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Randomized controlled trial of Siberian ginseng for chronic fatigue

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ABSTRACT

Background. Chronic fatigue greatly affects quality of life and is a common reason for consulting a physician. Since conventional therapy is often of limited help, fatigued patients may use herbal treatments. This randomized controlled trial evaluated the effectiveness of Siberian ginseng.

Method. Subjects were recruited from advertisements in Iowa (82%) and members of chronic fatigue syndrome support groups (18%). Potential subjects were required to have substantial fatigue $\geqslant$6 months with no identifiable cause. The mean change in a fatigue measure was compared for placebo and Siberian ginseng at 1 and 2 months. Comparisons were for all subjects and for subjects with characteristics previously identified in the literature as important for categorizing chronic fatigue.

Results. Ninety-six subjects were randomized to treatment groups, and 76 provided information at 2 months of follow-up. Fatigue among subjects assigned to either placebo or Siberian ginseng was substantially reduced during the study, but differences between treatment groups were not statistically significant in the full sample. Fatigue severity and duration had a statistically significant interaction with response to Siberian ginseng at the $P<0{\cdot}05$ level. Treatment was effective at 2 months for 45 subjects with less severe fatigue ($P=0{\cdot}04$ unadjusted for multiple comparisons) and for 41 subjects with fatigue for $\geqslant$5 years ($P=0{\cdot}09$ unadjusted for multiple comparisons).

Conclusion. Overall efficacy was not demonstrated. However, the findings of possible efficacy for patients with moderate fatigue suggests that further research may be of value.

INTRODUCTION

Fatigue is a common symptom (Wessely *et al.* 1997) that has a 'powerful adverse effect on quality of life' (Nelson *et al.* 1987). According to a National Ambulatory Medical Care Survey, it is the seventh most frequent chief complaint in primary care (National Center for Health Statistics, 1978). In this setting estimates of the percentage of 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 (Solberg, 1984; David *et al.* 1990; Wessely *et al.* 1997). Rarely is such fatigue caused by a medical illness that is not evident on initial examination (Sugarman & Berg, 1984; Kroenke *et al.* 1988; Cope, 1992). Yet fatigue tends to persist. For patients treated for this symptom at a primary care clinic, 50% to 75% still have fatigue at 1 year (Kroenke *et al.* 1988; Cathebras *et al.* 1992), and in one study, 59% who had fatigue for at least 6 months still had the problem after 30 months (Clark *et al.* 1995).

Most research on idiopathic chronic fatigue has evaluated the subset of patients with chronic

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fatigue syndrome (CFS). In addition to idiopathic chronic fatigue, CFS is also characterized by other somatic symptoms such as sore throat, painful lymph nodes, muscles aches, joint pain and headaches (Fukuda *et al*. 1994). The prevalence of CFS in primary care settings has recently been estimated to be 0·2% and 0·4% in two recent population studies (Steele *et al*. 1998; Jason *et al*. 1999) and 2·6% among patients in primary care (Wessely *et al*. 1997).

A review of CFS treatments concluded that cognitive behavioural therapy and graded exercise therapy proved somewhat beneficial, but evidence for benefits from pharmacological therapies is weak (Whiting *et al*. 2001). With the exception of a single trial of cognitive behaviour therapy (Ridsdale *et al*. 2001) there has been little if any research on treatments for patients who have idiopathic chronic fatigue but not CFS.

When conventional medicine fails, patients often turn to complementary and alternative therapies (Eisenberg *et al*. 1993). A herbal treatment widely touted for treatment of fatigue is Siberian ginseng (McMath, 1992; Weil, 1995; The Medical Advisor, 1996; Khermouch, 1997; Facts and Comparisons, 2000). Russian studies (that have been reported in one article (Farnsworth *et al*. 1985) but are not generally available in this country), found that Siberian ginseng improved the ability to perform physical labour, the quality of proofreading, the speed and quality of work by telegraphers in noisy conditions and the number of days lost to sickness among factory workers. It has been widely used by Russian athletes several weeks before an event to increase stamina, performance and concentration. It is prescribed by Russian physicians for asthenia and to improve the general health, resistance and energy of those who are weak, debilitated and stressed. Few side-effects are reported. To our knowledge no previous randomized controlled trials have investigated it as a treatment for fatigue.

METHOD

Treatment

The study was a 2-month, randomized, blinded, controlled trial in which subjects were given capsules containing either placebo or a standardized powdered extract of *Eleutherococcus senticosus* (Siberian ginseng). After 2 months all subjects were given Siberian ginseng as a reward for participating and to evaluate its long-term effect. The study design, method of subject recruitment, and data collection instruments were approved by the Institutional Review Board of the University of Iowa College of Medicine.

Both the extract of Siberian ginseng and placebo were supplied in four 500 mg capsules by Frontier Herbs of Norway, IA. The extract was standardized so that the active ingredients of Siberian ginseng (i.e. eleutheroside B and eleutheroside E) were 0·112% by weight according to an analysis performed on 15 March 1999. Four capsules provided 2·24 mg of eleutherosides. The database used by Frontier Herbs showed the usual concentration of eleutherosides B and E in the raw root vary considerably but typically range from 0·05% to 0·10%. Therefore, 2 mg a day of eleutherosides is equivalent to a dried root dosage of 2 to 4 g per day. Daily dosage recommendations for Siberian ginseng are typically in this range (Blumenthal, 1998; Gruenwald *et al*. 1998; Murray & Pizzorno, 1999) although some American sources recommend as much as 6 to 12 g a day (Murray & Pizzorno, 1991) and some Chinese sources recommend 9 to 27 g a day (Huang, 1994).

Siberian ginseng is a light brown, free-flowing powder that has a somewhat sweet flavour with bitter undertones. The placebo used in this study contained roasted white flour 80%, with fine-milling wheat germ added for fibrous taste (10%), fine milling-wheat bran added for colour enhancement (10%) and a bitter almond flavour adjusted so testers could not distinguish placebo from Siberian ginseng.

Subjects

Subjects with chronic, unexplained fatigue were recruited through advertisements in newspapers and Family Medicine residencies in eastern and central Iowa. In addition, we advertised in the newsletter of the Wisconsin Chronic Fatigue Syndrome Association and in a website listed by CoCure (Co-operate and Communicate for a Cure) that provides CFS information. In an effort to recruit additional minority subjects, we contacted churches and healthcare organizations in Iowa communities with the largest minority populations. Sites that recruited and

enrolled patients were the Preventive Intervention Center in Davenport Iowa and family practice residency programmes in Waterloo, Des Moines and Cedar Rapids. Subjects not close to one of the other cities were enrolled at the coordinating centre in Iowa City.

Screening

Volunteers were screened for eligibility first by telephone, then by a written questionnaire, and finally by review of laboratory test results and a form completed by the subject's personal physician. During the telephone screen, subjects were given the four-question Rand Vitality Index (RVI) (Brook *et al*. 1979; see Appendix A). The RVI is well validated and has been used in previous studies of chronic fatigue (Nelson *et al*. 1987; Valdini *et al*. 1988). It ranges from 4, which indicates low vitality and high fatigue, to 24, which indicates high vitality and low fatigue. Subjects were also asked about chronic diseases, medications and other possible causes of fatigue. Those who had unexplained fatigue $\geqslant$6 months and RVIs of $\leqslant$12 were mailed a consent form and baseline questionnaire. This represents greater fatigue than previous studies, which used a cut-off of 14 (Nelson *et al*. 1987; Valdini *et al*. 1988).

It is unknown whether in fatigued subjects there would be a difference in response between interviews and oral questionnaires. There is evidence, however, that some patients respond more honestly to impersonal questionnaires than interviews (Grossman *et al*. 1971; Lucas *et al*. 1977; Carr *et al*. 1983).

In addition to the RVI the baseline questionnaire included five other instruments: (1) 14 questions from the Mini International Neuropsychiatric Interview (Sheehan *et al*. 1998), which were modified to be a self administered screen for depression; (2) 12 questions from the Mood and Anxiety Symptom Questionnaire (MASQ), to measure the level of depressive symptoms (Watson *et al*. 1995); (3) 10 MASQ questions, to measure the level of anxiety (Watson *et al*. 1995); (4) the mental fatigue component of a fatigue instrument (Chalder *et al*. 1993); and (5) the 26-item Somatic Symptom Inventory (Barsky *et al*. 1992) supplemented by five additional questions specific for chronic fatigue syndrome. In addition, the questionnaire asked for information about demographics, fatigue onset, sleep and lifestyle or environmental factors that may have contributed to fatigue and medical history.

Each subject's physician indicated whether that subject had any chronic diseases. The physician also provided the subject's blood pressure and heart rate and the results of any of the following laboratory tests performed within 3 years of enrolment: liver function tests, thyroid stimulating hormone, electrolytes, complete blood count, creatinine, sedimentation rate, calcium and urine analysis. If the subject had not previously had one of these laboratory tests or the results were $>$3 years-old, the tests were ordered for the study.

In contrast to most research on idiopathic chronic fatigue, we did not select subjects on the basis of CFS for three reasons: (1) because chronically fatigued persons without CFS may use Siberian ginseng, it is important to evaluate its effectiveness in these individuals; (2) a mixture of subjects makes it possible to evaluate whether subjects with CFS show a difference in response to Siberian ginseng compared to subjects with idiopathic chronic fatigue; and (3) CFS is an uncommon form of idiopathic chronic fatigue and recruiting large numbers would have been difficult.

We excluded subjects who were pregnant or breast-feeding to prevent possible adverse effects on infants. Subjects were excluded if younger than 21 because many persons this age have life-style reasons for fatigue. They were also excluded if older than 65 when medical illness becomes increasingly common. Because of potential side-effects of Siberian ginseng, subjects were excluded if they had blood pressure greater than 140/85 or were taking digitalis or coumadin (McRae, 1996; Janetzky & Morreale, 1997). Other exclusion criteria included chronic diseases considered in the literature (Sharpe & Wilks, 2002) as exclusions for CFS (anemia, thyroid hormone abnormalities, cancer, heart disease, liver disease or autoimmune disorders), laboratory test abnormalities used in the literature (Sharpe & Wilks, 2002) to exclude CFS (complete blood count, erythrocyte sedimentation rate or C reactive protein, liver function tests, electrolytes, thyroid stimulating hormone, creatinine and urine analysis), life-style factors likely to cause the fatigue (multiple jobs, job plus a care-giver role, or rotating or night

shifts); use of medications that the subject or a screening pharmacist thought were a likely cause of fatigue, and evidence from screening or physician report of major depression. Some subjects who screen positive for major depression may not have it, but eliminating a few subjects unnecessarily does not invalidate the study results. Subjects with depressive symptoms were also excluded if they did not meet the criteria for major depression but responded affirmatively to the question: 'Is your depression more of a concern to you than your fatigue?'. These subjects are more likely than others to have fatigue caused by depressive symptoms.

Subjects on psychotropic medications were not excluded provided they did not currently meet criteria for major depression, their dose had been stable for 2 months, and, after consultation with their physician, they agreed not to change the dose for a minimum of 2 months. Subjects were withdrawn at the time they changed their dose of a psychotropic medication.

Our recruiting and exclusion policies should not have influenced the internal validity of the results because randomization was done after exclusion.

Randomization and concealment of treatment allocation

We randomized subjects in blocks of four for each site using numbers generated by SAS (SAS Statistical Software, 1999). In each block of four two subjects were randomly assigned to treatment and two to placebo. The statistician mailed bottles of medication to the subjects. The list of assignment was kept by the statistician, and not made available to subjects until they completed all 4 months of the study. Because the sites never knew which patients received Siberian ginseng, there was no possibility they could subvert the randomization.

Follow-up

Questionnaires were mailed at 1, 2, 3 and 4 months after the subject began the study therapy. For these monthly assessments subjects were asked to provide their blood pressure and resting heart-rate and respond to several scales from the baseline questionnaire. Subjects were instructed to answer these questions on the basis of how they had felt during the previous week. Subjects who failed to return questionnaires were called at least three times.

Subjects reported on the questionnaire any symptoms that could conceivably have been due to the treatment. Specific symptoms of concern were those associated with Panax ginseng (a herb sometimes considered to have properties similar to Siberian ginseng): insomnia, nervousness, palpitations, headaches, uterine bleeding and breast tenderness. Subjects rated these and other possible side-effects on a scale from absent to severe. A study coordinator contacted subjects reporting moderate or severe side-effects to discuss a dose reduction or withdrawal from the study.

As a measure of compliance at the 2-month assessment, subjects were asked to record the number of capsules that remained in their bottle(s). Subjects were considered compliant if at that time, the remaining capsules reported were consistent with missing no more than 2 days of treatment.

Analysis

Because the literature suggests that Siberian ginseng does not become effective for 5 weeks (Farnsworth *et al*. 1985), the primary outcome measure was the RVI after 2 months. Subjects varied as to when they completed questionnaires, and we included questionnaires completed at 6 to 10 weeks. A measure of fatigue reduction was a substantial improvement in the RVI (at least a seven-point increase). Outcomes other than fatigue were the sum of the frequency scores for certain somatoform symptoms and scales from the MASQ (Watson *et al*. 1995) for depression and anxiety.

We analysed data from all subjects regardless of whether or not they demonstrated full compliance with treatment. In a secondary analysis we included all subjects who had at least one assessment beyond baseline. If these subjects had more than one follow-up value, we included the value that was the closest to target interval of 42 to 70 days.

Baseline characteristics of the subjects considered in some of the analyses were demographic information (age, sex, race, ethnic group, marital status, socio-economic status, clinic where recruited); duration of fatigue; symptoms of anxiety and depression as measured

by the MASQ scales; history of a psychological illness; quality of sleep measured with five questions; previous diagnoses of CFS; depression; or fibromyalgia; and number of somatoform symptoms. Subjects were classified as CFS-like if at baseline they were bothered at least moderately by four 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, unrefreshed sleep and post-exertional fatigue lasting >24 h (Fukuda *et al.* 1994).

The statistical tests used were: paired t test (to assess changes from one time period to another); the two sample t tests (to compare outcomes between two treatment groups); and analysis of covariance (to compare treatments after adjusting for the RVI or other variables measured at baseline). The statistical tests were performed for all subjects and subjects in subgroups defined by compliance, CFS-like, acute onset, fatigue severity, fatigue duration, number of depressive symptoms and number of somatic symptoms. Onset was considered acute if subjects gave a date for the onset and it followed a specified disease, psychological stress, accident or surgery. Subjects were divided on the basis of continuous variables (fatigue severity and duration and depressive symptoms) into subgroups that included approximately 50% of the subjects. Compliant subjects were a subgroup of interest because, if Siberian ginseng is effective, it should be most effective among these subjects. Subgroups defined by depressive status, level of fatigue and duration of fatigue were previously suggested in an article defining CFS subjects, (Fukuda *et al.* 1994); subgroups defined by number of somatic symptoms were suggested in another article (Hickie *et al.* 1995). To reduce the size of the tables, we reported only results in the subgroup showing the largest effect size. We did not adjust P values for multiple comparisons because useful information may be lost from a study if critical P values are set very low to take multiple comparisons into account (Rothman, 1990). Since it is impossible to distinguish between statistically significant associations by chance and real association, it may be better to accept a higher probability that some apparent relationships are spurious. The purpose of the present study is to generate information about likely relationships. Relationships found to be statistically significant and medically plausible should then be examined in other settings.

We only counted as side-effects those symptoms that were reported as moderate or severe and began or became worse after the study began.

RESULTS

The number of subjects at each stage of the recruitment process is shown in Fig. 1. Of the 768 subjects who initially volunteered, 672 were excluded for reasons shown in Fig. 1, 96 were enrolled and 76 completed the randomized controlled trial. Prior to 2 months, 10 of 47 subjects were lost to follow-up in the placebo group and eight of 49 subjects were lost in the Siberian ginseng group. This suggests that the intervention did not increase lost to follow-up.

The baseline characteristics of enrolled subjects are shown in Table 1. Only two minority subjects completed 6 weeks of the study, and our search for additional ones was unsuccessful. The low percentage of minority patients in the study at least in part reflects their low percentage in Iowa. The average baseline value of the RVI was 8·0, which is closer to the extreme fatigue end of this scale (RVI $=4$) than to the extreme vitality end (RVI $=24$).

Subjects in both placebo and treatment groups improved substantially at the 1 month follow-up period, $P<0{\cdot}001$ for both groups. Roughly one-quarter of subjects had an increase in RVI of $\geqslant 7$. After 2 months, subjects on Siberian ginseng had an improvement in RVI of 0·66 more than subjects on placebo (adjusting for baseline RVI), but this difference was not statistically significant at the $P<0{\cdot}10$ level. The 95% confidence interval for the effect of Siberian ginseng ranges from an increase in RVI of 2·46 to a reduction of 1·14. Thus, it is unlikely that the true effect size of Siberian ginseng for all subjects was greater than 2·5.

Of the 20 subjects eliminated from the above analysis because they did not have measurements between 6 and 10 weeks after baseline, 10 had no measurements after baseline, seven only had measurements before 6 weeks and three only had measurements after 10 weeks. When we included the 10 subjects with follow-up outside of the target time interval, the effect size was 0·63 instead of 0·66.

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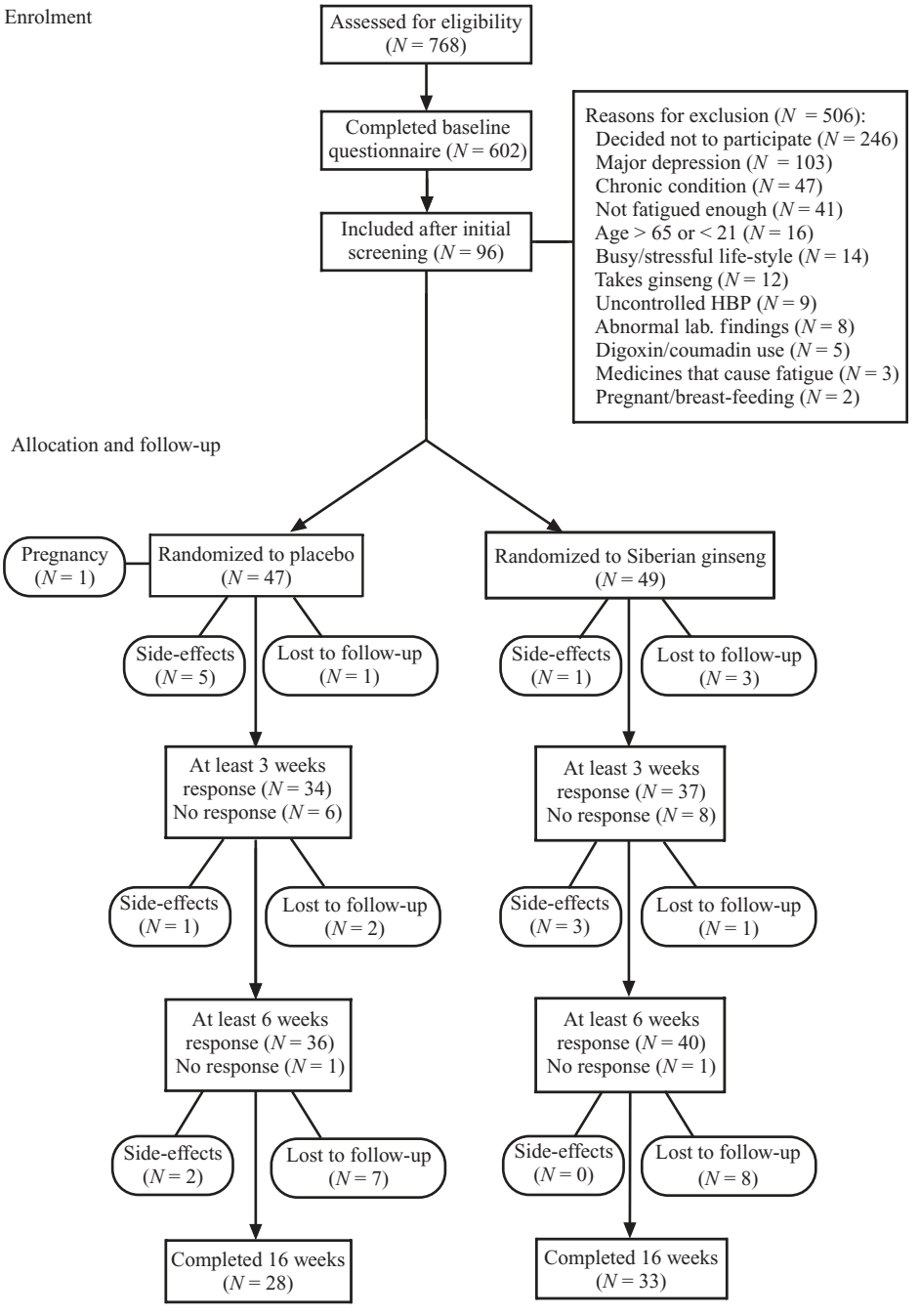

FIG. 1. Number of subjects at each stage.

We tested for interaction i.e. whether the subject characteristics used to define subgroups significantly altered the response to Siberian ginseng. We found interaction terms were statistically significant at the $P < 0{\cdot}05$ level for treatment with baseline fatigue and with duration of fatigue if these terms were measured on a continuum rather than as binary variables.

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Table 1. *Patient characteristics at baseline*

Characteristic	Placebo ($N=36$) (%)	Siberian ginseng ($N=40$) (%)
Age (in years)		
21–34	0·0	2·5
35–49	50·0	55·0
50–65	50·0	42·5
Female	83·3	77·5
Caucasian	100·0	97·4
Married	58·3	76·9 NS
Duration of fatigue (in years)		
0·50–0·99	5·6	2·5
1·00–4·99	38·9	40·0
5·00–9·99	25·0	22·5
10·00–19·99	16·7	30·0
⩾20·00	13·9	5·0
CFS-like	55·6	85·0**
Number of somatic symptoms†		
⩽5	11·1	5·0
6–10	30·6	20·0
11–19	44·4	65·0
20–29	13·9	10·0
Unclear thinking†	77·8	82·5
Rand Vitality Index (RVI)	8·3	7·8
Total MASQ depression	54·7	53·7
Source of subjects		
Davenport	25·0	20·0
Iowa City	44·4	50·0
Residency programmes in Waterloo, Des Moines, and Cedar Rapids	13·9	10·0
Website and support group	16·7	20·0

† A symptom is considered present if it bothered the subject at least a moderate amount.

** $P<0·01$; NS, not significant (but $P<0·1$).

Table 2 shows results of an analysis for treatment effect in the preselected subgroups as described in the Method section. For this purpose subjects were divided into two subgroups (e.g. long *v.* short duration of fatigue). To reduce the size of the tables we reported only results in the subgroup showing the largest effect sizes. The only covariate included in the tabulated analysis of covariance was the baseline RVI. With this analysis there was a statistically significant beneficial effect of Siberian ginseng ($P=0·03$), in subjects who were least fatigued at baseline (RVI from 8 to 12). Siberian ginseng was also associated with improvement at the $P<0·10$ level for the subgroup defined by distinct onset of fatigue and those with fatigue for ⩽5 years. We also performed analyses of covariance that included all factors independently associated with outcome. In these analyses Siberian ginseng was associated with the treatment effect for less fatigued patients at the $P=0·08$ level.

Fig. 2 shows mean RVI scores for moderately fatigued subjects over the blinded and open-label portions of the trial. Subjects initially assigned to placebo had an improvement in mean RVI of 2·0 after they were put on Siberian ginseng ($P=0·02$, paired t test for 2 months to 4 months). Subjects initially assigned to Siberian ginseng had a change in mean RVI from months 2 to 4 that was small and not statistically significant. Subjects were not provided information about time to onset of action of Siberian ginseng or their treatment assignment until they completed 4 months of the study.

In addition to evaluating the effect of treatment on fatigue, we examined the effect of treatment on factors strongly associated with fatigue: depressive symptoms measured by the MASQ scale for anhedonic depression and somatic symptoms as assessed by the Somatic Symptom Inventory. We did not find evidence of a treatment effect on depressive symptoms for all subjects or any subgroup. There was also no treatment effect on somatic symptoms in all subjects. However, in an analyses of covariance that adjusted for baseline value, treatment was associated with a decrease in somatic symptoms at the $P<0·05$ level in two subgroups: the most severely fatigue subjects (those with an RVI of <8) and more depressed subjects (those with total MASQ depression score in the upper half).

Changes in RVI were strongly associated with changes in depressive symptoms ($r=0·64$, $P<0·0001$) and with changes in the somatic symptoms ($r=0·47$, $P<0·0001$). There was no association of change in RVI with change in the MASQ anxiety score.

Table 3 shows side-effects reported by each treatment group at 1 month. After this time side-effects were greatly reduced. Although the percentage of subjects with new symptoms was high, the rates were similar for subjects assigned to Siberian ginseng and those assigned to placebo. There was a higher (but not significantly different) rate of breast tenderness and uterine bleeding in the intervention than in the control group, 14% *v.* 4% respectively. We also tested whether blood pressure was affected by Siberian ginseng. The mean change in systolic blood pressure from baseline to 1 month visit was 0·97 for the placebo subjects and −0·93 for

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Table 2. *Treatment effect at 2 months according to subgroup*

	Percentage substantial improvement		Mean RVI		Effect size†	*t*
	Placebo	S. ginseng	Placebo	S. ginseng		
All subjects	19 (7/36)	23 (9/40)	11·1	11·6	0·66	0·73
Compliers	18 (4/22)	29 (7/24)	11·4	11·3	0·32	0·26
Baseline RVI: 8–12	8 (2/24)	14 (3/21)	10·7	12·9	2·17	2·17*
Fatigue ⩽5 years	29 (6/21)	30 (6/20)	11·3	13·4	2·05	1·71 NS
CFS-like‡	20 (4/20)	26 (9/34)	10·2	11·8	1·67	1·43
Upper half of MASQ depression score	11 (2/18)	29 (7/24)	10·1	12·0	1·90	1·37
Upper half of somatic symptom score	27 (4/15)	29 (7/24)	10·1	12·0	1·90	1·37
Fatigue following specific problem§	13 (2/16)	24 (6/25)	10·6	11·2	2·08	1·69 NS

† Effect size is the difference in RVI between placebo and ginseng groups adjusted for baseline RVI.
‡ CFS-like are subjects with at least 4 of the symptoms in the Fukuda definition of CFS.
§ For example cold or flu, other well-defined diseases, psychological stress, accident, or surgery.
* $P<0·05$; NS, not significant (but $P<0·1$).

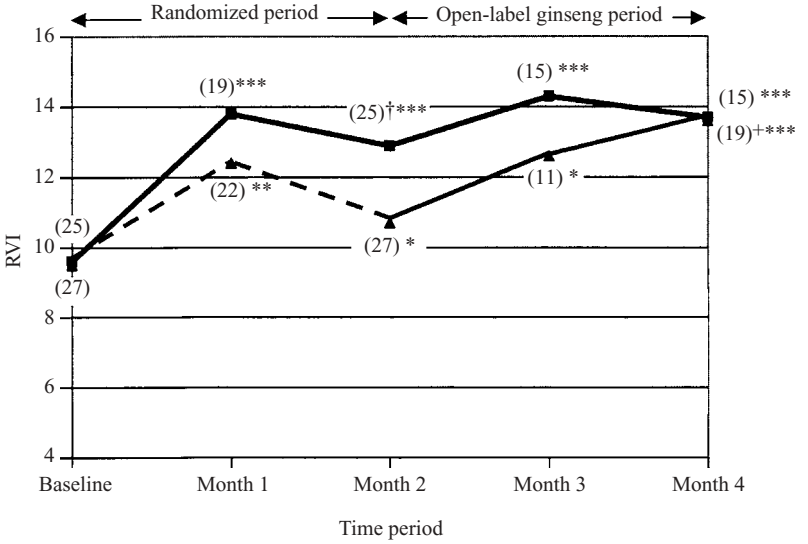

FIG. 2. Rand Vitality Index (RVI) for subjects with moderate fatigue according to time in study and therapy. (The numbers show the sample size for placebo (– – –) and Siberian ginseng (——).) For paired *t* test comparison with baseline RVI: * $P<0·05$; ** $P<0·01$; *** $P<0·001$. For paired *t* test comparison with baseline RVI at month 2: $^{+}$ $P<0·05$. For unpaired *t* test comparison of RVI at month 2 for Siberian ginseng and placebo subjects: † $P<0·05$.

the subjects on Siberian ginseng. The respective changes in diastolic blood pressure were −0·48 and −0·37. Neither of these differences were statistically significant.

DISCUSSION

The randomized controlled trial reported here evaluated Siberian ginseng for a diverse group of subjects with idiopathic chronic fatigue. For the 76 patients who completed the 2-month trial there was no evidence that Siberian ginseng reduced the fatigue. After 2 months, when the herb should have been effective, improvement was not statistically significant and the 95% confidence interval did not include an effect size >2·5 improvement in the RVI. The effect size was no greater for subjects who took the herb

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Table 3. *Side-effects at 1 month*

	Placebo ($N=36$)		Siberian ginseng ($N=41$)	
	New (%)	New & persistent (%)	New (%)	New & persistent (%)
Any				
Moderate or severe†	27·8	22·2	24·4	9·8
Severe† only	16·7	16·7	9·8	7·3
Nervousness				
Moderate or severe†	2·8	2·8	7·3	4·9
Severe† only	2·8	2·8	2·4	2·4
Headache				
Moderate or severe†	8·3	5·6	9·8	2·4
Severe† only	0·0	0·0	0·0	0·0
Breast tenderness				
Moderate or severe†	2·8	0·0	7·3	2·4
Severe† only	2·8	0·0	2·4	2·4
Other‡				
Moderate or severe†	16·7	13·9	17·1	12·2
Severe† only	11·1	11·1	7·3	7·3

† Severe includes subjects who rated the side-effect as severe or withdrew due to side-effects.

‡ Other includes: trouble sleeping, palpitations, uterine bleeding, fibromyalgia symptoms, nausea and burning muscles, constipation, itchy rash, vision trouble, extreme tiredness, tremors/chills, and inability to relax. Each side-effect in this category was present in at most two subjects in one of the treatment groups.

as prescribed than for other subjects. These results do not support a strong beneficial effect of the herbal preparation for all subjects.

Lost to follow-up rates were slightly higher in the placebo than the intervention groups suggesting that treatment effects did not contribute to lost to follow-up. When we included all subjects whose RVI was measured after baseline, even if it was not measured within the target follow-up interval, results were not affected. Therefore, it is unlikely that the true effect of treatment could be obscured by baseline differences between treatment and placebo subjects caused by lost to follow-up.

Because idiopathic chronic fatigue has diverse and multifactorial aetiologies (Cope, 1992; Blondel-Hill & Shafran, 1993), not all persons with this symptom may respond in the same way to an intervention. For this reason, we evaluated whether patient characteristics used to subclassify fatigue (Fukuda *et al*. 1994; Hickie *et al*. 1995; Hartz *et al*. 1998) may be associated with a differential response to treatment. The differential response was statistically significant at the $P<0{\cdot}05$ level for two of these factors, fatigue severity and duration. For subjects moderately fatigue at baseline, there was a significantly greater improvement at the $P<0{\cdot}05$ level for those on Siberian ginseng than those on placebo during the randomized controlled trial. In addition, when subjects with moderate fatigue were changed from placebo to Siberian ginseng, they also improved after 2 months. We did not see a similar improvement in the subjects who remained on Siberian ginseng for all 4 months of the study even though neither group of subjects knew whether they were on Siberian ginseng or placebo during the first 2 months of the study.

Although it is plausible that Siberian ginseng benefits only persons with less extreme fatigue, it is also possible that this association occurred by chance because we examined several subgroups. The influence of baseline fatigue on effect size needs to be substantiated in other settings to determine if degree of fatigue provides a classification of idiopathic chronic fatigue that is therapeutically meaningful for Siberian ginseng or other interventions.

This study had several limitations. One is an imprecise outcome measure. Not only is fatigue measured subjectively, but it varies greatly and is influenced by emotional state. In addition, our evidence suggests that it is responsive to placebo or possibly natural history (subjects may volunteer when fatigue is more distressing). Even though all subjects in this study had had fatigue for at least 6 months, the average improvement in the RVI from baseline to 1 month was substantial, highly significant, and highly variable. These limitations may obscure a moderate treatment effect unless sample sizes are large.

Another limitation is that we did not examine the effectiveness of varying doses of Siberian ginseng. It is possible that higher doses might be more effective. Since our study did not find evidence of side-effects that could not easily be controlled, it may be appropriate to study higher doses consistent with recommendations in some literature, (Murray & Pizzorno, 1991; Huang, 1994).

The need for systematic research on herbal therapies supported by cultural traditions has been widely recognized (Eisenberg *et al*. 1998; Ernst, 2002). Although the present study does not demonstrate overall efficacy, it suggests that

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further evaluation of Siberian ginseng may be warranted for persons with moderate fatigue.

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