Acute effects of tamoxifen and third-generation aromatase inhibitors on menopausal symptoms of breast cancer patients

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Endocrine treatments of breast cancer patients antagonize estrogen and may lead to consequences of estrogen deprivation including menopausal symptoms. We analyzed the changes in frequency and severity of menopausal symptoms in patients receiving tamoxifen or aromatase inhibitors and identified factors influencing these symptoms. One hundred and eighty-one consecutive postmenopausal breast cancer patients scheduled to start endocrine treatment were included in this prospective study. A menopause symptom questionnaire covering vasomotor, atrophic, psychological, cognitive and somatic symptoms was filled in at baseline, and after 1 and 3 months of therapy. Both first-line tamoxifen and aromatase inhibitors induced an increase in the occurrence and severity of hot flashes ($p < 0.0001$ and $p = 0.014$, respectively). Musculoskeletal pain and dyspareunia significantly increased under first-line non-steroidal aromatase inhibitors ($p = 0.0039$ and $p = 0.001$, respectively), while patients under tamoxifen had significant decrease in sexual interest ($p \leq 0.0001$). Younger age was associated with more hot flashes and vaginal dryness at baseline, and after 1 and 3 months of therapy (all $p < 0.02$). We conclude that there are significant differences between the early effects of tamoxifen and aromatase inhibitors on menopausal symptoms of breast cancer patients. Our results underscore the need for safe and effective non-hormonal interventions to alleviate vasomotor and musculoskeletal symptoms which were the most prevalent and severe symptoms. *Anti-Cancer Drugs* 15:753–760 © 2004 Lippincott Williams & Wilkins.

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Introduction

Endocrine treatments are widely prescribed for all stages of hormone receptor-positive breast cancer. These treatments are all primarily directed to induce estrogen deprivation through blocking estrogen at the receptor level, such as tamoxifen, or by inhibiting estrogen biosynthesis, such as aromatase inhibitors. These treatments may lead to acute and long-term consequences of estrogen deprivation including menopausal symptoms.

The occurrence of menopausal symptoms in breast cancer patients remains an issue of clinical concern. The discontinuation of hormone-replacement therapy (HRT) on diagnosis of breast cancer is at present more emphasized with recent publications confirming the detrimental effect of HRT on the breast [1–3]. The limited efficacy and questionable safety of most non-hormonal interventions [4–9] further complicate the treatment of menopausal symptoms in breast cancer patients. It is in this setting that identifying endocrine treatments associated with less menopausal side-effects is essential.

Treatment with the selective estrogen receptor modulator (SERM) tamoxifen is known to induce or intensify vasomotor symptoms, with hot flashes being the most frequent complaint reported by patients under tamoxifen [10–12]. Other menopause-associated symptoms such as vaginal dryness and dyspareunia have been described [13,14]. Nowadays, the third-generation non-steroidal aromatase inhibitors such as anastrozole and letrozole, and the steroidal-type exemestane are increasingly being

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used in the management of breast cancer. They have been shown to be equally effective or superior to tamoxifen in the metastatic setting [15–18] and are now challenging tamoxifen in the adjuvant setting [19].

To date, most comparative assessments of menopausal symptoms in patients receiving tamoxifen and aromatase inhibitors have been taken from randomized trials with response rates and survival as primary endpoints. In this setting, it is possible that non-life threatening but equally important side-effects may be overlooked or underestimated. Prospective studies primarily designed to analyze the effect of endocrine treatments on menopausal symptoms as recorded by the patient may better reflect differences in the impact of endocrine treatments on menopausal symptoms. Our aim was to analyze the early effects of tamoxifen and steroidal and non-steroidal aromatase inhibitors on the occurrence and severity of menopausal symptoms in postmenopausal breast cancer patients, and to identify factors influencing these symptoms.

Patients and methods

We conducted a prospective single-center study including all consecutive postmenopausal breast cancer patients who were scheduled to start endocrine treatment at the University Hospital Gasthuisberg, Leuven, Belgium. Postmenopausal status was defined as cessation of menses for more than 1 year. In case of doubt, follicle-stimulating hormone and estradiol levels were assessed, and had to be in the postmenopausal range. Women on HRT while being diagnosed with breast cancer had stopped therapy for at least 1 month prior to the start of this study. A straightforward menopause-specific questionnaire covering vasomotor, atrophic, psychological, cognitive and somatic symptoms which was developed and validated at our institute was used for this study [20]. This questionnaire included definitions of each menopausal symptom, and symptoms during the past 7 days were rated from 1 (no symptom), 2 (mild) up to 5 (intolerable symptom). Dyspareunia and decreased sexual interest were separate questions in the questionnaire used for this study. In the latest version (Fig. 1) currently used in our institute within the frame of prospective clinical trials, these items were lumped together under sexual problems, and the evaluation of sleeping problems was incorporated. Eligible patients filled in the questionnaire prior to the start of endocrine treatment, and after 1 and 3 months of therapy. The demographic information and baseline menopausal symptom questionnaires were filled-in by patients in the outpatient clinic, while the 1- and 3-month questionnaires were given with self-addressed envelopes and were filled in at home with written instructions on the appropriate dates of evaluation. Patients who failed to send the questionnaires within 1 week after the indicated dates were contacted by phone. The study was conducted according to the guidelines for clinical studies described in the Declaration of Helsinki (as revised by the World Medical Association, www.wma.net). The protocol was approved by the Ethical Committee for Clinical Studies and all participants provided written informed consent.

The policy for prescribing hormonal therapy in breast cancer patients is summarized hereafter. All patients who were eligible to receive adjuvant endocrine therapy were invited to participate in an on-going adjuvant hormonal therapy trial running at our institute. This was a randomized blinded treatment with equal chances of receiving either tamoxifen or letrozole, approved by the Committee for Medical Ethics, with patients providing written informed consent. Those who were not eligible or those who refused to participate were given the standard therapy, tamoxifen. In cases where there were contra-indications to adjuvant tamoxifen treatment, a non-steroidal aromatase inhibitor (letrozole or anastrozole) was prescribed. In patients with metastatic disease, those who were previously exposed to tamoxifen received an aromatase inhibitor, while hormone therapy-naive patients started with first-line tamoxifen. Third- and fourth-line endocrine therapy were the alternative aromatase inhibitor (steroidal for patients previously exposed to non-steroidal, and conversely) and fulvestrant (Faslodex). According to line and treatment received, four different treatment groups were created (Table 1). Groups 1–3 comprised patients receiving first-line therapy with either tamoxifen ($n = 49$), non-steroidal aromatase inhibitors anastrozole or letrozole ($n = 28$), or a blinded treatment ($n = 67$) with equal chances of receiving either tamoxifen or letrozole. Group 4 comprised those who were crossing-over from tamoxifen to either a steroidal or non-steroidal aromatase inhibitor due to breast cancer progression under tamoxifen ($n = 20$). The median duration of tamoxifen intake prior to crossing-over was 22 months (mean of 18 months). Formal statistical analysis was not possible in the remaining 17 patients who received an assortment of hormonal therapies in different lines. These patients were not included in the tables nor in the analysis.

Statistical analysis was performed with SAS (version 8). Categorical data analysis was done to determine the change in each menopausal symptom in the different treatment groups. For each treatment group, each symptom was analyzed separately by constructing frequency tables displaying in rows the proportions of patients reporting no symptom (1), mild to moderate symptoms (2–3) and severe to intolerable symptoms (4–5) over time from baseline to 1 and 3 months of therapy (columns). Since row and column variables are ordinal, the Mantel–Haenszel χ^2 statistic was used as a test for linear association for which

Fig. 1

Date: ____/ ____/ __ __
DD MM YY

Patient hospital file number _____
Institution: _____

In this questionnaire, you will find some complaints you may have experienced **during the past seven days**. Below you will find definitions of the symptoms which may guide you. **First, please read carefully the definition of each symptom**. Proceed to answer all the questions yourself by circling the number that best applies to you. There are no right or wrong answers. The information you will provide will remain strictly confidential.

- **Hot flashes –** transient episodes of feeling of warmth, redness on the face and chest, sweating and often accompanied by palpitations and anxiety sometimes followed by shivering
- **Vaginal dryness –** feeling of dryness of the vagina sometimes with itching, burning sensation or pain
- **Urinary problems –** frequent urination (even at night) and urgency, urine loss when coughing, sneezing and laughing
- **Emotional disturbance –** inner tension, despondency and tearfulness, nervousness, aggressivity, mood changes, lack of drive
- **Memory problems –** forgetfulness, difficulty in remembering new information, poor concentration
- **Joint and muscle pains –** pain predominantly in the finger joints, wrists, knees and feet or neck; other rheumatic symptoms like stiffness
- **Sexual problems –** loss of sexual interest, lack of sexual satisfaction, pain or discomfort with intercourse
- **Sleeping problems –** inability to obtain or maintain adequate sleep

During the past seven days:	**Not at all**	**Yes, w/ minor inconvenience**	**Yes, w/ moderate inconvenience**	**Yes, w/ severe inconvenience**	**Yes, intolerable**
a. Did you have **hot flashes** occurring during the day (7am-10pm)?	1	2	3	4	5
b. Did you have **hot flashes** occurring at night (10pm-7am)?	1	2	3	4	5
c. Have you had **vaginal dryness**?	1	2	3	4	5
d. Did you have **urinary problems**?	1	2	3	4	5
e. Did you feel **emotionally disturbed**?	1	2	3	4	5
f. Did you have **memory problems**?	1	2	3	4	5
g. Have you felt **joint and muscle pains**?	1	2	3	4	5
h. Did you have **sexual problems**?	1	2	3	4	5
i. Did you have **sleeping problems**?	1	2	3	4	5

- Are you currently taking treatments for menopausal symptoms? ☐Yes ☐No
  If yes, please indicate. . . . . .
  If no, would you like to receive treatment for menopausal symptoms? ☐Yes ☐No
  → **If yes**, please indicate the symptoms and rank them from most important to least important
  . . . . . .
- Have you experienced other menopausal symptoms not included in this questionnaire? ☐Yes ☐No
  If yes, please indicate. . . . . .

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corresponding p values are given. The strength and the direction of the association was determined by computing a γ statistic with corresponding 95% confidence interval (CI). Logistic regression was performed to detect variables influencing menopausal symptoms.

Table 1 Baseline medical and demographic characteristics

	No prior treatment			Prior treatment with tamoxifen
Treatment	Tamoxifen	Trial[a]	NSAI	(N)SAI
No. of patients	49	67	28	20
Mean age ± SD	61 ± 8.40	62 ± 7.95	62 ± 9.62	64 ± 11.05
Mean years menopause ± SD	12 ± 8.97	12 ± 8.90	14 ± 9.84	14 ± 11.24
Type of menopause				
natural	38	56	20	11
induced	11	11	8	9
Mean BMI ± SD	25 ± 4.85	26 ± 5.40	25 ± 5.21	27 ± 5.16
Partner status				
with partner	42	48	23	15
without partner	7	19	5	5
Educational level				
less than high school	34	37	18	11
high school/university	15	30	10	9
Employment status				
active	7	16	3	3
retired	42	51	25	17
Current status of treatment				
adjuvant	44	67	21	0
palliative	5	0	7	20
Karnofsky Index				
90–100	44	65	21	7
70–80	5	2	7	13

[a]Randomized double blind adjuvant trial with equal chances of receiving tamoxifen or letrozole. Abbreviations: NSAI: non-steroidal aromatase inhibitors (adjuvant letrozole $n=18$ and adjuvant anastrozole $n=10$); (N)SAI: non-steroidal and steroidal aromatase inhibitors (second-line letrozole $n=10$ and second-line exemestane $n=10$); Induced menopause: radiation, surgical and chemotherapy-induced menopause taken together.

Results

The baseline patient characteristics are summarized in Table 1. The one hundred and sixty-four women comprising the four treatment groups had a mean age of 62 years, were on average 10 years postmenopausal and had a mean body mass index (BMI) of 26 kg/m^2. One hundred and thirty-two (80%) received adjuvant hormonal treatment, while the remaining patients were treated for advanced disease. There were no significant differences between treatments groups in terms of age, years from menopause and mean BMI. At baseline, for any symptom, the proportions of patients being symptomatic (mild to severe or not) were not significantly different between the four groups (Fisher's exact test, p values 0.12–0.98).

The changes in menopausal symptoms from baseline to after 1 and 3 months of therapy are summarized in Table 2. After 1 and 3 months of therapy, both first-line treatments with either tamoxifen or non-steroidal aromatase inhibitors led to a significant increase in the occurrence and severity of hot flashes (Mantel–Haenszel χ^2 $p \leq 0.0001$, γ 0.58, 95% CI 0.38–0.78 and $p = 0.014$, γ 0.44, 95% CI 0.15–0.73, respectively). Similarly, patients participating in the blinded randomized trial (theoretically a 50/50 mixture of patients on tamoxifen or letrozole) reported a significant increase in the occurrence and severity of hot flashes ($p = 0.0003$, γ 0.38, 95% CI 0.20–0.57). The patients on first-line tamoxifen reported the highest percentage of severe to intolerable hot flashes after 3 months of therapy leading to treatment interruption in two of the 49 patients (4%). In those crossing-over from tamoxifen to a steroidal or non-steroidal aromatase inhibitor, no significant change occurred from baseline symptoms ($p = 0.62$).

The change in musculoskeletal pain was significant only in women receiving first-line non-steroidal aromatase inhibitors, anastrozole and letrozole ($p = 0.0039$, γ 0.45, 95% CI 0.19–0.70). Fifty percent of patients who were asymptomatic at baseline reported variable degrees of pain after 1 month of treatment with a marked increase in the number of patients reporting severe to intolerable symptoms after 3 months (from 7% at baseline to 36% after 3 months). Intolerable musculoskeletal pain at 3 months of therapy led to treatment interruption in two of the 18 patients receiving letrozole (11%). In the blinded randomized trial, a non-significant trend towards more symptomatic patients was seen after 1 and 3 months of therapy ($p = 0.0992$, γ 0.22, 95% CI 0.02–0.41). No significant change occurred in patients receiving first-line tamoxifen ($p = 0.33$) and in those crossing-over from tamoxifen to a steroidal or non-steroidal aromatase inhibitor ($p = 0.9225$).

Regarding the menopause-associated gynecological side-effects, a trend towards increased vaginal dryness was seen in women participating in the blinded randomized trial. There was a 15% increase in the number of patients reporting vaginal dryness after 3 months of therapy; however the intensity was mainly towards mild to moderate symptoms ($p = 0.0551$, γ 0.24, 95% CI 0.02–0.47). For both questions on dyspareunia and decreased sexual interest, 8% of the total number of patients

Table 2 Changes in menopausal symptoms after 1 and 3 months of therapy

Treatment	Percentage of patients reporting no symptom/mild to mod/severe to intolerable									p value[b]
	Baseline ($n=164$)			1 month ($n=163$)[c]			3 months ($n=162$)[c]			
Hot flashes										
Tam first-line	52	44	4	19	74	7	13	64	23	<0.0001
Trial[a]	45	51	4	25	64	12	21	59	21	0.0003
NSAI first-line	54	46	0	32	64	4	23	69	8	0.0141
(N)SAI previous Tam	50	50	0	42	53	5	47	47	5	0.6243
Musculoskeletal pain										
Tam first-line	56	40	4	43	45	12	40	53	6	0.3294
Trial[a]	51	41	9	30	60	10	32	54	13	0.0992
NSAI first-line	36	57	7	18	54	29	18	46	36	0.0039
(N)SAI previous Tam	31	53	16	21	53	26	21	58	21	0.9225
Vaginal dryness										
Tam first-line	65	27	8	63	28	9	53	32	15	0.1841
Trial[a]	80	20	0	68	29	3	65	32	2	0.0551
NSAI first-line	67	32	0	50	46	4	50	46	4	0.1893
(N)SAI previous Tam	75	25	0	74	26	0	79	21	0	NA
Dyspareunia[d]										
Tam first-line	74	18	8	63	27	10	50	38	12	0.1508
Trial[a]	78	20	2	57	34	9	55	33	12	0.0246
NSAI first-line	68	21	11	50	22	28	37	37	25	0.0010
(N)SAI previous Tam	75	25	0	69	15	15	92	8	0	0.3390
Decreased sexual interest[d]										
Tam first-line	53	37	10	43	43	13	21	32	47	<0.0001
Trial[a]	55	39	6	45	50	5	40	31	29	0.0022
NSAI first-line	63	21	16	50	28	22	31	37	31	0.1216
(N)SAI previous Tam	58	42	0	62	15	23	54	23	23	0.2957
Urinary problems										
Tam first-line	73	23	4	63	35	2	55	36	9	0.0761
Trial[a]	74	23	3	70	28	3	62	32	6	0.1100
NSAI first-line	61	39	0	57	43	0	50	35	15	0.1192
(N)SAI previous Tam	75	25	0	63	37	0	84	15	0	NA
Emotional disturbances										
Tam first-line	35	56	8	42	44	14	27	64	9	0.6570
Trial[a]	36	53	10	25	61	14	35	42	23	0.3620
NSAI first-line	45	50	5	47	53	0	53	47	0	0.3854
(N)SAI previous Tam	36	53	11	25	61	14	35	42	23	0.3620
Memory problems										
Tam first-line	79	18	2	58	40	2	60	34	6	0.0602
Trial[a]	77	22	1	58	39	3	60	35	5	0.0735
NSAI first-line	61	35	4	50	46	4	54	38	8	0.4808
(N)SAI previous Tam	60	40	0	68	32	0	63	32	5	0.6103

Values are shown as percentage of patients who reported no symptom (1), mild to moderate symptoms (2–3) and those who reported severe to intolerable symptoms (4–5) from baseline to 1 and 3 months of therapy.

[a]Randomized double-blind adjuvant trial with equal chances of receiving tamoxifen or letrozole.

[b]Mantel–Haenszel χ^2 statistic as a test for linear association for which corresponding p values are given.

[c]One patient did not return the questionnaire at 1-month evaluation; two patients did not complete the 3-month evaluation due to shifting to another treatment.

[d]For both questions, 8% of the total number of patients ($n=164$) consistently did not answer the questions, while 20% indicated the absence of sexual contact; analysis was done on the remaining patients. NA: statistics not applicable for this table where row or column sum is zero.

consistently did not answer the questions, while 20% indicated the absence of sexual contact. Excluding these patients, dyspareunia significantly increased in both the patients included in the blinded randomized trial and those receiving first-line non-steroidal aromatase inhibitors ($p = 0.0246$, γ 0.33, 95% CI 0.09–0.56; $p = 0.001$, γ 0.33, 95% CI 0.01–0.66, respectively). Those receiving first-line tamoxifen and those in the blinded randomized trial reported significantly decreased sexual interest after 3 months of therapy ($p \leq 0.0001$, γ 0.47, 95% CI 0.25–0.69; $p = 0.0022$, γ 0.27, 95% CI 0.03–0.50, respectively), with a stronger association towards more symptomatic patients and more intense symptoms in the tamoxifen group. Severe to intolerable vaginal dryness correlated with severe to intolerable intensity of dyspareunia ($p \leq 0.0001$). For urinary problems, memory problems and emotional disturbances, no significant changes were seen from baseline to after 1 and 3 months of therapy. Patients who reported severe to intolerable memory problems were likely to report the same intensity of emotional disturbances ($p \leq 0.0001$). Table 3 shows the prevalence of symptoms at baseline in the subgroup of endocrine therapy naive patients and summarizes the impact of 3 months first-line therapy with either tamoxifen or aromatase inhibitors.

Logistic regression was performed to detect variables influencing menopausal symptoms. Younger age was associated with more hot flashes and vaginal dryness ($p = 0.0021$ and $p = 0.0128$, respectively). Increasing years from menopause, artificially induced menopause (surgical-, radiation- and chemotherapy-induced meno-

Table 3 Endocrine therapy naive patients (groups 1–3, $n=144$) starting first-line tamoxifen or non-steroidal aromatase inhibitors: prevalence of menopausal symptoms at baseline and summary of changes after 3 months therapy

Symptom	Prevalence at baseline	Tamoxifen	Non-steroidal aromatase inhibitors
Hot flashes	74 (51%)	+ + +	+
Musculoskeletal pain	74 (51%)	=	+
Vaginal dryness	39 (27%)	=	=
Dyspareunia	37 (26%)	=	+ +
Decreased sexual interest	63 (44%)	+ + +	=
Urinary problems	41 (28%)	=	=
Emotional disturbances	88 (61%)	=	=
Memory problems	36 (25%)	=	=

The following p values are from the Mantel–Haenszel χ^2 statistic used as a test for linear association: $=p>0.05$; $+p \leq 0.01$; $++p \leq 0.001$; $+++p \leq 0.0001$.

pause taken together) and having a higher education (high school or university degree versus less than high school) were associated with more memory problems ($p = 0.0246$, $p = 0.0192$ and $p = 0.0058$ respectively). BMI showed an influence only on urinary problems such that women with a higher BMI were more likely to report urinary problems ($p = 0.010$). Women with partners were more likely to report decreased sexual interest compared to those who lived alone ($p = 0.021$).

Discussion

We analyzed the changes in frequency and severity of menopausal symptoms after 1 and 3 months of therapy with either tamoxifen or aromatase inhibitors. While all first-line treatments with any of these agents induced significant increases in hot flashes, the association towards more symptomatic patients and more intense hot flashes after 3 months of therapy was strongest in the tamoxifen group. The level of significance in the trial group is intermediate between the tamoxifen and the non-steroidal aromatase inhibitor group, corresponding to what is expected from an equal number of patients receiving tamoxifen and letrozole. Reported side-effects in randomized trials suggest that the third generation aromatase inhibitors anastrozole and exemestane may induce less hot flashes compared to tamoxifen [18,19], while the reported incidence of hot flashes under letrozole was similar to tamoxifen [17]. Nevertheless, hot flashes remain the most frequent menopausal symptom in patients receiving endocrine treatments and, although not considered a serious side-effect, increasing intensity may decrease patient compliance as also shown in other studies [21,22]. In the group crossing over from tamoxifen to either a steroidal or non-steroidal aromatase inhibitor after 22 months median duration of tamoxifen intake, the low incidence of hot flashes at baseline and the absence of severe to intolerable symptoms correspond with the observation that hot flashes tend to decrease over time in tamoxifen-treated patients [23].

The association of menopausal status with joint and muscle pain has been described [24]. The precise mechanism by which increased musculoskeletal pain occur in patients receiving non-steroidal aromatase inhibitors is not entirely clear. Taking into account the severe musculoskeletal pain in two patients receiving letrozole that led to treatment interruptions, the rapid resolution of symptoms after withdrawal and the greater reduction of estrogen levels with letrozole compared to other aromatase inhibitors [25,26], it is logical to think that sudden and profound estrogen suppression may be the explanation for this symptom. However, other causative factors should be explored. The lesser musculoskeletal pain observed in patients receiving tamoxifen is consistent with its known beneficial effects in preventing normal bone loss associated with natural menopause [27,28]. The absence of changes in musculoskeletal pain in patients crossing-over from tamoxifen to a steroidal or non-steroidal aromatase inhibitor may be explained by the weak estrogenic agonist effect of tamoxifen counteracting deep estrogenic depletion and its long half-life [29]. A washout period greater than the 3-month evaluation period in this study may be necessary to avoid carry-over effects and to better delineate what happens following tamoxifen.

Differences between steroidal and non-steroidal aromatase inhibitors have been reported. Exemestane, being steroidal in structure, is devoid of total cross-resistance with non-steroidal aromatase inhibitors after which it can still induce 24% of clinical benefit [30]. Moreover, it displays a favorable action (possibly androgen-mediated) on serum lipids [31] and on bone [32], in contrast to the reported effects of non-steroidal aromatase inhibitors on these organ systems [33–36]. However, whether these differences lead to a real clinical advantage with a decrease in cardiovascular events and bone problems remains to be demonstrated.

Compared to tamoxifen, less is known regarding the impact of aromatase inhibitors on menopause-associated gynecologic side-effects. Vaginal dryness and/or dyspareunia have not been included in the systematic evaluation of side-effects in studies using aromatase inhibitors [17–19,37]. Our results suggest that aromatase inhibitors induce more atrophic symptoms (vaginal dryness and dyspareunia) compared with tamoxifen, consistent with

the maximal estrogen suppression achieved with these agents [38–40]. The cause of decreased sexual interest is recognized to be multifactorial [41]. At variance from a publication linking decreased sexual interest with vaginal dryness and/or dyspareunia under tamoxifen treatment [14], our results on the contrary suggest that these symptoms may be unrelated at least during the first 3 months of therapy and that other factors may have greater influence on sexual interest. The absence of changes from baseline symptoms for memory problems, urinary problems and emotional disturbances is not unexpected in view of the chronic nature and possibly the multifactorial influence on these symptoms.

The significance of the data obtained in this study is not only limited to weighing differences in early side-effects between treatments, but also to better direct appropriate interventions to alleviate substantial menopausal symptoms particularly in breast cancer patients. Our results emphasize the need to develop targeted interventions for the most severe symptoms. Safe and effective systemic treatments are needed to alleviate hot flashes, musculoskeletal pain and decreased sexual interest, while local treatments may be necessary to alleviate dyspareunia. Effective prevention of bone loss by administration of biphosphonates is available and optimal scheduling in patients receiving aromatase inhibitors is currently being investigated.

While this present report analyzes the effects of tamoxifen and aromatase inhibitors early in the course of therapy, after 1 and 3 months, a reassessment after 1 year will give a deeper insight on the evolution of menopausal symptoms under the different groups. Given the present results, there are differences between the early effects of tamoxifen and aromatase inhibitors, and potential differences between the steroidal and non-steroidal type. Non-life threatening side-effects such as vasomotor or musculoskeletal symptoms which may reduce quality-of-life or affect patient compliance may be taken into account in clinical decisions in the choice between different drugs. This is particularly true in cases where agents may have minimal differences in efficacy, but exhibit marked differences in tolerance. Moreover, issues on acute and long-term side-effects will become more important in the preventive setting where younger and otherwise healthy high-risk women will be taking these drugs.

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