



## **TRANSDERMAL ESTRADIOL'S USE IN MENOPAUSE:** An Evidence-Based Affirmation

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A thorough literature review affirms that in peri- and postmenopausal (PMP) women, estradiol (E2) effectively relieves vasomotor (VMS) and vulvovaginal atrophy (VVA) symptoms, while increasing bone mineral density (BMD). Estrogen (E)/Estradiol (E2)-alone is associated with a reduced cardiovascular disease (CVD) event rate and breast cancer risk. Additionally, if the progesterone (preferably oral progesterone – OMP) dose balances E/E2's proliferative effects, there is no increase in endometrial cancer. In fact, transdermal estradiol (TD E2) therapy with OMP (especially in women with a uterus) may be continued beyond what current guidelines recommend. The most appropriate dose, duration, regimen, and route of administration is best determined by the clinician and patient while considering the risks and benefits.

### **Major Risks Associated with Estrogen Therapy**

Endometrial Hyperplasia and Cancer – Unopposed TD E2 increases endometrial hyperplasia and endometrial cancer risk

- The endometrial cancer risk is essentially eliminated with OMP dosing which balances TD E2's proliferative effects.

Breast Cancer - Estrogen/Estradiol-alone decreases breast cancer risk!

- Study results are confusing, and often inconsistent.
- TD E2 may be continued safely for > 10 years if meticulous surveillance and risk stratification is ongoing.
- A woman's age (< 60 or > 60) and years since menopause onset (< 10 years or > 10 years) probably have no impact on either breast cancer risk or breast cancer mortality.
- TD E2 combined with OMP does not increase breast cancer.

### **Risks Associated with Estrogen Deprivation**

VMS and VVA – FDA-approved E2 patches/gels are effective and the treatment of choice for both VMS and VVA symptoms

- TD E2 patch doses as low as 0.014mg/d relieve VMS and VVA symptoms.
- Low-dose DIVIGEL 0.25mg/d relieves VMS but takes longer than patches for significant symptomatic relief. Higher doses are clinically effective without delay.
- ESTROGEL 0.75mg/d, and 0.375mg/d (0.27mg/d did not), as well as ELESTRIN 0.52mg/d, relieve VVA symptoms.

*\*This material is educational and not an endorsement for a particular HRT dose or route of administration\**

## Risks Associated with Estrogen Deprivation, Continued

Osteoporosis – E2 patches and gels improve BMD, but only E2 patches are FDA-approved for BMD

- All FDA-approved TD E2 patches improve BMD and are FDA-approved for osteoporosis prevention.
- TD E2 gels are not FDA-approved for osteoporosis prevention, but show some effectiveness, i.e.  $\geq 0.75\text{mg/d}$  ESTROGEL.

Cardiovascular disease (CVD) – TD E2 decreases CVD, with no increase in stroke or venous thromboembolic events

- TD E2's mortality reduction is positively related to E2 exposure time.
- TD E2 patches (as low as  $0.025\text{mg/d}$ ) and gels ( $1\text{-}2\text{mg/d}$ ) have been associated with decreased CVD mortality.

Cognition – Results in the literature are inconsistent and the reasons for this are multifactorial

- ESTRADERM  $0.05\text{mg/d}$  and  $0.1\text{mg/d}$  improve cognitive performance in healthy, PMP women with mild-moderate AD.
- CLIMARA  $0.05\text{mg/d}$  improves cognitive performance in perimenopausal and recently menopausal women.
- MENOSTAR  $0.014\text{mg/d}$  does not improve cognitive performance in predominantly asymptomatic, older PMP women.



## WHAT ABOUT COMPOUNDED TD E2 CREAMS?

While TD E2 patches and gels have been proven to be effective, there are presently no outcome studies evaluating compounded products, including TD E2 creams. While they may be effective, there is no data on dosing, laboratory findings, and/or clinical success.

### EXECUTIVE SUMMARY

Since the 2002 Women's Health Initiative (WHI) publication, menopausal hormone therapy (MHT), especially E/E2 replacement therapy, has been hotly debated. The WHI's preliminary data releases changed physician practice patterns. Subsequently, hundreds, if not thousands, of studies, review articles, and meta-analyses, have been published trying to clarify MHT's role in women's health.

Precision Analytical (PA)'s goal is that you will use this TD E2 review as a guide when determining which hormone regimen is best for your patients. Extrapolate when you can, rationalize when you must, but always individualize care. Remember, results take time and the primary goal is always to do no harm.

Clinicians' two greatest concerns when considering MHT for an individual patient, are an increased breast cancer risk and an increased cardiovascular (CV) event rate. The evidence documents that estradiol, including transdermal estradiol (TD E2), neither increases breast cancer nor increases CV events, even when combined with oral micronized progesterone (OMP). TD E2-alone decreases breast cancer and CV events even when combined with oral micronized progesterone (OMP). TD E2-alone decreases breast cancer and CV event rates.

The studies cited below were performed with FDA-approved patches and gels. PA is not endorsing any specific product. Our goal is to accurately and precisely present the data. In fact, as you read, you will notice FDA-approved TD E2 patches and gels have evidence-based findings that are help-

ful. However, the MENOSTAR 0.014mg/d ultralow-dose patch is no longer available in the US.

What you will not see is data on compounded products. There are neither randomized, double-blind, placebo-controlled, trials (RCTs) using compounded creams with clinical outcomes, nor observational studies using compounded creams with clinical outcomes. In fact, we were able to find just one peer-reviewed publication<sup>1</sup> reporting serum E2 levels while on a compounded E2 cream product.

To be clear: this does not mean that compounded products are not effective; many key opinion leaders (KOLs) prescribe TD E2 creams, with presumed clinical success. When using compounded products, document "why" you chose a compounded product when there are FDA-approved options available.

Even though this paper focuses on TD E2, remember that the evidence documents and guidelines.<sup>2,3</sup> suggest that in women with a uterus, continuous OMP 200mg provides the most complete endometrial protection. In women without a uterus, oral (OMP), transdermal (TD Pg), or vaginal micronized progesterone (VMP) can be used if the desired outcome is achieved.

This paper will refer to: statistically significant as SS; postmenopause and postmenopausal as PMP; menopausal hormone therapy as MHT; oral as o; venous thromboembolism as VTE; deep venous thrombosis as DVT; pulmonary embolism as PE; synthetic estrogens as either o-CEE, Premarin, or o-E; bioidentical oral estradiol as o-E2; transdermal bioidentical estradiol as TD E2; progestins as

either MPA or others by name; oral natural micronized progesterone as OMP; vaginal progesterone as VMP; and progesterone as Pg.

The definition of “low-dose” TD E2 products that is widely accepted in the scientific literature is a dose that is less than a 0.05mg/d patch and less than an effective 0.0125mg/d gel, i.e., DIVIGEL 0.25mgs delivers E2 0.003mg/d.<sup>4</sup> In the literature, moderate or severe hot flashes are defined as at least 7 hot flashes a day or  $\geq 50$  hot flashes a week.<sup>5</sup> Out of necessity, Pg will be referred to many times in this paper.

### **Transdermal Estradiol (TD E2) is Safer than Oral Estrogen/Estradiol (E/E2)**

TD E2 is safer than o-CEE and o-E2. TD E2, compared to any o-E/E2, requires a lower effective dose to achieve the desired effect. At a lower effective dose, TD E2 results in more stable serum E2 levels and less estrogen tissue exposure without supraphysiologic liver concentrations.<sup>6,7,8</sup>

Oral E and o-E2 undergo extensive first-pass intestinal and hepatic metabolism. This results in protein production, including inflammatory proteins and binding proteins. All o-E's, because of increased clotting factors, increase thromboembolic risk. In contrast, TD E2, at commonly used doses, exerts minimal effects on inflammatory proteins, clotting factors, and/or binding proteins. TD E2 is a safer alternative to any o-E, including o-E2.<sup>6-8</sup>

Both the 2017 North American Menopause Society's (NAMS) position statement on hormone therapy,<sup>3</sup> and the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology Position Statement on Menopause – 2017 Update,<sup>2</sup> agree that TD E2 is a safer option.



### **Contraindications**

There are obvious absolute contraindications to TD E2 use, i.e., undiagnosed genital bleeding; suspected or known breast cancer; any E/E2 dependent cancer, such as endometrial cancer; venous thromboembolic disease (DVT, PE); etc.<sup>9</sup> Depending on the patient, some may be relative contraindications. Therefore, an ongoing risk-benefit analysis is warranted to individualize and optimize patient care.

### **Endometrial Hyperplasia and Endometrial Cancer**

It is well established that E/E2-only MHT increases endometrial hyperplasia and endometrial cancer risk.<sup>10</sup> Regardless of the dose and route of administration, when prescribing TD E2 therapy, i.e., TD E2 patches, gels,<sup>2,3</sup> or creams, the standard of care is to also prescribe OMP therapy.<sup>2,3,9</sup> Regardless of TD E2 dose, guidelines recommend, and evidence supports,<sup>11,12,13</sup> starting with OMP 200mg, either continuously or sequentially (12-14 days).<sup>2,3,9,13</sup>

The literature has identified three clinical variables and one laboratory finding which may help distinguish women with an increased likelihood of bleeding or spotting. These variables are younger age (<65), longer time since menopause (>15 years), obesity (BMI > 28), and a baseline serum E2 level < 5pg/mL.<sup>14</sup>

However, women with a baseline E2  $\geq 10$ pg/mL are significantly more likely to have a baseline proliferative endometrium than women with a baseline E2 < 5pg/mL or in the 5 to < 10pg/mL range.<sup>15</sup> In other words, if serum E2 is very low, you may see spotting and/or bleeding. If the baseline E2 level is  $\geq 10$ pg/mL, a high index of suspicion regarding a proliferative endometrium is warranted.

OMP 200mg (either continuously or sequentially for 12-14 days), which current guidelines suggest,<sup>2,3</sup> is for standard-dose or high-dose therapy. With either a low-dose (0.025mg/d), an

ultralow-dose (0.014mg/d) TD E2 patch, or a low-dose TD E2 gel (DIVIGEL 0.25mg/d), an argument can be made for prescribing either continuous lower dose OMP or VMP. The concern is that there is a paucity of long-term follow-up data and/or RCT data, especially in younger PMP women, using these lower dose combined regimens. If one chooses to use lower Pg doses, diligent follow-up is necessary.

- Unopposed TD E2 increases endometrial hyperplasia and cancer risk
- PROMETRIUM 200mg, either continuous or sequential (12-14 days), with standard-dose CLIMARA 0.05mg/d, is proven to prevent endometrial cancer
- There is a paucity of long-term follow-up data and/or RCT data on lower TD E2 and OMP doses and regimens

## BREAST DENSITY & BREAST CANCER

### Breast Density

Breast density is a mammographic finding based on differing proportions of fat, connective, fibroglandular, and epithelial tissue. Breast density is associated with a greater breast cancer risk than family history or other known factors. In fact, women with high mammographic breast density have a four- to six-fold higher breast cancer risk.<sup>6</sup>

E/E2 alone does not increase breast density. Only when E/E2 is combined with a progestogen, primarily synthetic progestins, does breast density increase. The breast density data with respect to OMP is mixed.<sup>17</sup>

- Increased breast density is an independent risk factor for breast cancer
- High mammographic density increases breast cancer risk four- to six-fold
- E2 does not increase breast density
- E/E2, and TD E2-alone, are associated with a decreased breast cancer mortality
- TD E2 + OMP does not increase breast cancer

### Breast Cancer

Breast cancer risk and MHT's relationship is complex. The results are confusing, and at times conflicting, created in part by the evidence and in part by its interpretation. In PMP women with normal mammography, estrogen-alone (CEE, o-E2, TD E2) does not increase breast cancer risk; it decreases breast cancer risk and mortality.

The landmark WHI's results were re-analyzed in 2018, finding a decreased breast cancer mortality (45%) when CEE-alone (0.625mg/d) was continued for 7.2 years with 18 years of cumulative follow-up (including the treatment phase) when compared to placebo.<sup>18</sup> This finding is an example of "... rationalize when you must..." Despite these findings, TD E2 is still safer. Oral CEE increases inflammatory markers and is procoagulant.<sup>6-8</sup>

The FINNISH observational trial that evaluated o-E2, TD E2 patches, and TD E2 gels, found that the longer a woman was exposed to E2 the greater the mortality benefit (up to 54% mortality reduction). FINNISH also noted that TD E2 can be continued safely, even in older PMP women, for > 10 years. FINNISH stated that time since menopause probably has no impact on either breast cancer risk or breast cancer mortality.<sup>19</sup>

However, two trials, the Million Woman's Study<sup>20</sup> and E3N,<sup>21</sup> document an increased breast cancer "relative risk," and the former documented an increased breast cancer mortality "relative risk." Both need cautious interpretation.<sup>18</sup>

When TD E2 is combined with OMP, there is also no increase in breast cancer risk.<sup>22,23,24</sup> There are no large, long-term RCTs, therefore we do not know definitively whether or not adding OMP to TD E2 decreases breast cancer incidence and mortality as seen with using E/E2 therapy by itself and mortality seen with E/E2-alone therapy.



## The Evidence

The WHI's initial and subsequent publications (RCTs and follow-ups) focused on the increased breast cancer incidence when CEE was combined with MPA. Hodis and Sarrel, in a 2018 review, critically evaluated breast cancer risk through the lens of the WHI studies. They found that when CEE (0.625mg/d) was combined with MPA (2.5mg/d), in the typical PMP population (women who have never used MHT), it had a null effect on breast cancer risk. In other words, the breast cancer incidence was not affected by CEE + MPA relative to placebo for up to 11 years. Similarly, in the woman who had previously taken hormones there was a null effect on breast cancer.<sup>18</sup>

Surprisingly, little attention was given to the WHI CEE-alone trial that documented a significant decreased breast cancer risk and mortality when CEE-alone (0.625mg/d) was compared to placebo. Women in the CEE-alone treatment arm showed a 21% non-significant reduction in breast cancer risk after a median 7.2 years of randomized treatment. When further analyzed by compliance, in those women who were taking their study pills and were at least 80% compliant, breast cancer risk was statistically significantly (SS) reduced by 32% relative to placebo.<sup>18</sup>

After a mean 10.7 years of follow-up (including the mean 7.2 years of intervention), the breast cancer risk was statistically significantly reduced by 23%, regardless of compliance status.

Subsequent data analysis noted a non-significant 20% reduction in breast cancer after a median 13.2 years of follow-up. But the most significant and overlooked CEE-alone trial finding was the 45% statistically significant breast cancer mortality reduction after 18 years of cumulative follow-up when compared to placebo.<sup>18</sup>

Other factors play a role in the significant mortality reduction seen with CEE-alone. Compared to women using CEE + MPA, women taking CEE-alone had higher unconjugated estrone (E1) levels, greater metabolism down the 2-OH pathway as opposed to the 16-OH pathway, and higher 4-methoxyestrone levels.<sup>23</sup>

Studies suggest breast cancer may be reduced in PMP women with more extensive metabolism along the 2-OH pathway rather than via the competing 16-OH pathway. This estrogen metabolism shift may impact breast cancer incidence and possibly breast cancer mortality. In addition, CEE alone may induce apoptosis, which can affect breast cancer risk.<sup>25</sup>

Methylation activity is also important. Catechol methylation prevents further catechol estrogen metabolism to catechol estrogen quinones, thereby deactivating the pathway that produces reactive and potentially mutagenic metabolites.<sup>25</sup>

What about breast cancer mortality? The Nationwide FINNISH Comparative Study, like the WHI CEE-alone trial, found a statistically significant breast cancer mortality reduction in women using E2-alone when compared to placebo or combined MHT. Any history of E2-based MHT exposure was associated with an up to 54% breast cancer mortality risk reduction.<sup>19</sup>

Finland prescribers exclusively use E2 (oral, transdermal patch, or gel). In women with a uterus, progestins are prescribed, not OMP (dose, type, and delivery system unknown). In all MHT users, breast cancer mortality was significantly reduced with exposure for 0-5 years, 5-10 years, and for > 10 years. Breast cancer pathology and hormone receptor status were not reported in the FINNISH data base.<sup>19</sup>

As expected in women between 50-59 years old, the mortality reduction was larger than for older women. Notably, in those women using E2-alone (data not differentiated by estradiol type), the mortality reduction was larger in all groups, com-

pared to combined MHT or placebo. Age at MHT onset was not related to breast cancer mortality.<sup>19</sup>

The FINNISH study, a large observational study, did not differentiate between the E2 delivery systems (oral, transdermal patches, or gels) and doses (1 or 2mg, 0.025mg-0.1mg, 0.5mg-1.5mg, respectively) when analyzing the data. Thus, delivery system and/or dose effect could not be analyzed. The authors reasoning was that their previous data analysis failed to show any marked difference between these factors and breast cancer risk. This study noted that TD E2, when used for > 10 years, was safe for the breast.<sup>19</sup>

In conclusion, breast cancer death risk is, as a mean of, 50% smaller among patients with previous exposure to MHT. Thus, in the Finnish population, breast cancer is fatal in 1 in 10 patients, whereas in women with a history of hormone therapy use, breast cancer is fatal in 1 in 20 patients.<sup>19</sup>

In a 2018 publication, Shufelt, et al.<sup>26</sup> analyzed the small WHI observational study (WHI-OS) database with an eight-year follow-up. The objective was to determine the invasive breast cancer incidence in relation to different estrogen-alone doses, formulations, and routes of delivery in hysterectomized women. An additional goal was to assess whether results varied by time since menopause onset (< 10 years, ≥ 10 years) for estrogen initiation.<sup>26</sup>

The WHI-OS analysis found that invasive breast cancer risk did not differ when comparing low-dose CEE < 0.625mg/d to standard-dose CEE 0.625mg/d. In addition, when compared to standard-dose CEE, TD E2 (doses and formulations not specified) was associated with a non-significant lower breast cancer risk.<sup>26</sup>

Shufelt, like Hodis,<sup>18</sup> stated that E/E2 did not increase breast cancer risk in women status post hysterectomy.

**Breast Cancer (BC) Studies Summarized**

| Studies                       | Study Drugs/Doses  | Results  |
|-------------------------------|--|--|
| WHI CEE-alone <sup>18</sup>   | <ul style="list-style-type: none"> <li>• CEE 0.625mg/d-alone treatment for 7.2 years</li> <li>• Placebo</li> </ul>   | <ul style="list-style-type: none"> <li>• Decreased BC incidence and 45% mortality reduction with 7.2 treatment years and 18 cumulative follow-up years</li> </ul>  |
| WHI: CEE + MPA <sup>18</sup>  | <ul style="list-style-type: none"> <li>• CEE 0.625mg/d + MPA 2.5mg/d treatment for 5.6 years</li> <li>• Placebo</li> </ul>   | <ul style="list-style-type: none"> <li>• Typical PMP woman, no previous MHT</li> <li>• Neutral effect when MPA added to CEE</li> <li>• In entire cohort, may or may not increase BC</li> </ul>   |
| WHI: WHI-OS <sup>26</sup>     | <ul style="list-style-type: none"> <li>• CEE 0.625mg/d</li> <li>• CEE &lt; 0.625mg/d</li> <li>• TD E2 dose and formulation unknown</li> </ul>                                    | <ul style="list-style-type: none"> <li>• CEE 0.625mg/d vs CEE &lt; 0.625mg/d: no difference in invasive BC risk</li> <li>• CEE 0.625mg/d vs TD E2: TD E2 demonstrated a nonsignificant lower BC risk</li> </ul>  |
| FINNISH-OS <sup>19</sup>      | <ul style="list-style-type: none"> <li>• O-E2 1 or 2mg/d</li> <li>• TD E2 patches 0.025mg-0.1mg/d</li> <li>• Gels 0.5mg-1.5mg/d</li> <li>• Placebo</li> </ul>                    | <ul style="list-style-type: none"> <li>• Up to a 54% mortality reduction; mortality reduction related to years of E2-alone use</li> <li>• BC fatal 1 in 10 without E2 and 1 in 20 with E2</li> </ul>   |
| Million Women's <sup>20</sup> | <ul style="list-style-type: none"> <li>• CEE, o-E2, TD E2, pellets – doses unknown</li> <li>• Never users</li> </ul>   | <ul style="list-style-type: none"> <li>• All increased BC relative risk and relative mortality risk</li> </ul>   |
| E3N <sup>21</sup>             | <ul style="list-style-type: none"> <li>• Primarily o-E2</li> <li>• Large percentage TD E2</li> <li>• Never users</li> </ul>  | <ul style="list-style-type: none"> <li>• Increased BC relative risk</li> </ul>   |
| WHI 2020 update <sup>66</sup> | <ul style="list-style-type: none"> <li>• CEE-alone vs placebo - treatment for 7.2 years, entire study group</li> <li>• CEE + MPA vs placebo - treatment for 5.6 years</li> </ul> | <ul style="list-style-type: none"> <li>• CEE-alone with ~7.2 years of treatment and 20 years cumulative follow-up: decreased BC incidence and decreased BC mortality</li> <li>• CEE + MPA with ~5.6 years of treatment and 20 years of cumulative follow-up: increased BC incidence, but NOT BC mortality</li> </ul> |

The authors concluded that TD E2 (all doses were included) may be a better choice than standard CEE 0.625mg/d, because TD E2 was associated with slightly less breast cancer risk. Furthermore, there was no statistically significant difference when taking into consideration time since menopause.<sup>26</sup>

Regrettably, the sample size limited the power for this comparison. Another limitation, in addition to the small number of women using TD E2, was the 8-year follow-up. Given that Hodis found a 45% breast cancer mortality reduction after 18 years of cumulative follow-up, one must wonder if a mortality benefit using TD E2 would have also been suggested if follow-up analysis was continued for 18 years.

Contrary to the above, two prospective observational cohort studies found higher breast cancer relative risk rates even when stratified by dose, delivery, and formulation.<sup>20,21</sup>

In the Million Women's Study, the breast cancer relative risk in current users at baseline increased with increasing total E2-based MHT duration. Breast cancer relative risk was increased in women using estrogen-alone therapy, regardless of dose or delivery, when compared to never users (range 1.24-1.65). Follow-up was only for 2.5 years (breast cancer incidence) and 4.1 years (breast cancer mortality), MHT use was defined at study entry, with no MHT information obtained at follow-up, and the doses and delivery methods were not specified.

There was no information regarding breast health at study onset. Also, death attributed to breast cancer and MHT use occurred 1.7 years after MHT initiation. The latter may be biologically implausible because on average, it takes approximately ten years for breast cancer cells to become evident.<sup>20</sup>

This short interval between breast cancer diagnosis and death suggests that some patients had undiagnosed advanced breast cancer at the time of MHT initiation.<sup>18</sup> In addition, one-third of women used more than one MHT regimen and, similar to the WHI, the comparator group had a lower breast cancer incidence than similar women in the general population.<sup>65</sup>

If the latter assumption is correct, MHT probably did increase the incident breast cancer relative risk, possibly by stimulating existing tumor growth. The Million Women's study<sup>20</sup> demonstrates, regardless of the results reliability, the need to ensure normal mammography prior to initiating therapy, as well as the need for diligent on-going surveillance.

In the E3N study,<sup>21</sup> TD E2 was the predominant estrogen prescribed, however, doses were unknown. In E3N's estrogen-only treatment arm, there was a significant increased breast cancer relative risk (relative risks 1.29 [95% confidence interval 1.02–1.65]) when compared to non-users.<sup>21</sup>

In addition, in the E2-only treatment group, approximately 72% used a combined MHT regimen. In the OMP/dydrogesterone group, 52% used estrogen/estradiol, combined with a progestin.<sup>21</sup>

Be cautious; observational study relative risks of  $\leq 2-3$  (Million Women's Study<sup>20</sup> and E3N<sup>21</sup>) may not be credible because of the high likelihood of biases, difficulty in interpreting, and confounding factors that are typically not included in the data analysis. These two observational studies had design and statistical analysis flaws.<sup>18</sup>

Even though Hodis' WHI-CEE reanalysis documented that CEE 0.625mg/d alone decreases breast cancer risk and mortality on follow-up,<sup>18</sup> TD E2 is still a better choice because an effective dose (menopausal symptom relief, BMD preservation, no side effects, or adverse events) generally produces lower serum E2 levels, which, over time, decreases E2 tissue exposure. In addition, TD E2 does not increase inflammatory markers



and is not pro-coagulant.<sup>6-8</sup>

Recently (2020), Chlebowski et al. published an additional WHI follow-up. Unfortunately, there was no attempt to address or correct the previously noted analytical flaws in the CCE + MPA study. However, the data continues to confirm that estrogen-alone decreases breast cancer incidence and breast cancer mortality. This finding can certainly be extrapolated to TD E2, which is a safer option. Despite this, the WHI continues to document an increased breast cancer incidence, but not mortality in the CEE + MPA arm when compared to placebo.<sup>67</sup>

Given the noted analytical issues, it is unclear what the CEE + MPA data means. This is okay because the data is not relevant to modern practice patterns. TD E2 is what guidelines/position statements<sup>2,3,9</sup> recommend because it is both efficacious and breast safe. Furthermore, adding either OMP<sup>17,23,24</sup> or VMP (indirect data)<sup>46</sup> does not increase breast cancer.

## COMORBIDITIES ASSOCIATED WITH ESTROGEN/ESTRADIOL DEFICIENCY

### Vasomotor Symptoms (VMS)

MHT is the gold standard for VMS relief.<sup>2,3</sup> Treatment efficacy increases with increasing E2 doses. However, low-dose (0.025mg/d)<sup>4</sup> and ultralow-dose TD E2 (0.014mg/d) patch<sup>5</sup> preparations are more tolerable, with less breast pain and irregular bleeding, as are TD E2 gel doses, when compared to the higher dose preparations. Gel doses are product specific.<sup>4</sup>

VMS, or hot flashes/flushes and sweats, are in many ways the quintessential menopausal symptoms. The FDA and guidelines agree that E2 is first-line therapy for VMS in the appropriate patients (no contraindications).<sup>2,3</sup> A standard-dose TD E2 patch (0.05mg/d) successfully treats VMS. Estradiol therapy (patches and gels), with or without OMP, decreases symptom frequency by 75% and significantly decreases symptom severity.

- TD E2 patch doses as low as 0.014mg/d (MENOSTAR) relieve VMS
- TD E2 gel doses as low as 0.25mg/d (DIVIGEL) and 0.52mg/d (ELESTRIN) relieve VMS (low-dose gels are product specific)
- With lower than standard patch and gel doses it may take longer to see effects
- OMP/VMP should be prescribed, even with lower TD E2 doses

There is no other pharmacological or nutraceutical product that provides equivalent symptomatic relief.<sup>3</sup>

Placebo-controlled trials have shown that low-dose oral (0.25mg/d) and TD E2 products (patches [0.025mg/d] and gels [product specific]) are effective in relieving VMS by 60% to 70%, with minimal adverse effects.<sup>5</sup> The question then becomes, what is the lowest TD E2 dose that can be used while minimizing any adverse consequences?

The following patch and gel products significantly improved moderate or severe hot flash severity and frequency when compared to placebo:

- All FDA-approved patch doses improve VMS, most reaching statistical significance by four weeks<sup>4,27,28</sup>
- Both low-dose DIVIGEL (0.25mg/d)<sup>4</sup> and ELESTRIN (0.52mg/d)<sup>29</sup> relieve VMS, reaching statistical significance at five weeks, not four weeks

However, do not assume a patch or gel treatment has failed if there is no symptomatic relief within four or five weeks. Many women require 8-12 weeks to achieve satisfactory VMS relief, especially given demographic, lifestyle, and HPA axis adaptability and resiliency differences. In women with a uterus, OMP/VMP is necessary for endometrial protection.<sup>10-12</sup>

There is not enough data to suggest these low and ultralow TD E2 doses, prescribed without OMP/VMP, do not induce endometrial hyperplasia and cancer.<sup>4</sup>

Low-dose and micro/ultralow-dose preparations successfully treat moderate or severe PMP VMS in women with and without a uterus, but it may take a few weeks longer than the higher dose preparations to obtain satisfactory results. Age should not preclude initiating therapy at these ultralow and low doses.

### **Genitourinary Syndrome of Menopause (GSM): Vulvovaginal Atrophy (VVA)**

Estradiol is the most effective treatment for moderate to severe VVA and its associated symptoms. In fact, unless contraindicated, it is the gold standard. All TD E2 products relieve VVA symptoms as well as show objective evidence of an improved vaginal maturation index (VMI).<sup>30,31,32</sup>

- TD E2 products relieve VVA symptoms
- TD E2 patch doses as low as 0.014mg/d are effective
- ELESTRIN gel 0.52mg/d and ESTROGEL 0.75mg/d and 0.375mg/d are effective
- The ESTROGEL 0.27mg/d does not provide adequate amounts of E2 to effectively improve VVA symptoms and/or VMI

Local estradiol, estriol, or DHEA should be considered in women without additional menopausal symptoms. With VMS, GSM symptoms, and/or concerns regarding osteoporosis risk, non-vaginal TD E2 formulations are the standard of care.<sup>32,33,34</sup>

What is the lowest dose that can be used while minimizing any adverse sequelae? All the following gel products significantly improved VMS, VVA, and objective vaginal parameters when compared to placebo:

- Low-dose ELESTRIN gel 0.52mg/d with trough serum levels ranging from 17pg/mL to 29pg/mL<sup>29</sup>

- ESTROGEL 0.75mg/d with serum levels of 33.0pg/mL<sup>33,34</sup>
- Low-dose ESTROGEL 0.375mg/d with serum levels of 21.8pg/mL<sup>34</sup>

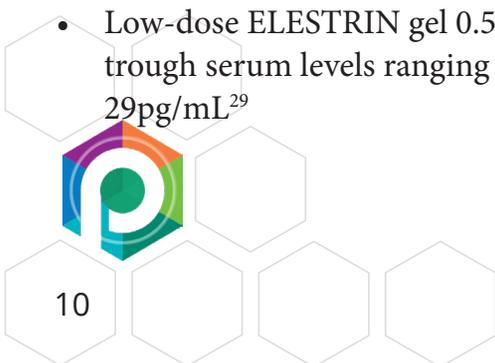
However, ESTROGEL 0.27mg/d with E2 serum levels of 11.65pg/mL, when compared to placebo, did not significantly improve symptoms or objective vaginal parameters, but did improve VMS.<sup>34</sup>

What about patch products? The MENOSTAR ultralow-dose 0.014mg/d patch (no longer available) was assessed in two separate studies. Each study's authors concluded that the MENOSTAR patch significantly improved VVA symptoms and objective vaginal parameters.

- Study 1: MENOSTAR (0.014mg/d) vs. ESTRING (0.0075mg/d) vaginal ring: both equally improved vaginal parameters. MENOSTAR significantly increased serum E2 levels with 6 and 12-week serum levels of 20.0pg/mL and 16.9pg/mL, respectively, when compared to the FDA-approved ESTRING. Symptoms were not assessed.<sup>35</sup>
- Study 2: MENOSTAR (0.014mg/d) vs Placebo: the MENOSTAR patch significantly improved VVA symptoms in addition to objective vaginal parameters, when compared to placebo, with 1 – and 2-year serum levels of 8.5pg/mL and 8.6pg/mL, respectively.<sup>32</sup>

PA has learned that the quality of study 2's laboratory assay has been called into question by analytical experts and has been discontinued. This does not take away from the findings that an ultralow-dose patch relieves VVA symptoms and objective vaginal parameters. It means that its effectiveness probably occurred at a higher serum E2 level than what ULTRA documented.

Study 1 documented the same patch's effectiveness at higher serum levels. Certainly, there are going to be patients who become clinically asymptomatic at low serum E2 levels (possibly not as low as 8.6pg/mL), as well as those women needing high-



er E2 levels to achieve clinical success (~ 30pg/mL). Therefore, MHT should be individualized.

## Osteoporosis

TD E2 patches improve BMD and are FDA-approved for osteoporosis prevention. Low-dose (0.025mg/d) ESTRADERM,<sup>36</sup> CLIMARA,<sup>37</sup> and ALORA<sup>38</sup> significantly improved BMD when compared to placebo, as did the ultralow-dose MENOSTAR 0.014mg/d patch.<sup>39</sup> Low-dose and ultralow-dose TD E2 gels are not FDA-approved for osteoporosis prevention.

However, using standard-dose ESTROGEL 0.75mg/d, BMD response was delayed. BMD did not improve at six months but did significantly improve at twelve months.<sup>40</sup>

With high-dose ESTROGEL 1.5mg/d, BMD significantly improved at both six and twelve months. This was at the expense of higher serum E2 levels, increased total E2 tissue exposure, and possibly increased side effects. This high ESTROGEL dose may not be a reasonable first choice.<sup>40</sup>

- TD E2 products improve BMD and are FDA-approved for osteoporosis prevention
- Low-dose (0.025mg/d) CLIMARA, ALORA, and ESTRODERM improve BMD vs placebo, as does the ultralow-dose (0.014mg/d) MENOSTAR
- Low-dose TD E2 gels are not FDA-approved for osteoporosis prevention
- Standard-dose ESTROGEL 0.75mg/d improves BMD, but response is delayed (1 year)

Recall that ESTROGEL 0.375mg/d does improve VMS and VVA symptoms;<sup>34</sup> however, this same dose was never studied for osteoporosis prevention. One must wonder if the 0.375mg/d dose had been evaluated for osteoporosis prevention, whether follow-up for  $\geq 2$  years would have yielded positive BMD findings.

Contrary to PMP, VMS, and/or VVA symptoms, where clinically meaningful results are easily determined, osteoporosis prevention is harder. The first and only symptom may be a fracture with its increased morbidity and potentially increased mortality. It had been previously suggested that the minimum serum E2 level needed to prevent PMP bone loss was 60pg/mL.

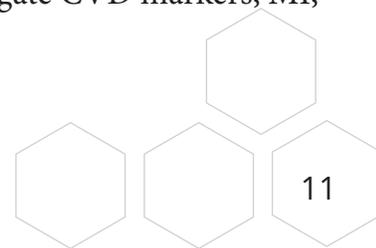
Achieving this high serum E2 level is probably not necessary given that the cited studies, as well as others, document that with both patches and gels, bone loss is prevented at much lower serum E2 concentrations. For example, at two years, ALORA 0.025mg/d increased BMD at serum E2 levels of 17pg/mL.<sup>38</sup> Also, at one year, ESTROGEL 0.75mg/d increased BMD at an E2 level of 33.5pg/mL.<sup>40</sup> Thus, BMD is maintained and bone loss prevented at lower serum E2 levels using all TD E2 patches compared to any TD E2 gel product.

For osteoporosis, DEXA scanning is an excellent tool; however, its usefulness is limited. Other markers should be evaluated and may include serum osteocalcin, serum bone-specific alkaline phosphatase, serum (or urine) estradiol levels, and urinary N-telopeptide.

## Cardiovascular Disease (CVD)

For most women, TD E2 probably provides cardiovascular (CV) protection. At present, there are no studies indicating a time limit on the administration of properly monitored MHT, including TD E2. TD E2 patch doses as low as 0.025mg/d, E2 gel doses of 1-2mg/d, and o-E2 doses of 1-2mg/d, are effective in decreasing CVD mortality risk in women, and this mortality reduction is positively related to hormone exposure time.<sup>41,42</sup>

Below is a summary of the studies discussed. It is important to note that the cited studies looked at different endpoints, surrogate CVD markers, MI, heart failure, and death.



| Cardiovascular Disease Studies Summarized            |  |   |
|--|--|---|
| Studies  | Study Drugs/Doses  | Results   |
| <b>Studies documenting mixed results</b>             |  |   |
| WHI <sup>43</sup>                                    | <ul style="list-style-type: none"> <li>• CEE-alone</li> <li>• Placebo</li> </ul>   | <ul style="list-style-type: none"> <li>• Women age 50-59 years old on CEE: 40% decreased MI risk and all-cause mortality compared to placebo</li> <li>• Women age 60-69: neutral effect on CV outcomes</li> <li>• Women age 70-79: trend towards increased CV events</li> </ul>   |
| ELITE <sup>46</sup>                                  | <ul style="list-style-type: none"> <li>• O-E2 1mg/d</li> <li>• O-E2 1mg/d + VMP GEL 45mg/d, days 1-10 (brand name unknown)</li> <li>• Placebo</li> </ul>   | <ul style="list-style-type: none"> <li>• Two study groups: &lt; 6 years PMP and ≥ 10 years PMP</li> <li>• PMP &lt; 6 years: o-E2 slowed CIMT progression, but only at the 5-year follow-up</li> <li>• PMP &gt; 10 years: no difference compared to placebo</li> </ul>   |
| <b>Studies documenting no CV benefit and no harm</b> |  |   |
| ELITE-post study analysis <sup>66</sup>              | <ul style="list-style-type: none"> <li>• PREMARIN 0.45mg/d + PROMETRIUM 200mg/d x 12d</li> <li>• CLIMARA 0.05mg/d + PROMETRIUM 200mg/d x 12d</li> <li>• Placebo</li> </ul>                             | <ul style="list-style-type: none"> <li>• Neither PREMARIN nor CLIMARA affected the rate of CIMT progression after 4 years</li> <li>• PREMARIN: trend toward reduced CAC accumulation</li> </ul>   |
| <b>Studies documenting CV benefits</b>               |  |   |
| DOPS <sup>47</sup>                                   | <ul style="list-style-type: none"> <li>• No uterus: O-E2 2mg/d</li> <li>• Yes uterus: O-E2 2mg/d x 12d; O-E2 2mg + 1mg NORETHISTERONE ACETATE x 10d; o-E2 1mg/d x 6 days</li> <li>• Placebo</li> </ul> | <ul style="list-style-type: none"> <li>• Recently PMP, treated 16 years</li> <li>• All treatment groups had a significantly lower coronary heart disease risk at both 10- and 16-years of follow-up</li> <li>• At 10 years, PMP women receiving o-E2 had a significantly reduced CV event risk such as heart failure and MI</li> </ul>  |
| FINNISH-OS <sup>41</sup>                             | <ul style="list-style-type: none"> <li>• O-E2 1-2mg/d</li> <li>• TD E2 patches 0.025mg-0.1mg/d</li> <li>• TD E2 gels 1-2mg/d</li> <li>• Never users</li> </ul>   | <ul style="list-style-type: none"> <li>• In E2 users, CAD-related death risk was reduced by up to 54% in a time-dependent manner</li> <li>• The longer a woman was prescribed and used an E2-based MHT, the greater the risk reduction</li> <li>• All risk reductions were comparable in PMP women initiating E2 &lt; age 60 and in women initiating therapy ≥ 60 years or older</li> </ul> |

## The Evidence

The WHI's subgroup analysis did confirm that CVD risk is influenced by a woman's age and time since menopause.<sup>43,44</sup> Therefore, the "timing hypothesis" began receiving attention. The hypothesis posits that age and time since menopause influence the MHT and CVD relationship, such that the risks are lower in women closer to menopause onset than in those distant from the menopause transition.

As a result, several clinical trials set out to confirm and clarify the timing hypothesis, including Kronos Early Estrogen Prevention Study (KEEPS),<sup>45</sup> Early versus Late Postmenopausal Treatment with Estradiol (ELITE),<sup>46</sup> and Danish Osteoporosis

Prevention Study (DOPS).<sup>47</sup> For study details, see PA's comprehensive TD E2 literature review.

KEEPS was a four-year RCT in healthy, recently PMP women that aimed to evaluate MHT's effects on atherosclerosis progression as measured by carotid intima-media thickness (CIMT) and coronary arterial calcification (CAC). PREMARIN (0.45mg/d) and CLIMARA (0.05mg/d), both combined with PROMETRIUM (200mg/d) x 12d/month, were evaluated vs placebo.<sup>45</sup>

After four years, neither the PREMARIN nor the CLIMARA patch affected the rate of CIMT progression. There was a trend for reduced accumulation of coronary artery calcium with PREMARIN. There were no severe adverse effects, including venous thrombosis.<sup>45</sup>

As opposed to KEEPS, both ELITE<sup>46</sup> and DOPS<sup>47</sup> studied o-E2, with ELITE balancing o-E's effects with VMP, and DOPS using an oral synthetic progestin (norethisterone acetate).

- TD E2 decreases CVD, with no increase in VTE or stroke
- TD patch doses as low as 0.025mg/d and TD E2 gel doses of 1-2mg/d may decrease CVD mortality risk
- TD E2's mortality reduction is positively related to E2 exposure time
- Know a woman's CVD risk prior to initiating MHT
- CVD risk changes; ongoing surveillance a must

All three studies concluded that MHT, including TD E2, is safe in all healthy, recently PMP women (natural or surgical).<sup>45-47</sup>

However, their results differed. KEEPS found no significant difference in the rate of CIMT progression when comparing the treatment arm to placebo.<sup>45</sup> This was thought to be due to a healthy study group and short study duration (four years).<sup>45,46</sup> ELITE,<sup>46</sup> on the other hand, did document significantly slower CIMT progression in the early o-E2 treated women (< six years since menopause onset) versus placebo at five years.<sup>46</sup>

It is surprising the ELITE authors did not highlight the fact that the older women (median age 63.6 years old) who initiated hormone therapy  $\geq$  ten years postmenopause (median 14.3 years), with similar demographics to the WHI study population, had no significant adverse cardiovascular events or other adverse events when compared to placebo.<sup>46</sup> This suggests that treatment may be continued for longer time periods, and, in those women who do not initiate MHT early, the perceived safety concerns have yet to be proven.

Recently, in a 2019 publication,<sup>66</sup> the ELITE study group in a post-trial analysis, evaluated the association between serum E2 levels and the atherosclerosis surrogate marker CIMT. They found that E2 levels were differentially associated with CIMT according to the timing of MHT initiation (early treatment arm < 6 years PMP, late treatment arm > 10 years PMP). With higher treatment serum

E2 levels, CIMT progression rate was decreased in the early PMP group (serum E2 48.2 +/- 35.4pg/mL) and increased in the late PMP group (serum E2 40.2 +/- 23.6pg/mL). The technology used to measure serum E2 was an ultrasensitive RIA method, not LC-MS/MS, which is the most accurate.<sup>66</sup>

We do not know how the o-E2 was metabolized, nor do we know anything about either treatment groups' inflammatory markers. Because we do not use o-E2, it is difficult to apply these results to current practice. However, it is a reminder that higher serum E2 levels (some in the premenopausal range) are not necessary and may be harmful.

Contrary to KEEPS<sup>45</sup> and ELITE,<sup>46</sup> DOPS<sup>47</sup> evaluated hard endpoints, not surrogate markers. They found that after ten years, women receiving o-E2 had a significantly reduced risk of cardiovascular events such as heart failure and MI, with no increased venous thromboembolism, cancer, or stroke risk.<sup>47</sup>

Since death is the most reliable CAD marker, a 2015 nationwide FINNISH study compared the death risk in almost half a million E2-based hormone therapy users with an age-matched female population. They assessed E2 (transdermal and oral) MHT regimens and the risk of death caused by coronary heart disease, stroke, or any disease. The MHT regimens (products unknown) included o-E2 1-2mg/d, TD E2 gel 1-2mg/d, or a TD E2 patch 0.025-0.1mg/d. Less than 1% used o-CEE and 90% used o-E2.<sup>41</sup>

They found that the risk for CAD-related deaths in E2 users was reduced by up to 54% in a time-dependent manner, meaning the longer a woman was exposed to an E2-based MHT, the greater the risk reduction.

In addition, all these risk reductions were comparable in PMP women initiating E2-hormone based therapy before age 60 years and women initiating therapy at age 60 years or older.<sup>41</sup>

The FINNISH study adds support to the growing body of evidence that E2-based therapy imparts significant cardiovascular benefits and that continuing therapy in all women, whether immediately PMP or older, and/or > 10 years postmenopause, is safe and effective.<sup>41</sup> Sixty years of age at the initiation of MHT is evidently not a threshold age, as suggested by the WHI sub-analyses and current guidelines.

What about VTE? TD E2, unlike o-E, does not increase the venous thromboembolic (VTE) risk, probably due to its lack of effect on the coagulation cascade, including thrombin generation and resistance to activated protein C, and does not increase stroke risk. It is cardioprotective, significantly reducing the myocardial infarction incidence and presumably death when compared with non-users.<sup>48</sup>

Consequently, the four concerns raised by the WHI publications—venous thromboembolic disease, myocardial infarction, stroke, and breast cancer—are minimized or negated by using TD E2.<sup>48</sup> Therefore, start TD E2-based MHT as early as possible,<sup>42</sup> do not hesitate to initiate TD E2 therapy in older women > 10 years PMP, and consider continuing indefinitely.<sup>41,42,47</sup> Time since menopause and age > 60 should cause pause, but not prevent MHT initiation or continuation. Remember, in women with a uterus, OMP/VMP is necessary to protect the endometrium,<sup>2,3,9,11,12</sup> and in all women ongoing cardiovascular, endometrial, breast, and bone surveillance is a must.

Finally, all women being considered for MHT should be screened for cardiovascular risk factors. In women with CVD risk factors, the work-up should probably include CIMT or CAC. Coronary calcium score is readily available and correlates well with coronary disease.<sup>43</sup>

All patients receiving MHT should be reevaluated at appropriate intervals, with appropriate testing, because CVD risk changes with age and lifestyle.

## Cognition

The ESTRADERM 0.05mg/d<sup>49</sup> and 0.1mg/d<sup>50</sup> patches both significantly improved cognitive function in women with mild-moderate AD when compared to placebo. The CLIMARA 0.05mg/d patch also significantly improved cognitive performance in perimenopausal and recently PMP women when compared to placebo.<sup>51</sup>

The latter findings contrast with KEEPS-Cog, where the CLIMARA 0.05mg/d patch had a neutral effect on cognition, but decreased amyloid- $\beta$  deposition, particularly in apolipoprotein e4 (APOE e4) carriers.<sup>52</sup> With ongoing follow-up, the latter should translate into positive clinical outcomes.

However, in older, asymptomatic, PMP women without AD, the MENOSTAR 0.014mg/d patch did not improve cognitive function.<sup>53</sup> The next page includes a summary of the studies discussed.

- ESTRADERM 0.05mg/d and 0.1 mg/d improve cognitive performance in older, healthy PMP women with mild-moderate AD
- CLIMARA 0.05mg/d improves cognitive performance in younger, symptomatic, perimenopausal, and recently menopausal women
- MENOSTAR 0.014mg/d does not improve cognitive performance in predominantly asymptomatic, older PMP women.
- A 0.025mg/d TD E2 patch's effectiveness on cognitive performance has yet to be studied

## The Evidence

The inconsistent results that exist in the literature regarding E/E2's effects on cognition are multifactorial. Reasons for the inconsistent results include



| Cognition Studies   |  |   |
|---|--|---|
| Studies   | Study Drugs/Doses  | Results   |
| <b>Studies documenting increased cognitive impairment</b> |  |   |
| WHIMS and WHIS-CA <sup>56,58,59</sup>                     | <ul style="list-style-type: none"> <li>• CEE 0.625mg/d alone</li> <li>• CEE 0.625mg/d + continuous MPA 2.5mg/d</li> <li>• Placebo</li> </ul>   | <ul style="list-style-type: none"> <li>• Significant increase in cognitive impairment in PMP women &gt; 65 years old</li> <li>• CEE alone – increased cognitive impairment not significant</li> </ul>   |
| <b>Studies documenting no benefit and no harm</b>         |  |   |
| WHIMS-Y <sup>59</sup>                                     | <ul style="list-style-type: none"> <li>• CEE 0.625mg/d + continuous MPA 2.5mg/d</li> <li>• Placebo</li> </ul>  | <ul style="list-style-type: none"> <li>• In younger PMP (treated 50-55 years old) women who initiate therapy soon after menopause, MHT is neither beneficial nor harmful</li> </ul>   |
| KEEPS-Cog <sup>52</sup>                                   | <ul style="list-style-type: none"> <li>• PREMARIN 0.45mg/d + PROMETRIUM 200mg/d x 12d</li> <li>• CLIMARA 0.05mg/d + PROMETRIUM 200mg/d x 12d</li> <li>• Placebo</li> </ul>                                       | <ul style="list-style-type: none"> <li>• Neither cognitive benefit nor harm for either MHT group</li> <li>• TD E2 patch decreased amyloid-β deposition, particularly in apolipoprotein e4 (APOE e4) carriers</li> </ul>   |
| ELITE-Cog <sup>62</sup>                                   | <ul style="list-style-type: none"> <li>• O-E2 1mg/d</li> <li>• O-E2 1mg/d + VMP GEL 45mg/d, days 1-10 (brand name unknown)</li> <li>• Placebo</li> </ul>   | <ul style="list-style-type: none"> <li>• Irrespective of when o-E2 was initiated, o-E2 did not affect verbal memory, executive function, or global cognition</li> </ul>   |
| Yaffe <sup>52</sup>                                       | <ul style="list-style-type: none"> <li>• MENOSTAR 0.014mg/d patch</li> <li>• Placebo</li> </ul>  | <ul style="list-style-type: none"> <li>• In older, PMP women TD E2 patch did not improve cognitive performance over a 2-year timeframe compared to placebo</li> </ul>   |
| <b>Studies documenting cognitive benefits</b>             |  |   |
| Cache County <sup>60,61</sup>                             | <ul style="list-style-type: none"> <li>• Unknown drugs, doses, routes of administration (2013, 2019 publications)</li> </ul>   | <ul style="list-style-type: none"> <li>• MHT use for long durations was positively associated with cognitive status</li> <li>• Older women had a greater benefit when compared with younger women</li> <li>• The later the onset of menopause, and the longer a PMP woman uses MHT, the greater the association with higher cognitive status later in life (especially true for older women)</li> </ul> |
| Asthana (2 separate studies) <sup>49,50</sup>             | <ul style="list-style-type: none"> <li>• Study 1 (1996): ESTRADERM 0.05mg/d vs Placebo</li> <li>• Study 2 (2001): ESTRADERM 0.1mg/d vs Placebo</li> </ul> <p style="text-align: center;">Small pilot studies</p> | <ul style="list-style-type: none"> <li>• Both studies: PMP women had mild-moderate cognitive impairment</li> <li>• ESTRADERM 0.05mg/d: Significantly improved attention and verbal memory compared to placebo</li> <li>• ESTRADERM 0.1mg/d: Significantly improved semantic, verbal, and visual memory compared to placebo</li> </ul>   |
| Joffe <sup>51</sup>                                       | <ul style="list-style-type: none"> <li>• CLIMARA 0.05mg/d</li> <li>• Placebo</li> </ul>  | <ul style="list-style-type: none"> <li>• Otherwise healthy, symptomatic, peri and PMP women without cognitive impairment</li> <li>• Significantly improved executive functioning when compared to placebo</li> </ul>  |

different study populations using different E/E2 formulations and doses, different endpoints which are tested using different methodologies and study duration.<sup>54,55,56,57</sup> The latter is especially important since Alzheimer's disease (AD) develops over a long time period and most studies are too short to really discern E2's protective effects.

Therefore, a lack of clarity is not surprising. Nevertheless, there is evidence that E2 improves cognitive performance in PMP women both without AD and with mild-moderate AD. However, we

must emphasize that cognitive improvement does not equal AD prevention.<sup>54,55,56,57</sup>

Higher estrone (E1) levels have been associated with poorer cognition, specifically working memory performance. The latter strongly supports TD E2's use with its physiologic estradiol (E2) estrone

(E1) ratio (1:1) as compared to any oral estrogen/estradiol, which, after hepatic and intestinal first-pass metabolism, generates much higher E1 levels and thus a higher, less physiologic E1:E2 ratio.<sup>8</sup>

Despite E2's positive effects on cognition, E2's role in preventing Alzheimer's disease (AD) continues to be controversial. Observational and epidemiologic studies suggest, similar to cardiovascular risk, an approximate 50% reduction in AD.<sup>54,55</sup> As opposed to CVD, where RCTs using E2 (including TD E2) demonstrate significant decreases in MI, heart failure, and presumably death,<sup>41,47</sup> the three most referenced RCTs using E2 in preventing AD do not demonstrate any decreased AD risk.<sup>56,57</sup>

What is MHT's role in cognition and dementia? Before the WHI's ancillary cognitive studies were discontinued and the results published, MHT was considered to be neuroprotective. However, the Women's Health Initiative Memory study (WHIMS) and Women's Health Initiative Study of Cognitive Aging (WHISCA) trials were a setback to this theory. Both studies' findings, like the WHI study, were unexpected, finding no cognitive advantage or decreased dementia risk in PMP MHT treatment groups. In fact, WHIMS concluded that CEE 0.625mg/d + MPA 2.5mg/d doubled the dementia incidence compared to placebo, and the later WHIMS CEE-alone (WHISCA) trial reported a 49% increase in the incidence of dementia.<sup>56,58,59</sup>

The WHIMS and WHISCA study participants were PMP women  $\geq 65$  years old. What if treatment was initiated earlier? Would this have produced different results? The latter is known as the "critical period" or "window of opportunity" hypothesis. This theory posits that MHT's cognitive benefits may be limited to MHT initiation close in time to menopause.<sup>56,58,59</sup>

The "critical period" hypothesis probably arose before the WHIMS and WHISCA results were available. Observational studies like the Cache County Study concluded that long-term PMP MHT (type, dose, and delivery methods

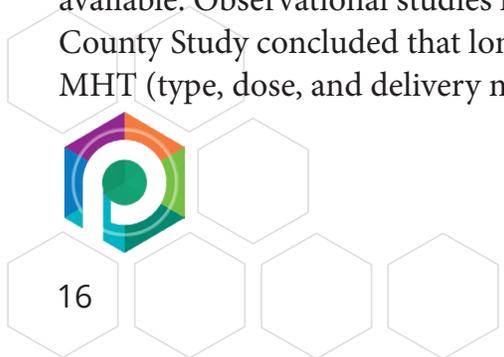
unknown) may be beneficial.<sup>56,58,60,61</sup> This ongoing study assesses reproductive estrogen/estradiol's lifetime exposure on cognitive function and AD development.

The 2013 Cache County publication detected a reduced AD risk (~ 37%) if MHT was started within five years of menopause and continued for more than ten years. An accompanying editorial noted "[b]ecause many women use HT for relatively brief durations around the menopause, the protective effect of ever-use therapy suggests the possibility of a "critical period" during the climacteric years, which are characterized by relatively rapid estrogen depletion."<sup>60</sup>

The most recent Cache County Study publication (2019) not only found that E/E2 exposure was positively associated with cognitive status, but also confirmed that MHT use for longer durations was positively associated with cognitive status. In addition, older women had a greater benefit when compared with younger women. Cache County concluded that the longer the endogenous estrogen/estradiol and MHT use, especially in older women, the greater the association with higher cognitive status later in life.<sup>61</sup>

A benefit of observational, longitudinal studies is their long-term follow-up. However, it is important to remember that many of these longitudinal studies, like the Cache County study, fail to document the estrogen/estradiol doses, formulations, or delivery methods. Therefore, the conclusions need careful interpretation and may be difficult to extrapolate to individual patients. What is clear is that E2 treatment need not be stopped at age 60 or 10 years postmenopause; it can be continued safely for a longer time if meticulous surveillance is ongoing.

What about randomized, double-blind, placebo-controlled trials? To test the "critical period" hypothesis, three highly publicized intervention trials (WHIMS-Young,<sup>59</sup> KEEPS-Cog,<sup>52</sup> and ELITE-Cog) were performed to assess MHT's cognitive effects if initiated soon after menopause.



All three studies documented that MHT is neither beneficial nor harmful.<sup>59,52,62</sup>

Are there any RCT's using TD E2 which documented cognitive improvement? Yes, there are. ESTRADERM, in two separate studies with the same authors, published in 1996 and 2001, was compared to placebo in older ( $\geq 65$  years) PMP women. The studies assessed the ESTRADERM .05mg/d (1996)<sup>49</sup> and 0.1mg/d (2001)<sup>50</sup> patch's effect on cognition in PMP women with mild-moderate AD.

- ESTRADERM 0.05mg/d patch (1996) with steady-state serum E2 levels ranging from  $\sim 55\text{pg/mL}$ - $100\text{pg/mL}$ <sup>49</sup> significantly improved attention and verbal memory when compared to placebo. And verbal memory significantly correlated with E2 plasma levels
- ESTRADERM 0.1mg/d patch (2001) with steady-state serum E2 levels ranging from  $\sim 70$ - $200\text{pg/mL}$ <sup>50</sup> significantly improved semantic, verbal, and visual memory when compared to placebo

In both studies, there were no adverse events either during the treatment phase or during follow-up. Similarly, E2's cognitive benefits diminished when treatment was terminated.<sup>49,50</sup>

What about TD E2's cognitive effects in healthy PMP women without AD? In 2006 publications, the CLIMARA patch<sup>51</sup> and the MENOSTAR patch<sup>53</sup> were both evaluated in PMP women without dementia. CLIMARA's 0.05mg/d patch was studied to determine which cognitive domains TD E2 therapy influenced and whether hot flashes and sleep played mediating roles in these effects.<sup>51</sup> MENOSTAR's 0.014mg/d patch's effect on cognition over a two-year timeframe was assessed in the ULTRA study group.<sup>53</sup>

- CLIMARA 0.05mg/d in young, healthy, symptomatic, peri and PMP women significantly improved executive functioning when compared to placebo.<sup>51</sup>
- MENOSTAR 0.014mg/d in healthy, older,

predominantly asymptomatic, PMP women did not improve cognitive performance over a two-year timeframe when compared to placebo.<sup>53</sup>

An outstanding question that has yet to be addressed is whether the relationship between low E2 levels, cognitive decline, and AD is due to low E2's direct neuronal effects or its indirect effects on other systems, including the HPA axis and the immune system.<sup>63,64</sup>

Inflammation is the root cause of many chronic diseases, including cardiovascular disease, inflammatory bowel disease, and osteoporosis, to name a few. As a result, it is plausible that inflammation may mediate the relationship between low E2 and cognition and may very well be a missing link as to why the evidence is inconsistent and confusing.

### Compounded E2 Creams

For those using TD E2 compounded products, this paper will hopefully guide you. Start slow, test, do not guess, and proceed with meticulous, ongoing surveillance. The following about compounded creams may be helpful:

- Generally, creams tend to absorb less than alcoholic gels, so E2 0.25mg-0.5mg/d is a reasonable starting dose
- Limited serum data implies that serum E2 levels do increase with E2 doses  $<1.0\text{mg/d}$ , but levels are variable, increasing and decreasing quickly, making urine a better option for monitoring
- Saliva testing should not be used to monitor creams as results are highly variable and do not represent clinical impact.
- Doses which raise urine E2 values out of the PMP range, but lower than the luteal range (0.7-1.8ng/mg for DUTCH), align with results documented in TD E2 patch and gel products that demonstrate clinical success. For more on TD E2 laboratory monitoring, see PA's recent position paper.

## PUTTING IT ALL TOGETHER

The TD E2 story does not end here; it is always evolving. The large RCTs that studied synthetic hormones should not be used as a roadmap to guide patient care decisions. However, large RCTs with long follow-up are unlikely to be performed; they are too costly.

Every woman without contraindications may benefit from MHT without significant risk. Clinicians: consider counseling eligible women regarding MHT's risks and benefits. Eligible women would be wise to strongly consider MHT heading into menopause. Certainly, the closer to menopause onset the greater the benefits.

In women with a uterus, OMP is necessary to completely protect the endometrium. In all women, ongoing cardiovascular, endometrial, breast, and bone surveillance is a must. Treatment dose and duration, along with a risk assessment, should be individualized and monitored on a regular basis. A hormone practice is never "one size fits all."

Remember, women spend approximately one-third of their lives in menopause; there is no rush to get TD E2 dosing perfect when initiating treatment. High doses will potentially increase estradiol tissue exposure and adverse events. "Start low and go slow" to optimize estradiol's health benefits safely and effectively (VMS relief, VVA symptom relief, osteoporosis prevention, decreased cardiovascular risk, and improved cognition).

Finally, we look forward to future research investigating the viability of compounded TD E2 products and lower FDA-approved TD E2 doses, both with lower OMP doses, to determine the lowest effective doses and regimens that protect the endometrium and the breast, decrease menopausal symptoms, improve cognitive performance and cardiovascular outcomes, and, of course, doses and regimens that "do no harm."

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