

2 therapies lift mood in chronic fatigue syndrome

Usual depression and anxiety therapies may be ineffective



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Chronic fatigue syndrome (CFS) continues to puzzle and provoke. Years of research have failed to find a biomedical cause or to answer fundamental questions, such as “What is it?” and “Does it exist?”

Up to two-thirds of CFS patients have psychiatric disorders,¹ but psychiatrists are not the first physicians CFS patients usually see. Primary care physicians may ask you to help confirm the diagnosis, manage patients’ anxiety and depression, differentiate CFS from somatoform disorders, or provide psychotherapy for patients and their families.

Knowing what transpires in the referring physician’s office is key to helping a patient function despite CFS. This article describes:

- CFS clinical features and possible causes
- psychiatric comorbidities and exclusions
- cognitive behavioral therapy (CBT) and graded exercise, the only two therapies shown to improve CFS patients’ daily function.

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Table 1

CDC diagnostic criteria for chronic fatigue syndrome

At least 6 months of fatigue sufficient to
"substantially reduce" patient's level of activity

4 or more of 8 concurrent symptoms:

- Poor memory/concentration
- Sore throat
- Tender glands
- Myalgia
- Joint pain
- Recent-onset headache
- Unrefreshing sleep
- Excessive tiredness on exercise

No obvious medical or psychiatric causes, such
as eating disorders, psychosis, bipolar disorder,
melancholia, or substance abuse*

CDC: Centers for Disease Control and Prevention

* Many nonpsychotic psychiatric disorders (such as atypical depression) do not exclude a CFS diagnosis

Source: References 1 and 2

ANXIOUS, DEPRESSED, AND TIRED

Mr. A, age 43, is referred to you with anxiety and depressed mood associated with CFS, diagnosed 2 years ago. Fatigue predated Mr. A's depression and anxiety, which his primary care physician considers consequences of CFS.

Mr. A is married, has three children, and owns a successful accounting practice. CFS was diagnosed from the classic presentation: abrupt onset of fatigue despite good health and a promising career. Now, overwhelming fatigue reduces his productivity. He makes up for frequent rest breaks by working in snatches of time, even at 4 AM. He is spending little time with his wife and children.

DEFINING CFS

The Centers for Disease Control and Prevention (CDC) defined CFS in 1988 while investigating infectious causes of fatigue (*Table 1*).^{2,3} Epstein-Barr virus was thought to be the cause of CFS.

continued

Most patients who present to their primary care physicians with complaints of fatigue do not meet CDC criteria for CFS, however. These “non-CFS” patients are diagnosed as having “idiopathic chronic fatigue,” a term that is not particularly helpful because CFS remains an idiopathic disorder.

Clinical findings. As with Mr. A, many CFS patients’ fatigue begins suddenly, often with flu-like symptoms. Patients lose tolerance for exercise and alcohol and become unable to work or socialize at pre-illness levels.

Medical symptoms can overlap those of other conditions, such as fibromyalgia, chemical sensitivities, and irritable bowel disorder. These associations make the condition difficult to assess and contribute to some physicians’ difficulty in accepting CFS as a biomedical condition. Mistrust and a poor patient-physician relationship can result when the physician doubts the symptoms’ “medical” nature and the patient resents the implication that the suffering is “all in your head.”

What causes CFS? No consistent factor has been identified that explains the pathophysiology of

CFS symptoms. Many possibilities have been examined, but the evidence is confusing and contradictory.

A few preliminary studies suggest possible familial (shared environmental) and genetic components, but data are sparse and no more than suggestive.⁴ Findings of CNS studies are inconsistent, and the search for a change in immune function or an infectious agent has been fruitless despite some patients’ infection-like symptoms. The early hypothesis that Epstein-Barr virus was responsible has been disproved. Imaging studies, psychological testing, and neuroendocrine investigations have identified abnormalities in some patients with CFS. The most-promising findings point to abnormalities in the hypothalamic-pituitary-adrenal axis and in serotonergic neurotransmission,⁵ suggesting an abnormal stress response in some patients.

Could CFS and depression be one and the same? Or is depression a response to CFS?

CASE CONTINUED: TEST RESULTS: NORMAL

Mr. A has undergone extensive medical assessment (complete blood cell count; renal, hepatic, and thyroid function tests; calcium, phosphate, and glucose determinations; and urinalysis), which yielded normal results. Brain MRI findings were also normal; specifically, no evidence of multiple sclerosis.

Even so, he has had nonspecific symptoms of impaired concentration, sore throat, tender cervical nodes, muscle pain, and nonrefreshing sleep. Physical exertion can leave him drained for at least 1 or 2 days.

PSYCHIATRIC DISORDERS

As many as 66% of CFS patients may have one or more psychiatric comorbidities; the most common are generalized anxiety disorder, panic disorder, depression, and somatoform disorder.¹ Because CFS symptoms are regarded as being

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not fully explained by a known medical disorder, patients are often diagnosed as having an undifferentiated somatoform disorder. Either disorder could be diagnosed in some cases, but this differentiation sheds no new light on the condition.

CFS and depression. Could CFS and depression be one and the same? Proponents of that position point out the similarity of symptoms, loss of function, and—in at least some cases—favorable response to antidepressants. Opponents cite other factors such as:

- presence of sore throat, lymphadenopathy, and post-exercise fatigue
- differences in sleep patterns
- frequent absence of psychiatric illness before fatigue onset
- evidence of hypocortisolism (also seen in patients with melancholic depression) in some CFS patients.

Notably, other forms of depression (atypical depression) may also be associated with hypocortisolism, suggesting common pathophysiologic features.⁷ Another possibility is that the depression and anxiety experienced by CFS patients are a response to a chronic debilitating condition, as is seen in other chronic illnesses.⁸

PRIMARY CARE WORKUP

Complaints of long-lasting, debilitating fatigue should alert the primary care physician to CFS. Like somatization disorder, CFS requires a physical workup, though as few as 2% of CFS patients are found to have an undiagnosed medical illness that explains the symptoms.⁹ The evaluation's goal is not so much to find out what's causing the fatigue as to reassure the patient that all avenues are considered before the diagnosis is made. When this is accomplished well, the patient is likely to accept psychiatric referral or treatment, if needed.

Two-part initial evaluation. If the initial physical exam and laboratory work find no biomedical

Table 2

Two-part initial primary care evaluation of chronic fatigue

First session

- Focus on initial history
- Introduce concept of a biopsychosocial approach to problem
- Help patient understand that the disorder has no clear-cut cause, but its effects can be anticipated and addressed
- Ask patient to bring a relative or friend to next appointment and to keep notes on symptoms and functional difficulties to discuss at the second session

Second session

- Refine the history
- Note recent events
- Establish more-complete picture of patient's everyday life with help of relative's or friend's observations
- Focus on identifying comorbid psychiatric conditions and helping patient cope with chronic illness
- Consider referring patient to a mental health professional

cause for the patient's chronic fatigue symptoms, we recommend a two-part primary care evaluation. This includes a focused discussion with the patient about CFS (*Table 2*).¹⁰ Goals of the first session are to:

- establish a relationship that will survive difficult times
- teach the patient to think of complex medical problems as having psychological and social consequences, if not causes.

During the second encounter, the primary care physician may begin to consider whether he or she will need help managing the patient's psychiatric/psychological problems. Some physicians enjoy work of a psychological nature, whereas others prefer to refer to mental health professionals. Primary care treatment or referral to a psychiatrist, psychologist, or other psychotherapist depends on

both the physician and the individual patient.

Primary care physicians usually request a psychiatric consultation to confirm or rule out psychiatric conditions that exclude a CFS diagnosis (melancholic depression, bipolar disorder, schizophrenia, anorexia nervosa or bulimia, and recent substance abuse). They also may refer in cases of other common disorders with poorly explained symptoms such as fibromyalgia and chemical sensitivity disorder.

CASE CONTINUED: HIGH ANXIETY

Mr. A describes how fatigue is affecting his work and home life. He is especially worried that he will not be attentive enough to catch accounting errors by his employees.

Interestingly, his anxiety remits but fatigue continues when he goes on vacation. He has no history of melancholic depression, bipolar disorder, psychosis, or substance abuse.

PSYCHIATRIC ASSESSMENT

The referring physician should provide a full account of the medical workup. This:

- assures you that possible medical causes of fatigue have been excluded
- provides information on psychiatric history and previous treatments
- delineates information on initial treatment efforts.

Like the primary care workup, your assessment is more for gathering relevant data than for its interpretation. You will follow well-defined diagnostic criteria in making sense of the information, but the quality of your data depends on

the patient's willingness to describe his or her symptoms.

Realize how defensive a patient may feel about being given a vague and disputed diagnosis such as CFS. Because the diagnosis depends somewhat on examining his or her volitional contribution to the symptoms,⁶ your listening skills are key to building the patient-physician relationship. Taking the patient's suffering seriously is essential and may provide great relief.

When you confirm a CFS diagnosis, the next step is to identify any frequently occurring psychiatric comorbidities, such as nonmelancholic depression, anxiety, and somatoform disorders.

No psychotropics, including all classes of antidepressants, show efficacy for CFS core symptoms

PSYCHIATRIC TREATMENT

CBT and exercise. Only CBT and graded exercise therapy yielded "promising results" in a systematic review of all CFS treatments studied in 44 controlled treatment trials.¹¹ By comparison, evidence is inconclusive or insufficient to support the use of:

- immunoglobulins or hydrocortisone
- most psychotropics—including all classes of antidepressants.

CBT and graded exercise protocols have been used successfully in adult^{12,13} and adolescent¹⁴ CFS patients. Treatment is done in two steps:

- Patients learn about their illness, develop a realistic assessment of their limitations, and come to understand that physical activity will not harm them.
- Patients begin graded exercises designed to slowly extend their exercise tolerance and widen their range of daily activities.

Compared with controls, adult and adolescent CFS patients' fatigue and overall functioning improved significantly, and the adolescents'

school attendance improved.

Trained psychologists usually do this work, and your role is to be aware of the key part this approach plays in managing CFS patients and to set up appropriate referrals.

CASE CONTINUED: RELIEF AND ACCEPTANCE

Mr. A continues to see you and a therapist for treatment of mild depression and severe anxiety. His behavioral therapy focuses on helping him cope with how his illness limits his relationship to work and family. His therapist also explores with him the personal meanings of his new situation, his feelings about issues such as dependence, and limitations imposed on his life goals.

You start a trial of fluoxetine (up to 40 mg/d for several months) with minimal benefit. You then try nortriptyline, 25 mg nightly, and clonazepam, 0.5 mg bid. Although these drugs can be sedating, Mr. A reports feeling no more fatigued than he was before taking them. He improves slightly after 7 months but not enough that he wants to continue the medication.

Medications. Neither psychiatric nor other medication classes have shown efficacy in treating CFS core symptoms.¹⁵ One recent study¹⁶ found

Depression and anxiety in chronic fatigue syndrome patients may be a response to the debilitating illness. Take their suffering seriously to build a lasting treatment relationship. CBT and graded exercise have been shown to improve CFS patients' function.

BottomLine

continued

Related resources

- ▶ Afari N, Buchwald D. Chronic fatigue syndrome: a review. *Am J Psychiatry* 2003;160:221-36.
- ▶ Reid S, Chalder T, Cleare A, et al. Chronic fatigue syndrome. *Clin Evid* 2004;12:1578-93.
- ▶ Centers for Disease Control and Prevention. Chronic fatigue syndrome. <http://www.cdc.gov/ncidod/diseases/cfs/>.
- ▶ International Association for Chronic Fatigue Syndrome. <http://www.aacfs.org>.

DRUG BRAND NAMES

Citalopram • Celexa, others Fluoxetine • Prozac
Clonazepam • Lorazepam, others Nortriptyline • Aventyl, others

DISCLOSURE

The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

citalopram helped reduce chronic fatigue, but the study was small and uncontrolled. Although the subjects had chronic fatigue, not all met the formal definition of CFS for study inclusion.

Medication does play an important role in treating comorbid anxiety and depression. Usual psychopharmacologic strategies are appropriate. As in Mr. A's case, most psychiatrists use SSRIs as first-line medications, but side effects are probably the most useful guide to medication choice.

CASE CONTINUED: ADDITIONAL TREATMENT

Because medication has had little effect on Mr. A's anxiety and depressed mood, you suggest adding a graded exercise program to his treatment plan. He improves steadily over time and says he is pleased. Although progress is slow, he finds it reassuring to be accomplishing realistic goals. He realizes that you and the therapist do not have the answer to his illness, but

he trusts you and is comforted that you accept his condition and are willing to listen and help.

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