Menopause Update

What's New in 2022

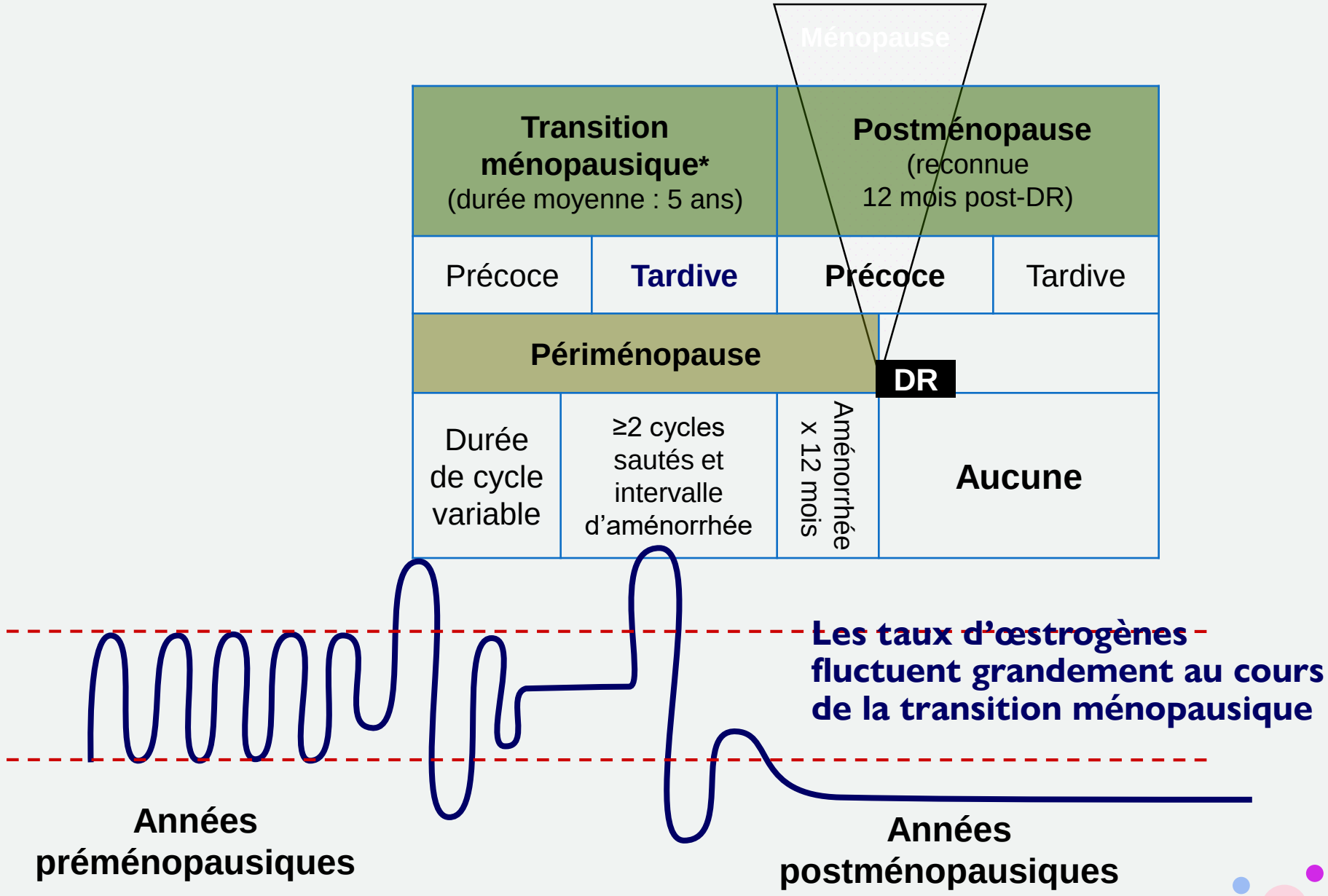
Cleve Ziegler, M.D.

Conflict of Interest

- Speaker and Advisory Board:
- Abbvie
- Biosyent
- Bayer
- Merck
- Organon
- Pfizer

Key Themes

- Understanding the difference between local and systemic effects of estrogen deficiency
- Women's Health Initiative 20 years later
- Evolving treatment paradigms AWAY from estrogen-progestin therapy
- Special Situations



Santoro N et coll. J Clin Endocrinol Metab, vol. 81, 1996, p. 1495-1501.
Kronenberg F. Ann N Y Acad Sci, vol. 592, 1990, p. 52-86.

Symptoms of Menopause:

- LOCAL
- SYSTEMIC

- Vaginal dryness
- Dyspareunia

- Hot Flashes
- Sweats

The Hallmark of Menopause

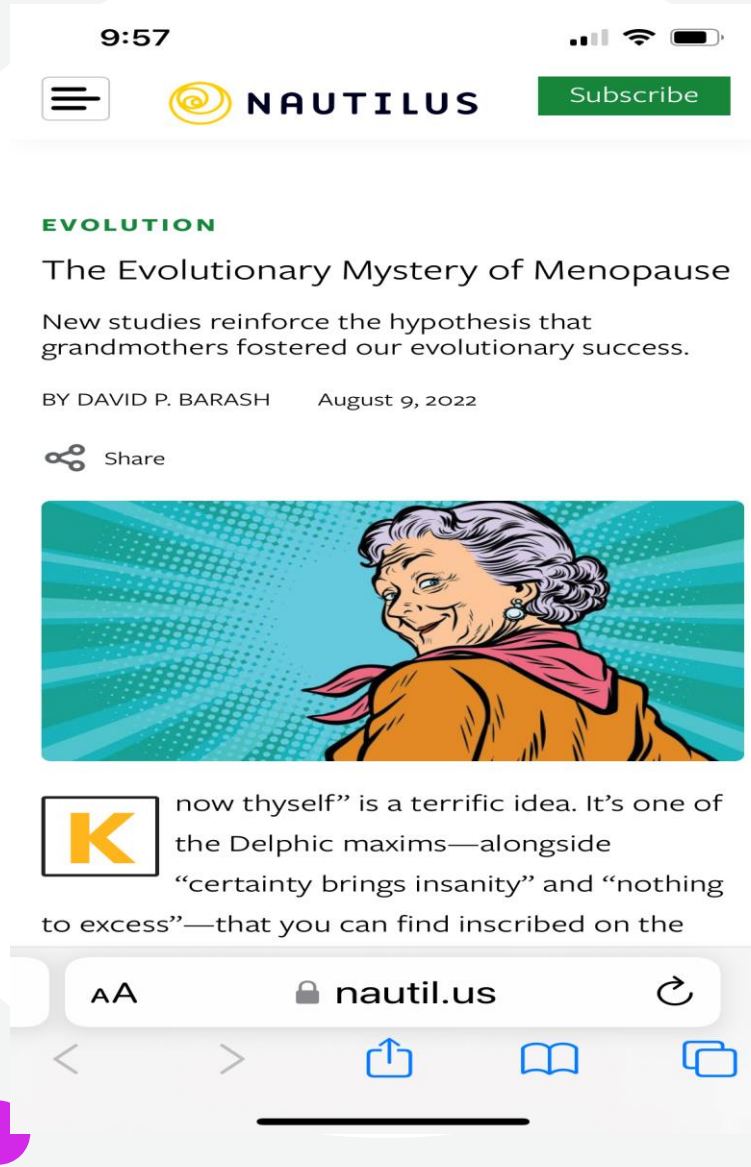
Vasomotor Symptoms (VMS):

- Hot flushes and night sweats affect 75% of peri/postmenopausal women

- VMS have been associated with:
  - Poorer health condition or poorer health status
  - Reduced work productivity
  - Impaired quality of life

NAMS. Menopause Practice: A Clinician's Guide, 5th Ed., 2014.

Menopause: Why?



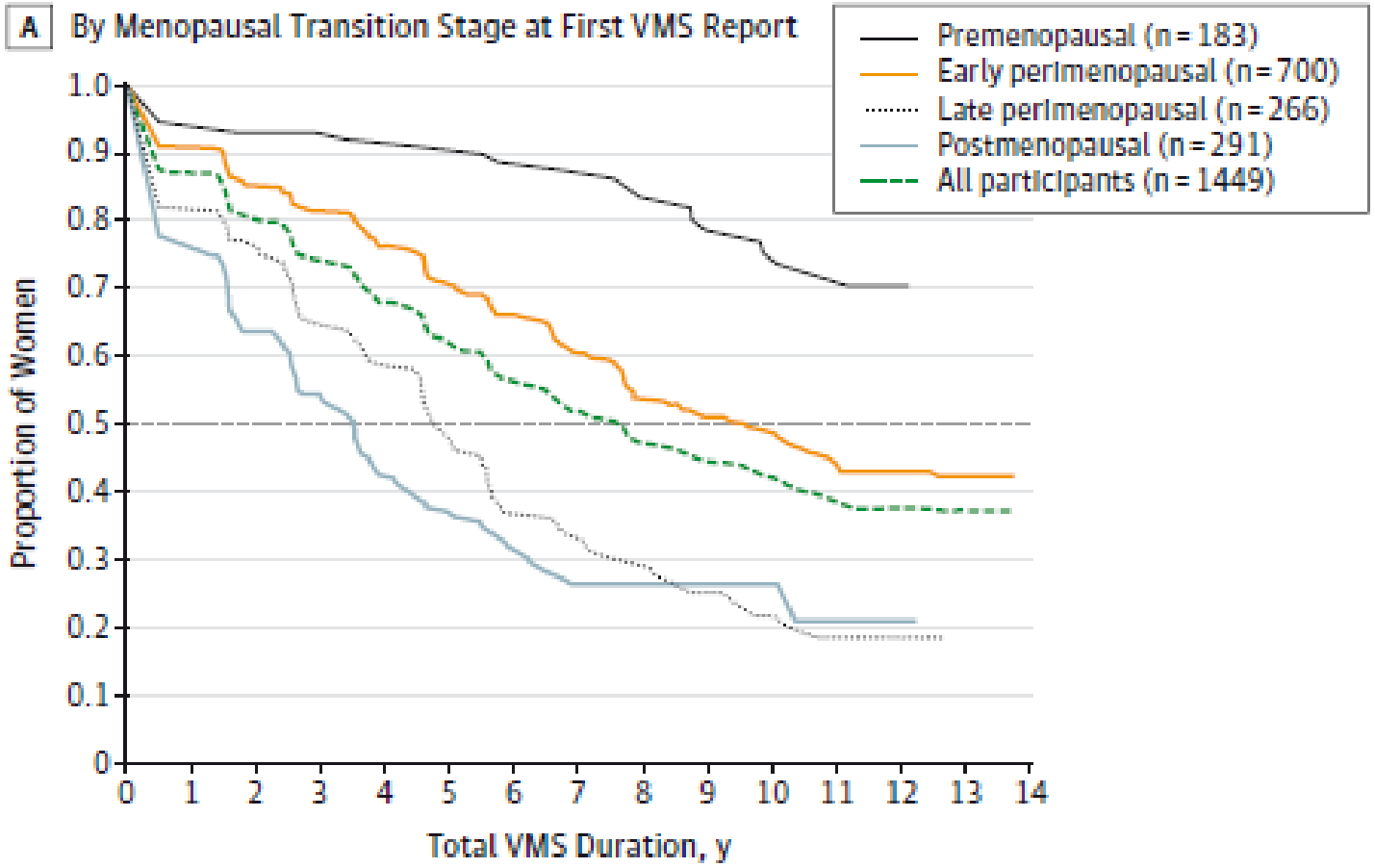
Normalising menopause

Martha Hickey and colleagues argue that social and cultural attitudes contribute to the varied experience of menopause and that medicalisation fuels negative perceptions

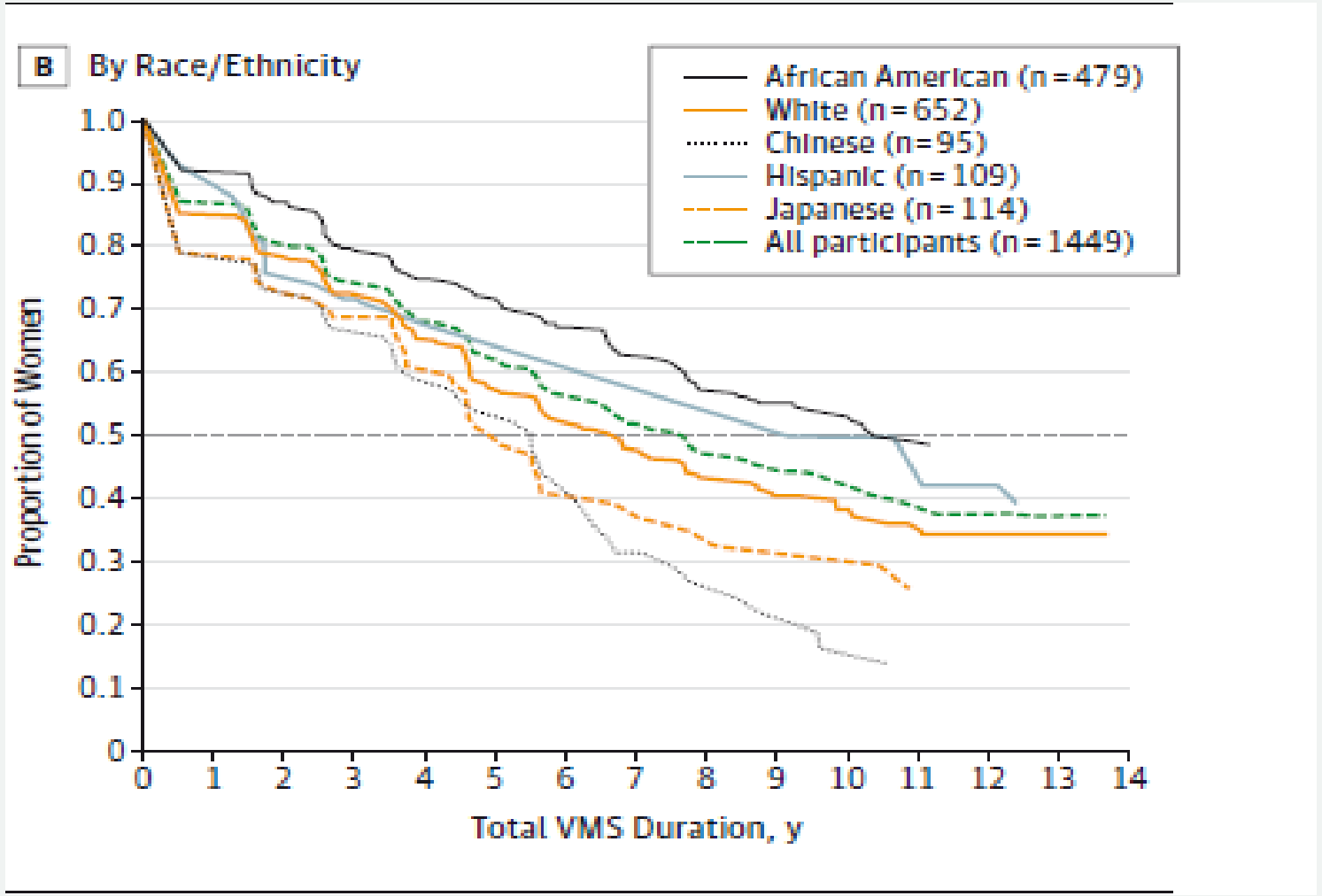
Martha Hickey, [1] Myra S Hunter, [2] Nanette Santoro, [3] Jane Ussher[4]

Key messages

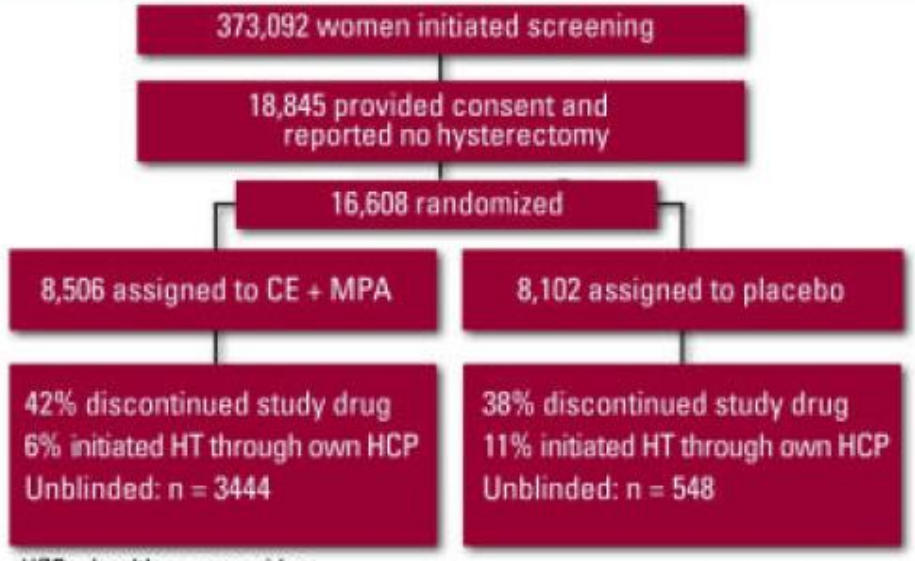
- Menopause is a natural event for half the population, but there is no universal experience
- Experience of menopause is shaped by social, cultural, and biological factors
- The medicalisation of menopause reinforces negative views about reproductive ageing
- Although some women with troublesome menopausal symptoms benefit from menopausal hormone therapy, other effective treatments are available and a narrow focus on symptoms fuels negative expectations
- Challenging gender based ageism, reducing stigma, and providing balanced information about menopause may better equip women to navigate this life stage



SWAN JAMA 2015


B
By Race/Ethnicity
African American (n = 479)
White (n = 652)
Chinese (n = 95)
Hispanic (n = 109)
Japanese (n = 114)
All participants (n = 1449)
Proportion of Women
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Total VMS Duration, y

The Women's Health Initiative (WHI): Estrogen + Progestin Arm



HCP = health care provider
MPA = medroxyprogesterone acetate

Rossouw JE, et al. *JAMA* 2002;288:321

WHI: Estrogen + Progestin Arm: Baseline Characteristics

Characteristic	CE + MPA (n = 8,506)	Placebo (n = 8,102)
Mean age at screening, y (SD)	63.2 (7.1)	63.3 (7.1)
Age group at screening, n (%)		
50–59 years	2,839 (33.4)	2,683 (33.1)
60–69 years	3,853 (45.3)	3,657 (45.1)
70–79 years	1,814 (21.3)	1,762 (21.7)
Hormone use, n (%)		
Never	6,280 (73.9)	6,024 (74.4)
Past	1,674 (19.7)	1,588 (19.6)
Current†	548 (6.4)	487 (6.0)

†Required a 3-month washout prior to randomization.

Rossouw JE, et al. *JAMA* 2002;288:321

WHI: Estrogen + Progestin Arm: Alarming Results?

	RR	%
Breast cancer	1.26	+ 26%
CHD	1.29	+ 29%
Stroke	1.41	+ 41%
PE	2.13	+113%
However...		
Colorectal cancer	0.63	- 37%
Hip fracture	0.66	- 34%
Endometrial cancer	0.83	- 17%
Death from other causes	0.92	- 8%

Rossouw JE, et al. *JAMA* 2002;288:321

Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence

*Collaborative Group on Hormonal Factors in Breast Cancer**

Summary

Background Published findings on breast cancer risk associated with different types of menopausal hormone therapy (MHT) are inconsistent, with limited information on long-term effects. We bring together the epidemiological evidence, published and unpublished, on these associations, and review the relevant randomised evidence.

Methods Principal analyses used individual participant data from all eligible prospective studies that had sought information on the type and timing of MHT use; the main analyses are of individuals with complete information on this. Studies were identified by searching many formal and informal sources regularly from Jan 1, 1992, to Jan 1, 2018. Current users were included up to 5 years (mean 1·4 years) after last-reported MHT use. Logistic regression yielded adjusted risk ratios (RRs) comparing particular groups of MHT users versus never users.

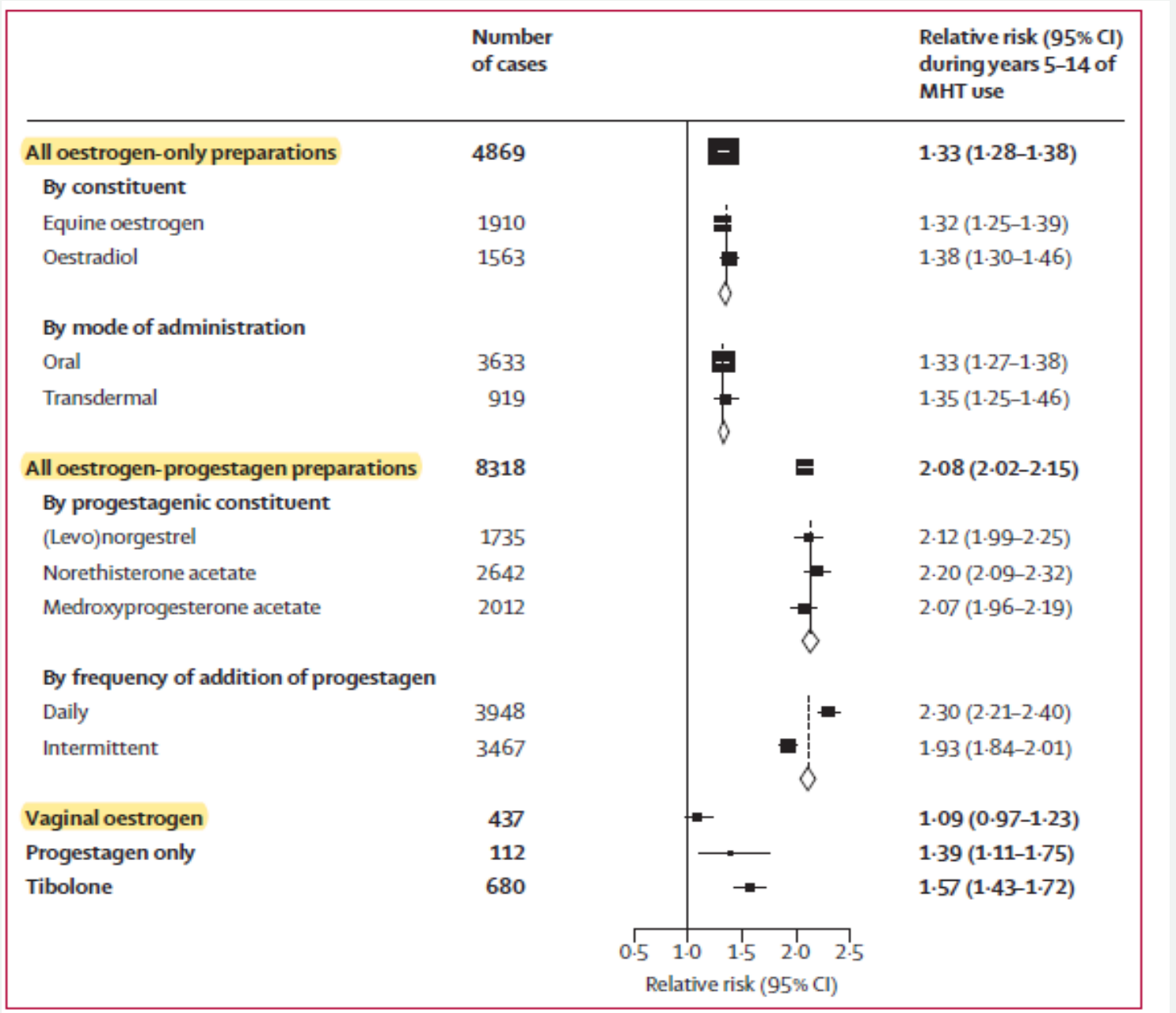


Figure 4: **Main types of MHT: relative risks during years 5–14 of current use**

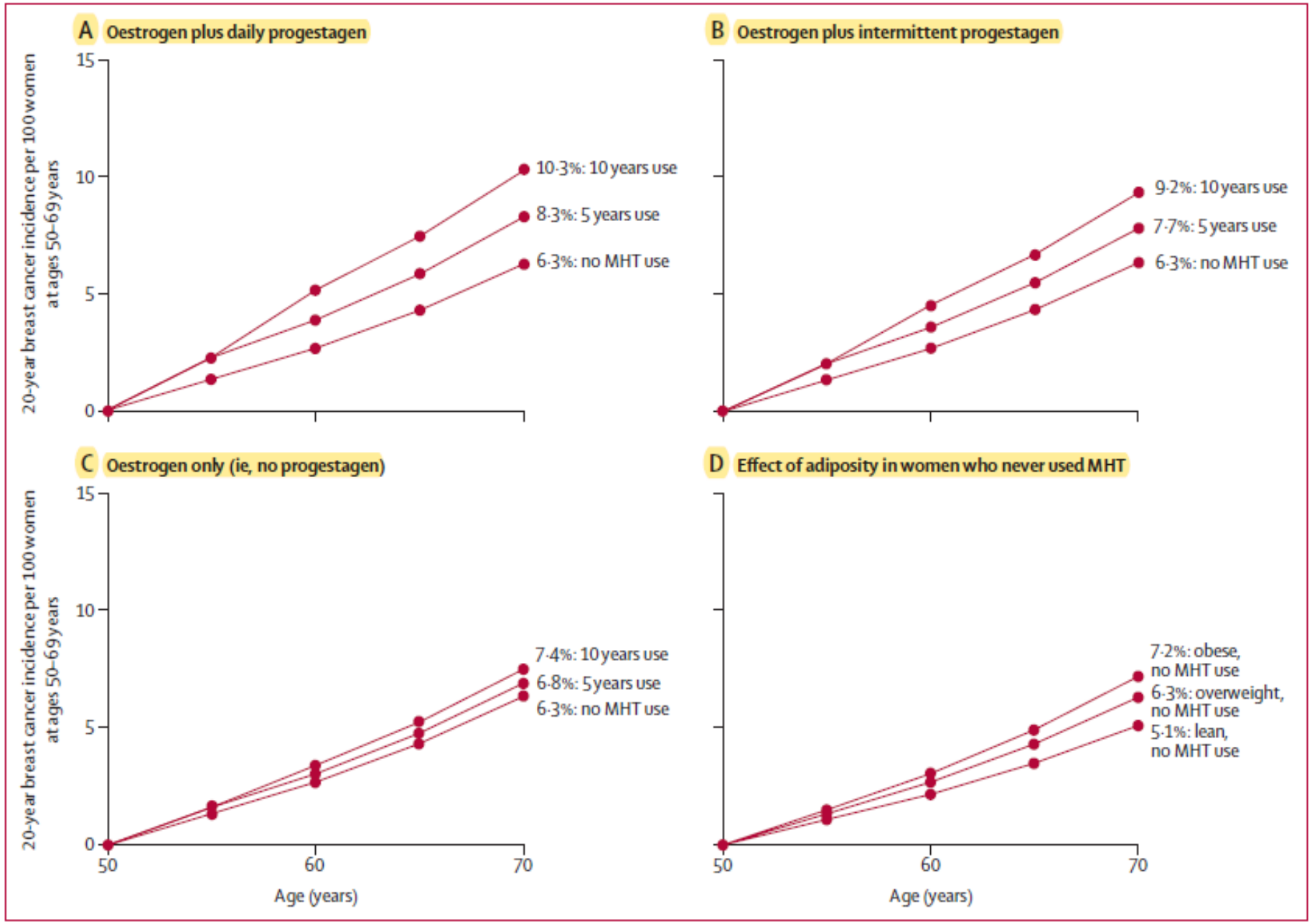
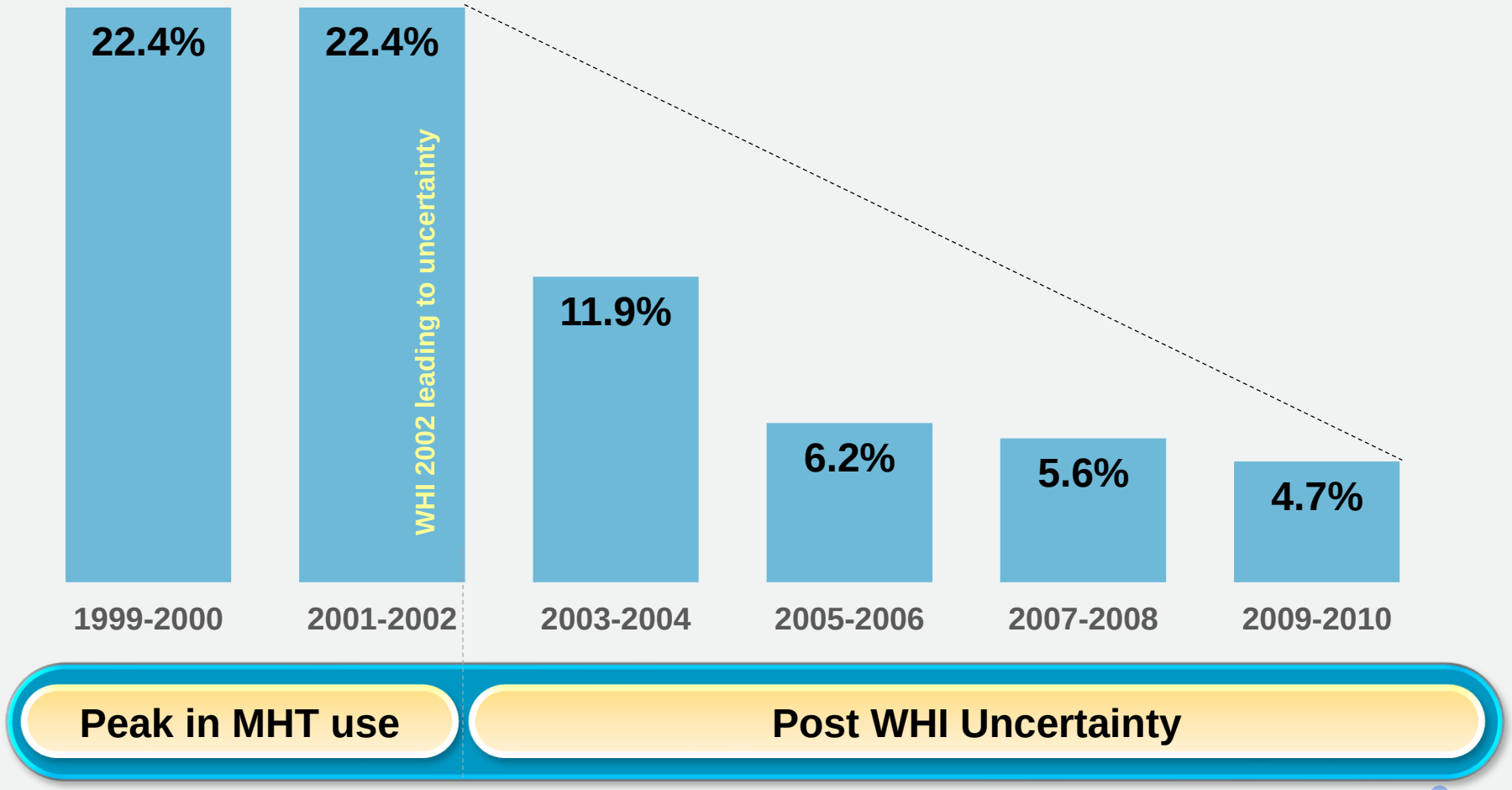


Figure 7: Effect of 5 years or of 10 years of MHT use, starting from age 50 years, on 20-year breast cancer incidence rates

Decline in Use of Hormone Therapy Over Time



Sprague et al. *Obstet Gynecol* 2012;120(3):595–603.

GYNECOLOGICAL ENDOCRINOLOGY
https://doi.org/10.1080/09513590.2022.2118254

Taylor & Francis
Taylor & Francis Group

REVIEW

Review of menopausal hormone therapy with estradiol and progesterone versus other estrogens and progestins

Shelli Graham[a], David F. Archer[b], James A. Simon[c], Kathleen M. Ohleth[d] and Brian Bernick[a]

[a]TherapeuticsMD, Boca Raton, FL; [b]Department of Obstetrics and Gynecology, Clinical Research Center, Eastern Virginia Medical School, Norfolk, VA; [c]School of Medicine, George Washington University, Washington, DC; [d]Precise Publications LLC, Far Hills, NJ

ABSTRACT

Objective: The objective of the present document was to review/summarize reported outcomes compared between menopausal hormone therapy (MHT) containing estradiol (E2) versus other estrogens and MHT with progesterone (P4) versus progestins (defined as synthetic progestogens).

Methods: PubMed and EMBASE were systematically searched through February 2021 for studies comparing oral E2 versus oral conjugated equine estrogens (CEE) or P4 versus progestins for endometrial outcomes, venous thromboembolism (VTE), cardiovascular outcomes, breast outcomes, cognition, and bone outcomes in postmenopausal women.

Results: A total of 74 comparative publications were identified/summarized. Randomized studies suggested that P4 and progestins are likely equally effective in preventing endometrial hyperplasia/cancer when used at adequate doses. E2- versus CEE-based MHT had a similar or possibly better risk profile for VTE and cardiovascular outcomes, and P4- versus progestin-based MHT had a similar or possibly better profile for breast cancer and cardiovascular outcomes. E2 may potentially protect better against age-related cognitive decline and bone fractures versus CEE; P4 was similar or possibly better versus progestins for these outcomes. Limitations are that many studies were observational and some were not adequately powered for the reported outcomes.

Conclusions: Evidence suggests a differential effect of MHT containing E2 or P4 and those containing CEE or progestins, with some evidence trending to a potentially better safety profile with E2 and/or P4.

ARTICLE HISTORY
Received 21 June 2022
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Published online 09 September 2022

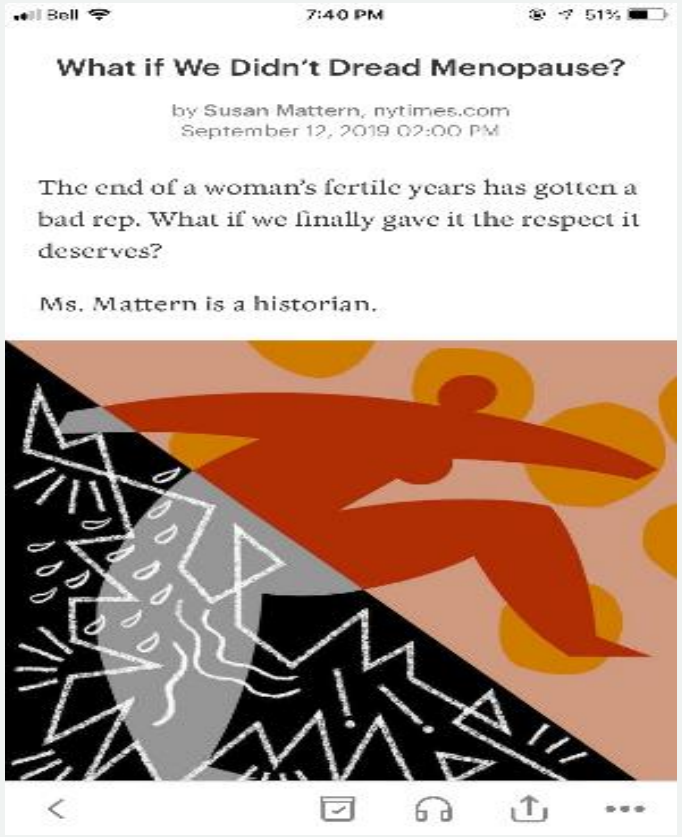
KEYWORDS
Estradiol; estrogens; menopause; progesterone; progestins

Lifestyle Modifications

Lifestyle Options?

- Data do not show that phytoestrogens, herbal supplements, and lifestyle modifications are efficacious for the treatment of vasomotor symptoms.

Alternative treatments?

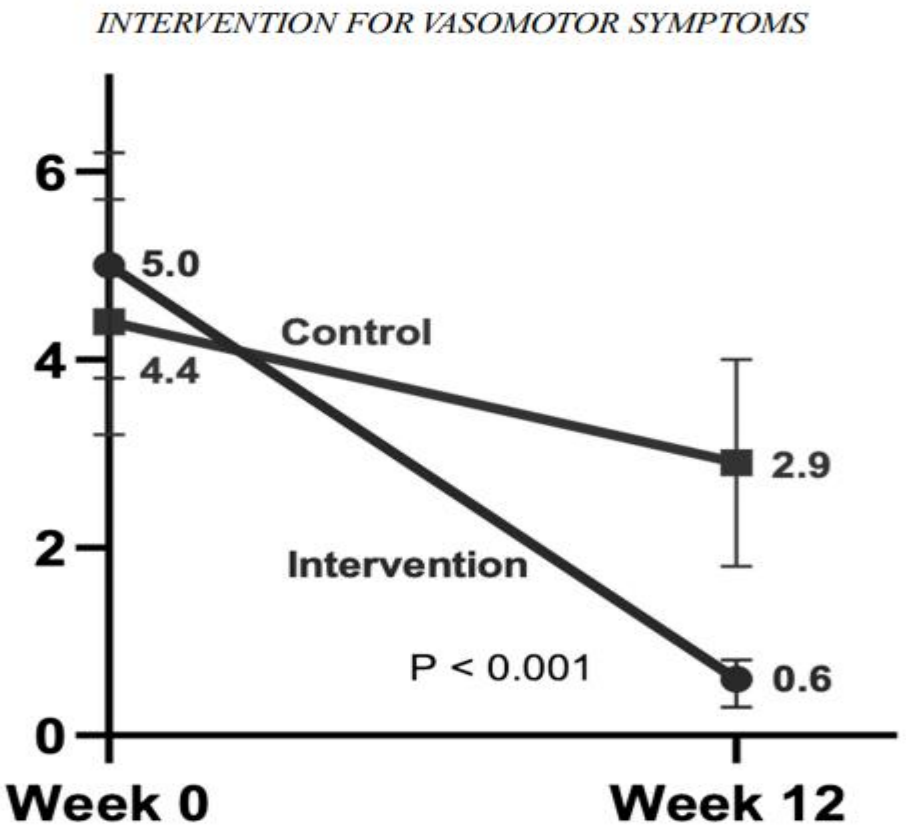


Menopause: The Journal of The North American Menopause Society
Vol. 00, No. 00, pp. 000-000
DOI: 10.1097/GME.0000000000002080

OPEN

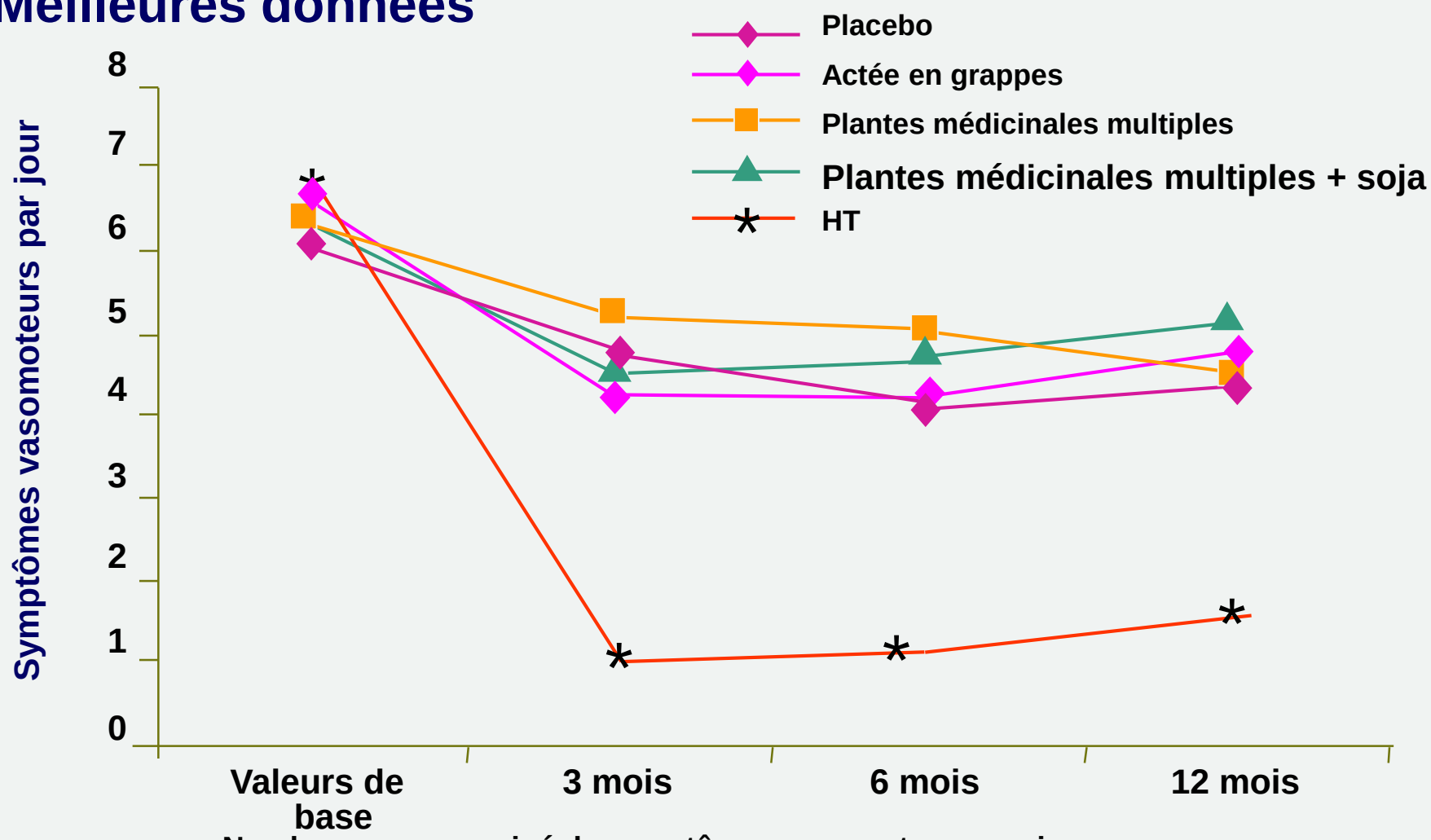
ORIGINAL STUDY

A dietary intervention for vasomotor symptoms of menopause: a randomized, controlled trial



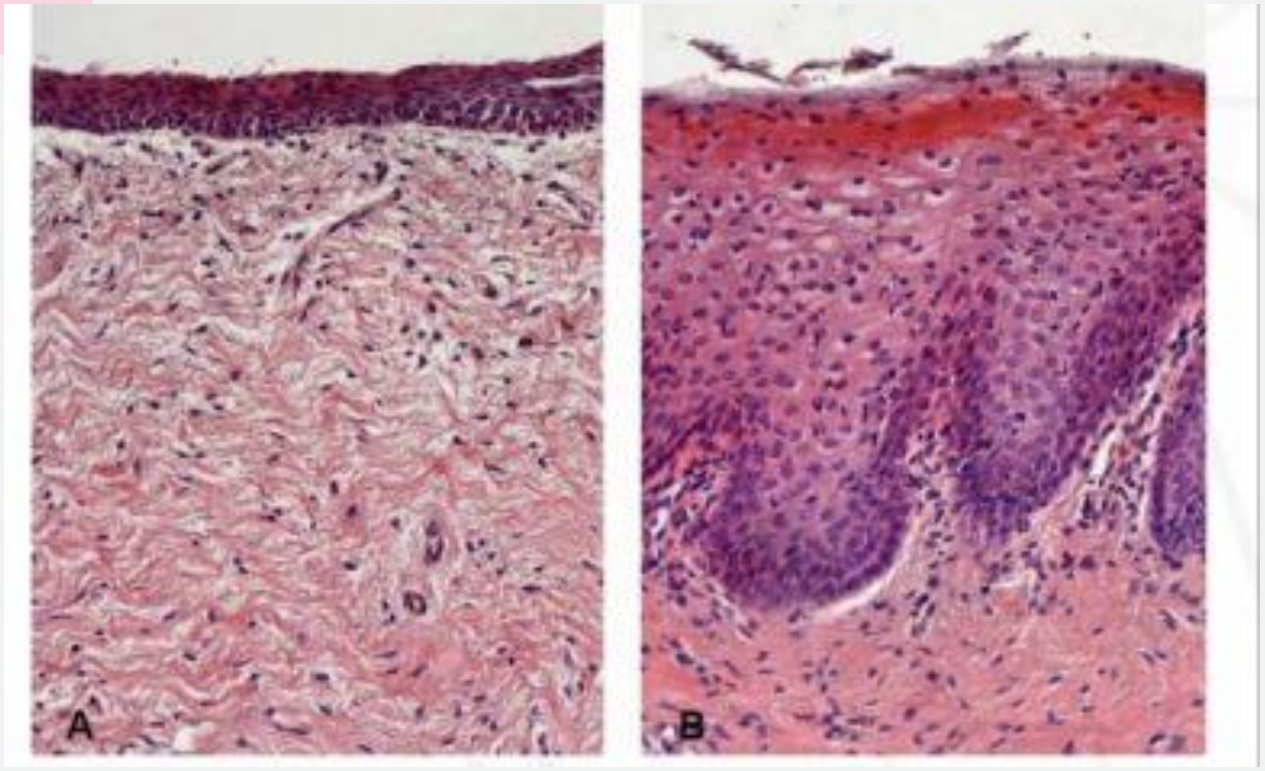
Soja et phytothérapie

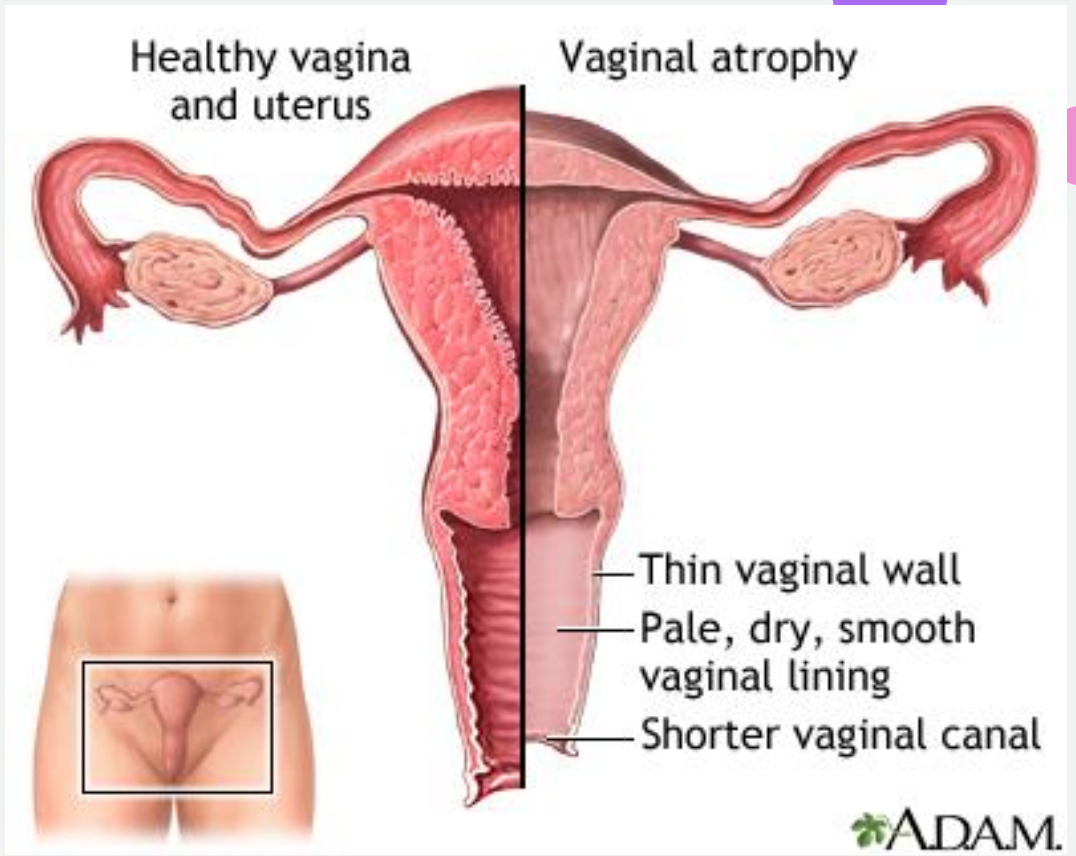
Meilleures données



Nombre moyen corrigé de symptômes vasomoteurs par jour, par groupe d'étude

Newton KM et coll. Ann Intern Med, vol. 145, 2006, p. 869-79. Reproduit avec permission.





Histology of GSM (Genitourinary Syndrome of Menopause)

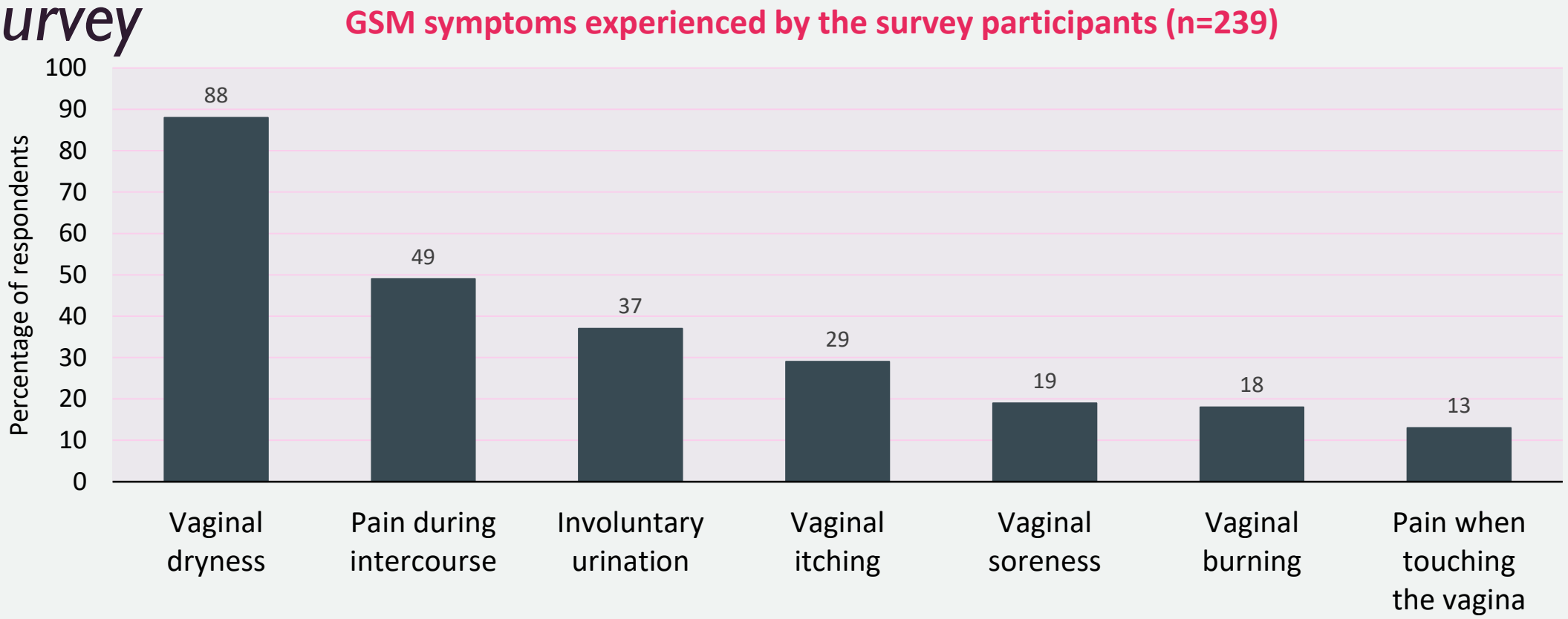
Signs and symptoms[1,2]

- Genital
  - VVA (vulvovaginal atrophy) and genitourinary atrophy
  - Vaginal discomfort, dryness, itching, and burning
- Sexual
  - Pain due to dryness during intercourse (dyspareunia)
- Urinary
  - Dysuria, urgency, and recurrent UTIs
- GSM does not include VMS (vasomotor symptoms, i.e. hot flashes and night sweats)

UTI: urinary tract infections. VMS: vasomotor symptoms. VVA: vulvovaginal atrophy.

1. Frank SM, et al. Menopause Int. 2013;19(1):20-27.
2. The North American Menopause Society. Menopause. 2020;27(9):976-992.

Vaginal dryness and dyspareunia are the most common GSM symptoms - *The VIVA survey*



VIVA: Vaginal Health Insights, Views and Attitudes. VVA: vulvovaginal atrophy.

Adapted from Frank SM, et al. Menopause Int. 2013;19(1):20-27.

Treatment types[1]

- OTC products
  - Lubricants and moisturizers
- Vaginal estrogen therapy
  - Vaginal creams, rings, and tablets
- Systemic Menopausal hormone therapy (MHT)
- Vaginal laser therapy

OTC: over-the-counter.

1. The North American Menopause Society. Menopause. 2020;27(9):976-992.

VAGINAL ESTROGEN PREPARATIONS

Estrone cream (plant source, single ingredient), alcohol and perfume-free:
0.5 to 1g OD x 2 weeks then 2-3 times/week

Conjugated equine estrogen cream:
0.5g OD x 2 weeks then 2-3 times/week

Estradiol ring:
Intravaginal, sustained release ring
2mg estradiol q 3 months

Intravaginal tablet:
10ug estradiol daily x 2 weeks, then 2-3 times/week

SOGC guidelines: Canadian Consensus Conference on Menopause and Osteoporosis, JOGC, № 171, February 2006

Cochrane Library

Cochrane Database of Systematic Reviews

Local oestrogen for vaginal atrophy in postmenopausal women (Review)

Lethaby A, Ayeleke RO, Roberts H

Educating patients on the safety of vaginal estrogen therapy

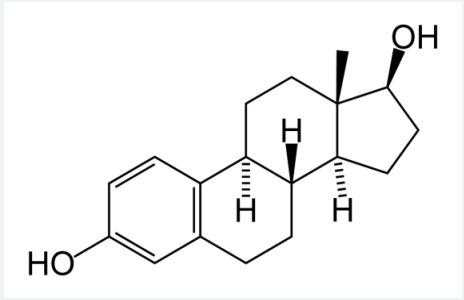
- Canadian women often associate vaginal estrogen with increased risk of breast cancer (31%) and blood clot or stroke (24%)[1]
- Vaginal estrogen therapy is safer than systemic MHT:
  - Serum estrogen levels are not significantly elevated following treatment[2]
  - VTE and CVD risk are not elevated[3-7]*
  - Existing clinical safety and efficacy data for GSM indication

CVD: cardiovascular disease. MHT: hormone replacement therapy. VTE: venous thromboembolism.
*Increased risk for VTE and CVD in WHI study is discussed in the Product Monographs for all products.

1. Frank SM, et al. Menopause Int. 2013;19(1):20-27.
2. Lee JS, et al. J Clin Endocrinol Metab. 2006;91(10):3791-3797.
3. Bhupathiraju N, et al. Menopause. 2018;26:603-610.
4. Collaborative Group on Hormonal Factors in Breast Cancer. Lancet. 2019;394:1159-1168.
5. Crandall CJ, et al. Menopause. 2018;25:11-20.
6. Crandall CJ, et al. Menopause. 2020;27(3):339-360.
7. Vinogradova Y, et al. BMJ. 2019;364:k4810.

Chemical Structures: Estradiol ≠ Ospemifene

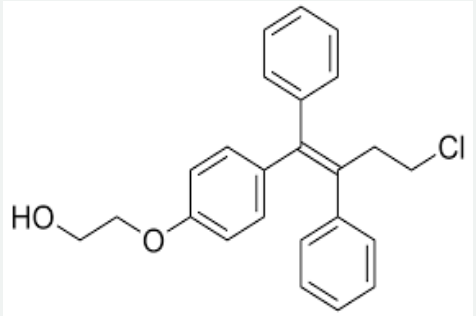
HORMONAL[1]
(cholesterol-based)



Estradiol

≠

ESTROGEN-FREE[2,3]
(triphenyl-ethylene)



Ospemifene

Ospemifene is one of several synthetically produced non-steroidal compounds with a similar structure to Tamoxifene and Toremifene[2-4]

1. World of Molecules Website. Estrogen Molecules. https://www.worldofmolecules.com/emotions/estrogen.htm. Accessed on June 6, 2018. 2. Maximov PY, Lee TM, Jordan VC. The Discovery and Development of Selective Estrogen Receptor Modulators (SERMs) for Clinical Practice. Current Clinical Pharmacology 2013; 8: 135-155. 3. Wurz GT, Kao CJ, DeGregorio MW. Safety and Efficacy of Ospemifene for the Treatment of Dyspareunia Associated with Vulvar and Vaginal Atrophy Due to Menopause. Clinical Interventions in Aging 2014; 9: 1939-1950. 4. Osphena [prescribing information]. Duchesnay 2019

OSPEMIFENE

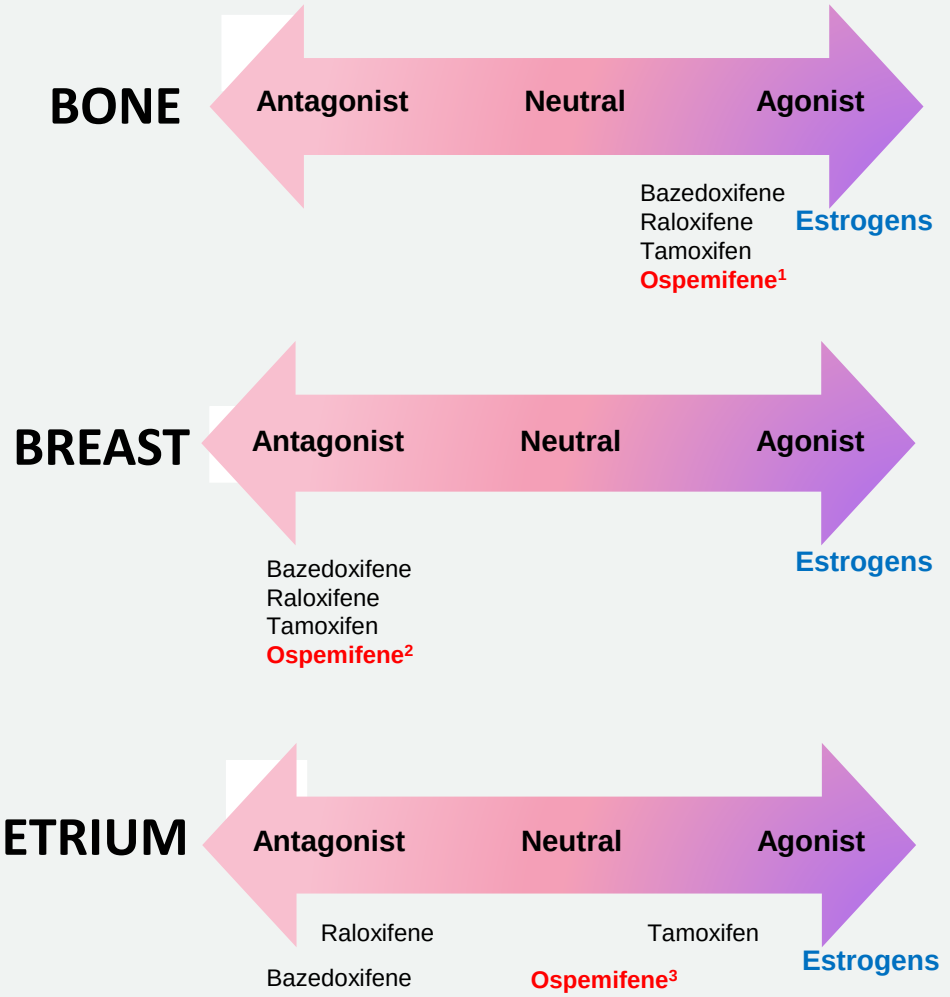
Osphena is an estrogen agonist/antagonist indicated in postmenopausal women for treatment of moderate to severe dyspareunia and/or vaginal dryness, symptoms of vulvar and vaginal atrophy (VVA), a component of genitourinary syndrome of menopause (GSM).[1]

Approved in 2021 by Health Canada
Approved since 2013 in US; more than 2.7 million of Px

4. OSPHENA® Product Monograph. July 15, 2021.

SERMs' Distinct Agonist-Antagonist selectivity

OSPEMIFENE IS DIFFERENTIATED BY ITS AGONISTIC ACTIVITY IN VAGINAL TISSUE[1,2]



[1]In bone turnover markers in clinical trials and in preclinical in vitro, in vivo animal models

[2]In preclinical in vitro, in vivo animal models and in human breast tissue explants

[3]Phase 3 clinical studies data

Modified from Hadji, Climacteric 2012;15:513–523.
1 .Wurz GT, Soe LH, DeGregorio MW. Ospemifene, Vulvovaginal Atrophy, and Breast Cancer. Maturitas 2013; accepted 2012: 1-6. 2.Maximov PY, Lee TM, Jordan VC. The Discovery and Development of Selective Estrogen Receptor Modulators (SERMs) for Clinical Practice. Current Clinical Pharmacology 2013; 8: 135-155.

Ospemifene- Key Features

- ☑ Restore the physiological changes associated with VVA:
  - Increase % superficial cells, decrease % parabasal cells
  - Decrease vaginal pH
  - Vulvoscopy analysis confirmed visual improvement of the vestibule/vulva

- ☑ Improve vaginal dryness and dyspareunia

- ☑ Improve sexual functions (FSFI)

- ☑ Greater adherence and persistence compared with non-ring local estrogen therapies


DEKA

Entering an "Era of Clarity"

Guideline Support for Prescribing MHT Today

2013

2014

2015

2016

2017

BMS Meeting the challenges of menopause

The Society of Obstetricians and Gynaecologists of Canada

The Endocrine Society

International Menopause Society

NAMS The North American Menopause Society

AACE

ACE

Menopause: The Journal of The North American Menopause Society
Vol. 29, No. 7, pp. 767-794
DOI: 10.1097/GME.0000000000002028

NAMS Position Statement

The 2022 hormone therapy position statement of The North American Menopause Society

Abstract

"The 2022 Hormone Therapy Position Statement of The North American Menopause Society" (NAMS) updates "The 2017 Hormone Therapy Position Statement of The North American Menopause Society" and identifies future research needs. An Advisory Panel of clinicians and researchers expert in the field of women's health and menopause was recruited by NAMS to review the 2017 Position Statement, evaluate new literature, assess the evidence, and reach consensus on recommendations, using the level of evidence to identify the strength of recommendations and the quality of the evidence. The Advisory Panel's recommendations were reviewed and approved by the NAMS Board of Trustees.

Hormone therapy remains the most effective treatment for vasomotor symptoms (VMS) and the genitourinary syndrome of menopause and has been shown to prevent bone loss and fracture. The risks of hormone therapy differ depending on type, dose, duration of use, route of administration, timing of initiation, and whether a progestogen is used. Treatment should be individualized using the best available evidence to maximize benefits and minimize risks, with periodic reevaluation of the benefits and risks of continuing therapy.

For women aged younger than 60 years or who are within 10 years of menopause onset and have no contraindications, the benefit-risk ratio is favorable for treatment of bothersome VMS and prevention of bone loss. For women who initiate hormone therapy more than 10 years from menopause onset or who are aged older than 60 years, the benefit-risk ratio appears less favorable because of the greater absolute risks of coronary heart disease, stroke, venous thromboembolism, and dementia. Longer durations of therapy should be for documented indications such as persistent VMS, with shared decision-making and periodic reevaluation. For bothersome genitourinary syndrome of menopause symptoms not relieved with over-the-counter therapies in women without indications for use of systemic hormone therapy, low-dose vaginal estrogen therapy or other therapies (eg, vaginal dehydroepiandrosterone or oral ospemifene) are recommended.

JAMA | US Preventive Services Task Force | RECOMMENDATION STATEMENT

Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Persons

US Preventive Services Task Force Recommendation Statement

US Preventive Services Task Force

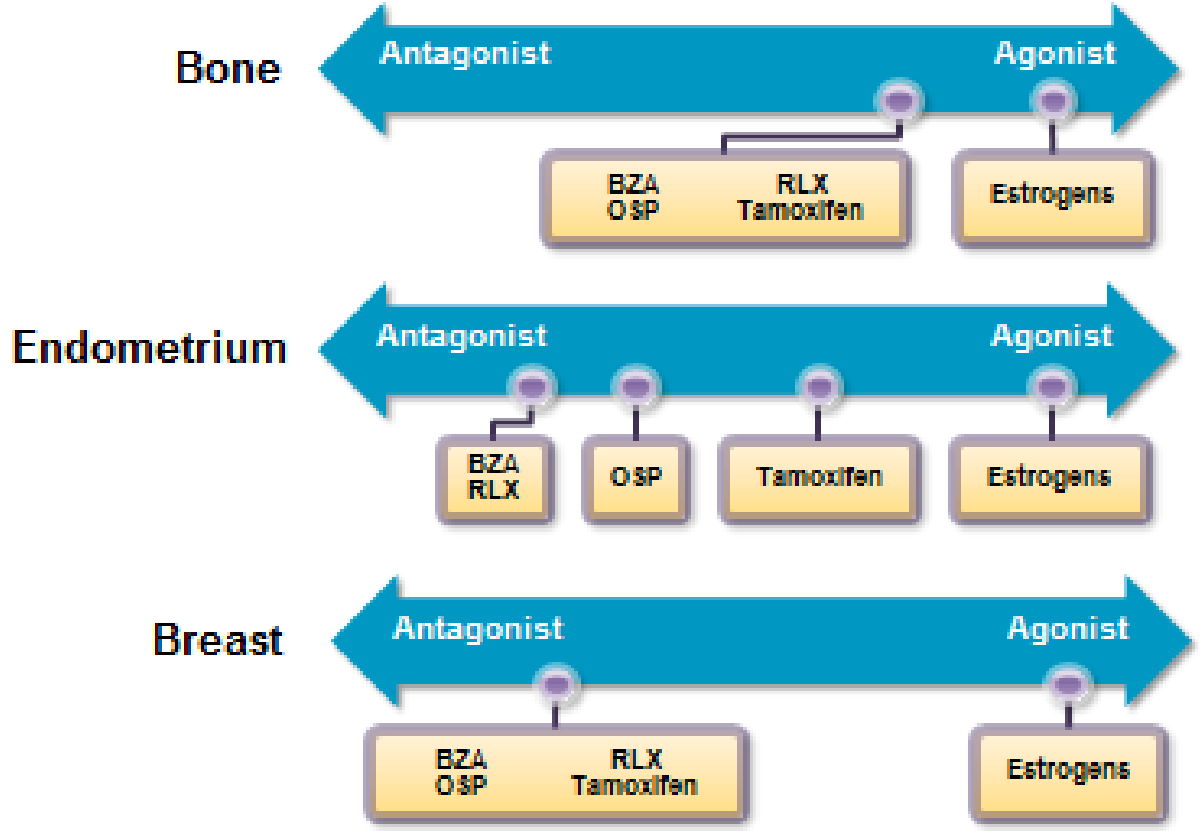
RECOMMENDATION The USPSTF recommends against the use of combined estrogen and progestin for the primary prevention of chronic conditions in postmenopausal persons. (D recommendation) The USPSTF recommends against the use of estrogen alone for the primary prevention of chronic conditions in postmenopausal persons who have had a hysterectomy. (D recommendation)

JAMA. 2022;328(17):1740-1746. doi:10.1001/jama.2022.18625

Summary of Recommendations

Population	Recommendation	Grade
Postmenopausal persons	The USPSTF recommends against the use of combined estrogen and progestin for the primary prevention of chronic conditions in postmenopausal persons.	D
Postmenopausal persons who have had a hysterectomy	The USPSTF recommends against the use of estrogen alone for the primary prevention of chronic conditions in postmenopausal persons who have had a hysterectomy.	D

Site of Action of SERMs



BZA, bazedoxifene; OSP, ospemifene; RLX, raloxifene; SERM, selective estrogen receptor modulator.
Adapted from Hadji. Climacteric 2012;15:513-22; and Maximov et al. Curr Clin Pharmacol 2013;8:135-55.

Tissue-Selective Estrogen Complexes (TSECs)

TSEC

The purposeful pairing of a SERM with one or more estrogens to achieve pharmacologic results based on their blended tissue-selective activity profile[1,2]

1. Komm. *Reprod Sci* 2008;15(10):984–92; 2. Berrodin et al. *Mol Endocrinol* 2009;23(1):74–85.

CE/BZA (DUAVIVE) Dosage & Administration

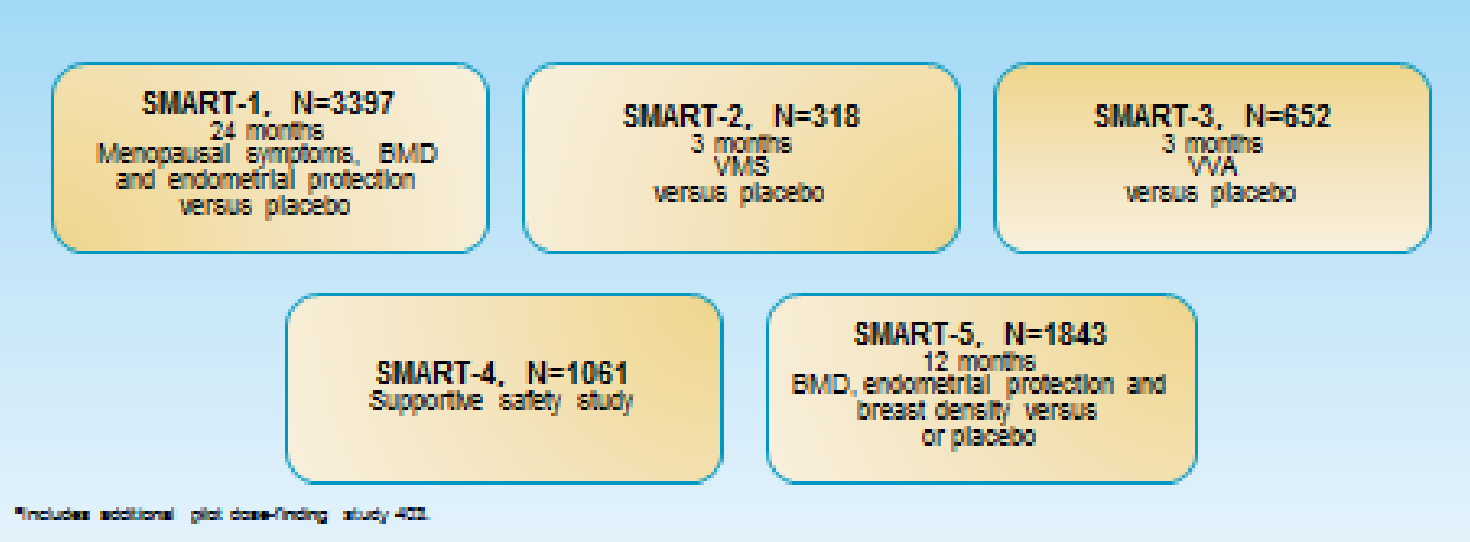
- One DUAVIVE tablet taken orally around the same time every day
- Tablet should be swallowed whole with fluid and not divided, crushed, chewed or dissolved in mouth
- Taken at any time of day, with or without food
- After opening foil pouch, product must be used within 45 days
- Duration of use should be consistent with treatment goals and benefits and risks for the individual

CE		SERM
Conjugated Estrogens 0.45 mg	+	Bazedoxifene 20 mg (Selective Estrogen Receptor Modulator)

CE/BZA Global Clinical Development Program

Selective estrogens, **M**enopause, **A**nd **R**esponse to **T**herapy (SMART) Trials

Clinical studies conducted worldwide in more than 7500 women[1-5,a]
Studies assessed CE 0.45 mg/BZA 20 mg and placebo



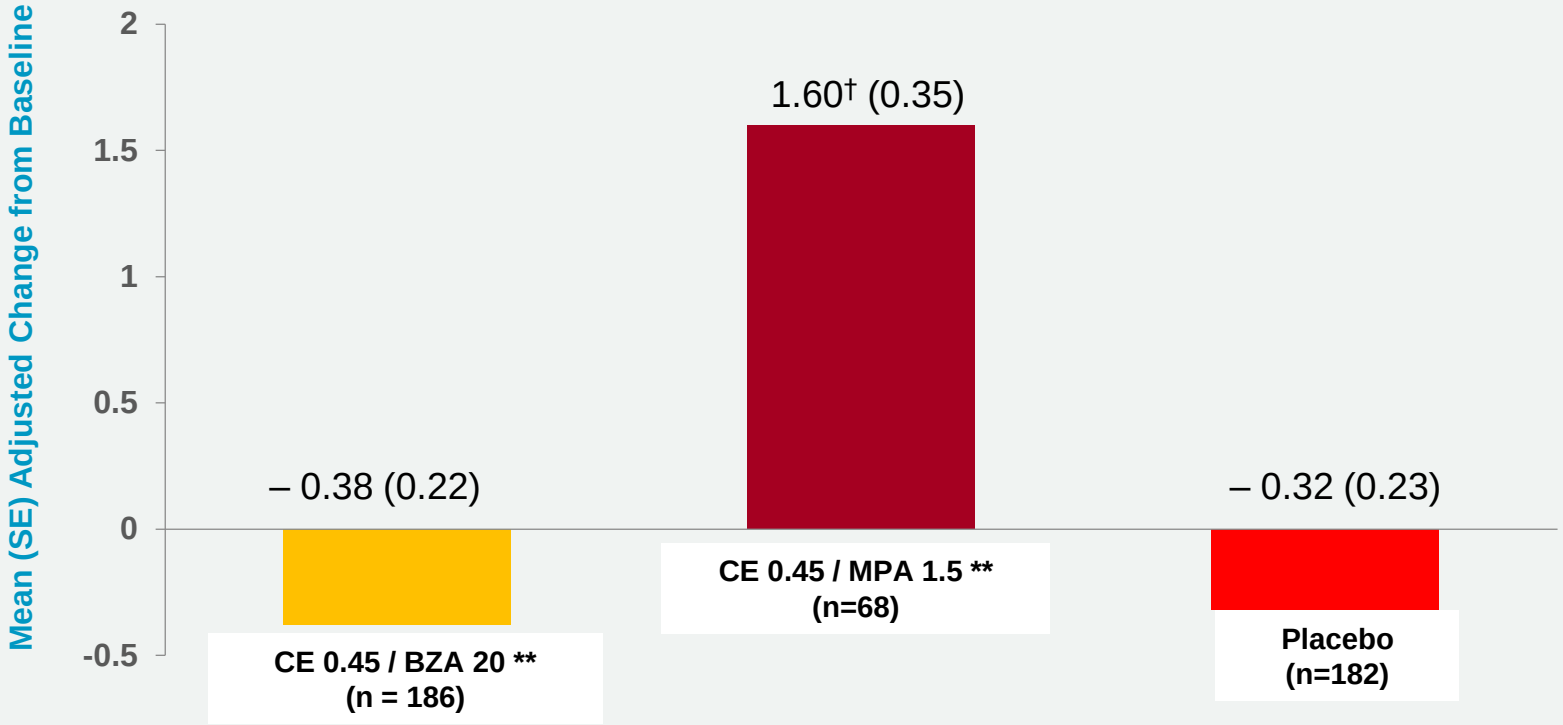
[a]Includes additional pilot dose-finding study 403.

BMD, bone mineral density; CE/BZA, conjugated estrogens/bazedoxifene; VMS, vasomotor symptoms; VVA, vulvovaginal atrophy.

1. Lobo et al. *Fertil Steril* 2009;92:1025-38; 2. Pinkerton, et al. *Menopause* 2009;16:1116-24; 3. Kagan et al. *Menopause* 2010;17:281-9; 4. Minkin et al. *Climacteric* 2012;15:338-46; 5. Pinkerton et al. *Obstet Gynecol* 2013;121:959-68.

Change in Breast Density at 1 Year*

Neutral effect of CE/BZA, but not CE/MPA, on adjusted change from baseline in % breast density vs. placebo (P<0.001) at year 1



*Modified intent-to-treat population included all participants enrolled in the breast density substudy who took ≥1 doses of the study drug, had a baseline breast density evaluation and had ≥1 postbaseline evaluations. †P<0.001 vs. placebo. ** All doses mg/day
Note that CE/BZA and placebo arms not significantly changed from baseline despite negative values.
BZA, bazedoxifene; CE, conjugated estrogens; MPA, medroxyprogesterone acetate; SE, standard error.

Pinkerton et al. *Obstet Gynecol* 2013;121(5):959-68; Pinkerton et al. *Menopause* 2009;16(6):1116-24.

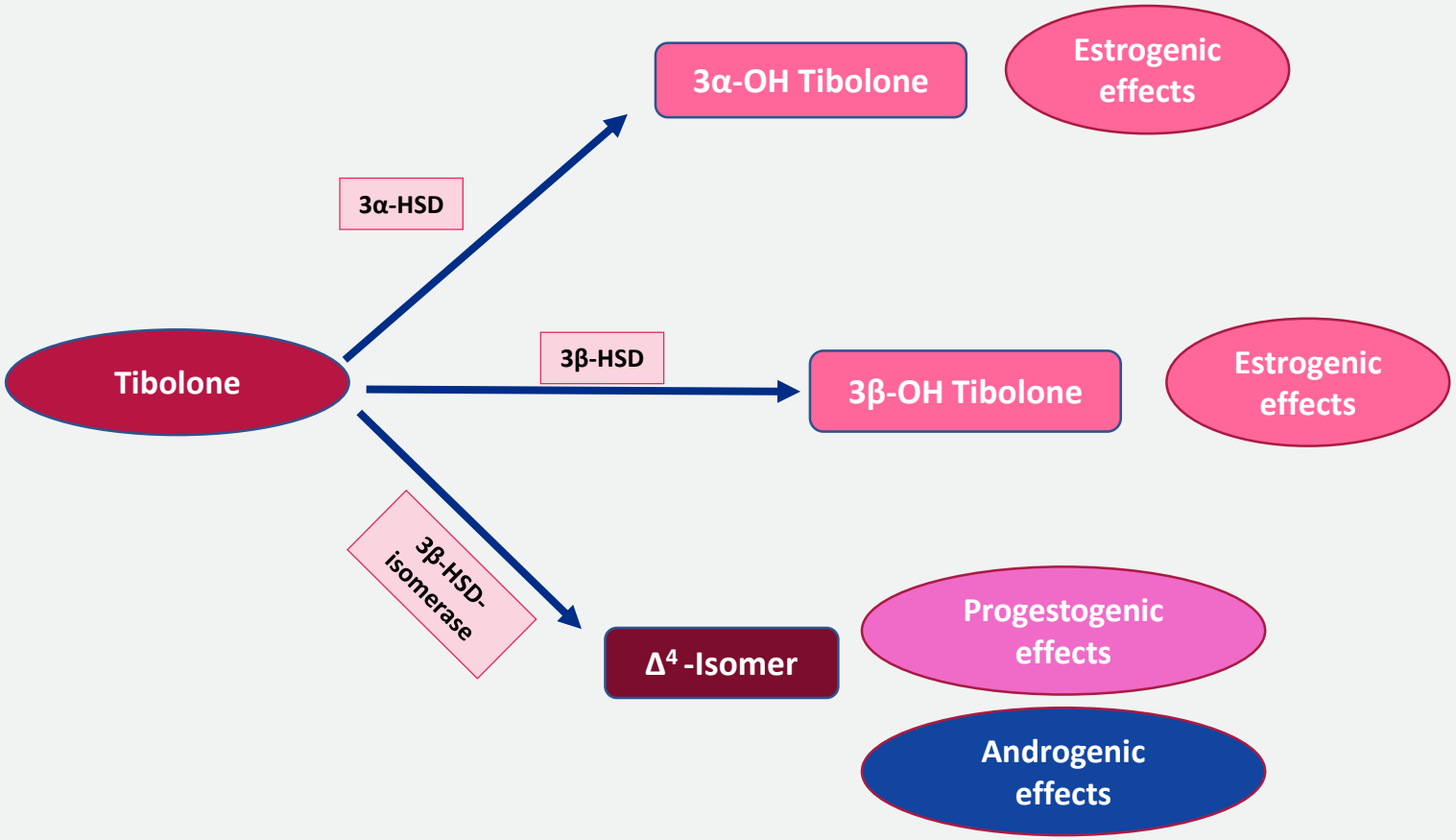
ᶜTibella® (Tibolone)

- Tibolone is a well-established treatment for climacteric complaints and prevention of osteoporosis in post-menopausal women in Europe and Australia.
- Used in Europe since 1988, available in 90+ countries.*

In Canada, ᶜTibella® is approved for short-term treatment of vasomotor symptoms due to estrogen deficiency in postmenopausal women, more than one year after menopause

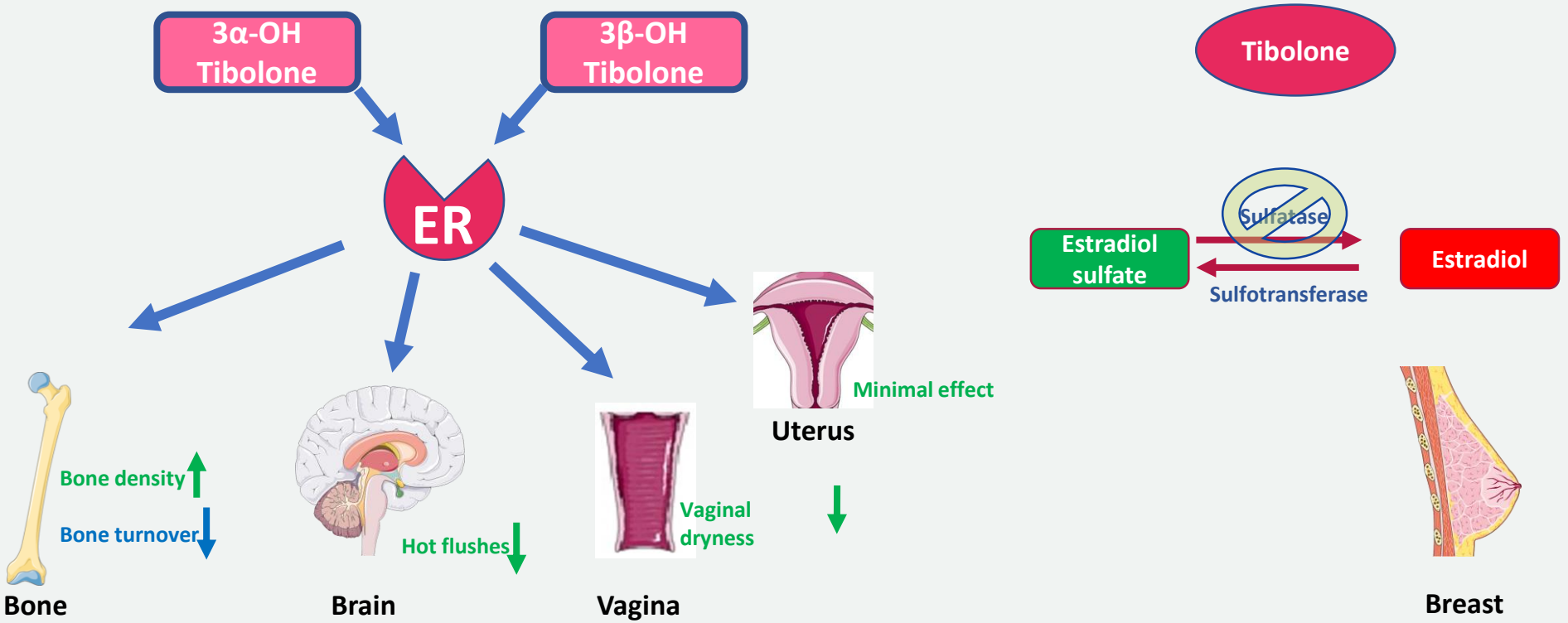
* 45 countries have indication for prevention of osteoporosis

Molecule Properties



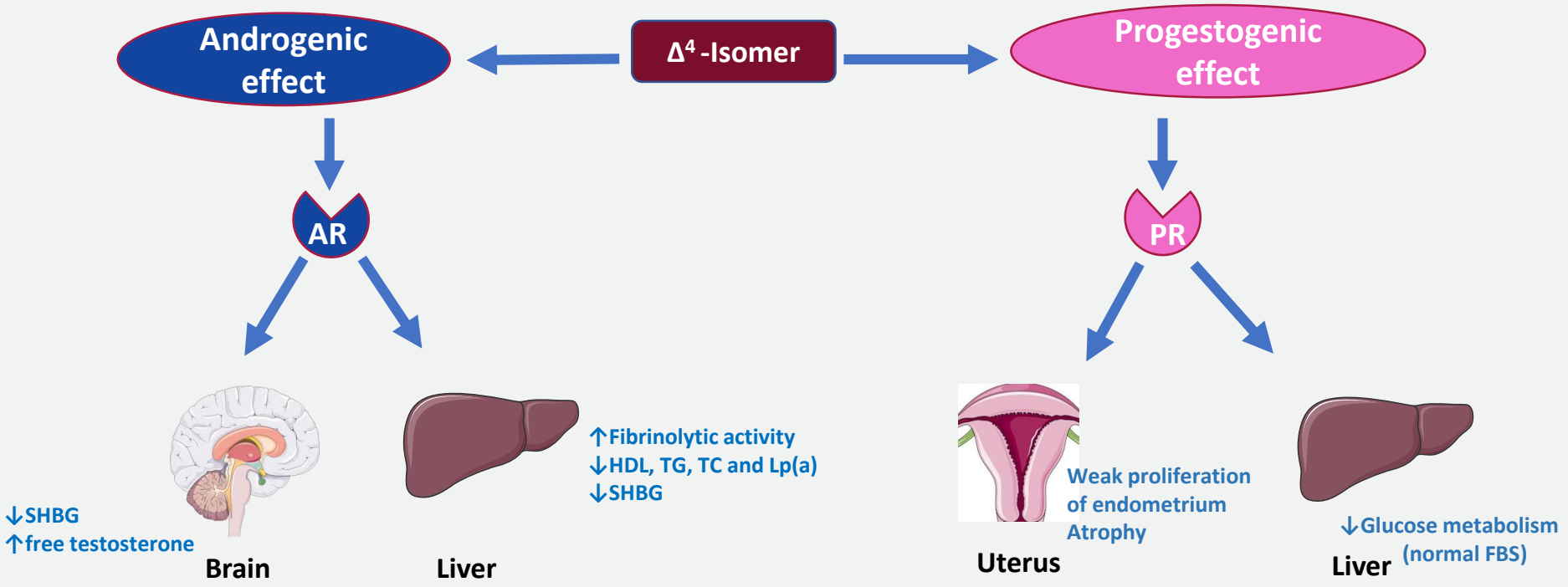
*Due to its androgenic effects, tibolone is a Schedule IV controlled substance under the Controlled Drugs and Substances Act.

Estrogenic Effect



- Campisi R and Marengo FD. Cardiovascular Effects of Tibolone: A Selective Tissue Estrogenic Activity Regulator. Cardiovascular Drug Reviews 2007; 25(2):132–145.
- Erel CT, Senturk LM, Kaleli STibolone and breast cancerPostgraduate Medical Journal 2006;82:658-662
- Modelska et al. Tibolone for postmenopausal women: systematic review of randomized trials. J Clin Endocrinol Metab. 2002; 87(1):16-23.

Progestogenic and Androgenic Effects



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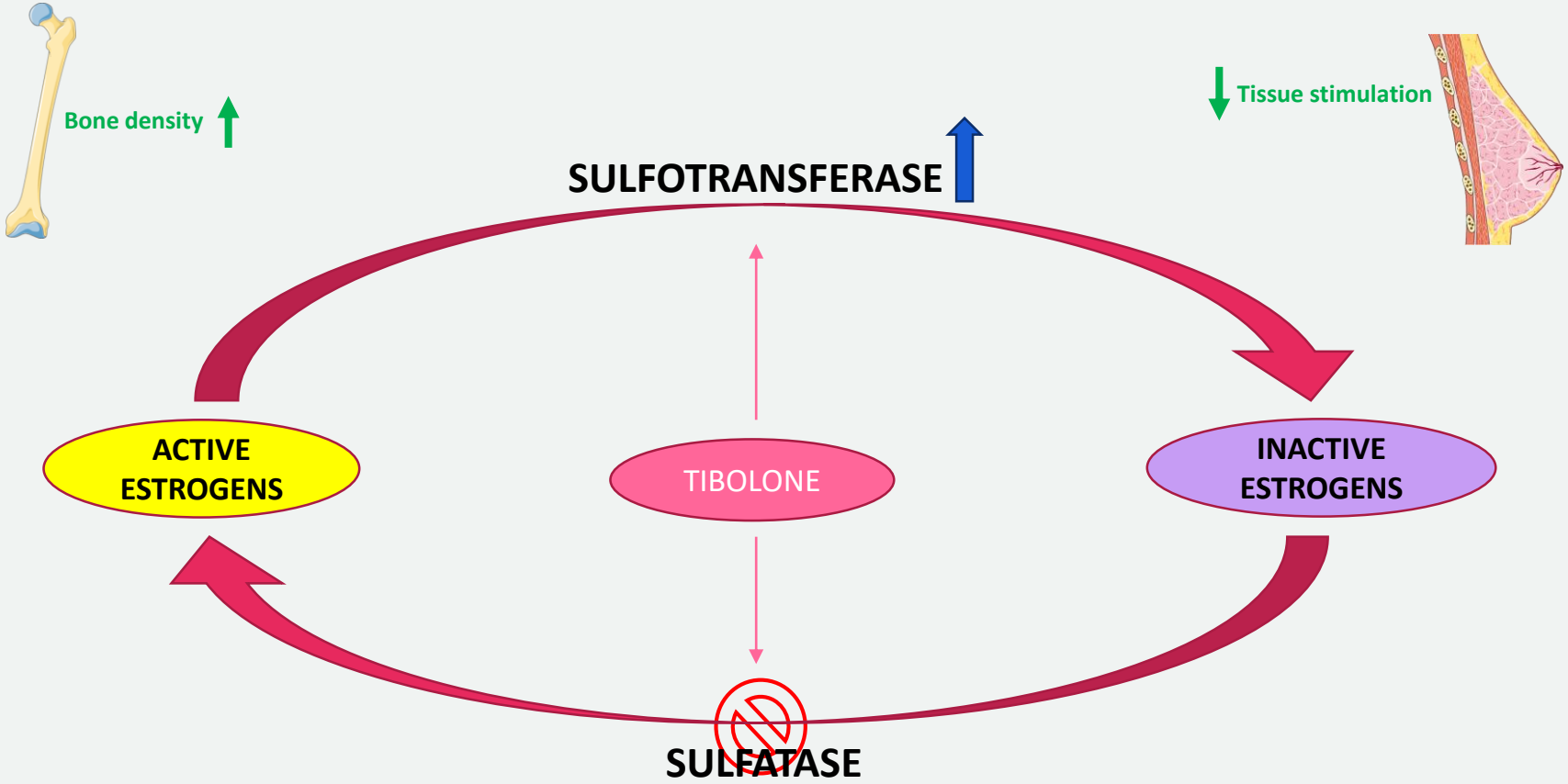
- Modelska et al. Tibolone for postmenopausal women: systematic review of randomized trials. J Clin Endocrinol Metab. 2002; 87(1):16-23.

Selective Tissue Estrogenic Activity Regulator (STEAR)



Tibolone selectively inhibits Sulfatase enzyme in the breast but not in the bone

Kloosterboer HJ. Maturitas 2004; 49(1):S5-S15.

Clinical Trials

LIBERATE

2 years, N=3148
TIBOLONE VS PLACEBO
VMS, BC, CVS

LIFT

3 years, N=4538
TIBOLONE VS PLACEBO
Osteoporosis, BC, Endometrial Ca, Stroke and VTE

OPAL

3 years, N=866
TIBOLONE VS CEE/MPA
Osteoporosis, BC, Endometrial Ca, CVS

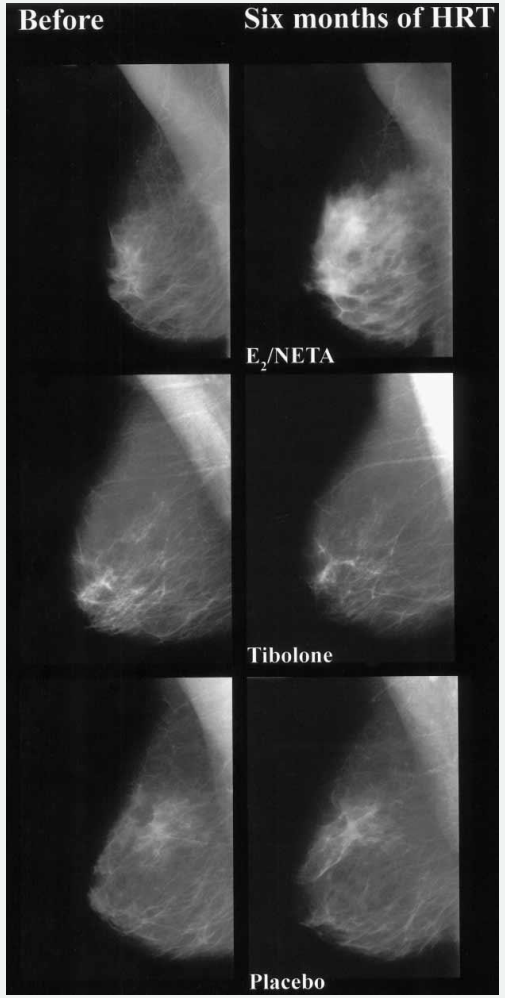
THEBE

2 years , N=3240
TIBOLONE VS CEE/MPA
Endometrial Ca, breast pain

LIFT= The Long-Term Intervention on Fractures with Tibolone study
OPAL= The Osteoporosis Prevention and Arterial effects of tiboLone study
LIBERATE= Livial Intervention following Breast cancer: Efficacy, Recurrence, And Tolerability Endpoints
THEBE= The Tibolone Histology of the Endometrium and Breast Endpoints

Effect of Tibolone on Mammographic Breast Density

- A prospective, randomized, double-blind placebo-controlled study
- N=166, (50-70) yr
- BMI (20-30) kg/m^2
- Tibolone 2.5 mg, (E2/NETA) 2mg/1mg, or placebo.
- Mammograms baseline and 6 months
- Wolfe classification and by the percentage area of the breast that had a dense pattern.
- Results
  - In conclusion, tibolone seems to exert little stimulation of breast tissue



Number of women with an increase in mammographic density after 6 months

	Wolfe increase	Percentage classification increase
E2/NETA	22/48 (**46%**)	24/48 (**50%**)
Tibolone	1/51 (**2%**)	3/51 (**6%**)
Placebo	0/55 (**0%**)	0/55 (**0%**)

Lundstrom et al. Am J Obstet Gynecol. 2002 Apr;186(4):717-22.

Sexual Dysfunction: Tibolone Vs CEE/MPA (2-2)

Sexual Function Scores

Sexual Domains	Tibolone			CEE/MPA			Control		
	Before	After	P value	Before	After	P value	Before	After	P value
Desire	2.80+1.06	3.66+0.74	**<0.001***	2.58+0.86	2.66+1.07	NS	2.68+0.96	2.75+1.12	NS
Arousal	3.11+1.13	3.68+0.99	**<0.001***	3.08+1.13	2.81+1.31	NS	2.90+1.57	2.70+1.52	NS
Lubrications	3.80+1.48	4.58+1.26	**<0.001***	4.93+1.95	4.93+1.95	**<0.001**	3.63+1.83	3.65+1.81	NS
Orgasm	3.81+1.24	4.40+1.13	**<0.001***	3.60+1.30	3.25+1.66	NS	3.60+1.64	3.45+1.56	NS
Pain improvement	3.68+1.44	4.70+1.29	**<0.001***	4.05+1.40	5.21+1.82	**<0.001**	4.00+1.31	3.94+1.79	NS
Satisfaction	4.31+0.97	4.61+0.77	**0.03**	4.37+0.98	4.28+0.96	NS	4.06+1.31	4.02+1.21	NS
Total score	21.52+5.72	25.66+4.87	**<0.001**	21.28+5.20	23.11+7.61	NS	20.89+7.06	20.5+7.12	NS

* $p<0.001$ compared to CEE/MPA

Tibolone significantly improved sexual function scores in all domains and total score, while CEE/MPA improved only lubrications and pain improvement scores

Ziaei et al, Climacteric 2010;13:147-156

OXFORD

JNCI J Natl Cancer Inst (2022) 114(10): djac112

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Article

Systemic or Vaginal Hormone Therapy After Early Breast Cancer: A Danish Observational Cohort Study

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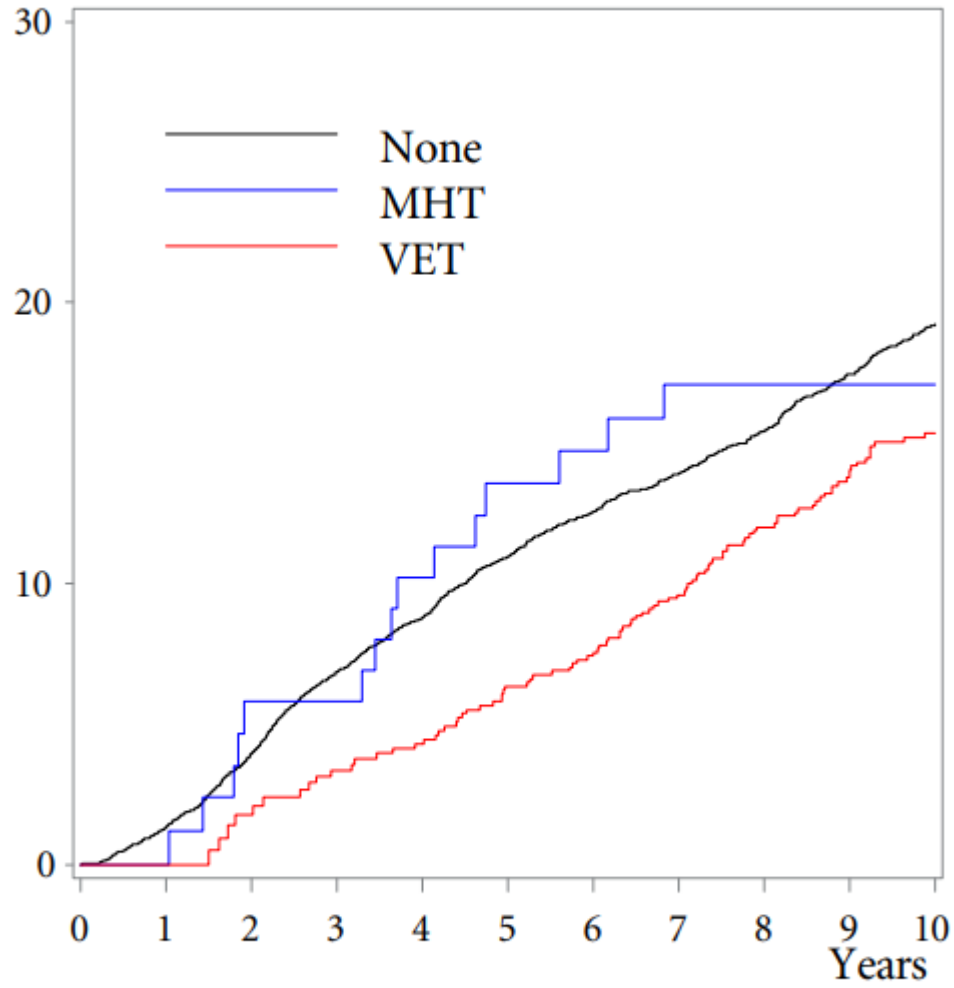
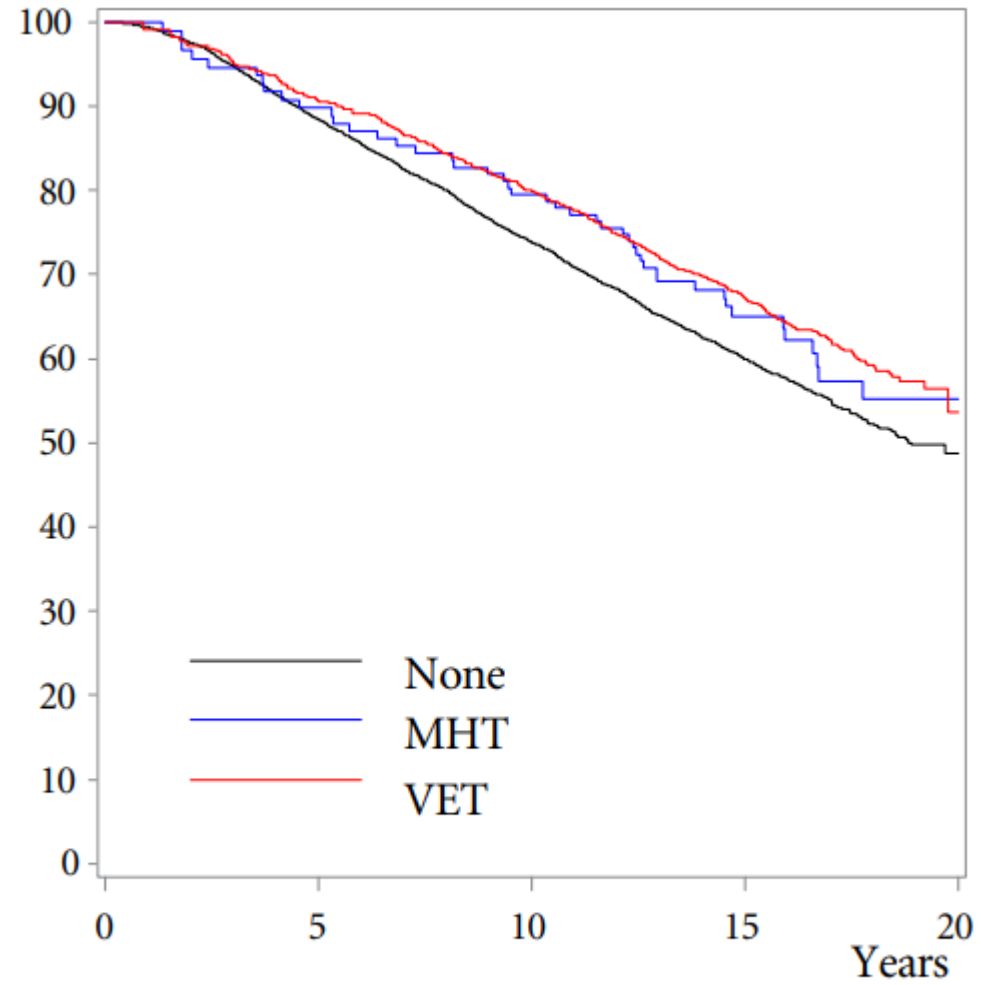
Abstract

Background: Women treated for breast cancer (BC) often suffer genitourinary syndrome of menopause. These symptoms may be alleviated by vaginal estrogen therapy (VET) or menopausal hormone therapy (MHT). However, there are concerns of risks of recurrence of BC and death following treatment. **Methods:** Our study included longitudinal data from a national cohort of postmenopausal women, diagnosed 1997-2004 with early-stage invasive estrogen receptor–positive nonmetastatic BC, who received no treatment or 5 years of adjuvant endocrine therapy. We ascertained prescription data on hormone therapy, VET or MHT, from a national prescription registry. We evaluated mortality and risk of recurrence associated with use of VET and MHT vs non-use using multivariable models adjusted for potential confounders. **Results:** Among 8461 women who had not received VET or MHT before BC diagnosis, 1957 and 133 used VET and MHT, respectively, after diagnosis. Median follow-up was 9.8 years for recurrence and 15.2 years for mortality. The adjusted relative risk of recurrence was 1.08 (95% confidence interval [CI] = 0.89 to 1.32) for VET (1.39 [95% CI = 1.04 to 1.85 in the subgroup receiving adjuvant aromatase inhibitors]) and 1.05 (95% CI = 0.62 to 1.78) for MHT. The adjusted hazard ratios for overall mortality were 0.78 (95% CI = 0.71 to 0.87) and 0.94 (95% CI = 0.70 to 1.26) for VET and MHT, respectively. **Conclusions:** In postmenopausal women treated for early-stage estrogen receptor–positive BC, neither VET nor MHT was associated with increased risk of recurrence or mortality. A subgroup analysis revealed an increased risk of recurrence, but not mortality, in patients receiving VET with adjuvant aromatase inhibitors.



None	8461	7328	6127	4734	3440	1877
MHT	0	83	82	72	61	34
VET	0	293	603	701	696	452



None	8461	6585	4929	1972
MHT	0	96	99	55
VET	0	805	1264	735