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A 35-Year-Old Woman with Somatic Symptoms

Case Study and Commentary: Robyn K. Goshorn, MD, FACP, and Elizabeth A. Rice, MD

DR. LIANG:

Patients who experience somatic symptoms characterized by pain, distress, and disability rather than discernible, disease-specific abnormalities are said to have functional somatic syndromes. These disease states are quite challenging but nevertheless important for primary care providers to recognize; symptoms occur commonly, often persist despite therapy, cause significant disability, and consume tremendous health care resources. For example, 20% of consultations in the United Kingdom,¹ 25% of referrals in the Netherlands,² and 35% of referrals in the United Kingdom³ are directly attributable to functional somatic syndromes and their symptoms. Inpatients also have been reported to experience somatic symptoms.⁴

Generally, patients with functional somatic syndromes have few, if any, detected structural lesions or biochemical changes accompanying their symptoms.⁵ Female patients are much more likely to experience functional somatic syndromes than are male patients.^{6,7} The term "hypochondria" is a common lay description of functional somatic syndromes. Some medical descriptions with a similar connotation include psychosomatic syndrome, somatization, and abnormal illness behavior.⁸

Although some belief may persist that these disorders are not real, it is clear that the suffering of affected patients is very real; consequently, functional somatic disorders deserve attention and careful assessment. Affected patients generally have a higher prevalence of emotional distress and related disorders than do patients with comparable medical conditions; they also experience high levels of disability.^{9,10} Functional disease syndromes include, but are not limited to, chronic fatigue syndrome, fibromyalgia, irritable bowel syndrome, premenstrual dysphoric disorder, temporomandibular pain, dysfunction syndrome, interstitial cystitis, atypical (noncardiac) chest pain, multiple chemical sensitivities, repetitive strain injury,¹¹ repeti-

tive stress injury, sick building syndrome, chronic whiplash, and Gulf War syndrome.¹²

The degree of objectivity in diagnosing each of these disorders is variable. For example, fibromyalgia is a condition that has been defined by objective terms alone,¹³ whereas premenstrual dysphoric disorder is defined using objective and subjective terms¹⁴ and multiple chemical sensitivities are defined by a completely subjective set of definitions.¹⁵ Although there has been much debate on the basic etiologies of these syndromes, it has been postulated that a spectrum of considerations may explain their typical characteristics. Generally, these syndromes may represent atypical forms of established psychiatric disorders,¹⁶ expressions of psychoemotional distress in a somatic formulation that is influenced by sociologic trends,¹⁷ or distinct disorders with specific symptoms and dysfunctions and individualized genetic and biologic features.¹⁸ Other studies have attempted to assess predisposing, precipitating, and perpetuating factors to describe these disease entities.¹⁹ Indeed, some have proposed that the existence of so many somatic disorders is largely the result of medical specialization, with the differentiation of specific functional somatic syndromes largely reflecting the tendency of specialists to focus upon those symptoms relevant to their specialty.²⁰

Treatment is difficult. Indeed, most standard therapies within the armamentarium of medicine are ineffective.²¹ Moreover, because of the debate on classification, most treatment assessments determining whether

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patients respond to specific therapies reflect, to a large extent, a particular subspecialty perspective on functional somatic syndromes.²⁰ This fact has limited the number of patients enrolled in clinical trials and increased the difficulty of determining underlying causes and effective treatments to address those causes.²⁰ Such difficulties are exacerbated by patient devaluation and dismissal of medically based evidence that conflicts with their beliefs regarding the disease, as well as by political, social, and economic considerations, including health insurance coverage for treatment.¹²

Overall, functional somatic syndromes cause significant morbidity in affected patients, who often turn to their primary care providers for relief of their symptoms. These physicians must be sensitive both to the nature of these disease states and to the patients who experience somatic symptoms. Psychological and socio-cultural factors should be reviewed, and a general biopsychosocial effort should be made in order to assist these patients.

DRS. GOSHORN AND RICE:

Syndromes of chronic fatigue, musculoskeletal pain, and multiple other somatic symptoms without objectively definable etiology or pathophysiology have been termed “functional somatic syndromes.”¹² These syndromes are a source of severe distress and disability for patients,^{22,23} and they present vexing diagnostic and therapeutic challenges for physicians. Patients with similar clinical syndromes have been described since the beginning of modern medical literature.²⁴ Such conditions have had many names over the years, including chronic Epstein-Barr virus syndrome, epidemic neuromyasthenia, Iceland disease, and chronic brucellosis syndrome. Some of these names reflect putative etiologies or pathophysiologies that subsequently have been shown to be incorrect. Currently, these syndromes are studied using the names chronic fatigue syndrome and fibromyalgia. The prevalence of chronic fatigue syndrome depends on the population being studied, the case definition used, and how the case definition is applied. Large community-based studies have estimated a point prevalence of between 75 and 560 cases per 100,000 persons.^{25,26} A study performed in 1992 in Australia estimated that chronic fatigue syndrome then cost \$59 million per year.²⁷

Despite a rapidly expanding body of research, chronic fatigue syndrome and fibromyalgia remain poorly understood in the general medical community.²⁸ Primary care physicians play an extremely important role in managing and shaping the course of these

illnesses. Wise decisions regarding the diagnostic evaluation and management of patients with chronic fatigue syndrome or fibromyalgia require the very best use of the art of medicine.

CASE STUDY

Initial Presentation

A 35-year-old female attorney of European ancestry goes to her primary physician with the chief symptom of fatigue.

History

She says that she had been in her usual state of good health until approximately 1 year ago. At that time, she began experiencing frequent colds and sore throats. She was under considerable situational stress because of the demands of her job and of taking care of her 2 children, age 2 and 4 years. Along with frequent respiratory infections, she had the gradual onset of fatigue and malaise. Over the course of the next 6 months the fatigue became so severe that she was forced to give up her well-paying and rewarding job as an attorney; she has not been able to return to work since that time. Sleep disturbance has been a prominent part of her illness. She describes both initial and middle insomnia and notes that her sleep is nonrefreshing, saying “I’m as tired when I wake up as I was when I went to bed.”

In addition to fatigue and sleep disturbance, she reports aching involving her arms, legs, back, and neck (saying “my whole body hurts”), dizziness or lightheadedness, intermittent nausea, and difficulty concentrating. She enjoys recreational reading but has largely given it up because she cannot remember what she reads from one page to the next. She remembers being bothered by relatively frequent headaches since her teenage years but says that generalized, steady, dull headaches have become more frequent, severe, and persistent over the past year.

During the past year the patient has been evaluated by 2 internists, 2 rheumatologists, and a neurologist. She has undergone multiple tests, but no specific diagnosis has been reached. Psychiatric evaluation has been recommended to her, but she is convinced that her illness is not emotional. She says that she has only recently begun to be depressed because her fatigue and other symptoms prevent her from doing many things that are enjoyable and important to her. She is tearful as she describes how her illness is preventing her from being an effective wife and mother. She says that, although her husband generally has been sensitive and supportive, his patience seems to be wearing thin, because the doctors have been unable to provide

an explanation for her ill health. Her law firm also has been supportive and lenient with her absence because, as they have told her, she has been “such an effective and productive member of the firm.”

She has never been hospitalized and has had no surgical procedures. She has never smoked. She has never had more than 1 or 2 alcoholic beverages per week, and she gave up alcohol completely several years ago because it made her feel “sick and dizzy.” She has never used recreational drugs. She reports no fever, change in appetite, weight loss or gain, or focal neurologic symptom.

Physical Examination and Laboratory Data

A thorough physical examination, including a complete neurologic examination, reveals no abnormality other than multiple musculoskeletal tender points. Results of a complete blood count; measurement of erythrocyte sedimentation rate and serum levels of alanine transaminase, total protein, albumin, globulin, alkaline phosphatase, calcium, phosphorous, glucose, creatinine, thyroid-stimulating hormone, and blood urea nitrogen; and urinalysis are all normal. The patient’s score on a Beck depression inventory is 11.

- **What is the differential diagnosis of chronic fatigue?**

Fatigue is a nonspecific symptom associated with a host of medical and psychiatric illnesses. It can also be a physiologic state related to sleep deprivation, overwork, and stress. When fatigue results from neoplastic, infectious, inflammatory, endocrine, hematologic, or cardiopulmonary disease, more specific signs and symptoms of the disorder usually dominate the patient’s clinical presentation. When prolonged fatigue is the primary symptom reported, several conditions should be considered during the history taking and physical examination (**Table 1**). Patients should be asked to distinguish between fatigue and sleepiness. True excessive daily sleepiness would raise concern about an underlying sleep disorder. The fatigue associated with chronic fatigue syndrome and fibromyalgia is central fatigue, or disinclination to activity, whereas the fatigue associated with adrenal insufficiency and most chronic medical illnesses is peripheral fatigue characterized by fatigability and weakness of muscles. The fatigue associated with chronic fatigue syndrome is unrelieved by rest, whereas the fatigue associated with physiologic fatigue states and most chronic medical conditions improves with rest but may recur with relatively minimal activity.

- **What diagnosis is suggested by this patient’s presentation?**

Table 1. Differential Diagnosis of Prolonged Fatigue

Psychiatric illness
Anxiety disorders, including posttraumatic stress disorder
Dysthymia
Major depression
Malingering
Somatoform disorder
Substance abuse
Physiologic states
Chronic situational stress
Deconditioning, prolonged bed rest
Poor sleep hygiene
Chronic medical illness
Adrenal insufficiency
Chronic allergic conditions
Chronic infection (including HIV, hepatitis B and C), toxoplasmosis
Chronic neurologic disease (especially multiple sclerosis)
Diabetes mellitus (especially when undiagnosed or poorly controlled)
Occult malignancy
Thyroid disease (including apathetic hypothyroidism in the elderly)
Sleep disorders (especially sleep apnea, nocturnal myoclonus, idiopathic hypersomnolence, narcolepsy)
Illnesses without objectively defined pathophysiology
Chronic fatigue syndrome
Fibromyalgia
Idiopathic chronic fatigue
Drug use
Anticonvulsant agents
Antihypertensive agents
Anxiolytic agents
Narcotic analgesics
Sedatives

Three features of this case are striking. First, the patient describes many symptoms of long duration involving multiple organ systems and multiple parts of the body. Second, these symptoms have not been associated with any objective, observable sign of disease. Third, thorough diagnostic evaluation has failed to determine an etiology for the symptoms. Based on her history of debilitating fatigue of more than 6 months’ duration, symptoms including unrefreshing sleep,

Table 2. CDC Research Case Definition of Chronic Fatigue Syndrome

1. Persistent or relapsing fatigue that
 - Is of new or definite onset (not lifelong)
 - Is not the result of ongoing exertion
 - Results in substantial reduction of occupational, educational, social, or personal activities
- AND
2. Concurrent occurrence of 4 or more of the following symptoms during 6 or more consecutive months of illness:
 - Self-reported functionally significant impairment of memory or concentration
 - Sore throat
 - Tender cervical or axillary lymph nodes
 - Muscle pain
 - Multijoint arthralgias
 - Headaches of a new type, pattern, or severity
 - Unrefreshing sleep
 - Postexertional malaise lasting more than 24 hours
- Exclusion criteria
- Any active medical condition that may explain the presence of chronic fatigue
 - Present or past diagnosis of depression with psychotic or melancholic features
 - Bipolar affective disorders
 - Any psychotic psychiatric disorder
 - Anorexia nervosa and bulimia nervosa
 - Alcohol or substance abuse occurring within 2 years of onset of chronic fatigue

Data from Fukuda et al.²⁹

CDC = Centers for Disease Control and Prevention.

diffuse musculoskeletal pain, difficulty concentrating, headaches, and postexertional malaise, and the absence of any active medical condition that would explain the symptoms, this patient's illness meets the Centers for Disease Control and Prevention (CDC) research case definition of chronic fatigue syndrome²⁹ (Table 2). Because of her history of widespread pain involving all 4 quadrants of the body for more than 3 months and the required number of tender points on physical examination, she also meets the criteria for the American College of Rheumatology's clinical definition of fibromyalgia¹³ (Table 3).

There is considerable overlap between the case definitions of chronic fatigue syndrome and fibromyalgia, and many patients concurrently meet criteria for both of

Table 3. American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia

1. History of widespread pain, above and below the waist, involving both sides of the body for at least 3 months
2. Pain in at least 11 of 18 specified tender point sites on digital palpation with an approximate force of 4 kg

Data from Wolfe et al.¹³

these conditions.³⁰ Chronic fatigue syndrome and fibromyalgia also tend to occur together with irritable bowel syndrome, migraine headaches, and multiple chemical sensitivity syndrome.³¹ The overlap in case definitions and clinical features among the functional somatic syndromes has led some authors to question whether these syndromes actually represent distinct entities.^{30,32}

- **What are the components of an adequate diagnostic evaluation in patients meeting criteria for fibromyalgia or chronic fatigue syndrome?**

Clinical Evaluation of Patients with Functional Somatic Syndromes

Patients with chronic fatigue syndrome are prone to disease at the same rate as the general population, but not more so. Fibromyalgia may be associated with another rheumatologic disease, but it does not predispose to the development of any other disease. It is essential that careful diagnostic evaluation of patients with functional somatic syndromes be performed to be sure all possible diagnoses have been detected. An adequate diagnostic evaluation includes 4 components.

First, thorough history and physical examination are as fundamental to the diagnostic evaluation of these patients as they are time consuming and labor intensive for the physician. Physical diagnosis is most effective when the examiner is looking for specific findings. Awareness of the differential diagnosis described above will enhance the diagnostic quality of the medical history and physical examination. Any objectively verifiable abnormality on physical examination or pertinent diagnostic clue from the history must be investigated carefully. Second, standard screening recommendations, including Papanicolaou smears, mammograms, endoscopic colon evaluation, and prostate-specific antigen test, should be followed. Third, the physician should use other screening laboratory tests judiciously, remembering that patients with these syndromes are rarely reassured by negative results of tests and that excessive use of diagnostic tests can encourage adaptation to the sick

role.³³ A specific battery of screening tests is required by the 1994 revised CDC case definition of chronic fatigue syndrome²⁹ (Table 4). This screening battery helps to rule out possible occult organic diseases. Any abnormality among these laboratory data must be evaluated carefully. Finally, concurrent psychiatric disorders, especially depression and anxiety disorders that are amenable to specific treatment, should be sought both at the beginning of treatment and over time. As the therapeutic alliance solidifies and trust develops, more detailed mental health exploration, either by the treating physician or by mental health professionals, is likely to become possible. For some patients, this exploration may lead to the core of the illness. For others, it may be helpful in dealing with comorbid psychiatric conditions and with the effects of chronic illness.

- **Does this patient meet criteria for depression or another psychiatric disorder?**

Depression

The case patient's report of depressed mood, insomnia, fatigue, and difficulty concentrating raises the possibility of a diagnosis of major depressive disorder. However, she notes that her depressed mood began after and as a result of the onset of her somatic symptoms and functional disability. Like most patients with chronic fatigue syndrome, she also reports no feelings of guilt or worthlessness and no anhedonia. Instead, she is eager to get back to her job, which she considers to be "rewarding." She states that she is highly motivated to pursue pleasurable activities and is extremely frustrated that her somatic symptoms interfere with these activities. She does not have thoughts of suicide or frequent thoughts of death. Instead, she expresses frustration that her illness is preventing her from "getting on with life."

The case patient has some symptoms of depression, but not enough to meet the full criteria for major depressive disorder. Such "subthreshold depression" is common among patients in primary care practice and is associated with functional impairment even after controlling for comorbid medical and psychiatric illness.^{34,35} Compared with general medical patients without depressive symptoms, patients with subthreshold depression have an increased risk for developing major depressive disorder in the future and an increased rate of comorbid psychiatric diagnoses.³⁴ Although some patients with subthreshold depression have a primary affective disorder, such as depression in partial remission, prodromal depression, or masked depression with somatic presentation, in other cases the depressive symptoms may be secondary to a chronic medical condition.

Table 4. Screening Laboratory Data Required by the 1994 CDC Revised Case Definition of Chronic Fatigue Syndrome

Complete blood count
Erythrocyte sedimentation rate
Serum levels
Alanine aminotransferase
Albumin
Alkaline phosphatase
Blood urea nitrogen
Calcium
Creatinine
Electrolytes
Globulin
Glucose
Phosphorous
Thyroid-stimulating hormone
Total protein
Urinalysis

Data from Fukuda et al.²⁹

CDC = Centers for Disease Control and Prevention.

Furthermore, the optimal management of subthreshold depression has not been defined,³⁶ and a high rate of spontaneous improvement appears to be common.³⁷

Patients with chronic fatigue syndrome and fibromyalgia often meet the *Diagnostic and Statistical Manual of Mental Health Disorders: DSM-IV-TR*³⁸ criteria for depression or anxiety disorders.^{33,39–41} However, the nature of the association between the emotional and physical symptoms remains unclear. Depression could be secondary to the effects of illness, and it could also be a comorbidity with a common pathophysiology. However, it is unlikely that chronic fatigue syndrome and fibromyalgia are merely somatic presentations of major depression. Phenomenologic differences separate chronic fatigue syndrome from typical major depression in that patients with chronic fatigue syndrome usually deny anhedonia and guilt.⁴² Also, the hypothalamic-pituitary-adrenal axis function abnormalities that characterize major depression are distinct from the abnormalities of this system that are found in fibromyalgia and chronic fatigue syndrome.^{43,44}

Somatoform Disorder

The concept of somatoform disorders is especially problematic in patients with chronic fatigue syndrome

and fibromyalgia, disorders that, at least as yet, have no objectively defined etiology and pathophysiology. The diagnosis of somatoform disorders depends on attribution of symptoms by the examiner to an emotional etiology. Johnson and colleagues compared a group of chronic fatigue syndrome patients with no psychiatric diagnosis for at least the previous 5 years with a group of patients with major depression but no medical diagnosis with regard to the *Diagnostic and Statistical Manual of Mental Health Disorders: DSM-III*⁴⁵ criteria for somatization disorder.⁴⁶ When chronic fatigue syndrome symptoms based on CDC criteria were coded as psychiatric, patients with chronic fatigue syndrome were far more likely than patients with major depression to meet criteria for full or subsyndromal somatization disorder. In contrast, when these symptoms were coded as medical, only about 10% of chronic fatigue syndrome patients met full criteria for somatization disorder, a number similar to that of the group of patients with classic major depression. When all symptoms beginning after the onset of chronic fatigue syndrome and attributed by the patient to the current illness were coded as medical, no patients met criteria for somatization disorder. The authors pointed out that the population was likely to be heterogeneous, including some patients with emotionally based tendencies to somatize and other patients with few or none of these tendencies. They concluded that the concept of somatoform disorders might be so arbitrary as to be rendered meaningless in controversial syndromes such as chronic fatigue syndrome.

Diagnosis

Based on the patient's clinical presentation and laboratory evaluation, the physician makes a diagnosis of chronic fatigue syndrome and fibromyalgia.

- **Are there any laboratory test results that are diagnostic for chronic fatigue syndrome and fibromyalgia?**

A growing body of research supports the contention of patients with chronic fatigue syndrome and fibromyalgia that their experience of illness is based on physical symptoms of an organic cause and not emotional or behavioral problems. Compared with healthy controls, patients who meet the chronic fatigue syndrome and fibromyalgia case definitions have been shown to have evidence of immune system dysregulation,^{47–50} neuroendocrine dysregulation,^{43,51–53} autonomic imbalance with neurally mediated hypotension,^{54,55} slow-wave-sleep abnormalities,⁵⁶ and altered pain perception.⁵⁷ Magnetic resonance imaging of the brain may show more subcortical white-matter hyperintensity in at least some subgroups of patients with chronic fatigue syn-

drome than is seen in healthy controls,⁵⁸ although the overlap is great and these findings are considered nonspecific.⁵⁹ Abnormalities of brainstem perfusion have been observed in some patients with chronic fatigue syndrome.⁶⁰

These findings as yet do not provide the basis for either an objective case definition or any diagnostic test. However, such observations should make clinicians who care for patients very uncomfortable with the word “functional”—a word that implies the absence of organic pathophysiology and relegates the patient's illness to the behavioral or emotional realm. Any response by the physician that denies the objective reality of the patient's experience, no matter how gently or sympathetically expressed, will inevitably make the patient feel misunderstood, abandoned, belittled, and defensive. At the same time, it is clear to every physician experienced in the care of patients with fibromyalgia and chronic fatigue syndrome that maladaptive behavioral and cognitive response to illness often perpetuate disability and may become the dominant feature of illness in these syndromes. As Dr. Nortin M. Hadler has pointed out so eloquently, “If you have to prove you are ill, you can't get well.”⁶¹

- **Is the diagnosis of chronic fatigue syndrome or fibromyalgia clinically helpful?**

Correct application of the case definitions for chronic fatigue syndrome and fibromyalgia implies that the patient's syndrome has no known etiology, no known pathophysiology, no definitive diagnostic test, no objective measure of severity, an uncertain prognosis, and no proven curative therapy. What clinical purpose could be served by a diagnostic label with such severe limitations?

In clinical use, the diagnostic labels chronic fatigue syndrome and fibromyalgia are double-edged swords. On the one hand, naming the illness can be extremely useful. From the therapeutic point of view, to name the illness is to objectify it, to make it potentially subject to control, and to set it apart as the enemy that the patient and physician can battle and eventually master together. On the other hand, if the limitations noted above are not clearly understood and reinforced directly and honestly, the diagnostic label can perpetuate sick-role behavior and become the dominant focus of the patient's life. The effect of the physician's words and body language in the initial diagnostic consultation go a long way toward determining the patient's response to these syndromes and his or her ultimate prognosis. The pressure of time in the busy clinic and limited knowledge of the functional somatic syndromes may result in a glib

and scientifically inaccurate explanation (eg, “You have Epstein-Barr virus disease”) that can encourage maladaptive and counterproductive responses to illness (eg, “I have to build up my immune system to get rid of the virus”). Less common but more pernicious is the manipulation of this vulnerable population for the financial gain of those selling unproved remedies or scientifically inaccurate self-help books. Establishing a trusting therapeutic alliance based on accurate information is the critical first step in the effective management of syndromes such as chronic fatigue syndrome and fibromyalgia.

- **What treatment options are available for this patient?**

Approach to Management

There is no universally effective treatment for chronic fatigue syndrome or fibromyalgia. Because we do not know the etiology and pathophysiology of these syndromes, treatment is, of necessity, empirical. Nevertheless, patients can benefit greatly by careful and artful treatment.

The literature regarding treatment of these conditions has become extensive and often difficult to interpret. The lack of a case definition based on objective findings makes it difficult to know if the patients in any single study are equivalent to the patients in another study. The absence of an objective measure of illness severity makes it difficult to assess outcome of treatment. A positive placebo response to therapeutic interventions is very common in chronic fatigue syndrome and fibromyalgia.⁶² Available therapeutic tools are far from ideal. These limitations notwithstanding, the physician caring for patients with these syndromes must attempt to derive a rational approach to therapeutics from available data and clinical experience. Such an approach has 3 components. First, the therapeutic value of interaction with a caring and competent physician cannot be overemphasized. As discussed above, education about the diagnosis—what it means and what it does not mean—prepares the patient in an essential way for a positive response to therapy. Second, any specific comorbidity that can be diagnosed, including depression and anxiety disorder, must be treated effectively. Third, while no therapy can be considered to be of proved efficacy in these syndromes, several treatment approaches are supported by some experimental data and much clinical experience. These approaches include pharmacotherapy, exercise, and cognitive behavioral therapy.

Pharmacotherapy. In our experience, tricyclic antidepressant agents often improve the quality of sleep,

reduce pain, and improve energy in patients with fibromyalgia and chronic fatigue syndrome. Several studies have also supported the efficacy of these drugs.^{63–67} Tricyclic antidepressant agents are known to increase time spent in stage IV sleep and to decrease transmission through the spinal cord pain filter. Their antidepressant effect also can be useful for treating comorbid depression, if present.

The effective use of tricyclic antidepressant agents requires considerable knowledge and clinical skill. Patients must be selected carefully for this treatment; those with underlying heart disease and those prone to significant orthostatic hypotension should be excluded. Patients must be educated about potential side effects, especially anticholinergic phenomena, including dry mouth and constipation. Morning grogginess can be minimized by gradual increase of dose and by splitting the dose or moving the dose to earlier in the day. Weight gain can be a major problem with amitriptyline, but it is less often noted with nortriptyline or desipramine. Although no studies of use of blood levels to monitor therapy in these syndromes are available, anecdotal reports have suggested that very low doses of tricyclic antidepressant agents are often therapeutic in patients with chronic fatigue syndrome and fibromyalgia. In contrast, our own anecdotal experience has been that patients with chronic fatigue syndrome often note symptomatic improvement with therapeutic blood levels of nortriptyline (50 to 150 ng/mL) and rarely respond to lower blood levels.

In our patient population, we have observed that selective serotonin reuptake inhibitors are helpful less often than tricyclic antidepressant agents for pain, fatigue, and sleep disturbance, although they may effectively manage comorbid depression. Some studies seem to support this impression,^{68–70} whereas other studies show benefit of citalopram and fluoxetine in treatment of fibromyalgia,^{60,71} particularly when used in combination with amitriptyline.⁷²

Evidence regarding efficacy of other antidepressants in treatment of chronic fatigue syndrome and fibromyalgia is very limited. One study of a monoamine oxidase inhibitor, moclobemide, found it less effective overall than amitriptyline.⁷³ Small studies of selegiline⁷⁴ and phenelzine⁷⁵ showed evidence of at best marginal improvement in symptoms. A small trial of nefazodone found enough evidence of benefit for patients with chronic fatigue syndrome to suggest further studies.⁷⁶ Venlafaxine is supported by anecdotal reports.⁷⁷ A small study of venlafaxine in fibromyalgia patients found evidence of benefit in those with a lifetime history of depression or anxiety.⁷⁸ Two randomized placebo-controlled

trials have indicated benefit of S-adenosylmethionine in treatment of fibromyalgia.⁶⁷

When musculoskeletal pain is a prominent feature of the syndrome, the literature suggests that addition of a nonsteroidal anti-inflammatory drug (NSAID) may enhance the benefits of tricyclic antidepressant agents⁷⁹; a trial of such a combination would be warranted. A placebo-controlled trial has demonstrated the efficacy of cyclobenzaprine in the management of pain and sleep disturbance in patients with fibromyalgia.⁸⁰ Another study found benefit of short-term use of tramadol,⁸¹ although no studies have addressed long-term use of this drug in treating fibromyalgia pain.

Based on the observation that patients with chronic fatigue syndrome have slightly low serum levels of cortisol,⁵¹ a trial was undertaken to study the effects of low-dose hydrocortisone replacement in patients with chronic fatigue syndrome.⁸² With doses of hydrocortisone ranging from 25 to 35 mg daily, this study found only minimal improvement that was outweighed by substantial adrenal suppression. A subsequent study using lower doses of hydrocortisone in the range of 5 to 10 mg daily appears promising.⁸³ However, many questions about low-dose hydrocortisone therapy remain, and further studies are needed before this approach can be generally recommended.

Immune globulin^{84,85} and fludrocortisone,^{86,87} administered intravenously, have failed to show benefit for patients with chronic fatigue syndrome. There is no valid experimental support for prescription of megadose vitamin therapy, magnesium, dietary supplements (or any dietary manipulation), ENADA (oral form of nicotinamide adenine dinucleotide), evening primrose oil, ginkgo biloba, coenzyme Q-10, or amino acids.

Exercise. Several studies have documented the benefits of aerobic exercise in patients with chronic fatigue syndrome and fibromyalgia.^{66,88–90} The key to successful prescription of exercise for treatment of these syndromes is to start with intensity and duration well within the patient's tolerance and to advance very slowly—slowly enough so that the exercise does not exacerbate symptoms. At the very least, an exercise program can overcome the effects of physical deconditioning, which is a common comorbidity in patients with fibromyalgia and chronic fatigue syndrome.⁹¹

Cognitive behavioral therapy. The psychiatric treatment technique of cognitive behavioral therapy has been shown to benefit at least some subgroups of patients with chronic fatigue syndrome and fibromyalgia. Initial studies of cognitive behavioral therapy in chronic fatigue syndrome showed equivocal results.⁹² However, later studies using longer treatment courses

(13–15 hours versus 6 hours) and different control treatments (usual medical care or relaxation techniques versus injections) showed significant improvement in physical functioning.^{93,94} There also appeared to be benefits with regard to fatigue, anxiety, and mood, although these benefits were not as robust. It is important to point out that all of these studies used 1-on-1 therapy. Cognitive behavioral therapy has been studied less thoroughly in patients with fibromyalgia. One study involving 22 patients and a treatment period of 30 months showed improvement in several areas of concern.⁹⁵

Formal cognitive behavioral therapy may not be readily available in all clinical settings. Nevertheless, many of the techniques used in this treatment, including patient education, correction of patients' maladaptive beliefs about their condition, and support for positive coping behaviors, can be appropriated to the standard clinical encounter.

Request for Leave of Absence

As the physician and patient discuss the treatment options, the patient says she feels she cannot continue her work as an attorney and requests support for a medical leave of absence from her law firm.

- **What is the appropriate role for the physician in supporting the patient's request for disability benefits?**

Support for short-term disability. In cases such as this one, determining disability status can be especially vexing because the functional somatic syndromes by definition have no objectively definable basis for diagnosis or measurement of severity. Physicians, as well as employers, friends, and family members, may be suspicious of patients' claims of disability, because patients with these syndromes superficially appear healthy. However, as discussed above, a growing body of evidence suggests that objective pathophysiology may well underlie these syndromes. Schizophrenia and peptic ulcer disease are examples of diseases that were once thought to be caused by emotional disturbance because of limited scientific understanding of their pathophysiology.

Studies have shown similar levels of physical disability for patients with fibromyalgia, rheumatoid arthritis, and ankylosing spondylitis and similar levels of cognitive disability for patients with fibromyalgia and major depression.^{96,97} By self-report, patients with chronic fatigue syndrome perceive themselves to be more disabled than do patients with congestive heart failure, type 2 diabetes mellitus, recent myocardial infarction, and multiple sclerosis.⁹ Symptoms of fibromyalgia tend to remain stable over time.⁶⁰ Severely ill patients with

chronic fatigue syndrome frequently do not improve over years of follow-up.⁹⁸

Obviously, in this case, the physician's first goal is to help the patient get well so she can return to her normal activities, including work. Because treatment in the case patient is just beginning, it is reasonable to remain optimistic that her condition will improve. Therefore, it would be appropriate to consider temporary disability or medical leave of absence, if possible, until her response to treatment becomes clear. Bennett has described well how chronic pain and fatigue can cause impairment of ability to work.⁹⁶ Chronic pain and fatigue may cause disability through (1) difficulty sustaining repetitive motor tasks; (2) decreased physical efficiency (ie, inability to maintain adequate pace of work); (3) decreased mental sharpness; (4) fear of poor performance; (5) difficulty in conforming to usual working hours; and (6) difficulty dealing with work-place stressors (eg, temperature extremes, rigid time/performance expectations, excessive noise). In her work as an attorney, the patient would be affected particularly by items 2 through 6. Her case for short-term (3–6 months) disability compensation could be supported on this basis.

Initiation of Therapy and Follow-up

The physician initiates therapy with nortriptyline 10 mg daily 30 minutes before bedtime, and the dose is increased by 10 mg every third day to 50 mg daily. The patient is instructed to begin an exercise program using her home treadmill starting at 2 miles per hour and 0% grade for 1 minute twice daily, a level of exercise she is confident she can tolerate without exacerbation of symptoms. She is to increase the duration of each session by 30 seconds per week for the next 4 weeks. If she feels she is not tolerating the exercise, she is told to reduce the duration but not to stop the exercise completely. The physician reassures her that even if she overdoes it and exacerbates her symptoms, no permanent damage will be done.

At the time of her first follow-up visit 4 weeks later, the patient is tolerating 50 mg of nortriptyline without difficulty; a therapeutic blood level of nortriptyline has been reached at 95 ng/mL. The patient has been able to exercise for only 1 minute twice daily without exacerbating symptoms. She believes her sleep, energy level, and musculoskeletal pain have improved slightly, and she feels somewhat encouraged. At the time of her second follow-up visit, the patient reports that she feels better than she has in more than a year. Her sleep seems deeper and more refreshing, her energy has improved, and her pain has decreased.

Five Months After Presentation

At a follow-up visit 5 months after initiation of therapy, the patient reports that improvement in her symptoms has not been sustained despite maintenance of a therapeutic nortriptyline level. For the past 6 weeks, she has noticed no benefit from treatment, and her symptoms have become as severe as they were initially. She has given up her exercise program because it made her "feel worse."

Follow-up During the Next 18 Months

Over the next 18 months, trials of venlafaxine, cyclobenzaprine, low-dose hydrocortisone, and NSAIDs prove unhelpful. The patient attempts to restart her exercise program but is unable to advance beyond the minimal level without exacerbation of symptoms. Referral for cognitive behavioral therapy is investigated, but the closest available site of treatment is more than 120 miles from the patient's home; she does not feel that she can make trips of that distance. After almost 2 years of illness, she decides to file for Social Security disability benefits.

- **How can physicians provide a reasonable and defensible opinion regarding long-term disability for patients with functional somatic syndromes?**

Long-Term Disability

The Social Security Act requires, in general, that disability be established on the basis of objective medical evidence and not on the patient's statement of symptoms alone. However, in 1999, Social Security Ruling 99-2P established that chronic fatigue syndrome could be considered a medically determinable impairment when it is accompanied by certain medical criteria or laboratory findings.⁹⁹ The ruling mentions several examples of findings that could be considered to establish objectively a diagnosis of chronic fatigue syndrome, including palpably swollen or tender lymph nodes, recurrent or persistent nonexudative pharyngitis, persistent and reproducible muscle tenderness on repeated examinations, Epstein-Barr virus capsid antigen titer equal to or greater than 1:5120, Epstein-Barr virus early antigen titer equal to or greater than 1:640, abnormal results on a magnetic resonance imaging brain scan, and neurally mediated hypotension, as shown by tilt-table testing.

These particular examples mentioned in the ruling underline the complexity of trying to objectify disability status in this syndrome that, by definition, has no objective pathology. Enlarged lymph nodes and recurrent pharyngitis were dropped from the CDC research case definition of chronic fatigue syndrome in the 1994

revision, because these findings were almost never present. In fact, the persistent presence of enlarged lymph nodes would very strongly imply some other diagnosis, such as lymphoma or HIV infection. In the 1980s, studies showed that patients with chronic fatigue syndrome had higher than usual titers of antibodies against Epstein-Barr virus, although the overlap with titers of healthy controls was great and the antibody titers did not correlate with symptoms.^{43,100} Epstein-Barr virus antibody measurements serve no purpose in the diagnosis or management of patients with chronic fatigue syndrome or fibromyalgia, and there is no value in measuring them. Reproducible tender points or muscle tenderness would serve as an objective finding under the ruling, even if the findings did not meet requirements for the American College of Rheumatology criteria for diagnosis of fibromyalgia. Nonspecific abnormalities on brain imaging, neuropsychological testing, and physical examination could also serve to validate chronic fatigue syndrome as a medically determinable impairment, although such findings would be of questionable clinical significance. For syndromes that have no objectively demonstrable pathology, the administrative law judge ultimately must determine the credibility of the claimant and the validity of the claim of disability under the rules of the Social Security Administration. Comprehensive records from the primary physician that document the nature and course of the illness over time and its functional impact on the patient's life can be very helpful to the judge in this regard.

In summary, with regard to disability in the functional somatic syndromes, the primary physician should be sure to complete each of the following steps: (1) carefully establish the diagnosis; (2) maintain an optimistic outlook while pursuing all appropriate treatment options; (3) document the patient's symptoms and self-reported functional impairment over time; (4) document any ancillary evidence of functional impairment including reports from family, employers, or other observers; (5) consider whether neuropsychological testing, brain imaging studies, or other special tests would clarify the clinical situation; and (6) provide all of the above information to the Social Security Administration or other insurer when requested.

Epilogue

The patient is granted Social Security disability benefits. Her condition remains unchanged 2.5 years after her initial visit.

- **How should patients with functional somatic symptoms be monitored?**

Regular follow-up of patients with functional somatic syndromes is important for several reasons. First, the physician must remain alert for any new signs or symptoms or objective findings that could signal a new diagnosis. Second, periodic reassessment of the patient's empirical treatment regimen is desirable. Repeat trials of standard therapeutic options, including exercise regimens, may become appropriate depending on the patient's condition. Third, patients desperate for relief often resort to unproved remedies. The physician should be available to counsel the patient regarding the scientific status of such unproved remedies as antifungal therapy, vitamins, food supplements, and over-the-counter drugs such as evening primrose oil, coenzyme Q-10, ENADA, and many others. Finally, it is important to remain alert for any new axis I psychiatric diagnosis that may develop so that appropriate treatment may be started.

SUMMARY

Fortunately, most patients with the functional somatic syndromes are not as refractory to therapy as this patient was, and many improve enough to return to work, school, and family and social responsibilities. Knowledgeable and caring physicians can provide education, guidance with coping strategies, counsel regarding the value of therapeutic exercise, and judicious prescription of empirical pharmacologic therapy. We must hope that advances in scientific understanding of the etiologies and pathophysiologies of these syndromes will allow more definitive therapy in the future. **HP**

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