Il ginecologo e la paziente con tumore della mammella

Le terapie ormonali e la gestione post terapia oncologica

Nicoletta Biglia
SSDU Breast Unit Ospedale Mauriziano Umberto I
Università di Torino

EPIDEMIOLOGY

Breast cancer (BC) affects **up to one in eight women** who survive up to the age of 85 years in Western countries.

Four out of five new cases of BC are diagnosed in women over 50 years, with the peak in the **50–64 years** age range.

The survival rate of BC patients has significantly increased due to earlier diagnosis and advances in adjuvant treatment: at 5 years after initial diagnosis is 89%.

Thus addressing survivors' post-treatment needs is critical to providing quality health care

SEER 2011

QOL after breast cancer

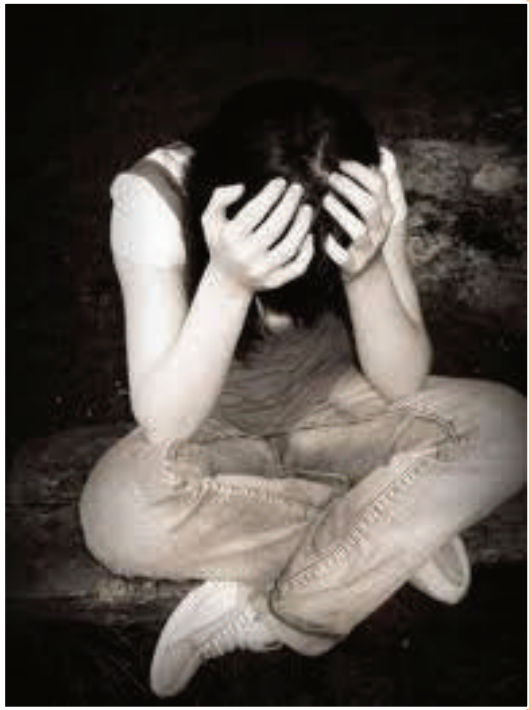
Many of breast cancer (BC) survivors suffer from symptoms, which result directly from BC treatment with chemotherapy, tamoxifen, aromatase inhibitors, ovarian suppression.

These women experience:

- **Vasomotor symptoms**

(hot flashes, night sweats, palpitations)

- **Vaginal dryness**
- **Sexual dysfunction**
- **Cognitive dysfunction**
- **Poor sleep and tiredness**
- **Osteoporosis**
- **Fertility problems …**



Up to 20% of BC patients consider stopping or actually cease endocrine therapy due to side effects.

Hickey, Ann Oncol 2008

Loprinzi, Lancet Oncol 2008

Published Ahead of Print on December 7, 2015 as 10.1200/JCO.2015.64.3809
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2015.64.3809

JOURNAL OF CLINICAL ONCOLOGY | ASCO SPECIAL ARTICLE

American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline

Carolyn D. Runowicz, Corinne R. Leach, N. Lynn Henry, Karen S. Henry, Heather T. Mackey, Rebecca L. Cowens-Alvarado, Rachel S. Cannady, Mandi L. Pratt-Chapman, Stephen B. Edge, Linda A. Jacobs, Arti Hurria, Lawrence B. Marks, Samuel J. LaMonte, Ellen Warner, Gary H. Lyman, and Patricia A. Ganz

Hot Flushes

- Women can experience menopausal symptoms if chemotherapy results in premature cessation of ovarian function or as an adverse effect of endocrine therapies.

- **Vasomotor symptoms are typically more severe in younger survivors** because of the abrupt change in hormones and, when present, can have a significant impact on QoL.

- **For younger women on endocrine therapies, 50% to 70% will likely experience hot flushes while on tamoxifen.**

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Summary of Long-Term and Late Effects by Treatment Type

Treatment Type	Long-Term Effects	Late Effects
Hormonal therapy		
Tamoxifen	• Hot flushes • Changes in menstruation • Mood changes • Increased triglycerides • Vaginal dryness • Decreased libido • Musculoskeletal symptoms/pain • Cholesterol elevation	• Increased risk of stroke • Increased risk of endometrial cancer • Increased risk of blood clots • Osteopenia in premenopausal women • Increased risk of osteoporosis • Increased risk of fractures
Aromatase inhibitors		
General psychosocial long-term and late effects	• Depression • Distress—multifactorial unpleasant experience of psychological, social, and/or spiritual nature • Worry, anxiety • Fear of recurrence • Fear of pain • End-of-life concerns: Death and dying • Loss of sexual function and/or desire • Challenges with body image • Challenges with self-image • Relationship and other social role difficulties • Return-to-work concerns and financial challenges	

Sexual Function after Breast Cancer

J Sex Med 2011

Mary Panjari, MD, Robin J. Bell, MD, and Susan R. Davis, MD

Monash University Medical School, Alfred Hospital- Women's Health Program, Department of Medicine, Prahran, Vic., Australia

✓ The BUPA Foundation Health and Wellbeing after Breast Cancer Study is a prospective cohort study of **1,684 women recruited (2004-2006) within 12 months of diagnosis with BC.**

Over 80% of all the women in our study declared that their sex life before BC was good and satisfying

At the time of completing the FQ1 on 1,011 women studied:

70% = sexual problems
77% = vasomotor symptoms

Women experiencing sexual function problems:

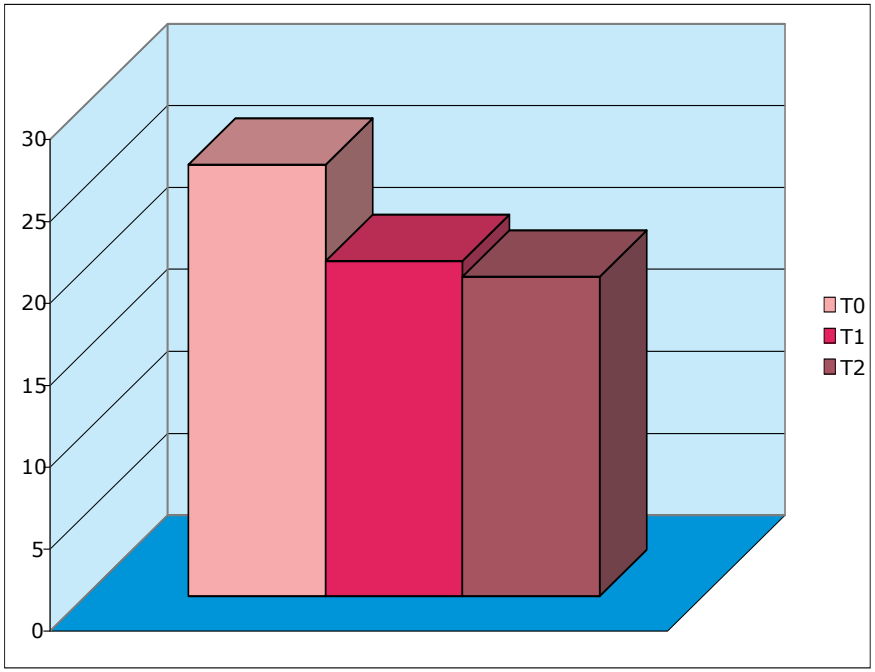
- were become ***postmenopausal since diagnosis*** (P = 0.02),
- experienced ***vasomotor symptoms*** (P < 0.01),
- used ***aromatase inhibitors*** (P = 0.03).

Effects of Surgical and Adjuvant Therapies for Breast Cancer on Sexuality, Cognitive Functions, and Body Weight

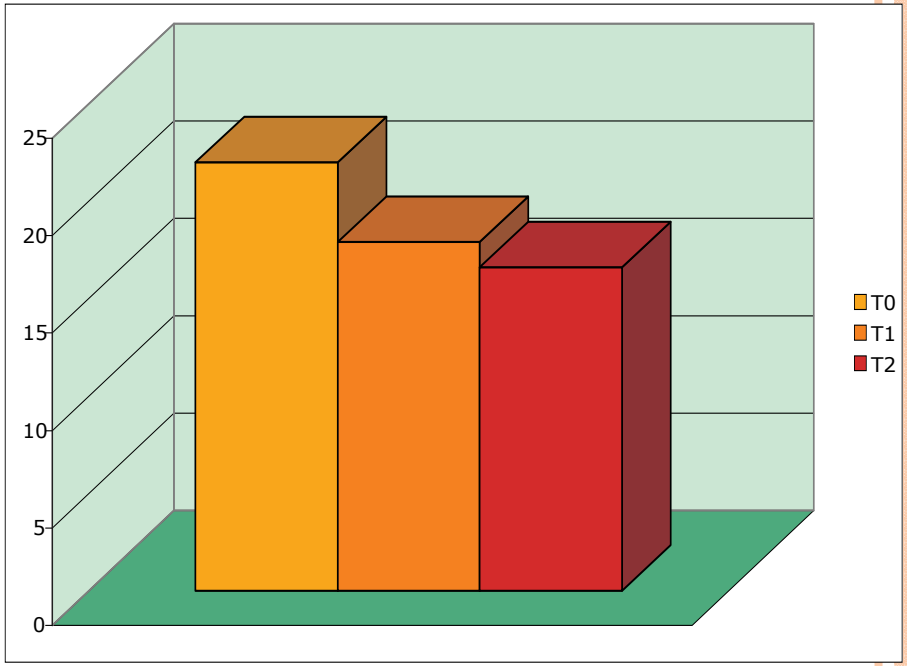
Nicoletta Biglia, MD, PhD,* Giulia Moggio, MD,* Elisa Peano, MD,* Paola Sgandurra, MD,* Riccardo Ponzone, MD,* Rossella E. Nappi, MD,† and Piero Sismondi, MD, PhD*

J Sex Med 2009

< SEXUAL ACTIVITY



RELATION WITH PARTNER



For 50% of sample, baseline scores are below normality range → not satisfying sexual life also before adjuvant therapy.

After 6 months and 1 year of adjuvant therapy, explicit **erotic cues**, typical of male sexuality, are even less effective in exciting.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Sexual Health

-Sexual complaints are a common problem among breast cancer survivors

They include:
- sexual desire disorder/decreased libido (23%-64% of patients)
- arousal or lubrication concerns (20%-48% of patients)
- orgasmic concerns (16%-36% of patients)
- dyspareunia (35%-38% of patients).

- Patients who **receive chemotherapy** tend to have more of these sexual concerns than those treated only with surgery and/or radiation
- **Treatment with aromatase inhibitors** may cause vaginal dryness, dyspareunia (which can be severe), menopausal symptoms, and loss of sexual desire.

HRT AFTER BREAST CANCER

Menopause: The Journal of The North American Menopause Society
Vol. 19, No. 3, pp. 257-271
DOI: 10.1097/gme.0b013e31824b970a

POSITION STATEMENT

The 2012 Hormone Therapy Position Statement of The North American Menopause Society

Estrogen Therapy/EstrogenProgestogen Therapy
" Is contraindicated in women with a history of hormone-sensitive cancer "

Updated 2013 International Menopause Society recommendations on menopausal hormone therapy and preventive strategies for midlife health

T. J. de Villiers, A. Pines, N. Panay†, M. Gambacciani‡, D. F. Archer**, R. J. Baber††, A. A. Gompel***, V. W. Henderson†††, R. Langer‡‡‡, R. A. Lobo****, G. Plu-Bureau and D. W. Sturdee‡‡‡‡, on behalf of the International Menopause Society*

There is a **lack of safety data supporting the use of MHT** (estrogen therapy or estrogen – progestogen therapy) in breast cancer survivors.

Hormone Replacement Therapy: An Increased Risk of Recurrence and Mortality for Breast Cancer Patients?

J Adv Pract Oncol

Jul/Aug 2015

MOLLY LUPO, RN, MSN, ANP, NP-C, AOCNP* JOYCE E. DAINS, DrPH, JD, RN, FNP-BC, DPNAP, FAANP, and LYDIA T. MADSEN, PhD, RN, AOCNS*

	Initial author[b]	Type of study	Statistics for recurrence[a]	Statistics for mortality
1	Holmberg (2004)	RCT	RH = 3.5 (1.5–8.1)	No analysis
2	Holmberg (2008)	RCT	RH = 2.2 (1.0–5.1)	No analysis
3	Fahlen (2013)	RCT	HR = 3.6 (1.2–10.9)	No significant findings
4	Marsden (2000)	RCT	No analysis	No data
5	Decker (2003)	Prospective	Descriptive data	t-test; $p < .03$
6	Peters (2001)	Prospective	Descriptive data	No analysis
7	Vassilopoulou-Sellin (1999)	Prospective	Descriptive data	No analysis
8	Brewster (2007)	Retrospective	HR = 2.10 (1.21–3.64) HR = 1.78 (1.27–2.50)	No analysis
9	Dew (2003)	Retrospective	No significant findings	No analysis
10	Le Ray (2012)	Retrospective	No significant findings	No data
11	O'Meara (2001)	Retrospective	No significant findings	No significant findings
12	Durna (2002)	Retrospective	RR = 0.18 (0.04–0.75)	No significant findings
13	Beckmann (2001)	Retrospective	No significant findings	No significant findings
14	DiSaia (2000)	Retrospective	No data	Kaplan-Meier $p = .003$

Review investigating recurrence and mortality data among breast cancer survivors who have used HRT.

The observational studies found no statistical evidence to support an increased risk of breast cancer recurrence from HRT (small sample size, potential recruitment bias with inclusion of low-risk pts, short f-up period….)

On the contrary, RCTs (Habits trial and Stockolm trial) reported a significantly increased risk of breast cancer recurrence.

HRT after breast cancer

Some observational studies suggested that HT use **may not increase the risk of recurrent breast cancer.** These reports have been questioned because of the potential bias from the selection of women at lower risk of recurrence for HT use

Three randomised trials on HRT after breast cancer diagnosis

"Menopausal Hormone Therapy After Breast Cancer: The Stockholm Randomized Trial"
Stockholm *Breast Cancer Study Group.* 2005

" Increased risk of recurrence after HRT in breast cancer survivors"
HABITS Study Group J Natl Cancer Inst, 2008

Effects of tibolone on climacteric symptoms and quality of life in breast cancer patients
LIBERATE trial *Oncol Lancet, Jan 2009*

All closed prematurely due to concern about the safety of treatment

"HABITS (HORMONE REPLACEMENT THERAPY AFTER BREAST CANCER - IS IT SAFE?), A RANDOMISED COMPARISON: TRIAL STOPPED"

L Holmberg et al, Lancet, 2004

Breast cancer recurrence

HR	95%	CI
Global	1.8	1.03-3.1
HABITS study	3.3	1.5-7.4
Stockolm trial	0.82	0.35-3.9

In 1997 two independent randomised trials were started in Sweden to assess the effects of HRT after a diagnosis of breast cancer; in 2002 the organisers agreed to pool safety data.

Following an interim safety analysis which showed a significant risk of recurrence from HRT for the two trials combined, both studies were prematurely closed in December 2003.

However, there was significant heterogeneity between the studies.

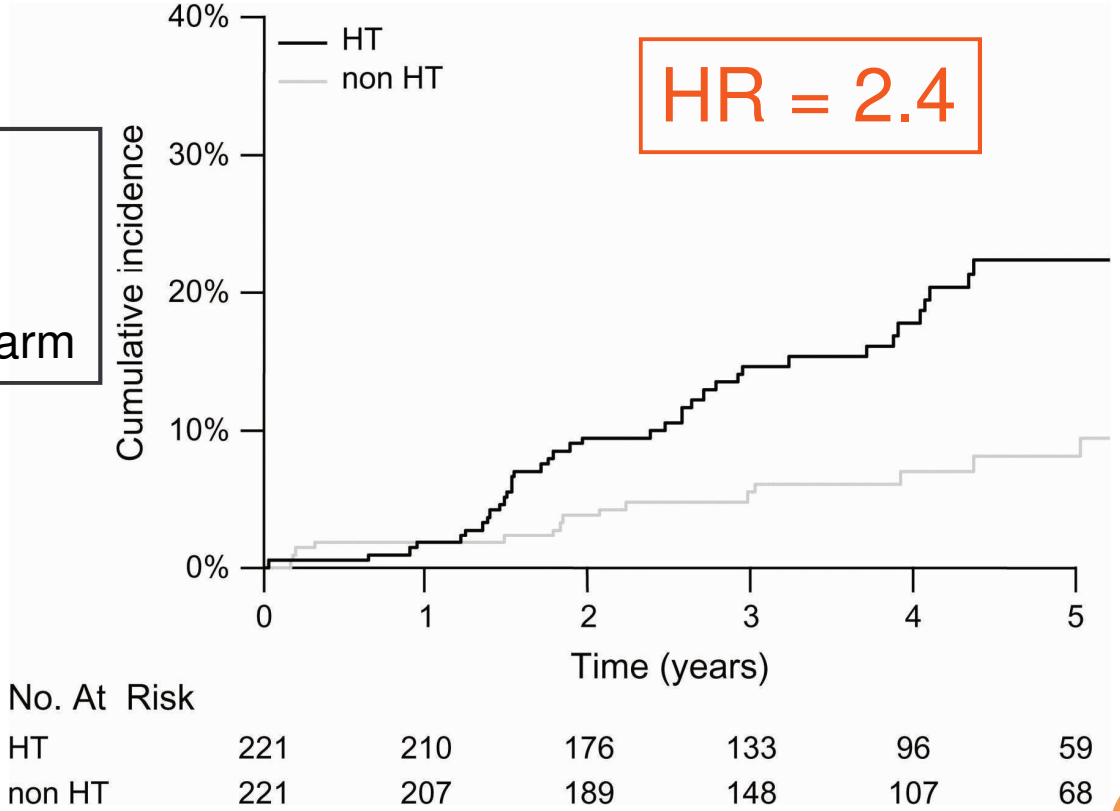
Increased Risk of Recurrence After Hormone Replacement Therapy in Breast Cancer Survivors

Lars Holmberg, Ole-Erik Iversen, Carl Magnus Rudenstam, Mats Hammar, Eero Kumpulainen, Janusz Jaskiewicz, Jacek Jassem, Daria Dobaczewska, Hans E. Fjosne, Octavio Peralta, Rodrigo Arriagada, Marit Holmqvist, Johanna Maenpa

On behalf of the HABITS Study Group

Median F-UP = 4 yrs

39 events in the HT arm
17 events in the non-HT arm



Holmberg L et al. JNCI J Natl Cancer Inst 2008;100:475-482

European Journal of Cancer (2013) 49, 52–59

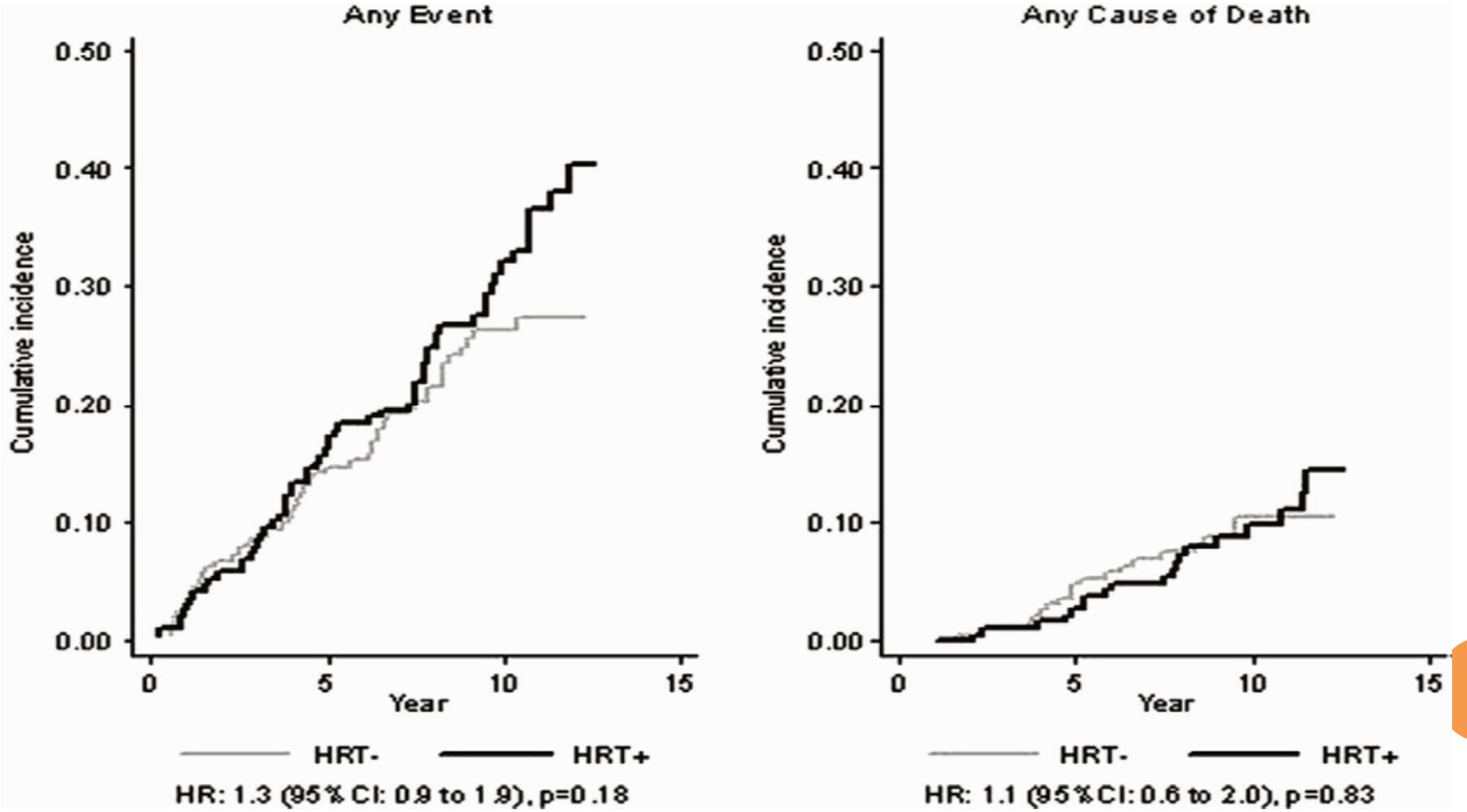
Available at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.ejcancer.info

Hormone replacement therapy after breast cancer: 10 year follow up of the Stockholm randomised trial

Mia Fahlén [a,b,*], Tommy Fornander [b], Hemming Johansson [b], Ulla Johansson [c], Lars-Erik Rutqvist [b], Nils Wilking [b], Eva von Schoultz [b]



REASONS FOR DIFFERENT RESULTS:

GREATER PROGESTOGEN EXPOSURE IN HABITS TRIAL (PREFERENTIAL USE OF CONTINUOUS COMBINED HRT)

LESS CONCOMITANT USE OF TAMOXIFEN IN HABITS TRIAL (21% VERSUS 52% IN STOCKOLM TRIAL)

SHORTER DURATION FROM PRIMARY TREATMENT SURGERY AND RANDOMISATION TO HRT IN HABITS TRIAL (2.1 YRS) AS COMPARED TO STOCKOLM TRIAL (2.6 YRS)

LIVIAL INTERVENTION FOLLOWING BREAST CANCER; EFFICACY, RECURRENCE, AND TOLERABILITY ENDPOINTS

•*Tibolone, a* **synthetic steroid**, *with a mixture of oestrogenic, progestogenic and androgenic properties.*
• *It is effective in reducing climateric symptoms in healthy post-menopausal women.*

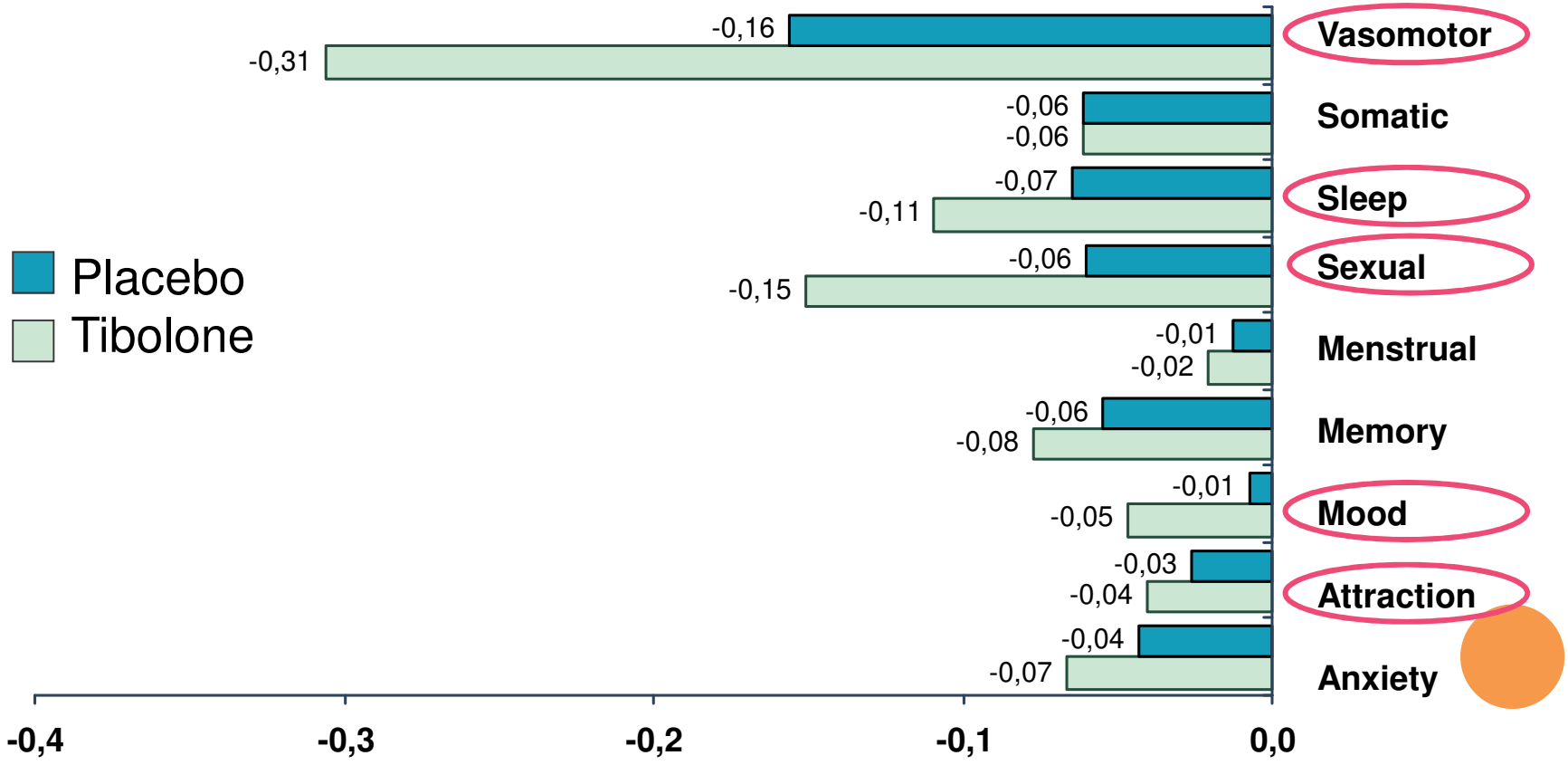
• **Experimental data have suggested an antiproliferative or neutral effect of tibolone on breast tissues**; *so the Liberate trial, a large multinational trial, was designed with more than 3148 women enrolled followed breast cancer diagnosis.*

LIBERATE QoL - Results

QUALITY OF LIFE

WOMEN'S HEALTH QUESTIONNAIRE (N=831)

After 1 year of treatment, a significant superiority of tibolone as compared to placebo was observed on QOL items

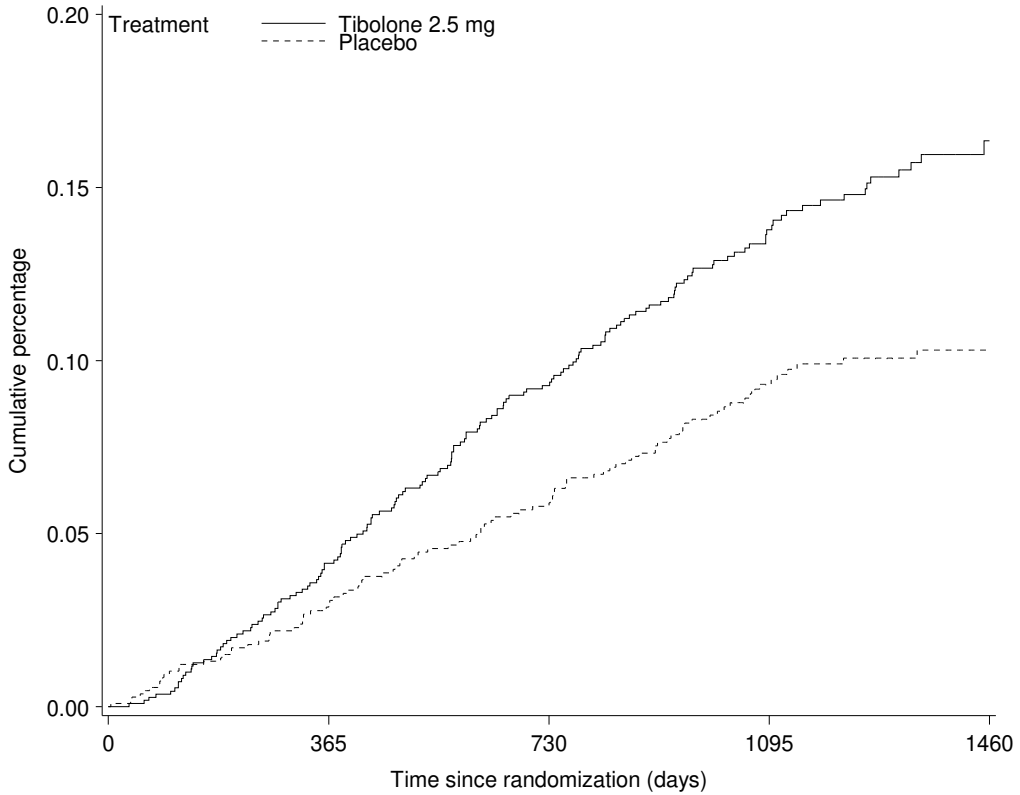


BREAST CANCER RECURRENCE (ITT)

	Tibolone (N =1556) n (%)	Placebo (N =1542) n (%)	HR [95% CI]	P-value
Overall	237 (15.2%)	165 (10.7%)	1.40 [1.14;1.70]	0.001
Location				
- Local	48 (3.1%)	33 (2.1%)	1.42 [0.91;2.21]	NS
- Contralateral	25 (1.6%)	17 (1.1%)	1.39 [0.74;2.59]	NS
- Distant	171 (11.0%)	121 (7.8%)	1.38 [1.09;1.74]	0.007

Kenemans P, et al. Lancet Oncol 2009

BREAST CANCER RECURRENCE (ITT)
ESTROGEN RECEPTOR STATUS POSITIVE (N=2185)



159 tibolone

99 placebo

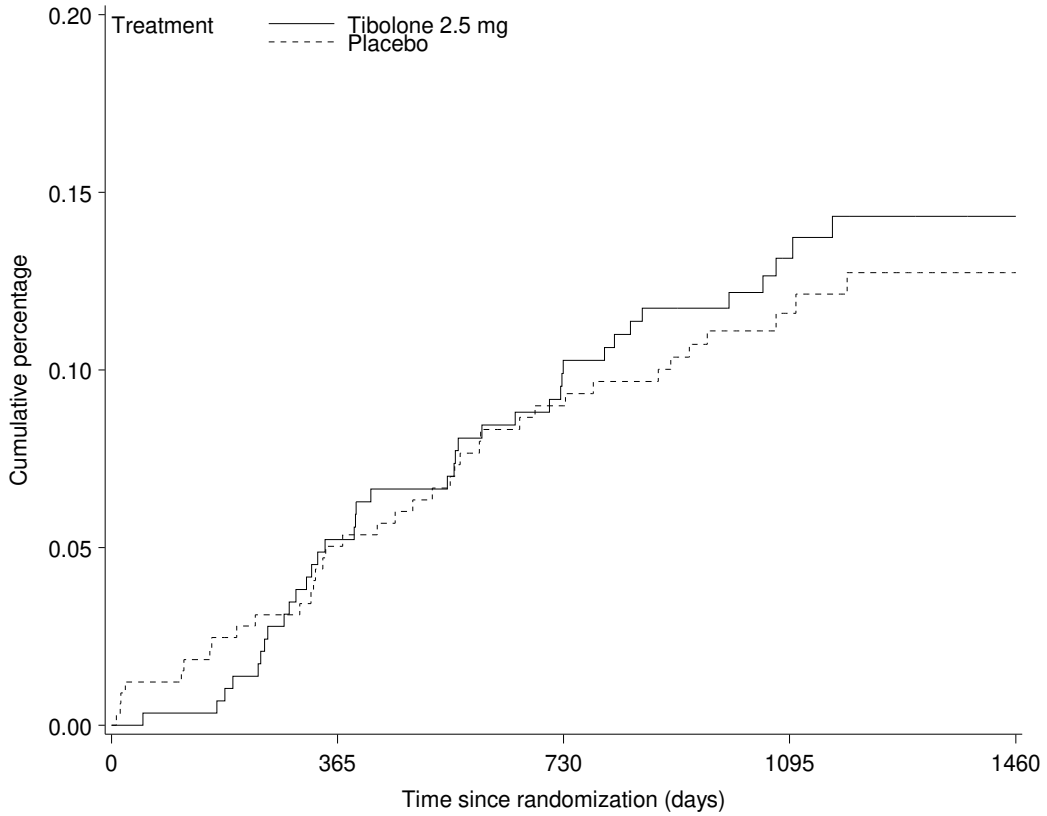
HR=1.56
95% CI: 1.22-2.01

Number at risk

Tibolone 2.5 mg	1112	1023	939	625	190
Placebo	1073	984	920	634	204

Kenemans P, et al. Lancet Oncol 2009

BREAST CANCER RECURRENCE (ITT)
ESTROGEN RECEPTOR STATUS NEGATIVE (N=623)



39 tibolone

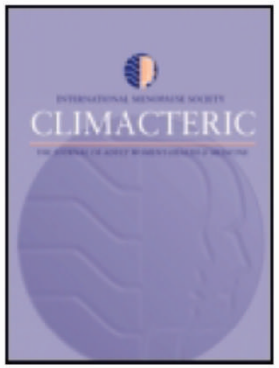
37 placebo

HR=1.15
95% CI: 0.73-1.80

Number at risk

Tibolone 2.5 mg	294	268	245	155	52
Placebo	329	293	270	165	47

Kenemans P, et al. Lancet Oncol 2009



Climacteric

Taylor & Francis
Taylor & Francis Group

ISSN: 1369-7137 (Print) 1473-0804 (Online) Journal homepage: http://www.tandfonline.com/loi/icmt20

2016 IMS Recommendations on women's midlife health and menopause hormone therapy

R. J. Baber, N. Panay & A. Fenton the IMS Writing Group

There is a lack of safety data supporting the use of MHT (estrogen therapy or estrogen–progestogen therapy) in breast cancer survivors.

So, the research has focused on non hormonal alternatives for menopausal symptoms in breast cancer survivors …

Alternative treatment for vasomotor symptoms

- **PHARMACOLOGICAL**
- **Antidepressant (SSRIs**: *fluoxetine, citalopram, paroxetine, sertraline and mirtazapine; **S**NRIs*: *venlafaxine and desvenlafaxine*; **Gabapentin**);
- **Phytoestrogen**
- **Black Cohosh**
- **Clonidine**
- **Vitamine E**

- **NON PHARMACOLOGICAL**
- ***Acupuncture, Yoga, paced respiration, Hypnosis, Diet…***

Loprinzi, Lancet Oncol 2008

Published Ahead of Print on December 7, 2015 as 10.1200/JCO.2015.64.3809
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Premature Menopause/Hot Flushes

Recommendation 3.12. It is recommended that primary care clinicians should offer SNRIs, selective serotonin reuptake inhibitors (SSRIs), gabapentin, lifestyle modifications and/or environmental modifications to help mitigate vasomotor symptoms of premature menopausal symptoms (LOE = IA).

Non-hormonal interventions for hot flushes in women with a history of breast cancer (Review)

2010

THE COCHRANE COLLABORATION®

Main results

Sixteen RCTs met our inclusion criteria. We included six studies on selective serotonin (SSRI) and serotonin-norepinephrine (SNRI) reuptake inhibitors, two on clonidine, one on gabapentin, two each on relaxation therapy and homeopathy, and one each on vitamin E, magnetic devices and acupuncture. The risk of bias of most studies was rated as low or moderate. Data on continuous outcomes were presented inconsistently among studies, which precluded the possibility of pooling the results. Three pharmacological treatments (SSRIs and SNRIs, clonidine and gabapentin) reduced the number and severity of hot flushes. One study assessing vitamin E did not show any beneficial effect. One of two studies on relaxation therapy showed a significant benefit. None of the other non-pharmacological therapies had a significant benefit. Side-effects were inconsistently reported.

Authors' conclusions

Clonidine, SSRIs and SNRIs, gabapentin and relaxation therapy showed a mild to moderate effect on reducing hot flushes in women with a history of breast cancer.

ANTIDEPRESSANT AND HOT FLUSHES

REVIEW

The efficacy and tolerability of SSRI/SNRIs in the treatment of vasomotor symptoms in menopausal women: A systematic review

Amy P. Handley, MSN, FNP-C (Associate Professor and Associate Dean)[1] & **Mary Williams**, PhD, RN (Nurse Practitioner)[2]

[1]College of Nursing, Brigham Young University, Provo, Utah
[2]Graduate Studies and Faculty, College of Nursing, Brigham Young University, Provo, Utah

2015

The **SSRIs and SNRIs can reduce hot flashes by 65% and begin working within the first week**.

Patient response is variable and if one drug does not improve hot flashes, another can be tried after a 1- to 2-week drug trial.

Paroxetine, citalopram, and escitalopram appear to have the fewest adverse effects.

ANTIDEPRESSANT AND HOT FLUSHES

SSRIs

Fluoxetine
Sertraline
Escitalopram
Paroxetine
Citalopram

SNRIs

Venlafaxine
Duloxetine

Evaluation of low-dose venlafaxine hydrochloride for the therapy of hot flushes in breast cancer survivors

N. Biglia[a,*], Riccardo Torta[b], R. Roagna[a], F. Maggiorotto[a], F. Cacciari[a], R. Ponzone[a], F. Kubatzki[a], P. Sismondi[a]

NaSSA

Mirtazapine

Mirtazapine for the Treatment of Hot Flushes in Breast Cancer Survivors: A Prospective Pilot Trial

Nicoletta Biglia, MD, PhD, Franziska Kubatzki, MD, Paola Sgandurra, MD, Riccardo Ponzone, MD, PhD, Davide Marenco, MD, Elisa Peano, MD and Piero Sismondi, MD, PhD

ANTICONVULSANT

Gabapentin

CLIMACTERIC 2009;12:310–318

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

N. Biglia, P. Sgandurra, E. Peano, D. Marenco, G. Moggio, V. Bounous, N. Tomasi Cont, R. Ponzone and P. Sismondi

Available online at www.sciencedirect.com
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Maturitas 52 (2005) 78–85
MATURITAS
THE EUROPEAN MENOPAUSE JOURNAL
www.elsevier.com/locate/maturitas

Current opinion

Evaluation of low-dose venlafaxine hydrochloride for the therapy of hot flushes in breast cancer survivors

N. Biglia [a,*], Riccardo Torta [b], R. Roagna [a], F. Maggiorotto [a], F. Cacciari [a], R. Ponzone [a], F. Kubatzki [a], P. Sismondi [a]

[a] Academic Gynaecological Oncology Department, University of Turin, IRCC (Institute for Cancer Research and Turin and Mauriziano Umberto I Hospital, Largo Turati 62, Torino 10128, Italy
[b] Department of NeuroScience, University of Turin, Turin, Italy

Received 10 September 2004; received in revised form 3 January 2005; accepted 4 January 2

Venlafaxine

Table 2
Mean hot flushes activity after 4 and at 8 weeks

Mean hot flashes number/week	
Baseline	80.4 (40 pts)
At 4 weeks	47.5 (30 pts)
Reduction at 4 weeks	−30.5 (−39.1%)
% Reduction	−39.1%
p	<0.001
At 8 weeks	36.0 (27 pts)
Reduction at 8 weeks	−41.2
% Reduction	−53.3%
p	<0.001

Venlafaxine is an **effective treatment for the relief of vasomotor symptoms** in patients previously treated for breast cancer.
A favourable effect is maintained **also in those patients using tamoxifen as adjuvant therapy**

ORIGINAL ARTICLE

Mirtazapine for the Treatment of Hot Flushes in Breast Cancer Survivors: A Prospective Pilot Trial

Mirtazapine

Nicoletta Biglia, MD, PhD, Franziska Kubatzki, MD, Paola Sgandurra, MD, Riccardo Ponzone, MD, PhD, Davide Marenco, MD, Elisa Peano, MD and Piero Sismondi, MD, PhD

Department of Gynaecological Oncology, University of Turin, Mauriziano "Umberto I°" Hospital and Institute for Cancer Research and Treatment of Candiolo (IRCC), Turin, Italy

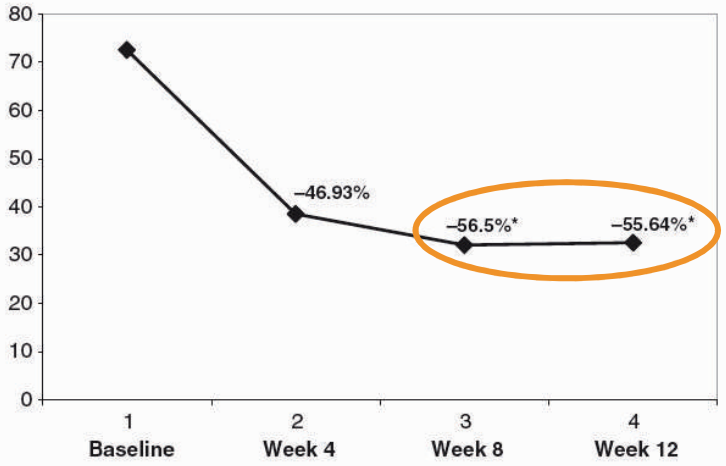


Figure 1. Mean hot flushes frequency reduction at 4, 8 and 12 weeks (*calculated on 20 patients).

Efficacy and safety of **mirtazapine 30 mg/ daily for 12 weeks** to reduce hot flushes (HF) in women with previous breast cancer
55.6% (p < 0.05) reduction in HF frequency and 61.9% (p < 0.05) reduction in HF score as compared to baseline.

Mirtazapine appears to be effective in reducing HF in breast cancer survivors. The more frequent side effect was somnolence

ANTIDEPRESSANT AND HOT FLUSHES

Duloxetina Vs Escitalopram

European Journal of Cancer Care

Original Article

Duloxetine and escitalopram for hot flushes: efficacy and compliance in breast cancer survivors

BIGLIA N., BOUNOUS V.E., SUSINI T., PECCHIO S., SGRO L.G., TUNINETTI V. & TORTA R. (2016) *European Journal of Cancer Care*

Table 2. Mean hot flushes (HF) activity baseline (T0) and after 4 (T1) and 12 weeks (T2) of treatment

	Duloxetine	Escitalopram
Weekly HF frequency (mean)		
T0	89.6	82.5
T1	39.7 (−56%; $P = 0.001$)	46.2 (−48.3%; $P < 0.001$)
T2	43 (−49.8%; $P = 0.003$)	39 (−53%; $P = 0.001$)
Weekly HF score (mean)		
T0	244.7	197.6
T1	86.6 (−62.6%; $P = 0.001$)	97 (−53.9%; $P < 0.001$)
T2	98.7 (−53.6%; $P = 0.003$)	80 (−60.4%; $P = 0.001$)

Duloxetine and Escitalopram showed **significant reduction** in HF frequency and in HF score with **no significant differences between two groups**

The beneficial effect is **fast**, with a **reduction of more than 50% of HF in the first month**.

ANTIDEPRESSANT AND HOT FLUSHES

Side effects

Treatment with SSRI/SNRIs may cause/complicate sexual dysfunction by reducing libido and causing anorgasmia

- Most studies in depressed populations report sexual function **does not vary by SSRI type**
- Others suggest that female orgasm disorder is most commonly associated with **paroxetine and venlafaxine**

ESCITALOPRAM 10-20 mg/day
did not affect overall sexual function and only minimally affected orgasmic response and lubrication, with no effect on sexually-related personal distress

Reed 2012

ANTIDEPRESSANT AND HOT FLUSHES

Treatment with SSRI/SNRIs may interfere with tamoxifen by inhibiting CYP2D6 enzyme

For women treated with tamoxifen, there may be a preference to avoid some SSRIs and SNRIs that are potent inhibitors of CYP2D6 enzyme with a potential consequent decrease in the efficacy of tamoxifen

- **among SSRIs**, **citalopram and escitalopram have a mild effect** and can be given with tamoxifen, unlike **paroxetine and fluoxetine, which both have large effect**

Handley and Williams 2015

- as regards **SNRIs, venlafaxine and desvenlafaxine are the safest choices** for tamoxifen users, whereas **duloxetine has a moderate effect**

Freeman et al. 2013

Although evidence supports SSRIs and SNRIs efficacy in reducing HFs *(Carroll & Kelley 2009; Handley & Williams 2015*), **only paroxetine has been approved** by the Food and Drug Administration (FDA) **for the treatment of moderate-to-severe vasomotor symptoms** associated with menopause

Orleans et al. 2014

Type of drug and dose	Effectiveness	Side effects	Interactions with tamoxifen
Paroxetine 10-25 mg/day (7.5 mg salt is the only SSRIs/SNRIs approved for the treatment of menopausal moderate-to-severe HFs by FDA) *(first-line option for HFs)* [15,16,17,21,23]	Up to 64% HFs score reduction, improvement also of sleep	- Nausea at the 20 mg dose - The low dosage has less toxicity - low withdrawal rate, in particular with low doses	Potent inhibitors of CYP2D6 enzyme; they should be avoided during tamoxifen use
Fluoxetine 10-30 mg/day (*second line option for HFs)* [16,17,21,22]	24% HFs score and 19% HFs frequency reduction	- 18% withdrawal rate - withdrawal due more to ineffectiveness of treatment rather than to side effects	
Sertraline 25 -100 mg/day (*second line option for HFs)* [16,17,21]	Modest effect on HFs	-10% dropout rate -nausea and decreased sexual function	Moderate effect on the CYP2D6 enzyme
Citalopram 10-20 mg/day *(first-line option for HFs)* [16,17]	Up to 49%–55% HFs score reduction	-20% withdrawal rate	Mild inhibitory effect on the CYP2D6 enzyme; they can be used in tamoxifen users
Escitalopram 10-20 mg/day *(first-line option for HFs)* [16,17]	47% HFs frequency and 24% reduction	-Best tolerability profile -withdrawal rate of 4% -nausea, weakness and drowsiness	

Biglia et al. 2018, submitted

Menopause: The Journal of The North American Menopause Society
Vol. 22, No. 11, pp. 1155-1174
DOI: 10.1097/GME.0000000000000546

POSITION STATEMENT

Nonhormonal management of menopause-associated vasomotor symptoms: 2015 position statement of The North American Menopause Society

Evidence from relatively short-term pharmaceutical trials (eg, 8-12 wk) suggests that there is a return of VMS when treatment is stopped. However, there are no available data on potential effects of withdrawing SSRIs or SNRIs after a period of 2 to 3 years when used for VMS in nondepressed women. Similar evidence is not available from nonpharmacologic, nonhormonal intervention trials.

Therapy should be carefully evauated on a regular basis (eg every 6-12 months) because data on long-term use are limited…..

Randomized clinical trials on gabapentin for hot flushes

Type of patients	Author, year of publication and type of study, number of patients (N)	Type of treatment	Type of measurement	Main results	Adverse events (AEs)
HEALTHY WOMEN	**Guttuso et al 2003**[29] Randomised, double-blind, placebo-controlled trial N=59	1) 900 mg oral gabapentin for 12 weeks vs placebo 2) Extension phase: gabapentin up to 2700 mg/day	Diary for HFs severity and frequency, composite score including both	1) 45% HFs frequency and 54% HFs score reduction from baseline, compared with 29% ($p<0.02$) and 31% ($p<0.01$) respectively for placebo 2) With the higher dose, further reduction of HFs (54% in HF frequency and 67% in the score)	-Somnolence, dizziness, rash -In 50% of gabapentin patients at least one AE (vs 27.6% for placebo) -13% withdrawal rate in the gabapentin group for AEs (vs 3% for placebo)
	Butt et al 2008[30] Randomised, double-blind, placebo-controlled trial N=200	900 mg gabapentin for 4 weeks	Diary for HFs severity and frequency, score including both	51% HFs score and 45.7% frequency reduction vs placebo (26.5% and 24.7%, respectively, $p < 0.001$)	More dizziness, unsteadiness and drowsiness in the gabapentin group vs placebo in the first treatment week, with later AEs reduction
BREAST CANCER SURVIVORS	**Pandya et al 2005**[31] Randomised, double-blind, placebo-controlled, multi-institutional trial N=420 BCSs	300 mg/d or 900 mg/d gabapentin vs. placebo over 8 weeks	Diary for HFs severity, frequency and duration	44% HFs frequency and 46% severity reduction in the 900 mg gabapentin group vs placebo (15% for both, $p < 0.0001$) → gabapentin is effective in HFs control at a dose of 900 mg/day	-Withdrawal rate of 12% at 4 weeks and 17% at 8 weeks for AEs -Significant worsening of appetite
	Biglia et al 2009[32] Randomized controlled trial N=115 BCSs	Oral gabapentin 900 mg/day (N=60) vs vitamin E 800 IU/day (N=55) for 12 weeks	1) For HFs: daily HFs diary 2) For sleep quality: PSQI 3) For other menopausal Symptoms: MRS 4) For QoL: SF-36 Health Survey	1) HFs frequency and score decreased by 57% and 67%, respectively ($p<0.05$) in the gabapentin group 2) Improvement in quality of sleep (PSQI score reduction: 21.33%, $p<0.05$).	The prescribed treatment with gabapentin was never started by 28.3% of BCSs and was interrupted by 28% of BCSs for AEs (dizziness and somnolence)

Biglia et al. 2018, submitted

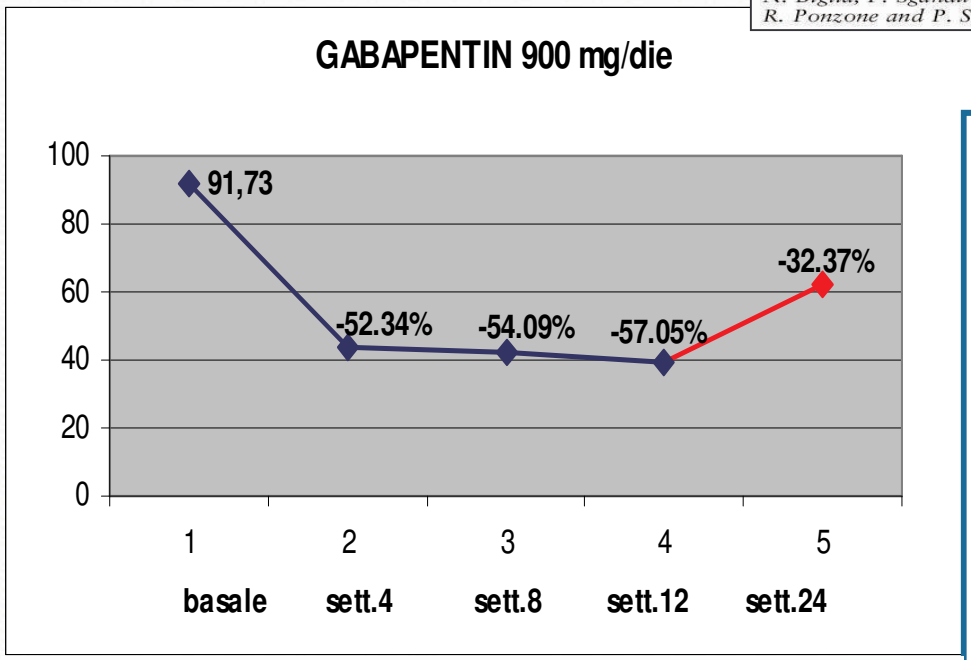
ANTIDEPRESSANT AND HOT FLUSHES

Gabapentin

CLIMACTERIC 2009;12:310–318

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

N. Biglia, P. Sgandurra, E. Peano, D. Marenco, G. Moggio, V. Bounous, N. Tomasi Cont, R. Ponzone and P. Sismondi



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.

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**

Hot flush frequency decreased by **57.05% in the gabapentin group**.

The effect of vitamin E was fairly small: hot flush frequency were reduced by **10.02%**

Gabapentin was also particularly effective in **improving the quality of sleep** (PSQI score reduction: 21.33%)

PHYTOESTROGENES

- Family of plant compounds with **estrogenic and antiestrogenic properties,** depending on dose and menopausal status.
- Phytoestrogens are found in many **fruits, vegetables and grains.** The most frequent sources of phytoestrogens for treatment of menopause are **soy beans and red clover** (Trifolium pratense). Both contain **isoflavones** that are the most oestrogenically potent phytoestrogens.

- These compounds structurally resemble oestradiol (E2) and are shown to have weak oestrogenic activity

- The estrogenic activity is **much less than 17-beta estradiol** and like other weak estrogens. Such as tamoxifen, they can act like SERMs.

PHYTOESTROGENES

efficacy

TABLE 1. *Efficacy of soy-derived isoflavones in hot flash treatment: controlled clinical trials*

Lead author	Trial design	Tx length	N (age)	Daily dosage	Hot flash decreases: Soy	Hot flash decreases: Control	Hot flash decreases: Significance
Soy foods							
Albertazzi[64]	R, DB, PC	12 wk	104 (45-62)	76 mg iso	45%	31%	S
Burke[65]	R, DB, PC	24 mo	241 (mean 51)	42 mg iso	42%	77%	NS
				58 mg iso	59%	77%	NS
Dalais[66]	R, DB, CO	12 wk	52 (45-65)	45 g soy grits (53 mg iso)	22%[a]	51%[b]	—
Knight[67]	R, DB, PC	12 wk	24 (mean 53)	77 mg iso	43%	20%	NS
Murkies[68]	R, DB	12 wk	58 (mean 54-56)	45 g soy flour 45 g wheat flour	40%	25%	NS
St. Germain[69]	R, DB, PC	24 wk	69 (42-62)	40 g iso-rich soy protein	57%	76%	NS
				40 g iso-poor soy protein	54%	76%	NS
Van Patten[70]	R, DB, PC	12 wk	123 (mean 54)	500 mL soy beverage (90 mg iso)	30%	40%	NS
Soy isoflavone supplements							
Faure[71]	R, DB, PC	16 wk	75 (mean 54)	soy iso extract (70 mg iso)	61%	21%	S
Han[72]	R, DB, PC	16 wk	82 (45-55)	150 g soy protein (100 mg iso)	27%	1%	S
Nikander[73]	R, DB, PC, CO	12 wk	62 (mean 54)	114 mg iso	10%	14%	NS
Penotti[74]	R, DB, PC	24 wk	62 (45-60)	72 mg iso	40%	40%	NS
Quella[75]	R, DB, PC, CO	4 wk	177 (18 to >50)	600 mg soy tablets (50 mg iso)	35%	38%	NS
Scambia[76]	R, DB, PC	6 wk	39 (mean 53-54)	400 mg soy extract (50 mg iso)	44%	24%	S
Upmalis[77]	R, DB, PC	12 wk	177 (55)	soy iso extract (50 mg iso)	28%	19%	NS

Superscript numbers refer to citations in the reference list. Tx, treatment; R, randomized; DB, double-blind; PC, placebo-controlled; OL, open-label; CO, crossover; iso, isoflavones; S, statistically significant vs control; NS, not statistically significant vs control.

[a]NS v baseline; no between-group comparison.

[b]S v baseline; no between-group comparison.

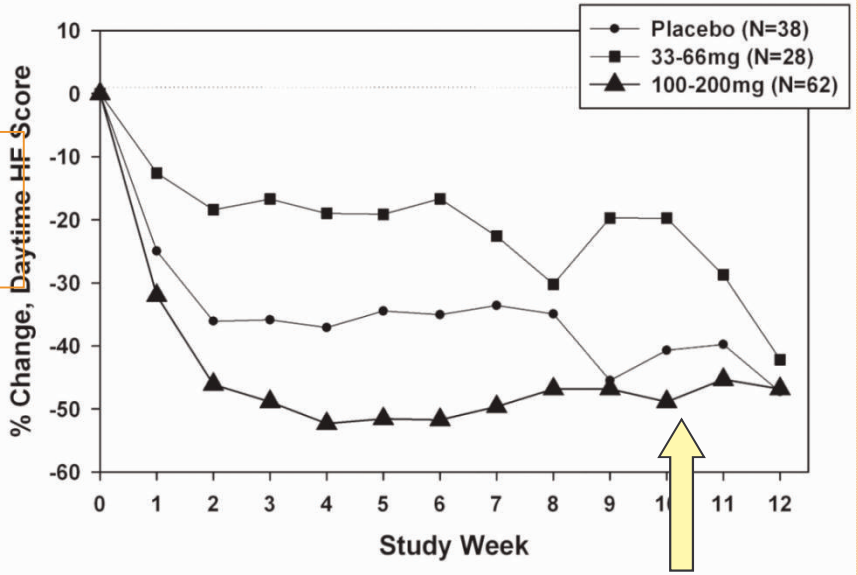
NAMS 2004

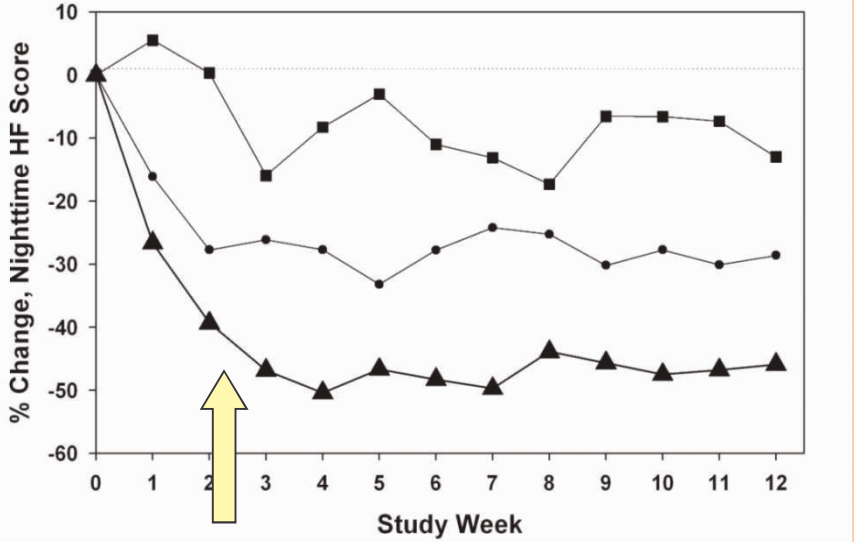
Published in final edited form as:
Menopause. 2013 September ; 20(9): 911–921. doi:10.1097/GME.0b013e3182829413.

THE IMPACT OF DOSE, FREQUENCY OF ADMINISTRATION, AND EQUOL PRODUCTION ON EFFICACY OF ISOFLAVONES FOR MENOPAUSAL HOT FLASHES: A PILOT RANDOMIZED TRIAL

Sybil L. Crawford, PhD[1], Elizabeth A. Jackson, MD[2], Linda Chu Lampe, PhD[3], Katherine Leung, MPH[1], and Judith K. Ockene, F

HF intensity scores were lowest in women randomized to the highest total daily dose (100-200mg) and to the highest dosing frequency (2-3 times daily)





Abstract

Objective—The relatively modest benefit in vasomotor symptom relief seen in clinical trials of isoflavones may reflect once-daily dosing as well as low percentages of participants able to metabolize daidzein to equol, a potentially more biologically active isoflavone. This pilot study examined whether symptom reduction was greater with more frequent administration as well as with higher daily doses. In addition, we explored possible effect modification by equol producer status.

Methods—We randomized 130 peri- (no menses in past three months) and postmenopausal (12+ months amenorrhea) women with an average of 5+ moderate/severe hot flashes per day to treatment arms with varying total daily isoflavone doses and dosing frequency, separately for equol producers and non-producers. Participants recorded daily frequency and severity of hot flashes. Analyses compared mean daily hot flash intensity scores (sum of hot flashes weighted by severity) by total daily dose and by dosing frequency. Dose- and frequency-related differences also were compared for equol producers and non-producers.

Results—Hot flash intensity scores were lowest in women randomized to the highest total daily dose (100-200mg) and in women randomized to the highest dosing frequency (2-3 times daily), with greater benefits in nighttime than in daytime scores. Dose-related and frequency-related differences were somewhat larger in equol producers than in non-producers.

PHYTOESTROGENES

Efficacy

Phytoestrogens for vasomotor menopausal symptoms (Review)

- 43 randomised controlled trials trials (4,364 ptz);
- **No women with previous breast cancer**

THE COCHRANE COLLABORATION®

- **No significant difference** overall in the frequency of HF between red clover extract and placebo.
- Some trials found that **alleviated the frequency and severity of HF and night sweats** when compared to placebo but **low quality and underpowered.**
- **Strong placebo effect**: reduction in frequency ranging from 1% to 59% with placebo.
- **No** evidence of **oestrogenic stimulation of the endometrium** when used for up to two years.

There is no evidence of effectiveness in the alleviation of menopausal symptoms with the use of phytoestrogen treatments.

Lethaby, 2013

PHYTOESTROGENES

Safety

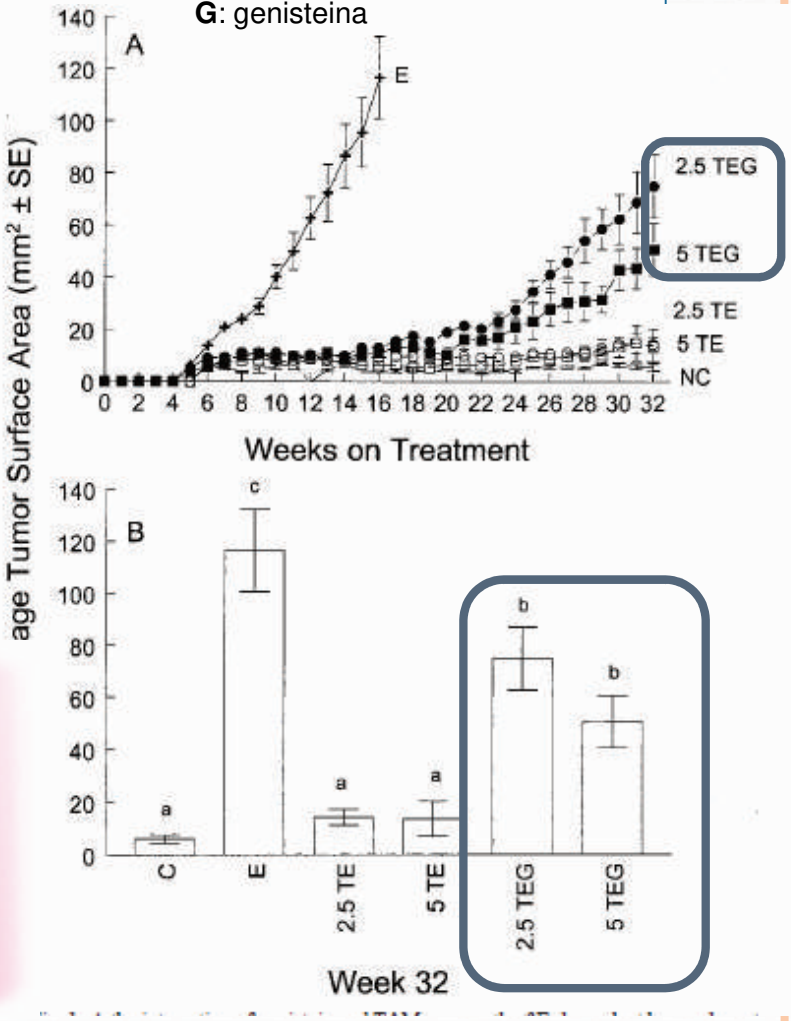
Dietary Genistein Negates the Inhibitory Effect of Tamoxifen on Growth of Estrogen-dependent Human Breast Cancer (MCF-7) Cells Implanted in Athymic Mice

Young H. Ju, Daniel R. Doerge, Kimberly F. Allred, et al.

Cancer Res 2002;62:2474-2477.

Treatment with TAM (2.5 TE and 5 TE) suppressed E2-stimulated MCF-7 tumor growth in ovariectomized athymic mice.
Dietary genistein negated/overwhelmed the inhibitory effect of TAM on MCF-7 tumor growth, lowered E2 level in plasma, and increased expression of E-responsive genes (*e.g., pS2, PR, and cyclin D1).*

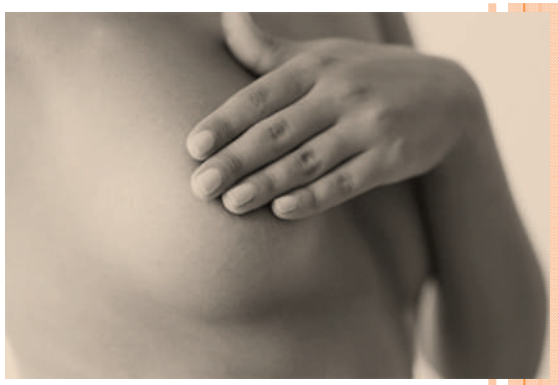
E: estradiol 2.5 o 5 mg
T: tamoxifene
G: genisteina



CONCLUSION Dietary intake of **genistein negated the protective effect of TAM.** Therefore, caution is warranted for postmenopausal women consuming dietary genistein while on TAM therapy for E-responsive breast cancer.

PHYTOESTROGENES

Safety



Genistein induces breast cancer-associated aromatase and stimulates estrogen-dependent tumor cell growth in *in vitro* breast cancer model

M.B.M. van Duursen[a,*], S.M. Nijmeijer[a], E.S. de Morree[a], P. Chr. de Jong[b], M. van den Berg[a]

[a] *Endocrine Toxicology, Institute for Risk Assessment Sciences, Utrecht University, Yalelaan 2, PO Box 80177, 3508 TD, Utrecht University, Utrecht, The Netherlands*
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Breast cancer

ABSTRACT

In breast cancer, the interaction between estrogen-producing breast adipose fibroblasts (BAFs) and estrogen-dependent epithelial tumor cells is pivotal. Local estrogen production is catalyzed by aromatase, which is differentially regulated in disease-free and tumorigenic breast tissue. The use of aromatase inhibitors to block local estrogen production has proven effective in treatment of estrogen-dependent breast cancer. However, a major problem during breast cancer treatment is the sudden onset of menopause and many women seek for alternative medicines, such as the soy isoflavone genistein. In this study, we show that genistein can induce estrogen-dependent MCF-7 tumor cell growth and increase breast cancer-associated aromatase expression and activity *in vitro*. We have previously developed an *in vitro* breast cancer model where the positive feedback loop between primary BAFs and estrogen-dependent MCF-7 tumor cells is operational, thereby representing a more natural *in vitro* model for breast cancer. In this model, genistein could negate the growth inhibitory action of the aromatase inhibitor fadrozole at physiologically relevant concentrations. These data suggest that soy-based supplements might affect the efficacy of breast cancer treatment with aromatase inhibitors. Considering the high number of breast cancer patients using soy supplements to treat menopausal symptoms, the increasing risk for adverse interactions with breast cancer treatment is of major concern and should be considered with care.

FITOESTROGENI

2012 American Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Survivors**, consente l'utilizzo di alimenti ricchi di soia** alle donne con anamnesi positiva per carcinoma mammario, ma **attenzione ai supplementi di isoflavoni** (dosi nettamente superiori)

"It is **not known** if isoflavone supplements can be **safely** consumed by women with breast cancer"

NAMS 2004

"Even if there are no data that soy, phytoestrogens or isoflavone products increase the risk of breast or endometrial cancer, **women with breast or endometrial cancer should consider consulting their oncologists before using them**"

NAMS 2014

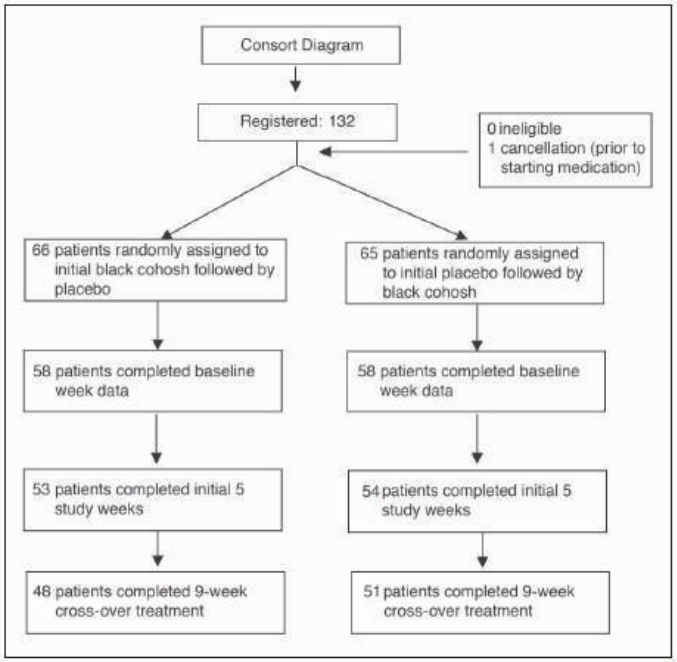
VOLUME 24 · NUMBER 18 · JUNE 20 2006

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase III Double-Blind, Randomized, Placebo-Controlled Crossover Trial of Black Cohosh in the Management of Hot Flashes: NCCTG Trial N01CC[1]

Barbara A. Pockaj, James G. Gallagher, Charles L. Loprinzi, Philip J. Stella, Debra L. Barton, Jeff A. Sloan, Beth I. Lavasseur, Radha M. Rao, Tom R. Fitch, Kendrith M. Rowland, Paul J. Novotny, Patrick J. Flynn, Elliott Richelson, and Abdul H. Fauq



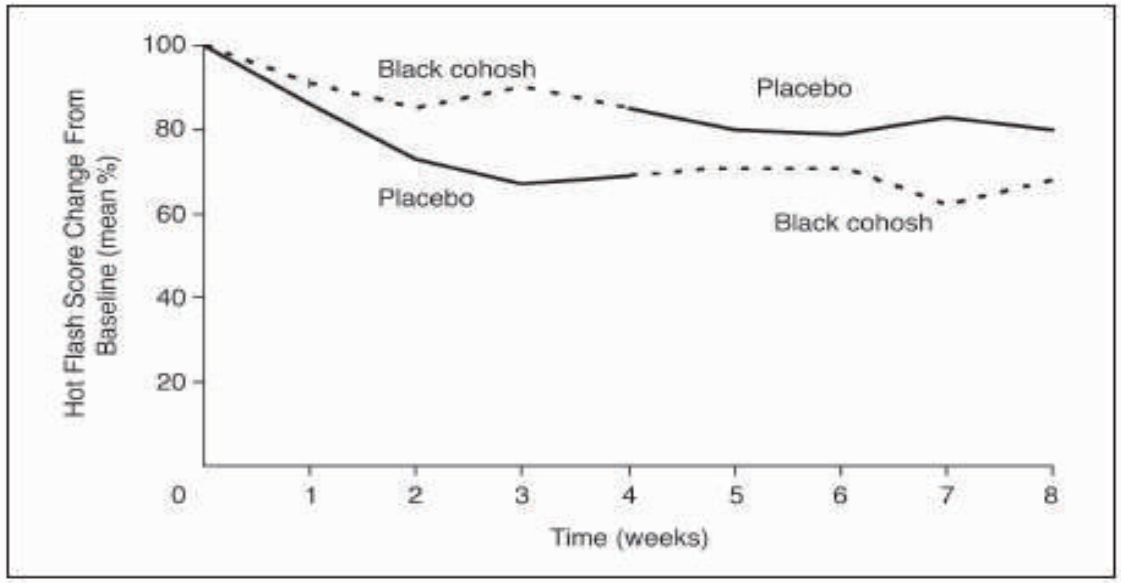


Fig 2. Hot flash score reductions from baseline over the study period. Week 0 represents the baseline week.

Patients receiving black cohosh reported a **mean decrease in hot flash score of 20% compared with a 27% decrease for patients on placebo (P .53).**

This trial failed to provide any evidence that black cohosh (40 mg/day) reduced hot flashes more than the placebo.

Black cohosh (*Cimicifuga racemosa*) in tamoxifen-treated breast cancer patients with climacteric complaints – a prospective observational study

A prospective observational study was carried out in **50 breast cancer patients** on tamoxifen treated with an isopropanolic extract of black cohosh (1–4 tablets, 2.5 mg) for 6 months.

Table II. MRS II and subscores.

	t1 day 1 (n=50)	t2 day 28±7 (n=47)	t3 day 90±14 (n=40)	t4 day 180±28 (n=35)	Last observation (n=47)
MRS II Score	17.6 (6.1)	14.0 (5.7)**	14.2 (5.1)**	13.8 (6.4)**	13.6 (6.5)**
Vegetativesomatic symptoms	8.1 (2.6)	6.8 (2.6)*	6.4 (2.0)*	6.5 (2.7)*	6.4 (2.8)*
Psychic symptoms	6.6 (3.6)	4.6 (2.8)*	5.0 (3.0)*	4.5 (2.9)*	4.4 (3.1)*
Urogenital symptoms	3.0 (2.5)	2.7 (2.1)	2.8 (2.2)	2.8 (2.5)	2.8 (2.4)

Mean (SD); *$p < 0.01$; **$p < 0.001$.

The reduction of the total MRS II score under black cohosh treatment from 17.6 to 13.6 was statistically significant.

Hot flashes, sweating, sleep problems, and anxiety improved, whereas urogenital and musculoskeletal complaints did not change.

Black cohosh extract seems to be a **reasonable treatment approach in tamoxifen treated breast cancer patients with predominantly psychovegetative symptoms.**

Rostock et al. Gynecol Endocrinol 2011; 27(10): 844–848

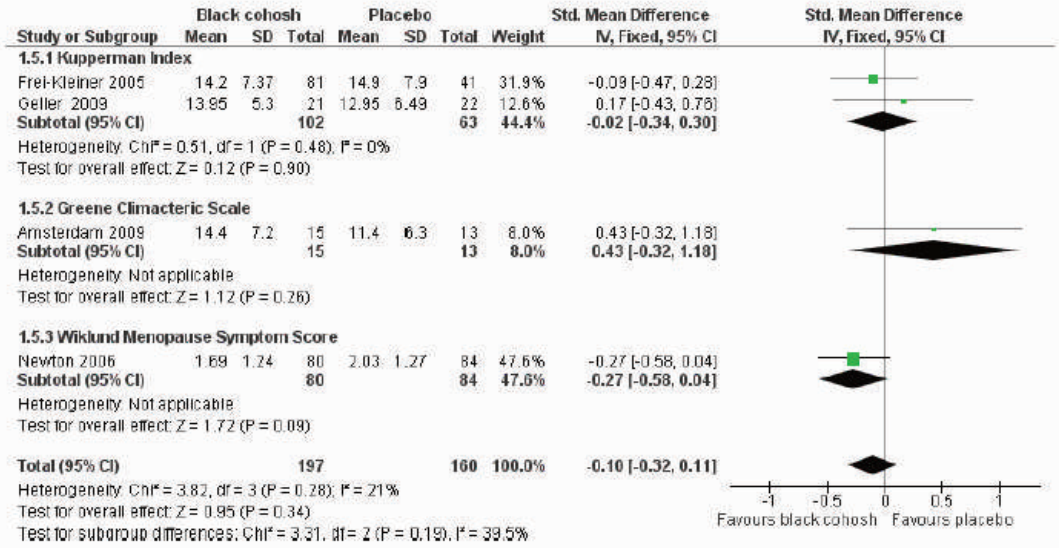
BLACK COHOSH

Efficacy

Black cohosh (*Cimicifuga* spp.) for menopausal symptoms (Review)

Leach MJ, Moore V

Figure 5. Forest plot of comparison: 1 Black cohosh versus placebo, outcome: 1.5 Menopausal Symptom Score.



THE COCHRANE COLLABORATION®

"There is currently insufficient evidence to support the use of black cohosh for menopausal symptoms in healthy women"

PHYTOESTROGENES

Early and locally advanced breast cancer – NICE guideline 2015

Evidence supporting the use of black cohosh for menopausal symptoms in breast cancer patients is lacking.

Published Ahead of Print on December 7, 2015 as 10.1200/JCO.2015.64.3809
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2015.64.3809

JOURNAL OF CLINICAL ONCOLOGY | ASCO SPECIAL ARTICLE

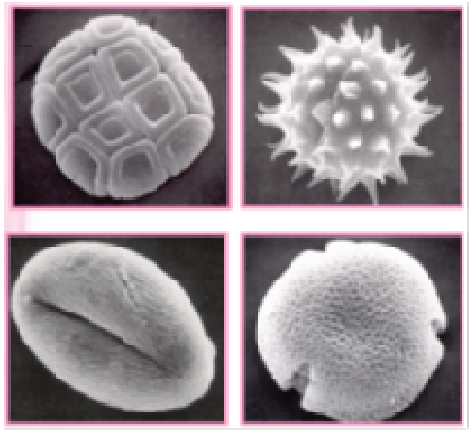
American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline

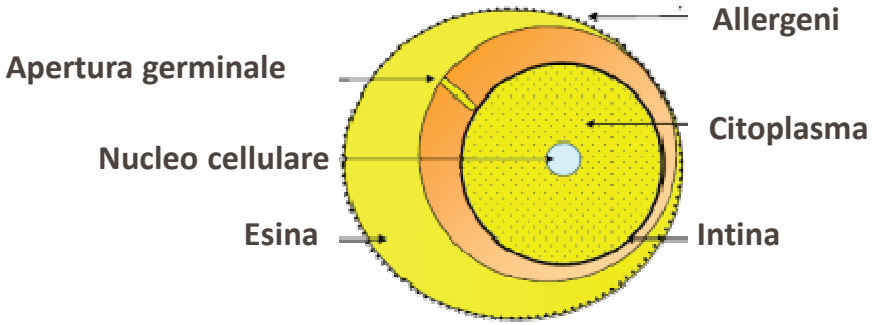
Carolyn D. Runowicz, Corinne R. Leach, N. Lynn Henry, Karen S. Henry, Heather T. Mackey, Rebecca L. Cowens-Alvarado, Rachel S. Cannady, Mandi L. Pratt-Chapman, Stephen B. Edge, Linda A. Jacobs, Arti Hurria, Lawrence B. Marks, Samuel J. LaMonte, Ellen Warner, Gary H. Lyman, and Patricia A. Ganz

Complementary therapies have been studied and some have been found to be *minimally effective* ...

Estratto citoplasmatico di polline con Vit E

- **Contiene 3 agenti attivi :**
  - **estratto di polline purificato**
  - **mix di polline citoplasmatico ed estratti di pistillo**
  - **Vitamina E**
- **I pollini ed i pistilli provengono da specie selezionate in Svezia**
- **La coltivazione e la raccolta vengono effettuate secondo le GMP (Good Manufacture Practices) dell'EMA**
- **La metodologia produttiva brevettata assicura una concentrazione standard di agenti attivi in ogni compressa**

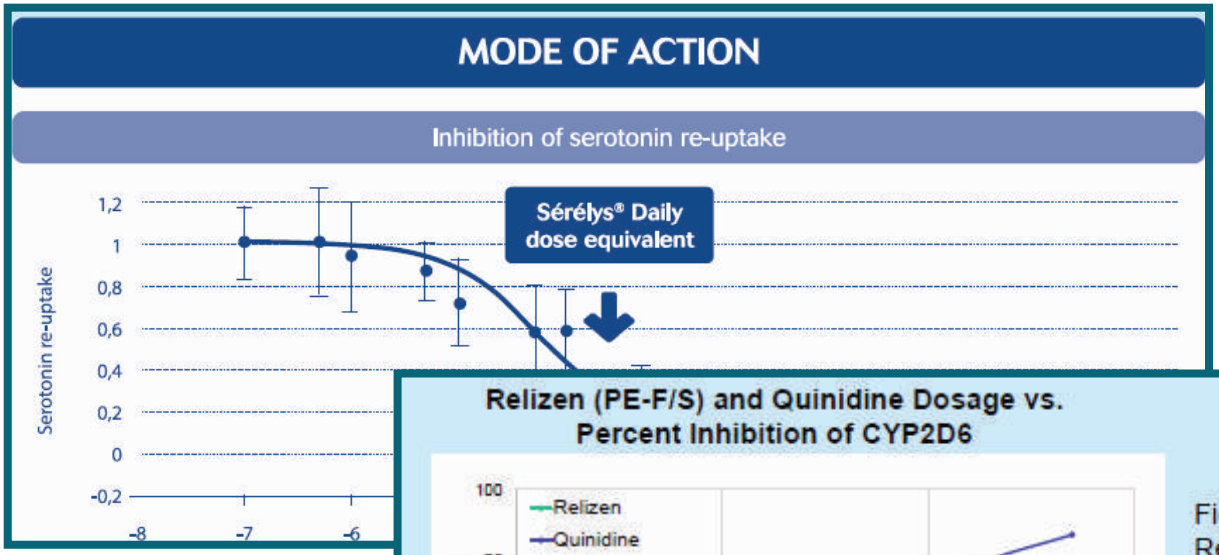




Elia D et al. *Genesis*. 2008 November; 135: 12-15

Meccanismo d'azione
Inibisce il re-uptake della serotonina (simil SSRI)

Inibizione del re-uptake della serotonina



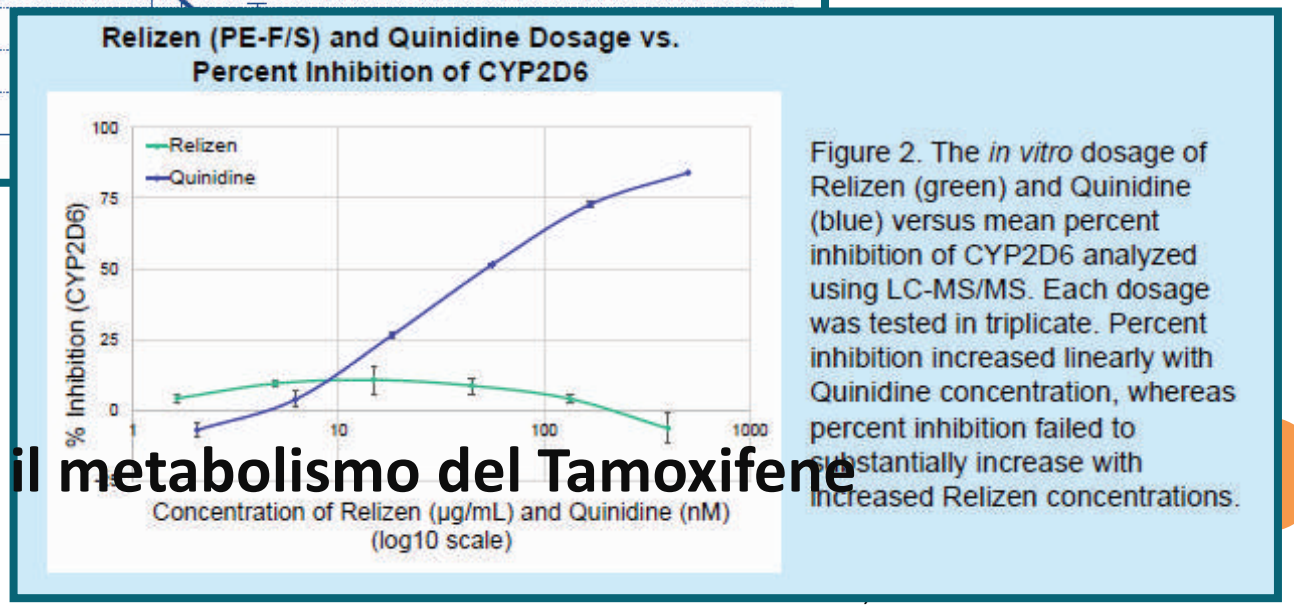


Figure 2. The *in vitro* dosage of Relizen (green) and Quinidine (blue) versus mean percent inhibition of CYP2D6 analyzed using LC-MS/MS. Each dosage was tested in triplicate. Percent inhibition increased linearly with Quinidine concentration, whereas percent inhibition failed to substantially increase with increased Relizen concentrations.

Senza ridurre il metabolismo del Tamoxifene

Goldstein et al-Menopause; vol 22,No11, 2015

Meccanismo d'azione NON ESTROGENICO

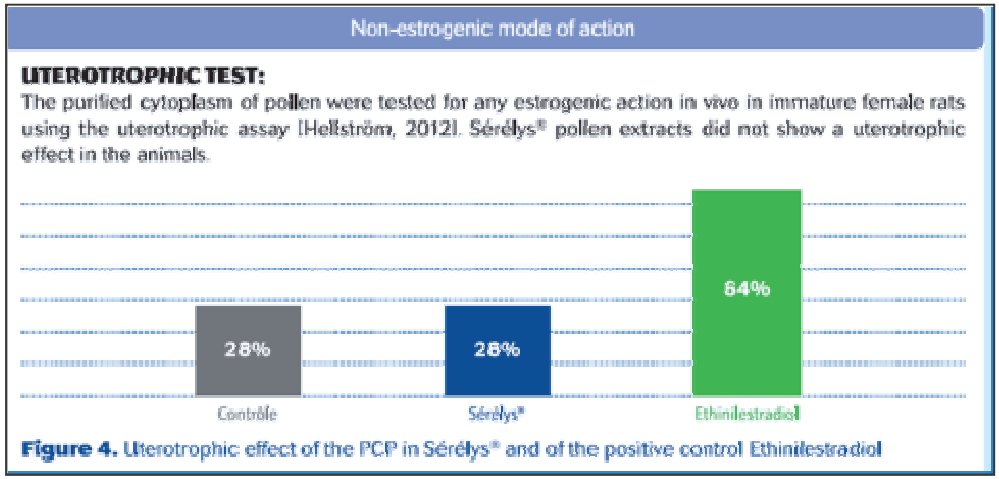
Non contiene fitoestrogeni

TABLE 1. *Concentration of common isoflavonoid phytoestrogens in the pollen extracts PI 82 and GC FEM*

Extract and batch	Isoflavonoid concentration in the extracts, ng/mg extract					
	Daidzin	Genistin	Daidzein	Genistein	Formononetin	Biochanin A
PI 82						
570005101	94	9	22	nd	nd	nd
570008101	79	15	nd	nd	nd	nd
570009101	48	9	nd	nd	nd	nd
GC FEM						
578907103	59	nd	14	nd	nd	nd
578908101	50	13	11	nd	nd	nd
578909101	28	nd	10	nd	nd	nd

nd, not detected.

E non ha alcun effetto uterotrofico



Hellstrom AC et al. *Menopause*, 2012.

Riduzione significativa della vampate di calore

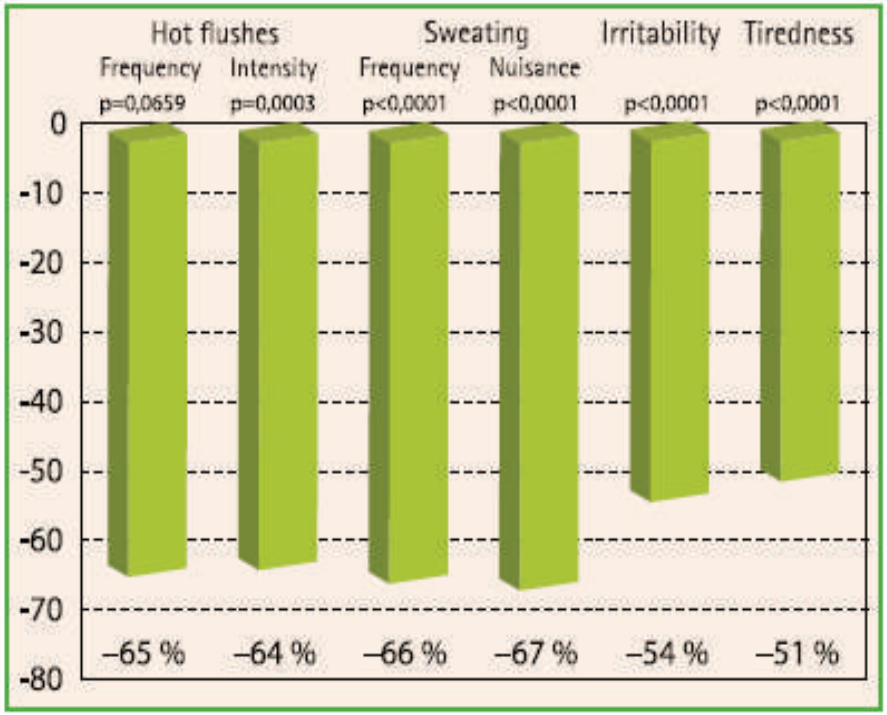


Figure 3: Reduction in symptoms on J84

Tutti i parametri studiati ed in particolare ***le vampate di calore e le sudorazioni notturne sono migliorati significativamente*** tra la prima visita (C1) e la seconda (C2), ***effettuata dopo 84 giorni***.

Elia D et al. *Genesis*. 2008 November; 135: pp 12-15

Purified polline extract for hot flushes – *in vitro* and clinical studies

		Author, year of publication and type of study	Number of patients (N) and type of treatment	Type of measurement	Main results
Efficacy in healthy women		**Winther et al 2005**[34] *Double-blind, placebo-controlled trial*	N=64 PPE 2/day per 3 months	-MRS -15 QoL parameters	-65% HFs reduction in the PPE group vs 38% in the placebo group ($p<0.006$) -Improvement in the QoL parameters (tiredness, dizziness , mood, libido, headache, irritability, mood swings and sensitiveness) in the PPE group compared to baseline ($p<0.031$)
Safety in breast cancer survivors	**No estrogenic activity**	**Winther et al 2005**[34] *Double-blind, placebo-controlled trial*	N=64 PPE 2/day per 3 months	-15 QoL parameters -Diary of menses -Blood samples for FSH, E2, TT, SHBG	-No changes in vaginal dryness parameter -No change in menses frequency -No change in blood levels of FSH, E2, TT, SHBG
		Hellstrom et al 2012[35] *In vitro study*		-High-performance liquid chromatography analyses of phytoestrogens in PPE -Estrogenic activity evaluation in the immature female rat uterotrophic bioassay with PPE	-PPE in the high dose of 500 mg kg/day contains low, subeffective concentrations of daidzin, daidzein, and genistin. Genistein, formononetin, and biochanin could not be detected. -No uterine growth in female rats with PPE
	No interference with CYP2D6 enzyme	**Goldstin et al 2015**[36] *In vitro study*		Test for potential inhibition of CYP2D6 enzyme by PPE at high concentrations in pooled human liver microsome with Quinidine as a reference.	-Negligible inhibition of CYP2D6 with PPE (-6.53% to 10.67%), whereas Quinidine completely inhibited the CYP2D6.

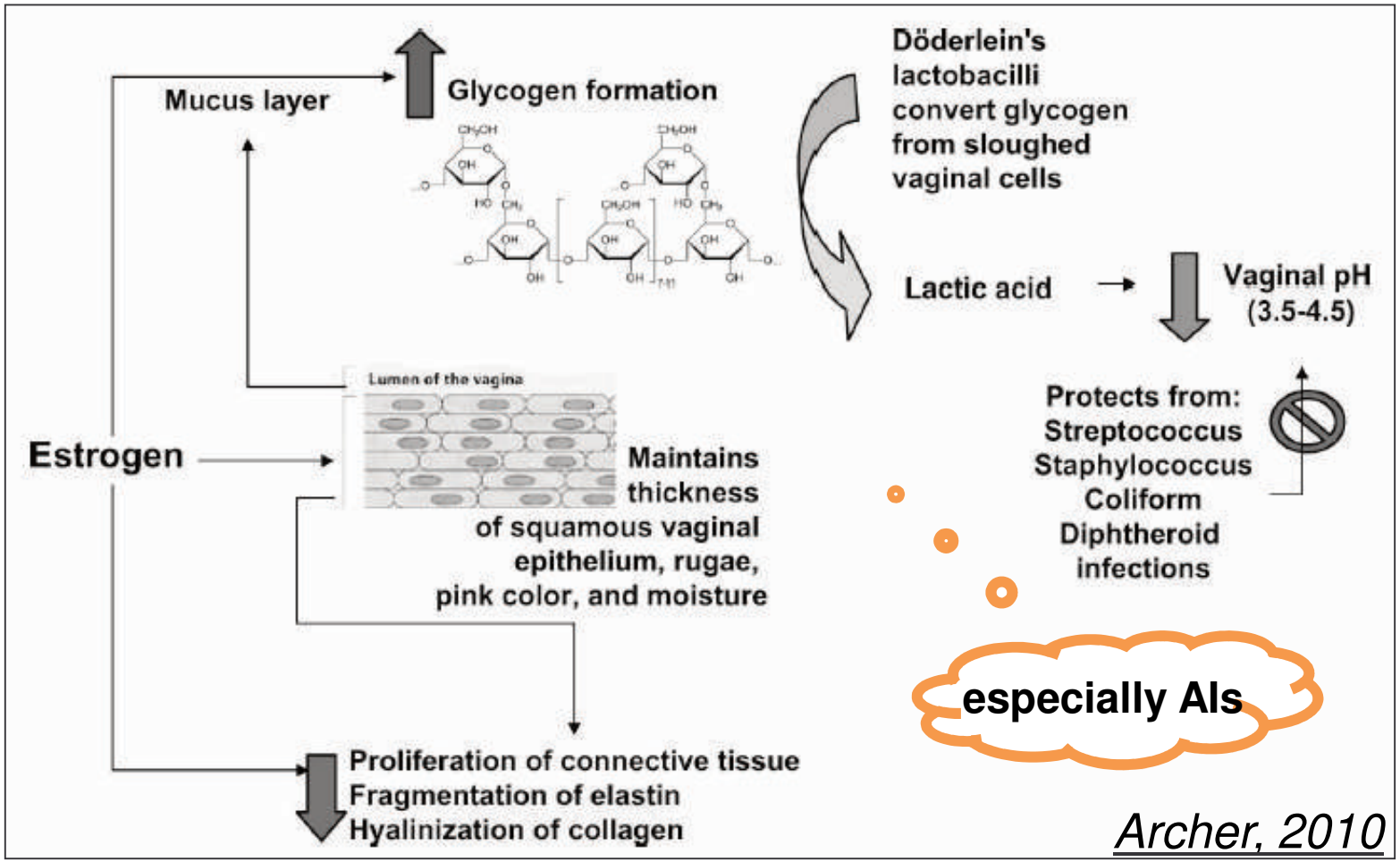
Biglia et al. 2018, submitted

VULVAR AND VAGINAL ATROPHY

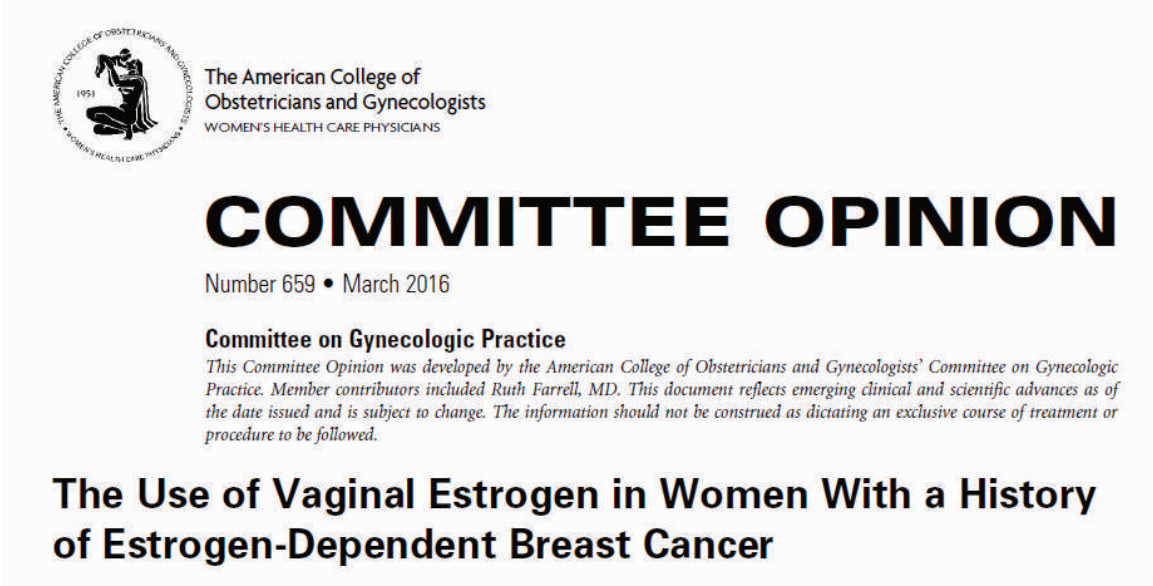
Vulvar and vaginal atrophy

about 60% of BC survivors

→ vaginal dryness,
→ dyspareunia,
→ atrophic vaginitis
→sexual problems.



Archer, 2010



The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

COMMITTEE OPINION

Number 659 • March 2016

Committee on Gynecologic Practice

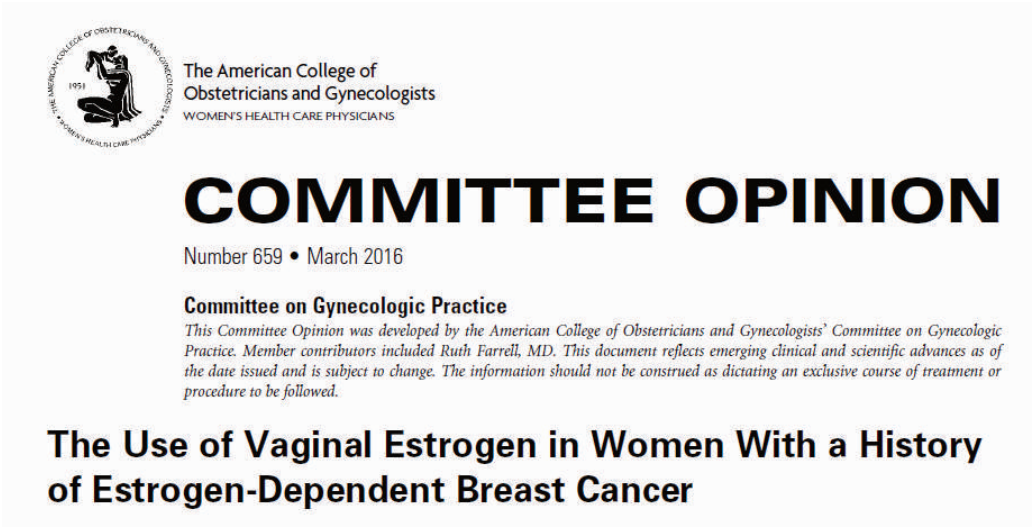
This Committee Opinion was developed by the American College of Obstetricians and Gynecologists' Committee on Gynecologic Practice. Member contributors included Ruth Farrell, MD. This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.

The Use of Vaginal Estrogen in Women With a History of Estrogen-Dependent Breast Cancer

• **Non hormonal approaches are the first-line choices** for managing urogenital symptoms or VVA during or after treatment for breast cancer. However, non hormonal methods (moisturizers, lubricants) may have limited and temporary effect on symptoms and QOL.

• Among women with a history of estrogen-dependent breast cancer **vaginal estrogen should be reserved for those patients who are unresponsive to non hormonal remedies.**

• The decision to use vaginal estrogen may be made in coordination with a woman's oncologist. Additionally, **it should be preceded by an informed decision-making and consent process** in which the woman has the information and resources *to consider the benefits and potential risks* of low-dose vaginal estrogen.



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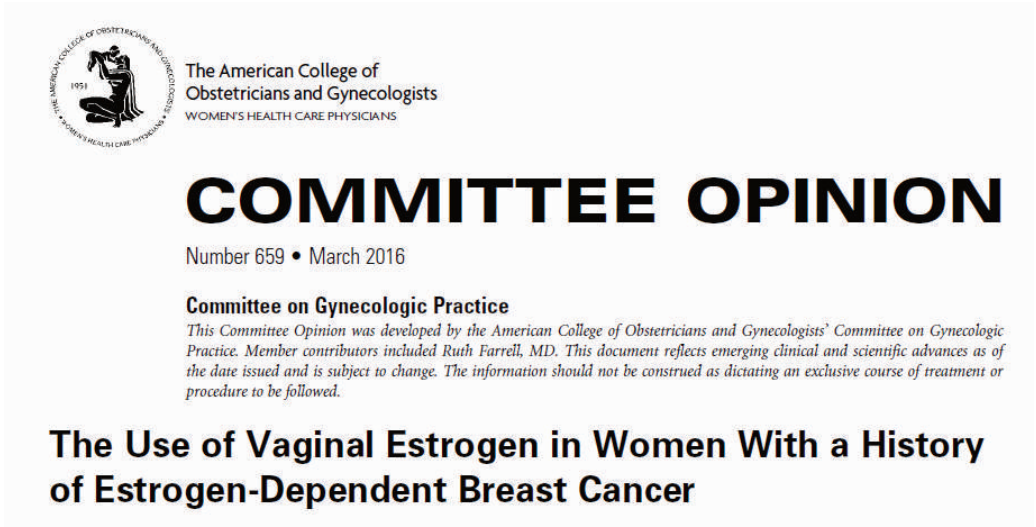
- Vaginal ET has been shown to provide symptomatic relief of VVA and generally delivers lower doses of hormone as compared to systemic HT, with minimal systemic absortion.
- There are many available preparations of vaginal estrogens with different doses and potency. Studies show that the use of low-dose or ultra low-dose vaginal ET does not result in sustained serum estrogen levels exceeding the normal menopausal range.
- Data do not show an increased risk of cancer recurrence among BC survivors who use vaginal estrogen to relieve urogenital symptoms;
- However, the study population is small and the study period short.

Reference	Type of Study	Study Population	Main Outcome	Treatment	Study Period	Results
O'Meara et al, 2001[48]	Retrospective case-control study	43% (75 patients) of 174 BCSs using HRT (compared with 2581 BCSs not using HRT)	Recurrence and mortality	LET (CEE and dienestrol)	457 person-years	Risk of recurrence or mortality not increased
Dew et al, 2003[49]	Cohort study	69 BCSs treated for VVA (compared with 1403 BCSs who did not require treatment for VVA)	Recurrence	36 BCSs vaginal estriol creams and pessaries; 33 BCSs estradiol 25-mg tablets	1 year (median time; range, 0.1-5)	No increase in the recurrence rate
Kendall et al, 2006[47]	Prospective clinical study	7 Postmenopausal BCSs treated with AIs	Serum E2, FSH, LH levels	Vaginal estradiol 25 mg tablets	12 weeks	Serum E2 levels increase from baseline levels <5 pmol/L to a mean 72 pmol/L at 2 weeks; however, a decrease to a mean of 16 pmol/L was observed after 1 month; significant further increases were seen in 2 BCSs
Biglia et al, 2010[50]	Prospective clinical study	26 Postmenopausal BCSs using SERMs or AIs (BCSs receiving AIs were excluded from LET administration)	• Efficacy: improvement of VVA evaluated using the Vaginal Symptoms Score, Profile of Female Sexual Function, Vaginal Health Index, and Karyopycnotic Index • Safety: endometrial thickness and serum FSH, LH, E2, E1, TT and SHBG levels	10 Women, vaginal estriol cream 0.25 mg; 8 women, vaginal estradiol tablets 12.5 mg; 8 women, nonhormonal polycarbophil-based vaginal moisturizer (2.5 g)	12 weeks	• Efficacy: low-dose LET is effective for VVA relief, and nonhormonal moisturizer only provides transient benefit • Safety: minimal increase of serum hormone levels with LET
Wills et al, 2012[51]	Prospective study	48 Postmenopausal BCSs and women at risk of breast cancer during AI or SERM treatment	Serum E2 levels	24 Control participants (receiving AIs only); 14 women, intravaginal 25 mg estradiol tablet; 10 women intravaginal estradiol ring (7.5 mg/d)	≥3 Months	LET increases E2 levels, regardless of whether the preparation is by tablet or slow-release ring. Mean E2 levels before insertion and 12 weeks after insertion in BCSs who were using the ring were significantly greater than in control participants; levels before insertion for BCSs who were receiving tablets were not increased compared with control participants, suggesting that E2 increases with use of tablets might not be continuously sustained
Donders et al, 2014[52]	Phase I clinical study	16 Postmenopausal BCSs who were receiving AIs	Serum E1, E2, E3 levels	Ultra—low-dose estriol 0.03 mg and *Lactobacillus acidophilus* vaginal tablets	3 Months	Small and transient increase in serum E3 level, but not in E1 or E2 levels; VVA resolved or improved in all women
Pfeiler et al, 2011[53]	Prospective randomized clinical study	10 BCSs who were receiving AIs	Serum E2 or E3 levels	Vaginal 0.5 mg estriol	2 Weeks	Serum levels of E3 and E2 were not increased



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The Use of Vaginal Estrogen in Women With a History of Estrogen-Dependent Breast Cancer

- *The use of vaginal estrogens may be appropriate for women who use tamoxifen. Low and temporary increase of estrogen levels do not appear to increase recurrence risk in these women, because of a competitive interaction with the estrogen receptor.*
- *Concern remains about recurrence risk in women who use aromatase inhibitors (AIs).*
- *Tipically, AIs decrease circulating E2 levels from 20 pg/ml to less than 1-3 pg/ml.*
- *Studies have demonstrated an initial increase of serum estradiol also with the use of low-dose vaginal estrogen among women treated with AIs.*
- *Some Authors note that even a small increase in systemic E2 levels may have a detrimental effects on recurrence risk, though these levels were not sustained over time and increased cancer recurrence was not noted.*

Caution: Vaginal estradiol appears to be contraindicated in postmenopausal women on adjuvant aromatase inhibitors

A. Kendall[1], M. Dowsett[1], E. Folkerd[1] & I. Smith[2*]

Ann Oncol 2006

The serum estradiol levels in 7 women on adjuvant AI therapy for early breast cancer using standard dose of E2 vaginal tablets (estradiol 25mcg administered daily for 2 weeks then twice weekly) at day 14 raised from a median level of 3 to 72 pmol/l; at day 28 there was a drop in E2 levels to less than 35 pmol/l (median 16 pmol/l).

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Patient	Concurrent AI	Serum estradiol levels on Vagifem (pmol/l)				
		Baseline	Week 2	Week 4	Week 7–10	Week >12
1	Letrozole	<3.0	220	40	219	
2	Letrozole	<3.0	232	31	20	<3.0
3	Letrozole	3.5	77	16	3	
4	Anastrozole	<3.0	46		<3.0	<3.0
5	Exemestane	7.4	67	16	137	
6	Anastrozole	<3.0	<3.0	<3.0		
7[a]	Anastrozole	3.2	83		14	

"The vaginal estradiol tablet 25 mcg significantly raises systemic estradiol levels, at least in the short term. This reverses the estradiol suppression achieved by aromatase inhibitors in women with breast cancer"

Ultra-low-dose estriol and *Lactobacillus acidophilus* vaginal tablets (Gynoflor®) for vaginal atrophy in postmenopausal breast cancer patients on aromatase inhibitors: pharmacokinetic, safety, and efficacy phase I clinical study

Donders et al., 2014

Phase I study: assessed circulating estrogens in **16 breast cancer patients on aromatase inhibitor** with VVA using vaginal ultra-low-dose 0.03 mg estriol (E3) and Lactobacillus combination vaginal tablets (a daily vaginal tablet for 28 days followed by a maintenance therapy of 3 tablets weekly for 8 weeks)

The vaginal atrophy resolved or improved in all women. The product was well tolerated

Compared with baseline, serum estrone and estradiol did not increase in any of the women at any time following vaginal application. Serum estriol transiently increased after the first application in 15 of 16 women, with a maximum of 168 pg/ml 2–3 h post-insertion. After 4 weeks, serum estriol was slightly increased in 8 women with a maximum of 44 pg/ml.

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Published Ahead of Print on December 7, 2015 as 10.1200/JCO.2015.64.3809
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2015.64.3809

JOURNAL OF CLINICAL ONCOLOGY | ASCO SPECIAL ARTICLE

American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline

Carolyn D. Runowicz, Corinne R. Leach, N. Lynn Henry, Karen S. Henry, Heather T. Mackey, Rebecca L. Cowens-Alvarado, Rachel S. Cannady, Mandi L. Pratt-Chapman, Stephen B. Edge, Linda A. Jacobs, Arti Hurria, Lawrence B. Marks, Samuel J. LaMonte, Ellen Warner, Gary H. Lyman, and Patricia A. Ganz

Sexual Health

It is recommended that primary care clinicians:

(a) should assess for signs and symptoms of sexual dysfunction or problems with sexual intimacy

(b) should assess for reversible contributing factors to sexual dysfunction and treat when appropriate

(c) should offer non hormonal, water-based lubricants and moisturizers for vaginal dryness (first line treatment)

(d) should refer for psychoeducational support, group therapy, sexual counseling, marital counseling, or intensive psychotherapy when appropriate

Hormonal therapies, such as a low-dose estrogen vaginal tablets or an estradiol vaginal ring, may be recommended for vaginal dryness because of urogenital atrophy, although results commonly take approximately 6 to 12 weeks.

The safety of these therapies in women with a history of breast cancer is not well established at this time. The level of estrogen absorption is variable, which raises concerns in patients who have a history of breast cancer.

Use of hormonal therapies for women on aromatase inhibitors is not recommended.

Treating dyspareunia secondary to vaginal atrophy and stenosis with vaginal dilators or pelvic floor relaxation techniques may be helpful.

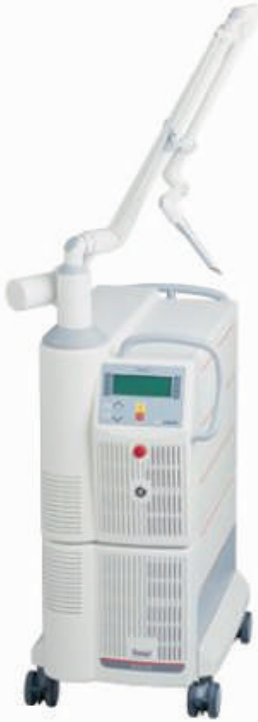
Genitourinary Syndrome of Menopause in Breast Cancer Survivors: Are We Facing New and Safe Hopes?

Nicoletta Biglia,[1] Valentina E. Bounous,[1] Luca G. Sgro,[1] Marta D'Alonzo,[1] Silvia Pecchio,[1] Rossella E. Nappi[2]

Clinical Breast Cancer, Vol. 15, No. 6, 413-20 © 2015

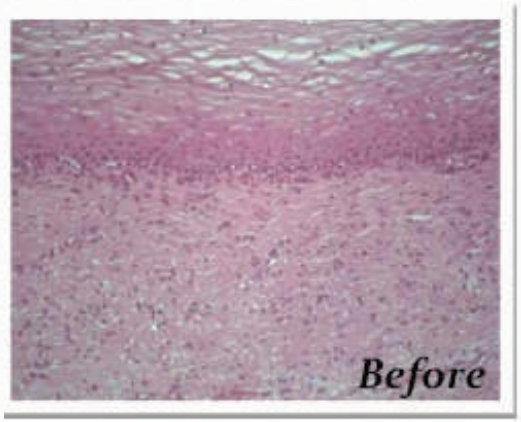
Table 2 Different Options for Genitourinary Syndrome of Menopause Treatment in BCSs

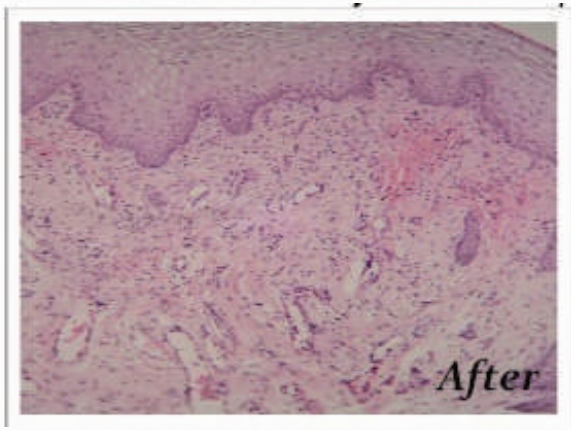
Pharmacological Intervention
Nonhormonal vaginal moisturizers and lubricants (first-line therapy; transient benefit, low compliance)
Low-dose vaginal estrogens (LETs) (for BCSs who do not respond to nonhormonal intervention, after discussion of risk and benefits; caution in women receiving AIs. Great efficacy, even at ultra-low doses)
Oral ospemifene (no clinical trials available in BCSs; in healthy women the efficacy is comparable with LETs, no endometrial or breast stimulation after 12 months of therapy)
Androgen therapy (experimental; concerns regarding possible aromatization of androgens to estrogen in BCSs)
Nonpharmacological Interventions
Vaginal laser (no clinical trials available in BCSs; short follow-up for evaluating its efficacy in healthy women)
Couple counseling
Management of psychosocial distress
Regular sexual activity
Need for larger clinical trials: • Vaginal dilators of graduated size • Pelvic floor physical therapy • Topical liquid lidocaine



The laser therapy has been recently introduced also in gynaecology as a new non hormonal option for the treatment of VVA

It acts inducing the production of new collagen, extracellular matrix and elastic fibers through a controlled heat shock response.

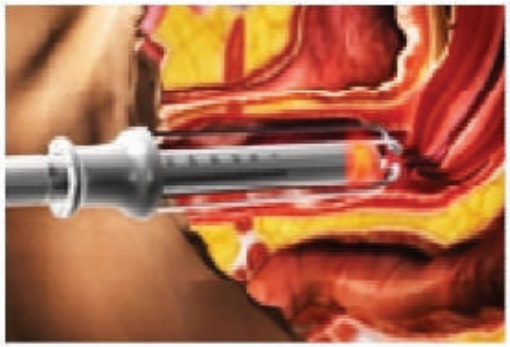


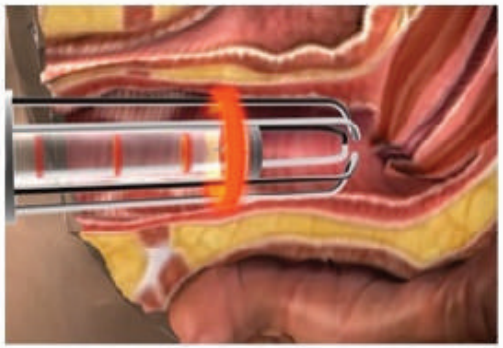


Menopause: The Journal of The North American Menopause Society
Vol. 22, No. 8, pp. 845-849
DOI: 10.1097/gme.0000000000000401

Histological study on the effects of microablative fractional CO_2 laser on atrophic vaginal tissue: an ex vivo study

Stefano Salvatore, MD,[1] Umberto Leone Roberti Maggiore, MD,[1] Stavros Athanasiou, MD,[2] Massimo Origoni, MD,[1] Massimo Candiani, MD,[1] Alberto Calligaro, MD,[3] and Nicola Zerbinati, MD[4]





Laser procedure is an efficient, easy-to-use, quick, well tolerated and safe procedure

Table 1 Differences between CO_2 and Er:YAG lasers in the treatment of genitourinary syndrome of menopause (GSM) (A. Gaspar, as presented at FIGO 2012, personal communication)

	CO_2	Er:YAG
Absorption in water	15 × less than Er:YAG	15 × more than CO_2
Optical penetration	50 µm	3–5 µm
Mechanism of action	ablation	thermal diffusion
Aggressiveness of treatment	always partial necrosis and associated adverse effects	surface of mucosa is not ablated (damaged)
Depth of penetration	3 mm or more	200–500 µm
Operative time (min)	20	15
Pain level during treatment on scale of 0–10	5	0
Pain level post treatment on scale of 0–10	3–5	0
Treatment zone	vaginal canal	vaginal canal and introitus
Tissue-healing phase	20 days	2 days
Return to normal sexual activity	10 days	3 days
Laser release	operator-dependent	uniform and controlled

Climacteric

ISSN: 1369-7137 (Print) 1473-0804 (Online) Journal homepage: http://www.tandfonline.com/loi/icmt20

A 12-week treatment with fractional CO_2 laser for vulvovaginal atrophy: a pilot study

S. Salvatore, R. E. Nappi, N. Zerbinati, A. Calligaro, S. Ferrero, M. Origoni, M. Candiani & U. Leone Roberti Maggiore

CLIMACTERIC 2015;18(Suppl 1):43–48

Rationale and design for the Vaginal Erbium Laser Academy Study (VELAS): an international multicenter observational study on genitourinary syndrome of menopause and stress urinary incontinence

M. Gambacciani, M. G. Torelli*, L. Martella†, G. L. Bracco‡, A. G. Casagrande**, E. Albertin††, S. Tabanelli‡‡, M. Viglietta***, G. D'Ambrogio†††, G. Garone‡‡‡ and M. Cervigni****

CO2 LASER PROCEDURE AT OUR INSTITUTION

Aim

To evaluate the effects of fractional CO_2 laser in the treatment of vulvo-vaginal atrophy (VVA) in 87 post menopausal women. Among these, 13 were breast cancer survivors

Methods

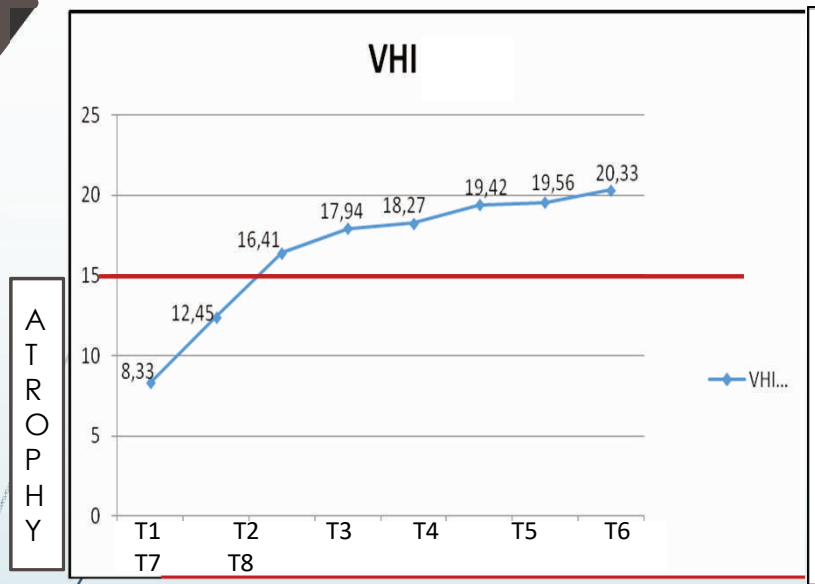
The study was conducted between April 2014 and April 2016 at *Sedes Sapientiae* Institute of Turin

Type of evaluations:

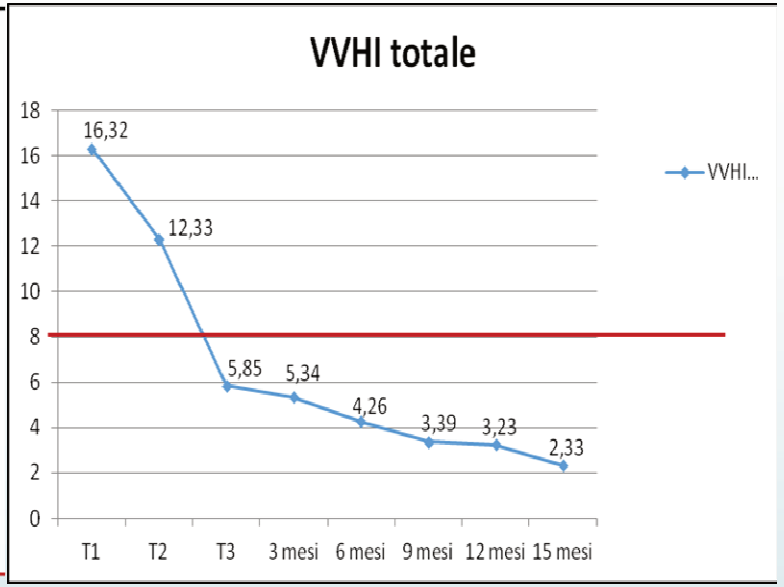
- Subjective measures (DIVA, questionnaire of treatment satisfaction and about the degree of pain encountered during the procedure)
- Objective measures (VHI e VVHI, VAS for dyspareunia and vaginal atrophy)

PHASES	SCREENING	FIRST LASER APPLICATION	SECOND LASER APPLICATION	THIRD LASER APPLICATION	3 MONTHS FU	6 MONTHS FU	9 MONTHS FU	12 MONTHS FU	15 MONTHS FU
Weeks	T0	T1	T2	T3	T4	T5	T6	T7	T8
Pap-test	*								
Inclusion/ Exclusion criteria	*								
Gynecological visit	*								
VHI	*		*	*	*	*	*	*	*
VVHI	*		*	*	*	*	*	*	*
VAS	*		*	*	*	*	*	*	*
DIVA	*				*				
Questionnaire of treatment satisfaction					*				
Questionnaire about the degree of pain encountered in the procedure		*	*	*					

Results: VHI and VVHI



ATROPHY



- At T1 the mean VHI score (8.33) was indicative of atrophy
- Also at T2 the mean VHI score (12.45) was indicative of atrophy
- At T3 the mean VHI score (16.41) was indicative of resolution of the atrophy
- VHI score improved at T4, T5, T6, T7 and T8

- At T1 the mean VVHI score (16.32) was indicative of atrophy
- Also at T2 the mean VVHI score (12.33) was indicative of atrophy
- At T3 the mean VVHI score (5.85) was indicative of resolution of the atrophy
- VVHI score improved at T4, T5, T6, T7 and T8

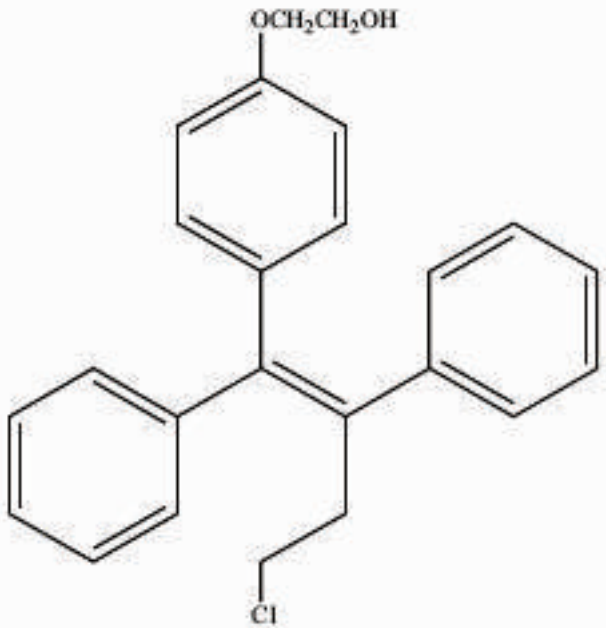
OSPEMIFENE

..was originally developed as a treatment for postmenopausal osteoporosis

Approved for the treatment of moderate to severe symptomatic VVA in postmenopausal women who are not candidates for local estrogen therapy

Wurz, Maturitas 2012

Ospemifene Drug Summary

Drug Name:	Ospemifene
Phase of Development:	NDA Submitted April 2012
Indication:	Postmenopausal Vulvovaginal Atrophy
Pharmacology/Mechanism of Action:	Selective Estrogen Receptor Modulator (SERM) (estrogen receptor agonist/antagonist)
Route of Administration:	Oral
Chemical Structure:	

Ospemifene and breast cancer: preclinical data

Berga SL; *Reprod Sci*. 2013 Oct;20(10):1130-6

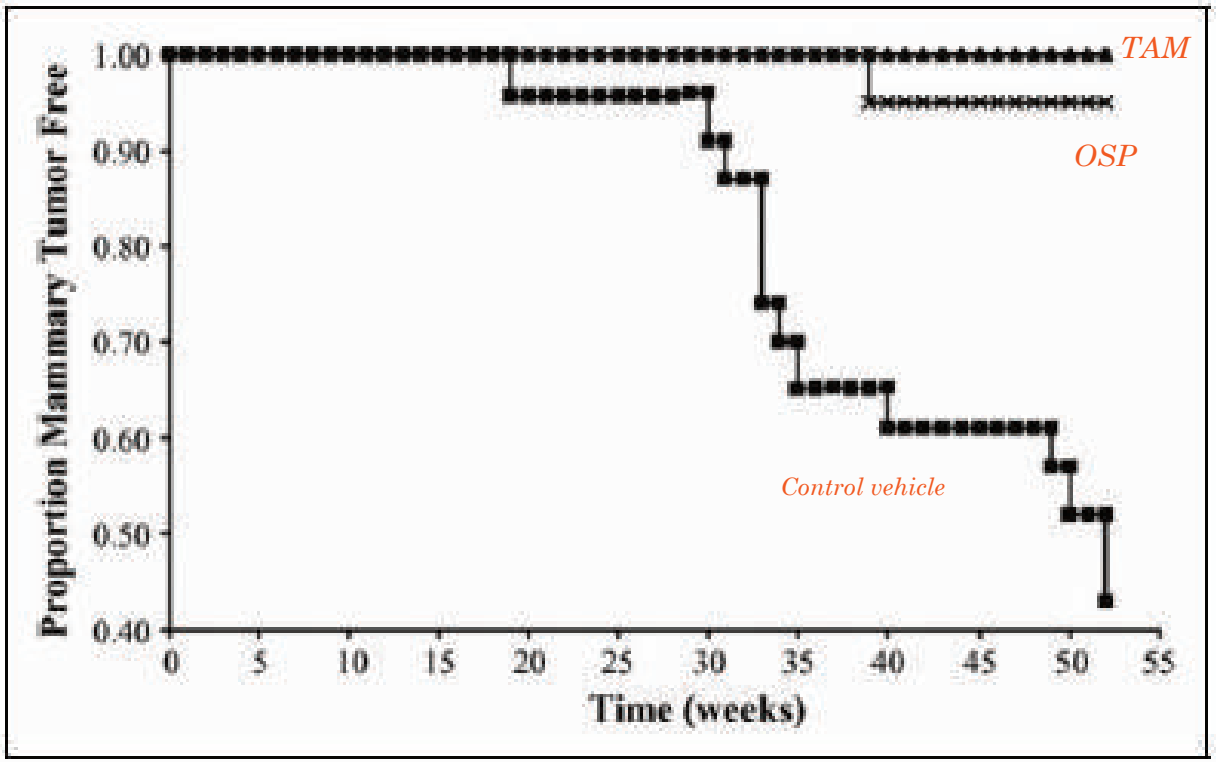
Table 2. Overview of Preclinical Data for Ospemifene in the Breast.

Study	Experimental Model	Key Results
Qu et al[14]	MCF-7 ERα$^+$ breast cancer cells grown in vivo in nude mice	Ospemifene suppressed expression of pS2, an estrogen marker
Taras et al[9]	MCF-7 ERα$^+$ breast cancer cells grown in vivo in nude mice	Ospemifene inhibited the growth of ER-dependent MCF-7 cells; no effect on ER-independent MDA-MB-231 cells
Qu et al[14]	DMBA-induced mammary carcinoma in intact and ovariectomized rats	Ospemifene inhibited tumor growth in a dose-dependent manner (by 12%, 59%, and 79%-88% in the 1-, 10-, and 50-mg/kg groups, respectively)
Wurz et al[10]	DMBA-induced mammary carcinoma in Sencar mice	Ospemifene significantly reduced DMBA-induced mammary carcinomas, similar to tamoxifen
Namba et al[8]	DCIS mouse model	Growth of transplanted cells and incidence of tumors were significantly reduced in mice treated with either ospemifene or tamoxifen compared with untreated mice
Burich et al[33]	MTag.Tg mouse breast cancer model	Ospemifene delayed the development of breast tumors, and average tumor volumes were smaller

Abbreviations: DMBA, dimethylbenzanthracene; DCIS, ductal carcinoma in situ; ER, estrogen receptor.

Ospemifene and breast cancer: preclinical data

Both Ospemifene and tamoxifene reduced the number of DMBA-induced mammary carcinoma in female mice model as compared with untreated mice



G.T. Wurz et al. Journal of Steroid Biochemistry & Molecular Biology 97 (2005) 230–240

Ospemifene - Special warnings and precautions

Endometrium

no increase in vaginal bleeding or spotting.

incidence of endometrial hyperplasia 0.3% (95% CI upper limit 1.74%)

Breast cancer

In women with previous breast cancer, should be used, for the treatment of VVA, only after the treatment of breast cancer, including adjuvant therapy, has been completed

No evidence of negative endometrial effect

NO contra-indication after treatment for breast cancer

CONCLUSION

Recent guide lines underscore the importance of addressing health and QOL issues of breast cancer survivors

- *Hormone therapy (HT) is contraindicated in breast cancer survivors*
- *Antidepressants and gabapentin are an option for women with hot flushes who are not candidates for HT, including breast cancer survivors*
- *Data are inconclusive regarding the efficacy of isoflavones. The safety of isoflavone supplemetation in women with breast cancer is not estabilished.*

CONCLUSION

Vaginal atrophy:

- *Non hormonal lubricants and moisturisers should be considered first line in breast cancer survivors*
- *Low-dose vaginal ET improves vaginal symptoms in the majority of treated women.*
  Their use in BC survivors must follow an informed consent process.
  Use caution in women receiving aromatase inhibitors
- *Ospemifene is an option for women with previous breast cancer suffering from VVA. Its use is allowed only after adjuvant therapy is completed*
- *Laser therapy is a new non hormonal option for the treatment of VVA; efficacy data are promising, but observation period is limited.*

Grazie per l'attenzione!