CLIMACTERIC 2009;12:310–318

Non-hormonal treatment of hot flushes in breast cancer survivors: gabapentin vs. vitamin E

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Key words: HOT FLUSHES, MENOPAUSAL SYMPTOMS, BREAST CANCER SURVIVORS, GABAPENTIN, VITAMIN E

ABSTRACT

Objectives To assess the efficacy and the tolerability of gabapentin 900 mg/day compared to vitamin E for the control of vasomotor symptoms in 115 women with breast cancer. The secondary objective was to evaluate the effect of the treatments on the quality of sleep and other aspects of the quality of life.

Methods A hot flush diary was completed daily; sleep quality and other menopausal symptoms were assessed with the Pittsburgh Sleep Quality Index (PSQI), the Menopause Rating Scale (MRS) and the SF-36 Health Survey.

Results The prescribed treatment with gabapentin was never started by 28.3% of the patients and was interrupted by 28% for side-effects (dizziness and somnolence). Among the women allocated to vitamin E, 16.36% never started therapy and 34.78% dropped out because of inefficacy. Hot flush frequency and score decreased by 57.05% and 66.87%, respectively ($p < 0.05$) in the gabapentin group. The effect of vitamin E was fairly small: hot flush frequency and score were reduced by 10.02% and 7.28%, respectively ($p > 0.05$). Gabapentin was also particularly effective in improving the quality of sleep (PSQI score reduction: 21.33%, $p < 0.05$).

Conclusion Gabapentin appears to be effective for the treatment of hot flushes with a favorable effect on quality of sleep. Vitamin E has only marginal effect on vasomotor symptoms.

INTRODUCTION

Hot flushes are the most commonly reported menopausal symptom in women receiving systemic therapy for breast cancer. Hot flushes may significantly compromise quality of life by disrupting sleep and by exerting a negative influence on work and other daily activities. In a survey on 200 women treated for breast cancer within the last 5 years, sleep disturbances were reported by 86% of the patients and were described as moderate or severe by more than 50% of them[1]. Although vasomotor symptoms are the most common complaint, many of these women also experience bothersome psychological symptoms, including nervousness, anxiety

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ORIGINAL ARTICLE

DOI: 10.1080/13697130902736921

Received 18-08-2008
Revised 25-11-2008
Accepted 01-01-2009

and depression. In the survey by Gupta and colleagues[1], more than half of the interviewed women felt depressed and about a third were taking, or had used in the past, antidepressant drugs. In this regard, it is not possible to establish the relative contribution of abrupt menopause and breast cancer diagnosis in the pathogenesis of depression.

Estrogen and progestogen supplementation (HT) is the mainstay in the treatment of menopause-related problems, resulting in a 80–90% reduction in hot flushes, but it is considered to be contraindicated for patients with a history of hormone-dependent tumors[2]. The prospective placebo-controlled HABITS trial, which tested the safety of HT in breast cancer survivors, was prematurely stopped due to the detection of an increased risk of recurrence among estrogen users (hazard ratio 2.4, 95% confidence interval (CI) 1.3–4.2)[3].

Newer antidepressants belonging to the category of selective serotonin reuptake inhibitors, such as venlafaxine[4], have been established as an alternative for alleviating hot flushes in breast cancer patients. Also mirtazapine, a noradrenergic and selective serotoninergic antidepressant, appears to be effective in reducing hot flushes in these women[5]. The use of antidepressants might also provide further benefits on mood alterations and sleep difficulties.

Gabapentin is a GABA analog used in the treatment of epilepsy, neurogenic pain, restless-leg syndrome, essential tremor, bipolar disorder and migraine prophylaxis. A beneficial effect of gabapentin on hot flushes was first reported in anecdotal case reports[6] and subsequently confirmed in three randomized, double-blind, placebo-controlled trials, in healthy women[7,8] and in women treated for breast cancer[9].

In the present study, we assessed the efficacy and the tolerability of gabapentin 900 mg/day compared to vitamin E for the control of vasomotor symptoms in women with breast cancer, the majority of whom concurrently received chemotherapy and/or hormonal adjuvant therapy. Vitamin E was chosen as a placebo equivalent on the basis of the previous experience showing that this compound has only minimal effect on hot flushes in breast cancer patients, but is not toxic and is devoid of side-effects[10]. The persistence of the effect of gabapentin on hot flushes after drug discontinuation is also investigated. The secondary objective of the study was to evaluate the effect of gabapentin on the quality of sleep and other aspects of the quality of life, possibly related to breast cancer diagnosis and premature menopause.

METHODS

We enrolled 115 postmenopausal women attending the outpatient clinic for menopausal problems and meeting the following criteria: previous breast cancer surgically treated at least 1 year before, no evidence of systemic disease, eight or more hot flushes per day, postmenopausal status (amenorrhea for more than 12 months or amenorrhea for 6–12 months with a serum follicle stimulating hormone (FSH) level greater than 40 mIU/ml and estradiol less than 20 pg/ml or bilateral oophorectomy or ovarian suppression by gonadotropin releasing hormone (GnRH) analogs). Adjuvant therapy with tamoxifen, aromatase inhibitors or GnRH analogs was allowed, provided that it was started at least 2 months before. Exclusion criteria were use of any antidepressant treatment, progestogens or any other medication to treat hot flushes within the previous 3 months, concomitant chemotherapy, uncontrolled hypertension (diastolic blood pressure >95 mmHg and/or systolic blood pressure >160 mmHg), impaired renal or hepatic function, diabetes.

At study enrolment, patients were randomly allocated to one of two treatment groups: vitamin E 800 IU/day or gabapentin 900 mg/day by oral route (Neurontin 300 mg capsules) for a period of 12 weeks. Treatment allocation was done by use of a randomization table. Gabapentin titration was done over the first week: one capsule at bedtime for 3 days, one capsule twice daily for 3 days, one capsule three times daily thereafter. Serum FSH, luteinizing hormone and estradiol were assessed at baseline and at week 12. Complete blood chemistry was assessed at the same time, although clinical trials do not indicate that routine monitoring of laboratory parameters is necessary for the safe use of gabapentin.

All participants provided written informed consent at the screening visit.

Each participant filled a 1-week self-report diary on hot flushes at study entry and during the 12 weeks of drug administration. Treatment efficacy was assessed by two measures: frequency (total number of hot flushes) and severity score, calculated by assigning scores of 1, 2, 3 and 4, respectively, to mild, moderate, severe and very severe hot flushes. This hot flush diary had been already validated in a series of previous publications[11]. Each value was obtained by averaging of data collected over 1 week. Differences and

percentage changes from baseline to weeks 4, 8 and 12 were calculated. In order to assess the duration of treatment efficacy, patients were requested to fill the hot flush diary for 3 months after treatment discontinuation. At the end of each week of therapy, patients were asked to report any side-effects.

Sleep quality was evaluated using the Pittsburgh Sleep Quality Index (PSQI), a validated instrument used to assess the quality and patterns of sleep in the adult[12]. It differentiates 'poor' from 'good' sleep by measuring seven areas: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction over the last month.

Menopausal symptoms were assessed using the Menopause Rating Scale (MRS), a self-administered standardized questionnaire, and the results were evaluated for psychological, somatic and urogenital symptoms; a composite score was obtained summing up the scores of these three aspects[13]. Quality of life was evaluated using the Short Form-36 Health Survey[14], which was conceived to analyze eight of the most important concepts of health: four related to physical health and four to mental health components. For each concept of health (general health, physical functioning, mental health, social functioning, vitality, bodily pain, role functioning/physical, and role functioning/emotional), a score is calculated and then transformed into a global score, ranging from 0 to 100 and expressed as a percentage; a global score $\geq$87.9 indicates excellent health, while a score $\leq$10.9 indicates poor health.

Statistical considerations

Statistical analyses were performed by using the SPSS software for Windows (SPSS, Chicago, Illinois, USA). Statistical significance was determined by using an α level of 0.05 and two-sided tests.

The sample size was calculated under the assumptions of the detection of a 50% reduction in hot flush frequency, with 80% power at a two-sided α level of 0.05. These assumptions using a dependent-samples *T* test required at least 20 evaluable patients.

To compare hot flush frequency and score after 4, 8 and 12 weeks of treatment with the basal value and PSQI, MRS and SF-36 Health Survey score modifications, the dependent-samples *T* test was used and the Shapiro–Wilk test to confirm that the sample originated from a normal population. When normality of data was not confirmed, the Wilcoxon Signed-Rank test was used.

The comparison between the two groups (vitamin E and gabapentin) was performed with variance analysis (ANOVA). For non-normally distributed variables, a non-parametric analysis was performed with the Mann–Whitney *U* test.

RESULTS

Between June 2005 and November 2007, 115 women with breast cancer were enrolled and randomly assigned to gabapentin ($n = 60$) or vitamin E ($n = 55$). The median age of the participants was 50 years (range 28–76 years), but more than 50% were less than 50 years old. Clinical and hot flush characteristics at baseline are shown in Table 1 and are comparable in the two groups. The baseline hot flush frequency per day was 13 for patients treated with gabapentin and 12 for those treated with vitamin E; the corresponding weekly hot flush scores were 235 and 202, respectively. In half of the cases, the duration of vasomotor symptoms lasted more than 9 months.

The majority of women in this study were receiving tamoxifen during treatment with gabapentin or vitamin E. About 60% of the women enrolled had a iatrogenic menopause induced by GnRH analogs or previous chemotherapy.

Withdrawals

Seventeen women (28.3%) in the gabapentin group and nine women in the vitamin E group (16.36%) withdrew from the study after signing the informed consent and recording basal data, and never began therapy. The most frequently reported reasons were the reluctance to take antiepileptic drugs, the fear of adverse effect on cognitive functions or general side-effects for the gabapentin group and the refusal to add another drug to the adjuvant therapy prescribed for breast cancer for the vitamin E group. Of the remaining 43 women who started the treatment with gabapentin, 12 (28%) stopped after 2 weeks because of somnolence and dizziness and were excluded from data analysis, while one (2%) dropped out after 1 month for lack of beneficial effect. Data at 1 month of therapy with gabapentin are available for 31 women; 30 patients completed the study period of 3 months. None of the 46 women who started vitamin E therapy stopped for troublesome side-effects, but 16 (34.78%) dropped out during the first month

Table 1 Patient baseline characteristics (only patients actually treated). Data are given as *n* (%) or mean

	Gabapentin *n (%)*	*Vitamin E* *n (%)*	*p Value*
Age 28–49 years	18 (58%)	18 (60%)	NS
Age ≥50 years	13 (42%)	12 (40%)	NS
Months from menopause	22	24	NS
Body mass index (kg/m^2)	25.2	24.8	NS
Iatrogenic menopause	19 (61%)	18 (60%)	NS
Natural menopause	7 (23%)	6 (20%)	NS
Surgical menopause	5 (16%)	6 (20%)	NS
Tamoxifen or other hormone therapy	27 (87%)	26 (86%)	NS
Hot flushes duration (>9 months)	17 (54.8%)	17 (56%)	NS
Daily hot flushes frequency	13	12	NS
Weekly hot flushes frequency	91	86	NS
Weekly hot flushes score	235	202	NS
Serum FSH (mIU/ml)	60	62	NS
Serum estradiol (pg/ml)	10	10	NS
Serum LH (mIU/ml)	30	32	NS

FSH, follicle stimulating hormone; LH, luteinizing hormone; NS, not significant

because of inefficacy against vasomotor symptoms.

Vasomotor symptoms

Gabapentin

After the first 4 weeks of treatment, there was a significant decrease in vasomotor symptoms as compared to baseline values; the mean decrease in weekly hot flush frequency was 52.34% (absolute change 48.01; 95% CI 23.51–72.52; $p < 0.05$) and the mean reduction of weekly hot flush score was 62.62% (absolute change 147.21; 95% CI 73.4–221; $p < 0.05$). A further increase in efficacy was observed after 8 weeks of gabapentin, when the mean decrease in hot flush number and score were, respectively, 54.09% (absolute change 49.61; 95% CI 27.82–73.71; $p < 0.05$) and 65.52% (absolute change 154.03; 95% CI 88.77–225.62; $p < 0.05$); the effect remained stable during the last month of therapy. At 3 months after the end of therapy, the hot flushes were more frequent and severe compared to the treatment period, even if they did not reach baseline values. We observed a reduction of 32.37% (absolute change 29.69; 95% CI 10.67–51.03; $p < 0.05$) in frequency and of 39.84% (absolute change 93.65; 95% CI 37.26–156.37; $p < 0.05$) in score as compared to pretreatment values (Table 2).

Table 3 shows the distribution of patients whose hot flush activity decreased by varying

Table 2 Gabapentin: mean hot flush frequency and score reduction as compared to baseline values

	Weekly hot flush frequency	*Weekly hot flush score*
Baseline ($n = 31$)		
Mean	91.73	235.1
Week 4 ($n = 31$)		
Mean	43.72	87.89
Absolute change	48.01	147.21
95% CI	23.51–72.52	73.4–221.0
Reduction	−52.34%	−62.62%
p	<0.05	<0.05
Week 8 ($n = 30$)		
Mean	42.12	81.07
Absolute change	49.61	154.03
95% CI	27.82–73.71	88.77–225.62
Reduction	−54.09%	−65.52%
p	<0.05	<0.05
Week 12 ($n = 30$)		
Mean	39.4	77.90
Absolute change	52.33	157.2
95% CI	29.64–77.34	85.8–234.93
Reduction	−57.05%	−66.87%
p	<0.05	<0.05
Week 24 ($n = 30$)		
Mean	62.04	141.45
Absolute change	29.69	93.65
95% CI	10.67–51.03	37.26–156.37
Reduction	−32.37%	−39.84%
p	<0.05	<0.05

95% CI, 95% confidence interval

Table 3 Reduction of hot flush frequency and score with gabapentin at 4, 8 and 12 weeks. Data are given as *n* (%)

	Hot flush frequency			*Hot flush score*		
Reduction	*Week 4*	*Week 8*	*Week 12*	*Week 4*	*Week 8*	*Week 12*
<25%	9 (29)	5 (16.5)	5 (16.5)	5 (16)	3 (10)	3 (10)
25–50%	10 (32.5)	10 (33.5)	8 (26.5)	10 (32)	6 (20)	7 (23.5)
>50%	12 (38.5)	15 (50)	17 (57)	16 (52)	21 (70)	20 (66.5)

amounts over the treatment period. After the 1st month of therapy, 32.5% of patients experienced a reduction in hot flush frequency, ranging from 25% to 50%, and 38.5% of patients a decrease greater than 50% as compared to basal values. Over the next 4 weeks of treatment, 50% of women reported a reduction greater than 50% in the number of hot flushes; these results remained unchanged during the 3rd month of treatment.

The beneficial effect of gabapentin was more pronounced in the case of severe hot flushes; a greater than 50% decrease of hot flush score was observed in 52% and 70% of these patients after 1 and 2 months, respectively.

At the end of the study, greater than 66% reductions of hot flush frequency and score were reported by 6% and 10% of the patients, respectively, and corresponding greater than 75% reductions were reported by 16% and 30% of the patients, respectively.

Vitamin E

The effect of vitamin E on vasomotor symptoms is fairly small; after 4 weeks of treatment, the average reduction in hot flush frequency was 11.1% (absolute change 9.64; 95% CI −2.25–21.53), not statistically significant as compared to basal values, and these data did not change during the further 2 months of treatment. The hot flush score showed a non-significant decrease of 7.28% (absolute change 14.7; 95% CI −3.49–32.89) at the end of the study period (Table 4).

Table 4 Vitamin E: mean hot flush frequency and score reduction as compared to baseline value

	Weekly hot flush frequency	*Weekly hot flush score*
Baseline ($n=30$)		
Mean	86.9	202.1
Week 4 ($n=30$)		
Mean	77.26	184.26
Absolute change	9.64	17.84
95% CI	−2.25–21.53	−5.6–41.28
Reduction	−11.1%	−8.83%
p	0.08	0.1
Week 8 ($n=30$)		
Mean	76.8	183.2
Absolute change	10.1	18.9
95% CI	−2.89–23.09	−6.75–44.55
Reduction	−11.63%	−9.56%
p	0.09	0.11
Week 12 ($n=30$)		
Mean	78.2	187.4
Absolute change	8.7	14.7
95% CI	−1.07–18.47	−3.49–32.89
Reduction	−10.02%	−7.28%
p	0.0	0.08

95% CI, 95% confidence interval

Quality of life

Sleep quality, measured by the PSQI, was significantly improved in the gabapentin group; at the end of the study, the total score decreased by 21.33% (absolute change 1.67; 95% CI 0.9–2.43; $p < 0.05$). After 12 weeks, 40% of the women observed an improvement in time to fall asleep and 13% in time staying asleep, while 16% obtained fewer awakenings.

With regard to the MRS questionnaire, which evaluates psychological, somatic and urogenital symptoms in menopausal women, there was a decrease in total score of about 14.92% (absolute change 2.08; 95% CI 0.23–3.93; $p < 0.05$) after 4 weeks of gabapentin use, and the improvement in the somatic subscale was even greater. The continuation of the treatment for other 2 months did not modify these results.

The analysis of the SF-36 questionnaire revealed that the health-related quality of life slightly improved in all women treated with gabapentin, with a significant increase in the mental health component score of 13.72% (absolute change −8.32; 95% CI −13.78 to −2.86; $p < 0.05$) at the end of the treatment period as compared to the baseline week. The corresponding value for the physical health component was +10.87% (absolute change −6.53; 95% CI −12.12 to −0.92; $p < 0.05$) (Table 5).

Table 5 Pittsburg Sleep Quality Index score (PSQI), Menopause Rating Scale score (MRS), SF-36 Health Survey Mental and Physical component scores with gabapentin

	PSQI	*MRS*	*SF-36 Mental (%)*	*SF-36 Physical (%)*
Baseline ($n=31$)				
Mean	7.83	13.95	60.64	60.06
Week 4 ($n=31$)				
Mean	6.58	11.87	68.28	66.33
Absolute change	1.25	2.08	−7.64	−6.27
95% CI	0.56–1.93	0.23–3.93	−13.04 to −2.24	−10.61 to −1.91
Reduction	−15.97%	−14.92%	12.59%	10.43%
p	<0.05	<0.05	<0.05	<0.05
Week 12 ($n=30$)				
Mean	6.16	11.75	68.96	66.59
Absolute change	1.67	2.2	−8.32	−6.53
95% CI	0.9–2.43	0.0–4.41	−13.78 to −2.86	−12.12 to −0.92
Reduction	−21.33%	−15.78%	13.72%	10.87%
p	<0.05	<0.05	<0.05	<0.05

95% CI, 95% confidence interval

In the group of women receiving vitamin E, the evaluation of total scores of PSQI, MRS and SF-36 after 4 and 12 weeks of treatment did not show any significant modification as compared to pretreatment values.

The most common adverse events in the gabapentin group were somnolence and dizziness, which caused the dropout from the study of 12/43 women (28%); five of the 43 women who started the treatment suffered from dry mouth, nervousness and modest weight gain. None of the aforementioned side-effects occurred in women receiving vitamin E.

On the other hand, only one woman (2%) withdrew because of inefficacy in the gabapentin group, as compared to 35% (16/46 patients) in the vitamin E group.

DISCUSSION

The results of this non-placebo-controlled, non-blinded study confirm that gabapentin 900 mg/day is effective for relieving hot flushes in patients previously treated for breast cancer. Many of these patients were young (<50 years of age) and suffering from iatrogenic premature menopause; furthermore, they were frequently receiving concurrent tamoxifen, which may worsen vasomotor symptoms. The beneficial effect of gabapentin appeared within 4 weeks of therapy, with a reduction of hot flush frequency of 52.34%, and persisted across all age groups, although the highest benefit was reported by younger women suffering from more severe vasomotor symptoms due to iatrogenic menopause.

On the contrary, vitamin E had a negligible effect on vasomotor symptoms in these patients; women treated with this compound obtained a reduction of about 10% in the number of hot flushes per day during the whole study period, and 34.78% of them withdrew because the treatment was perceived as not helpful. Our data on vitamin E are consistent with those of a previous trial on 120 breast cancer patients[10] showing similar reduction in hot flush frequency for vitamin E and placebo (25% vs. 22%) after 4 weeks. The benefit obtained with vitamin E was marginal: one less hot flush per day than with placebo. Our study confirms, however, that vitamin E is devoid of significant side-effects and may be used as a placebo in trials evaluating the effect of new drugs on vasomotor symptoms.

Our data on gabapentin are comparable to those obtained by Pandya and colleagues[9] in a large placebo-controlled trial carried on in a group of breast cancer survivors with similar characteristics (mean age 55 years; mean number of hot flushes per day 8.7; currently taking tamoxifen 69%), showing a reduction in hot flush frequency of 49% after 2 months of treatment at the same dosage. In Pandya's trial, gabapentin was prescribed for 8 weeks; in our study, the period of treatment was extended to 12 weeks, but the continuation of the gabapentin did not further improve the percentage of responding women. After 1 month, 38.5% of the women enrolled experienced a greater than 50% reduction in hot

flush frequency; this figure increased to 50% after the 2nd month of therapy, but remained steady during the 3rd month. A similar behavior of hot flush frequency and score during a 3-month treatment period was observed by Guttuso and colleagues in a trial on 30 healthy postmenopausal women treated with gabapentin at the same dosage[7].

The benefit obtained in our trial with gabapentin 900 mg/day appears to be even higher for the severity of hot flushes. At the end of the treatment period with gabapentin, we observed a 66.87% reduction (absolute change 157.2; 95% CI 85.8–234.93; $p < 0.05$) of the hot flush score. In the randomized trial of Butt and colleagues[8], carried out on 193 healthy postmenopausal women, the hot flush score decreased by 51% after 4 weeks.

With regard to the dose, we decided to use 900 mg of gabapentin per day on the basis of the previous experience of Pandya who showed that a lower dosage had only a marginal effect on vasomotor symptoms[9]. However, higher doses of gabapentin might be more effective. Evidence in support of this hypothesis comes from the study by Guttuso and colleagues[7]. During the second open-label part of this study, when patients were allowed to adjust their own gabapentin dosage from 300 to 2700 mg/day, 75% of them self-adjusted to a dose between 900 and 2700 mg/day. Higher doses were associated with a 67% reduction of the hot flush score, which compares favorably with the 54% reduction obtained with 900 mg/day, and were not associated with increased frequency of side-effects.

The efficacy of gabapentin on vasomotor symptoms after its discontinuation is an unexplored aspect. Although we observed that the beneficial effect of the drug did not fully persist over time, hot flushes did not return to baseline values. This could be explained by 'getting used to' hot flushes by enrolled women or by the physiological decrease of vasomotor symptoms with passing time since menopause.

Hot flushes are the major menopausal symptoms for breast cancer survivors; however, several other problems have been shown to decrease the quality of life of these women. We published a survey where insomnia was cited as a relevant problem by 43% of patients during chemotherapy and by 31% of women undergoing hormonal therapy[15].

In the survey by Gupta[1], menopausal symptoms were causing physical inconvenience, affecting social life, and having a negative impact on the employment of 71%, 56% and 42% of the patients, respectively. While vasomotor symptoms were most strongly associated with the feeling of physical inconvenience, psychological symptoms, such as feeling depressed, nervousness and impaired memory, were most strongly associated with effects on employment and had a detrimental effect on social life.

Most studies investigating the side-effects of breast cancer treatments use generic quality-of-life instruments, which are unable to provide enough information on menopausal symptoms. We used the Menopausal Rating Scale (MRS), a validated scale for measuring menopausal symptoms and assessing their effects on quality of life[13], and the SF-36 Health Survey, which evaluates both mental and physical components of health[14].

Our data showed that, besides hot flushes, only the quality of sleep may really benefit from gabapentin treatment among all the variables considered. With regard to sleep quality, the 21.33% (absolute change 1.67; 95% CI 0.9–2.43) reduction of the PSQI obtained in our study after 3 months of therapy is statistically significant. Overall, the baseline score of 7.83 in the PSQI[12] in our series indicated a rather poor sleep quality and it is likely that, at least for some of these women, even a small improvement in quality of sleep may be perceived as a fairly good benefit. A beneficial effect on sleep quality was reported also by Guttuso and colleagues in a population of healthy postmenopausal women treated with gabapentin[7].

The menopausal symptoms evaluated using the MRS showed a small but significant improvement (total score reduction 15.78%; absolute change 2.20; 95% CI 0.0–4.41) after 12 weeks of gabapentin use. For comparison, studies conducted on patients using HT (which was not allowed in our breast cancer patients) reported improvement in total MRS score of about 36% after HT; in particular, significant declines were observed in the psychological and somatic subscales[16].

In the SF-36 questionnaire, both mental and physical components of health showed small but significant improvements in all women treated with gabapentin. It is unlikely that side-effects of the drug may have influenced the results obtained on quality of life, since they appeared in the initial 2 weeks of therapy and were transient.

Adverse events of gabapentin in our series were similar to those found in other studies and were mostly represented by somnolence and dizziness during the initial few weeks of therapy. In our experience, gabapentin's side-effects can be

reduced by adopting a gradual titration and by taking medication with meals. Although it is well known that these symptoms are transient, 12/43 women (28%) withdraw from the study during the 1st month of therapy. Somnolence is reported by 20% and dizziness by 13% of the women enrolled by Guttuso and colleagues, who report a drop-out rate for adverse events of 13%[7]. Pandya and colleagues suggest that they might have underestimated the adverse effects of gabapentin and that the withdrawal rates of 12% at 4 weeks and of 17% at 8 weeks might be due entirely to the side-effects of the treatment[9]. In the trial by Butt and colleagues, women taking gabapentin reported greater dizziness (18%), unsteadiness (14%) and drowsiness (12%) at week 1 as compared to those taking placebo, but these symptoms improved by week 2 and returned to baseline levels after 1 month of therapy[8].

The compliance with gabapentin in the present study was adversely affected by patients' reluctance to use this drug for the indication of relief from vasomotor symptoms. In fact, even though hot flushes are a troublesome problem in our sample (with a mean of 13 hot flushes per day and a poor sleep quality), a high percentage (28.3%) of the women enrolled did not start the treatment after having signed the informed consent. When asked about the reasons, the more frequent answers were: the reluctance to use a drug indicated also for psychiatric disorders, the fear of impairing cognitive functions, and, in a few cases, the contrary advice of their general practitioner.

The high dropout rate probably did not affect the study results since the frequency and severity of basal vasomotor symptoms were similar in the group of women who never started the treatment and in those who completed it. Moreover, the small size of the sample may account for the lack of statistical significance of some questionnaires.

Maybe surprisingly, 16% of women in the vitamin E group decided not to take the drug; their decision was motivated either by reluctance to receive other drugs beside those required for breast cancer or by a lack of confidence in the efficacy of the drug.

Finally, we decided to prolong the duration of gabapentin for 3 months, although there are no data on long-term use with this drug for hot flush relief. On the other hand, long-term use of gabapentin for other indications has not been associated with significant side-effects.

CONCLUSION

Gabapentin at the dosage of 900 mg/day is effective for the treatment of hot flushes in breast cancer survivors. Gabapentin also has additional favorable effects on quality of sleep and on several other aspects related to premature menopause. As expected, vitamin E has only marginal effect on vasomotor symptoms and no effect on the other menopausal symptoms. Treatment benefits do not persist after discontinuation of the drug. Literature data in healthy menopausal women suggest that higher doses might be more effective. Further studies in breast cancer patients are warranted, evaluating the efficacy and tolerability profile with different doses.

Conflict of interest The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Source of funding Nil.

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