Published in final edited form as:
Support Care Cancer. 2010 February ; 18(2): 179–187. doi:10.1007/s00520-009-0642-2.

Pilot study of *Panax quinquefolius* (American ginseng) to improve cancer-related fatigue: a randomized, double-blind, dose-finding evaluation: NCCTG trial N03CA

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Abstract

Purpose—This pilot trial sought to investigate whether any of three doses of American ginseng *(Panax quinquefolius)* might help cancer-related fatigue. A secondary aim was to evaluate toxicity.

Methods—Eligible adults with cancer were randomized in a double-blind manner, to receive American ginseng in doses of 750, 1,000, or 2,000 mg/day or placebo given in twice daily dosing over 8 weeks. Outcome measures included the Brief Fatigue Inventory, vitality subscale of the Medical Outcome Scale Short Form-36 (SF-36), and the Global Impression of Benefit Scale at 4 and 8 weeks.

Results—Two hundred ninety patients were accrued to this trial. Nonsignificant trends for all outcomes were seen in favor of the 1,000- and 2,000-mg/day doses of American ginseng. Area under the curve analysis of activity interference from the Brief Fatigue Inventory was 460–467 in the placebo group and 750 mg/day group versus 480–551 in the 1,000- and 2,000-mg/day arms, respectively. Change from baseline in the vitality subscale of the SF-36 was 7.3– 7.8 in the placebo and the 750-mg/day arm, versus 10.5– 14.6 in the 1,000- and 2,000-mg/day arms. Over twice as many patients on ginseng perceived a benefit and were satisfied with treatment over those on placebo. There were no significant differences in any measured toxicities between any of the arms.

Conclusion—There appears to be some activity and tolerable toxicity at 1,000–2,000 mg/day doses of American ginseng with regard to cancer-related fatigue. Thus, further study of American ginseng is warranted.

Keywords

Panax quinquefolius; American ginseng; Cancer-related fatigue; Botanicals

Background and significance

Definition and prevalence of cancer-related fatigue

Cancer-related fatigue has been defined by a panel of the National Comprehensive Cancer Network as “a persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning” [1]. One of the distinguishing characteristics of cancer-related fatigue, compared to other fatigue, is that it is not relieved by sleep or rest [1–3] and patients report being “unusually” or overwhelmingly tired [1–4]. Cancer-related fatigue is out of proportion to the amount of physical activity and hence is often accompanied by negative affect or distress [1–4].

Fatigue is one of the most common unmanaged symptoms in people diagnosed with cancer and exists in those receiving chemotherapy, radiation therapy, biologic therapies, and in those having completed treatment [1, 2, 5, 6]. The prevalence of fatigue is reported to be between 59–96% in patients undergoing chemotherapy, 65–100% in patients receiving radiation therapy, and 30% in long term survivors [7–9].

Evidence-based interventions

Few randomized controlled trials of nonpharmacologic or pharmacologic interventions for improving fatigue in cancer patients have been performed. Of the nonpharmacologic interventions, exercise has the strongest evidence base for treating fatigue [10, 11]. Most studies have used home-based walking, three to five times per week for 30 min each time [2, 12, 13]. Other interventions with some evidence of efficacy include restorative therapy such as communing with nature, dietary management, sleep therapy, and activity management

[10–13]. However, though preliminary evidence is positive, large randomized trials are needed to properly define the role and effect size of many of these interventions in clinical practice.

Several pharmacologic agents have been explored, such as methylphenidate [14–18], corticosteroids, anabolic steroids, antidepressants, donepezil [19], L-carnitine, modafanil [20], and amantadine, a drug which as shown some efficacy in relieving fatigue related to multiple sclerosis [11]. However, few of these agents have been studied in large placebocontrolled trials and, so far, of those that have been studied, none have been proven to be helpful and ready for general clinical practice.

The evidence for ginseng

Within the context of traditional Chinese medicine, ginseng is generally viewed as an "adaptogen", a substance which can help reduce the impact of environmental stress. There are different species of ginseng, the two most common being Asian *(Panax ginseng)* and American *(Panax quinquefolius)*, both from the genus *Panax* of the Araliaceae family of plants [21, 22]. Both Asian and American ginseng have a common mixture of active ingredients, the most important being ginsenosides, in varying amounts, strengths, and ratios and both ginseng preparations are thought to have broad and similar activity [21–23].

Studies with ginseng often do not denote the specific species of ginseng nor the ginsenoside constituents, which makes it very difficult to accurately summarize the literature with respect to scientific thoughts. Despite this weakness, there are several studies looking at ginseng for fatigue.

Most of the preliminary data, both in animals and in pilot studies with humans, have been with Asian ginseng. Studies in mice have shown that Asian ginseng has improved fatigue related to stress using the forced swimming test as well as electroshock stress [24, 25]. One large study evaluating Asian ginseng in combination with vitamins and minerals, in 232 patients who had functional fatigue for over 10 years, concluded that the ginseng formula improved a fatigue symptom score statistically significantly more than did a vitamin placebo [26]. Furthermore, an abstract presented at the 2003 American Society of Clinical Oncology meeting evaluated Asian ginseng in chemonäive people with cancer. It reported that ginseng significantly improved total and average fatigue levels, as measured by the Brief Fatigue Inventory, even though the sample size was quite small (N=20) [27].

Though much of the published research evaluating properties of ginseng with respect to fatigue has been done with Asian ginseng, there are some important considerations in favor of studying American ginseng for cancer-related fatigue. These issues include the fact that both species have similar ginsenosides [28, 29], the positive experience of American ginseng in research with respect to toxicities [30], and the quality assurance available with respect to the product.

As noted above, both species of ginseng (Asian and American) have many of the same ginsenosides but in different ratios. With respect to fatigue, one study looked at the specific ginsenosides attributable to the ergogenic properties of ginseng [31]. These investigators found that either the Rb1 or Rg1 ginsenoside was necessary to enhance activity performance in mice. Without either of these ginsenosides, the ginseng was not effective [31]. Both American and Asian ginseng have both of these ginsenosides; American has more Rb1, while Asian has more Rg1 [28, 29]. Therefore, operating under the hypothesis that either Rb1 or Rg1 was the active ginsenosides related to fatigue, either Asian or American ginseng would have the potential to impact fatigue.

American ginseng is currently being studied fervently with respect to diabetes [32]. Doses up to 3,000 mg have been studied with no significant toxicity being reported [22]. The only reported side effect in the literature attributed to American ginseng has been insomnia [32, 33]. In addition, American ginseng has been shown to have antiproliferative effects in breast tissue and is beginning to be studied in colon cancer [34–36].

Finally, the availability and quality control of American ginseng may be better, as Asian ginseng is difficult to find and many products studied have been found to be inadequate [37]. American ginseng grown in some areas of the USA is subject to strict pesticide use standards for agricultural products. Specifically, American ginseng from Wisconsin, which was used in this pilot trial, has been tested by the US Environmental Protection Agency and is governed by the Ginseng Board of Wisconsin which has been working with the US Department of Agriculture to develop grading standards to ensure consistency of ginseng marketed as Wisconsin ginseng in the USA [38].

Due to the high prevalence of fatigue and the limited number of effective interventions, the purpose of this pilot trial was to investigate three doses of American ginseng *(P. quinquefolius)*, to evaluate the potential for alleviating cancer-related fatigue and to examine toxicity. This pilot trial was designed to delineate an appropriate dose of American ginseng to study in a more definitive phase III placebo-controlled trial.

Materials and methods

Eligibility

To be eligible for this trial, adult patients had to have a history of cancer-related fatigue as defined by a score of 4 or more on a screening question about fatigue level, that went from 0 (no fatigue) to 10 (fatigue as bad as you can imagine). Other causes of fatigue, such as uncontrolled pain, insomnia, and hypothyroidism, were to be ruled out. Participants had to be experiencing fatigue for at least 1 month and had to have a life expectancy of 6 months or more.

Randomization

Participants were stratified according to stage of disease (stage I/II versus III/IV versus unknown), gender, baseline fatigue score (4–7 versus 8–10), and current treatment (chemotherapy versus not and radiation therapy versus not). Randomization was computer generated and assignments were made using a dynamic allocation procedure balancing marginal distribution of the stratification factors. Participants were randomized to receive a placebo versus 750, 1,000, or 2,000 mg per day of *P. quinquefolius*. The total milligrams were divided into twice daily dosing to be taken in the morning and midafternoon with food. All participants and treating study personnel were blinded to treatment assignments. Informed consent was obtained through all local Institutional Review Boards according to federal regulations.

Intervention

American ginseng is also known by a number of names (North American ginseng, Ontario ginseng, Canadian ginseng, western ginseng, and Wisconsin ginseng, for example), depending on where it was grown. The ginseng used in this study was Wisconsin ginseng. A 4-year-old root was used and the product was fingerprinted by an independent company, Covance, in Madison, WI, USA. The ginseng met with quality control for pesticides and contaminants. It also contained 5% ginsenosides, with Rb1 being the most prevalent ginsenosides, with 24,000 ppm, compared to 3,230 ppm of Rg1. Other ginsenosides present in this product included (in declining amounts) Re (22,800 ppm), Rc (8,130 ppm), Rd (7,080

ppm), Rb2 (1,160 ppm), and Rf (<850 ppm). The root was made into capsules via Good Manufacturing Practices by Beehive Botanicals in Hayward, WI, USA. Matching placebo was also made by Beehive Botanicals and consisted of long grain white rice flour. Both placebo and Wisconsin ginseng were supplied for this trial by the Ginseng Board of Wisconsin and the Ginseng Research Institute of America (Wausau, WI, USA).

Outcome measures

The primary outcome measure was the Brief Fatigue Inventory (BFI) developed by Mendoza and colleagues [39]. As this was a pilot trial, efficacy trends for the three dose levels were examined. Secondary outcome measures included the vitality subscale of the Medical Outcome Scale Short Form-36 (SF-36) [40], the Pittsburgh Sleep Quality Index (PSQI) [41], the Global Impression of Change [42], and the Linear Analogue Self Assessment Scale [43–46], which has been validated for application in cancer patient clinical trials by the North Central Cancer Treatment Group.

Toxicities were evaluated with a symptom experience diary, which is a self-report diary of potential side effects of ginseng. It measured the severity of the side effects experienced on a 0 to 10 scale with 0 being not a problem to 10 being “as bad as it can be”. Toxicities graded per the National Cancer Institute Common Terminology Criteria for Adverse Events (Version 3.0) every other week during treatment included agitation, anxiety, insomnia, thrombosis, nausea, and vomiting.

All primary and secondary outcome measures were completed at baseline and at 4 and 8 weeks after starting study treatment. Self-reported toxicities were completed weekly and provider-graded toxicities were evaluated every other week.

Statistical analysis

The primary endpoint was the total activity interference as measured by the area under the curve (AUC) of the summated BFI activities of daily living items. The average AUC for the placebo arm was compared to the average AUC for the collective ginseng treatment arms, using a single two sample *t* test with a two-sided alternative. Subsequent testing for differences in efficacy among the three ginseng dose levels was carried out by paired comparison procedures. Confidence intervals were constructed for the mean reduction in total AUC fatigue score for each treatment group. Understanding that this was designed as a pilot study, the trial was powered for a total of 256 patients with 192 patients in the ginseng arms and 64 patients in the placebo arm providing 80% power to detect a difference of 41% times the standard deviation, using a two sample *t* test. This is considered a moderate effect size [47]. The study was powered to look at the three ginseng arms combined and not look at individual differences in the doses. To examine differences between specific arms, there was 80% power to detect 61% times the standard deviation, which is a large effect.

The analytical procedures detailed for the primary endpoint were also applied to the secondary endpoints, including the usual fatigue question from the BFI. Supplementary analyses involved a *t* test and Wilcoxon procedures at each time point as well as a repeated measure of analysis of variance and generalized estimating equations linear model, using data from all time points for the average fatigue score, sleep quality score, sleep latency, sleep duration, overall quality of life, and various domains, and the vitality subscale of the SF-36 [48].

All scales were transformed to 0 to 100 point scales for improved ability to compare effects and determine clinical significance. Toxicities were compared across treatment groups using chi-square testing.

Results

A total of 290 patients were randomized on this trial from October 21, 2005 to July 5, 2006. Patient flow is illustrated in the CONSORT diagram in Fig. 1. One hundred seventy-five completed the double blind 8-week phase of the study, with 39 to 48 patients per arm. Baseline characteristics, shown in Table 1, were well balanced with the randomization and stratification process. There were no statistically significant differences between the arms in these variables at baseline.

The primary endpoint of AUC activity interference (p=0.21) and secondary endpoint of usual fatigue (p=0.08) were not statistically significantly different between the collective ginseng arms versus placebo. However, planned subset analyses revealed a trend for greater positive effects with the highest dose of ginseng, 2,000 mg/day, over placebo, with the 2,000-mg arm having an effect size of over 50% times the standard deviation (Table 2).

The mean change from baseline for all secondary endpoints at weeks 4 and 8 are shown in Tables 3 and 4, respectively. The mean scores for the vitality subscale of the SF-36 demonstrate that there was a greater effect on fatigue in the highest two doses (1,000 and 2,000 mg/day) of ginseng. An increase in quality of life as measured by the overall physical, emotional, mental, and spiritual well-being scales were also evident in the higher dose levels. This trend is not evident for improvement in sleep as measured by the PSQI, where the placebo arm showed the most improvement in sleep.

There were no statistically significant differences between the study arms, in the numbers of patients who withdrew from the study (Fig. 1). Investigator-reported toxicities were spread fairly evenly throughout the treatment arms, including placebo, as is shown in Table 5. In addition, there were no statistically significant differences by arm for the following self-reported side effects evaluated per the symptom experience diary: nausea, dizziness, nervousness, headache, trouble falling asleep, and trouble staying asleep.

More than twice as many participants on the 1,000- and 2,000-mg/day doses of ginseng perceived a moderate to very much better improvement in fatigue at the end of the 8-week study period compared to those on placebo as shown in Fig. 2. In addition, more participants on the higher doses of ginseng were satisfied with their treatment for fatigue than those on placebo. These data were obtained while patients were still blinded to their treatment assignment.

Discussion

This pilot trial evaluated Wisconsin ginseng in a heterogeneous group of patients with cancer, ranging from those with localized resected disease to those with advanced incurable cancer. Overall, this study suggested that Wisconsin ginseng, at a dose of 750 mg/day, did not provide any benefit over that seen with a placebo. However, the two highest doses of Wisconsin ginseng (1,000 and 2,000 mg/day) did appear to decrease fatigue more than did a placebo, as measured by various scales of fatigue, vitality, and well being.

Perhaps the most compelling preliminary evidence from this current trial is that more than twice the patients who were on the higher doses of ginseng perceived a benefit for their fatigue, with 40% of patients who actually completed treatment with the 1,000- and 2,000-mg doses perceiving a moderate to very much better benefit as compared to 17% of the participants who were on the placebo arm. If the magnitude of benefit suggested by this pilot trial experience is observed in a larger more definitive trial, Wisconsin ginseng has the potential to help over 220,000 survivors based on conservative estimates from the literature that 30% to 60% of cancer survivors experience fatigue through at least 1 year past

diagnosis and the fact that there was an estimated 1.4 million people diagnosed with cancer in 2006.

In this study, there were no significant toxicities apparent in the active arms compared to the incidences seen in those taking the placebo. This was true despite the fact that many of these participants had advanced disease and were taking cytotoxic treatment for their disease.

It is curious that there was not a clear trend for a linear dose effect on all endpoints. Further study is needed to clarify this issue. The reason for the variability in this may be due to the challenges in measuring fatigue or may be due to the heterogeneous sample. However, the effect sizes seen are consistent with the potential for meaningful clinical activity and, coupled with low toxicity, suggest that this herb be studied further.

One of the difficulties in studying herbal or dietary supplements is the lack of regulation and hence standardization of product. Plant products are affected by growing conditions including climate, soil, fertilizers, and pesticides [21, 37]. In addition, the harvesting and processing of plants can alter their biologic viability. In any one crop of ginseng, the percentage of ginsenosides can vary and can be further influenced by the manufacturing process. There is evidence to suggest that the strength of effect of ginseng may be related to the percentage of ginsenosides [49]. This principal was supported in this study in that there was suggestion of a dose response that is that with more ginsenosides, a greater effect was observed.

The precise pharmacokinetic activity of Wisconsin ginseng is not yet known [21]. Ginsenosides, the active constituents of ginseng, are steroidal saponins. Therefore, each ginsenoside, as well as other nonginsenoside constituents of ginseng such as polysaccharides and peptides, may have more than one effect on any given tissue [21]. There are animal model studies suggesting that Wisconsin ginseng can directly affect the brain through activating intracellular steroid receptors [21], regulating gamma-aminobutyric acid (GABAergic) neurotransmission [50] and/or providing neuroprotection in various brain regions [51]. The ability to modulate important neurotransmitters, such as dopamine, noradrenalin, serotonin, and GABA may be one explanation for how ginseng may help cancer-related fatigue.

Thus, given the multiple potential effects of Wisconsin ginseng and the present, very preliminary, data suggesting that the higher doses studied may be helpful in cancer-related fatigue, it appears worthwhile to more clearly and definitively evaluate the benefits of the effects of Wisconsin ginseng in a larger, more definitive, placebo-controlled clinical trial. Such a trial is actively recruiting patients in the North Central Cancer Treatment Group.

Acknowledgments

This study was conducted as a collaborative trial of the North Central Cancer Treatment Group and Mayo Clinic and was supported in part by Public Health Service grants CA-25224, CA-37404, CA-63849, CA-63848, CA-35267, CA-35431, CA-35269, CA-52352, CA-37417, CA-35415, CA-35103, CA-35119, CA-35195, CA-35448, CA-60276, CA-35101, CA-35113, CA-35103, and CA-35090.

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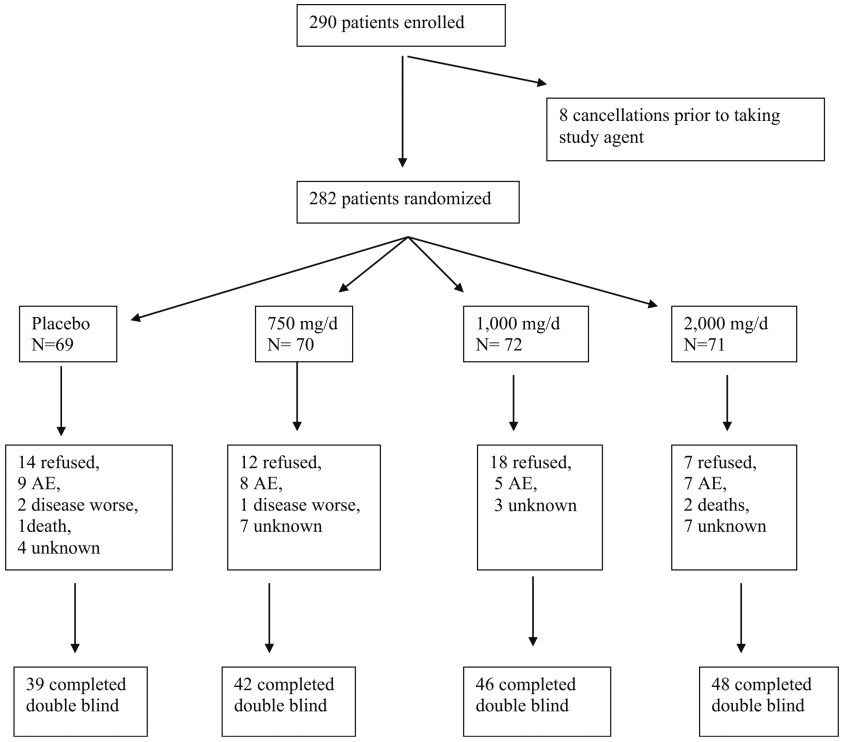

Fig. 1.
CONSORT diagram

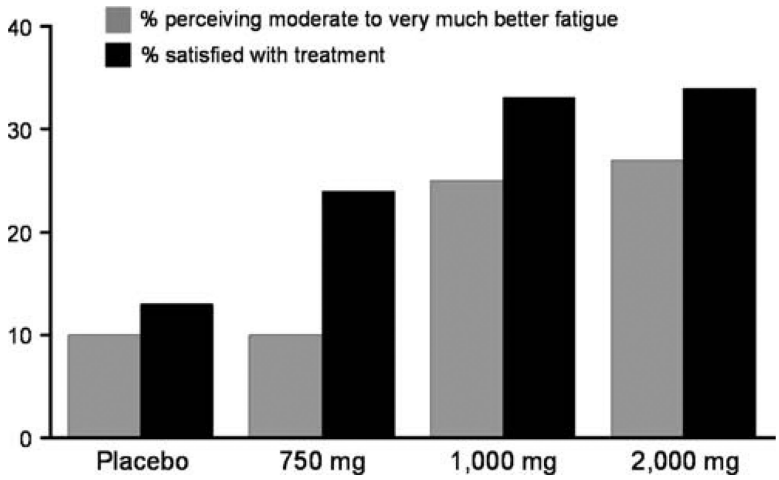

Fig. 2.
Perception of benefit

Table 1

Demographics

	Placebo (*n*=69)	750mg (*n*=70)	1,000mg (*n*=72)	2,000mg (*n*=71)	Total (*n*=282)
Age					
n	69	70	72	71	282
Mean (SD)	62 (13)	58 (11)	60 (12)	62 (11)	60 (12)
Race					
White	66 (96%)	64 (91%)	70 (97%)	67 (94%)	267 (95%)
Black or African American	2 (3%)	3 (4%)	0 (0%)	3 (4%)	8 (3%)
Native Hawaiian or other Pacific Islander	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (0.4%)
Asian	0 (0%)	1 (1%)	1 (1%)	1 (1%)	3 (1%)
American Indian or Alaska Native	1 (1%)	1 (1%)	0 (0%)	0 (0%)	2 (1%)
Gender					
Female	45 (65%)	46 (66%)	47 (65%)	48 (68%)	186 (66%)
Disease stage					
I/II	22 (32%)	21 (30%)	24 (33%)	23 (32%)	90 (32%)
III/IV	44 (64%)	45 (64%)	44 (61%)	42 (59%)	175 (62%)
Unknown	3 (4%)	4 (6%)	4 (6%)	6 (9%)	17 (6%)
Baseline Fatigue Score					
4-7	50 (73%)	50 (71%)	50 (70%)	51 (72%)	201 (71%)
8-10	19 (28%)	20 (29%)	22 (31%)	20 (28%)	81 (29%)
Current chemotherapy					
Yes	39 (57%)	39 (56%)	42 (58%)	40 (56%)	160 (57%)
Current radiation therapy					
Yes	12 (17%)	12 (17%)	14 (19%)	13 (18%)	51 (18%)
Type of cancer					
Breast	24 (35%)	29 (41%)	26 (36%)	30 (42%)	109 (39%)
Colon	7 (10%)	7 (10%)	5 (7%)	10 (14%)	29 (10%)
Lung	8 (12%)	8 (11%)	10 (14%)	9 (13%)	35 (12%)
Combination/unknown/other	30 (44%)	26 (37%)	31 (43%)	22 (31%)	109 (39%)
Menopausal status					
Premenopausal	7 (10%)	7 (10%)	7 (10%)	6 (9%)	27 (10%)
Postmenopausal	34 (49%)	35 (50%)	37 (51%)	39 (55%)	145 (51%)
Hysterectomy without oophorectomy	4 (6%)	4 (6%)	3 (4%)	3 (4%)	14 (5%)
Previous radiation therapy					
Yes	23 (50%)	16 (33%)	19 (39%)	14 (30%)	72 (38%)
Previous chemotherapy					
Yes	30 (65%)	32 (67%)	34 (69%)	28 (60%)	124 (65%)

Table 2

Efficacy results: mean BFI AUC with 95% confidence intervals at 8 weeks (higher numbers are better)

Endpoints	Placebo (95% CI)	750mg ginseng (95% CI)	ES (%)	1,000mg ginseng (95% CI)	ES (%)	2,000mg ginseng (95% CI)	ES (%)	*P* value, SD
Activity interference	460 (405-515)	467 (409-524)	4.2	480 (429-531)	12	551 (506-597)	56	0.08, 163
Usual fatigue	410 (360-460)	425 (373-177)	10	448 (408-488)	27	491 (449-532)	57	0.08, 143

95% CI 95% confidence interval, *ES* effect size, *SD* standard deviation

Table 3

Change from baseline at week 4 (higher numbers are better)

Endpoint	Placebo	750mg ginseng	ES (%)	1,000mg ginseng	ES (%)	2,000mg ginseng	ES (%)	*P* value, SD
Vitality subscale	4.1	3.5	−3	13.6	50	10.4	33	0.06, 19
Physical well being	−1.0	−0.5	2	2.2	13	7.3	33	0.23, 25
Emotional well being	−0.5	−0.5	0	0.0	2	6.9	34	0.12, 22
Mental well being	2.4	−1.0	−15	−6.1	−37	4.7	10	0.06, 23
Spiritual well being	0.0	−3.6	−17	−0.8	−2	5.1	24	0.05, 21
Social activity	4.6	−0.2	−20	8.2	15	2.2	−10	0.10, 24
Sleep	7.4	0.7	−39	5.3	−12	1.4	−51	0.61, 17

ES effect size, *SD* standard deviation of change from baseline

Table 4

Change from baseline at week 8 (higher numbers are better)

Endpoint	Placebo	750mg ginseng	ES (%)	1,000mg ginseng	ES (%)	2,000mg ginseng	ES (%)	*P* value, SD
Vitality subscale	7.3	7.8	3	14.6	37	10.5	17	0.39, 19
Physical well being	5.6	5.3	−1	12.0	26	6.5	4	0.65, 25
Emotional well being	3.6	3.0	−3	6.1	11	9.4	26	0.47, 22
Mental well being	4.4	3.3	−5	0.7	−16	7.5	13	0.55, 23
Spiritual well being	2.9	3.9	5	2.9	0	6.3	16	0.47, 21
Social activity	10.3	9.2	−4	16.1	26	9.4	−4	0.51, 24
Sleep	12.9	−1.4	−8.4	10.1	−16	2.9	−59	0.10, 17

ES effect size, *SD* standard deviation of change from baseline

Table 5

CTC graded toxicities—numbers of patients

Toxicity	Grade	Placebo	750mg	1,000mg	2,000mg	P value
Agitation	Grade 1 (*N*)	7	6	6	6	0.38
	Grade 2 (*N*)	0	1	0	0	
	Grade 3 (*N*)	0	0	0	1	
Anxiety	Grade 1 (*N*)	7	6	6	10	0.38
	Grade 2 (*N*)	2	5	3	1	
	Grade 3 (*N*)	0	0	0	1	
Insomnia	Grade1 (*N*)	28	22	19	19	0.57
	Grade 2 (*N*)	2	5	5	3	
	Grade 3 (*N*)	2	4	1	1	
Nausea	Grade1 (*N*)	13	14	17	16	0.64
	Grade 2 (*N*)	2	8	8	5	
	Grade 3 (*N*)	1	2	1	1	
Vomiting	Grade1 (*N*)	3	5	7	5	0.29
	Grade 2 (*N*)	0	5	5	4	
	Grade 3 (*N*)	2	2	1	1	