Dr. Karen Toews

Dr. Grace Frankel

The Seven Dwarves of Menopause

A "Choose your own Adventure" on hot topics in menopause

Conflicts of Interest

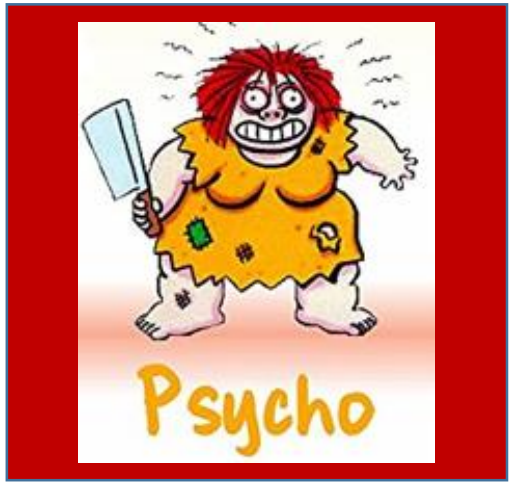
Together, we may reflect all the signs and symptoms of menopause and apologize if they occur during the session

We wish someone would sponsor us….

Objectives

- Discuss 4 “hot topics” in menopause utilizing an evidence-based approach and audience participation
- Highlight a useful tool for patient assessment of menopause-associated symptoms
- Maybe even have a bit of fun…..

Choose Your Own Menopause Adventure!



CONTINUE

HORMONE THERAPY WHEN PATIENTS HAVE A BREAST CANCER HISTORY

What do we do?

Case Study

Brenda is a 55 yo woman with a history of breast cancer. She completed a course of chemotherapy and radiation one year ago and is presently on letrozole. She presents to your office today c/o hot flashes, vaginal dryness and pain with intercourse.

Can we prescribe hormone replacement therapy for Brenda?

"The use of systemic hormone therapy in survivors of breast cancer is generally not advised."

-NAMS 2017 Hormone Therapy Position Statement

Menopause. 2017 Jul;24(7):728-753.

Stockholm Trial: 10-year Follow-Up

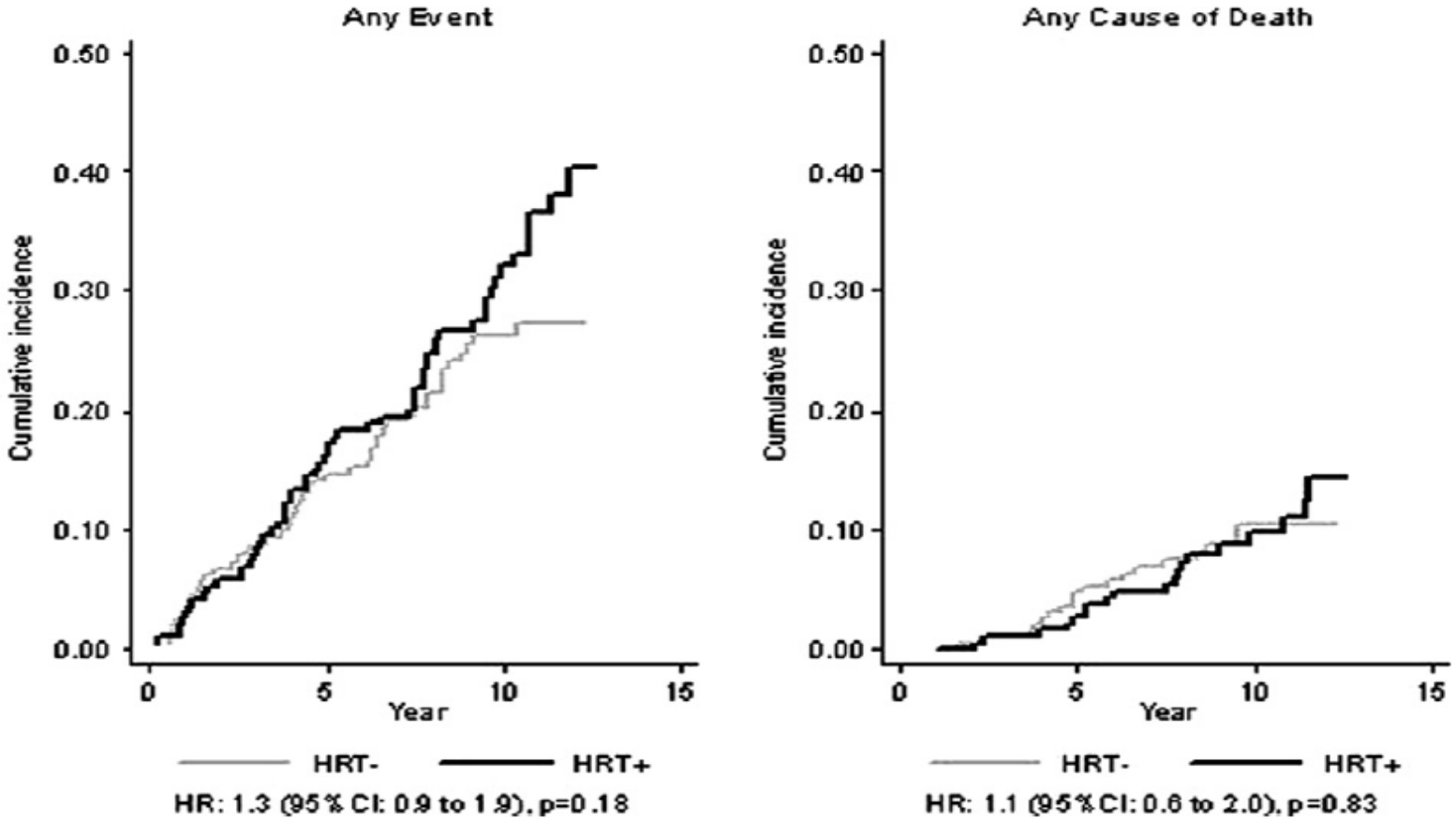
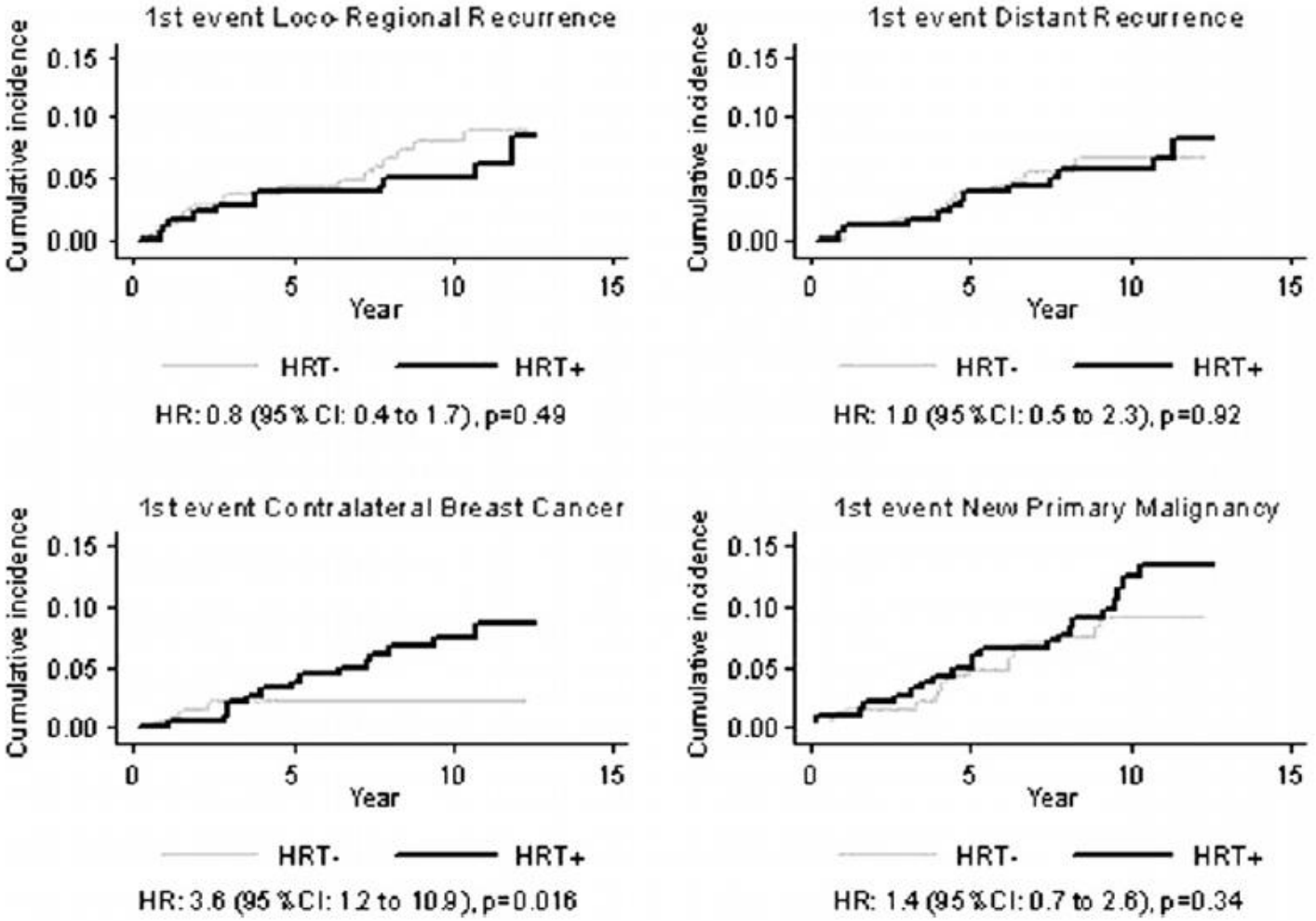


Fig. 1. Cumulative incidence of any breast cancer recurrence and cause of death versus time during follow-up in the Stockholm trial.

Eur J Cancer. 2013 Jan;49(1):52-9

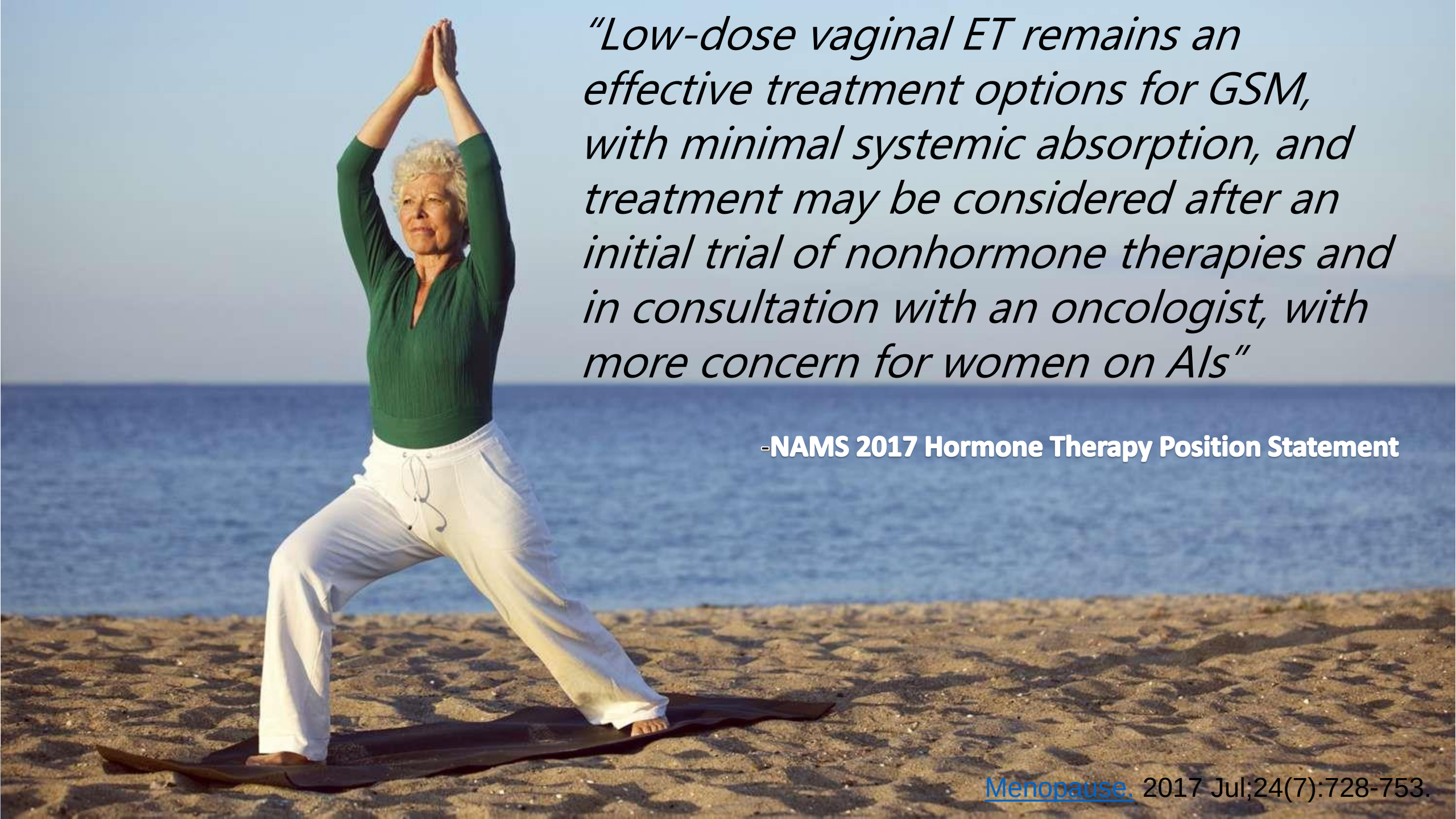
Stockholm Trial: 10-year Follow-Up



Study Conclusion

In some women with severe menopausal symptoms an impaired quality of life may outweigh the potential risks from hormone replacement therapy

Fig. 2. Cumulative incidence of first events of breast cancer recurrence versus time during follow-up in the Stockholm trial. Eur J Cancer. 2013 Jan;49(1):52-9



"Low-dose vaginal ET remains an effective treatment options for GSM, with minimal systemic absorption, and treatment may be considered after an initial trial of nonhormone therapies and in consultation with an oncologist, with more concern for women on AIs"

-NAMS 2017 Hormone Therapy Position Statement

Menopause. 2017 Jul;24(7):728-753.

Local estrogen therapy and risk of breast cancer recurrence among hormone-treated patients: a nested case–control study

Isabelle Le Ray · Sophie Dell'Aniello · Franck Bonnetain · Laurent Azoulay · Samy Suissa

Females >18 years between 1998-2008 with first breast cancer on tamoxifen or AI

917 Cases
Breast Cancer Recurrence

8885 Controls
No breast cancer recurrence

Exposure:
Local Hormone therapy
(Vaginal estrogens including tablets, creams and pessaries)

1. AI or Tamoxifen alone
2. Local HT with AI or tamoxifen
3. Used local HT *after* AI or Tamoxifen

Breast Cancer Res Treat (2012) 135:603–6

Table 3 Breast cancer recurrence with concurrent use of tamoxifen or AI with local hormonal treatments

	Cases ($n = 917$)	Controls ($n = 8885$)	Crude RR (95 % CI)	Adjusted RR (95 % CI)[a]
Tamoxifen or AI only, *n* (%)	896 (97.7)	8,611 (96.9)	1.00	1.00 (Reference)
Concurrent use of tamoxifen or AI with LHT, *n* (%)	19 (2.1)	252 (2.8)	0.74	0.78 (0.48–1.25)
Use of hormonal treatment after end of tamoxifen or AI use, *n* (%)	2 (0.2)	22 (0.2)	0.89	0.97 (0.22–4.18)

AI aromatase inhibitors, *LHT* local hormonal treatment, *RR* risk ratio

[a] Adjusted for obesity (BMI $\geq$ 30), smoking, excessive alcohol use, history of oophorectomy, previous use of hormone replacement therapy, anti-depressants (other than CYP2D6 substrates), anti-diabetic agents, NSAIDS (other than CYP2D6 substrates), benzodiazepines, antipsychotic drugs (other than CYP2D6 substrates), CYP2D6 inhibitors and statins

Table 4 Breast cancer recurrence with concurrent use of tamoxifen with local hormonal treatments

	Cases ($n = 811$)	Controls ($n = 7950$)	Crude RR (95 % CI)	Adjusted RR (95 % CI)[a]
Tamoxifen only, *n* (%)	790 (97.4)	7,688 (96.7)	1.00	1.00 (Reference)
Concurrent use of tamoxifen with LHT, *n* (%)	19 (2.3)	240 (3.0)	0.78	0.83 (0.51–1.34)
Use of hormonal treatment after end of tamoxifen use	2 (0.2)	22 (0.3)	0.90	0.95 (0.22–4.14)

LHT local hormonal treatment, *RR* risk ratio

[a] Adjusted for obesity (BMI $\geq$30), smoking, excessive alcohol use, history of oophorectomy, previous use of hormone replacement therapy, anti-depressants (other than CYP2D6 substrates), anti-diabetic agents, NSAIDS (other than CYP2D6 substrates), benzodiazepines, antipsychotic drugs (other than CYP2D6 substrates), CYP2D6 inhibitors and statins

Only 12 patients on AI

Breast Cancer Res Treat (2012) 135:603–6

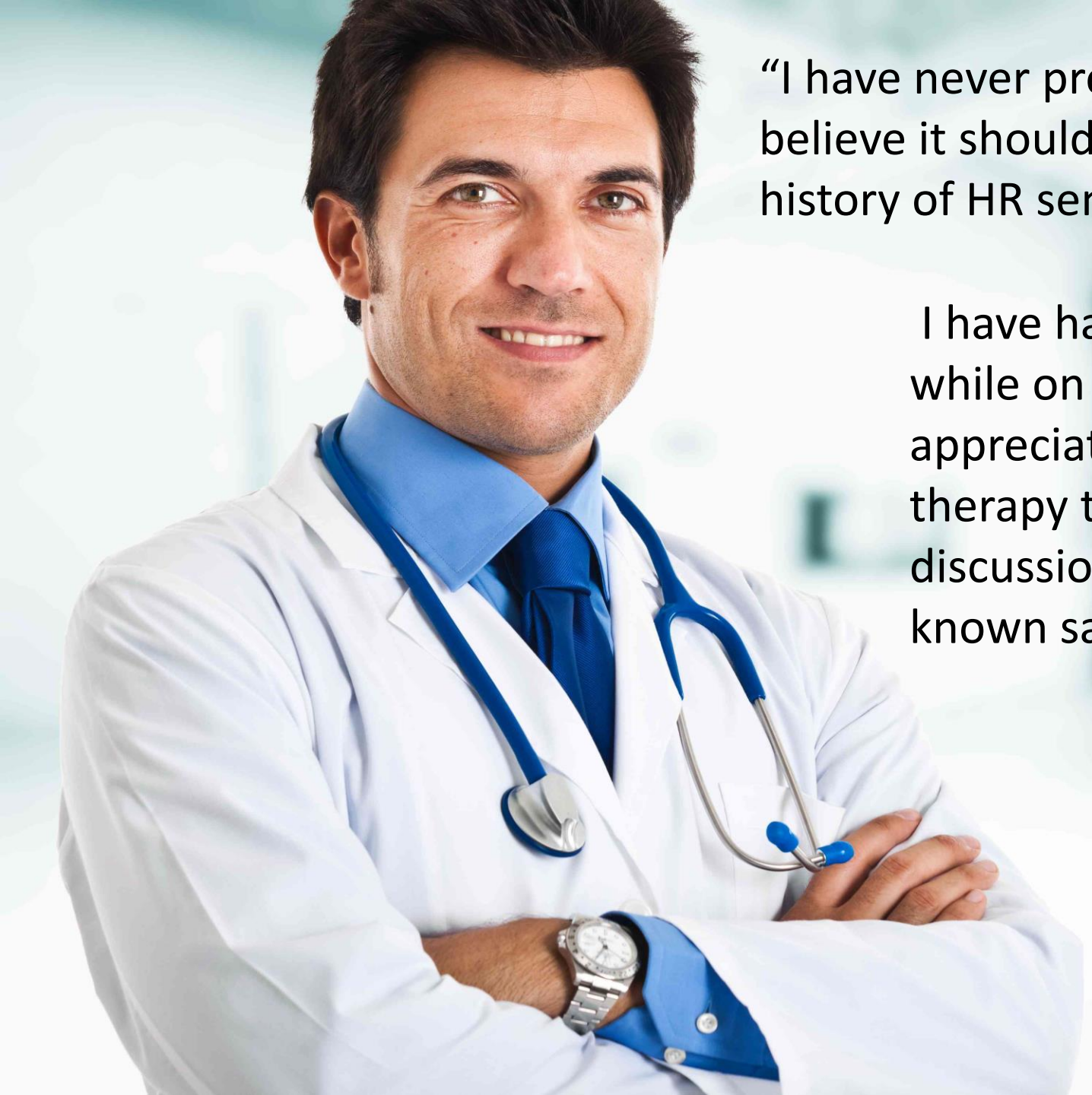
Local estrogen therapy and risk of breast cancer recurrence among hormone-treated patients: a nested case–control study

Isabelle Le Ray · Sophie Dell'Aniello · Franck Bonnetain · Laurent Azoulay · Samy Suissa

Author Conclusion:

"Given its lack of effect on the recurrence rate of BC, the indication of local estrogenic treatment should be discussed in endocrine treated patients with vaginal symptoms"

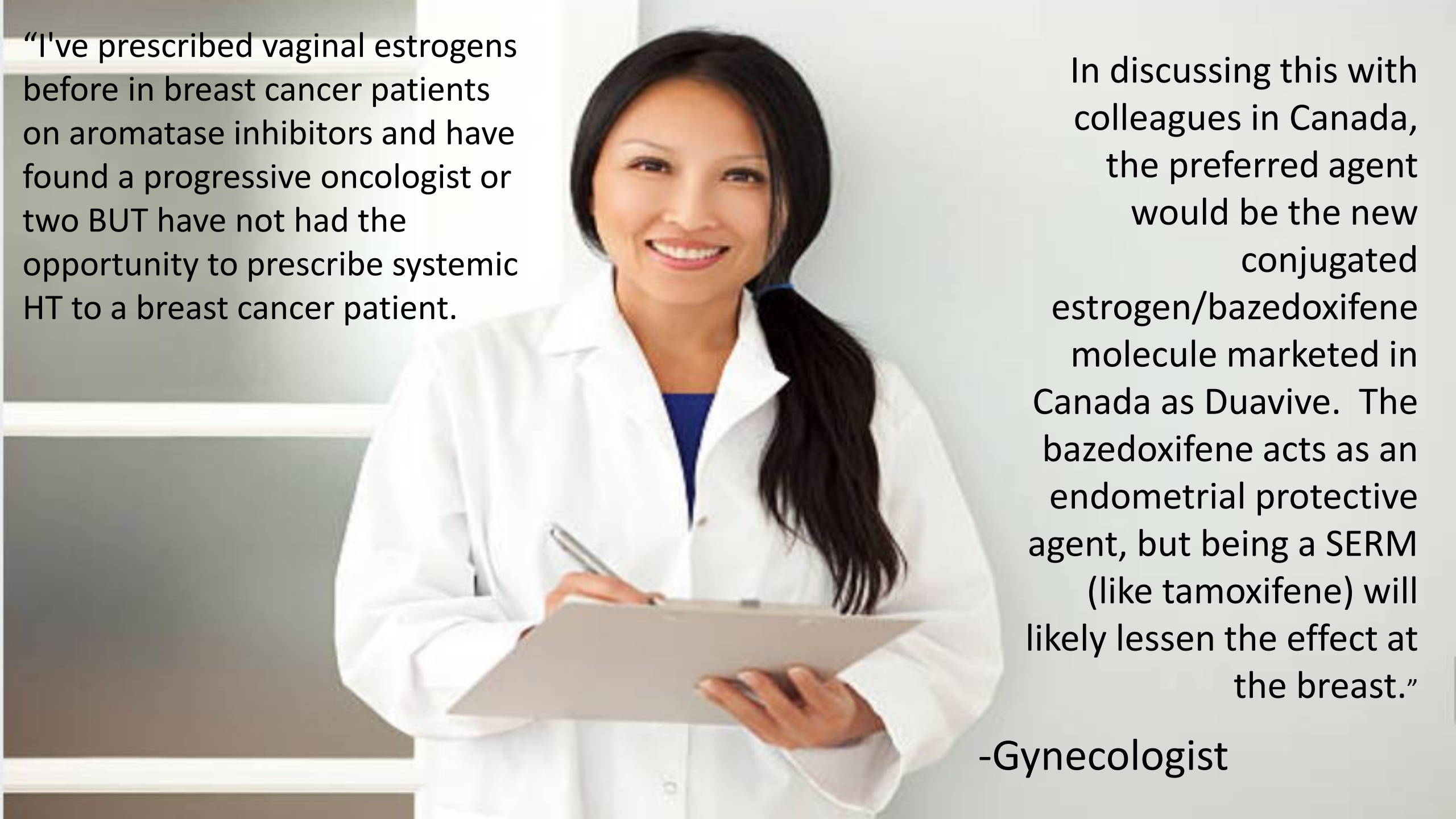
Breast Cancer Res Treat (2012) 135:603–6



“I have never prescribed systemic HT, and do not believe it should ever be prescribed, in a woman with a history of HR sensitive Breast Cancer.

I have had patients prescribed a topical HT while on AI in the past, and would greatly appreciate a referral prior to starting the therapy to allow a risk benefit ratio discussion, even in regards to the lack of known safety.”

-Oncologist



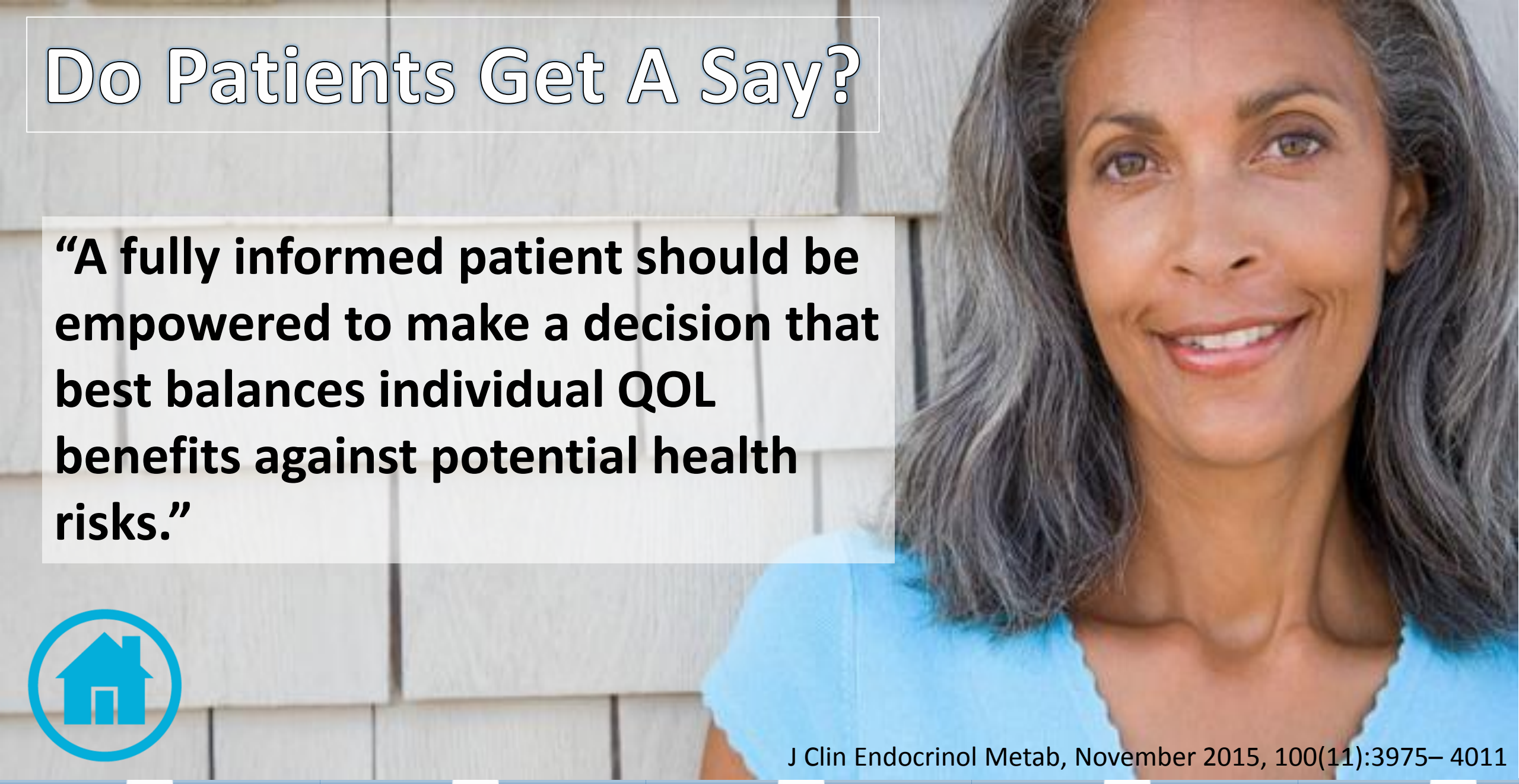
“I've prescribed vaginal estrogens before in breast cancer patients on aromatase inhibitors and have found a progressive oncologist or two BUT have not had the opportunity to prescribe systemic HT to a breast cancer patient.

In discussing this with colleagues in Canada, the preferred agent would be the new conjugated estrogen/bazedoxifene molecule marketed in Canada as Duavive. The bazedoxifene acts as an endometrial protective agent, but being a SERM (like tamoxifene) will likely lessen the effect at the breast.”

-Gynecologist

Do Patients Get A Say?

“A fully informed patient should be empowered to make a decision that best balances individual QOL benefits against potential health risks.”



J Clin Endocrinol Metab, November 2015, 100(11):3975– 4011

BIOIDENTICAL HORMONES

And the things patients tell me…….

ENDOCRINE SOCIETY

Hormone Science to Health

POSITION STATEMENT

COMPOUNDED BIOIDENTICAL HORMONE THERAPY

Table 1

	FDA-approved Hormone Therapy	Compounded "Bioidentical" Hormone Therapy
Molecular structure	Similar or identical* to human	Identical to human
FDA oversight	Yes	No
Dosage	Monitored; accurate and consistent	Not monitored; may be inaccurate or inconsistent
Purity	Monitored; pure	Not monitored; may be impure
Safety	Tested; risks known	Not FDA tested; risks unknown
Efficacy	Tested and proven	Not FDA tested; unproven
Scientific evidence	Existent; conclusive	Insufficient

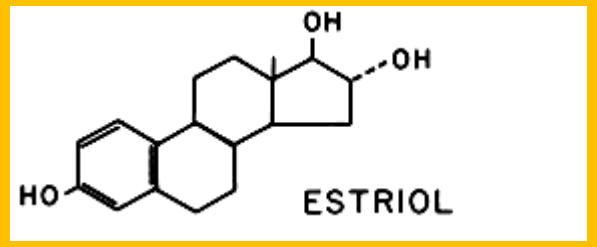
*A few "bioidentical" hormones—those available from retail pharmacies, such as estradiol and progesterone—are produced under FDA supervision and are monitored for dosage and purity. However, even FDA-monitored "bioidentical" hormones have not been examined in head-to-head RCT with clinical outcomes such as cardiovascular events and fracture, and, therefore, have unproven safety and efficacy.

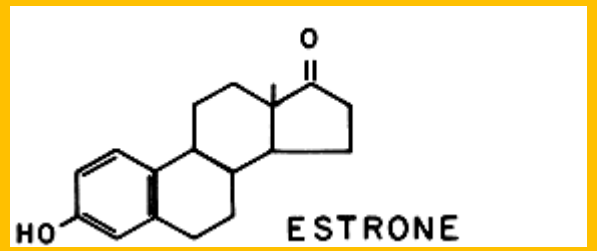
Position statement: Endocrine Society Sept 26, 2017 https://www.endocrine.org/advocacy/priorities-and-positions/bioidentical-hormones

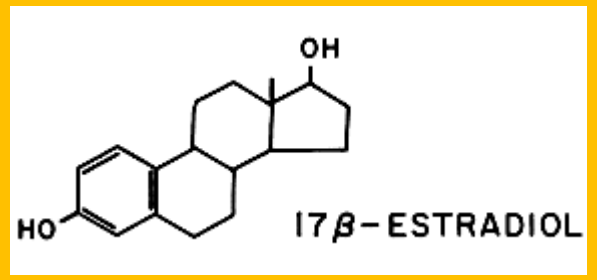
“I’m only going to take ‘natural’ hormones, like those from plants. I don’t want any chemicals poisoning my body…”

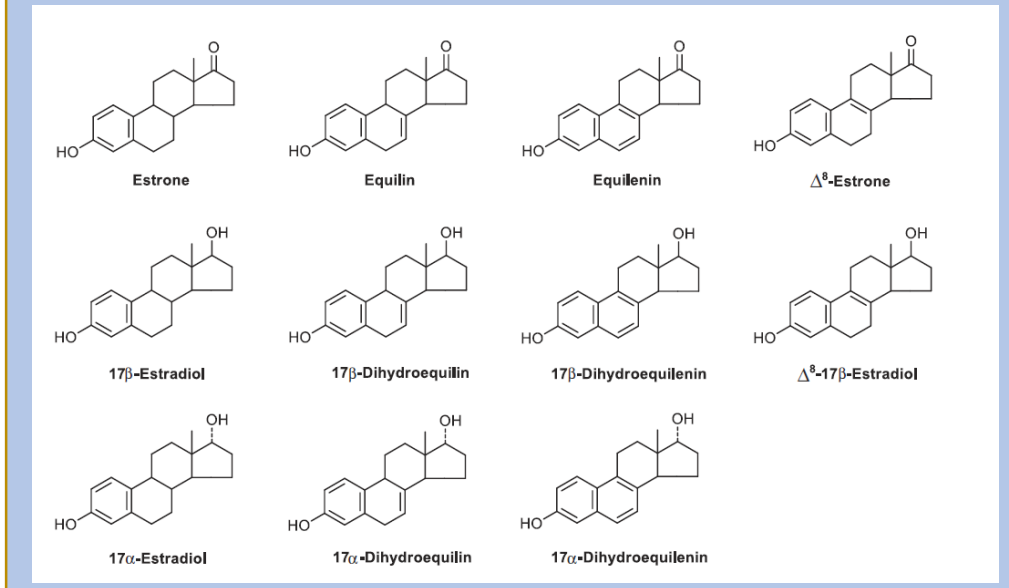
Pharmaceutical Preparations

Endogenous

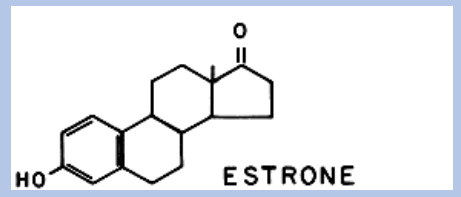




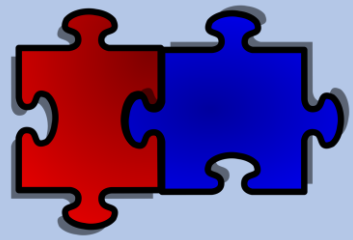


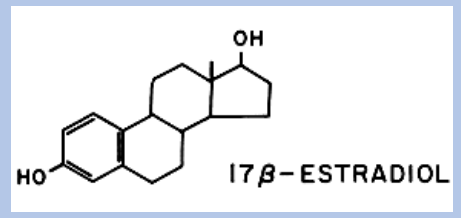


Premarin® (conjugated equine estrogens)
ORAL: Tablet
Vaginal: Cream

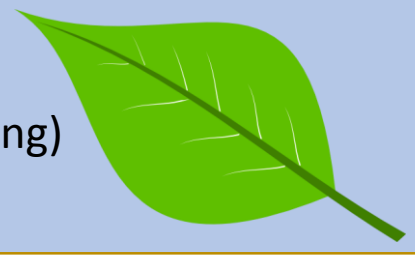


Vaginal: Estragyn® (cream)

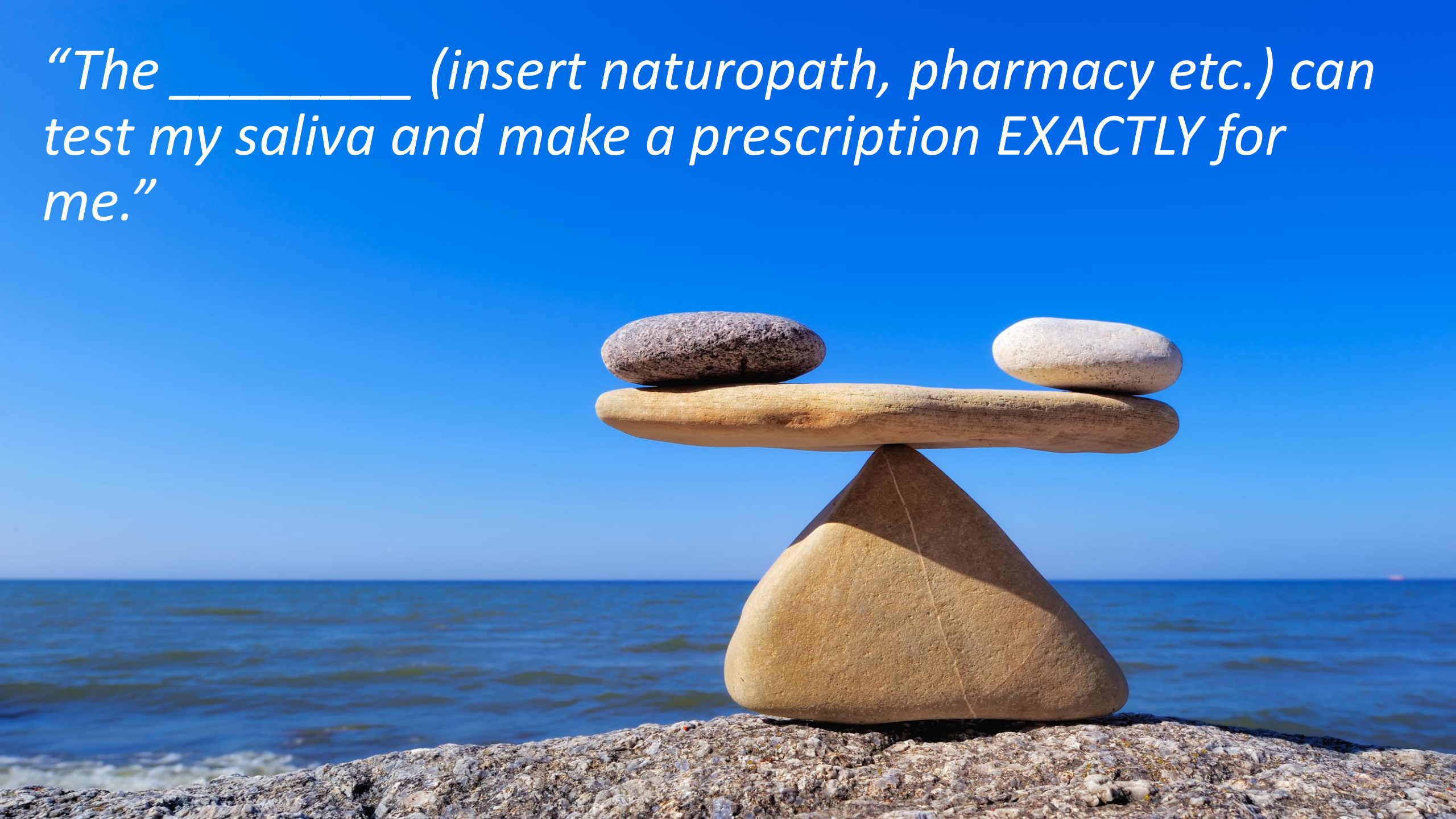




ORAL: Estrace® (Lupin®) micronized
PATCH: Climera®, Estradot®
Vaginal: Vagifem® (tablet), Estring® (ring)



“The _____ (insert naturopath, pharmacy etc.) can test my saliva and make a prescription EXACTLY for me.”



Actually, no, they can't….

- Vary with **time of day**, **diet** and **inter-assay variability**
- Must correlate with:
  - Clinical signs/symptoms
  - Follow a dose-response curve
  - Serum levels

Menopause. 2004 May-Jun;11(3):356-67

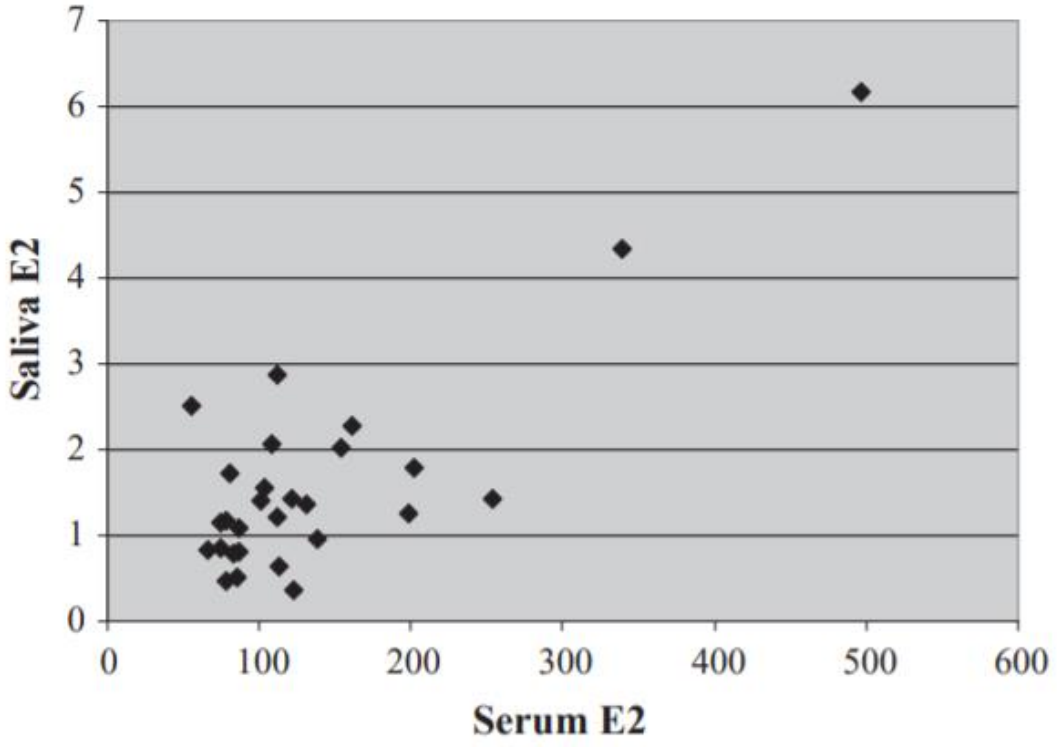


Fig. 1. Serum E2 by saliva E2 values in 28 ET using postmenopausal women ($r = 0.81$, $p < 0.0001$).

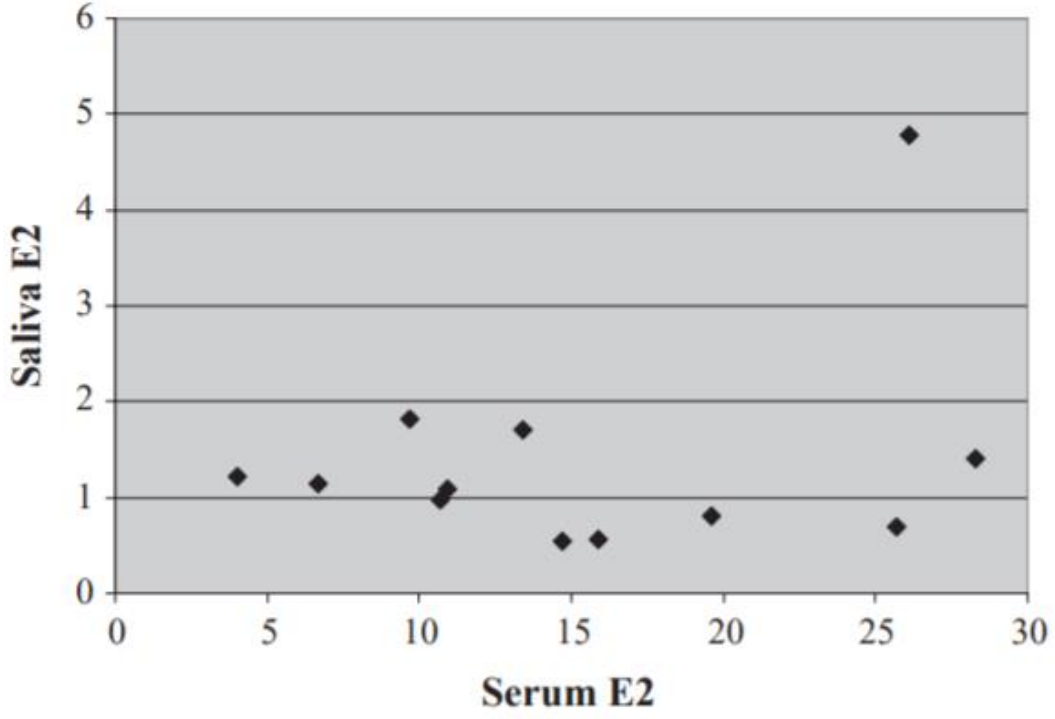


Fig. 2. Serum E2 by saliva E2 values in 12 ET non-using postmenopausal women ($r = 0.32$, $p < 0.31$).

Prog Neuropsychopharmacol Biol Psychiatry. 2005 Jun;29(5):727-32.

TABLE 4. *Gonadal saliva steroid concentrations in women*

Hormone	Unsupplemented concentration (pg/mL)	Supplemented concentration (pg/mL)
Estradiol		
Premenopausal		
Basal	0.5-5	Oral: 2-20
Ovulatory	3-8	Patch: 1-5
Postmenopausal	<1.5	Cream/gel: 10-50
Estriol		
Premenopausal	4.4-8.3	Oral: 20-40
Postmenopausal	3-5.4	Cream: 300-500
Estrone		
Premenopausal and postmenopausal	−5.4	
Progesterone		
Premenopausal		
Basal	<0.1 ng/ml	Oral: 0.1-0.5 ng/mL
Ovulatory	−0.5 ng/ml	Cream/gel: 1.0-10 ng/mL
Postmenopausal	<0.05 ng/ml	
Testosterone unsupplemented		
20–29	17-52	
30–39	15-44	
40–49	13-37	
50–59	12-34	
>60	>11-35	

Adapted from Reference 54.

Menopause. 2004 May-Jun;11(3):356-67

“I’d rather pay for a compound; I know where it’s coming from and I trust my _____ (insert naturopath, pharmacist etc.).”

How do I interpret this Rx?

Good N' Natural Clinic
123 Almond Way
Winnipeg, MB R2N1N7

Date: Jan 27, 2018
Patient: Suzanne Sommers
Address: 55 Grass Lane

Rx:

BiEst transdermal gel 2.5mg (9:1)
Apply as directed daily
M: 50g Repeats: 2

Dr. B. Free
Bernard Free (#56789)

TABLE 2. **Common Compounded Bioidentical Hormone Therapy Preparations**[a,b]

Preparation	Ingredients	Dose
Tri-estrogen	Estriol Estrone Estradiol (8:1:1 ratio)	1.25-2.5 mg/d
Bi-estrogen	Estriol Estradiol (8:2 or 9:1 ratio)	1.25-2.5 mg/d
Estriol	Estriol	2.0-8.0 mg/d
Progesterone	Progesterone	100-200 mg/d

[a] Data were compiled from multiple compounded bioidentical hormone therapy Web sites and pharmacies on the Internet and from Boothby et al[15]; however, this summary is not a comprehensive listing of all available products.

[b] All preparations are available in oral, transdermal, sublingual, or vaginal routes of administration, with the exception of progesterone, which is also available as an injectable medication.

Menopause. 2004 May-Jun;11(3):356-67

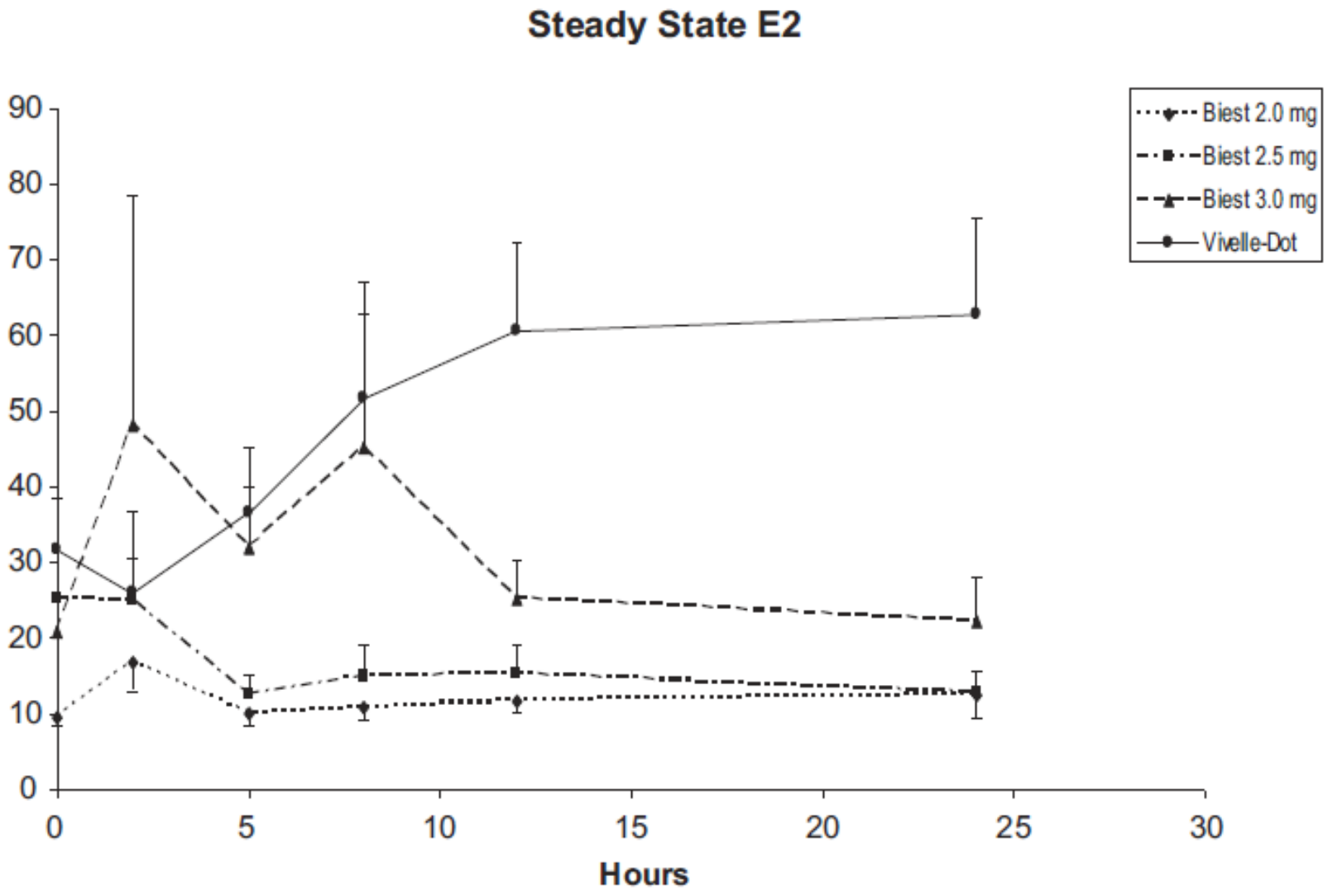


Fig. 3. Mean estradiol across groups – steady-state (Days 15/16) curves.

n= 40 menopausal women

4 arms:
Biest 2.0mg (80:20) 1.6mg/0.4mg
Biest 2.5mg (80:20) 2mg/0.5mg
Biest 3.0mg (80:20) 2.4mg/0.6mg
Estradiol patch 0.05mg

E1, E2, E3 levels over 16 days (blood sampled Day 1 and Days 15 and 16: 1 hr prior, 2, 5, 8, 12, 18 and 24 hours)

Maturitas. 2013 Apr;74(4):375-82.

Cost of Compounding “Bioidentical Hormones”

Biest 50:50 0.5mL/dose daily (45mL)	$120/90 days
Estrogel® 2.5g daily (80g/tube)	$130/90 days

Bioidentical Hormones are derived from plants, such as yam or soy and are chemically and functionally identical to human hormones. Bioidentical Hormones produce the same responses in the body as hormones made by the body without increased risk of allergic reaction and sensitivities.

Our approach is to individualize treatment plans for each patient based on medical history, physical examination, symptoms and laboratory analysis. The prescription is tailored to the exact amount of each hormone needed for the individual's balance. We focus on Bioidentical Hormone restoration and optimization.

MOOD IN MENOPAUSE

Case Study

Carol is a 48 year old woman who presents to your office reporting fatigue, depressed mood, poor sleep and memory changes. She would like her “hormones checked” and becomes angry with you when you suggest treatment for depression.

How can you help Carol?

HT for Depression?

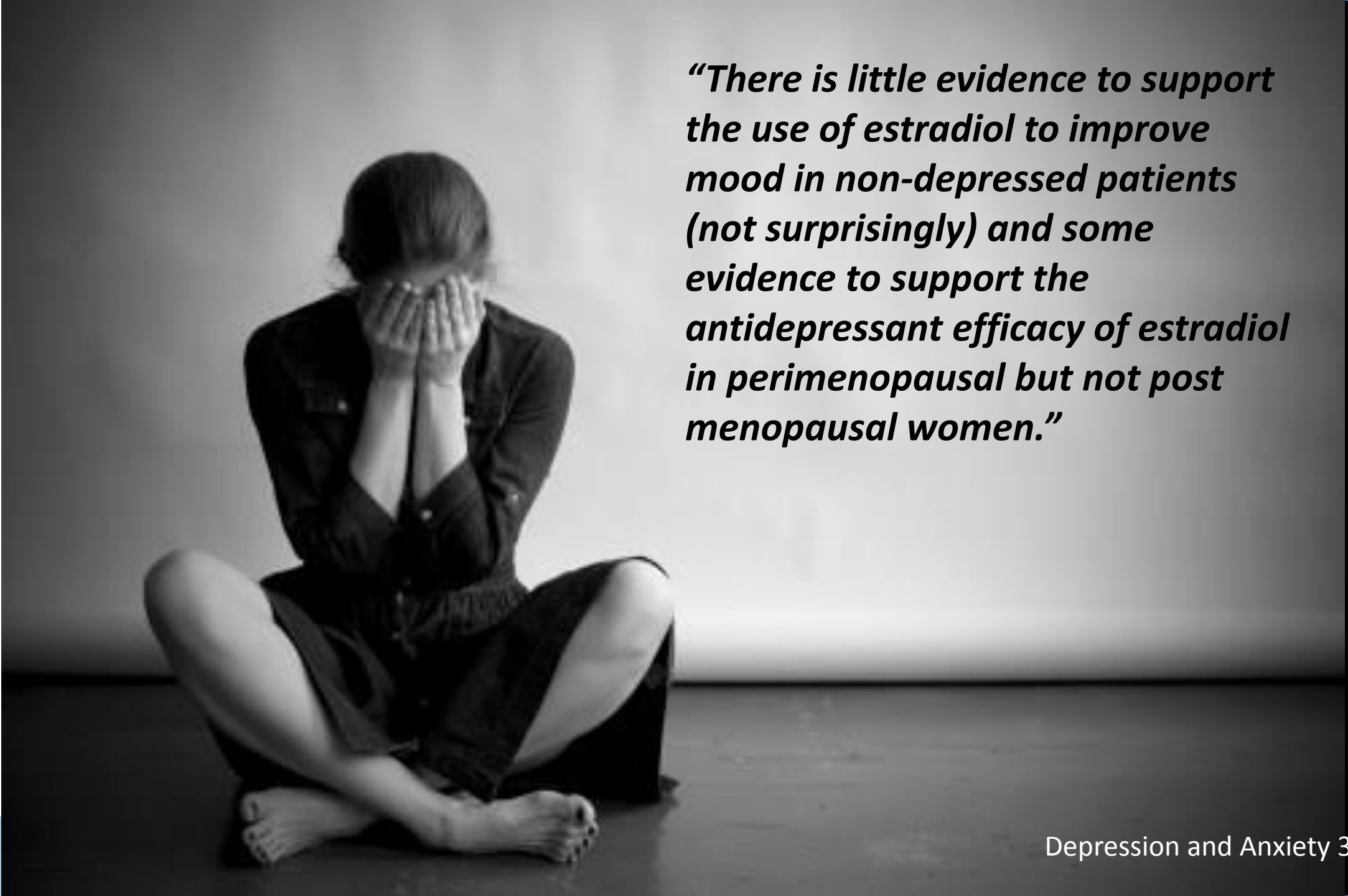
"Evidence is insufficient to support HT use in the treatment of clinical depression."

"In small RCTs, ET was effective in improving clinical depression in perimenopausal but not postmenopausal women."


POSITION STATEMENT

The 2017 hormone therapy position statement of The North American Menopause Society

Menopause: The Journal of The North American Menopause Society Vol. 24, No. 7, pp. 728-753



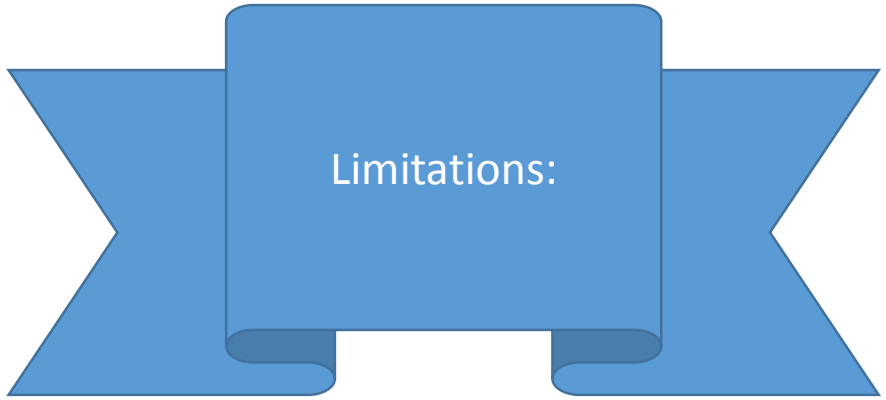
"There is little evidence to support the use of estradiol to improve mood in non-depressed patients (not surprisingly) and some evidence to support the antidepressant efficacy of estradiol in perimenopausal but not post menopausal women."

Depression and Anxiety 32:539-549, 2015

Efficacy of Estradiol for the Treatment of Depressive Disorders in Perimenopausal Women

A Double-blind, Randomized, Placebo-Controlled Trial

Cláudio de Novaes Soares, MD, PhD; Osvaldo P. Almeida, MD, PhD; Hadine Joffe, MD; Lee S. Cohen, MD



Patients

- 50 patients with depression (26 major, 11 dysthymia and 13 minor depression)
  Randomized to 17B estradiol 100mcg patch vs placebo for 12 weeks
  Depression severity determined by the MADRS

Results

- Remission of depression was observed in 17 (68%) of women treated with 17B estradiol compared with 5 (20%) in the placebo group (*p<0.01)*

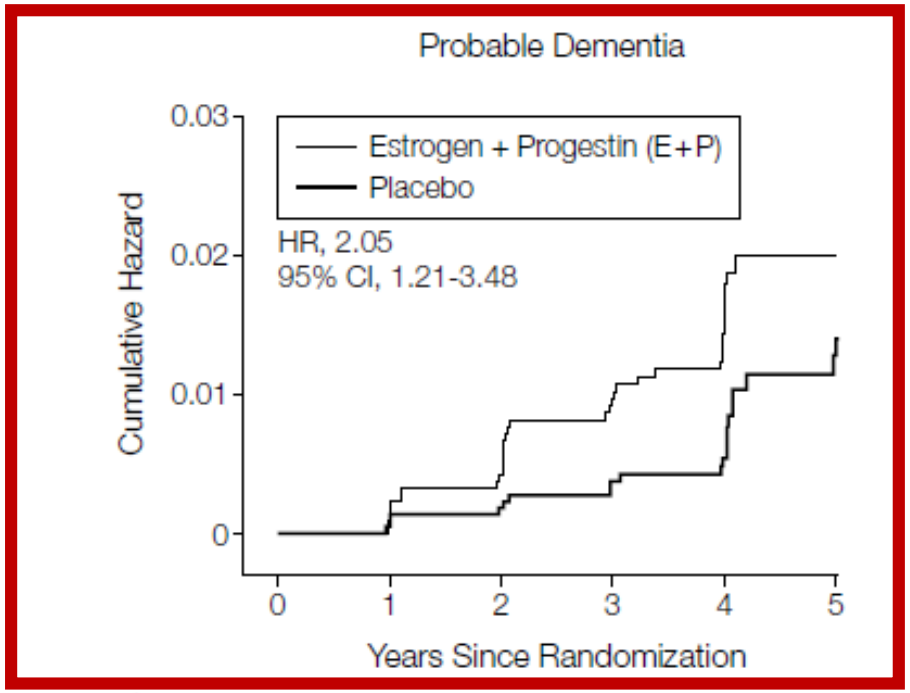
Arch Gen Psych 2001;58 (6): 529-534

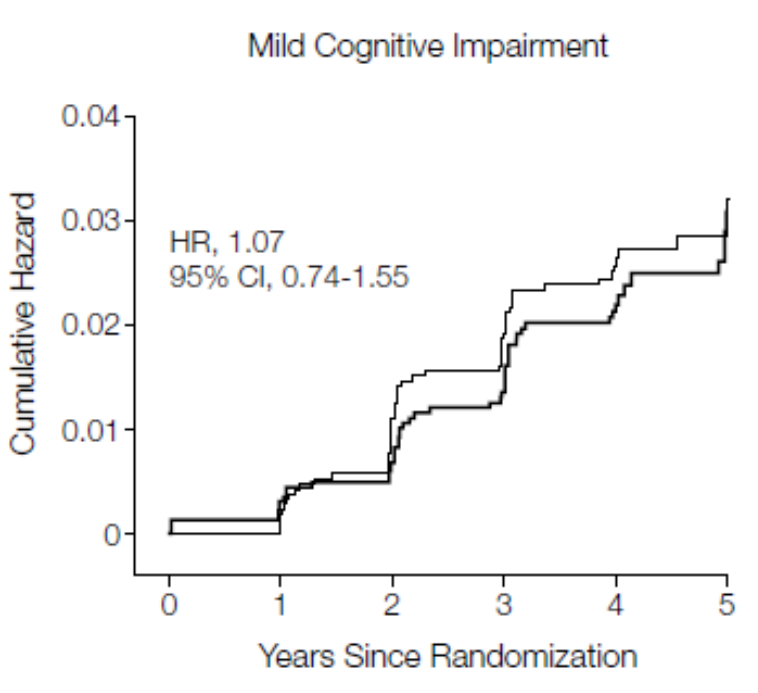
“HT cannot be recommended at any age to prevent or treat a decline in cognitive function or dementia.”

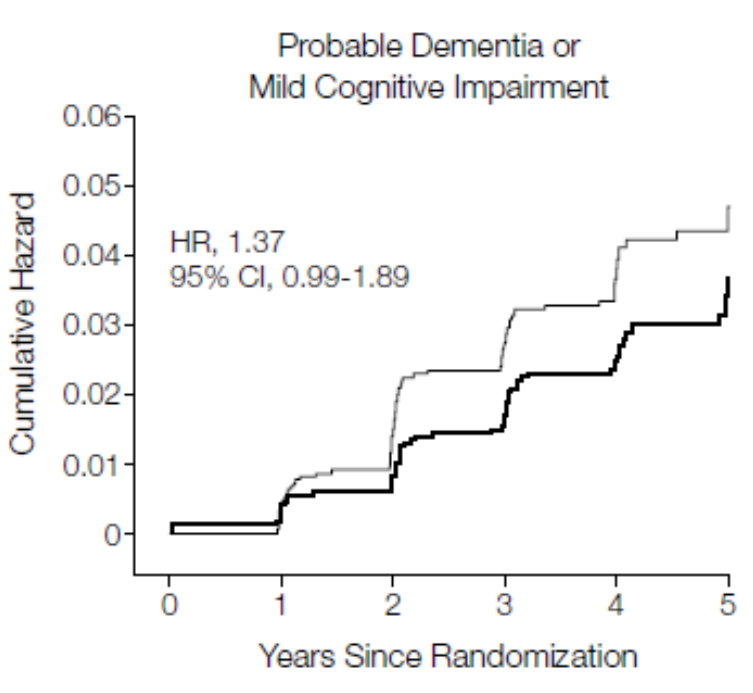
-NAMS 2017 Position Statement

Menopause: The Journal of The North American Menopause Society Vol. 24, No. 7, pp. 728-753

Figure 2. Cumulative Hazards Ratios for a Diagnosis of Probable Dementia and Mild Cognitive Impairment







No. at Risk																
E+P	2229	2117	2047	1947	1349	406	2229	2116	2036	1930	1337	408	2229	2112	2026	1915	1325	401
Placebo	2303	2206	2138	2007	1416	485	2303	2202	2129	1988	1395	479	2303	2200	2125	1984	1392	477
No. of Events																		
E+P	5	7	8	11	4		5	18	18	11	4		10	24	24	17	7	
Placebo	3	2	3	3	9		7	8	18	12	6		9	10	20	13	9	

CI indicates confidence interval; HR, hazard ratio. Data shown only through 5 years of follow-up because numbers at risk are too small after this point for precise estimates.

JAMA 2003;289:2651-2662

What about surgical menopause?

P	19 women TAH and BSO
I	10mg IM delestrogen monthly
C	Sesame oil IM
O	Blood samples for estradiol and memory testing

TABLE II. MEAN (±SEM) MEMORY TEST SCORES FOR THE TWO TEST TIMES

	ESTROGEN GROUP		PLACEBO GROUP	
	Preoperative Baseline	Post-Treatment	Preoperative Baseline	Post-Treatment
Immediate Paragraph Recall	19.0 ± 2.3*	25.8 ± 2.2*	23.1 ± 2.9	24.6 ± 2.9
Delayed Paragraph Recall	15.9 ± 2.1	21.1 ± 2.4	16.7 ± 3.4	21.2 ± 3.3
Visual Reproduction – Immediate Recall	10.1 ± 0.7	10.0 ± 0.8	11.3 ± 0.8	10.1 ± 1.2
Visual Reproduction – Delayed Recall	8.7 ± 1.0	8.5 ± 1.0	9.3 ± 1.0	7.1 ± 1.2
Associate Learning – Immediate Recall	31.7 ± 1.4	31.3 ± 1.4	30.8 ± 1.6*	25.3 ± 1.7*
Associate Learning – Delayed Recall	11.8 ± 0.5	11.4 ± 0.6	12.3 ± 0.7*	10.0 ± 0.9*
Digit Span	6.0 ± 0.4	6.1 ± 0.4	6.6 ± 0.3	6.9 ± 0.4

*significant within-group difference at $p < 0.05$.

Short-Term memory benefits?

Well that’s depressing!
Is there anything we can do?

EXERCISE!

- Patients:
  N=60, aged 60-70 years
- Intervention:
  Exercise with rhythmic musical background vs no treatment
- Outcomes (6 months)
  Geriatric Depression Scale
  Hamilton Anxiety Scale

Journal of Clinical Nursing 21; 923-928, 2011

Table 2 Symptoms of depression

	n	Initial	Final	Difference initial–final
Control group (*n* = 30)				
Moderate depression	11	11·87 ± 0·56	11·93 ± 1·01	+0·06
Severe depression	19	17·23 ± 1·22	16·85 ± 0·98	−0·38
Exercise group (*n* = 27)				
Moderate depression	10	12·02 ± 1·11	9·76 ± 1·02	−2·26*
Severe depression	17	17·34 ± 0·87	13·49 ± 1·82	−3·85**

*$p < 0·05$; **$p < 0·01$.

Table 3 Symptoms of anxiety

	n	Initial	Final	Difference initial–final
Control group (*n* = 30)				
Minor anxiety	11	7·20	7·12	−0·08
Major anxiety	19	16·37	17·01	+0·64
Exercise group (*n* = 27)				
Minor anxiety	10	7·33	5·27	−2·06*
Major anxiety	17	16·76	15·02	−1·74**

*$p < 0·01$; **$p < 0·05$.

Journal of Clinical Nursing 21; 923-928, 2011

NEW AND SEXY DRUGS FOR MENOPAUSAL SYMPTOMS

DUAVEE®

CONJUGATED ESTROGENS/ BAZEDOXIFENE 0.45 MG/20 MG TABLETS

Put moderate-to-severe hot flashes due to menopause in their place with DUAVEE

DUAVEE IS FOR POSTMENOPAUSAL WOMEN WITH A UTERUS

DUAVEE should be taken for the shortest time possible and only for as long as treatment is needed. You should talk to your doctor or other healthcare professional (HCP) regularly to see if treatment is still needed.

Don't just GRIN & BEAR IT — talk to your doctor

Talk to your doctor or other healthcare professional (HCP) about whether treatment may be right for you. They are there to listen and, more importantly, to help. So don't be shy about speaking up — start the conversation today.

GET YOUR CONVERSATION GUIDE

SCROLL DOWN TO LEARN MORE

http://www.duavee.com/

TSECs (Tissue Selective Estrogen Complex)

- Bazedoxifene = Selective Estrogen Receptor Modulator (SERM)
  - In Combo with CE = **Tissue Selective Estrogen Complex (TSEC)**

- Bazedoxifene in combo with CE has **selective estrogenic effects**
  - Beneficial effects in vaginal tissue, bone and for vasomotor menopausal symptoms
  - **Minimizes estrogen effects in endometrial and breast tissue**

SERMs and Indications/Effects

SERM	Indication	Effects on target tissues			
		Bone	**Breast**	**Endometrium**	**Vagina**
The IDEAL SERM	**<u>Doesn't exist</u>**	Agonist	Antagonist (or neutral)	Antagonist (or neural)	Agonist

Modified From Table 1 in: Expert Opin. Pharmacother. (2015) 16(17):2703-2714

SERMs and Indications/Effects

SERM	Indication	Effects on target tissues			
		Bone	**Breast**	**Endometrium**	**Vagina**
The IDEAL SERM	**<u>Doesn't exist</u>**	Agonist	Antagonist (or neutral)	Antagonist (or neural)	Agonist
Tamoxifen	Treat or reduce breast cancer	Agonist	Antagonist	Agonist ☹	Variable Agonist
Raloxifene	Treat and prevent OP in postmenopausal women, reduce risk of breast cancer	Agonist	Antagonist	Neutral or Antagonist	Neutral ☹
Ospemifene (Osphena®)	Moderate-Severe dyspareunia (GSM)	Agonist	Neutral	Partial Agonist ☹	Agonist
Bazedoxifene (Duavee®)	In combo with CE: vasomotor symptoms of menopause	Agonist	Neutral or Antagonist	Antagonist	Antagonist ☹

Modified From Table 1 in: Expert Opin. Pharmacother. (2015) 16(17):2703-2714

The SMART Trials (Phase III)

CE/Bazedoxifene combo

Dose-Finding Safety

SMART-1 (2 year)

- N=3544
- 40-75 years intact uterus
- **Endometrial hyperplasia and BMD**
- 8 groups
  - CE/BZA 0.625/10mg 0.45/10mg 0.625/20mg 0.45/20mg 0.625/40mg 0.45/40mg raloxifene 60mg Placebo
  - 0.625 or 0.45mg CE plus BZA 20mg minimum needed to prevent endometrial hyperplasia
  - Increase in BMD with treatment vs placebo

Fertil Steril 2009;92:1025–38

VM Symptoms

SMART-2 (12 weeks)

- N=332
- Postmenopausal women, intact uterus
- **Daily # of hot flushes**
- CE/BZA 0.45/20 mg
- CE/BZA 0.625/20mg
- Placebo
- 74% reduction in CE/BZA 0.45/20 mg group (10.3 to 2.8/day)
- 80% reduction in CE/BZA 0.625/20mg group (10.4 vs 2.4/day)
- 51% reduction in placebo group (10.5 to 5.4/day)
- NNT = 3-4 patients (versus placebo)

Menopause: 2009;16(6) 1116-24

GSM Symptoms

SMART-3 (12 weeks)

- N=664
- **Vulvovginal symptoms** of menopause
- CE/BZA 0.625/20mg
- CE/BZA 0.45/20mg
- BZA 20mg
- Placebo
- Both BZA/CE combinations were associated with increased cell turnover and lubrication (ASEX score) but no difference in QOL scores
- When looking at symptoms scores, questionable if truly met statistical significance (p=0.048)

Menopause: 2010;17(2) 281-289

Endometrial safety and BMD

SMART-4 (1 year+1year F-Up)

- N=1061
- Postmenopausal, uterus intact age 40-64 years
- **Endometrial safety and effects on BMD**
- CE/BZA 0.625/20mg
- CE/BZA 0.45/20mg
- CE 0.45/MPA 1.5mg
- Placebo
- 1.1% endometrial hyperplasia with CE/BZA 0.625/20mg compared with none for other groups
- CE/BZA combos increased total hip BMD and lumbar spine BMD as compared with other groups

CLIMACTERIC 2013;16:338–346

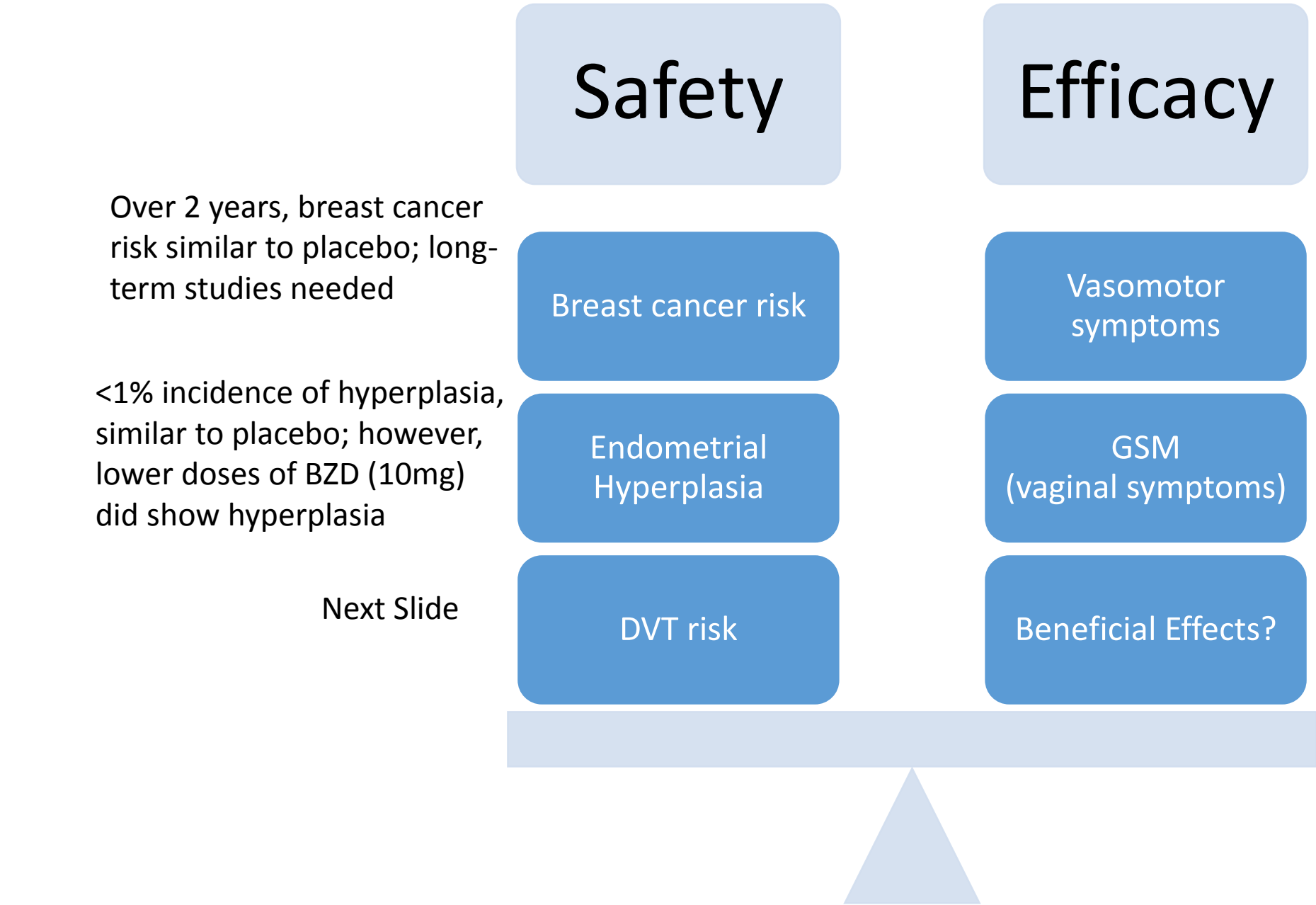
Breast Safety

SMART-5 (1 year)

- N=1843
- Postmenopausal, uterus intact age 40-64 years
- **Breast density, BMD, endometrial safety** and other parameters
- CE/BZA 0.625/20mg
- CE/BZA 0.45/20mg
- CE 0.45/MPA 1.5mg
- Placebo
- BZA/CE combo was non-inferior to placebo in terms of breast density (CE/MPA significantly increased breast density form baseline)

Obstet Gynecol 2013;121:959–68

J Clin Endocrinol Metab, February 2014, 99(2):E189–E198



Over 2 years, breast cancer risk similar to placebo; long-term studies needed

<1% incidence of hyperplasia, similar to placebo; however, lower doses of BZD (10mg) did show hyperplasia

Next Slide

Reduced hot flushes by 8-9 per day vs 2.5-5/day in placebo group
(note: placebo rates ~50%)

Not approved for GSM; some benefits in vaginal cell turnover/lubrication, but clinical symptom improvement questionable

Approved for postmenopausal bone loss prevention; Reduced bone loss @ 1 year vs placebo, but did not perform as well as CE/MPA combo

Therapeutics and Clinical Risk Management 2016:12;549-562

Cardiovascular Risk: A Comparison

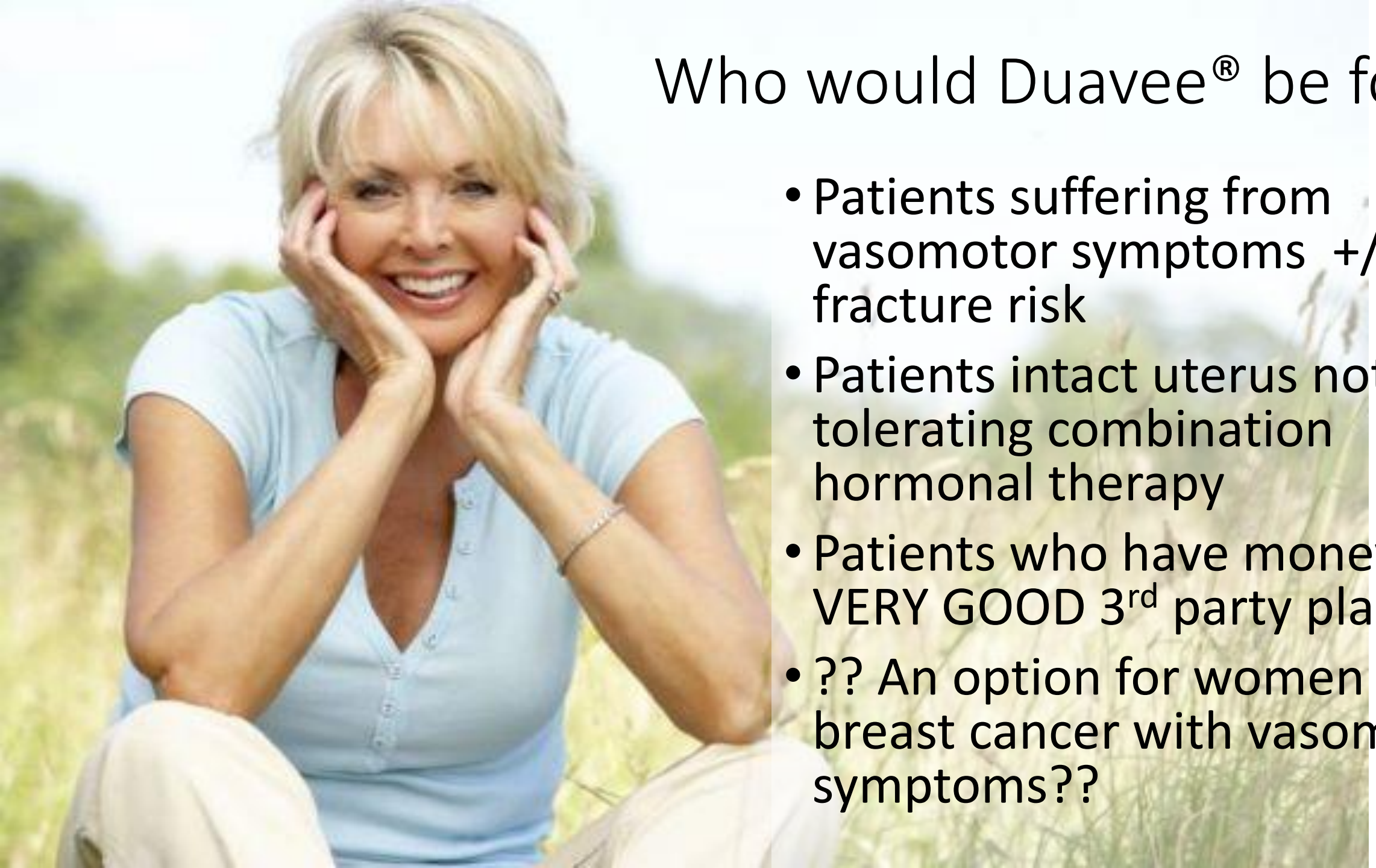
Table 6 Incidence of venous thromboembolism, ischemic stroke, and coronary heart disease: comparison of CE 0.45 mg/BZA 20 mg with historical data from the Women's Health Initiative (WHI) on CE/MPA and CE alone

	Incidence rate per 1000 woman-years							
	SMART studies		*WHI (50–59-year age group)*[30,35]		*WHI (50–59-year age group)*[30,36]		*BZA Osteoporosis Trial*[*37]	
	CE 0.45 mg/BZA 20 mg	*Placebo*	*CE/MPA*	*Placebo*	*CE*	*Placebo*	*BZA 20 mg*	*Placebo*
Venous thromboembolism	0.3	0.6	1.9	0.8	1.6	1.2	2.3	1.6
Coronary heart disease	2.6	2.0	2.2	1.7	1.7	2.7	NR	NR
Ischemic stroke	0.4	0.0	1.5	1.0	1.5	1.7	1.9	2.0

BZA, bazedoxifene; CE, conjugated estrogens; MPA, medroxyprogesterone acetate; SMART, Selective estrogens, Menopause, And Response to Therapy; NR, not reported

*, Mean age, 66.5 years in both the BZA 20 mg and placebo groups; data based on 5 years of follow-up

CLIMACTERIC 2015;18:503–511



Who would Duavee® be for?

- Patients suffering from vasomotor symptoms +/- fracture risk
- Patients intact uterus not tolerating combination hormonal therapy
- Patients who have money or a VERY GOOD 3rd party plan
- ?? An option for women after breast cancer with vasomotor symptoms??

Cost Comparisons (Intact uterus)

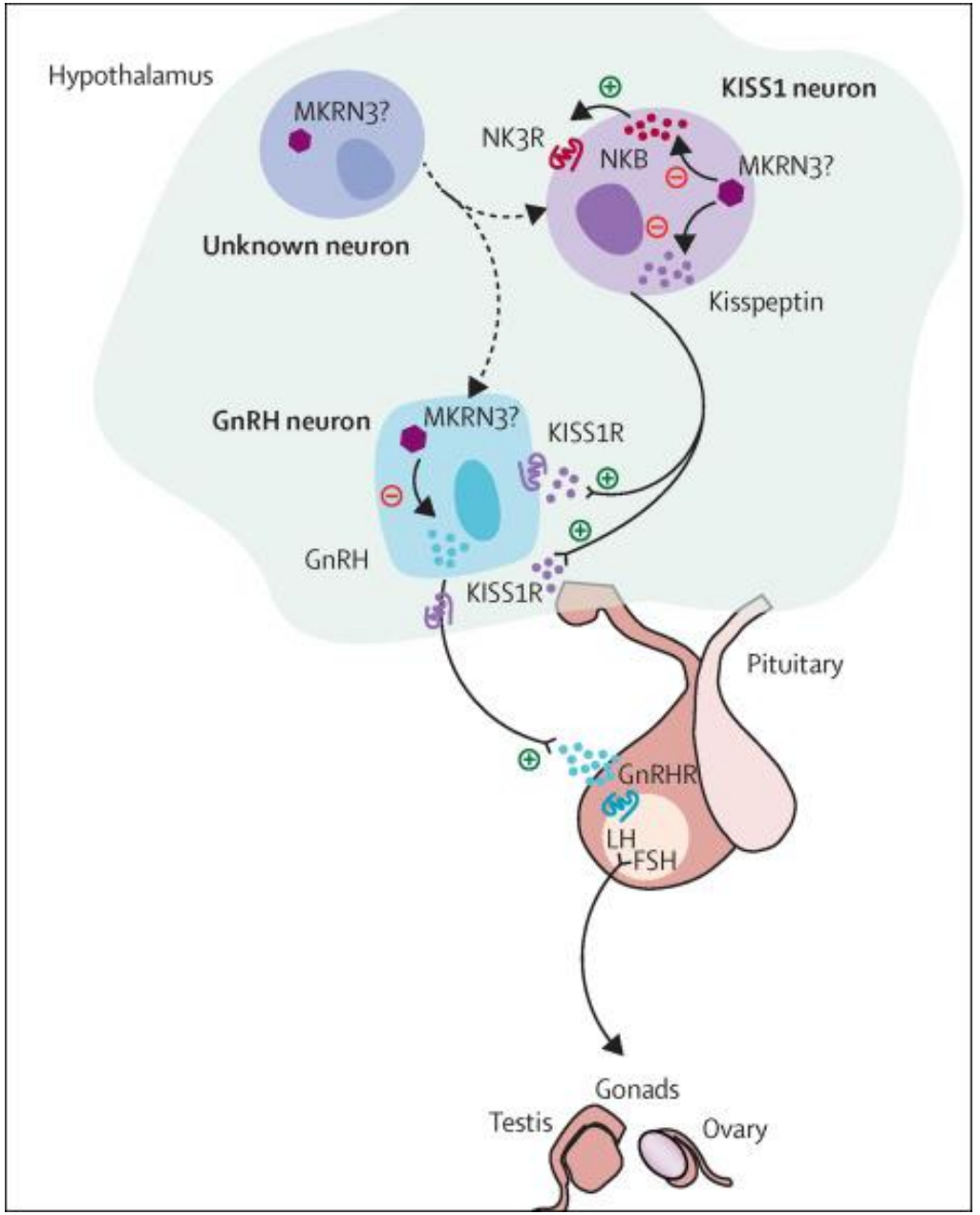
Drug/Combo	Cost for a 1 year supply
PO Estradiol + MDPA	$150 + $80 = $230
PO Estradiol + Prometrium (micronized MDPA)	$150 + $500-1000 depending on dose = TOTAL $650-$1150
Estradiol PATCH (generic) + progestin	~$320 + $230-$1000 = $550-$1320
Combination HT (controversial) Activelle® (Estradiol hemihydrate + norethindrone) Angeliq® (Estradiol + drospirenone)	 $700 $350
Duavee® (CE/bazedoxifene)	$1260

CE=conjugated estrogens, HT = hormone therapy, MDPA = medroxyprogesterone acetate

Sources: RxFiles Hormonal Therapy for Menopause Sept 2017 and McKesson Product Catalog [Accessed Sept 28, 2017]

NK3RAs – Hot off the Press

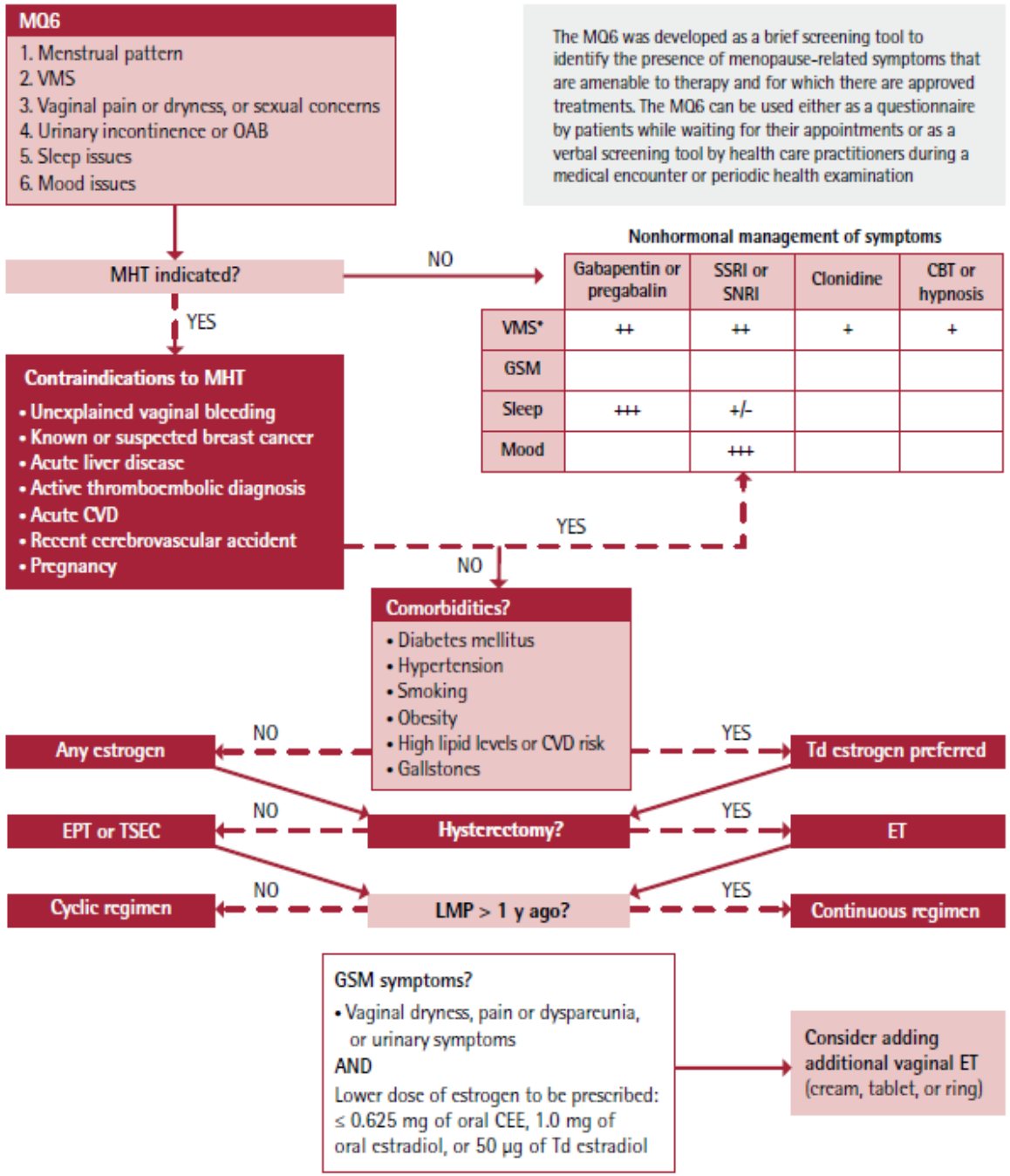
- Neurokinin 3 receptor antagonists (AZD4901)
- Phase II clinical trial underway NCT02668185
  - N=30 female patients, 40-62 years old with ≥7 hot flushes/day
  - AZD4901 x 4 weeks vs placebo
  - Primary Outcome: Mean Hot Flush Frequency
  - Secondary Outcomes: Hot flush severity, interference, bother; serum gonadotropins and estradiol concentrations, skin conductance monitoring



https://clinicaltrials.gov/ct2/show/NCT02668185?term=neurokinin+receptor+antagonists&cond=menopause&rank=1

WHERE DO WE GO FROM HERE?

Figure 2. Evidence-based algorithm for management of menopausal symptoms



Primary Care MQ6

1. • Any changes in your periods?
2. • Are you having any hot flushes?
3. • Any vaginal dryness, pain or sexual concerns?
4. • Any bladder issues or incontinence?
5. • How is your sleep?
6. • How is your mood?

Can Fam Physician. 2017 Apr;63(4):295-298

THANK YOU!
QUESTIONS?

EXTRAS

HORMONAL THERAPY for MENOPAUSE (MP): Chart [37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53 (SOGC'14); NAMS'17, AACE'17]

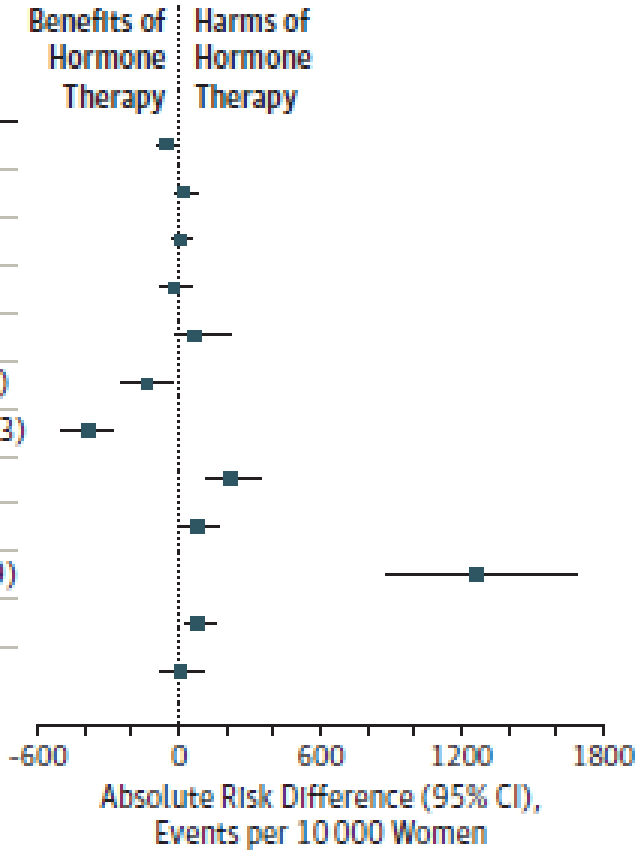
L Regier BSP BA Sep 2017

Hormonal Therapy See Online Extras 💻 for more pearls.	Source	Generic Name	TRADE Name / Strength	Equivalent / Usual Dose	$/Yr
• Hormone therapy expected to ↓vasomotor symptoms by 50-100%. Use for shortest duration possible at lowest effective dose. CEE 0.625mg ≈ estradiol, 1mg oral, ≈ 50mcg transdermal patch. Estrogen regimens are generally ⅓ to ½ the estrogen found in oral contraceptives. **Pearls**: ❶ Add progestogen to estrogen if no hx of hysterectomy, to prevent endometrial cancer. ❷ Consider topical/transdermal estrogen if ↑CVD risk/smoking/HTN/DM/gallstones. ❸ If last menstrual cycle was < 1yr ago, use 10-14 days progestogen per month; otherwise use continuous HT to avoid monthly withdrawal bleed. See Online Extras 💻 for further bleeding pearls. • **AE**: Breast tenderness, headache, mood changes. Tapering useful when discontinuing to ↓AE.[54] **Serious & rare**: DVT, pulmonary embolism, stroke, ?dementia. **CI**: history of breast cancer, CHD, stroke/TIA, VTE, liver disease, endometrial cancer, unexplained vaginal bleeding. Raynaud's may be caused/worsened by unopposed estrogen. Harms > benefit over 5+ years?[WHI; NNH=88] See *Weighing Benefits & Harms* below.[55,56] Less risk in younger <50-59yr ♀? • **DI**: 3A4 substrate (↑ estrogen level by 3A4 inhibitors; ↓ level by 3A4 inducers); weak 1A2 inhibitor. **AE risk ↑ as age ↑; reassess need for tx regularly.** **?Timing hypothesis**: ↑ CV harm in those started late (10+ yrs post menopause) vs within 6 yrs					
ESTROGEN: ORAL •↓dose = ↓AE (e.g. uterine bleed, breast tenderness, breast cancer risk)	equine	Conjugated equine est. (CEE)	**PREMARIN** 0.3, 0.625, 1.25 mg tab (0.45 KEEPS)	0.625mg po daily [WHI]	185
	plant	Micronized estradiol-17β	**ESTRACE, g** Lupin 0.5, 1, 2mg (scored tabs)	1mg po daily [WELL-HART, Elite]	152 g, [179]
ESTROGEN: TRANSDERMAL/TOPICAL •Avoids 1st pass effect. Compared to oral: ↓risk in liver disease; ↓lipid effect (↓LDL, ↔/↑HDL, ↓↓TGs; ↓gallbladder dx; ↓VTE; [ESTHER] equal efficacy for vasomotor symptoms and in preserving bone density. •**patch**: rotate sites (abdomen/thighs/buttocks) •**gel**: **do not rotate sites** (arm, abdomen or thigh)	plant	Estradiol-17β **Patch**	**ESTRADOT** 25, 37.5, 50, 75, 100mcg/d Matrix ☎▼	50mcg twice/wk [smallest size]	372
			SANDOZ-ESTRADIOL DERM 50,75,100 mcg/d Matrix (Inter-changeable) ☎▼	50mcg twice/wk	315
			OESCLIM 25, 50 mcg/d Matrix ☎▼	50mcg twice/wk	347
			CLIMARA 25, 50, 75, 100 mcg/d Matrix ☎▼	50mcg **weekly** [KEEPS]	350
	plant	Estradiol-17β **Topical Gel**	**DIVIGEL 0.1%** 0.25mg(0.25g), 0.5mg(0.5g), 1mg(1g) {thigh area} ☎▼	0.25mg(0.25g) daily (as directed)	290
			ESTROGEL 0.75mg/1.25g {to each arm daily} ☎▼	2.5g(1.5mg) daily (as directed)	530
•**Compounded Estrogen Cream:** with estradiol + estriol ± estrone; controversial - promoted as "bio-identical/safer" [eg. BI-EST, TRI-EST cream], but no advantages, quality control issues, & expensive. [SOGC]					
ESTROGEN: VAGINAL –with ↑tx transmucosal absorption↓ •For **urogenital** sx's: atrophy/dryness/stress incont.[Cody'09] •Adjust to lowest dose that controls symptoms. •**Less systemic** effect (but creams may require progesterone) •OK even in breast cancer hx if failed non-hormonal tx.[ACOG'16]	equine	Conjugated estrogens	**PREMARIN Vag. Cr** 0.625mg/g [Off-label use: apply to nostrils to ↓ nosebleeds]	0.5-2g pv HS(cyclic [3wk/1wk] ✱)	195-600
	synth	Estrone vaginal cream	**ESTRAGYN Vag. Cr** 1mg/g ✗ ⊗	0.5-4g pv HS(cyclic [3wk/1wk] ✱)	200-1230
	plant	Estradiol-17β **Vaginal Tab**	**VAGIFEM Vag. tab** 10,25mcg [D/C by company] {initial: 1tab vag daily x2wk}	1 tab per vag twice/wk	463
	plant	Estradiol-17β **Vaginal Ring**	**ESTRING Vag. Ring** 2mg (7.5mcg/day)	vaginally every 90 days	350
PROGESTOGENS: ORAL • **Required** if intact uterus & on estrogen. •Cyclic regimen ↑bleeding, bloating vs continuous • þ concern •?levonorgestrel IUD **MIRENA** if oral tx not tolerated few trials.[57]	synth	Medroxyprogesterone (MPA) •may ↓HDL	**PROVERA** 2.5, 5, 10 mg scored tabs ♣ daily dosing for amenorrhea (14days tx q 3 months an option ??use limited) ←	2.5mg po daily [WHI] 5-10mg po X10-14 d/mo	77 70-90
	plant	Micronized progesterone •less breakthrough bleeding	**PROMETRIUM, g** 100mg cap • sedating (give at HS); ?↓AE ☎ 🤰 {Teva-Progesterone contains peanut oil}	100-200mg po HS 200-300mg x10-14 d/mo [KEEPS]	566-1073 465-668
•**Compounded Progesterone cream** 2.5, 5 &10%; ? absorption, serum levels & efficacy (apply to thigh, inside of upper arm, abdomen). Does not provide endometrial protection. ✗ ⊗				Apply ~ 1g daily	~ 260
Combination Hormone Therapy Offers convenience of progestin and estrogen in single dosage form. Continuous progestin regimen prevents withdrawal bleeding. Benefits called into question following large scale RCTs (HERS, WHI, WHIMS, HABITS), but **controversial** (see *Benefits and Harms* below).		**Combination Tab** **EH** = estradiol hemihydrate	**ACTIVELLE** EH 1mg + norethindrone 0.5mg tab ✗ ⊗ **ACTIVELLE LD** EH 0.5mg + norethindrone 0.1mg tab ✗ ⊗ **ANGELIQ** E2 1mg + drospirenone 1mg tab ✗ ⊗	1 tab po daily	700 700 349
		Combination Patch **E2** = Estradiol-17β	**ESTALIS** E2 50mcg/d + norethindrone 140mcg or 250mcg Matrix ☎▼ **CLIMARA Pro** E2 45mcg/d + levonorgestrel 15mcg Matrix ✗ ▼	apply one patch twice/week apply one patch weekly	405 415
ANDROGENS (T=testosterone) •for symptoms of androgen deficiency post bilateral oophorectomy & post-menopause; ↓ abdominal fat & TBW.[58] •studies re. optimal prep, dose & long-term safety are lacking		Testosterone undecanoate	**ANDRIOL, g** 40mg cap (data lacking in ♀)	40mg po alternate days	155g, [245]
		Testosterone Vag. Ointment	**T**-propionate **2%**; Micronized-**T 0.125%** **compounded** ✗ ⊗	M-T 0.125%: 0.2-0.4ml per vag. daily	500
		Testosterone Gel	**ANDROGEL** 1% gel (data lacking in ♀) ✗ ⊗	♂ 2.5-5g daily	90-165

Figure 3. Absolute Risk Reductions or Increases for Women Treated With Estrogen Alone and With Estrogen Plus Progestin

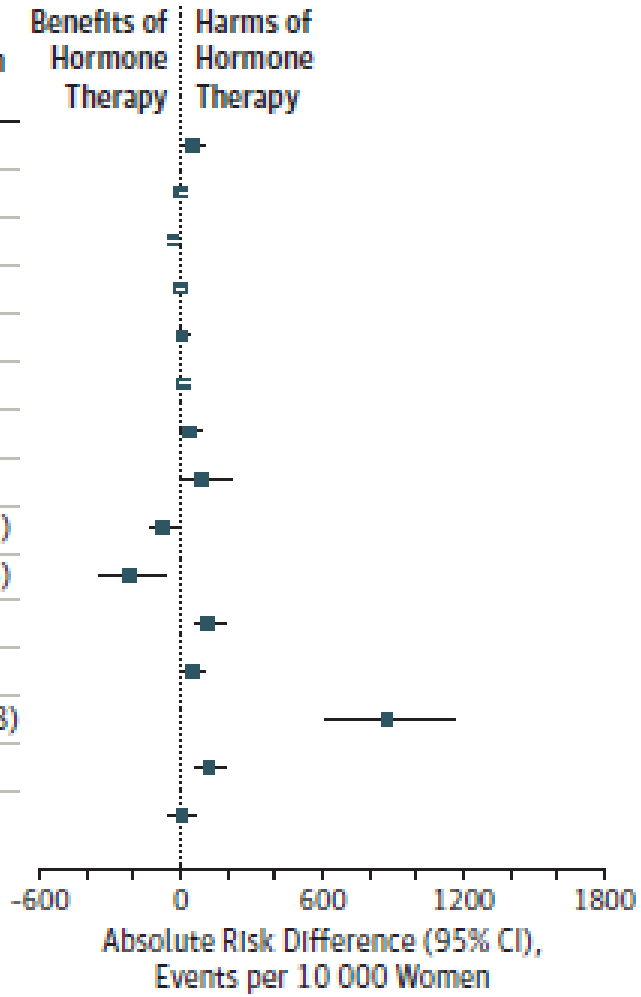
A Estrogen alone

Outcome	No. of Trials	Strength of Evidence	No. of Events/Total No.		RR (95% CI)	Absolute Risk Difference, Events per 10 000 Women (95% CI)
			Treatment	Placebo		
Breast cancer (invasive)	1[13]	Moderate	104/5310	135/5429	0.79 (0.61-1.01)	-52 (-97 to 3)
Colorectal cancer	1[13]	Low	65/5310	58/5429	1.15 (0.81-1.63)	16 (-20 to 73)
Lung cancer	1[13]	Low	62/5310	61/5429	1.04 (0.73-1.48)	5 (-30 to 54)
Coronary heart disease	3[23,29,31]	High	203/5596	224/5714	0.95 (0.79-1.14)	-20 (-82 to 55)
Dementia (probable)	1[77]	Low	28/1464	19/1483	1.49 (0.84-2.66)	63 (-21 to 213)
Diabetes	1[13]	Moderate	449/4900	527/5017	0.87 (0.77-0.98)	-137 (-242 to -21)
Fractures (osteoporotic)	1[13]	High	544/5310	767/5429	0.73 (0.65-0.80)	-382 (-495 to -283)
Gallbladder disease	1[39]	Moderate	228/4141	143/4235	1.63 (1.33-2.00)	213 (111 to 338)
Stroke	1[13]	Moderate	169/5310	129/5429	1.33 (1.06-1.67)	79 (14 to 160)
Urinary incontinence	1[41]	Moderate	557/1526	368/1547	1.53 (1.37-1.71)	1261 (880 to 1689)
Venous thromboembolism	1[13]	Moderate	137/5310	98/5429	1.43 (1.11-1.85)	78 (20 to 153)
All-cause mortality	3[23,29,31]	High	340/5923	342/6038	1.01 (0.88-1.17)	6 (-74 to 96)

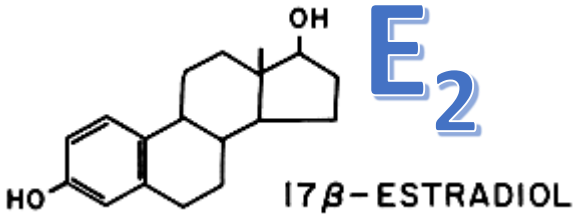


B Estrogen + progestin

Outcome	No. of Trials	Strength of Evidence	No. of Events/Total No.		RR (95% CI)	Absolute Risk Difference, Events per 10 000 Women (95% CI)
			Treatment	Placebo		
Breast cancer (invasive)	1[13]	High	206/8506	155/8102	1.27 (1.03-1.56)	52 (6 to 107)
Cervical cancer	1[65]	Low	8/8506	5/8102	1.52 (0.50-4.66)	3 (-3 to 23)
Colorectal cancer	1[13]	Moderate	50/8506	75/8102	0.64 (0.44-0.91)	-33 (-52 to -8)
Endometrial cancer	1[13]	Low	27/8506	30/8102	0.86 (0.51-1.44)	-5 (-18 to 6)
Lung cancer	1[13]	Moderate	78/8506	70/8102	1.06 (0.77-1.46)	5 (-20 to 40)
Ovarian cancer	1[13]	Low	24/8506	16/8102	1.43 (0.76-2.69)	9 (-5 to 33)
Coronary heart disease	3[18,32,71]	High	205/9506	155/8712	1.23 (1.00-1.52)	41 (7 to 93)
Dementia (probable)	1[45]	Moderate	40/2229	21/2303	1.97 (1.16-3.33)	88 (15 to 213)
Diabetes	1[37]	Moderate	328/8132	373/7742	0.84 (0.72-0.97)	-77 (-135 to -15)
Fractures (osteoporotic)	5[16,18,31,34,35]	High	903/10464	1092/10035	0.80 (0.68-0.94)	-221 (-353 to -66)
Gallbladder disease	1[39]	Moderate	228/7308	135/6895	1.59 (1.29-1.97)	116 (57 to 190)
Stroke	1[13]	High	159/8506	109/8102	1.39 (1.09-1.77)	53 (12 to 104)
Urinary incontinence	1[41]	Moderate	834/2675	563/2507	1.39 (1.27-1.52)	876 (606 to 1168)
Venous thromboembolism	1[13]	Moderate	209/8506	102/8102	1.95 (1.54-2.47)	120 (68 to 185)
All-cause mortality	3[31, 34, 35]	Moderate	384/9990	368/9590	1.01 (0.88-1.17)	4 (-48 to 68)

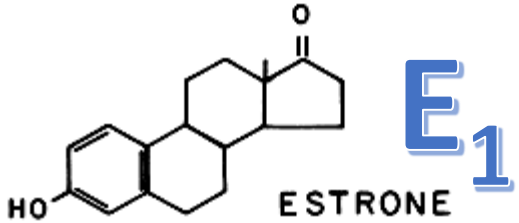


Get Those Hormones Straight!



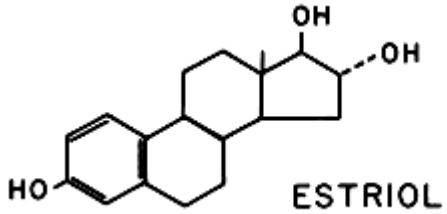
E_2

From ovaries
Predominant estrogen *before* menopause



E_1

From ovaries
Highest *after* menopause



E_3

Short-acting, least potent
(1/80th of E_2)
Metabolized from others
High in pregnancy

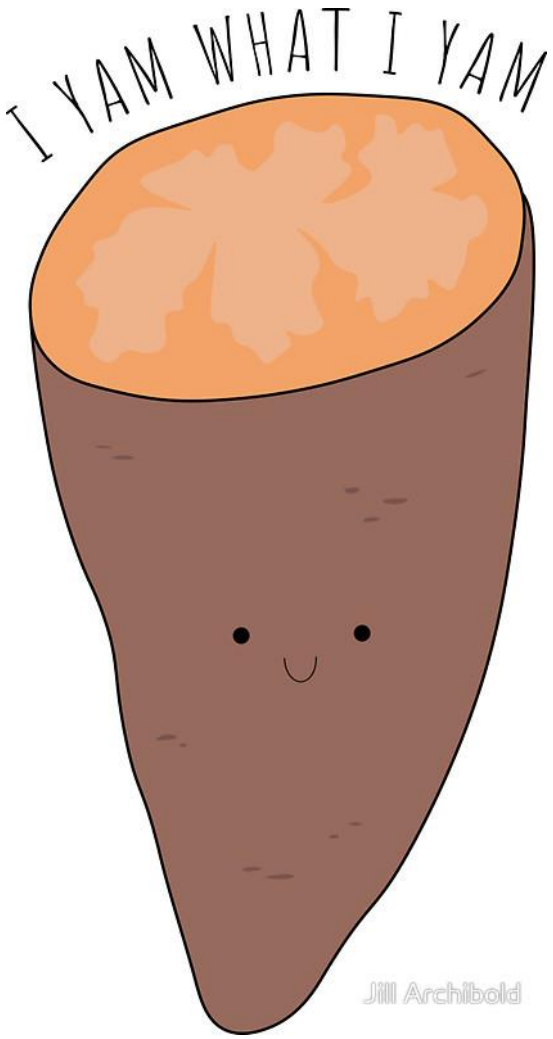
17-β Estradiol

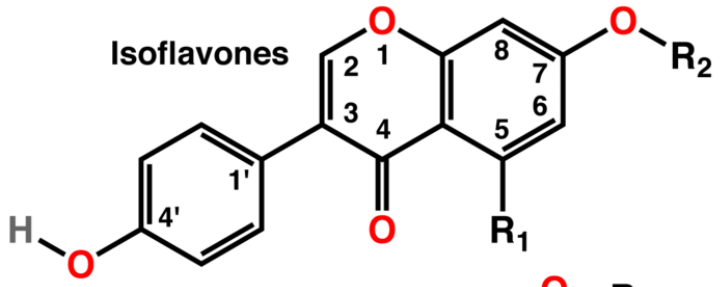
Most potent, most active

α (Alpha) receptors	β (Beta) receptors
Endometrium Breast cancer cells Ovary	Bone Kidney Lung Endothelium
17-β estradiol (high) Estrone (moderate) Estriol (weak)	17-β estradiol (high) Estriol (weak)

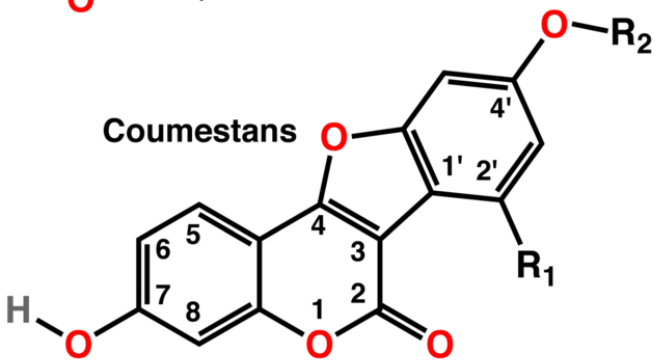
Journal of Steroid Biochemistry & Molecular Biology 142 (2014) 16–29
Menopause. 2004 May-Jun;11(3):356-67

Plant-Based Estrogens

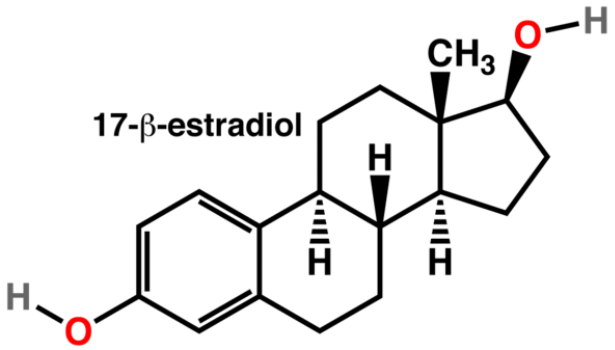




	R_1	R_2
daidzein	H	H
formononetin	H	CH_3
genistein	OH	H
biochanin A	OH	CH_3

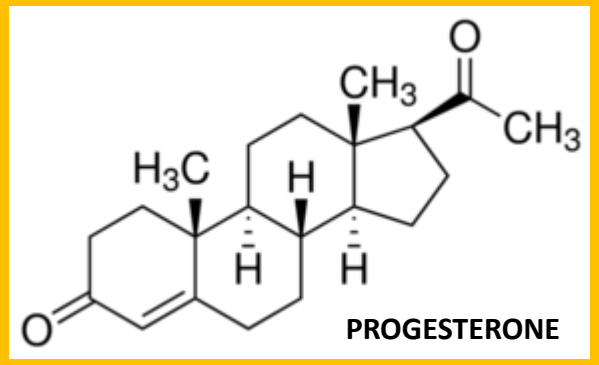


	R_1	R_2
coumestrol	H	H
4'-methoxycoumestrol	H	CH_3
repensol	OH	H
trifoliol	OH	CH_3

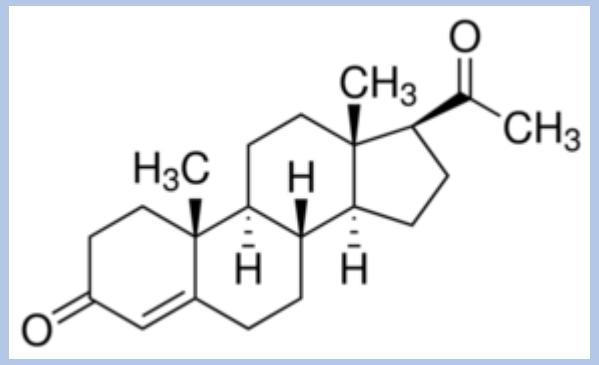


Pharmaceutical Preparations

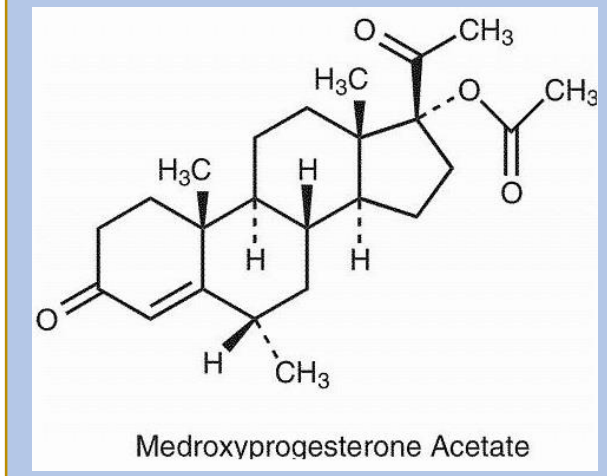
Endogenous



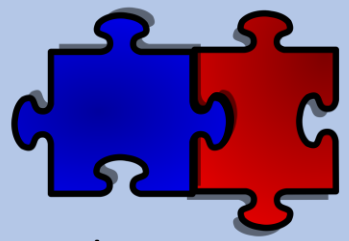
PROGESTERONE



Prometrium® (micronized progesterone)



Medroxyprogesterone Acetate



Medroxyprogesterone acetate (MPA)

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