and were found to have high titers of IgG antibodies to Epstein-Barr virus (EBV). However, subsequent research^[8] refuted a correlation between titers of EBV antibodies and severity of symptoms in CFS, and showed that patients with CFS did not have significantly higher titers to EBV compared with healthy control subjects.

Although a number of other viral pathogens (such as the Coxsackie virus, human herpes virus 6, cytomegalovirus, measles, and the human T-cell lymphotropic virus [HTLV-II]) have also been implicated as etiologic agents for CFS, there is no consistent or conclusive data to suggest any causal relationships.^{[9] [10] [11]} It is now believed that CFS is not specific to one pathogenic agent but could be a state of chronic immune activation, possibly of polyclonal activity of B-lymphocytes, initiated by a virus. Patients with CFS can show different lymphocyte and cytokine profiles depending on the nature of their illness and its time of onset.

IMMUNOLOGIC

Many of the symptoms seen in patients with CFS, such as disabling lethargy, myalgias, and cognitive impairment, are similar to the effects observed with high dosage treatments of cytokines including interleukin-2 and alpha interferon.^{[12] [13]} Given that CFS may be an illness of immune dysregulation, numerous studies^{[14] [15] [16] [17] [18]} have attempted to identify abnormalities in circulating immune complexes, increased interferon activity, cytokine levels, lymphocyte cell markers, or natural killer cells. However, the data are inconsistent.^{[14] [15] [16] [17] [18]} Nevertheless, the implication of immune disorder in patients with CFS is supported by reports that lymphocyte markers (including CD4+ cell counts and adhesion molecules) may be increased in patients with CFS. These findings, however, have been inconsistent among studies.^{[17] [19]}

In a recent study,^[18] patients with CFS showed normal natural killer cell numbers but low natural killer activity. Researchers suggested that this is a result of an inability to replenish activated natural killer cells.^[18] This hypothesis may explain how a triggering event, such as a viral infection, could produce a cascade of immune and neuroendocrine abnormalities. The varied nature of illness onset and infectious agents could produce different immune profiles among patients with CFS. Although the data supporting this

hypothesis remain speculative, this finding suggests that at least a subset of CFS patients may have immune dysregulation.

AUTONOMIC NERVOUS SYSTEM

Evidence supports that CFS may be an illness mediated by the central nervous system. Patients with **chronic fatigue syndrome** present with cognitive deficits in concentration, attention, and short-term memory. More specifically, persons with neurally mediated hypotension experience periods of light-headedness, syncope, and fatigue after periods of orthostatic stress (erect posture). Studies^{[19] [20]} investigating this phenomenon as a cause of CFS have not produced consistent results.

When treatments specific to neurally mediated hypotension were administered to patients with CFS, the results were inconclusive. The use of fludrocortisone (Florinef) alone had no beneficial effect. Although use of low-dose hydrocortisone resulted in a slight improvement of symptoms, the risk associated with chronic use of corticosteroids outweighed the therapeutic benefits.^{[21] [22]} Other therapeutic interventions that have been suggested include: salt loading to increase vascular volume by increasing dietary sodium chloride; beta blockers to inhibit the epinephrine rush that accompanies hypotension; and alpha adrenergics to increase vascular resistance.^{[19] [20] [21] [22]}

Diagnostic imaging studies have also provided preliminary data to suggest that patients with CFS may have neurologic abnormalities. Magnetic resonance imaging has shown the presence of cerebral lesions in white matter, predominantly in the frontal lobes.^[23] Regional cerebral flow studies^[24] using single photon emission computed tomography analysis have shown impaired regional cerebral blood flow in patients with CFS compared with healthy control subjects. A later study^[25] using positron emission tomography analysis compared patients who had CFS and no history of depression with clinically depressed patients who had no history of CFS; the study found altered frontal cortical metabolism in both patients with CFS and patients with depression compared with healthy control subjects. Whether the functional impairment in patients with CFS is caused by a concurrent psychiatric illness is still inconclusive.

PSYCHIATRIC

Because CFS lacks definitive organic causes, it is often dismissed by physicians as either a psychosomatic illness or a manifestation of clinical depression. This occurrence is reinforced by reports that patients with CFS are more prone to depression than healthy subjects and are often excessively emotional.^[26] Studies have shown that two thirds of patients with CFS have signs of major depressive illness and one half of all patients with CFS have experienced at least one episode of major depression. Although there is some overlap in symptoms presented by patients with CFS and those with depression, patients with CFS also show symptoms that are not typical of clinical depression, such as sore throat, lymphadenopathy, and postexertional malaise. Patients with CFS lack feelings of anhedonia, guilt, and decreased motivation classically seen in patients with depression.^[26]

^[27]

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MUSCULAR

Patients with CFS often complain of myalgias and arthralgias, but exhibit no diagnostic signs of musculoskeletal disorder. A study^[28] investigating muscular function in patients with CFS reported reduced work capacity compared with healthy control subjects. There have also been reports^{[29] [30]} that patients with CFS show decreased cognitive performance after maximal physical activity compared with healthy control subjects.

ALLERGIC

A recent study^[31] suggested that patients with CFS have a higher occurrence of allergies compared with normal populations. Although it has been reported that the increased incidence of atopic illness among patients with CFS is the result of an increased use of allergy tests on this population by physicians,^[32] most studies show that patients with CFS are more susceptible to atopic disease. Given the association between CFS and allergies, there is a strong possibility that allergies are essential to the pathology of CFS. Not only do patients with CFS present with positive skin tests to allergens, but they also have elevated levels of circulating eosinophilic cationic proteins compared with healthy subjects.^[33] Rhinitis is a common atopic illness that affects 20 to 30 percent of the population, and allergic rhinitis has been shown to disrupt sleep.^[34] It is not yet known whether this disrupted sleep pattern contributes to the pathology of CFS.

Given the ambiguity surrounding CFS, the current suggested management includes exercise, optimal diet, appropriate sleep hygiene, low-dose tricyclic antidepressants and/or a selected serotonin reuptake inhibitor, combined with cognitive-behavior therapy.

It is generally accepted that the neuroendocrine-immunologic network plays a role in the pathogenesis of CFS. Therefore, it is reasonable to hypothesize that allergens, similar to infectious agents, could serve as a triggering event for the many symptoms specific to CFS. Given the interactions among the hypothalamic-pituitary-adrenal axis, neural and immune system, an allergen, similar to an infectious agent, can initiate a variety of symptoms along with severe fatigue, as is seen in patients with CFS. Exacerbations of allergic disease, such as rhinitis, could affect cytokine levels and natural killer cell function, thereby producing the abnormal immunologic and endocrine profiles seen in

patients with CFS. More recent data suggest that the rhinitis in CFS is not allergy induced but is instead thought to be secondary to the neuroendocrine disorders commonly found in CFS.^[35]

Treatment

Because there is no known cause of CFS, current treatment remains symptomatic with a focus on management rather than cure. Numerous clinical trials of pharmacologic agents have been conducted but no definitive therapeutic benefit has been identified.

Tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) are common therapy for patients with CFS. Tricyclic antidepressants have proven to be effective in reducing clinical depression and improving sleep patterns and are reportedly beneficial for patients with chronic fatigue. Although clinical trials^[29] of tricyclic antidepressants have not produced definitive results, it is believed that along with their antidepressive effect they also promote stage 4, nonrapid eye movement sleep and stimulate the descending inhibitory pathways of pain control. While anecdotal evidence and small noncontrolled studies support the use of the SSRIs fluoxetine (Prozac) and bupropion (Wellbutrin), placebo-controlled trials of these drugs have not significantly benefited patients with CFS.^{[36] [37]} A recent investigation^[34] of nicotinamide-adenine dinucleotide (NADH) therapy reported promising results. The authors of this report^[34] stipulated that a decreased adenosine triphosphate level, when alleviated by NADH therapy, improves muscle atrophy and neuroendocrine abnormalities.

Reports of subtle hypocortisolism in patients with CFS has spurred interest in treatment with mineralocorticoids and corticosteroids. In a randomized control study^[38] of 32 patients, researchers successfully demonstrated a response to low-dose hydrocortisone (five to 10 mg daily). Fatigue was improved and disability was reduced without significant short-term adverse events.^[38]

Cognitive behavior therapy is a psychotherapeutic treatment postulating that patients with CFS may perceive their physical symptoms as insurmountable, thereby precluding any hope for recovery. Cognitive behavior therapy examines both the patient's cognition and behavior to identify unhealthy coping skills. Recent studies have produced promising results. Other psychologic treatments such as support groups and a positive physician-patient relationship have proven to be beneficial in the long-term management of CFS.^[39]

The role of exercise in treating patients with CFS has recently been emphasized. Long-term physical inactivity can lead to physical deconditioning that further complicates the symptoms of CFS and has detrimental effects on mood, energy level, and both neural and immune functioning. While investigations into the effect of graded aerobic exercise on improving cognitive and motor functioning in patients with CFS have not produced definitive results, a graded exercise program is usually recommended in the treatment of CFS.^{[29] [30]}

Given the ambiguity surrounding CFS, the current suggested management includes exercise, optimal diet, appropriate sleep hygiene, low-dose tricyclic antidepressants and/or an SSRI, combined with cognitive-behavior therapy. Alleviating allergy symptoms and stress may decrease the intensity and frequency of exacerbations, thereby improving the quality of life for persons with CFS. Multidisciplinary intervention, consisting of medical, psychiatric, behavioral, and psychologic evaluations and therapy has been demonstrated to be effective at restoring gainful employment.^[5]

Final Comment

CFS has been the subject of intense investigation, but its etiology and clinical course remain unknown. As the search for more effective treatment and, hopefully, a cure continues, future researchers may be drawn toward a holistic approach to CFS, specifically as an interaction among neural, endocrine, and immune systems. Symptoms and treatment may differ from patient to patient depending on illness onset and genetic predisposition. Treatment of concomitant disorders such as migraine headache, irritable bowel syndrome, depression, panic disorder, and fibromyalgia may significantly improve the quality of life of the affected patient.^[6] Future technologic advances in neuroimaging, genotype profiling, immune assays, and pharmacologic therapy may bring greater consistency to scientific research and the possibility of improved therapy for patients with CFS.

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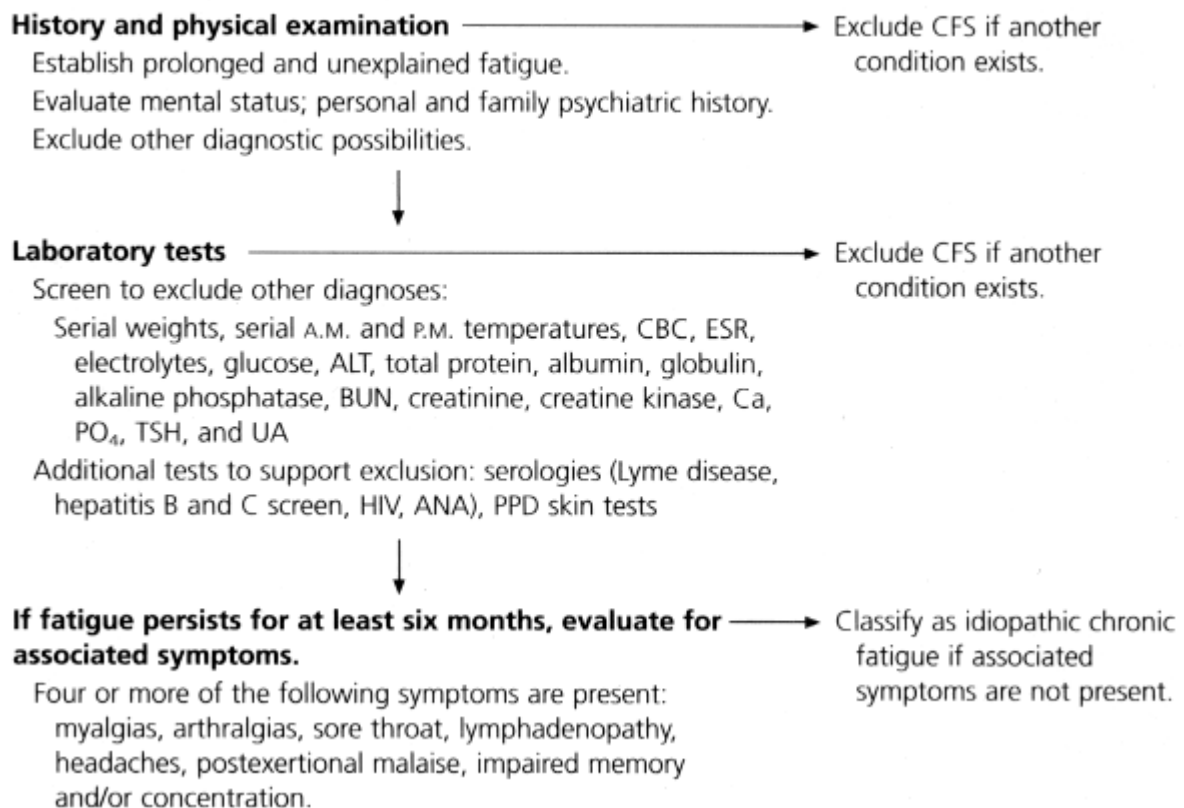
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Figure 1. Algorithm for the evaluation of a patient for chronic fatigue syndrome. (CFS = chronic fatigue syndrome; CBC = complete blood cell count; ESR = erythrocyte sedimentation rate; ALT = alanine aminotransferase; BUN = blood urea nitrogen; Ca = cancer; PO₄ = phosphate radical; TSH = thyrotropin-stimulating hormone; UA = urinalysis; HIV = human immunodeficiency virus; ANA = antinuclear antibodies; PPD = purified protein derivative) Information from references 3^[3] 4^[4] 5^[5] through 6^[6].

Evaluation for Chronic Fatigue Syndrome



Important notes and advice on the significance and limitation of this report

- 1. It is very important for patients to understand their own medical problems and have a healthy and positive attitude toward their illness. It has been proven that active patients' participation is an integral and vital part for most effective therapies. Often times, the patients have an instinct or feeling about their own problems that is better than the judgment of anyone else including their physicians'. A Therefore, you should read the information carefully and try to have a correct and objective assessment of your condition. This will help you to ask the most relevant questions to your doctors and avoid any possible mistakes in diagnosis and management of your disease. Information of the latest understanding and discoveries about your condition will empower you and your physicians to make the most sensible decision about your health and disease.**
- 2. It is also very important for you to fully understand the limitations about the information that we provide in this report. Please note that without examining the patient and knowing the complete details of the patient's history, family history, test results, complete symptoms, treatments, medication, etc, it is impossible for us to make any diagnosis of the specific condition that the patient may suffer. Please do not take this report as the definitive answer to your specific medical problem. The information provided is merely for you to gain a better understanding of the diseases and conditions that may be related to your unique situation. Always consult with your qualified physicians before taking any actions about your illness.**
- 3. You should also be aware that the available knowledge about our body and diseases are limited and are rapidly changing. There are many unknowns about the abnormal states and even the normal functions of the human body. Many diseases and symptoms are listed as cause-unknown in the most up-to-date and authoritative text books of medicine, but in fact, most of them are caused by some factors that the medical community has not yet discovered a . Even though medical research has accumulated a tremendous amount of knowledge about the thousands of diseases, it is save to say that there are much more awaiting to be discovered than those we already known. Every year, month or even week, there are many medical research findings published in the literature that advance our knowledge about how our body functions and dysfunctions and how to manage and treat different diseases. Therefore, on the one hand, you should accept the limitation of our current knowledge and appreciate that you and your physicians may have known all there is to know about your disease. On the other hand, you should always**

strive to know more and find out the latest advances about the understanding and treatment of your condition.

- 4. You should also have a realistic grasp of the many names, procedures and diagnoses that the medical doctors use in describing your disease. The medical names and terms are simply ways for the doctors to define and label a set of conditions that may have a common cause or common pathological changes. But in reality, there are many diseases and conditions of the patients that are not clear-cut, and cannot be fit into a certain name or definition. Many patients suffer from a combination of abnormalities or borderline lesions that cannot be clearly defined or diagnosed with a simple term. Each patient is different and unique. Each illness is a result of the unique body condition and circumstance the particular patient has encountered and reacted. Every patient should be evaluated and treated individually. Please do not be disappointed if there is no specific medical term associated with your specific case or more than one possibility exists for your condition. This is probably the norm rather than the exception. Your goal is not to find a disease name that has a perfect fit to your condition, but to understand the complexity of your situation and make your body return to the broad normal range that you can function and live normally.**
- 5. Even though we are trying our best in finding the most relevant and accurate information about your condition, we cannot guarantee the completeness and accuracy of the research that we performed on your question. It is possible that we may have missed some important information in our report. We also cannot verify the accuracy of all the information that are published in text books, journals and literatures from which we obtained our information and prepared the report. The patients are advised to consult with their physicians and make their own judgment of the knowledge that we provide. You may check with us periodically to follow the most recent advances in your field of interest.**
- 6. We emphatically state that we cannot be held responsible for any actions the patients or their physicians take upon reviewing our reports and any consequences that may be derived thereafter. We should not be held responsible for any damages that may be caused by interpreting or misinterpreting the reports provided thereof.**

The End