Menopause: The Journal of The North American Menopause Society
Vol. 16, No. 2, pp. 307-314
DOI: 10.1097/gme.0b013e31818572a0

Effects of *Hypericum perforatum* (St. John's wort) on hot flashes and quality of life in perimenopausal women: a randomized pilot trial

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Abstract

Objective: The aim of this pilot double-blind, randomized clinical trial, which initially targeted breast cancer survivors, was to obtain preliminary evidence of the effect of *Hypericum perforatum* extract (St. John's wort extract) compared with placebo on symptoms and quality of life of symptomatic perimenopausal women. We also assessed practical difficulties in recruiting women to such a trial.

Methods: Symptomatic perimenopausal women aged 40 to 65 years who experience hot flashes (three or more per day, Heart and Estrogen/Progestin Replacement Study scale) were randomly assigned to receive ethanolic St. John's wort extract (900 mg TID) or placebo. The women were asked to keep a daily diary during the week before randomization and during the week before the 3-month follow-up (primary outcome) to record hot flash frequency and intensity. A hot flash score (frequency × severity) was calculated. The Menopause-Specific Quality of Life questionnaire was used to assess menopause-specific quality of life.

Results: Forty-seven women were randomized. After 12 weeks of treatment, a nonsignificant difference favoring the St. John's wort group was observed in the daily hot flash frequency (St. John's wort, -2.3 ± 3.6; placebo, -1.0 ± 2.2; $P = 0.11$) and the hot flash score (-3.8 ± 8.3 and -1.8 ± 6.5, respectively; $P = 0.10$). After 3 months of treatment, compared with the placebo group, women in the St. John's wort group reported significantly better menopause-specific quality of life ($P = 0.01$) and significantly fewer sleep problems ($P = 0.05$).

Conclusions: *Hypericum perforatum* may improve quality of life in ways that are important to symptomatic perimenopausal women, but these results need to be confirmed by a larger clinical trial.

Key Words: *Hypericum perforatum* – Perimenopausal women – Hot flashes – Quality of life – Menopause-Specific Quality of Life questionnaire – Pilot trial.

Hot flashes can be a major problem in women with diminished ovarian function as a result of natural menopause or breast cancer therapy. Hot flashes are experienced by more than 50% of perimenopausal women, and among such women, 20% report that hot flashes negatively affect quality of life.

Received April 29, 2008; revised and accepted June 13, 2008.

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Fundings/support: Financial support for this study was provided by the Quebec Breast Cancer Foundation.

Financial disclosure: None reported.

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Women treated for breast cancer are an important subgroup of perimenopausal women for whom management of menopausal symptoms can be particularly problematic. Chemotherapy may induce or speed up ovarian failure. In addition, women who receive tamoxifen citrate, a specific modulator of estrogen receptors, report menopausal symptoms more frequently than do women who receive a placebo.[1,2] Estrogens are not a recommended approach to treating menopausal symptoms for women with breast cancer, whereas other therapies, already not optimal for healthy women, may be even more complicated for breast cancer survivors. Moreover, the extensive media attention paid to the results of the Women's Health Initiative trial incited many women and health professionals to consider using nonhormonal therapies, including natural health products (NHPs), rather than hormone therapy (HT). Among French-speaking women in Quebec, the total number of long-term and new HT users declined by 28% and 50%, respectively, after the publication of the Women's Health Initiative trial results.[3] Because of a lack of confidence in conventional therapies, an increasing number of perimenopausal women, both with and without breast cancer, are turning to nonmedicinal alternatives.[4]

The use of NHPs is a major phenomenon in Canada. Statistics Canada conducted a general health survey in 2000 to 2001 to evaluate NHP use among 11,424 adult Canadians 18 years or older.[5] More women than men reported using NHPs (11.5% vs 7.1%), whereas 50% more middle-aged or older Canadians than young adults used NHPs. Middle-aged women used NHPs the most, with St. John's wort being one of the 10 most popular. According to a Canadian descriptive survey of 251 breast cancer patients in a single Canadian cancer center, 43% used complementary and alternative medicine (CAMs), the most common being vitamins and herbal therapies.[6]

Information on the efficacy and safety of CAM for menopausal symptoms is limited. A recent systematic review published in 2006 evaluated 70 randomized controlled trials (RCTs) conducted among both healthy women and breast cancer survivors to assess the effectiveness of CAM therapies in the management of menopausal symptoms. The data from several trials were insufficient to provide support for CAM in the management of menopausal symptoms. Data on adverse effects and safety issues were also limited, and most trials lacked consistent or clear reporting.[7]

We were particularly interested in testing the efficacy of an NHP in the treatment of menopausal symptoms in the breast cancer survivor population. Although several other nonhormonal treatments for menopausal symptoms are available, they are not considered optimal for perimenopausal women who either have had breast cancer or have not. We first considered testing black cohosh, which is currently widely used by women, despite the fact that there is no evidence-based clinical proof of effect. However, in an abstract presented at the 94th Annual Meeting of the American Association for Cancer Research, black cohosh was reported to be associated with a greater likelihood of recurrence of lung metastases in 96 mice.[8] Although we were unable to obtain further information about this study, doubt about the safety of this product in the breast cancer population led us to assess other NHPs as potential treatments for menopausal symptoms in the survivor population.

Serotonin and norepinephrine reuptake inhibitors (SSRIs/SNRIs), which were originally developed to treat depression and are now used to treat menopausal symptoms in women with a contraindication for HT, were another possibility. However, the systematic review and meta-analysis by Nelson et al[9] suggested that they showed only modest efficacy and, indeed, that SSRIs were less efficacious than estrogens. In addition, cost and adverse effects may limit their use by many women.

In contrast, St. John's wort (*Hypericum perforatum*), an NHP that has been shown to be effective for mild to moderate depression in randomized trials and a recent meta-analysis, may have potential for treating menopausal symptoms in both breast cancer survivors and healthy women.[10] Among healthy women, St. John's wort is well tolerated and has a more favorable adverse effect profile than do many synthetic antidepressants. A large-scale surveillance study of 14,245 patients indicated that the frequency of adverse effects associated with St. John's wort was 10 times lower than that with synthetic antidepressants.

Although the mechanism of action of St. John's wort is not known, hypericin and hyperforin, the two main active ingredients, may be responsible for the antidepressant effect. Based on the findings of studies using cellular and animal models, the effect of St. John's wort may be partly due to the inhibition of monoamine oxidase and the recapture of serotonin. Hyperforin may also play a role by inhibiting interleukin-6, enhancing the production of cortisol, which is found in higher concentrations in the blood of persons with depression.[11]

An open-label study of 111 perimenopausal symptomatic women conducted without controls investigated the ability of St. John's wort to relieve psychological and vegetative symptoms.[12] The women, who were not receiving HT, received a standardized extract of St. John's wort for 12 weeks (900 mg *H perforatum*, three times daily). Outcomes were evaluated using the Menopause Rating Scale and the Clinical Global Impression Scale. Substantial improvements in menopausal symptoms and psychological, psychosomatic, and sexual scores were observed after 5 and 12 weeks of beginning St. John's wort.

Although promising, major methodological limitations of this clinical study make it impossible to draw any definitive conclusions as to the efficacy of St. John's wort. However, we believe that the results support the need for a double-blind randomized controlled clinical trial with a large sample and sufficient follow-up to determine the efficacy of St. John's wort for treating menopausal symptoms among symptomatic women. We conducted a pilot randomized controlled trial to obtain the information needed for the design and organization of such a large-scale trial. In particular, we were interested in identifying potential difficulties in recruiting breast cancer survivors, a population for whom treatment of menopausal symptoms is more limited because HT is not recommended in this population.

METHODS

Participants

This trial targeted perimenopausal women with menopausal symptoms of sufficient severity for them to request therapeutic intervention. Women aged 40 to 65 years were recruited from October 2003 to September 2005 from the general population through advertising in a local newspaper, flyers posted in clinics treating perimenopausal women and in a breast cancer center, and, finally, by clinicians involved in breast cancer. The study population was initially limited to women who had had breast cancer, but we found that only a small percentage of such women met trial inclusion criteria. One of the most important reasons for ineligibility was that more than 50% of the breast cancer survivors who expressed interest in participating were already using antidepressants. After 3 months, the steering committee decided to also

extend the pilot trial to healthy perimenopausal women who had never had breast cancer.

Women eligible for the pilot trial were the following: those who said they had hot flashes three or more times a day in response to the Heart and Estrogen/Progestin Replacement Study scale question "During the past week, including today, did hot flashes bother you or interfere with your life?",[13] those who had serum follicle-stimulating hormone (FSH) concentrations of 40 mIU/mL or more, those who had had at least 6 months of amenorrhea in the year preceding study entry, and those who had a normal mammogram in the preceding 2 years.

Women were excluded if they had used St. John's wort or antidepressants within the preceding 6 months, ingested phytoestrogens from soybean or soy product food supplements (soy flour, soy milk, and flax seeds) on a regular basis, had received HT (systemic HT or local estrogens) in the preceding 3 months, had a history of recurrent or metastatic cancer, had uncontrolled hyperthyroidism or hypothyroidism or a severe psychiatric disorder, used or planned to use other agents for treating hot flashes (eg, clonidine, megestrol acetate, venlafaxine, belladonna alkaloids), or used other oral herbal therapies or medications (eg, monoamine oxidase inhibitors) that could cause potential interactions with St. John's wort. All participants provided written informed consent. The human research review boards of Hôpital St. François d'Assise, Centre Hospitalier Universitaire du Québec and Hôpital St.-Sacrement, Centre Hospitalier Affilié Universitaire du Québec approved the protocol.

Protocol

This pilot trial was randomized, double blind, and placebo controlled and included 3 months of follow-up after the start of treatment or placebo. Randomization was computer generated by the Clinical Unit of the Hôpital St. François d'Assise Research Centre.

The trial included three visits to the Centre Menopause Québec:

1. A first visit (visit 1) at which the trial was presented, risks and benefits were described, and informed consent was obtained;
2. The baseline visit 1 month later (visit 2) during which self-report measurements on menopausal symptoms were completed relative to the preceding 7 days and randomization was performed for those women shown to meet the final eligibility criterion, namely reporting three or more hot flashes daily in the preceding week;
3. A third visit 3 months after randomization and the start of treatment or placebo (visit 3), during which outcome measurements were collected.

At visit 1, in addition to obtaining written informed consent, several other measurements were obtained. The research nurse measured the weight, height, waist circumference, and blood pressure of the women using a standardized protocol. Women also underwent a physical examination, and a 10-mL blood sample was taken to measure hormone levels (thyroid-stimulating hormone, 17β-estradiol, luteinizing hormone and FSH). These latter measures were also repeated at visits 2 and 3. The analyses were performed at the Clinical Biochemistry Laboratory of Hôpital St. François d'Assise. As participants were required to abstain from using HT or any other medications for menopausal symptoms, including clonidine, bellergal, and vitamin E, during the trial, the research nurse verified the use and dose of such medications at this and subsequent visits. Finally, a food frequency questionnaire was used to evaluate the dietary intake of phytoestrogens (lignans and isoflavones) in the preceding month.

At visit 2, mammogram and/or gynecological examination, including Papanicolaou tests, were performed if these examinations had last been performed more than 2 years earlier. Women with more recent examinations provided copies of the results, which were added to their medical files. At this visit and visit 3, participants self-administered a short questionnaire on sociodemographic characteristics, regular physical exercise, calcium supplementation, tobacco and alcohol consumption, and quality of life.

The main study outcome, frequency and intensity of hot flashes, was recorded by the women, who completed a daily hot flash diary every day during 7 days preceding visit 2 and again for the 7 days preceding visit 3. In the diary, they recorded the number of hot flashes and the intensity of each hot flash (scored as mild, moderate, severe, or very severe). During the week preceding visit 3 (3-month follow-up), women were also asked to record any adverse reactions or adverse effects using the questions for this purpose included as part of the diary.

TABLE 1. *Baseline characteristics*

	St. John's wort (n = 20)	Placebo (n = 22)
Age, y	53.4 ± 4.8	54.0 ± 5.8
Breast cancer survivor		
No	9 (45.0)	7 (31.8)
Yes	11 (55.0)	15 (68.2)
With tamoxifen	6 (30.0)	9 (40.9)
Without tamoxifen	5 (25.0)	6 (27.3)
Daily no. of hot flashes in preceding week	6.9 ± 4.5	7.7 ± 4.5
Daily hot flash score	11.5 ± 10.0	14.3 ± 9.3
Body mass index, kg/m^2	26.4 ± 3.9	26.1 ± 3.6
MENQOL score	3.6 ± 1.2	3.8 ± 1.0
SF-12		
PCS	46.7 ± 5.3	46.6 ± 4.8
MCS	38.7 ± 4.5	40.5 ± 4.6
General fatigue	1.5 ± 0.3	1.7 ± 0.4
Sleeping problem score	1.7 ± 0.8	1.7 ± 0.6
FSH IU/L	73.6 ± 39.8	57.5 ± 30.4
Time since onset of menopause		
≤5 y	10 (50.0)	12 (54.6)
>5 y	10 (50.0)	10 (45.5)
Prior hysterectomy	5 (25.0)	8 (36.4)
Smoker	2 (10.0)	2 (9.1)
Physical activity ≥3 times/week	9 (45.0)	15 (68.2)

Values are presented as mean ± SD or n (%). MENQOL, Menopause-Specific Quality of Life; PCS, Physical Component Summary; MCS, Mental Component Summary; FSH, follicle-stimulating hormone.

Women were randomly assigned to receive either 900 mg of St. John's wort (300 mg TID) or placebo (TID) for 3 months. All participants, staff, investigators, and statisticians were blinded to the treatment assignments for the duration of the study. Compliance with treatment was assessed in two ways. First, participants were asked to record their daily intake of tablets on diary cards. Second, they were asked to return unused tablets at the follow-up visit.

Menopause-specific quality of life was evaluated using the Menopause-Specific Quality of Life (MENQOL) questionnaire. The MENQOL[14] is composed of 30 questions with a six-point scale used to rate the severity of the symptoms experienced in the preceding month. The questions cover four domains (vasomotor, physical, psychosocial, and sexual). The domains are scored from 0 to 8, with a difference of 0.5 being the smallest clinically important change.[15-17] Two MENQOL items (hot flashes and night sweats) from the vasomotor domain were also used as independent indicators of outcome. Higher MENQOL scores indicate worse outcomes. The internal consistencies (α coefficient) of these three domain scores at each administration were 0.80 or greater. The Medical Outcomes Study SF-12, which focuses on overall health-related physical and mental health,[18] was also used as a generic measure of quality of life to determine how comparable the groups were at the start of the study. Higher scores on the SF-12 physical and mental component summaries (PCS-12 and MCS-12, respectively) indicate better health-related quality of life. General fatigue was evaluated by four questions from the 15-item Multidimensional Fatigue Inventory, which has been validated in Canadian French (internal consistencies ≥0.90 in these women).[19] Sleep problems were estimated with the Sleep Problem Scale ($\alpha \geq 0.79$).[20]

St. John's wort

Colba Laboratories Inc (St. Laurent, QC, Canada) donated the St. John's wort and placebo tablets. The tablets were sent to the Hôpital St.-François d'Assise pharmacy. The pharmacist was responsible for both quality assurance of the tablets and their secure distribution for the trial. Participants took either one St. John's wort tablet (lot 040304-02C) containing 300 mg dry *H perforatum* extract standardized to 0.3% hypericin extracted in 50% ethanol or one placebo tablet, three times a day. The tablets were taken at mealtime. The hypericin was extracted and quantified in the laboratory of Dr Boulanger at the horticultural research center of Université Laval by high-performance liquid chromatography analyses, a method similar to that developed by the Institute for Nutraceutical Advancement (Ann Arbor, MI) (http://www.nsf.org/business/ina/index.asp?program=INA). A 3-month supply of tablets was provided to each participant at visit 2 (the randomization visit).

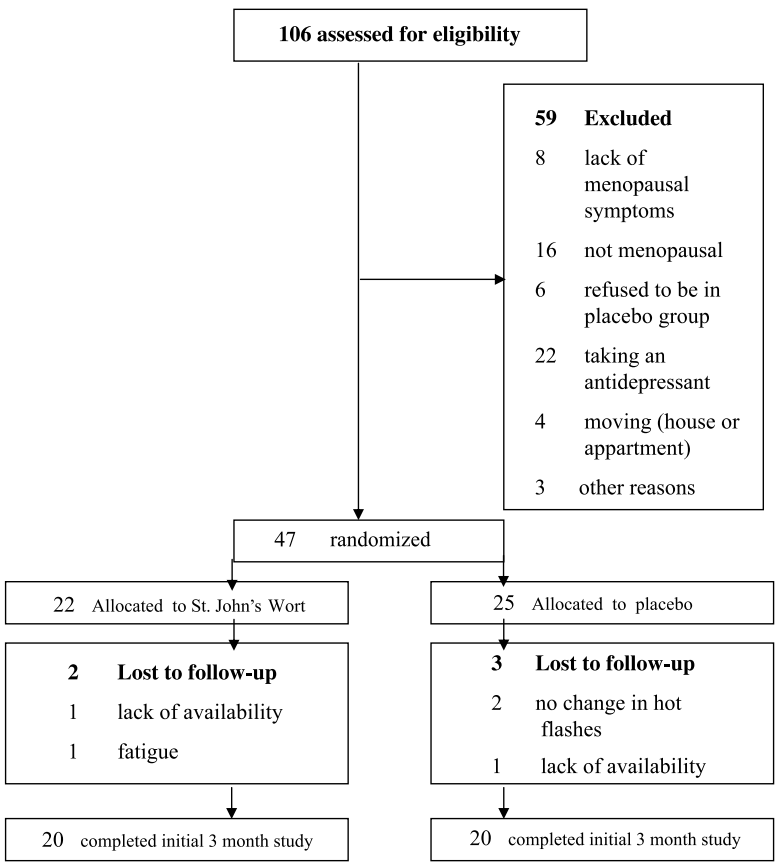

FIG. 1. Patient flow diagram.

TABLE 2. *Mean ± SD and paired differences in the number of hot flashes and the hot flash scores*

Outcome	Baseline	Month 3	Difference	Between-group effect size	*P*	
					Within groups, baseline vs month 3	Between groups, St. John's wort vs placebo
No. of hot flashes per day in preceding week						
St. John's wort (n = 20)	6.9 ± 4.5	4.6 ± 4.1	−2.3 ± 3.6	−0.53	0.01	0.11
Placebo (n = 22)	7.7 ± 4.5	6.7 ± 4.0	−1.0 ± 2.2		0.04	
Hot flash score per day						
St. John's wort (n = 20)	11.5 ± 10.0	7.7 ± 8.4	−3.8 ± 8.3	−0.53	0.06	0.10
Placebo (n = 22)	14.3 ± 9.3	12.5 ± 0.9	−1.8 ± 6.5		0.21	

Analyses

Because breast cancer survivors were very comparable with women without breast cancer for all of the principal baseline characteristics, all subsequent analyses were done only without stratification for whether participants had had breast cancer (Table 1). The severity and the frequency of hot flashes were analyzed separately. Baseline hot flash values (sum of the number of hot flashes during 1 week) were calculated based on the frequencies recorded in the 7 days preceding visit 2, whereas the 3-month values were calculated based on the frequencies recorded in the 7 days before visit 3 (last week of the treatment period). The severity of the hot flashes was calculated by dividing the sum of the number of hot flashes during the week weighted by severity [(1 × number of mild hot flashes) + (2 × number of moderate hot flashes) + (3 × number of severe hot flashes) + (4 × number of very severe hot flashes)] by the total number of hot flashes. There were no missing data for these variables.

The analyses were based on the intention-to-treat principle. The within-group differences comparing baseline and 3-month measures were calculated using the paired *t* test. The difference between the placebo and St. John's wort groups at 3 months was calculated using Student's *t* test. For descriptive purposes, means were used to describe the average (±SD) scores for the main outcomes and each quality-of-life domain according to time and treatment group. Intragroup and intergroup differences were computed as *d*, the standardized mean difference, or effect size (ES).[21] Effect sizes of 0.20 to 0.49 are generally regarded as small; 0.50 to 0.79 as medium; and 0.80 or more as large.[22]

We used SAS version 9 (SAS Institute, Cary, NC) for the statistical analyses. Two-sided $P \leq 0.05$ was considered statistically significant.

RESULTS

Participant flow

Between October 2003 and September 2005, 106 women were assessed for eligibility, and 59 were excluded (Fig. 1). The principal reasons for exclusion included taking antidepressants (n = 22), not being perimenopausal (n = 16), lacking menopausal symptoms (n = 8), not interested in being in the placebo group (n = 6), moving (n = 4), and other reasons (n = 3). Forty-seven women were randomized, 22 into the St. John's wort group and 25 into the placebo group.

Compliance and feasibility

Overall, compliance with the study protocol was very good, supporting the feasibility of a full-scale trial. The self-report medication diary indicated that 90% of the women in both arms took at least 75% of the medication. Of the 47 randomized women, only 5 dropped out of the study before the 3-month follow-up, 2 in the St. John's wort group and 3 in the placebo group. The reasons for dropping out were no change in hot flashes (n = 2), lack of availability (n = 2), and fatigue (n = 1). Forty-two women completed the 3 months of treatment (or placebo), 20 in the St. John's wort group and 22 in the placebo group.

TABLE 3. *Means ± SD at baseline and month 3 and the paired differences in the four Menopause-Specific Quality of Life domains*

Score	Baseline	Month 3	Difference	Between-group effect size	*P*	
					Within groups, baseline vs month 3	Between groups, St. John's wort vs placebo
Menopause-specific quality of life						
St. John's wort (n = 20)	3.6 ± 1.2	2.9 ± 1.0	−0.7 ± 1.0	−0.80	0.003	0.01
Placebo (n = 22)	3.8 ± 1.0	3.7 ± 1.0	−0.1 ± 0.9		0.66	
Vasomotor domain						
St. John's wort (n = 20)	5.0 ± 1.8	4.2 ± 1.7	−0.8 ± 1.8	−0.69	0.06	0.03
Placebo (n = 22)	5.5 ± 1.3	5.3 ± 1.6	−0.2 ± 1.2		0.42	
Physical domain						
St. John's wort (n = 20)	3.5 ± 1.5	2.8 ± 1.1	−0.7 ± 0.9	−0.57	0.003	0.06
Placebo (n = 22)	3.7 ± 1.3	3.6 ± 1.4	−0.1 ± 1.0		0.56	
Psychosocial domain						
St. John's wort (n = 20)	2.9 ± 1.4	2.2 ± 1.1	−0.8 ± 1.4	−0.75	0.02	0.01
Placebo (n = 22)	3.2 ± 1.4	3.1 ± 1.2	−0.1 ± 1.0		0.69	
Sexual life domain						
St. John's wort (n = 20)	3.2 ± 2.0	2.4 ± 1.4	−0.8 ± 1.8	−0.10	0.07	0.69
Placebo (n = 22)	3.0 ± 2.2	2.6 ± 2.0	−0.3 ± 2.2		0.4	

TABLE 4. *Means ± SD at baseline and month 3 and the paired differences in sleep problems and general fatigue*

Variable	Baseline	Month 3	Difference	Between-group effect size	*P*	
					Within groups, baseline vs month 3	Between groups, St. John's wort vs placebo
Sleep problems						
St. John's wort (n = 20)	1.7 ± 0.8	1.2 ± 0.8	0.5 ± 0.8	−0.67	0.009	0.05
Placebo (n = 22)	1.7 ± 0.6	1.6 ± 0.6	0.07 ± 0.58		0.589	
General fatigue						
St. John's wort (n = 20)	1.5 ± 0.3	1.5 ± 0.3	0.01 ± 0.25	−0.05	0.83	0.16
Placebo (n = 22)	1.7 ± 0.4	1.7 ± 0.3	0.01 ± 0.39		0.89	

Description of sample

There were no significant baseline differences between the two groups in terms of main outcomes, frequency and severity of hot flashes, age, body mass index, years since menopause, number of women with a prior hysterectomy and/or breast cancer history, general fatigue, sleep disorder, or PCS-12 and MCS-12 scores (Table 1). No significant differences were reported for mean FSH levels ($P = 0.15$) or for the proportions of women engaging in regular physical activity ($P = 0.13$).

Effect of St. John's wort on hot flash frequency and scores

Although the differences between the two groups at the follow-up visit (visit 3) did not reach statistical significance, the St. John's wort group reported a decrease of at least two hot flashes on average (−2.3 ± 3.6) compared with a decrease of one hot flash in the placebo group (−1.0 ± 2.2; $P = 0.11$) and an almost four-point drop on average hot flash score, which incorporated frequency and intensity (−3.8 ± 8.3), compared with almost two points in the placebo group (−1.8 ± 6.5; $P = 0.10$) (Table 2). The effect size of St. John's wort on hot flash frequency and hot flash score was 0.53. With use of a 30% improvement in the number of hot flashes as a clinical criterion, 50.0% of the women in the St. John's wort group had such an improvement compared with 22.7% in the placebo group ($P = 0.07$).

Effect of St. John's wort on MENQOL scores

Among women who took St. John's wort, a clinically significant reduction in mean MENQOL scores was seen at 3 months compared with baseline for the global menopause-specific quality of life and for all four domains of the MENQOL questionnaire, and most of these declines were statistically significant (Table 3). Only small and statistically insignificant changes for these variables were observed for the placebo group. The mean differences between the groups were statistically significant or almost so for global quality of life ($P = 0.01$) and for three of the four MENQOL domains, vasomotor ($P = 0.03$), physical ($P = 0.06$), and psychosocial ($P = 0.01$), but not for the sexual life domain ($P = 0.69$).

TABLE 5. *Adverse events reported during the 3-month treatment period*

Type of adverse event	No. of patients with adverse events[a]	
	St. John's wort 900 mg/d (n = 20)	Placebo (n = 22)
All adverse events	11	18
Loss of appetite	1	0
Somnolence (lethargy)	4	3
Nausea (sickness)	1	4
Dizziness	1	2
Dry mouth	0	7
Constipation	5	4
Other adverse events	3	5

[a]Women may have experienced more than one adverse event.

Effect of St. John's wort on sleep problem scores and general fatigue

A statistically significant reduction in mean sleep problem scores was observed from baseline to month 3 among those in the treatment group but not those in the placebo group (St. John's wort, −0.5 ± 0.8, $P = 0.009$; placebo, −0.07 ± 0.58, $P = 0.59$), with the result that sleep problems had decreased borderline significantly at 3 months in the treatment group compared with the placebo group ($P = 0.05$) (Table 4). However, there were no reductions over time in either group with respect to general fatigue.

Safety and tolerance

Adverse events reported to have occurred during the treatment phase are listed in Table 5. The most frequently reported adverse events were constipation, which affected five of the women in the St. John's wort group and four of the women in the placebo group. Adverse events such as fatigue, dry mouth, and abnormal sweating were observed more often in the placebo group than in the St. John's wort group.

No noteworthy changes were observed in vital signs or physical condition as measured by the nurse.

DISCUSSION

Our results indicate that ingesting an *H perforatum* ethanolic extract for 12 weeks resulted in an apparent reduction in the mean number of hot flashes and hot flash scores compared with placebo. Furthermore, a 30% improvement in the number of hot flashes was reported by 50% of the women in the St. John's wort group but only 23% in the placebo group. However, because the size of the cohort in our pilot study was small and the variability of hot flash frequency and hot flash intensity scores was high, it was difficult to detect statistically significant differences between

the two groups. Our study included women with breast cancer, but these women were not analyzed separately because the two groups were very similar at baseline (data not shown) and the sizes of each group were too small to allow analyses stratified by whether the participants were breast cancer survivors.

Quality of life is an essential component in evaluating the overall effect and benefits of treatments for perimenopausal women. In the present study, the difference between the two treatment groups was statistically significant for global menopause-specific quality of life and for three of the four MENQOL domains (vasomotor, physical, and psychosocial). We analyzed our data in two different ways and observed a significant clinical effect on quality of life with St. John's wort with both approaches. According to Whelan et al,[15] Guyatt et al,[23] and Wyrwich et al,[17] the smallest clinically important change is a score difference of 0.5 in each MENQOL domain. In our study, we observed a difference in within-group score change over time that exceeded this 0.5 criterion for global menopause-specific quality of life (0.7 point) and the vasomotor (0.8 point), physical (0.7 point), and psychosocial (0.8 point) domains. However, there was no significant or clinically relevant difference in the score for the sexual life domain. This might be due to the fact that most of the women did not have a sexual partner. We also assessed the clinical significance of the reductions in symptoms and the improvement in quality of life by assessing the effect size. Except for the sexual life domain, all reductions were equal to or above the threshold for a medium (or 0.53) effect size, suggesting that St. John's wort had a beneficial clinical effect.

Our results suggest that sleep disturbance, a common and distressing symptom in perimenopausal women, may be alleviated by St. John's wort. In fact, we observed a statistically borderline significant reduction in the mean sleep problem score in the St. John's wort group compared with the placebo group (ES, 0.67).

The improvement in menopause-specific quality of life in our study is in keeping with the findings of 37 of 39 clinical trials that showed that St. John's wort is superior to a placebo or is equivalent to antidepressant medications for mild to moderate depression and has minimal adverse effects compared with some antidepressants.[24] However, most studies were conducted on populations that were not perimenopausal. We postulate that St. John's wort can modulate depression, mood, and/or quality of life, thus altering the perception of hot flashes. However, we observed no correlation between the global menopause-specific quality-of-life score and hot flash frequency (data not shown).

Our study has several strengths. This pilot trial was rigorously conducted and was randomized, double blind, and placebo controlled. It specifically evaluated the effect of St. John's wort in a perimenopausal population, a population that includes women both with and without a past history of breast cancer. This is of interest because breast cancer survivors are a group for whom treatment of menopausal symptoms can be particularly problematic. We investigated a wide range of possible outcomes of treatment with St. John's wort. The dose in the 300-mg tablet of hypericum extract standardized to 0.3% hypericin extracted in 50% ethanol three times a day used in our trial is similar to that used in most published studies. Finally, to ensure safety and reliability of the trial and given the wide variability in herbal medicinal products available on the market and their variable quality and content, we first analyzed the content of the tablets used in the trial to make sure that they contained 0.3% hypericin.

Only two other clinical studies have assessed the effects of St.-John's wort in perimenopausal women. In one, an open-label study by Grube et al[12] published in 1999, the effects on menopausal symptoms, sexual well-being, and psychological symptoms were assessed. However, this was a non–placebo controlled clinical study involving 111 premenopausal or postmenopausal women with menopausal symptoms who received one tablet of St. John's wort three times a day for 12 weeks. The authors reported that psychological and vasomotor symptoms had improved. However, because the study lacked methodological rigor and had major limitations, the results must be interpreted with caution. In the other study, Uebelhack et al[25] investigated a combination of St. John's wort and black cohosh for the treatment of menopausal symptoms (hot flashes, irritability, minor depression, mood swings, and insomnia) with a cohort of 911 premenopausal, perimenopausal, and postmenopausal women with psychological disorders. The authors reported that this combination of botanicals had a synergistic effect, but the specific effect of St. John's wort could not be isolated.

No pharmacological or nonpharmacological treatments currently available for the treatment of menopausal symptoms are as efficacious as HT. Although the systematic review and meta-analysis of double-blind randomized controlled trials of nonhormonal therapies by Nelson et al[9] provide some evidence for a modest effect by SSRIs on reducing the frequency and intensity of hot flashes, they are less effective than HT. The combined estimate of the meta-analysis indicated that SSRIs lead to a reduction of approximately one hot flash a day compared with the placebo. The study populations may not be similar and direct comparisons with our results cannot be made, but interestingly, the amplitude of the effect observed in our pilot trial is very similar to that reported by Nelson et al.

Despite their modest effect, SSRIs and/or SNRIs are currently regarded as the most promising nonhormonal treatment for hot flashes in women with breast cancer. However, we think that it is important to keep in mind that the long-term effects of SSRIs and/or SNRIs may ultimately prevent their use by many survivors. A study by Jin et al[26] raised concerns about the possible interaction between SSRIs and tamoxifen because they inhibit the cytochrome P450 enzymes that play a major role in converting tamoxifen to its active metabolites. Moreover, a recent general community cross-sectional health survey with a cohort of 25,315 patients suggested that participants taking SSRIs are more likely to be obese and have

hypercholesterolemia, factors that are both known to be associated with a higher risk of breast cancer, and association of these factors with risk of recurrence is also being investigated.[27] These observations raise concerns about using SSRIs for breast cancer survivors and support the importance of a large-scale trial using St. John's wort with breast cancer survivors included as part of the trial. We note, however, that we had trouble recruiting women for our pilot trial because of frequent use of antidepressants generally and particularly by breast cancer survivors. Of the 106 women assessed for eligibility, 59 did not meet the inclusion criteria; fully one third of these (22 of 59) were excluded because they were taking antidepressants, and 20 of 22 breast cancer survivors were excluded for this reason. As we use more aromatase inhibitors up front instead of tamoxifen for adjuvant treatment of early breast cancer and because there does not seem be an interaction between antidepressant and aromatase inhibitors, breast cancer survivors might use antidepressant more often for hot flash symptoms in the future. Given this observed prevalence of antidepressant use, recruitment for such a trial would require a large number of collaborating centers.

Finally, although we observed changes in most menopausal symptoms that were consistent with St. John's wort having a beneficial clinical effect using 900 mg daily of dry *H perforatum* extract, studies seem to now indicate that it may be hyperforin that inhibits the reuptake of monoamines and may thus be the pharmacologically active component, and not hypericin as was originally thought.[11]

CONCLUSIONS

In conclusion, a large clinical trial is required to determine the true efficacy of a well-characterized *H perforatum* extract in the treatment of symptomatic perimenopausal women with and without a past history of breast cancer.

Acknowledgments: The authors thank the many individuals who contributed to this research project, especially the participants. Special thanks are extended to the physicians at the Centre des Maladies du Sein Deschènes-Fabia, Lucile Turcot-Lemay, for her statistical support, and the nurses who assisted with the study. We are grateful to Colba Laboratories Inc for donating the *H perforatum* extract and the placebo and to the Quebec Breast Cancer Foundation for providing financial support.

REFERENCES

1. Israel D, Youngkin EQ. Herbal therapies for perimenopausal and menopausal complaints. *Pharmacotherapy* 1997;17:970-984.
2. Land SR, Wickerham DL, Costantino JP, et al. Patient-reported symptoms and quality of life during treatment with tamoxifen or raloxifene for breast cancer prevention: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. *JAMA* 2006;295:2742-2751.
3. Guay MP, Dragomir A, Pilon D, Moride Y, Perreault S. Changes in pattern of use, clinical characteristics and persistence rate of hormone replacement therapy among postmenopausal women after the WHI publication. *Pharmacoepidemiol Drug Saf* 2007;16:17-27.
4. Wright J. *Use and Dangers of Alternative Medicines and Practices*. Vancouver, BC, Canada: Angus Reid Group Inc, CTV/Angus Reid Group Poll 1997.
5. Singh SR, Levine MA. Natural health product use in Canada: analysis of the National Population Health Survey. *Can J Clin Pharmacol* 2006;13:e240-e250.
6. Rakovitch E, Pignol JP, Chartier C, et al. Complementary and alternative medicine use is associated with an increased perception of breast cancer risk and death. *Breast Cancer Res Treat* 2005; 90:139-148.
7. Nedrow A, Miller J, Walker M, Nygren P, Huffman LH, Nelson HD. Complementary and alternative therapies for the management of menopause-related symptoms: a systematic evidence review. *Arch Intern Med* 2006;166:1453-1465.
8. Davis VL, Jayo MJ, Hardy ML, et al. Effects of black cohosh on mammary tumor development and progression in MMTV-neutransgenic mice. Paper presented at: 94th Annual Meeting of the American Association for Cancer Research; June 11-14, 2003; Washington, DC. Abstract 44.
9. Nelson HD, Vesco KK, Haney E, et al. Nonhormonal therapies for menopausal hot flashes: systematic review and meta-analysis. *JAMA* 2006;295:2057-2071.
10. Schulz V. Safety of St. John's wort extract compared to synthetic antidepressants. *Phytomedicine* 2006;13:199-204.
11. Müller WE. Current St. John's wort research from mode of action to clinical efficacy. *Pharmacol Res* 2003;47:101-109.
12. Grube B, Walper A, Wheatley D. St. John's wort extract: efficacy for menopausal symptoms of psychological origin. *Adv Ther* 1999; 16:177-186.
13. Hlatky MA, Boothroyd D, Vittinghoff E, Sharp P, Whooley MA. Quality-of-life and depressive symptoms in postmenopausal women after receiving hormone therapy: results from the Heart and Estrogen/Progestin Replacement Study (HERS) trial. *JAMA* 2002;287:591-597.
14. Hilditch JR, Lewis J, Peter A, et al. A menopause-specific quality of life questionnaire: development and psychometric properties. *Maturitas* 1996;24:161-175.
15. Whelan TJ, Goss PE, Ingle JN, et al. Assessment of quality of life in MA.17: a randomized, placebo-controlled trial of letrozole after 5 years of tamoxifen in postmenopausal women. *J Clin Oncol* 2005; 23:6931-6940.
16. Di Maio M, Perrone F. Quality of life in elderly patients with cancer. *Health Qual Life Outcomes* 2003;1:44.
17. Wyrwich KW, Fihn SD, Tierney WM, Kroenke K, Babu AN, Wolinsky FD. Clinically important changes in health-related quality of life for patients with chronic obstructive pulmonary disease: an expert consensus panel report. *J Gen Intern Med* 2003;18:196-202.
18. Gandek B, Ware JE, Aaronson NK, et al. Cross-validation of item selection and scoring for the SF-12 Health Survey in nine countries: results from the IQOLA Project. International Quality of Life Assessment. *J Clin Epidemiol* 1998;51:1171-1178.
19. Fillion L, Gelinas C, Simard S, Savard J, Gagnon P. Validation evidence for the French Canadian adaptation of the Multidimensional Fatigue Inventory as a measure of cancer-related fatigue. *Cancer Nurs* 2003; 26:143-154.
20. Jenkins CD, Stanton BA, Niemcryk SJ, Rose RM. A scale for the estimation of sleep problems in clinical research. *J Clin Epidemiol* 1988;41:313-321.
21. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. New York, NY: Academic Press, 1969.
22. Maunsell E, Pogany L, Barrera M, Shaw AK, Speechley KN. Quality of life among long-term adolescent and adult survivors of childhood cancer. *J Clin Oncol* 2006;24:2527-2535.
23. Guyatt GH, Osoba D, Wu AW, Wyrwich KW, Norman GR. Methods to explain the clinical significance of health status measures. *Mayo Clin Proc* 2002;77:371-383.
24. Clement K, Covertson CR, Johnson MJ, Dearing K. St. John's wort and the treatment of mild to moderate depression: a systematic review. *Holist Nurs Pract* 2006;20:197-203.
25. Uebelhack R, Blohmer JU, Graubaum HJ, Busch R, Gruenwald J, Wernecke KD. Black cohosh and St. John's wort for climacteric complaints: a randomized trial. *Obstet Gynecol* 2006;107:247-255.
26. Jin Y, Desta Z, Stearns V, et al. CYP2D6 genotype, antidepressant use, and tamoxifen metabolism during adjuvant breast cancer treatment. *J Natl Cancer Inst* 2005;97:30-39.
27. Raeder MB, Bjelland I, Emil Vollset S, Steen VM. Obesity, dyslipidemia, and diabetes with selective serotonin reuptake inhibitors: the Hordaland Health Study. *J Clin Psychiatry* 2006;67:1974-1982.

