REVIEW

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# A common-sense approach to chronic fatigue in primary care

## ABSTRACT

Since chronic fatigue is so common, long-lasting, and fraught with functional and emotional consequences, early intervention can limit overuse of health care resources and forestall disability. To help patients, we must intervene before chronicity is established or iatrogenic harm has occurred. Care that integrates medical and psychologic concepts, together with symptom management, can prevent significant secondary impairment in most cases.

## KEY POINTS

Primary care physicians should manage most of the care of persons with chronic fatigue, with referral to specialists only when specifically indicated.

By definition, chronic fatigue syndrome and idiopathic chronic fatigue must have no identifiable cause; therefore, every patient who complains of chronic fatigue should undergo a limited physical and psychiatric evaluation.

Cognitive behavioral therapy has shown some success. In this approach, patients are encouraged to set goals to increase their activity level, and to gain insight into their thought processes and outside influences that reinforce the sick role.

CHRONIC FATIGUE remains a mystery. Nobody really knows what causes it[1]; in fact, by definition, it has no identifiable cause. Like low back pain, headache, and fibromyalgia—all common conditions that physicians encounter every day—it occupies a gray area of medicine where psychosocial issues complicate our neat theories of physical causes and effects.

This does not mean that chronic fatigue is not real, or that patients with it do not suffer, or that physicians cannot help. However, the most effective treatment may not consist of drugs, but rather of listening and talking and helping the patient gain insight into his or her condition—psychosocial as well as physical.

Chronic fatigue syndrome is best regarded as a descriptive term for a type of clinical presentation. There is increasing evidence that effective interventions are possible, even in the absence of a complete understanding of the pathophysiologic mechanisms involved. Good clinical care integrating medical and psychologic concepts, together with symptom management, may prevent significant secondary impairment in most patients.

## CASE DEFINITION

"Fatigue" describes a variety of symptoms related to failure to sustain some form of physical activity, a common experience that limits our activities and achievements.[2] In most cases, fatigue is transient, explained by prevailing circumstances, relieved by rest, and of little cause for concern. For some people, however, fatigue can be chronic and disabling enough to prompt a visit to a physician.

**Chronic fatigue** is defined as self-reported persistent or relapsing fatigue lasting 6 or more consecutive months but not necessarily associ-

**TABLE 1**

**Aims of assessment**

To clarify the nature of the complaint and consider alternative diagnoses

To assess the current disability

To elicit the beliefs and fears of the patient and family about symptoms, diagnosis, and treatment

To elicit the beliefs of the patient and family about the role, benefits, and consequences of rest and activity

To identify psychological distress

To formulate the problem in terms of predisposing, precipitating and perpetuating factors

SOURCE: WESSELY S. CHRONIC FATIGUE SYNDROME. J ROYAL COLL PHYSICIANS LONDON 1996; 30:497–504. WITH PERMISSION

ated with functional impairment.[1] The International Chronic Fatigue Study Group[1] recognizes two grades of chronic fatigue that has no identifiable medical or psychiatric cause: chronic fatigue syndrome and idiopathic chronic fatigue (FIGURE 1). Of the two, chronic fatigue syndrome is more severe and less common.

## EPIDEMIOLOGY

**No etiologic theory of chronic fatigue has been proved**

Chronic fatigue seems to be common, but estimating its true prevalence is difficult. Most epidemiologic data on chronic fatigue have been extrapolated from records of patients attending specialty clinics or based on physician identification or recall. Accordingly, such data are influenced by numerous forms of selection bias.

**Chronic fatigue.** Two studies[3,4] reported that chronic fatigue affects 11% to 24% of patients in general medical practice.

**Chronic fatigue syndrome.** Analyses of community-based samples and of records in primary care clinics have estimated the prevalence of chronic fatigue syndrome at 75 to 267 cases per 100,000.[5] Bates et al[6] screened all patients in a general medical practice at a US urban hospital and estimated the prevalence at 3 to 10 cases per 1,000, depending on the definition used. A recent prospective primary care study in England[7] found an overall prevalence of chronic fatigue syndrome of 2.6%, falling to 0.5% if comorbid psychological disorders were excluded.

On the basis of these data, the CDC recently added chronic fatigue syndrome to its list of priority 1 and reemerging infectious diseases, indicating that it is now a top CDC priority.

In different series of patients with chronic fatigue syndrome, the mean age was 27 to 42 years and the female-male ratio varied from 4:1 to 1:1.[8–11] Although studies in patients attending specialty clinics seem to indicate that chronic fatigue syndrome mostly affects affluent white people, studies performed in community or primary care settings show it is an equal-opportunity disease.[7,10,12,13]

## ETIOLOGIC THEORIES

Etiologic theories abound for chronic fatigue syndrome. Some say it is a sequela of infection,[14] while others attribute it to immunologic activation,[15–19] psychiatric disorders,[20–23] central nervous system disorders,[24,25] neurally mediated hypotension,[26] neurohormonal abnormalities,[27] or muscle dysfunction. However, there is no convincing evidence that any one of these plays a major causative role. At present most investigators agree that a multifactorial etiology is most likely, and symptoms remain largely unexplained.

## CLINICAL APPROACH TO CHRONIC FATIGUE IN PRIMARY CARE

The rational diagnostic and therapeutic approach to chronic fatigue does not hinge on making a specific diagnosis of chronic fatigue syndrome or idiopathic chronic fatigue. An open mind and compassionate attitude are the pillars of diagnostic and treatment planning. TABLE 1 summarizes the aims of assessment,[28] and FIGURE 1 summarizes the overall approach.

### Differential diagnosis

A combined medical and psychiatric assessment is required in every case of chronic fatigue. The first step is to exclude easily diagnosable and sometimes treatable conditions such as:

**Thyroid disease.** The thyroid-stimulating hormone (TSH) level serves as a good screening test.

**Sleep disorders.** Ask specific questions to

## Clinical evaluation and management of chronic fatigue

Self-reported persistent or relapsing fatigue lasting 6 or more consecutive months

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**Evaluate** by history, physical, and mental status examination and appropriate laboratory tests

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**Exclude** if another cause for chronic fatigue is found (ie, chronic liver disease, infection, neoplasm, inflammatory disease)

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**Classify** as either chronic fatigue syndrome or idiopathic chronic fatigue (see "Aims of assessment," TABLE 1)

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**Chronic fatigue syndrome**

Inclusion criteria

Clinically evaluated, medically unexplained fatigue of at least 6 months' duration that is:

- Of new onset (not lifelong)
- Not the result of ongoing exertion
- Not substantially alleviated by rest
- The reason for a substantial reduction in previous level of activities

Plus 4 or more of the following symptoms:

- Subjective memory impairment
- Sore throat
- Tender lymph nodes
- Muscle pain
- Joint pain
- Headache
- Unrefreshing sleep
- Postexertional malaise lasting more than 24 hours

Exclusion criteria

- Active, unresolved or suspected disease
  - Untreated hypothyroidism
  - Sleep apnea, narcolepsy
  - Unresolved cases of hepatitis B or C virus infection
- Psychotic, melancholic, or bipolar depression (but not uncomplicated major depression)
- Psychotic disorders (any past or current diagnosis)
  - A major depressive disorder with psychotic features
  - Schizophrenia of any subtype
- Dementia
- Anorexia or bulimia nervosa
- Alcohol or other substance misuse
- Severe obesity

**Idiopathic chronic fatigue**

Clinically evaluated, unexplained chronic fatigue that fails to meet criteria for chronic fatigue syndrome

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**Management**

- Establish a therapeutic alliance with the patient
- Use modified cognitive behavior therapy
- Prescribe a graded exercise program
- Advise the patient to schedule activity
- Treat as appropriate with SSRIs or low-dose tricyclics, and analgesics if indicated
- Negotiate a return to work
- Refer to a specialist if necessary

SOURCE: ADAPTED FROM FUKUDA K, STRAUS SE, HICKIE I, ET AL. THE CHRONIC FATIGUE SYNDROME: A COMPREHENSIVE APPROACH TO ITS DEFINITION AND STUDY. ANN INTERN MED 1994; 121:953–958.

**FIGURE 1**

TABLE 2

**Approximate charges for laboratory tests recommended by the National Institutes of Health for patients with debilitating chronic fatigue**

| TEST | COST* |
|---|---|
| General health panel blood test† | $85.00 |
| Erythrocyte sedimentation rate | $4.90 |
| Urinalysis | $4.37 |
| Thyroid-stimulating hormone level | $23.00 |

*Medicare reimbursement for a Cleveland, Ohio area teaching hospital, with facility and professional fees included where applicable; reimbursement may vary by institution
†Includes complete blood count with differential, serum urea nitrogen, creatinine, sodium, potassium, chloride, carbon dioxide, glucose, calcium, phosphorus, alanine aminotransferase, alkaline phosphatase, total protein, albumin, and globulin

**A detailed laboratory investigation is usually not helpful**

try to uncover obstructive sleep apnea or narcolepsy, which may be confused with chronic fatigue syndrome. Examples: Do you feel sleepy in the daytime? Does your partner tell you that you snore? That you stop breathing? Do you fall asleep in inappropriate situations? If the history suggests a sleep disorder, the patient should be referred to a polysomnography laboratory for a formal sleep study.

**Psychiatric disorders.** Several standardized screening tests such as the General Health Questionnaire or combinations of tests such as the Zung Self-rating Anxiety Scale, the Symptom Checklist-90, and the Beck Depression Inventory can help identify patients who may be suffering from a primary psychiatric disorder.[29] While borderline results on any of these tests have limited sensitivity and specificity for diagnosing psychiatric illness, markedly abnormal results can be useful in identifying patients with high levels of emotional distress.

If you are uncertain about the presence of a confounding psychiatric problem, referral to a psychologist or psychiatrist who is familiar with chronic fatigue is appropriate.

**Other chronic diseases** that may readily explain fatigue should also be considered, such as infection, inflammatory diseases, chronic liver disease, and neoplasms.

### Laboratory testing

Unless there are specific indications from the history or physical examination, a detailed laboratory investigation is not usually helpful in cases of chronic fatigue. A National Institutes of Health (NIH) panel has recommended a group of relatively inexpensive diagnostic tests (TABLE 2).[1] We believe that tilt-table testing should be considered if the patient gives a history of syncope, light-headedness, diaphoresis, abdominal discomfort, blurred vision, or nausea associated with fatigue.

## TREATMENT

Treatment remains largely empiric, since no specific treatment for chronic fatigue has proven effective in adequately large controlled clinical trials. Nevertheless, a growing body of data suggests that some therapies are useful, while others are not.

**Antidepressant medications** have gained widespread theoretic and clinical support for treating chronic fatigue syndrome, despite a lack of controlled studies. Newer antidepressants have better side effect profiles than the tricyclic antidepressants and less likelihood of serious medical consequences from overdosage. Case reports and uncontrolled studies suggest that fluoxetine, a selective serotonin reuptake inhibitor (SSRI), is beneficial in chronic fatigue syndrome. However, results from placebo-controlled studies were inconclusive—one study found evidence of efficacy,[30] but the other did not.[31]

**Cognitive behavioral therapy** (CBT) has been tried with apparent success in chronic fatigue syndrome. Recent randomized controlled trials[32,33] suggest that cognitive behavioral therapy leads to measurable sustained functional improvement in chronic fatigue syndrome and is acceptable to patients.

The interventions reported to date have generally involved several key elements, including:

- Goal-setting (increased activity levels, increased social and pleasurable events)
- Education about the illness
- Gradual exposure to activities the patient used to engage in but now avoids because of chronic fatigue

- Restructuring of potential cognitive errors involving misinterpretation of events or stimuli. (Symptoms such as fatigue and myalgia engender a state of "learned helplessness," and seem potent and uncontrollable. Through cognitive behavioral therapy, the belief that "the symptoms are controlling me" should give way to "I am in control of my symptoms," not necessarily "I no longer experience symptoms.")
- Evaluation of possible social, family, or personal reinforcers of disability.

**Exercise.** Patients with chronic fatigue must balance two opposing needs. On one hand, they must engage in some physical activity or they will suffer worsening fatigue from muscle atrophy and cardiovascular deconditioning. On the other hand, a sudden burst of physical activity can precipitate a relapse (ie, postexertional fatigue). Therefore, a cautious controlled increase in activity should be part of a multidimensional approach. This was confirmed in a prospective randomized controlled study by Fulcher and White,[34] in which both fatigue and functional capacity were significantly better after completing a supervised graded exercise treatment.

**Mineralocorticoids** and other supportive measures can be tried for patients with documented neurally mediated hypotension. In a randomized, double-blind, placebo-controlled trial,[35] patients with chronic fatigue syndrome took low doses of hydrocortisone. Symptoms improved, but at the expense of significant adrenal suppression.

**Other treatments.** Immune-based therapies such as immunomodulators[36] or intravenous immunoglobulin[37,38] lack convincing evidence of efficacy, and should therefore be avoided. Data are also limited from clinical trials of magnesium[39] and fish oil.[40] So far no significant success has resulted from the use of an antiviral agent (ie, acyclovir).[41]

## COURSE OF ILLNESS AND PROGNOSIS

Many patients with chronic fatigue syndrome appear to improve slowly, but the symptoms rarely disappear completely. Bombardier et al[42] found that, 1.5 years after the initial evaluation, 64% of patients with chronic fatigue said they had improved, as did 61% of those with full-blown chronic fatigue syndrome. However, only 2% reported complete resolution of symptoms. Patients initially diagnosed with chronic fatigue syndrome reported greater symptom severity and a lower level of functioning at follow-up than did patients with idiopathic chronic fatigue.

Consistently reported risk factors for poor prognosis are older age, chronic illness, comorbid psychiatric disorders, and the belief that the illness is due to physical causes.[43]

## ROLE OF THE PRIMARY CARE PHYSICIAN

Since chronic fatigue is so common, long-lasting, and fraught with functional and emotional consequences, we believe that early intervention may not only limit overuse of health care resources but also possibly forestall some degree of disability. To help patients, we must intervene before chronicity is established or iatrogenic harm has occurred.

Generalists are more than "gatekeepers": they know the patient and the difficulties he or she is experiencing and are ideally situated to provide empathy and education, which are crucial in gaining the patient's trust and cooperation.

Thus, we do not believe that referral to a specialist should be routine. The primary care physician remains the mainstay of management, in collaboration with other members of the primary care team such as physiotherapists, social workers, and psychologists.

Referral to a specialist may be indicated only if patients develop severe, prolonged, or complex disabilities and when there is an increased probability of an alternative diagnosis. Further investigations may include objective neuropsychological and exercise tolerance testing, evaluation of comorbid psychiatric disorders, and thorough assessment of pain severity and its impact on daily activities.

**Patients should start by walking for 5 minutes, 5 days a week**

## WORK AND DISABILITY

Compared with the 4.5% to 5.6% of the general population who claim to be unable to work,[44] the work disability rate among patients with chronic fatigue syndrome is considerable. Primary care physicians should seek

to promote rehabilitation by advising, whenever possible, that patients return to work early on, with duties and hours restricted to suit the needs of the individual. Return to work, like all other activities, needs to be gradual and planned.

## PRACTICAL RECOMMENDATIONS

In our experience, more than 80% of patients with medically unexplained chronic fatigue who are treated according to the following regimen achieve meaningful improvement. We therefore suggest this general approach for patients with chronic fatigue.

- **Talk to the patient.** Explore his or her beliefs about the illness, and stressors, moods, and coping behavior. Written handouts, counseling about diet and nutrition, and referral to support groups can bolster the patient's intellectual, physical, and emotional resources.
- **Prescribe graded, low-intensity exercise.** Patients should start by walking for 5 minutes at 50% of their predicted maximal heart rate, at least 5 days a week. Every 1 or 2 weeks, increase the duration by 1 or 2 minutes up to a goal of 20 minutes.
- **Consider SSRI antidepressants** for patients who are clearly depressed (even if mildly) and in those complaining of prominent neurocognitive dysfunction.
- **Give nonnarcotic analgesics** (ie, acetaminophen, tramadol) **and nonsteroidal anti-inflammatory drugs** to treat the myalgias, arthralgias, and headaches that often occur in chronic fatigue syndrome.
- **Give low-dose tricyclic agents or doxepin** 30 minutes to 1 hour before bedtime as adjunctive agents for selected patients with difficulties in falling or staying asleep.
- **Consider referral** to an experienced psychiatrist for patients with evidence of an active mood disorder (whether primary or secondary), as well as those with persistently abnormal mood states despite treatment with SSRIs. Also consider referral to a chronic fatigue specialist for further evaluation, such as a formal sleep study or tilt-table testing, for patients whose histories suggest a primary sleep disorder or neurally mediated hypotension.
- **Reevaluate every 8 to 12 weeks** to assess compliance and to monitor the status of major complaints.

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