A Randomized Trial Of Fluoxetine In A Patient With Persistent Fatigue

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Chronic fatigue syndrome is a disorder of unknown cause that is characterized by debilitating fatigue for at least 6 months. Formal criteria for the diagnosis of this syndrome were established in 1988 by the Centers for Disease Control (CDC).[1] Even though fatigue ranks among the most common problems in primary care,[2] most persons afflicted with fatigue fail to satisfy the Centers for Disease Control criteria for chronic fatigue syndrome. In fact, in one study of 135 patients with persistent fatigue, only 6 met the criteria for chronic fatigue syndrome.[3] While the cause and treatment of chronic fatigue syndrome remain open to speculation, even less is known about patients with persistent fatigue who do not meet CDC criteria for chronic fatigue syndrome.

Because many chronic fatigue syndrome patients and patients with persistent fatigue experience mood changes[4] and major depression,[5] it has been speculated that chronic fatigue syndrome in some patients might result from neurochemical mechanisms similar to those observed in major depression.[6] While this mechanism might explain the cause of chronic fatigue syndrome in some patients, it is likely that there are also other causes of chronic fatigue syndrome, which would explain why none of a variety of pharmacological agents used thus far has been successful on the whole population of patients with persistent fatigue.[7]

Although treatment approaches are often established by randomized clinical trials, treatment decisions in chronic fatigue syndrome cannot be guided by such trials because they have not yet shown an effective treatment.[8] In addition, treatment decisions that are generalized from studies with different eligibility criteria might be unwarranted for a specific patient.

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Recently a method for determining, in a relatively unbiased and objective manner, whether a promising but unproven method of treatment actually works for an individual has been discussed.[9-11] We report the results of a single-patient randomized controlled trial assessing the effectiveness of the treatment of chronic fatigue with the serotonergic antidepressant fluoxetine.

Case History

A 45-year-old man came to our office complaining of a 7-month history of severe fatigue. His fatigue began gradually after an L4-5 and L5-S1 laminectomy for lumbar disc disease. The surgery and the postoperative period were uneventful. He reported no history of fevers, chills, night sweats, change in weight, or back pain in addition to the expected degree and duration of postoperative discomfort. With the exception of mild childhood asthma, the patient denied any other important medical illnesses.

At the onset of his fatigue, the patient thought he might have had a tick bite while in a geographical region known to have Lyme disease. Aside from his fatigue, the patient had no history of neurologic symptoms, cardiac complaints, or joint pain. A detailed review of systems was negative. The patient specifically denied sore throat, adenopathy, generalized myalgia or arthralgia, headache, forgetfulness, or confusion.

The patient had recently become unemployed. He denied depressed or anxious mood, trouble with concentration, feelings of guilt, constipation, changes in libido, anhedonia, anorexia, or insomnia. He estimated that his fatigue reduced his energy level by 75 to 90 percent. He was unable to perform any but the simplest tasks of daily living. He denied use of alcohol or other drugs and was taking no medications. There was no family or personal history of psychiatric illness. The patient reported a stable and happy marriage.

A comprehensive physical examination revealed a 5-foot 10-inch man weighing 191 pounds. His temperature, blood pressure, and

heart rate were normal. He appeared fatigued but not wasted or obviously depressed. His examination was notable only for a well-healed midline scar in the lower back, mild abdominal obesity, and 0.5-cm, mobile, nontender lymph nodes in both inguinal areas.

Results from the laboratory examination included normal findings for erythrocyte sedimentation rate, complete blood count, thyroid stimulating hormone level, and a comprehensive chemistry panel. Lyme disease immunoglobulin M and immunoglobulin G antibody titers by enzyme-linked immunosorbent assay were less than the limit of detectability.

After his first visit he developed a pruritic eczematous rash in the area of his presumed tick bite, which did not have the characteristics of erythema chronicum migrans. A consulting dermatologist believed the rash to be a nonspecific eczematous dermatitis that was unrelated to the patient's fatigue. It cleared without recurrence after the use of topical corticosteroids.

Because there was no apparent external cause for his fatigue, and because many patients with chronic fatigue syndrome have been found to have an underlying affective disorder, we decided to address the possibility of depression masked as fatigue.

Methods

An accepted approach to treatment of a disease in a patient when there is no known effective treatment is to undertake a randomized controlled treatment trial (n of 1), in this case comparing the effects of medication with those of placebo. Fluoxetine was chosen because it is a serotonin reuptake inhibitor that does not cause side effects, such as those caused by tricyclic antidepressants, which would cause the patient to distinguish between treatment and placebo.

Most studies of fluoxetine treatment in patients with depression have indicated that patients respond between weeks 3 and 8 of treatment. Recent evidence indicates that most patients who will ultimately respond to treatment show improvements in depressive symptomatology within the first 2.5 weeks of treatment, and many show some changes within the first week.[12-15]

After giving informed consent to the randomized clinical trial, the patient received two bottles, marked "A" and "B," of identically appearing capsules containing 20 mg of fluoxetine or placebo. The patient, his wife, and the physician were blinded to the contents of the bottles, and the physician was blinded to the order of their administration. The patient completed a 3-week course of each medication without a washout period.

The patient and his wife independently rated his overall energy and activity level at the onset of the study and at the end of each treatment period using a five-item scale; estimating his energy and activity level to be 1–25 percent, 26–50 percent, 51–75 percent, 76–100 percent, or in excess of 100 percent of his premorbidity energy and activity level.

Results

During the first 2 weeks on medication A the patient had a gradual but marked decrease in his fatigue, which was virtually absent by the third week. In the 2 weeks after switching to medication B, he experienced a marked increase in fatigue until it reached his prestudy base line. His wife reported the same effects, even though the patient made a point of not discussing how he felt directly with her during this period. The patient and his wife both scored his global energy and activity level to be 1 to 25 percent at the onset of the study, 76 to 100 percent at the end of treatment A, and 1 to 25 percent at the end of treatment B. When the code was broken, it was found that medication A was fluoxetine and B was placebo. The patient was prescribed fluoxetine 20 mg/d, again with resolution of his fatigue. He continued taking fluoxetine for 6 months. Within 2 months after stopping, he had a recurrence of fatigue without other symptoms; the drug was prescribed again, and he is currently asymptomatic.

Conclusion

This report describes a single-patient randomized placebo-controlled trial of fluoxetine in a patient who had persistent, severe fatigue. This relatively specific serotonergic antidepressant had a dramatically ameliorative effect on the patient's symptom of fatigue, even though the patient did not meet the *Diagnostic and Statistical Manual of Mental Disorders* III-R[16] criteria for major depression, dysthymia, or other affective disorders. Because many chronic fatigue syndrome patients have unrecognized affective disorders that are only recognized during a focused psychiatric in-

terview by a trained individual,[17] the possibility of an affective disorder as the cause of the patient's fatigue, and his response to fluoxetine, remains plausible.

The single-patient randomized clinical trial has been described extensively in the literature.[9-11] We believe that this approach is particularly useful in a condition with characteristics similar to chronic fatigue syndrome. The lack of a specific external cause and the absence of a test-proven treatment leave the physician few options. The single-patient randomized clinical trial can alleviate some of the physician's uncertainty regarding the risk-to-benefit ratio of a new treatment. In addition, these trials hold the promise of adding to our knowledge about the syndrome.

This report shows that the single-patient randomized clinical trial can be easily and practically applied to a common clinical condition, such as persistent fatigue, in which promising ideas and therapies might exist but are as yet unproved.

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