GENERAL PRACTICE

CONFERENCE & EXHIBITION

MENOPAUSE: YOUR MENU OF TREATMENTS FOR PAUSING THE SYMPTOMS – MHT UPDATE 2017

Dr AnnaBurrows

medical specialist in gynaecology

Hey !

Premarin®

(conjugated estrogens)

EQUINE

vaginal cream

› That's right. It's made with horse pee.

THE MENOPAUSE TRANSITION

- Vasomotor
- Irregular Bleeding
- Urinary Incontinence
- Sleep disturbance
- Dyspareunia
- Depression
- Anxiety
- Labile Mood
- Fatigue
- Headache
- Myalgias
- Arthralgias
- Weight gain
- Poor memory
- Dry Skin
- Dry eyes
- Vaginal Dryness
- Thin scalp hair
- Hirsutism

PIVOTAL STUDIES

- WHI (Women's Health Initiative) RCT 1993-2002
- PEPI (Post menopausal Estrogen/Progestin Interventions) 1989-94
- HERS (Heart and Estrogen Replacement) 1993-98
- NHS (Nurses Health Study)
- SWAN (Study of Women's Health Across the Nation) 1996-current
- MWS (Million Women Study) 1996- current
- WISDOM (Womens International Study of long Duration Estrogen after Menopause 1992-2002
- ELITE (Early Vs Late Intervention trial Estradiol) 2004-2013
- KEEPS (Kronos Early Estrogen Prevention Trial) 2005-2012
- Harvard mood study 1995-2006
- DOPS Danish Oestoporosis prevention Study 1990-2008

WOMEN'S HEALTH INITIATIVE

ISSUES TO ADDRESS

1. What is the effect of HRT on hot flushes, the genitourinary syndrome of menopause (also formerly known as vaginal atrophy) and other menopause symptoms?

2. What are the risks or risk reduction for osteoporosis, cardiovascular disease, breast, endometrial and colon cancer?

3. Does HRT slow the decline in cognitive function and prevent Alzheimer's disease?

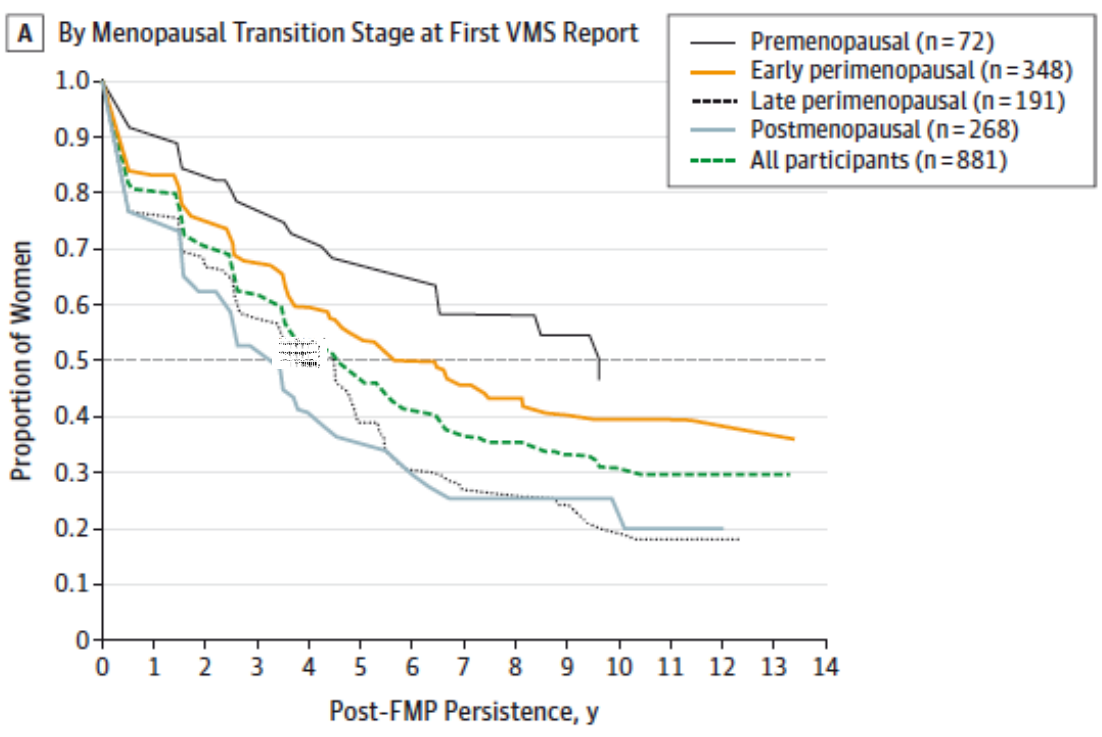
4. What recommendations should women be given – what to take and for how long?

We now have a consensus on the use of MHT

- **Treatment of Symptoms of Menopause: An Endocrine Society Clinical Practice Guideline.** J Clin Endocrinol Metab 2015; 100:3975-4011
- **Menopause Clinical Guideline. National Institute for Health and Care Excellence. (NICE Guideline)** JAMA Intern Med 2016;176:1205-6
- **2016 IMS Recommendations on women's midife health and Menopausal Hormone Therapy** Climacteric 2016;19:109-50
- **NAMS 2017 Position Statement on MHT** Menopause 2017 June
- **Global Consensus Statement on Menopausal Hormone Therapy** Climacteric 2016;19:313-315

VASOMOTOR SYMPTOMS

How long do hot flushes last?



Data from SWAN

- 1449 women with frequent VMS
- **Frequent VMS** *lasted more than 7 years for more than 50% women*

Avis N et al JAMA 2015;175:531-9

Prevalence of VMS in Australia
Community survey of 2020 women.
VMS in:
32% of peri menopausal women
75% of post menopausal women < 55
42% of women aged 60-65

Gartoulla P et al Menopause 2015;7:694-701

SLEEP DISTURBANCES

POOR SLEEP

- 45% Perimenopausal Women

CAUSES

- Hot Flushes
- Nocturia
- Anxiety
- Depression
- Primary Sleep Disorders

SLEEP DISTURBANCES

OESTROGEN in HYPOGONADAL WOMEN

- Improved sleep quality
- Improved length of REM sleep
- Improved latency (time from awake to sleep – the lightest of the non –REM sleep)

PRIMARY SLEEP DISORDERS

- Arousals in second half of night
- Look for other causes – apnoea, restless legs, anxiety and depression

DEPRESSION

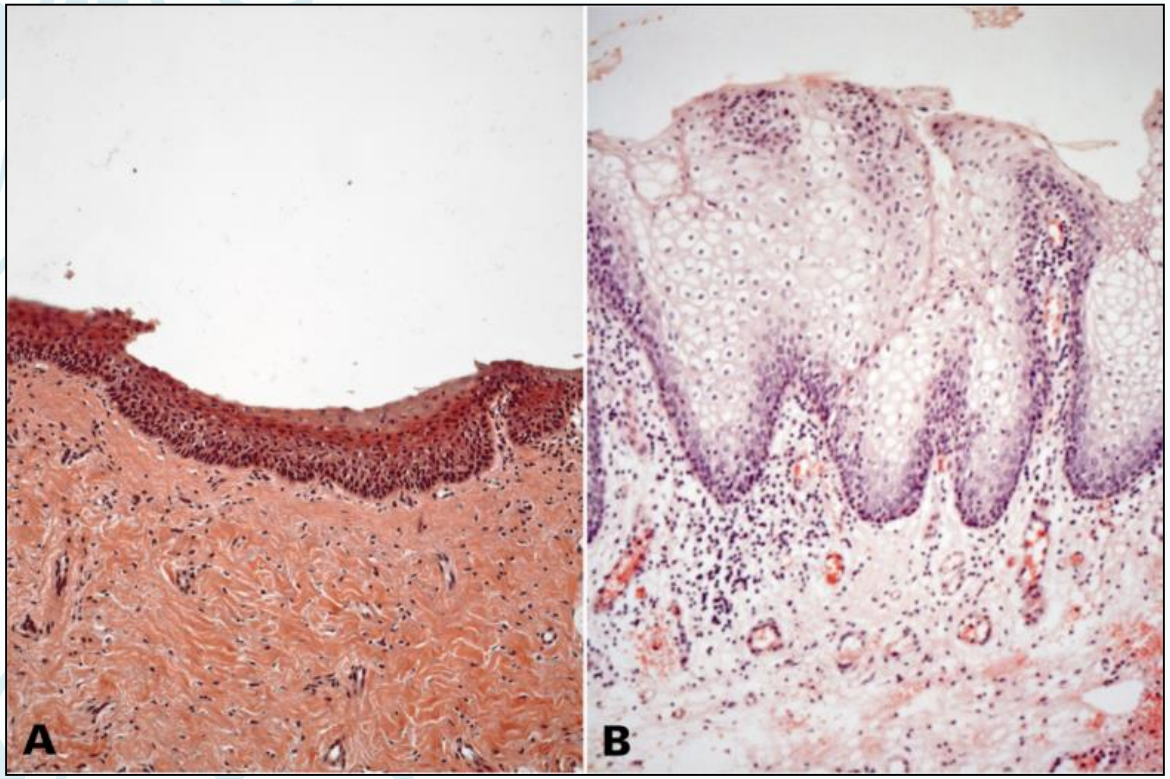
- Harvard Study of Moods – depression during the menopausal transition
- SWAN (Study of Women's Health Across the Nation) – increased psycholgic distress
- Depression more likely:

1. Latter phases of perimenopause
2. History of postnatal depression and PMDD
3. Sleep disorders and hot flushes

DEPRESSION

- Treatment with transdermal oestradiol success
- KEEPS (Krono Early Prevention Study) :
- HRT can improve
  1. Depression
  2. Anxiety
  3. Sexual function
- Consider SSRI's

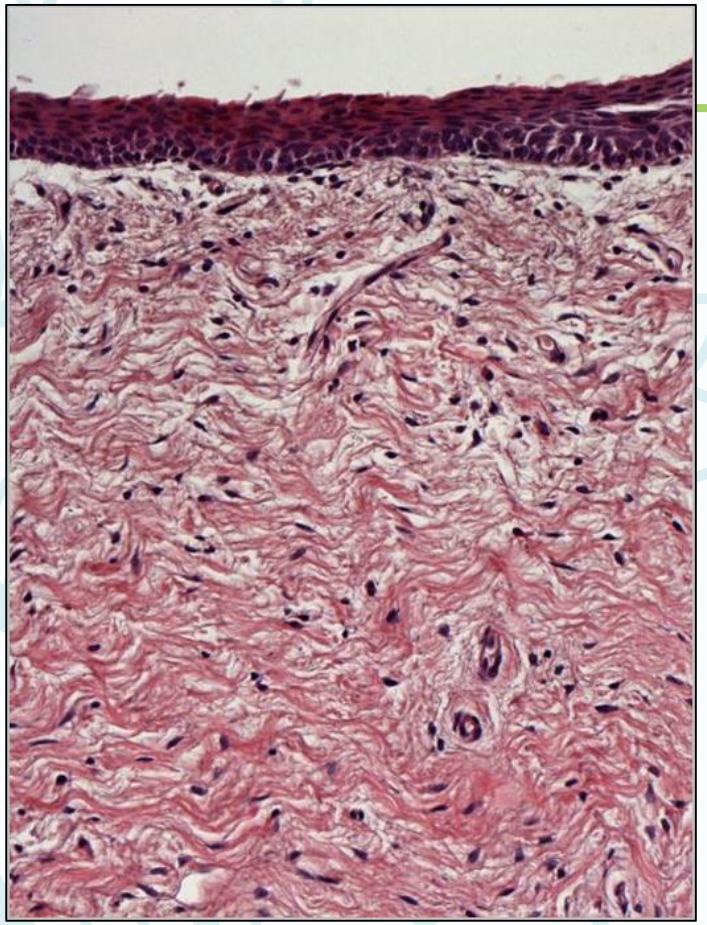
GENITOURINARY SYNDROME OF MENOPAUSE (ATROPHY)

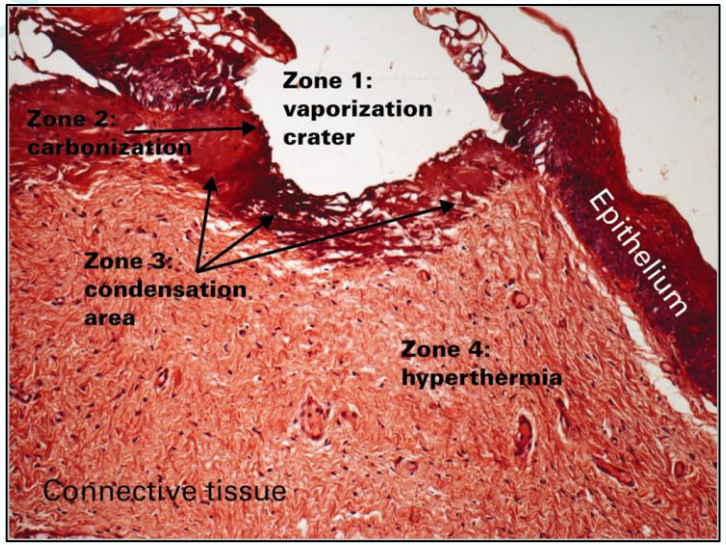


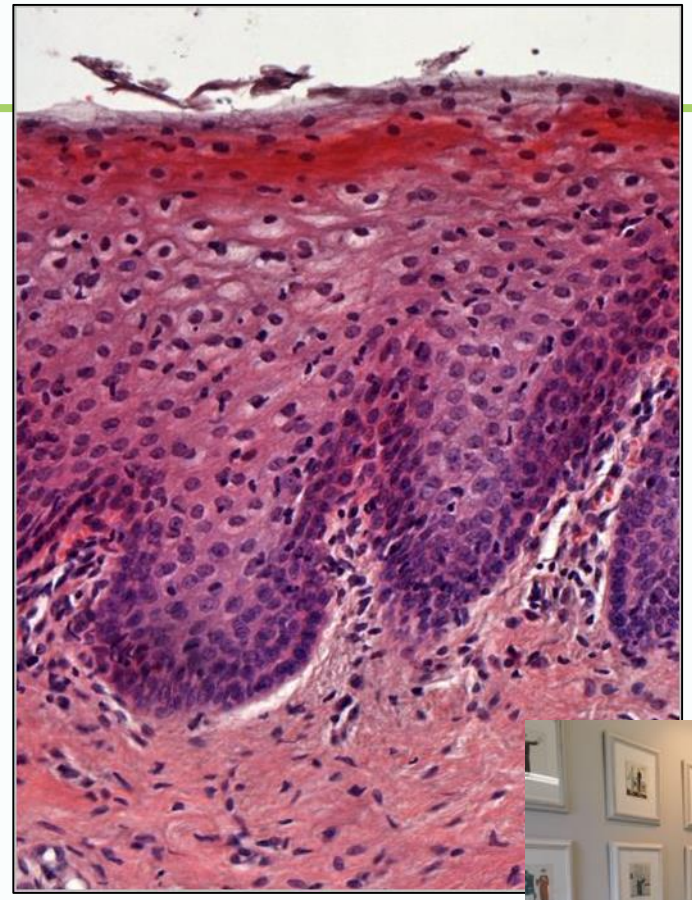
(H&E). (A): POST MENOPAUSAL ATROPHY. Reduced vessels, thinner epithelium with lack of glycogen.

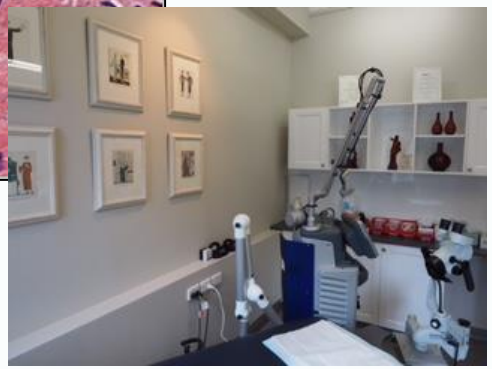
(B): HEALTHY PRE MENOPAUSAL VAGINAL MUCOSA. The mucosa is well supplied with blood and the epithelium consists of a larger number of cell layers, particularly rich in glycogen.

FRACTIONAL CO2 LASER









SEXUAL DYSFUNCTION

OSTEOPOROSIS

- Oestrogen deficit results in increased osteoclast activity and bone resorption.
- Bone mass peaks third decade of life
- Accelerated loss starts 2 years before menopause and can continue for 2-4 years
- Oestrogen will reduce fractures by 65%’

OSTEOPOROSIS

WHI

- HRT vs placebo
- RR 0.66 hip fracture
- RR 0.66 vertebral fracture
- RR 0.77 fragility fractures any site

- Consider alternatives to HRT if no other indication than primary prevention of osteoporosis

- Calcium and Vit D

CARDIOVASCULAR DISEASE

- Accounts for 30.7% of female deaths
- The lifetime risk of dying from ischaemic heart disease is 10 times that of risk of dying from:
  - Breast cancer
  - Reproductive cancer
  - Osteoporotic fracture
- American Heart Association does not recommend HRT to be used for primary prevention of heart disease

CARDIOVASCULAR DISEASE

- Observational and randomized studies suggest younger women starting HRT at menopause are **not** at increased risk
- KEEPS Study 2012
- DOPS Study 2012 (BMJ)
- Elite Study 2014 (younger women attenuation carotid intima-media thickness)

BREAST CANCER

- Oestrogen may promote pre-existing breast cancer
- Unknown if it will induce the growth of new cancers.
- Nurses' Health Study – slight increased risk
- WHI (CCE /MPA) combined HRT
  - Excess 8 cases /10 000 users per year
  - WHI (CCE alone) no increased risk

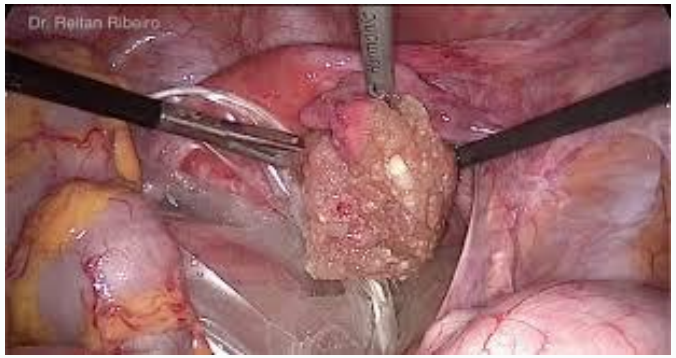
- Epidemiologic meta analysis of 21 Studies – increased risk over time
- Iowa Women's Health Study and other – no increased risk
- Million Women Study (observational) - increased risk

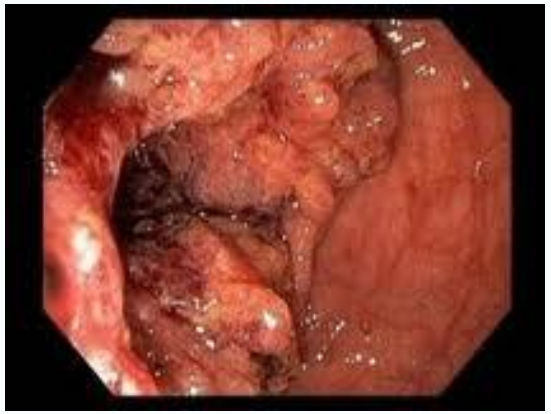
BREAST CANCER

- No randomized studies to evaluate different progestogens
- BRAC 1 and 2
  - Prophylactic oophorectomy
  - HRT improves quality of life
  - HRT does not increase risk of genetically determined breast cancer
- History of breast cancer avoid HRT
- Family history (first degree relative with pre-menopausal breast cancer)
  - HRT will not increase the risk

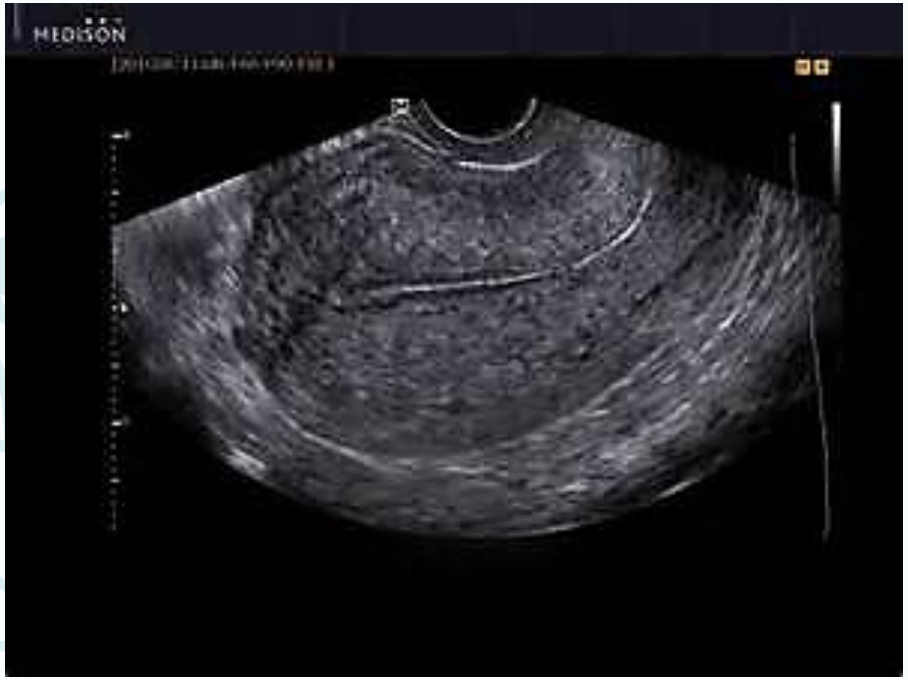
OVARY / COLON CANCER

No consistent risk with HRT has been demonstrated

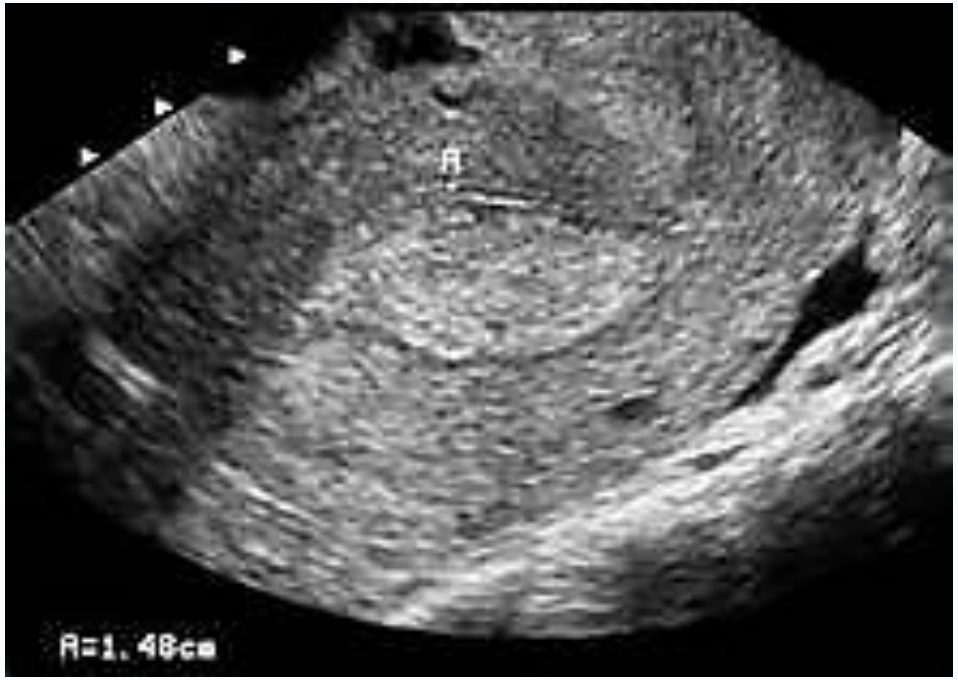




ENDOMETRIAL CANCER



THIN ENDOMETRIUM



ABNORMAL ENDOMETRIUM

NEUROLOGICAL FUNCTION

ALZHEIMER'S DISEASE

Dr. Alois Alzheimer

VENOUS THROMBOEMBOLISM

Evidence from RCT's – increased risk with current oral use on any HRT Vs Placebo

Thus there is an important trade-off regarding risks and benefits of HRT.

VENOUS THROMBOEMBOLISM

- National Collaborating Centre for Women's and Children's Health concluded
  - November 2015 Guidelines

1. Oral HRT increases VTE risk and can occur immediately (with or without progesterone)
2. Transdermal HRT does not significantly increase this risk
3. Risk increases substantially with age
4. Risk discontinues when HRT stopped

STARTING HRT

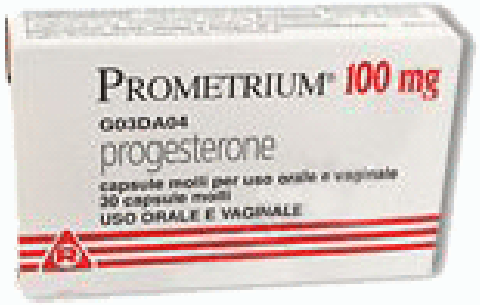
RELATIVE CONTRAINDICATIONS

- Chronic liver disease
- severe hypertriglyceridaemia
- endometriosis

ABSOLUTE CONTRAINDICATIONS

- hormone related cancer or active liver disease
- history of hormone – induced thromboembolism
- history of pulmonary embolism (not caused by trauma)
- undiagnosed vaginal bleeding
- pregnancy

PREPARATIONS



BREAST CANCER HISTORY

Adverse side effects appear to be related to synthetic progestogens

- Progestogens are necessary for protection of the endometrium.
- Progestogens may cause undesirable side effects
  - Fluid retention, Aching legs, Mood changes
  - Breast tenderness
- Progestogens may
  - Decrease glucose tolerance
  - Attenuate the beneficial effects of oestrogen on lipids
  - Attenuate any cardiovascular benefits of oestrogen only therapy
  - Increase mammographic density
  - Increase the risk of breast cancer when combined with oestrogen as MHT

Stanczyk F et al Endocrine Reviews 2013; 34:171-208
Sitruk Ware R Maturitas 2008;61:151-157
Sitruk Ware R and Nath A. Rev Endocr Metab Disord 2011;12: 63-75

The ideal TSEC combination would balance positive and negative effects

Positive Effects	Without Negative Effects

• Central nervous system
  • ↓ vasomotor effects
• Skeleton
  • Stabilisation of bone loss
  • ↑ bone mineral density (BMD)
• Vagina
  • ↓ Dryness, irritation, or dyspareunia
	• Uterus
	  • Neutral endometrial stimulation
	  • Neutral effect on breakthrough bleeding
	• Breast
	  • Neutral preclinical effect at ERs of breast
	  • No increase in breast density
	  • No increase in breast pain
	• Cardiovascular
	  • No increase in risk of cardiovascular disease

Conjugated Oestrogens and Bazedoxifene

Combining the established efficacy of estrogens with a SERM to protect against endometrial effects of estrogens[1]

Conjugated Estrogens (CE)

- Composed of multiple estrogens and are agonists of ER-α and –β[2]
- Established efficacy and benefit/risk profile in treating VMS and preventing bone loss[3]
- Over 60 years of experience in MHT[4]
- Shown to be the most suitable in preclinical studies for pairing with bazedoxifene[5-7]

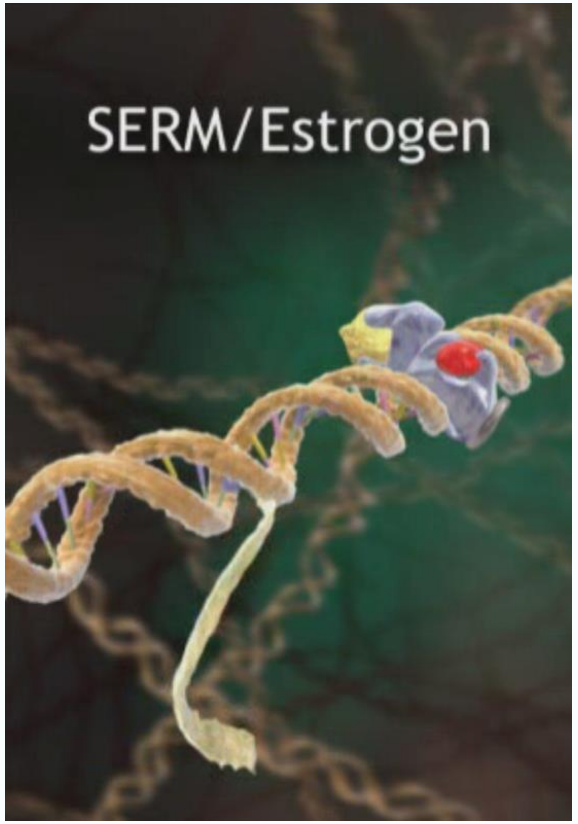
Bazedoxifene (BZA)

- Selected for its unique pharmacologic profile, and effects on VMS and endometrium in particular; as demonstrated by pre-clinical studies studying a number of different SERMs[5,6]
- Bazedoxifene reduces the risk of endometrial hyperplasia that can occur with the conjugated estrogens component alone. **Thus progestins are not needed[2]**

1. Komm BS, et al. *J Cell Physiol.* 2013;228:1423–1427; 2. Duavive Data Sheet ; 3. Berrodin TJ, et al. *Mol Endocrinol.* 2009;23:74-85;
4. Weismiller D. *Prim Care Clin Office Pract.* 2009;36:199-226; 5. Crabtree J, et al. *Mol Cell Endocrinol*. 2008;287:404-6;
6. Kharode Y, et al. *Endocrinolology*. 2008;149:6084-6091; 7. Peano B, et al. *Endocrinology* 2009;150:1897–1903.

Duavive: The first TSEC

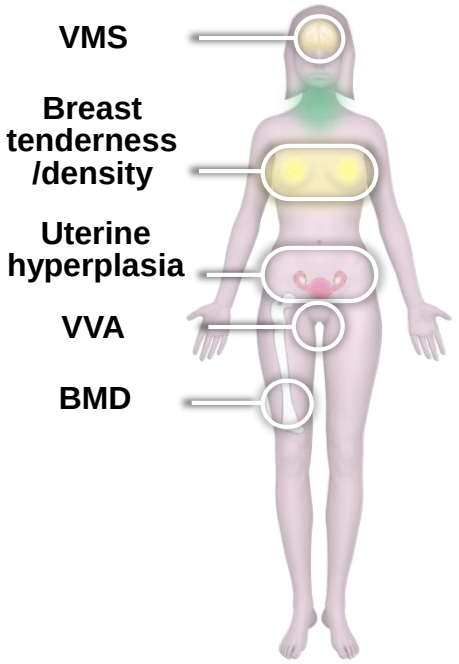
- DUAVIVE is the first TSEC, partnering CE (0.45mg) with BZA (20mg) in a specific ratio.
- DUAVIVE uses BZA instead of a progestin to protect the uterine lining.
- The outcome of this tissue-selective activity is distinct from administering either component alone.
- Thus, the TSEC provides reliefs symptoms of VMS, while protecting uterine tissues from hyperplasia associated with estrogens alone so there is no need for progestin.



The effects of Duavive differ from the effects of its two constituents

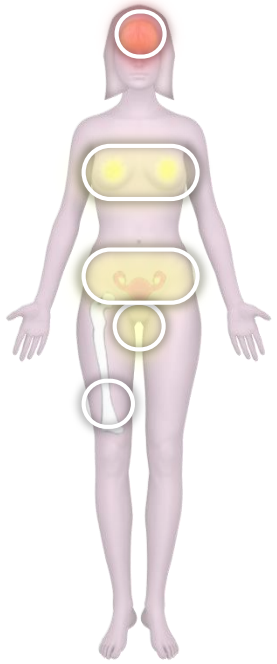
CE

Composed of Multiple oestrogens
ER -α and -β agonists



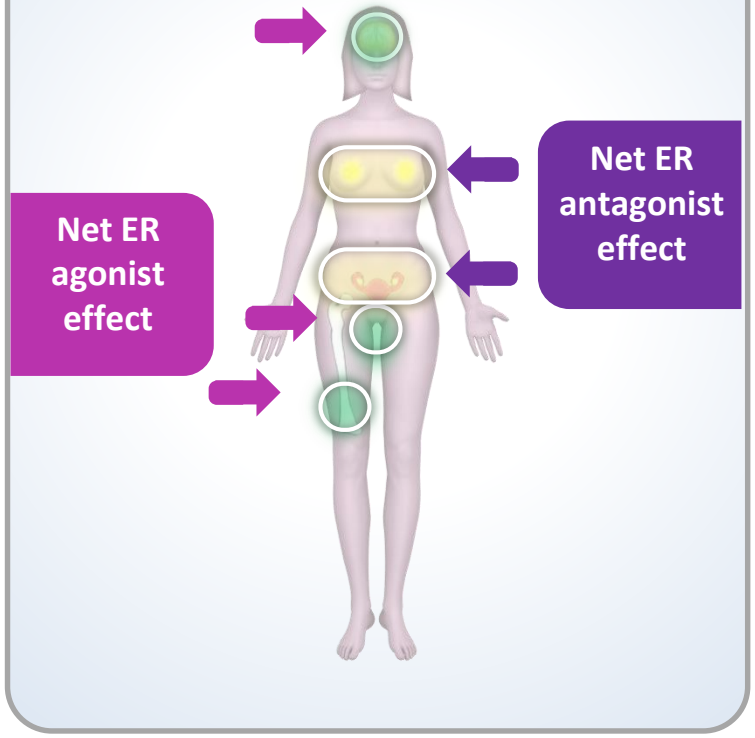
BZA

Estrogen agonist/antagonist
Tissue-dependent agonism/antagonism



DUAVIVE (CE/BZA TSEC)

Composite action of CE and BZA
Effect specific to target tissue



Clinical profile

- Neutral
- Less favorable
- More favorable

Duavive Clinical Trial Program (over 7500 women included)

SMART 1

SMART 1, N=3,397
24 months
Menopausal symptoms and
endometrial protection
vs placebo

SMART 2

SMART 2, N=318
3 months
VMS
vs placebo

SMART 3

SMART 3, N=652
3 months
VVA
vs placebo

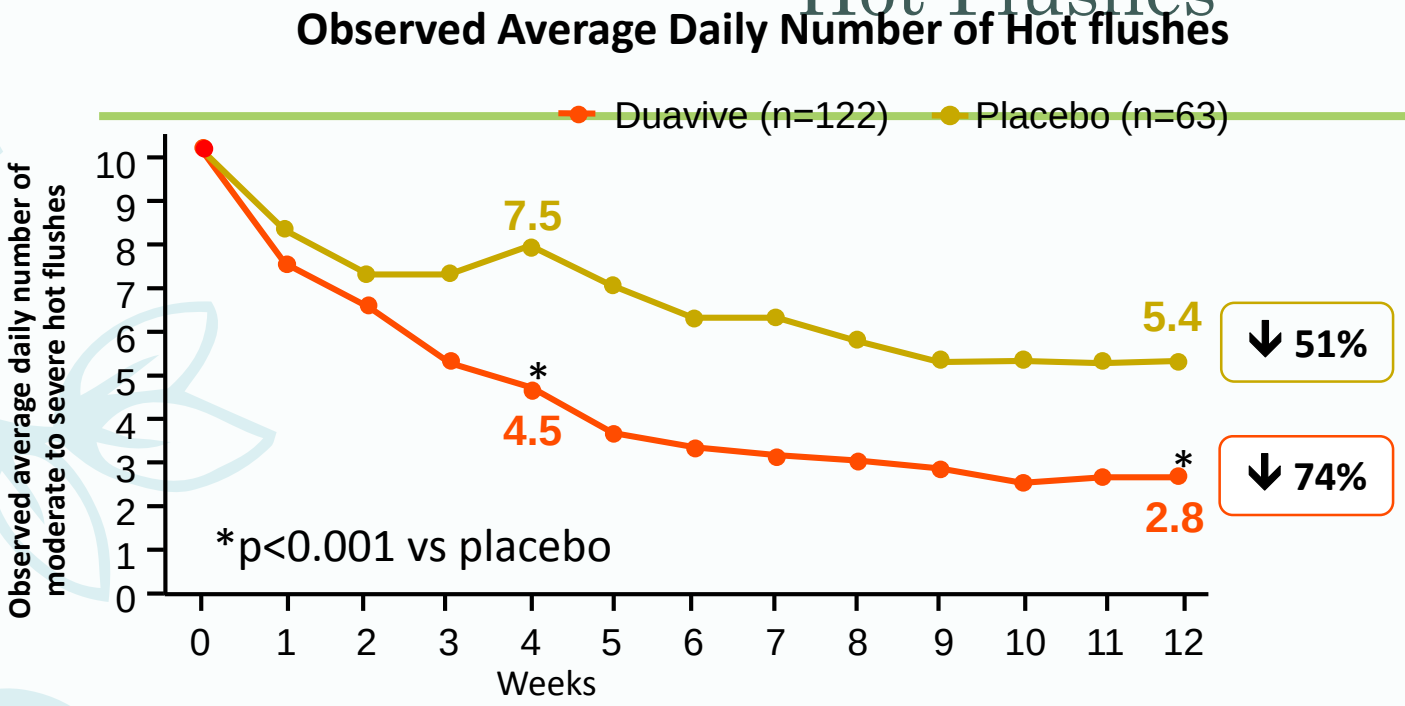
SMART 5

SMART 5, N=1,843
12 months
BMD, endometrial protection and breast density vs placebo
placebo

SMART 4

SMART 4, N=1,061
Supportive safety study
12 months, 1 year extension
Endometrial protection
and BMD vs placebo

Reduction in Daily Number of Moderate to Severe Hot Flushes



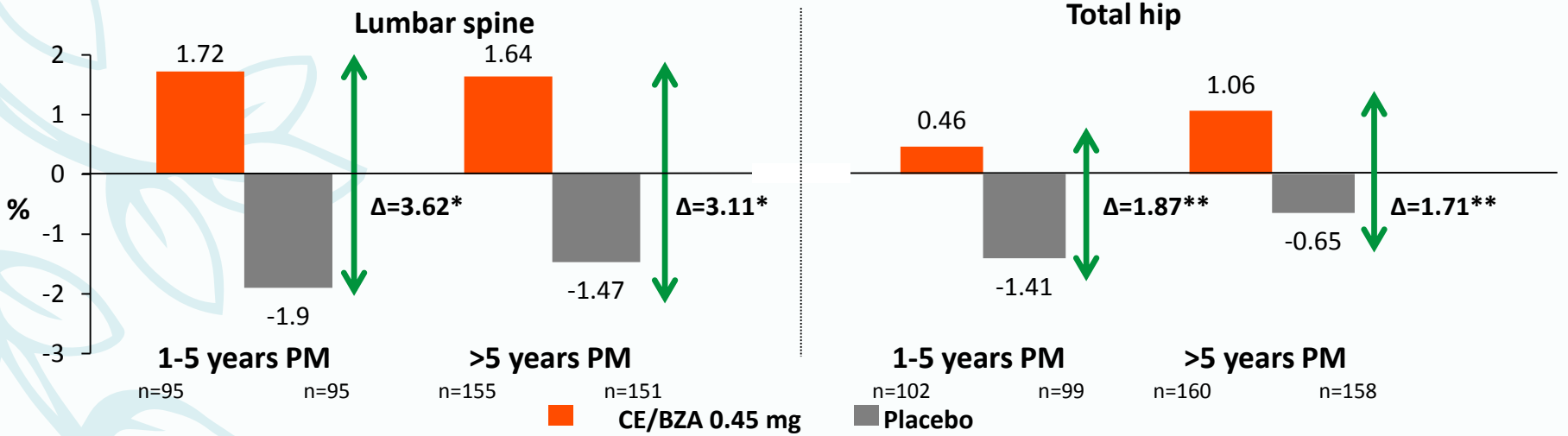
Primary analysis at weeks 4 and 12; prespecified secondary endpoints at all other weeks

Pinkerton JV, et al. Menopause. 2009;16(6):1116-1124.
*Based on data analysis using analysis of covariance (ANCOVA) model.

Effect on BMD Following 1 and 2 Years of Treatment (SMART 1 & SMART 5)

- Significant increases in lumbar spine and total hip BMD at 24 months for both doses in SMART 1, in women both less and greater than 5 years post-menopause[1]

Mean Change from Baseline in BMD at 24 Months Post Treatment in SMART 1



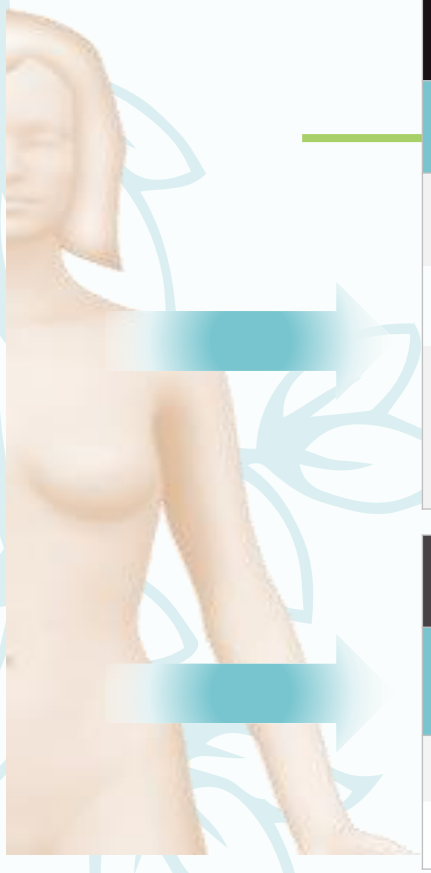
*P<0.001 **P<0.05 (excluding those subjects with missing source documentation, treatment differences are 1.96 and 1.73% respectively)

- Significant increases in lumbar spine and total hip BMD at 12 months in women 1-5 years post menopause (PM)[2]

1. Lindsay R, et al. *Fertil Steril*. 2009;92:1045-1052; 2. Pinkerton JV, et al. *J Clin Endocrinol Metab.* 2013.

1. Duavee PI; 2. Pickar J, et al. Abstract presented at NAMS 2013; 3. Pinkerton JV, et al. *Obstet Gynecol.* 2013;121:959-68; 4. Pfizer Inc. Data on file.

Effects on Breast & Endometrium



Breast tolerability profile similar to placebo following up to 2 years of treatment with DUAVIVE[1-3]			
Pooled analysis of SMART clinical trials	**0.45 mg (n=1,585)**	**0.625 mg (n1,583)**	**Placebo (n=1,241)**
Breast cancer incidence up to 2 years (per 1,000 woman-years)	1.00 (CI 0.00–3.21)	0.00 (CI 0.00–1.54)	1.40 (CI 0.00–4.17)
Incidence of reported breast pain/tenderness up to 12 weeks	9.8–11.5%	9.8–10.2%	8.1–11.2%
Incidence of abnormal mammogram at month 12	2.58%	2.60%	3.16%
Mean change in breast density at month 12 (SMART 5)*	-0.38%	-0.44%	-0.32%

Incidence of endometrial hyperplasia occurred in <1% of women following up to 2 years of treatment with DUAVIVE[1,4]				
Study	**Incidence at month 12 (n/N)**		**Incidence at month 24 (n/N)**	
	0.45 mg	**0.625 mg**	**0.45 mg**	**0.625 mg**
SMART 1	0.00% (0/336)	0.32% (1/314)	0.68% (2/294)	0.74% (2/271)
SMART 5	0.30% (1/335)	0.27% (1/368)	--	

*n= 186, n=191 and n=182 for DUAVIVE 0.45 mg, 0.625 mg and placebo respectively.

What's New? Duavive

DUAVIVE is a TSEC (tissue selective oestrogen complex)

- 0.45 mg conjugated oestrogens- of equine origin
- 20 mg Bazedoxifene SERM (a selective oestrogen receptor modulator)

*proven prevention/treatment of osteoporosis

*antagonistic effect on breast (less mastalgia)

Mirkin et al J Women's health 2016- reduced breast pain vs than CE/MPA

*antagonistic effect on endometrium (protective)

Climacteric 2013, J Clin Endocr Metab – reduced bleeding at 1 year vs CE/MPA

Duavive

INDICATION vasomotor symptoms of menopause

- Effective relief of vasomotor symptoms
- Post menopause use leads to high rates of amenorrhoea
- Does not show the unwanted effects of oestrogen on the breast and uterus
- Limited data in women over 65
- Long term safety and efficacy data re DVT etc is extrapolated from other SERMS and oestrogen in the WHI study

Duavive and Breast Cancer

The effect of DUAVIVE on the risk of breast cancer is unknown.*

- Women should receive yearly breast examinations by an HCP and perform monthly breast self-examinations.
- Mammograms should be scheduled based on patient age, risk factors and prior mammogram results.
- Duavive is contraindicated in women with known, suspected or past history of breast cancer.
- The Women's Health Initiative (WHI) trial found no increase in the risk of breast cancer for women using estrogen only therapy but a small increased risk with long term use of CE plus medroxyprogesterone (MPA).
- Breast cancer risk appears to be related to the addition of synthetic progestogens and duration of use.

* Duavive Product Information. Australia

The risk of Venous Thromboembolism (VTE)

- SERMS (including BZA) and estrogens individually increase the risk of VTE.
- In clinical trials of up to 2 years duration in post menopausal women with CE/BZA, cases of VTE were rare and not greater than placebo.
- Hormone therapy is associated with a 1.3-2 fold risk of developing VTE. The occurrence of such an events is greatest in the first year of treatment.
- Patients with known thrombophilic states have an increased risk of VTE and hormone therapy may add to this risk.
- Duavive is contraindicated in these patients.
- If a VTE develops after initiating therapy or is suspected Duavive should be discontinued immediately.
- Women should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (e.g. painful swelling of a leg, sudden pain in the chest dyspnoea.

*VTE=deep vein thrombosis, pulmonary embolism and retinal vein thrombosis

Duavive Product Information, Australia

Indications for using Duavive.

Indication

- **DUAVIVE is indicated for the treatment of moderate to severe vasomotor symptoms associated with menopausal women with a uterus.**
- Duavive should be used for the shortest duration consistent with treatment goals and risks for the individual women.
- Experience in women older than 65 years is limited.

Dosing

- One tablet orally once daily, with or without food
- May be taken at the same time as calcium or vitamin D supplements, as necessary

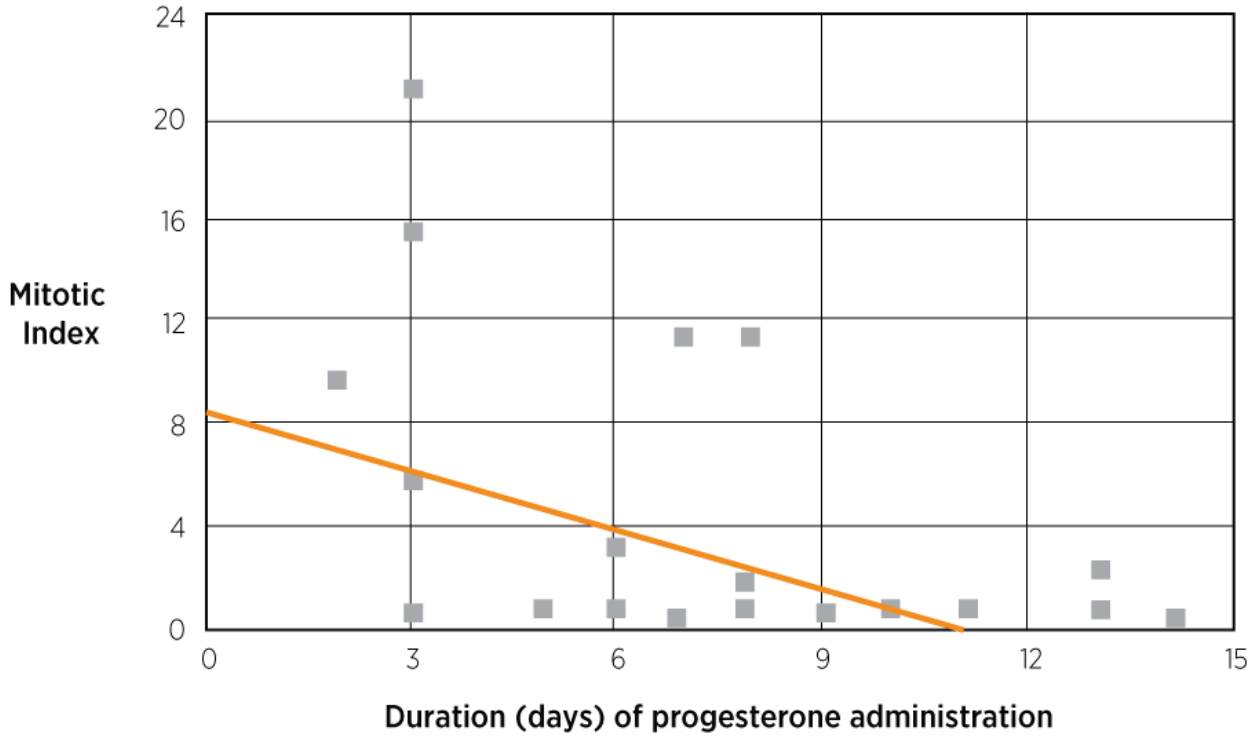
Duavive Product Information

MICRONISED PROGESTERONE

– PROMETRIUM

Anti-proliferative effects of progesterone

Regression of mitotic index compared with days of micronised progesterone administration.



Adapted from Moyer et al. *Fertil Steril 1993*

Achieving Endometrial Atrophy with Micronised Progesterone in Oestrogen Replacement Therapy

200 mg/day for 1st 12 days (PEPI 1996)
or
100 mg/day for days 1-25 (Darj et al 1991)

Endometrial atrophy (or quiescent)

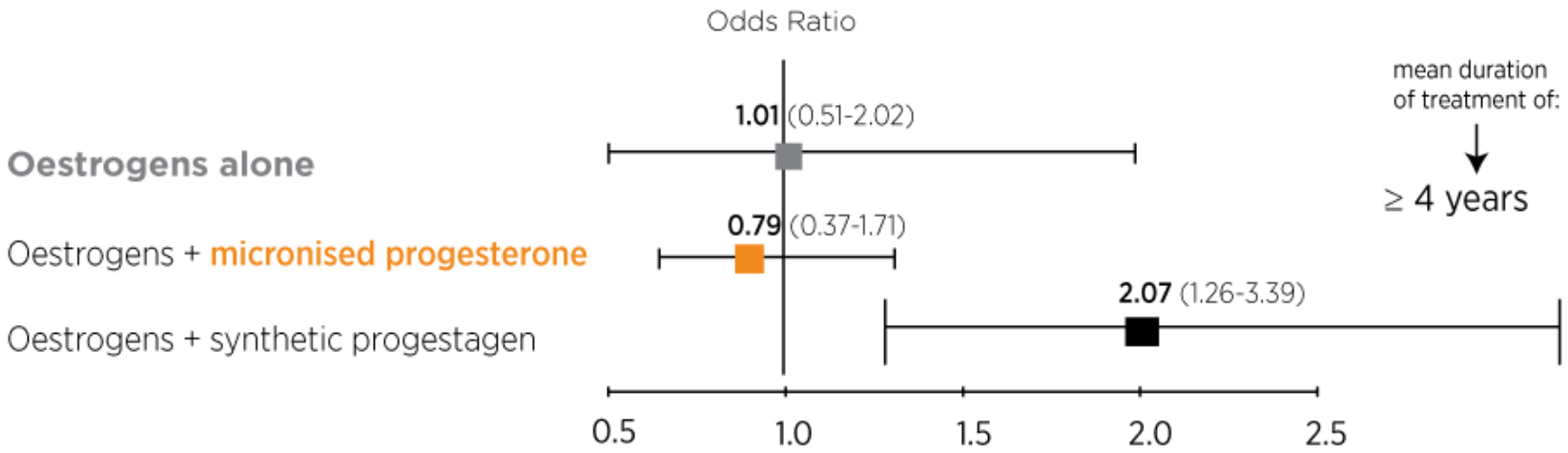
Study Group for the PEPI Trial. JAMA 1996;275(5):370-375
Darj et al. Maturitas 1991;13:109-115

MICRONISED PROGESTERONE

–BREAST SAFETY

Breast Cancer Risk and HRT – CECILE Study

Odds ratios for breast cancer among current users of menopausal hormone therapy with treatment duration ≥4 years

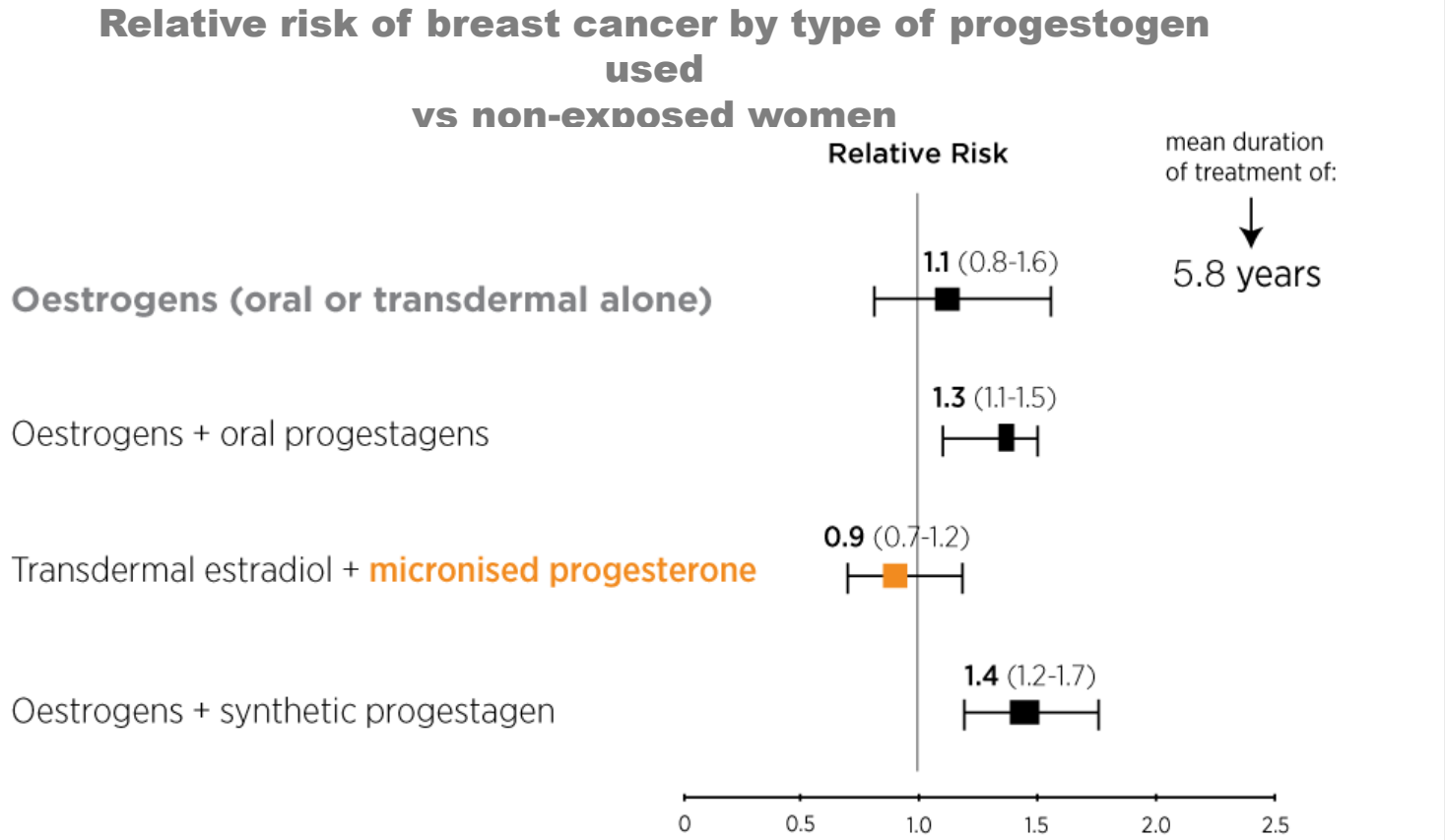


Adapted from Cordina-Duverger E, PLoS One 2013

Odds ratios adjusted for study area/ age at reference date / age at menarche / parity / age at first full-term pregnancy / breast feeding /history of benign breast disease / family history of breast cancer in first-degree relatives / BMI / oral contraceptive use

Cordina-Duverger E et al. PLoS One 2013;8(11) e78016

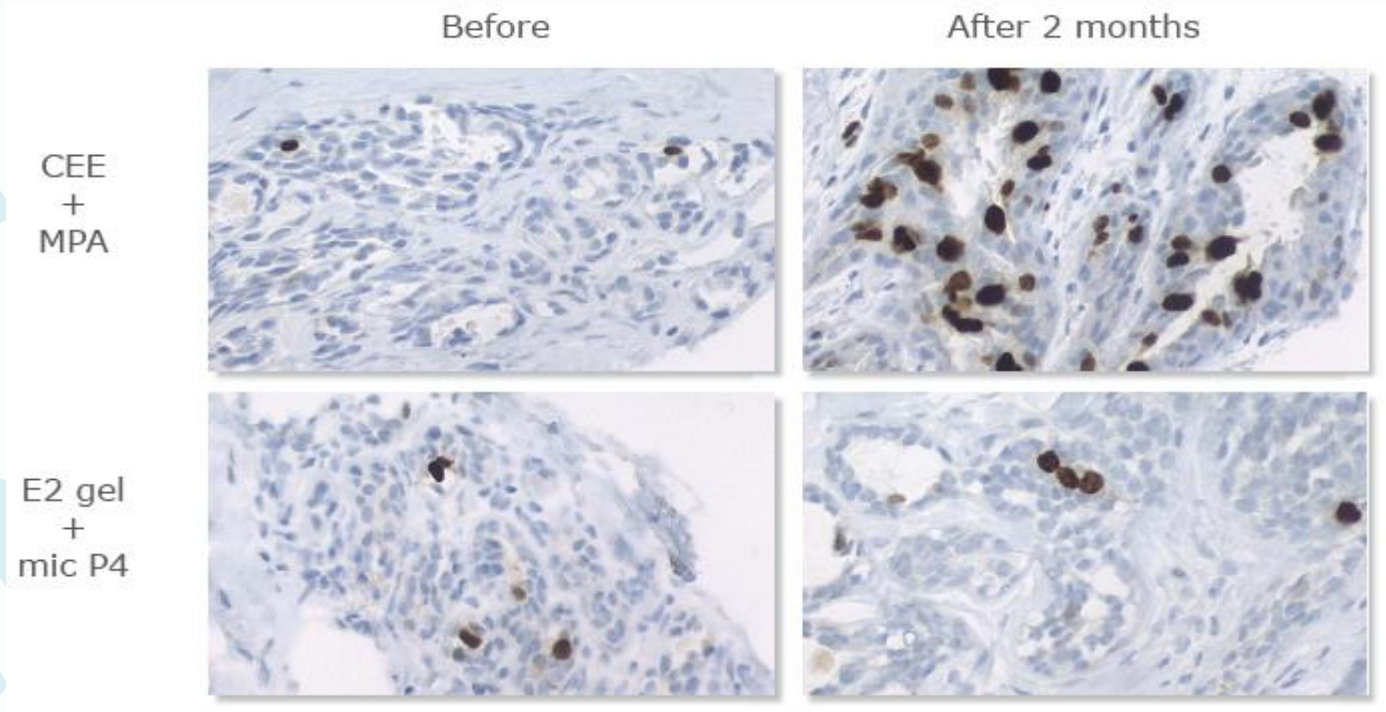
Breast Cancer Risk and HRT – E3N Study



The test for heterogeneity between micronised progesterone and synthetic progestins was significant (p <0.001).

Adapted from Fournier A et al. 2005

Effects of percutaneous E2 - oral mic.P4 versus oral CEE + MPA on breast cell proliferation and bcl-2 protein in healthy women



Breast histologic findings from two individual women before (left) and after (right) 2 months of sequential treatment with either oral conjugated equine oestrogens–MPA (top) or percutaneous E2–oral micronised P (bottom). Nuclei of proliferating cells staining brown by Ki-67 MIB-1 antibody. (Original magnification X200)

Breast cancer and progestogen: Guidelines

- "…It is not clear whether there is a class effect from the progestogen or whether the specific agent used influences breast cancer risk. Data from a large observational study suggest that **EPT with micronised progesterone carries a low risk of breast cancer with short-term use** but carries an increased risk of breast cancer with all EPT formulations with long-term use."[1]

- "Emerging data …..report that **progesterone** (and perhaps **dydrogesterone**) in combination with oestrogen does **not increase breast cancer risk** if given for 5 years or less." (Level of Evidence C)[2]

- **A large European observational study** suggested that **micronised progesterone** or dydrogesterone used in association with oral or percutaneous estradiol may be associated with **a better risk profile** for breast cancer than synthetic progestogens.[3]

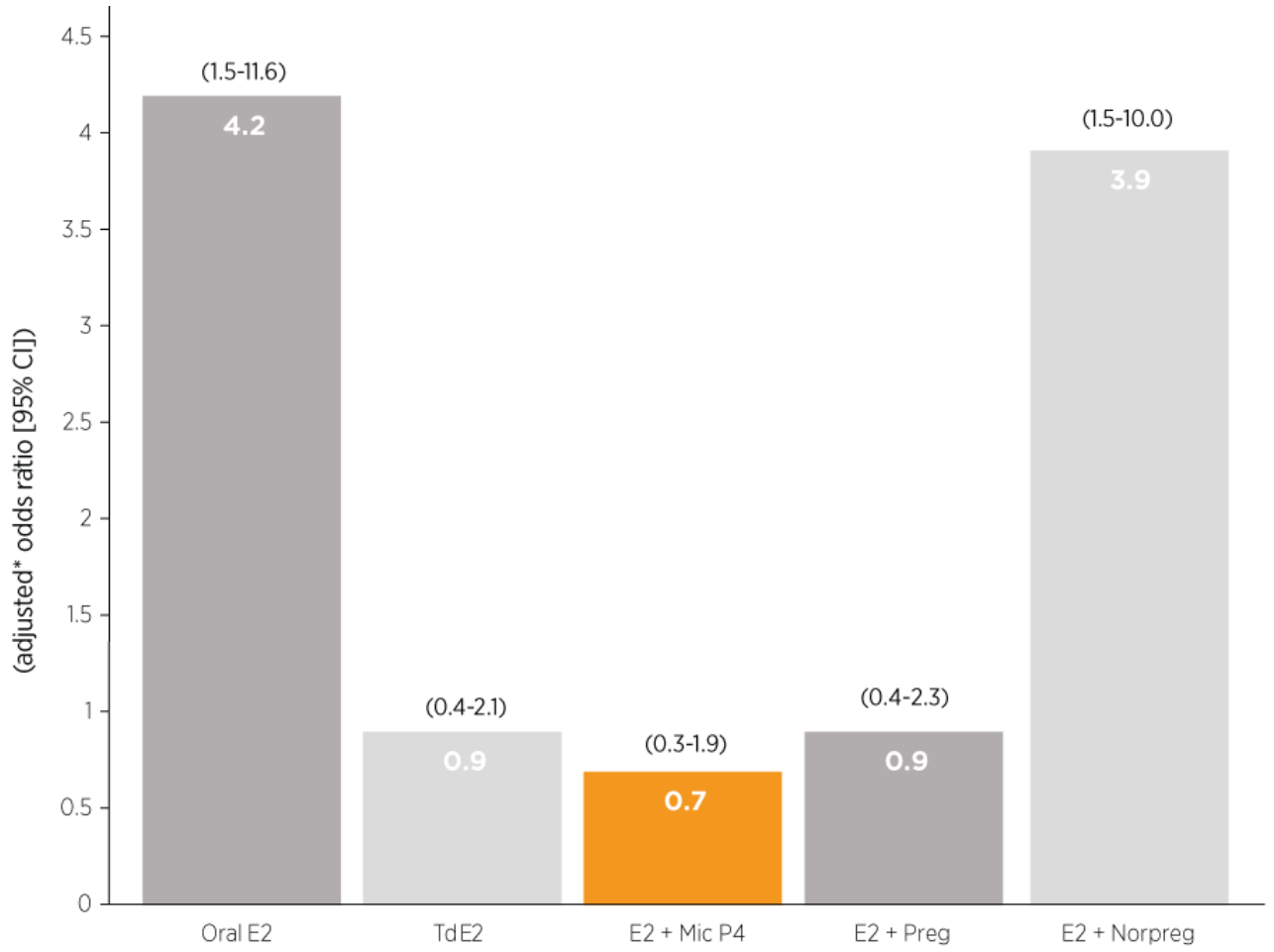
- The risk may be lower with micronised progesterone or dydrogesterone than with a synthetic progestogen.

1. Schmidt P. Menopause. 2012; 19(3): 257-271
2. Santen RJ. JCEM.2010:95,(1):S1-S66
3. De Villiers TJ et al. Climacteric 2013;16:316–337

MICRONISED PROGESTERONE

VENOUS THROMBOEMBOLISM RISK

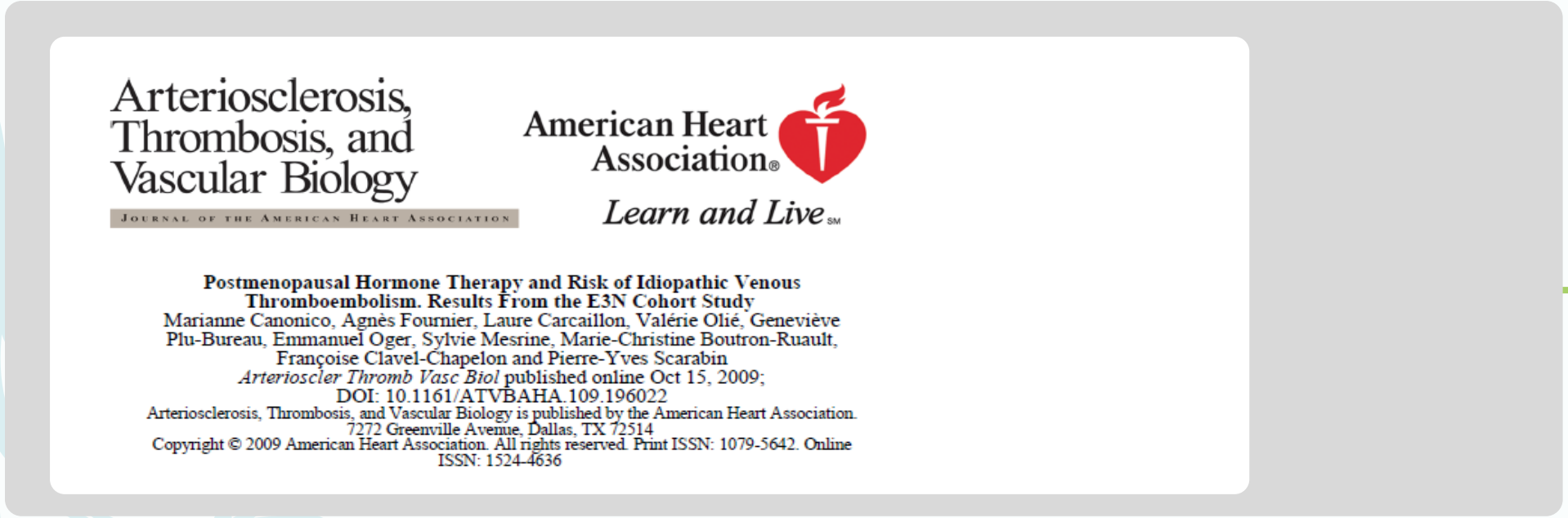
Impact of Hormone Therapy on VTE Risk by Route of Oestrogen Administration and Type of Progestogens **(ESTHER study)**



*Adjusted for obesity status, familial history of VTE, history of varicose veins, education, age at menopause, hysterectomy and cigarette smoking. Td E2 (Transdermal estradiol), Mic P4 (micronised progesterone), Preg (Pregnane derivatives), Norpreg (Norpregnanes derivatives)

Adapted from **Canonico M, et al.** *Circulation 2007*

Canonico M, et al. *Circulation 2007;**115**:840-845*



Arteriosclerosis, Thrombosis, and Vascular Biology

Journal of the American Heart Association

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Postmenopausal Hormone Therapy and Risk of Idiopathic Venous Thromboembolism. Results From the E3N Cohort Study

Marianne Canonico, Agnès Fournier, Laure Carcaillon, Valérie Olié, Geneviève Plu-Bureau, Emmanuel Oger, Sylvie Mesrine, Marie-Christine Boutron-Ruault, Françoise Clavel-Chapelon and Pierre-Yves Scarabin

Arterioscler Thromb Vasc Biol published online Oct 15, 2009;

DOI: 10.1161/ATVBAHA.109.196022

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Conclusions

"In this large study (from **E3N cohort study**), we found that route of oestrogen administration and concomitant progestogens type are two important determinants of thrombotic risk among postmenopausal women using hormone therapy.

Transdermal oestrogens alone or combined with progesterone might be safe with respect to thrombotic risk."

Canonico et al. *Arterioscler Thromb Vasc Biol. 2010;30:340–345*

Anything else on the horizon?

OSPEMIFENE (not available here)

60 mg vaginal preparation

New SERM used for the treatment of vulvar and vaginal atrophy

FDA approval in USA in Feb 2013

Evidence shows improved pH and vaginal maturation but only 2 x 12 week RCT's

Not recommended for breast cancer patients (J Clin Endocriol Metab 2015)

Anything else on the horizon?

PRASTERONE (vaginal DHEAS) (not available here)

USA FDS approved prasterone (INTRAROSA) in 2016

For dyspareunia, vaginal insertion

Two twelve week trials looking at pain after intercourse

Some improvement over placebo

Higher incidence of vaginal discharge and abnormal pap

“Although DHEA is included in some dietary supplements, the efficacy and safety has not been established for diagnosing, curing, mitigating , treating, or preventing any disease.”

Using Menopausal Hormone Therapy

- MHT is the most effective treatment for moderate to severe menopausal symptoms and is most beneficial before the age of 60 years or within 10 years after menopause.
- ***The dose and duration of MHT should be consistent with treatment goals***.
- Estrogen only is appropriate therapy for women after a hysterectomy.
- Estrogen plus a progestogen should be used when the uterus is present.
- Topical low dose estrogen is preferred for those women whose symptoms are limited to vaginal dryness and dyspareunia.
- Current safety data do not support the use of MHT in breast cancer survivors.

(Global Consensus Statement. De Villiers et al Climacteric 2016;19:313-315)

(IMS Recommendations. Baber et al Climacteric 2016;19: 109-150)

Global Consensus Statement

- RCT and observational data provide strong evidence that estrogen only MHT may decrease coronary disease and all-cause mortality in women younger than 60 years of age and within 10 years of menopause
- *Data on estrogen – progestogen therapy in this population show a similar trend but with less precision*
- The risk of breast cancer in women over 50 years associated with MHT is a complex issue but *is primarily associated with the addition of a progestogen to estrogen therapy and to the duration of use*

(Global Consensus Statement. De Villiers et al Climacteric 2016;19:313-315)

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Thank you!