

## **Menopause conundrums**

*OED:*

Conundrum (noun): a confusing and difficult problem or question

PCRM Fertility and Reproductive Medicine Symposium  
Wednesday June 12, 2018

## **Competing Interests**

I am a member of the DuaVive National  
Advisory Board (Pfizer Canada).

I have no other competing or potentially  
competing interests.

## Objectives

*At the end of this presentation, attendees should be able to*

1. Describe the use of different hormone therapy regimens in perimenopausal and postmenopausal women;
2. Outline the options for women in Canada;
3. Outline the risks and benefits of hormone therapy regimens in postmenopausal women

## MHT after a diagnosis of breast cancer

### *The HABITS Trial*

- 221 women treated with HT and 221 controls were followed for a median 4 years
- 39 women in the HT arm and 17 controls developed a new breast cancer event (HR 2.4; 95% CI 1.3 to 4.2)

### *The Stockholm Randomized Trial*

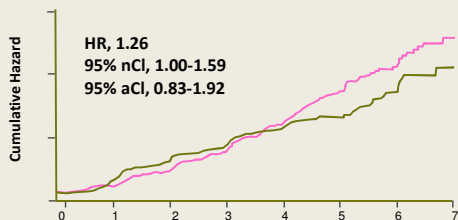
- 187 women treated with HT and 190 controls followed for a median 4.1 years
- 11 women in the HT arm and 13 controls developed a new breast cancer event (OR 0.82; 95% CI 0.35 to 1.9)

Holmberg L et al. J Natl Cancer Inst 2008;100:475-82  
 Von Schoultz E et al. J Natl Cancer Inst 2005;97:533-5

# WHI: Breast cancer findings

## Continuous CEE+MPA

**INVASIVE BREAST CANCER**  
Higher risk for CEE+MPA

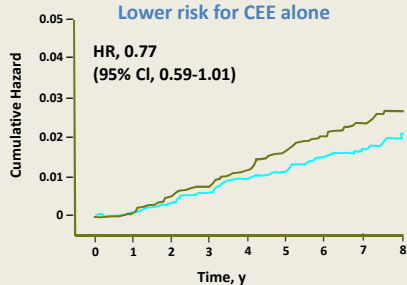


No. at Risk							
8506	8378	8277	8150	7000	4234	2064	801
8102	8001	7891	7772	6619	3922	1740	523

— CEE+MPA — CEE — Placebo

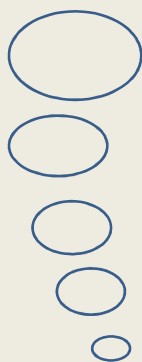
## CEE in women with hysterectomy

**INVASIVE BREAST CANCER**  
Lower risk for CEE alone



No. at Risk									
CEE	5310	5225	5160	5077	4986	4896	3957	2271	1011
Placebo	5429	5348	5265	5183	5077	4958	4007	2332	1110

1.WHI Writing Group. JAMA 2002;208:321-33  
2.WHI Steering Committee. JAMA 2004;291:1701-12



## Risk of breast cancer in women using different forms of hormone therapy

Table 3. Relative risk of invasive breast cancer among postmenopausal women using hormone therapy

Therapy	Cases	Controls	OR <sup>1</sup>	95% CI	<i>p</i>
No user <sup>2</sup>	5,473	17,956	1.00	(Reference)	
Estradiol-only therapy	991	3,300	1.01	0.93–1.09	0.88
Progestagen-only therapy	138	476	0.97	0.80–1.17	0.73
LNG-IUS <sup>3</sup>	329	708	1.53	1.33–1.75	0.001
Estradiol-progestagen therapy	1,731	4,243	1.36	1.27–1.46	0.001
Estradiol plus LNG-IUS	287	473	2.07	1.78–2.41	0.001
Mixed therapy <sup>4</sup>	927	2,534	1.22	1.12–1.33	0.001
Tibolone	80	178	1.36	1.15–1.96	0.003

Lyytinen HK et al. Int J Cancer 2010;126:483-9

## Serum levonorgestrel in women with LNG-IUS and women using a levonorgestrel-only pill

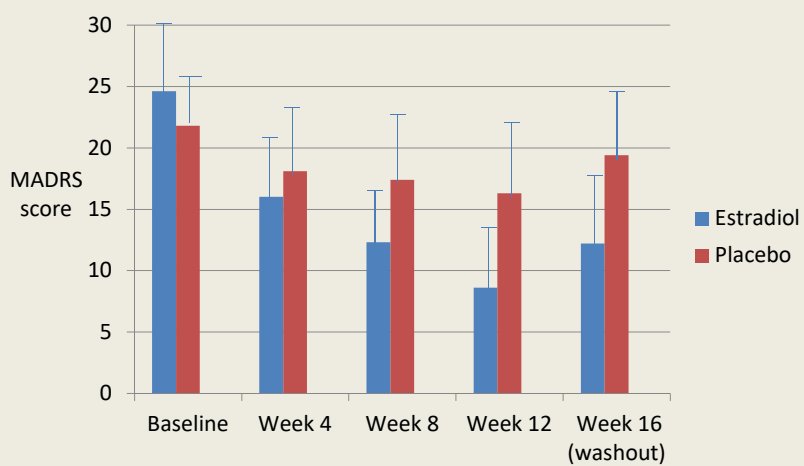
Study	Levonorgestrel serum level (pmol/L)
Levonorgestrel 30 µg pill	
Weiner et al. [25]	800
LNG-IUS	
Ratsula et al. [26]	455
Suhonen et al. [27]	480–640
Lockhat et al. [9]	1062
Nilsson et al. [28]	640–1601
Xiao et al. [29]	960–1601
Raudaskoski et al. [20]	1504

Ewies AA. Gynecol Endocrinol 2009;25:668-73

## Estrogen regulation of bioenergy in the brain

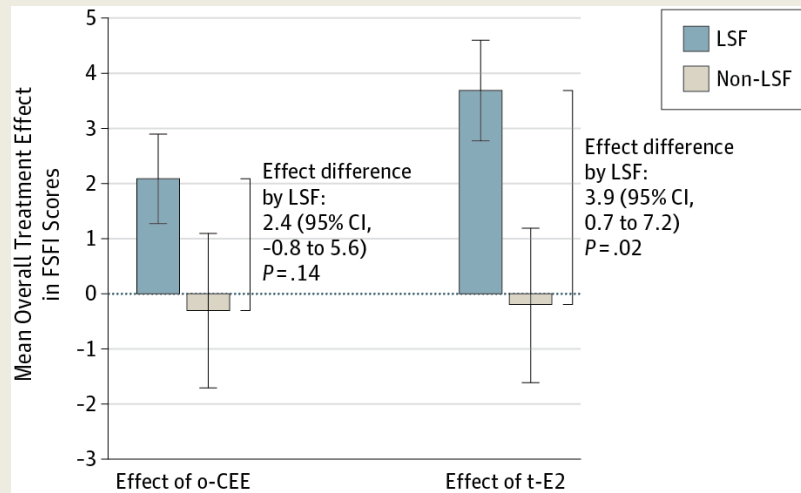
Brinton RD et al. *Nat Rev Endocrinol* 2015;11:393-405

## TD estradiol vs placebo in 50 women with perimenopausal depression



Soares CN et al. *Arch Gen Psychiatry* 2001;58:529-34

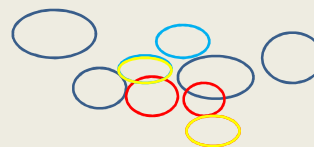
## Effect of oral and transdermal estrogen on sexual function (KEEPS)



Taylor HS et al. *JAMA Int Med* 2017;177:1471-9

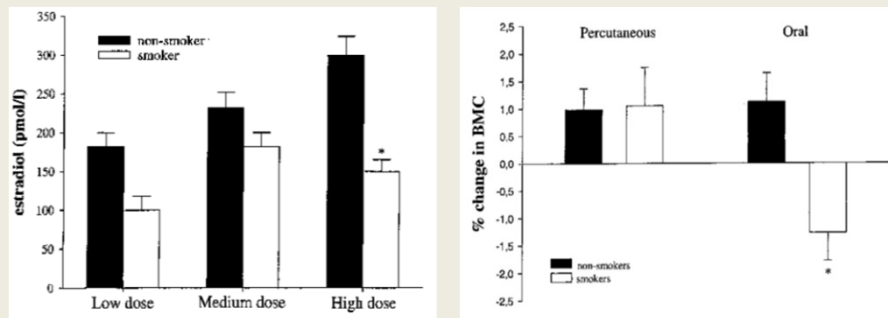
## Changes in neurological function associated with menopause

- Change in cognitive function
- Mood change (chiefly depression)
- Sleep disturbance
- Vasomotor symptoms





## Estrogen therapy in smokers and non-smokers



Tanko & Christiansen *Menopause* 2004;11:104-9

## Common compounded bioidentical hormone preparations

<u>Preparation</u>	<u>Ingredients</u>	<u>Dose</u>	<u>Routes of administration</u>
TRI-EST	Estriol (80%), Estrone (10%), Estradiol (10%)	1.25-2.5 mg/day	Oral, transdermal, sub-lingual, vaginal
BI-EST	Estriol (80-90%) Estradiol (10-20%)	1.25-2.5 mg/day	Oral, transdermal, sub-lingual, vaginal
ESTRIOL	Estriol	2.0-8.0 mg/day	Oral, transdermal, sub-lingual, vaginal
PROGESTERONE	Progesterone	20-200 mg/day	Oral, transdermal, sub-lingual, vaginal, injectable



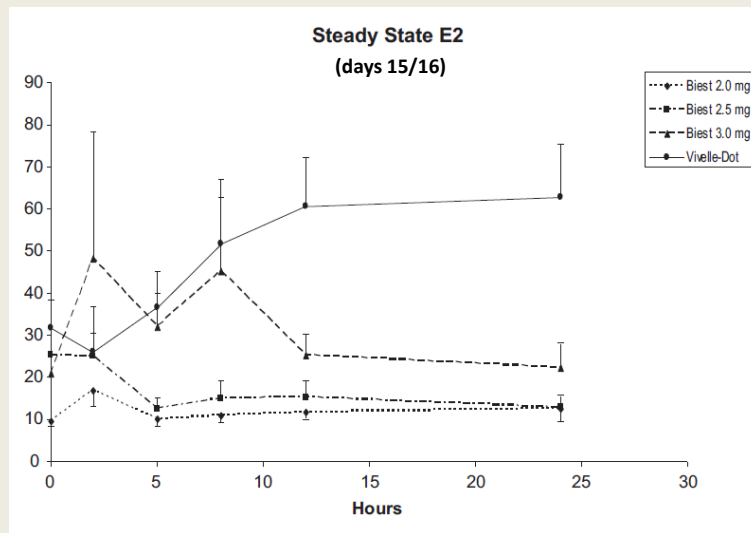
## Binding affinity of estrogen subtypes

	<u>Estrogen receptor-<math>\alpha</math></u>	<u>Estrogen receptor-<math>\beta</math></u>
17 $\beta$ -Estradiol	100	100
Estrone	60	37
Estriol	14	21

Boothby LA et al. Menopause 2004;11:356-67

## Serum estradiol levels, patch vs compounded estrogen

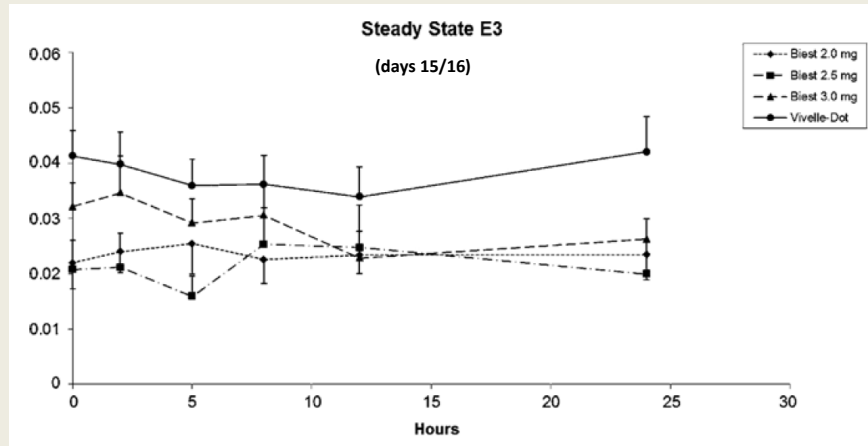
40 postmenopausal women randomized to 50  $\mu$ g TD estradiol patch or Bi-Est cream



Sood R et al. Maturitas 2013;74:375-82

## Serum estriol levels, patch vs compounded estrogen

40 postmenopausal women randomized to 50 µg TD estradiol patch or Bi-Est cream



Sood R et al. Maturitas 2013;74:375-82

## Use of compounded estrogens

### *For:*

- Some estrogenic effect
- “Individualized therapy”

### *Against:*

- Variable estrogen content, most of it being estriol
- Limited and variable absorption
- No safety data
- Most studies of effect are uncontrolled – hence effect may be mostly placebo
- Cost

## Current HT options marketed in Canada

### *Estrogens (oral)*

- Conjugated estrogens (Premarin, CES, Congest)
- Estradiol-17 $\beta$  (Estrace)

### *Estrogens (transdermal)*

- Estradiol-17 $\beta$  (Climara, Divigel, Estradot, Estrogel, Oesclim, Sandoz Estradiol Derm)

### *Estrogens (vaginal)*

- Estradiol-17 $\beta$  (Vagifem, Estring)
- Conjugated estrogens (Premarin)
- Estrone (Estragyn)

## Current HT options marketed in Canada

### *Progestogens (oral)*

- Medroxyprogesterone acetate (Provera)
- Micronized progesterone (Prometrium)
- Norethindrone (Micronor)\*
- Norethindrone acetate (Norlutate)\*
- Dienogest (Visanne)\*

## Current HT options marketed in Canada

### *Estrogen-progestin combinations (oral)*

- Estradiol/norethindrone acetate (Activelle, Activelle LD)
- Estradiol-17 $\beta$ /drospirenone (Angeliq)
- Conjugated estrogens/medroxyprogesterone acetate (Premplus)

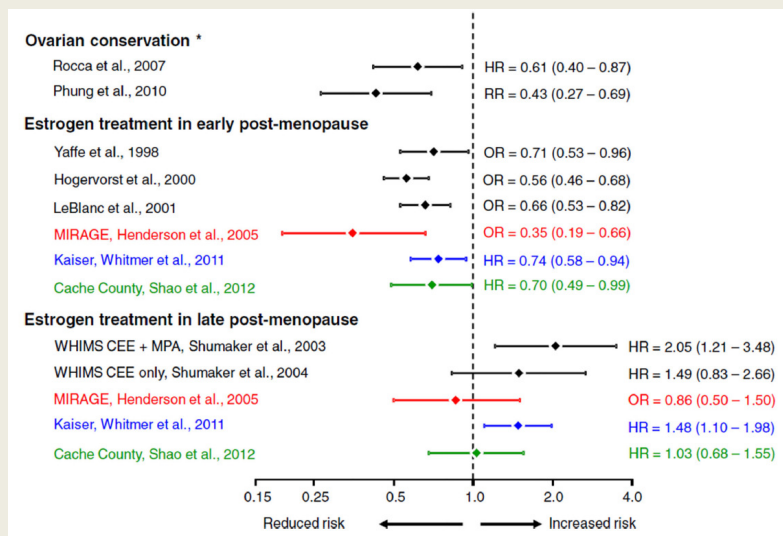
### *Estrogen-progestin combinations (transdermal)*

- Estradiol-17 $\beta$ /norethindrone acetate (Estalis)
- Estradiol-17 $\beta$ /levonorgestrel (Climara Pro)

### *Estrogen-SERM combination*

- Conjugated equine estrogens/bazedoxifene (DuaVive)

## Effect of estrogen on cognitive decline or dementia



Rocca WA et al. *Mol Cell Endocrinol* 2014;389(0):7-12

## The risks and benefits of EPT

### Risks

- Venous thromboembolism
- Stroke (inconsistent data)
- Breast cancer ( $\geq 5$  years' use, likely progestogen-specific)
- Ovarian cancer (putative)
- Endometrial cancer (putative; progestogen-specific)
- Gallbladder disease

### Benefits

- Bone density
- Colon cancer
- Quality of life