The Effectiveness of Citalopram for Idiopathic Chronic Fatigue

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Background: Chronic fatigue greatly affects quality of life and is a common reason for physician visits. Patients with chronic fatigue are often treated with antidepressants.

Method: Prior to enrollment, all subjects had substantial fatigue for 6 months or more that was not explained by depression, organic illness, or lifestyle behaviors. Patients already taking an antidepressant were excluded from the study. Two designs were used. (1) Thirty-one subjects were given placebo for 1 week and then citalopram, 20 to 40 mg/day, for 2 months. Statistical testing evaluated whether fatigue (measured with the Rand Vitality Index) was reduced after citalopram was started. (2) Fatigue changes for subjects taking citalopram were compared with fatigue changes after 1 month and 2 months for 76 similar subjects taking an ineffective treatment.

Results: In design 1, fatigue for subjects taking citalopram was significantly and substantially reduced when subjects were switched from placebo to citalopram, $p < .05$. Benefits at 2 months were greatest for subjects who had fatigue less than 5 years, $p < .01$, and women, $p < .01$. In design 2, fatigue scores for subjects taking citalopram were not significantly better than the comparison group for all subjects but were significantly better at 2 months for subjects with less severe fatigue at baseline, $p = .005$, and for women, $p = .08$. Depression scores were not significantly better for citalopram subjects overall ($p > .10$) but were for certain subgroups. For all subjects, citalopram was associated with greater decrease in headaches and muscle aches at 1 month, $p < .01$.

Conclusion: Citalopram may improve fatigue and symptoms associated with fatigue for some patients.

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Fatigue is common[1] and has a powerful adverse effect on quality of life.[2] According to a National Ambulatory Medical Care Survey, it is the seventh most frequent chief complaint in primary care.[3] Estimates of the percentage of primary care patients who have had fatigue for at least 1 month range from 5% to 47% depending on the definition of fatigue and the source of patients.[1,4,5] Commonly, it is found that about a quarter of patients in primary care clinics have chronic fatigue, i.e., fatigue for at least 6 months.[6] Rarely is such fatigue caused by a medical illness that is not evident on initial examination.[7–9] Yet fatigue tends to persist. Of patients treated for fatigue at a primary care clinic, 50% to 75% still have fatigue at 1 year,[7,10] and in one study, 59% of 78 patients who reported fatigue for at least 6 months still had fatigue after $2^1/_2$ years.[11]

The most often investigated subtype of idiopathic chronic fatigue is chronic fatigue syndrome (CFS). CFS is characterized by several other somatic symptoms such as impaired concentration, sore throat, tender lymph nodes, muscle aches, joint pain, and headaches.[12] CFS is much less common than other forms of idiopathic chronic fatigue. Estimates of CFS frequency in population-based studies range from 0.037%[13] to 2.6%.[1] Although the distinction between CFS and other forms of idiopathic chronic fatigue is important to patients, little is understood about the etiology of CFS. Many investigators have suggested that CFS is a heterogeneous condition,[14–16] and subjects may differ with respect to etiology, course, and response to treatment. A review of treatments for CFS concluded that cognitive-behavioral therapy and graded exercise therapy proved somewhat beneficial.[17] Because these therapies are difficult to implement and improvement is limited for many patients, an effective pharmacologic therapy would be an attractive alternative.

Antidepressants are a logical choice for pharmacologic therapy because depression causes fatigue and may be unapparent or atypical. In addition, neurochemical mechanisms responsible for depression may also cause chronic fatigue.[18] Support for the association between depression and fatigue comes from the high correlations between changes in depression scores and changes in fatigue ($r = 0.38$, $p < .0001$), even in subjects who do not meet criteria for clinical depression.[15]

The studies of antidepressants for the treatment of CFS give mixed results. Although open-label trials found doxepin effective in 70% of patients with CFS,[19] fluoxetine in almost all subjects,[20] and sertraline in 65% of patients,[21] 2 randomized controlled trials (RCTs) of fluoxetine did not demonstrate effectiveness.[22,23] One of these studies did not even find that fluoxetine reduced depressive symptoms in CFS subjects.[22] Results may differ among studies because of the inadequacy of the open-label design. It is also possible, however, that treatment effectiveness varies with different subjects and that subjects in different settings or recruited with different strategies may give different results. In the present study, we evaluated whether the selective serotonin reuptake inhibitor (SSRI) citalopram is more effective than placebo in the treatment of chronic fatigue and whether effectiveness varies among selected subgroups. Citalopram was selected because it has a relatively benign side effect profile and quick action (1–4 weeks). In contrast to the previous European studies, the present study was conducted in the midwestern United States and included subjects with idiopathic chronic fatigue who did not meet criteria for CFS. Our study used an observational design that has many of the advantages of an RCT.

METHOD

Forest Laboratories (New York, N.Y.) provided sufficient funding to study the effectiveness of citalopram for the treatment of idiopathic chronic fatigue in 31 patients. Because 31 subjects were inadequate to perform an RCT, we utilized data from a concurrent RCT of Siberian ginseng for the treatment of idiopathic chronic fatigue to compare subjects taking citalopram to other subjects. The reluctance of some subjects to take an antidepressant prevented a 3-arm trial of citalopram, Siberian ginseng, and placebo. The Institutional Review Board of the University of Iowa, College of Medicine, approved all data collection.

Subject Recruitment and Data Collection

Subjects with chronic (longer than 6 months) unexplained fatigue were recruited from newspaper advertisements in Iowa City and Davenport, Iowa, and by a medical record search for idiopathic chronic fatigue patients at Marshfield Clinic in Marshfield, Wis. Subjects without contraindications were offered a choice to participate in an open-label study of citalopram or an RCT of an herbal treatment, Siberian ginseng. Contraindications for the citalopram study were current use of an antidepressant, and contraindications for the Siberian ginseng study were uncontrolled hypertension or use of digitalis or warfarin.[24,25] Subjects for the Siberian ginseng study were also recruited from other sources including family medicine residency programs in Iowa, CFS support groups, and a Web site.

Volunteers were screened for eligibility first by telephone, then with a written questionnaire, and finally with review of laboratory test results and a form completed by the subject's personal physician. During the telephone screen, subjects were given the 4-question Rand Vitality Index,[26] which rates fatigue and energy levels. It has been well validated and has been used in previous studies of chronic fatigue.[2,27] The index ranges from 4, which indicates extremely low vitality or high fatigue, to 24, which indicates high vitality. Subjects were also asked about chronic diseases, medications, and other possible causes of fatigue. Subjects who had unexplained fatigue for 6 months or more and scored 12 or less on the Rand Vitality Index were mailed a consent form and baseline questionnaire. Our criteria selected subjects that were more fatigued than previous studies that used criteria of 14 or less on the Rand Vitality Index.[2,27]

In addition to the Rand Vitality Index, the baseline questionnaire included 5 other instruments: (1) 14 questions from the Mini-International Neuropsychiatric Interview (MINI),[28] which were modified to be a self-administered screen for depression; (2) 12 questions from the Mood and Anxiety Symptom Questionnaire (MASQ) to measure degree of anhedonic depressive symptoms[29]; (3) 10 MASQ questions to measure degree of anxiety[29]; (4) the mental fatigue component of a fatigue instrument[30]; and (5) the 25-question Somatic Symptom Inventory[31] supplemented by 5 additional questions specific for CFS. In addition, the questionnaire asked for information about demographics, fatigue onset, sleep, lifestyle or environmental factors that may have contributed to fatigue, and medical history.

Each subject's personal physician listed the subject's chronic diseases and provided results for any of the following laboratory tests performed within 3 years of enrollment in the study: liver panel, thyroid-stimulating hormone, electrolyte panel, complete blood count, creatinine, erythrocyte sedimentation rate, calcium level, and urinalysis. Laboratory tests were performed if recent results were not available from the physician.

Inclusion/Exclusion Criteria

In contrast to most research on idiopathic chronic fatigue, we did not use CFS as an inclusion criterion for 3 reasons: (1) physicians want to know the effectiveness of treatments for chronically fatigued persons without CFS; (2) a mixture of subjects with and without CFS makes it possible to evaluate whether CFS subjects respond to citalopram differently than other subjects with idiopathic chronic fatigue; and (3) CFS is an uncommon form of idiopathic chronic fatigue, and recruiting large numbers of CFS subjects would have been more difficult.

We excluded subjects who were pregnant or breast-feeding to prevent possible adverse effects to infants. Subjects were excluded if younger than 21 years of age, because many persons in this age group have lifestyle reasons for fatigue. Subjects were also excluded if they were

older than 65 years, when medical illness becomes increasingly common. Other exclusion criteria consisted of all medical, psychological, or lifestyle factors that could explain fatigue such as chronic diseases (e.g., anemia, untreated abnormalities in thyroid hormone, cancer, heart disease, liver disease, or connective tissue disorders), evidence of chronic illness from laboratory tests, or the use of medications likely to cause fatigue. Subjects were excluded if they believed their fatigue was primarily caused by any of the following lifestyle factors: poor sleep hygiene, young children, long working hours, or night/swing-shift work. Exclusion criteria after the study began were changes in psychoactive medications or other medication (e.g., thyroid) that could affect energy.

Because it is well known that antidepressants reduce fatigue in patients with major depression,[32] we excluded those patients. Evidence of major depression was obtained from the MINI or physician report of major depression. Subjects with depressive symptoms who did not meet criteria for major depression were not excluded unless the depressive symptoms were of greater concern to the subject than the fatigue.

Treatment and Follow-Up

Subjects who qualified for the citalopram study were followed at 1 of 3 clinical sites: the Preventive Intervention Center in Davenport, Iowa; the Department of Family Medicine at the University of Iowa, College of Medicine Iowa City; or Marshfield Clinic in Marshfield, Wis. Subjects returned to the clinic for follow-up at 1 week, 5 weeks, and 9 weeks after the initial visit. They were followed by telephone at 2 and 3 weeks after the initial visit. At the initial visit, subjects were given 10 placebo tablets that were prepared by Forest Laboratories and appeared identical to citalopram. At the 1-week follow-up visit, subjects were given 35 tablets of citalopram, 20 mg. The 3-week phone call assessed whether the citalopram dose should be increased to 40 mg/day. Doses were increased when side effects were not significant and the Rand Vitality Index was 12 or lower. At the 5-week visit, subjects were given enough citalopram to last 35 more days.

Each clinic follow-up visit was used to assess the following: (1) Rand Vitality Index, (2) a 7-point global improvement scale[33] that ranged from "very much worse" to "very much improved," (3) 12 MASQ questions for anhedonic depression, and (4) 3 somatic symptoms (headache, muscle aches, and faintness/dizziness), which are highly correlated with changes in fatigue over a 2-year period.[15] As a measure of compliance, the clinic nurse or pharmacist recorded the number of capsules that remained in the subjects' medication bottles. Subjects were considered compliant at a visit if they had not missed more than 2 doses since the previous visit.

Subjects whose Rand Vitality Index assessed with a telephone interview remained at 12 or lower after taking citalopram for 2 to 3 weeks and who did not have significant side effects had a citalopram dose increase to 40 mg. If this dose caused increased side effects, the citalopram dose was again reduced to 20 mg.

Analysis

The primary outcome measure was the Rand Vitality Index after 1 month and 2 months of taking citalopram (i.e., 5 weeks and 9 weeks into the study). Secondary outcome measures included the following.

Responses to the global improvement scale. Subjects who answered much improved or very much improved on the scale were considered to be substantially improved. The few subjects missing the global improvement score were also considered substantially improved if their Rand Vitality Index increased by 7 (the median change for subjects indicating much improved on the global improvement scale).

Improvement on the MASQ scale for anhedonic depression. Each of the 12 MASQ symptoms was scored from 1 (not at all) to 6 (extremely) on the basis of severity.

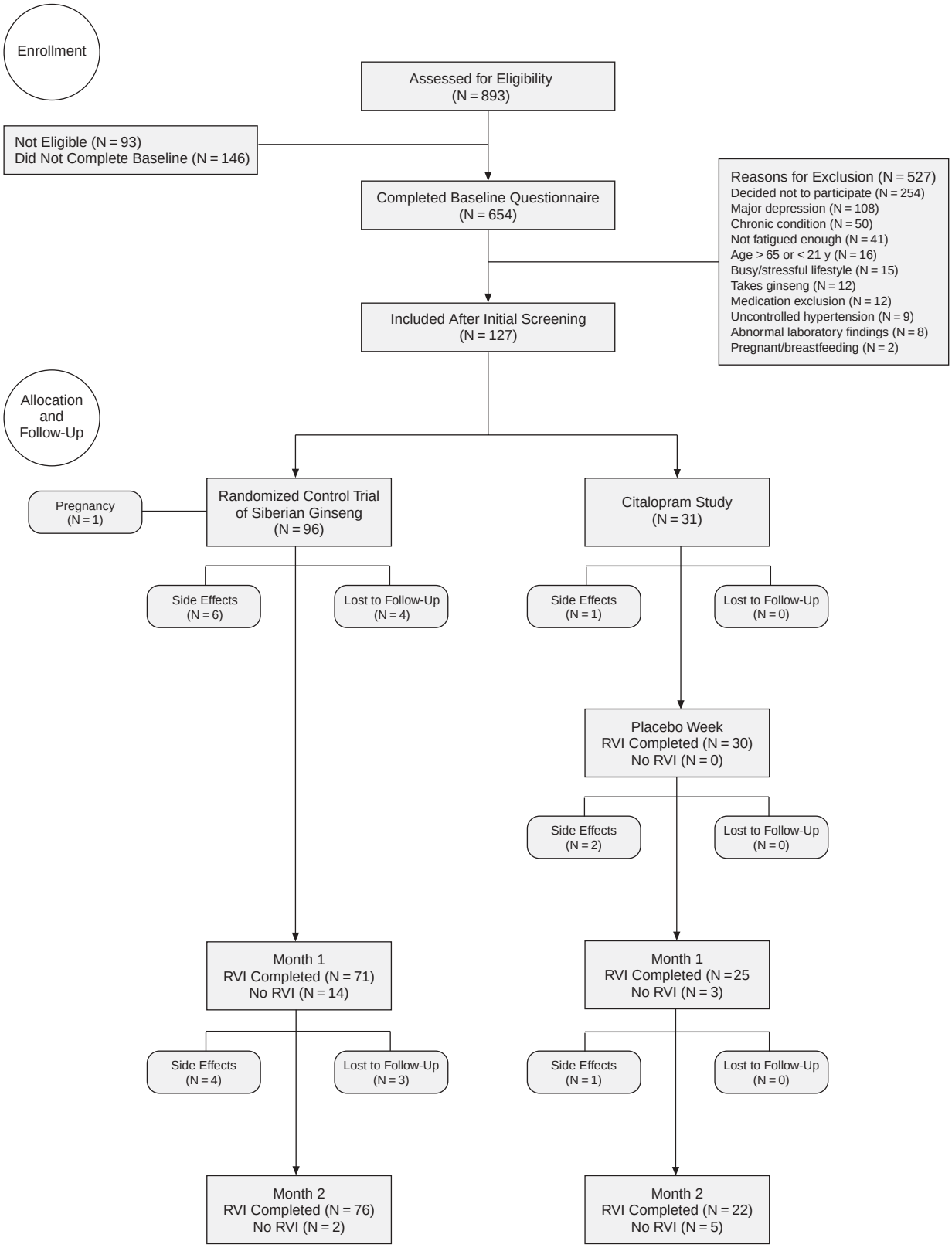
The somatic symptom score for 3 somatic symptoms previously found to covary with fatigue. Each symptom was scored from 1 (not at all) to 6 (extremely) on the basis of how much the symptom bothered the subject. The scores were added together to form the total score.

Outcomes for subjects taking citalopram were compared with 3 control groups: (1) the outcome for the same subjects after treatment for 1 week with placebo, (2) the 1-month outcome for subjects in the Siberian ginseng study who were treated with Siberian ginseng or placebo, and (3) the 2-month outcome for subjects in the Siberian ginseng study treated with placebo only. Subjects treated with Siberian ginseng were included in the comparison group at 1 month, when Siberian ginseng was clearly not effective, but not at 2 months, when it may have been effective for some subjects.

The paired t test was used to assess changes in the same group of subjects from 1 time period to another. The analysis of covariance was used to compare citalopram and control subjects after adjusting for baseline level of the outcome variable and number of days on treatment. Adjusted means for the outcome measures were obtained from SAS analysis of covariance.[34]

Statistical tests were performed for all subjects and subgroups defined by each of the following subject characteristics: compliance, gender, fatigue severity, CFS-like status, type of onset, MASQ depressive symptom score, and duration of fatigue. Subjects were classified as CFS-like if they were bothered at least moderately by 4 or more of the following symptoms: sore throat, painful lymph nodes, muscle aches in many places throughout the body, joint pain, headaches, inability to concentrate, unrefreshing sleep, and post-exertional fatigue lasting more than 24 hours.[12] Onset was considered acute if subjects gave a date

Figure 1. Number of Study Subjects at Each Stage



Abbreviation: RVI = Rand Vitality Index.

Table 1. Comparison of Chronic Fatigue Patient Characteristics Across Treatment Groups[a]

Characteristic	Citalopram (N = 27)[b]	Placebo/ Siberian Ginseng (N = 85)[b]	Placebo Only (N = 40)[b]
Baseline Rand Vitality Index, mean	8.3	8.1	8.3
Age, N (%)			
21–34 y	2 (7.4)	2 (2.4)	1 (2.5)
35–49 y	12 (44.4)	47 (55.3)	21 (52.5)
50–65 y	13 (48.2)	36 (42.4)	18 (45.0)
Women, N (%)	20 (74.1)	69 (81.2)	34 (85.0)
White, N (%)	26 (96.3)	81 (97.6)	40 (100)
Married, N (%)	19 (70.4)	59 (70.2)	25 (62.5)
Duration of fatigue, N (%)			
0.50–0.99 y	1 (3.7)	5 (5.9)	3 (7.5)
1.00–4.99 y	11 (40.7)	33 (38.8)	16 (40.0)
5.00–9.99 y	9 (33.3)	19 (22.4)	9 (22.5)
10.00 y or more	6 (22.2)	28 (32.9)	12 (30.0)
CFS-like, N (%)[c]	16 (59.3)	60 (70.6)	23 (57.5)
Depressive symptom score, mean	48.1	47.1	47.8
Number of somatic symptoms, N (%)[d]			
5 or fewer	5 (18.5)	7 (8.2)	4 (10.0)
6–10	5 (18.5)	23 (27.1)	14 (35.0)
11–29	17 (63.0)	55 (64.7)	22 (55.0)
Source of subjects, N (%)			
Marshfield Clinic	6 (22.2)	0	0
Davenport	15 (55.6)	19 (22.4)	9 (22.5)
Iowa City	6 (22.2)	40 (47.1)	18 (45.0)
Other[e]	0	26 (30.6)	13 (32.5)

[a]Subjects taking citalopram did not differ significantly from subjects in the comparison group for any characteristics except for source, $p < .001$.
[b]The sample size reported for each group was the total of the following: the number of subjects responding in both month 1 and month 2 (N = 20 for citalopram), the number responding in month 1 only (N = 5 for citalopram), and the number responding in month 2 only (N = 2 for citalopram).
[c]CFS-like subjects have at least 4 of the symptoms in the Fukuda et al.[12] definition of CFS.
[d]A symptom was considered present if it bothered the subject at least a moderate amount.
[e]Includes residency programs in Waterloo, Des Moines, and Cedar Rapids, Ia., and recruitment from the Web site, CFS support groups, or the Wisconsin Chronic Fatigue Association.
Abbreviation: CFS = chronic fatigue syndrome.

for the onset and the onset followed a well-defined disease, psychological stress, accident, or surgery. Subjects were divided on the basis of MASQ depressive symptom score and duration of fatigue into 2 subgroups that each included approximately 50% of the subjects.

Compliant subjects were a subgroup of interest, because if citalopram is effective, it should be most effective among these subjects. The other subgroups were chosen because they may represent subjects with different fatigue etiologies who respond differently to citalopram. Subgroups defined by depressive status, level of fatigue, and duration of fatigue were suggested for subgrouping CFS subjects.[12] To reduce the size of the tables, we report only results in the subgroup showing the largest effect size. To determine whether any factors used to define subgroups significantly influenced the effect size of citalopram, we tested for interaction in the analysis of covariance.

At baseline and at each follow-up visit, subjects were asked specifically about the following side effects that have been reported for patients taking citalopram: nausea/vomiting, sleepiness, dry mouth, dizziness, insomnia, diarrhea, and sexual dysfunction. They were asked to rate the severity of each of these symptoms on a 4-point scale from none to severe. At follow-up visits, subjects were also asked whether the symptoms had worsened since baseline. A symptom was considered a significant side effect if it was rated as moderate or severe, the severity was rated greater than at baseline, and the subject considered that the symptom had worsened. The subject was also asked at every follow-up visit about new symptoms that could possibly be side effects of treatment. These symptoms were considered clinically significant side effects if they were rated as moderate or severe.

RESULTS

Recruitment and follow-up of subjects are summarized in Figure 1. Of 893 subjects assessed, 127 were enrolled and 112 completed the Rand Vitality Index after 1 or 2 months of therapy. No citalopram subjects were lost to follow-up, but 1 subject who returned to the clinic for follow-up visits did not complete the Rand Vitality Index within the allowed time intervals for either the 1- or 2-month follow-up period.

Characteristics of the subjects in the 3 treatment groups are shown in Table 1. The mean baseline value of the Rand Vitality Index is 8.2, which is much closer to the extreme fatigue end of this scale (Rand Vitality Index = 4) than to the extreme vitality end (Rand Vitality Index = 24). The high percentage of female subjects shown in the table occurs in most studies of chronic fatigue. A low percentage of subjects had few somatic symptoms, and a high percentage met our criteria for CFS-like. Except for place of recruitment, characteristics for subjects in the citalopram and comparison groups did not differ significantly. In particular, there was no difference in depression scores for the 3 groups, indicating that subjects with more depressive symptoms were no more likely to choose the citalopram arm of the study.

At 1 month, 15 subjects in the citalopram treatment group were taking 20 mg/day of citalopram and the other 10 were taking 40 mg/day. At 2 months, 12 of 22 patients were taking the 20-mg/day citalopram dose. Five of the subjects who had been taking 40 mg/day of citalopram had a dosage reduction by 2 months due to side effects.

Table 2 shows changes in the Rand Vitality Index for subjects taking citalopram. Analyses were performed on all subjects and on subjects in preselected subgroups as described in the Method. Changes from the end of the 1-week placebo period to later time periods were statistically significant ($p < .05$) for all subjects combined and

Table 2. Changes in the Rand Vitality Index (RVI) for Subjects With Chronic Fatigue Taking Citalopram

Group[a]	Baseline Mean (N)	Placebo Mean (N)	Placebo to Month 1 Mean Change (N)	Placebo to Month 2 Mean Change (N)
All subjects	8.3 (27)	10.6 (27)	1.8* (25)	2.0* (22)
Compliers	8.1 (20)	10.2 (20)	1.9 (18)	2.3* (15)
Women	8.7 (20)	10.8 (20)	3.0** (19)	2.9** (18)
Baseline RVI 8–12	9.9 (17)	12.4 (17)	1.8 (15)	2.6* (14)
Fatigue for ≤ 5 years	8.2 (15)	10.6 (15)	2.5* (15)	3.3** (12)
CFS-like[b]	8.0 (16)	10.1 (16)	1.5 (16)	1.5 (12)
Lower half of MASQ depression score	9.5 (12)	11.3 (12)	2.9* (11)	2.3 (10)
Fatigue following specific problem	7.8 (15)	9.9 (15)	2.2 (15)	1.7 (11)

[a]The sample size reported for each group was the total of the following: the number of subjects responding in both month 1 and month 2 (N = 20 for citalopram), the number responding in month 1 only (N = 5 for citalopram), and the number responding in month 2 only (N = 2 for citalopram).
[b]CFS-like subjects have at least 4 of the symptoms in the Fukuda et al.[12] definition of CFS.
*p < .05 using a paired t test for difference between placebo week and month 1 or 2.
**p < .01 using a paired t test for difference between placebo week and month 1 or 2.
Abbreviations: CFS = chronic fatigue syndrome, MASQ = Mood and Anxiety Symptom Questionnaire.

Table 3. Mean Adjusted Rand Vitality Index (RVI)[a]

	Month 1			Month 2		
Group	Citalopram Mean (N)	Placebo/ Siberian Ginseng Mean (N)	Adjusted Means Difference	Citalopram Mean (N)	Placebo Mean (N)	Adjusted Means Difference
All subjects	12.3 (25)	11.7 (71)	0.6	12.3 (22)	11.1 (36)	1.2
Compliers	11.9 (18)	11.9 (39)	0.0	13.4 (15)	11.7 (22)	1.7
Women	13.3 (19)	11.7 (58)	1.5	13.5 (18)	11.4 (30)	2.1*
Baseline RVI 8–12	14.0 (15)	13.0 (41)	1.0	14.7 (14)	10.8 (24)	3.9**
Fatigue for ≤ 5 years	13.1 (15)	12.7 (37)	0.4	13.6 (12)	11.5 (20)	2.0
CFS-like[b]	11.3 (16)	11.0 (48)	0.3	11.3 (12)	10.3 (20)	1.0
Lower half of MASQ depression score	13.6 (11)	12.4 (34)	1.2	13.8 (10)	11.5 (15)	2.4
Fatigue following specific problem[c]	11.9 (15)	10.8 (37)	1.2	11.8 (11)	10.3 (16)	1.5

[a]Means are adjusted by the baseline RVI.
[b]CFS-like subjects have at least 4 of the symptoms in the Fukuda et al.[12] definition of CFS.
[c]E.g., cold or flu, other well-defined diseases, psychological stress, accident, or surgery.
*p = .08.
**p = .005.
Abbreviations: CFS = chronic fatigue syndrome, MASQ = Mood and Anxiety Symptom Questionnaire.

for subjects in certain subgroups. The changes were relatively large for women and for subjects with shorter duration of fatigue. Improvement for women was significantly greater than improvement for men at both month 1 and month 2, p < .01. Change in the Rand Vitality Index score from month 1 to month 2 for the 11 subjects taking 20 mg of citalopram was 0.09, and change in the Rand Vitality Index for 9 subjects whose dose increased to 40 mg was –1.44, a decrease in vitality or increase in fatigue. Neither change was statistically significant at the p < .10 level with a paired t test.

As shown in Table 2, the mean improvement from baseline to placebo was 2.3 on the Rand Vitality Index, p < .0001, by the paired t test. Subjects' improvement was 1.8 from the end of the placebo to the end of 1 month of citalopram treatment, p = .04. The subgroup with the largest improvement after starting citalopram was women, whose Rand Vitality Index improved by 3.0, p = .003. We performed a correlation to evaluate whether response to placebo was associated with response to citalopram. The correlation between improvement on placebo and additional improvement after beginning citalopram was –0.49, p = .01, i.e., subjects who improved more on placebo tended to improve less on citalopram.

Table 3 compares citalopram and control groups for adjusted means of the Rand Vitality Index at 1 month and 2 months of treatment. Because the covariable for days on treatment was not statistically significant, it was not included in the analysis of covariance. At 1 month, differences between treatment groups were small and not statistically significant. At 2 months, the difference between treatment groups was not significant for all subjects but was large and statistically significant for the less severely fatigued subjects, p = .005, and of statistical significance for women, p = .08 (cutoff = p < .10).

We tested whether subject characteristics used to define subgroups significantly modified the response to citalopram, i.e., we tested for an interaction between treatment and characteristics of the subjects. We found that treatment effectiveness at month 2 was significantly modified by level of baseline fatigue, i.e., citalopram was more effective with higher baseline levels of the Rand Vitality Index, p = .001. Citalopram was also more effective for women than for men at month 1, p = .08. Other

Table 4. Mean Adjusted Anhedonic Depression Score[a]

	Month 1			Month 2		
Group	Citalopram Mean (N)	Placebo/ Siberian Ginseng Mean (N)	Adjusted Means Difference	Citalopram Mean (N)	Placebo Mean (N)	Adjusted Means Difference
All subjects	31.2 (23)	33.6 (67)	–2.4	31.9 (22)	33.8 (28)	–1.9
Compliers	30.7 (16)	32.5 (37)	–1.8	30.4 (15)	32.2 (19)	–1.8
Women	29.2 (17)	33.7 (54)	–4.5*	30.4 (18)	34.0 (24)	–3.6
Baseline RVI 8–12	29.3 (14)	33.0 (38)	–3.7***	30.0 (14)	35.3 (20)	–5.3**
Fatigue for > 5 years	32.9 (9)	35.0 (33)	–2.1	32.5 (10)	35.8 (15)	–3.3***
CFS-like[b]	31.9 (15)	34.6 (47)	–2.7	31.7 (12)	36.6 (14)	–4.9***
Upper half of MASQ depression score	35.4 (13)	37.5 (33)	–2.1	33.9 (12)	38.7 (16)	–4.8
Fatigue following specific problem[c]	31.7 (14)	34.7 (36)	–3.0	31.0 (11)	33.9 (13)	–2.9

[a]Means are adjusted for the baseline anhedonic depression score.
[b]CFS-like subjects have at least 4 of the symptoms in the Fukuda et al.[12] definition of CFS.
[c]E.g., cold or flu, other well-defined diseases, psychological stress, accident, or surgery.
*p = .01.
**p = .05.
***p < .10.
Abbreviations: CFS = chronic fatigue syndrome, MASQ = Mood and Anxiety Symptom Questionnaire, RVI = Rand Vitality Index.

Table 5. Adjusted Means for Key Somatic Symptoms[a]

	Month 1			Month 2		
Group	Citalopram Mean (N)	Placebo/ Siberian Ginseng Mean (N)	Adjusted Means Difference[b]	Citalopram Mean (N)	Placebo Mean (N)	Adjusted Means Difference[b]
All subjects	7.1 (25)	9.4 (70)	–2.3*	7.5 (22)	8.3 (31)	–0.8
Compliers	7.2 (18)	9.3 (39)	–2.1*	7.2 (15)	8.0 (22)	–0.8
Women	7.2 (19)	9.8 (57)	–2.6*	7.7 (18)	8.6 (26)	–0.9
Baseline RVI 8–12	6.9 (15)	8.6 (40)	–1.7***	6.1 (14)	8.5 (21)	–2.4**
Fatigue for ≤ 5 years	6.3 (15)	9.1 (36)	–2.7*	7.0 (12)	8.0 (15)	–1.0
CFS-like[c]	7.9 (16)	10.5 (48)	–2.7*	8.6 (12)	10.4 (17)	–1.8
Upper half of MASQ depression score	7.2 (14)	10.4 (34)	–3.2*	8.5 (12)	8.1 (17)	0.4
Fatigue following specific problem[d]	7.2 (15)	9.7 (37)	–2.5*	8.2 (11)	9.0 (14)	–0.8

[a]Key somatic symptoms found previously to be associated with change in fatigue were headache, muscle aches, and dizziness. Means are adjusted for baseline score.
[b]The difference between means for the given time period adjusted for somatic symptom score at baseline.
[c]CFS-like subjects have at least 4 of the symptoms in the Fukuda et al.[12] definition of CFS.
[d]E.g., cold or flu, other well-defined diseases, psychological stress, accident, or surgery.
*p < .01.
**p < .05.
***p < .10.
Abbreviations: CFS = chronic fatigue syndrome, MASQ = Mood and Anxiety Symptom Questionnaire, RVI = Rand Vitality Index.

subject characteristics used to define subgroups did not significantly modify the effect of citalopram.

Not shown in Table 3 are the percentages of subjects with substantial improvement in fatigue who answered much improved or very much improved on the global improvement scale: 32% at month 1 and 32% at month 2 for the citalopram subjects and 18% at month 1 and 19% at month 2 for the control group. Although differences between these percentages were large, they were not statistically significant.

As shown in Table 4, citalopram did not have a statistically significant effect on depressive symptoms at month 1 or month 2 for all subjects combined. Citalopram was associated with improvement in depressive symptoms for women at month 1, p = .01, and for several groups at 2 months.

Table 5 shows that citalopram had a statistically significant effect on the key somatic symptoms during month 1. In an analysis not shown, we found that for all subjects at month 1, citalopram was strongly associated with less severe headaches, p = .01, and muscle aches, p = .005, but had less impact on dizziness, p = .11.

Changes in fatigue from baseline were strongly correlated with both changes in depression scores ($r = 0.58$, $p < .0001$, at month 1 and $r = 0.63$, $p < .0001$, at month 2) and changes in key somatic symptom scores ($r = 0.30$, $p = .003$, at month 1 and $r = 0.44$, $p < .0001$, at month 2).

Side effects for citalopram are compared with placebo in Table 6. Although the overall rates of moderate or severe side effects were not significantly different, 3 subjects taking citalopram and none taking placebo had moderate or severe insomnia and sexual dysfunction. All subjects recovered their sexual function, but 2 subjects with severe insomnia withdrew from the study and the third continued to have severe insomnia.

Table 6. Side Effects[a]

	Placebo (N = 36)		Citalopram (N = 30)		Persistent With Citalopram[b]	
Side Effect	N	%	N	%	N	%
Any						
Moderate or severe	10	28	11	37	7	23
Severe only	6	17	7	23	5	17
Insomnia						
Moderate or severe	0	0	3	10	3	10
Severe only	0	0	3	10	3	10
Sexual dysfunction						
Moderate or severe	0	0	3	10	0	0
Severe only	0	0	2	7	0	0
Nausea/vomiting						
Moderate or severe	1	3	2	7	2	7
Severe only	1	3	2	7	2	7
Hot flashes/sweating						
Moderate or severe	0	0	2	7	2	7
Severe only	0	0	1	3	1	3
Sleepiness						
Moderate or severe	0	0	2	7	1	3
Severe only	0	0	1	3	0	0
Decreased appetite						
Moderate or severe	0	0	2	7	1	3
Severe only	0	0	1	3	1	3
Headaches						
Moderate or severe	3	8	1	3	1	3
Severe only	0	0	1	3	1	3
Other[c,d]						
Moderate or severe	8	22	5	17	3	10
Severe only	6	17	3	10	3	10

[a]A symptom is considered a side effect if it is moderate or severe and has worsened since baseline.
[b]Side effects of 3 subjects who withdrew from the study are considered persistent.
[c]Other in the citalopram group includes the following side effects that each occurred in 1 subject: frequent urination, lack of motivation, lethargy, diarrhea, and dizziness.
[d]Other in the placebo group includes the following side effects that each occurred in 1 subject: nervousness, uterine bleeding, breast tenderness, fibromyalgia symptoms, burning muscles, constipation, itchy rash, and vision trouble.

DISCUSSION

Energy levels improved somewhat following treatment with placebo and improved further when subjects were given citalopram instead of placebo. The percentage of subjects with a substantial improvement was greater for citalopram than for the comparison group, 32% versus 18%, but neither this difference nor differences in final Rand Vitality Index were statistically significant. However, evidence was stronger for treatment effectiveness in subgroups. Among subjects with less severe fatigue at baseline, those given citalopram improved more than controls at 2 months, $p = .005$, and women taking citalopram had greater improvement at 2 months than women taking placebo, $p = .08$. For these same 2 subgroups, subjects taking citalopram had fewer symptoms of anhedonic depression than placebo subjects at both 1 and 2 months of therapy. For all subjects, citalopram was associated with fewer headaches and muscle aches after 1 month of therapy, $p < .01$. Anhedonic depression scores and somatic symptom scores may be intrinsically associated with fatigue since changes in these scores were significantly associated with changes in fatigue at both 1 and 2 months, $p < .01$.

This study combined 2 data sets. Although the combination of data from 2 studies is not equivalent to an RCT, there are several features of the design that strengthen this study. (1) The 2 data sets used the same procedures for subject selection and data collection and were collected during the same time period. The differences between subject selection criteria for the 2 studies related to contraindications for citalopram or Siberian ginseng or refusal to take an antidepressant. (2) The data collection used the same procedures as are used in RCTs. (3) Detailed data were collected for the subjects at baseline. (4) Subjects in the treatment groups did not differ on the basis of baseline characteristics. (5) Baseline information was used to adjust outcome comparisons. Because of these design features, this observational study was much better than many.

In general, results from this study are consistent with previous work. In particular, the significant improvement of subjects on citalopram treatment and the lack of effectiveness in comparison to a control group are similar to findings from previous studies of SSRIs for treatment of CFS.[19–23] The effectiveness of citalopram for subjects with less severe fatigue is a new finding. Since the previous studies[19–23] only included subjects with CFS, they may have included few subjects with less severe fatigue.

Our finding of the effectiveness of citalopram for symptoms of muscle aches and headaches is also consistent with previous studies of antidepressants for these symptoms.[35–40] However, these symptoms were not studied in CFS subjects, and our results differ from a previous study that did not find citalopram effective for headaches.[41]

Previous studies of the effectiveness of an SSRI for depression treatment in CFS subjects gave conflicting results; one study found an effect[23] but another did not.[22] In our study, which excluded subjects with major depression, depressive symptoms were improved in certain subgroups, especially those with less severe fatigue. Subgroup effects may explain the discrepancy between previous studies.

Our study was not an RCT, which would be necessary for proving the effectiveness of a fatigue treatment. However, it did benefit from a comparable control group that had placebo therapy. Although the validity of this kind of observational study has not been thoroughly assessed, observational studies have been found to be valid in many contexts[42,43] and should be valuable for selecting subgroups for future studies.

A difficulty with any study of fatigue is the imprecise outcome measure. Fatigue is not only measured subjectively but also is subject to many influences that cause considerable variation. Increasing the difficulty in detecting treatment effect is a placebo effect that may be larger

than the treatment effect. These difficulties increase the sample sizes and study duration necessary to detect a treatment effect.

Because there was evidence for effectiveness at only 1 time period for each of 2 subgroups, this study cannot be said to support the effectiveness of citalopram for idiopathic chronic fatigue. There is little question, however, that idiopathic chronic fatigue has diverse and multifactorial etiologies,[9,44] and, therefore, these subgroups may well have different etiologies of fatigue or response to citalopram. Only additional studies can clarify whether citalopram is effective in certain subgroups such as women and subjects with moderate fatigue.

In summary, there was some evidence suggesting that citalopram benefited subsets of persons with idiopathic chronic fatigue. Further studies of how to characterize the persons benefited may improve the understanding and treatment of chronic fatigue.

Drug names: citalopram (Celexa), doxepin (Sinequan and others), fluoxetine (Prozac and others), sertraline (Zoloft), warfarin (Coumadin and others).

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