The chronic fatigue syndrome generally occurs acutely, reduces activity by more than 50% without obvious cause, and lasts for at least 6 months. Recent studies have shown that there is frequently an overlap with fibromyalgia. Most fatigued patients do not have the "chronic fatigue syndrome"; multiple conditions need to be ruled out before making this diagnosis. A definite association with the Epstein-Barr virus or other infections has not been proven. The finding of a psychological problem does not necessarily indicate a causal relationship to the chronic fatigue syndrome.

Is chronic fatigue more common today than it once was?

No, I don't think so. I think that the attention that it is getting in the press nowadays is a reflection of the society we live in and differences in expectations. Fifty years ago, people expected to become fatigued at a certain point in their lives. But now, people expect to have the same energy levels in their 40s that they had in their 20s.

It is important to distinguish between chronic fatigue and "the chronic fatigue syndrome." The syndrome is more common in women and is said to be more prevalent in members of the medical profession. More highly educated persons seem more likely to be affected, but this impression may just reflect our society and its stresses.

What is chronic fatigue syndrome?

The currently accepted definition is fatigue that occurs fairly acutely, reduces activity by more than 50% without any other obvious cause, and is of at least 6 months' duration. Many other causes must be ruled out, including significant psychiatric disorders — usually depression — infections, inflammatory diseases, and adverse drug reactions (Table 1).

The patient usually has a fairly sudden onset of fatigue and reports frequent low-grade temperatures, sore throat, and enlarged lymph nodes. Generalized headaches and sleep disturbance — insomnia or hypersomnia — are common accompaniments. Problems with mental function — irritability, confusion, and difficulty with concentration, comprehension, mental arithmetic, and memory — also are characteristic. Because numbness, tingling, myalgias, muscle weakness, and arthralgias are common, the patient often sees a rheumatologist first.

There are few diagnostic signs, because fatigue is a subjective complaint. However, unless the patient has nearly all of the subjective criteria, at least two of the three objective features must be present:

- low-grade fever (oral 37.6 to 38.6°C)
- nonexudative pharyngitis
- palpable lymph nodes in the anterior or posterior cervical or axillary lymph nodes.

Because there is no known tissue pathology, chronic fatigue syndrome is not a disease entity in the generally accepted meaning of the term.

What is the nature of the relationship between chronic fatigue and fibromyalgia?

Chronic fatigue is characteristic of the patient with fibromyalgia-fibrositis. Indeed, the
Chronic fatigue syndrome

continued

The patient with “chronic fatigue syndrome” usually has a fairly sudden onset of fatigue and reports frequent low-grade temperatures, sore throat, and enlarged lymph nodes.

A constellation of diagnostic signs

Figure. The chronic fatigue syndrome is characterized by fatigue of at least 6 months’ duration that is of acute onset and is accompanied by subjective signs, such as cognitive dysfunction, sleep disorders, and myalgias. To meet the diagnostic criteria, low-grade fever, nonexudative pharyngitis, and/or palpable lymph nodes must also be present.

Illustration for Modern Medicine by John W Karapelou

Fatigue is often more of a problem than the musculoskeletal pain. On the other hand, myalgia and arthralgia are part of the definition of chronic fatigue syndrome, so there is considerable overlap.

How do the diagnostic criteria for fibromyalgia compare with those for chronic fatigue syndrome?

It is perceived that fibromyalgia and chronic fatigue syndrome have a remarkable degree of “internal consistency” in their presentations. For this reason, it has been possible to view each as a distinctive syndrome.
Chronic fatigue syndrome

Chronic fatigue is characteristic of the patient with fibromyalgia; myalgia and arthralgia are part of the definition of chronic fatigue syndrome; the overlap is considerable.

Recently, criteria have been developed to aid in the diagnosis of each syndrome. A consensus definition for the chronic fatigue syndrome has been published, as have the results of a large multicentre trial that have resulted in criteria for fibromyalgia.

The recommended criteria for fibromyalgia turn out to be disarmingly simple: widespread musculoskeletal pain - all four quadrants - accompanied by 11 or more characteristic tender points.

Another recent study applied fibromyalgia criteria to patients with a diagnosis of the chronic fatigue syndrome. The result: 70% of chronic fatigue patients met the criteria for fibromyalgia. It is now evident that there is a considerable overlap between these two conditions. This will be an important area for further research that attempts to pinpoint specific psycho-physiological dysfunction.

What is the relationship between chronic fatigue syndrome and viral infections?

Recent studies indicate that a chronic form of Epstein-Barr virus [EBV] infection is only rarely associated with the chronic fatigue syndrome. Coxsackie B virus and cytomegalovirus infections also have been associated with the syndrome, but no cause-and-effect relationship has been established. B cell cytotropic virus, which is a retrovirus akin to HIV, has been linked to some cases of chronic fatigue syndrome. Unlike HIV, which infects T cells, the B cell lymphocytotropic virus infects B cells. This virus was associated with an outbreak of fatigue illness in the Lake Tahoe area in the USA. Currently, there is no proof that any one virus is causally related to the chronic fatigue syndrome.

Are any laboratory tests helpful?

I certainly do not favour “blind” testing for acute-onset chronic fatigue. A thorough history and examination should suggest appropriate tests. It is reasonable to do basic tests such as a complete blood count, a chemistry screen, urinalysis, and an erythrocyte sedimentation rate. Most patients undergo thyroid function tests.

Usually the sed rate is not elevated in chronic fatigue syndrome. In fact, it may be abnormally low. A significantly elevated sed rate may be an indication to consider other aetiologies.

In the patient who shows significant physical dysfunction, it is often instructive to evaluate the level of aerobic fitness by assessing the maximum oxygen consumption (V\text{O}_2\text{max}) when exercised to volitional exhaustion. Most of these patients become rapidly deconditioned, and the V\text{O}_2\text{max} quantitates aerobic unfitness and helps initiate a programme of gentle aerobic conditioning.

EBV panels are inconsistent from lab to lab and person to person over a period of time. Even if the patient is labelled as having a chronic EBV or other viral infection, the diagnosis is immaterial because we have no generally accepted treatments.

Is psychological testing routinely done?

Routine tests are seldom indicated; they are often a substitute for thought. In the patient who has no abnormal physical findings - including the tender areas of fibromyalgia - or abnormal basic investigations, I consider referral for formal psychological testing.

Usually, we find evidence of excessive somatization, hypochondriasis, phobias, anxiety states, and depression. However, the finding of a psychological problem does not necessarily indicate a causal relationship to the chronic fatigue syndrome. Many patients with chronic problems that seem to defy a precise diagnosis become anxious and depressed as a reaction to their illness.

Once the diagnosis is made, what can we do for the patient?

We don't have a magic bullet for curing fatigue. People sometimes forget that as they age, they fatigue more readily. Sometimes it is enough just to point this out to a patient who, for example, manages a family
and a job, participates in marathons, and goes to night school. We shouldn’t overlook the possibility of chronic fatigue syndrome in these people, but most fatigue patients do not have the constellation of symptoms and signs said to be characteristic of the “chronic fatigue syndrome.”

If the patient has chronic fatigue with no cause, then it is important to discuss his or her fears, what he wants to do, and what his fatigue prevents him from doing. Sometimes formal counselling is indicated to help the patient achieve more realistic expectations about his physical capacity and to generate a more positive approach to the problem.

It is important to involve the patient in a programme that encourages activity. These patients are usually inactive and quickly become deconditioned. Patients often don’t realize that it takes only a few weeks of inactivity to become significantly deconditioned. We educate the patient about the importance of conditioning and try to increase his $V_o_{max}$ incrementally. It has to be increased slowly to minimize the muscle pain that most experience when commencing exercise after a period of inactivity.

**Are there other treatment measures?**

Significant depression should be treated. If depression is severe, with profound psycho-motor retardation or manic-depressive episodes, I refer to a psychiatrist. Less severe depression may often be effectively treated with antidepressants (Table 2). Most are taken at bedtime, an exception being fluoxetine (Prozac), which should be taken in the morning. In anecdotal reports, fluoxetine seems effective in ameliorating the fatiguing aspect of depressive illness.

Many persons with chronic fatigue have sleep disturbances. If there is a history of nonrefreshing sleep— that is, sleeping a normal number of hours but waking up feeling tired—we might try a low-dose tricyclic antidepressant, such as amitriptyline HCl (Tryptanol, et al), 10 to 25 mg at bedtime. This has proved helpful in people with fibromyalgia.

The possibility of primary sleep pathologies such as nocturnal myoclonus, sleep apnoea, and narcolepsy should always be given some consideration. They have not been frequently reported in this group of patients, but specific treatments are available.

**What is the prognosis?**

The patient cannot expect a cure. To a large extent, the prognosis depends upon the patient having an intelligent understanding of his predicament and his level of motivation. If the patient falls into a pattern of “chronic illness behaviour,” then the prognosis is

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**TABLE 1**

Chronic fatigue syndrome: differential diagnosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
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<tbody>
<tr>
<td>Psychiatric disorders, such as depression</td>
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<tr>
<td>HIV infection</td>
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<tr>
<td>Chronic fungal infection</td>
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<tr>
<td>Protozoan infection</td>
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<tr>
<td>Lyme disease</td>
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<tr>
<td>Chronic or subacute bacterial diseases</td>
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<tr>
<td>Autoimmune disease</td>
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<tr>
<td>Malignancy</td>
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<tr>
<td>Chronic inflammatory diseases, such as sarcoidosis</td>
</tr>
<tr>
<td>Neuromuscular diseases, such as myasthenia gravis</td>
</tr>
<tr>
<td>Endocrine disease, such as hypothyroidism</td>
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<tr>
<td>Drug dependency or abuse</td>
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<tr>
<td>Chronic cardiopulmonary disease</td>
</tr>
<tr>
<td>Renal insufficiency</td>
</tr>
<tr>
<td>Haematological disease, such as anaemia</td>
</tr>
<tr>
<td>Toxic agents</td>
</tr>
<tr>
<td>Adverse drug reactions</td>
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</tbody>
</table>

Source: Prepared for MODERN MEDICINE by Robert M Bennett, MD.
Even if the patient is labelled as having a chronic Epstein-Barr virus infection, the diagnosis is immaterial because we have no treatment.

Chronic fatigue syndrome: a diagnostic puzzle

This timely interview raises a number of important issues:
- What is chronic fatigue syndrome?
- Is it a discrete illness?
- Is it caused by a virus or other infection?
- What is the role of depression?
- How is it diagnosed?
- Can it be treated?

Dr Bennett answers many of these questions in a thought-provoking manner. In so doing, he points up our own uncertainty when we in this field are asked similar questions.

Ten to 30% of all patients who seek medical attention in general clinics report episodes of fatigue that significantly affect their lives for 3 consecutive months. The vast majority of these patients do not have a recognized medical illness. So do they all have chronic fatigue syndrome?

Diagnostic criteria

Chronic fatigue syndrome represents a symptom complex rather than a clearly delineated disease. Thus, as Dr Bennett explains, “It is important to distinguish between chronic fatigue and the chronic fatigue syndrome.” But current working definitions of chronic fatigue syndrome have not been adequately tested. Some definitions have been so exclusionary as to make them impractical. For example, the working case definition excludes from the diagnosis any patient with depression. Nevertheless, depression is common in any chronic medical illness.

Definitions have also not accounted for other overlapping disorders, such as fibromyalgia, that could cause chronic fatigue. Although there are no definitive laboratory tests for either fibromyalgia or chronic fatigue syndrome, there are certain findings in fibromyalgia, such as tenderness at uniform anatomical sites, that have stood up as sensitive and specific diagnostic criteria. Therefore, it is important that better criteria for the diagnosis of chronic fatigue syndrome be proposed and then tested in large patient populations, including patients who meet criteria for fibromyalgia as well as for depression.

We should also ask the question: why should we label a chronically fatigued patient as having a syndrome? Isn't this much ado about nothing? After all, we all suffer from excess fatigue at one time or another during our lives. For us to tell the patient that he or she has a syndrome may merely reinforce an attitude of sickness or hopelessness. Many doctors believe that in these ill-defined areas, patients are better off without a diagnosis and that they should simply be told to get on with their lives.

Unfortunately, many such individuals are not satisfied with this approach and therefore they do not get better – neither physically nor emotionally – no matter how well intentioned they or their doctors may be. This is the group of individuals who are truly “patients,” and defining them as such is justified in view of the functional impairment from their symptoms.

Defining the illness

The problem is that we still have not adequately defined the subset of the population that has chronic fatigue syndrome in terms of “illness.” It is necessary to delineate such a definition before adequate understanding and treatment of chronic fatigue can be developed.

DON L GOLDENBERG, MD
Director, Arthritis/Fibrositis Centre and Chief of Rheumatology, Newton-Wellesley (Mass) Hospital, USA.
Follow up at least once a year. The spectrum of problems in chronic fatigue syndrome often changes, demanding further investigations and usually a lot of reassurance.

The patient most likely to improve is the one who perceives the explanation of reduced expectations as useful information and cooperates in improving aerobic fitness, improves the quality of sleep, and accepts the contribution of psychological problems. Most patients do not return to their former level of vigour, but they can lead reasonably full, productive lives.

Do some patients clear completely over a year or two?

Yes, but they are in the minority.

How often should we recheck the patient?

With any patient who has fibromyalgia or chronic fatigue, it is important to follow up at least once a year. A minority of patients will eventually develop an obvious illness to account for their symptoms.

More important, the spectrum of problems in chronic fatigue syndrome often changes, demanding further investigations and usually a lot of reassurance. Unless the patient knows that he has a “return base,” he is likely to go off on a fruitless journey of doctor-shopping. Also, if the patient knows that he will be scrutinized regularly, he is more likely to comply with management recommendations.

### TABLE 2

<table>
<thead>
<tr>
<th>Drug therapy for depression associated with chronic fatigue syndrome</th>
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<tbody>
<tr>
<td>Antidepressant</td>
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<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Amitriptyline HCI</td>
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<tr>
<td>Tryptanol, et al</td>
</tr>
<tr>
<td>Amoxapine</td>
</tr>
<tr>
<td>Demolox</td>
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<tr>
<td>Fluoxetine HCI</td>
</tr>
<tr>
<td>Prozac</td>
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<tr>
<td>Nortriptyline HCI</td>
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<tr>
<td>Aventyl, et al</td>
</tr>
<tr>
<td>Pheneizine</td>
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<tr>
<td>Nardil</td>
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<tr>
<td>Tranylcypromine</td>
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<tr>
<td>Parate</td>
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<tr>
<td>Trazodone HCI</td>
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<tr>
<td>Molipaxin</td>
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</tbody>
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Source: Prepared for MODERN MEDICINE by Robert M Bennett, MD.

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References


Suggested reading