Prospective Observational Study of Treatments for Unexplained Chronic Fatigue

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Background: Unexplained chronic fatigue is a frequent complaint in primary care. A prospective observational study design was used to evaluate whether certain commonly used therapies for unexplained chronic fatigue may be effective.

Method: Subjects with unexplained chronic fatigue of unknown etiology for at least 6 months were recruited from the Wisconsin Chronic Fatigue Syndrome Association, primary care clinics, and community chronic fatigue syndrome presentations. The primary outcome measure was change in a 5-question fatigue score from 6 months to 2 years. Self-reported interventions tested included prescribed medications, non-prescribed supplements and herbs, lifestyle changes, alternative therapies, and psychological support. Linear regression analysis was used to test the association of each therapy with the outcome measure after adjusting for statistically significant prognostic factors.

Results: 155 subjects provided information on fatigue and treatments at baseline and followup. Of these subjects, 87% were female and 79% were middle-aged. The median duration of fatigue was 6.7 years. The percentage of users who found a treatment helpful was greatest for coenzyme Q10 (69% of 13 subjects), dehydroepiandrosterone (DHEA) (65% of 17 subjects), and ginseng (56% of 18 subjects). Treatments at 6 months that predicted subsequent fatigue improvement were vitamins (p = .08), vigorous exercise (p = .09), and yoga (p = .002). Magnesium (p = .002) and support groups (p = .06) were strongly associated with fatigue worsening from 6 months to 2 years. Yoga appeared to be most effective for subjects who did not have unclear thinking associated with the fatigue.

Conclusion: Certain alternative therapies for unexplained chronic fatigue, especially yoga, deserve testing in randomized controlled trials.

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The symptom of fatigue is worthy of study. It has a "powerful adverse effect on quality of life"^{1(p175)} and is a primary reason for seeking medical care.¹ For sufferers, the problem tends to persist; 58% to 72% of persons who have fatigue for at least 3 months continue to have fatigue after 1 year,²⁻⁵ and 59% still have fatigue after $2^{1/2}$ years.⁵

Most research on treatment for fatigue has evaluated the subset of patients with chronic fatigue syndrome (CFS). In addition to unexplained chronic fatigue, CFS is also characterized by other somatic symptoms such as sore throat, painful lymph nodes, muscle aches, joint pain, and headaches.⁶ Treatments evaluated for CFS include conventional, medically prescribed therapies such as antidepressants,^{7–9} anti-infective agents,^{10,11} and immunologic agents.^{12,13} Most treatments have been ineffective.^{14–16} However, there is evidence that cognitive-behavioral therapy and graded exercise therapy are somewhat helpful.¹⁷ With the exception of a single trial of cognitivebehavioral therapy,¹⁸ there has been little research on treatments for patients who have unexplained chronic fatigue but not CFS.

Because medical treatments for chronic fatigue have not been adequate, patients often try alternative therapies.¹⁹ Many of these are recommended on CFS Web sites, including acupuncture,²⁰⁻²² herbal therapies such as ginseng or astragalus,²¹ dietary supplements such as essential fatty acids^{23,24} or magnesium,²⁵ yoga,^{19,22} and other supplements such as nicotinamide adenine dinucleotide (NADH).²⁶ There has been minimal research evaluating these therapies.^{23,27,28} The purpose of the present observational study was to identify therapies that may be worth testing in a randomized controlled trial.

METHOD

Data for this study were from a prospective 2-year study of 159 persons over the age of 17 years with fatigue of unknown etiology for at least 6 months. Study subjects were recruited from 3 sources: (1) members of the Wisconsin Chronic Fatigue Syndrome Association, Sun Prairie, Wis., (2) patients in participating primary care medical clinics, and (3) persons from the community who attended presentations on CFS. Patients from the medical clinics responded to signs in the clinics that asked for volunteers. These patients were not necessarily being treated for fatigue. The collection of data from study participants was approved by the institutional review boards of the Medical College of Wisconsin, Milwaukee, and the University of Iowa, Iowa City, and all persons who participated in the study signed a consent form.

Subjects were excluded if they did not meet our criteria for substantial fatigue or they reported other illnesses that might account for their fatigue: cancer, diabetes, heart disease, chronic bronchitis or emphysema, renal disease, rheumatoid arthritis, or systemic lupus erythematosus. The presence of these diseases was determined from responses to a questionnaire that asked whether or not they had ever been told by a doctor that they had any of several specific chronic illnesses or a chronic illness that was not on the list.

Subjects provided information at 3 time periods. When subjects were enrolled in the study, they provided baseline information about fatigue, demographic characteristics, medical conditions, lifestyle, sleeping habits, and psychological characteristics. At 6 months and at 2 years of follow-up, they also provided information about fatigue, somatic symptoms, and any herbal or prescription medications they were currently taking. At this time, patients were asked to note whether they had tried any of a list of 16 lifestyle changes or alternative therapies within the past 6 months and whether these therapies had been helpful.

We measured the degree of fatigue by summing the responses to questions about the frequency of the following 5 characterizations of energy level: (1) full of pep or energy; (2) tired, worn out, used up, or exhausted; (3) woke up feeling fresh and rested; (4) fatigue has interfered with my work, family, or social life; and (5) fatigue has been one of my 3 most disabling symptoms. The first 3 of these questions came from the Rand Vitality Index,²⁹ and the fourth and fifth questions were taken from the Fatigue Severity Scale.³⁰

The 3 questions about the frequency of fatigue (questions 2, 4, and 5) were scored "1" for none of the time, "2" for a little of the time, "3" for some of the time, "4" for a

good bit of the time, "5" for most of the time, and "6" for all of the time. The 2 questions relating to the frequency of having high energy (questions 1 and 3) had reverse scoring (i.e., from 6 to 1). Thus, higher scores represented greater rather than less fatigue.

The possible range of the total score was from 5 to 30. Subjects were excluded from the study if their total score at baseline was less than 17.5, which is an average score midway between "some of the time" and "a good bit of the time." The threshold used for this study was chosen because it corresponds to the threshold level used by the Rand Vitality Index to define fatigue.^{4,31} We used a score of 25 or higher to indicate severe fatigue. This score indicates that the subjects answered the 5 fatigue questions so that the average response for each aspect of fatigue was "most of the time."

Subjects were asked about 5 somatic symptoms used as criteria for CFS (headache, muscle aches or pains, sore throat, painful lymph nodes, and joint pain) and 8 other somatic symptoms (backache, indigestion, diarrhea, constipation, other stomach or intestinal discomfort, mild fever or chills, muscle weakness, and dizziness or lightheadedness). The subjects scored the frequency of each somatic symptom in the past 4 weeks on a scale from 1 ("none of the time") to 6 ("all of the time"). A score of 5 was "most of the time." Total scores were obtained for the 5 somatic symptoms for CFS, the 8 other somatic symptoms, and all 13 symptoms. These scores were used as outcome measures and risk factors. As a way of describing patient status, we also reported the number of somatic symptoms that were scored from 4 to 6, i.e., they occurred a good bit of the time.

The depressive symptom scale was made up of 8 symptoms from the Zung Self-Rating Depression Scale³² (downhearted, blue, and sad; more irritable than usual; trouble sleeping; tired; finding it easy to do the things they used to; hopeful about the future; feeling useful and needed; and enjoying the things they used to) and 4 additional items from the Medical Outcomes Study Short-Form 36-item questionnaire (SF-36)³³ (so down in the dumps that nothing could cheer them up, nervous, feeling calm and peaceful, and happy). Instead of the wording from the Zung scale for "tired," we used the wording from the SF-36 (tired, worn out, used up, or exhausted). Another item on both the Zung and SF-36 scales was "downhearted, blue, and sad."

Subjects were asked to respond to questions on the depressive symptom scale using the 1 to 6 frequency scale described previously. For positive items (e.g., calm and peaceful), the scale was reversed so that a higher score signified that a positive state occurred less frequently. The depressive symptom score that was used as an outcome measure or risk factor was then calculated as the number sum of the responses to the 12 questions. Patients who answered that they felt depressed or had anhedonia most of the time or all of the time were considered to have possible depression.³⁴ For these patients, we reported the number of depressive symptoms that had a score of 5 or 6.

Statistical Methods

The primary outcome measure was the fatigue score at one time period subtracted from the fatigue score at the following time period; a negative change implies that fatigue had been reduced. To make the results more clinically relevant, we also examined the percentage of patients who had a substantial change in fatigue. We classified substantial improvement as a drop in fatigue score of 5 or more points (a mean improvement of at least 1 level for each of the 5 fatigue questions) and substantial worsening as an increase in fatigue score by 4 or more points. These cutoff points represent the 10th and 90th percentiles of the distribution of the change in fatigue score, i.e., by this definition about 10% of subjects showed a substantial improvement and 10% showed substantial worsening. Secondary outcome measures were the change in somatic symptom score and the change in depressive symptom score.

We did not have treatment information available at baseline. We examined the association of each treatment at 6 months with change in the outcome measure from baseline to 6 months and from 6 months to 2 years. We also examined the association of treatment at 2 years with changes in the outcome measure from 6 months to 2 years. Associations were tested with regression analysis. The dependent variable in the analysis was change in the outcome measure. The independent variables were (1) an indicator variable for the use of treatment at a given time, (2) the value of the outcome measure at the earlier time, and (3) the following variables found to be associated with prognosis in a previous study³⁵: unclear thinking, somatic symptoms not associated with CFS, frequent awakening, marital status, hours of sleep at night, and length of follow-up. Adjusting the change scores for the outcome measure at baseline is mathematically identical to comparing the outcome measures adjusted for the baseline measure, which some researchers have recommended.³⁶

The effect size was the regression coefficient of the indicator variable for a given therapy, which is equivalent to the difference between the improvement in fatigue scores for subjects on the therapy and subjects not on the therapy after adjusting for the prognostic factors. To examine whether a risk factor for prognosis may influence the association between an intervention and outcome, we added to the regression equation an interaction term for the intervention and the risk factor. Chi-square tests for differences between proportions were used to evaluate an association of treatment with the percentage of subjects who had substantial improvement.

Each of the 38 treatments evaluated in this study was tested independently. We did not adjust p values for mul-

Table 1. Demographic and Fatigue-Associated Characteristics at the 6-Month Assessment of Patients With Unexplained Chronic Fatigue

	All Patients
Characteristic	(N = 155)
Female, %	87
Minority race, %	7
Age group, y, %	
18–29	8
30–55	79
56–86	13
Income < \$20,000, %	28
Currently married, %	57
Education, %	
High school	13
Some college or vocational training	39
College graduate	48
Not employed, %	49
Severe fatigue, %	47
No. of somatic symptoms,	
median (10th, 90th percentiles)	
Chronic fatigue syndrome criteria (out of 5)	2.0 (0, 4.0)
Other somatic symptoms (out of 8)	3.0 (0, 5.0)
No. of depressive symptoms (out of 12),	
median (10th, 90th percentiles)	5.0 (3.0, 8.0)

tiple comparisons, because it is impossible to distinguish between statistically significant associations by chance and real association, and useful information may be lost from a study if critical p values are set very low to take multiple comparisons into account.³⁷ With or without correcting for multiple comparisons, all associations found to be significant in this study need to be confirmed in other observational studies and randomized controlled trials.

RESULTS

There were 330 people who expressed interest in participating in this study; 290 returned a baseline questionnaire. Of those 290 subjects, 56 were excluded due to having one of the medical conditions listed in the method, 30 were excluded because their fatigue score was below 17.5 at baseline, 26 did not complete a questionnaire after 6 months of follow-up, and 19 were excluded because their 6-month fatigue score was less than 17.5. Thus, there were 159 subjects eligible for this study. Four of the 159 subjects did not return a 2-year follow-up questionnaire. These 4 subjects had baseline fatigue scores of 23, 26, 26, and 29, which did not differentiate them from the other 155 subjects.

Study subjects had a median fatigue score of 24 with a range of 18 to 30. The mean change in fatigue score was -0.70 with a range from -13 to 10. The range in follow-up time after the 6-month assessment was from 1.3 to 2.5 years with a median follow-up of 1.5 years, 10th percentile of 1.4 years, and 90th percentile of 1.8 years.

The demographic characteristics of the subjects are shown in Table 1. The majority of subjects were female (87%) and white (93%) with a median duration of fatigue

Figure 1. Distribution of Fatigue Score Changes From 6 Months to 2 Years in Patients With Unexplained Chronic Fatigue $(N = 159)^a$



^aThe changes in fatigue score used to define the categories are as follows: "substantially worse" is an increase of 4 or more, "somewhat worse" is an increase of 3, "minimal change" is -2 to +2, "somewhat improved" is a decrease of 3 or 4, and "substantially improved" is a decrease of 5 or more.

of 6.7 years. Most subjects (79%) were between the ages of 30 and 55 years, and over half (57%) were married. In general, they were well educated with almost half of the subjects (48%) having a college degree. A high percentage (28%) had a family income less than \$20,000, and almost half (49%) were unemployed. Also shown in Table 1 is information about the severity of fatigue, somatic symptoms, and depression. Almost half of the patients had severe fatigue; 50% reported that most of the time they had 5 of 13 somatic symptoms, and 50% reported that most of the time they had 5 of 12 depressive symptoms.

The distribution of fatigue score changes is shown in Figure 1. The majority of the subjects (62%) showed minimal change in fatigue over the follow-up period, i.e., a change in either direction of 2 or fewer points in the fatigue score. A higher percentage of subjects showed improvement (24%) rather than worsening (14%) over time. This difference was statistically significant at p = .03.

Table 2 lists the treatments that were commonly used by the study subjects for treatment of fatigue. Rows are sorted by the most commonly used therapy within a category. Information in the columns is as follows: (1) the name of the therapy, (2) the percentage of patients who had the therapy and the total number asked, and (3) the number and percentage of patients who reported that they had previously benefited from the therapy. The most commonly tried prescription medicine was alprazolam, but only 13% of those who tried it found it helpful. The most commonly prescribed category of medications was antidepressants; 26 subjects (42% of those who tried them) found these medications were helpful. The percentage of users who found a treatment helpful was greatest for coenzyme Q10 (69% of 13 subjects), dehydroepi-

Table 2. Therapies Used at 6-Month Assessment for the Treatment of Unexplained Chronic Fatigue in 155 Patients				
Intervention	Asked, N ^a	Tried Therapy, %	Rated Helpful in the Past, N	Tried Therapy, %
Prescribed medicines				
Alprazolam	155	10	2	13
Amitriptyline	155	8	4	33
Fluoxetine	155	8	4	31
Clonazepam	155	6	5	50
Categories of medicines ^b				
Antidepressants	155	40	26	42
Pain medications	155	23	5	14
Hormones	155	20	12	39

Fluoxetine	155	8	4	31
Clonazepam	155	6	5	50
Categories of medicines ^b				
Antidepressants	155	40	26	42
Pain medications	155	23	5	14
Hormones	155	20	12	39
Antianxiety medications	155	15	3	13
Sleep medications	155	15	9	39
Thyroid medications	155	14	8	38
Immunoglobulin therapy	146	14	2	13
Antihistamines	155	11	5	29
Antihypertensives	155	8	2	15
Antiseizure medications	155	8	5	42
Muscle relaxants	155	8	4	33
Nonprescribed therapies				
Ginseng	155	12	10	56
DHEA	155	11	11	65
Magnesium	155	9	6	43
Coenzyme O10	155	8	9	69
Calcium	155	6	0	0
Melatonin	155	6	4	40
Nonprescribed categories				
Vitamins	155	48	21	28
Herbs	155	25	13	33
			Rated Verv	Tried
			Helpful in	Therapy.
Lifestyle changes			the Past, N	%
Sleep more	142	84	28	24
Light exercise	146	82	20	18
Increase recreational	140	74	10	0
activities	144	/4	10)
Decrease stress	145	70	35	34
Decrease work	145	63	28	31
Vigorous exercise	141	43	8	13
Dietary changes	146	38	10	18
Lose weight	141	36	5	10
Alternative therapy				
Herbal remedy	145	45	9	14
Homeopathy	146	25	8	22
Chiropracty	145	24	8	23
Yoga	146	18	6	22
Acupuncture	146	16	7	30
Counseling				
Support groups	144	37	10	19
Psychotherapy	144	34	8	16
35				

^aBecause questions were added about some therapies after the study began, the number of subjects asked whether they used a therapy varied.

^bEach of the categories of medicines includes the use of any medication of that type. For example, fluoxetine is included in the antidepressants category even though it is listed individually. Abbreviation: DHEA = dehydroepiandrosterone.

androsterone (DHEA) (65% of 17 subjects), and ginseng (56% of 18 subjects). Other medications and supplements were more often reported as helpful when they were tried, but the high success rates were based on small sample sizes. The lifestyle changes reported as being helpful for the most people were decreasing stress, decreasing work, and sleeping more. Several alternative therapies (acu-

Table 3. Statistically Significant Associations of Treatment
and Fatigue Change in 155 Patients With Unexplained
Chronic Fatigue ^a

	Treatment	Treatment at 2 Years	
	Fatigue Change 0 to 6 Months	Fatigue Change 6 to 24 Months	Fatigue Change 6 to 24 Months
Treatment	(N) ^b	(N) ^b	$(N)^{b}$
Prescribed medicine			
Amitriptyline			$-1.90(10)^{c}$
Categories of medicines			
Antianxiety medications	$-1.06(23)^{c}$		
Sleep medications	$1.00(23)^{c}$		
Immunoglobulin therapy	$-1.28(15)^{c}$		
Antihistamines	$-1.04(17)^{c}$		
Nonprescribed therapies			
Calcium			$-2.76(8)^{d}$
Magnesium	$-1.18(14)^{c}$	$2.80(14)^{d}$	
Coenzyme Q10			$1.71 (13)^{c}$
Nonprescribed categories			
Herbs			1.48 (32) ^d
Vitamins		$-0.90(75)^{c}$	
Lifestyle changes			
Vigorous exercise		$-0.92(60)^{c}$	-1.71 (71) ^d
Lose weight	-0.71 (51) ^c		
Alternative therapy			
Yoga		$-2.10(27)^{d}$	$-1.31(27)^{c}$
Counseling			
Support group		$1.09(53)^{c}$	

^aThe association is shown as effect size for treatment, i.e., the difference between the change in fatigue scores for subjects on the treatment and subjects not on the treatment after adjusting for the prognostic factors. A negative effect size means that treatment was associated with a decrease in fatigue.

^bN is the number of patients on treatment.

 ${}^{c}p < .10.$ ${}^{d}p < .05.$

Symbol: ... = no significant associations at that time period.

puncture, chiropractic care, yoga, and homeopathy) were reported as being effective by 20% to 30% of the subjects.

Some of the complementary and alternative therapies often were used together. We found that of subjects who had used yoga at the 6-month assessment, 52% also had used acupuncture (odds ratio [OR] = 7.0, p < .0001), 51% had used homeopathy (OR = 4.7, p = .0003), and 48% had used chiropracty (OR = 4.1, p = .001). Complementary and alternative medicines that were significantly more often used in combination with magnesium were calcium (OR = 15.1, p < .0001), chiropracty (OR = 6.2, p = .001), DHEA (OR = 6.0, p = .002), coenzyme Q10 (OR = 5.9, p = .004), homeopathy (OR = 3.6, p = .02), and acupuncture (OR = 3.5, p = .03). Therapies used with acupuncture were chiropracty (OR = 9.6, p < .0001), homeopathy (OR = 9.1, p < .0001), DHEA (OR = 7.3, p =.0002), ginseng (OR = 6.3, p = .0005), and coenzyme Q10 (OR = 4.0, p = .02). Homeopathy was also associated with the use of chiropracty (OR = 9.5, p < .0001) and DHEA (OR = 5.0, p = .003).

As described in the Method, treatments at 6 months were tested for an association with fatigue changes from baseline to 6 months and from 6 months to 2 years; treat-





ments at 2 years were tested for an association with fatigue changes from 6 months to 2 years. The statistically significant associations are shown in Table 3. The table shows that losing weight, antianxiety medications, immunoglobulin therapy, antihistamines, and magnesium at 6 months were associated with fatigue improvement from baseline to 6 months. None of these treatments were associated with fatigue improvement at subsequent time periods, and magnesium and support groups were strongly associated with fatigue worsening from 6 months to 2 years (p = .002 and p = .06, respectively). The association of efforts to lose weight at 6 months with previous improvement of fatigue was consistent with fatigue improvement causing patients to make an effort to lose weight.

Treatments at 6 months that predicted subsequent fatigue improvement were vitamins (p = .08), vigorous exercise (p = .09), and yoga (p = .002). Treatments at 2 years that were associated with improvement in the previous 18 months were amitriptyline (p = .06), calcium (p = .06) .01), vigorous exercise (p = .001), and yoga (p = .06). Of course, vigorous exercise at 2 years could easily be a response to previous fatigue improvement.

We also examined whether treatments used at 2 years but not 6 months were associated with improvements from 6 months to 2 years. Subjects who began taking calcium and hormone therapy after 6 months had greater fatigue improvements than other subjects at the p < .05 level. However, the comparison was based on few subjects (only 5 in each case) who had used these therapies at 2 years but not at 6 months.

More information about the distribution of fatigue changes for those who tried yoga is described in Figure 2. Twenty-five percent of subjects who practiced yoga at both baseline and follow-up experienced substantial improvement in their fatigue, while only 9% of those who were taking yoga at only 1 time period and 8% who never tried yoga experienced substantial improvement. The p value for this association was .07. The mean change

in fatigue for those who consistently used yoga in both time periods was an improvement of 2 points on the fatigue scale compared with .42 for other patients (p = .07).

To find clues to the factors underlying the association of yoga and changes in fatigue, we used univariate t tests and χ^2 tests to examine how patients who practiced yoga differed from other patients. We found 2 differences that were statistically significant at the p \leq .05 level: patients who practiced yoga had more somatic symptoms not used to define CFS (p = .03) and greater baseline fatigue (p = .05) than patients who did not.

We also examined whether yoga might be associated with a greater benefit for some subjects than for others by testing the interaction of yoga with patient characteristics associated with prognosis. After adjusting for other baseline factors, the interaction was statistically significant between yoga and unclear thinking at baseline (p = .03). For the 53 subjects with no unclear thinking at baseline, the adjusted change in fatigue score was -4.8 (N = 9) if they had tried yoga and -0.7 (N = 44) if they had not, i.e., the effect size was -4.1 (p = .006) compared with an effect size for yoga of only -1.2 (p > .10) for subjects with unclear thinking at baseline.

In addition to fatigue, we also considered change in depressive symptoms and change in somatic symptoms as outcomes. The only treatment at 6 months that predicted change in depressive symptoms from 6 months to 24 months of follow-up was yoga, p = .02. No treatments at 6 months predicted an improvement in somatic symptoms at 2 years.

DISCUSSION

This was an exploratory questionnaire study in which the results are based on few subjects. The 155 subjects in this study had moderate to severe fatigue with a median duration of more than 6 years. Subjects had tried a variety of interventions to increase their energy. The therapies most often reported as helpful prior to baseline were less stress (N = 35), less work (N = 28), more sleep (N = 28), and antidepressants (N = 26). The therapies most likely to be reported as effective by those who tried them were coenzyme Q10 (69% of 13 subjects), DHEA (65% of 17 subjects), and ginseng (56% of 18 subjects). The only therapies associated with subsequent improvement in fatigue after a median follow-up of 1.5 years were vitamins (p = .08), vigorous exercise (p = .09), and yoga (p = .09).002). Yoga was associated with the greatest improvement (mean improvement in fatigue score of 2 points compared with .42 for the other subjects). Twenty-five percent of subjects who practiced yoga at 6 months and 2 years had substantial improvements in fatigue compared with only 8% of the 103 subjects who did not practice yoga at any time. It appeared that yoga had a greater effect on subjects who had clear thinking at 6 months than on subjects who

did not have clear thinking; p < .05 for the interaction. The fatigue score for the 9 subjects who had clear thinking at baseline and practiced yoga improved 4.1 points more than the fatigue score of the other 44 subjects who had clear thinking at baseline.

The therapies most often reported to be effective by the subjects were not associated with measured change of fatigue during any time period. However, because our information on fatigue changes did not correspond to the time of therapy, the effectiveness of some therapies may not be apparent in this study.

There are several possible explanations for the 3 therapies found to be significantly associated with prognosis. One is that many treatments were studied and some ineffective treatments may be significant by chance alone. Support for this possibility is that magnesium use was as strongly associated with increased fatigue as yoga was with less fatigue. Because any findings from this study need to be validated by other studies, however, we decided not to adjust for multiple comparisons. This adjustment would have increased the likelihood that potentially effective interventions would be ignored.

A second possible explanation is that persons who choose certain therapies have a different prognosis than others. Although outcomes were adjusted for known prognostic factors, certain therapies may be a marker for unknown prognostic factors. For example, subjects who are sometimes able to exercise vigorously or practice yoga may have a different type of fatigue than subjects who do not have these abilities. Also, subjects who take vitamins or practice yoga may have certain attitudes or self-care behaviors that influence the progression of fatigue. However, the factors that we found to be associated with the use of yoga (more somatic symptoms and greater baseline fatigue) should have been associated with worse prognosis rather than better prognosis. Additional information about the types of people who practice yoga may suggest important risk factors that can help with the understanding of factors associated with the perpetuation of chronic fatigue.

A third limitation of the study was that the fatigue and depression scales were abbreviated forms of validated scales. Use of the full scales may have changed the results or made the results easier to understand.

A fourth possibility, of course, is that some therapies are effective. Yoga had an association with improvement in fatigue of p = .002. Although we did not find previous studies that tested yoga for subjects with unexplained chronic fatigue, a nonrandomized crossover trial³⁸ showed that pranayama (a form of yoga that involves breathing techniques and stretching) produced a significantly greater increase in self-reported mental and physical energy than relaxation or visualization. Yoga has also been shown in randomized controlled trials to have a positive effect either alone or in combination with traditional therapy for a variety of physical conditions including asthma,^{39,40} chronic bronchitis,⁴¹ lipid status of those with coronary risk,⁴² hypertension,⁴³ coronary atherosclerosis,⁴⁴ epilepsy,⁴⁵ and carpal tunnel syndrome.⁴⁶ Mental conditions benefited by voga in randomized controlled trials include anxiety and depression,47 obsessive-compulsive disorders,⁴⁸ and well-being and improved quality of life.⁴⁹ An effect of yoga on depression and anxiety may explain its effect on subjects with unexplained chronic fatigue who do not have cognitive disabilities. A previous study found that these CFS subjects were more likely to have had a psychological disorder.⁵⁰ Unfortunately, we did not collect information about the type of yoga or frequency of use. Without this information, we were not able to identify those forms of yoga that may be most effective or the reasons they may be effective.

In conclusion, the practice of yoga was associated with substantial improvement in persons who had previously suffered from fatigue for an extended period of time. It may be most effective for those who do not have problems with unclear thinking and those who practice for many months. Although the results from this study are not definitive, they suggest that further study of yoga as a therapy for unexplained chronic fatigue may be worthwhile.

Drug names: alprazolam (Xanax and others), fluoxetine (Prozac and others), clonazepam (Klonopin and others).

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