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## Menopause & Estrogen Hormone Therapy

Updated: February 2019

The saga is finally over. Estrogen replacement therapy in the post-menopausal years of a woman's life is not only **safe**, it has clearly been shown to be **protective** for heart disease, breast cancer, colon cancer, dementia, osteoporosis and all causes of death.

For the past **17 years** women and healthcare providers alike have been paralyzed by fear that estrogen therapy increased a woman's chance of developing breast cancer and having heart disease. The Woman's Health Initiative (**WHI Study**) was published in **2002** (Ref. #1) and made front-page headlines around the world. The result: Over 40 million women in the U.S. alone stopped taking estrogen and entered "hot-flash hell". The **warnings** continue today: "estrogen is harmful" and "should only be used to treat severe menopausal symptoms and only for the shortest period of time". These messages come from our governmental health agencies, medical insurance companies, medical schools and medical residency programs (responsible for teaching physicians learning primary care, internal medicine and Ob-Gyn). The subsequent damage done to 10's of millions of women's health and their quality of life is immeasurable and cannot be undone, but it can be stopped.

In this article, I hope to clarify the confusion and myths surrounding menopause and estrogen hormone replacement. Further, I will explain the role of estrogen in reducing the risk of heart disease, stroke, breast cancer, osteoporosis and diabetes. I will outline the *evidenced-based* medical research that validates the importance and the safety of estrogen replacement therapy in women.

First, however, I would like to review some basic information about menopause and why estrogen is so important for the health of women during their post-menopausal years. **Menopause** is diagnosed when a woman ceases to menstruate for one year. This occurs as the result of the ovaries reaching the end of their ability to ovulate (for fertilization and pregnancy) and to produce the hormone, estrogen. The average age of menopause occurs at about 51 years, but can range from the early 40's to the late 50's. Over 2 million women reach menopause each year in the U.S. and this number will *double* in the next 25 years. It is important to note that the average life expectancy of women living beyond the onset of menopause did not occur until after the 1920's. For example, the following is the average life expectancy of women born in:

**1920:** 51 yrs.    **1930:** 61 yrs.    **1960:** 74 yrs.    **2010:** 80 yrs.    **2018:** 81 yrs.

**Peri-menopause** is diagnosed when a woman still has menstrual cycles, but they vary in frequency and length and may be associated with psychological, emotional and/or physical symptoms (discussed later). These symptoms or disturbances are directly due to declining ovarian production of estrogen, progesterone and testosterone. This lowering of her blood estrogen levels may be periodic or continuous and is why many women who are "still menstruating" can be estrogen deficient and experience menopausal symptoms.

**Menopause** or '**post-menopause**' has been a significant health issue for **only the past 75 years** and is due to the fact that today a woman's life expectancy extends well beyond her ability to procreate.

History reveals how menopausal aged women were viewed and treated in the past by both their culture and the medical establishment. For example, in 1686 in Salem, Massachusetts 14 women were executed for being 'witches' (known as the famous Salem Witch Trial); 13 were of menopausal age. It wasn't until 1821 that a French physician coined the term 'menopause' and called it a "condition". In 1872 the English medical society classified menopausal women with mood and memory problems as having "incurable dementia".

A moving testimonial (that continues to be all too common today) can be read on my website:  
[www.gordongunnd.com](http://www.gordongunnd.com): “*Estrogen and My Sense of Well-Being*”.

### A Brief History of Estrogen:

- 1930:** Germany: Estrogen discovered in pregnant mares’ urine and found to improve menopausal symptoms.
- 1942:** Ayerst received a patent and FDA approval for Premarin (estrogen) use for hormone therapy (ERT)
- 1965:** “Feminine Forever” published by Dr. Robert Wilson extolling the benefits of estrogen by preserving youth, beauty and a full sex life for menopausal women.
- 1977:** Medical journal reports of possible link between estrogen and breast cancer and uterine cancer.
- 1990’s:** Over 90% of women in their 50’s in the U.S. with a hysterectomy were taking estrogen. It was the ‘**standard of care**’ in the U.S. **Estrogen** (primarily, Premarin) was the most frequently prescribed drug in U.S. and reached \$1 billion in sales.
- 1991:** National Institutes of Health (NIH) launched the **Women’s Health Initiative (WHI) Study**.

### Women’s Health Initiative (WHI) Study.

A brief review of the WHI Study is important because of the overwhelming impact it has had on women in the free world since 2002. The WHI Study was funded to the tune of one billion dollars was designed to test the effect of postmenopausal estrogen and progesterone hormone therapy, (along with diet, calcium and Vitamin D) on a women’s future risk of heart disease, bone fractures, stroke, breast cancer and colorectal cancer. The investigating authors (including countries outside the U.S.) enrolled **161,808 “healthy”** postmenopausal women between the ages of 50-79 years and who were not taking hormones when they entered the study.

When the WHI Study was launched in 2001 by the National Institutes of Health (“NIH”), women enrollees were randomly assigned to one of three groups (or arms).

1. **Estrogen alone** (Premarin) (E Arm); these patients had a prior hysterectomy
2. **Estrogen+Provera** (medhydroxyprogesterone) (E+P Arm); patients still had their uterus
3. **Placebo** (P Arm) – received no hormone

However, there were **significant flaws in the study’s design** (learned after publication):

- The authors generalized their conclusions, applying them to all women and their recommendations implied that all the study participants had just entered menopause when they enrolled, which is far from the truth. In fact, the average age of the women selected for the Study was **63 years!!** - 12 years AFTER menopause had occurred. Further, the **fact** is only **10%** of the Study participants were under the age of 60 yrs. when they entered the study. The physical changes and resulting health damage to the estrogen dependent tissues of a woman’s body (due to the absence of estrogen for 12 years) had already occurred.
- The Study’s 161,808 participants were **NOT** representative of **healthy women**:
  - 70% were seriously **overweight** (34%) or **obese** (35%)
  - 36% were under treatment for **hypertension** (high blood pressure)
  - Nearly 50% were either current or past **smokers**

**Then, in 2002** the WHI Study was suddenly stopped by a few of the researchers (unbeknownst to many of the investigators involved in the research effort) and reported *their* initial conclusions in the Journal of the American Medical Association (JAMA) (Ref. #1). Their report immediately made the headlines of all the news agencies throughout the world: “**Estrogen Linked to Invasive Breast Cancer and Heart Attacks**”.

The authors reported their primary conclusions after comparing both the *Estrogen Arm* and the *Estrogen+Provera Arm* to the *Placebo Arm* as follows:

- **(E+P) Arm:** had a slight increased risk of heart disease, stroke, blood clots, and breast cancer.
- **(E alone) Arm:** had a slight decreased risk of breast cancer (this was not reported at the time) and colon cancer and osteoporosis, no benefit on heart attacks and a slight increased risk of stroke and blood clots.
- “**These findings apply to all women, regardless of age or health status**”

The wide spread reports in the “**Breaking News**” **Headlines** were understandably interpreted by women around the world: ***Estrogen caused an increased risk of invasive breast cancer and heart attacks.***

What both the **Authors** of the WHI Study and the **Media *failed to clarify*** was this initially reported increase in risk occurred **ONLY** in the (E+P) Arm, but **NOT** in the Estrogen Arm. It was the synthetic progesterone (Provera) that initially appeared to be associated with this small increase (not statistically significant and later proved to be false). Note: *Provera* (brand name for medhydroxyprogesterone) is a synthetic progesterone and remains today FDA approved. Bio-identical progesterone was not commercially available in the 1990’s.

What was also neglected by the media and was **NEVER** clarified by the reporting authors was that the estrogen alone (E) Arm had a decreased incidence of both breast and colon cancer and osteoporosis and had a neutral effect on heart disease events. [Remember: the average age of these women was 63 years when they entered the Study; the damage to arteries was already well underway.]

**NOTE:** I will point out later in this article that, in fact, estrogen therapy when started in the peri-menopausal years, significantly **DECREASES** (by up to 40%) the risk of heart disease, stroke **AND** breast cancer, along with all-cause mortality!!

The impact of the WHI Study and the media’s handling of this news in 2002 resulted in “*Hot Flash Hell*” and it occurred throughout the free world. **Fear** caused women to stop their HRT. **Uncertainty** caused physicians to stop prescribing hormones. Within two years the rate of estrogen and hormone prescription refills in the U.S. decreased from 61 million in 2001 to 21 million in 2004 – an estimated decrease of 40 million women. It was a tsunami of panic from which the resulting disaster is only now beginning to slowly recover.

### **What has been the Long-Term Impact of the 2002 WHI Study Report?**

There is a generation of women from 2002 to 2019 who have purposely avoided or been denied hormone therapy as a result of fear, uncertainty and misinformation. Since 2002 the medical teaching institutions, governmental health agencies and medical insurance companies’ position have taken (and continue to take) is: ‘HRT is harmful, causes breast cancer and heart disease and should only be used for severe menopausal symptoms and only for the shortest period of time’. The **impact** of this de-facto denial of estrogen usage by the medical establishments is illustrated in a **2013** mathematical analysis of the WHI Estrogen (E) Arm. The authors concluded: “Between the years 2002–2011 among women aged 50-59 in the U.S., who were denied and not treated with ERT, there was an excess of 18,600 to 91,600 deaths that might have been avoided!

### **In 2017 Two Paradigm Shifts Occurred About Estrogen’s Role on Long-Term Health of Women?**

#### **July 2017:**

**NAMS** (North America Menopause Society) published their “**NAMS 2017 UPDATED POSITION STATEMENT ON HRT**”. The lead author (JoAnn Pinkerton, MD, Executive Director of NAMS and Professor of Obstetrics and Gynecology, University of Virginia) stated the following:

- “Their (NAMS) prior 2012 Position Statement on HRT is **NOT Valid**”,
- Further, “the concept of the lowest dose HRT for the shortest period of time was **inadequate or even harmful** for some women”
- “the use of hormone replacement therapy (HRT) for menopausal and postmenopausal women guarantees to make healthcare providers and the women they treat **more comfortable using HRT**, when women want it to improve their quality of life”.
- “For women, younger than 60 years or who are within 10 years of menopause onset and have no contraindications, the benefit-risk ratio of hormone therapy is **most favorable** for treatment of:
  - ❖ Bothering VMS (hot flashes and night sweats)
  - ❖ Elevated risk for bone loss or fracture
  - ❖ Longer durations of hormone therapy should be for documented indications, persistent vasomotor symptoms or bone loss”.

- What About Older Women over 60 years of age and the Extended Use of HRT?
  - ❖ “When HRT is initiated in women who are 10 or more years out from their menopause or when they are 60 years of age or older, the benefit/risk ratio of HRT is less favorable than it is for younger women”.
  - ❖ “Once women discontinue HRT, there is a 50% chance that vasomotor symptoms (“VMS”) will return, regardless of their age or how long they've been using it. Thus, extended use of HRT may be expected to continue to relieve persistent VMS”.
  - ❖ "With discontinuation of HRT, virtually all women will lose bone-mineral density, with increased risk of bone fractures and excess mortality from hip fracture”.
  - ❖ “Moreover, there is **no evidence to support discontinuation of HRT after the age of 65**”.
  - ❖ "Decisions about longer duration of therapy should be individualized ...with shared decision-making, documentation, and periodic reevaluation.”
  - ❖ “Risks of longer use of HRT may be minimized with lower doses of both estrogen and progestogens, the use of transdermal therapies to avoid hepatic (liver) first-pass effect, or the combination of conjugated estrogen paired with the SERM bazedoxifene (Duavee), which down-regulates and protects the lining of the uterus (endometrium) without the need for a progestogen.”.
- What About Hormone Therapy for **BRCA 1/2** Carriers?
  - ❖ In women who carry the BRCA 1/2 mutation, both of which place them at very high risk for breast and ovarian cancer: “Observational studies suggest that hormone therapy **does not alter their risk** for breast cancer any further in women with a family history.”
  - ❖ In BRCA-positive women without breast cancer who have undergone pre-menopausal risk-reducing removal of her ovaries:
    - “Observational data suggest that systemic HRT ..... may **decrease** health risks associated with premature loss of estrogen **without increasing breast-cancer risk.**”

## September 2017:

The second article was published (in JAMA) by the authors of the original WHI Study of 2002, in which they updated their findings. They NOW stated (and without any apology):

“NEITHER the estrogen alone (E) Arm, **NOR** the estrogen+progesterone (E+P) Arm, were associated with ANY increase in all-cause mortality OR cause-specific mortality, including cardiovascular disease mortality, cancer mortality and other major causes of mortality after 18 years of follow-up!”

## So, Why in 2019 are the Medical Establishments, Governmental Agencies and Insurance Companies still ‘Out of Touch’ regarding HRT in Women?

- ❖ **Ignorance!!** A recent report by NAMS illustrates this fact. In 2016-2017 NAMS conducted a continuing medical education (CME) program, enrolling 34,501 physicians, nurse practitioners, and physician assistants who worked in an Ob-Gyn setting. JoAnn Pinkerton, MD, executive director of North American Menopause Society presented the following results at the NAMS Annual Meeting on October 11, 2017:

The findings:

- Pre-testing revealed that an average of ONLY 50% of the participants had an accurate understanding of the WHI Study data and the appropriate use of HRT for postmenopausal women.
- After completion of the study program, post-testing achieved a passing score of just 70%.
- 30% of practitioners still lacked an understanding of the usage, benefits and options of HRT – after taking the course!

COMMENT: It is my opinion that women who seek information and guidance regarding menopause and hormone replacement should not delay in consulting with their physician or other healthcare provider. Women need and deserve accurate and unbiased information from their physicians who should respect and support their health patients’ decisions. Women are the ultimate decision makers regarding their health, not the healthcare professionals. If they do not receive the information and support, they are requesting, they should consider finding another provider.

➤ **Denial.**

COMMENT: In spite of all the reported observational and random controlled studies available in 2019 the governmental agencies, insurances companies (including Medicare), and the medical professional teaching institutions in the U.S. still do not endorse the safety and benefits of estrogen therapy in post-menopausal women. Even the available and revalidated proven research data do not seem to alter the ingrained negative beliefs about ERT. Nietzsche is quoted as stating: “convictions are more the enemy of the truth than lies”.

It is my position that as a physician responsible for the health and well-being for my patients, I have the responsibility to continue to learn, educate my patients as to what the unbiased body of evidence shows and then support whatever decision they make.

**Why is Estrogen So Important in Women’s Health?**

Estrogens directly influence the normal body functions in all mammals, including humans. Estrogen works by attaching to *estrogen receptors* located on the surface of the cells of all normal tissues in the female body. This influences the function of all these cells and is primarily important for, but not limited to:

- Reproduction
- Cardiovascular Health
- Bone Integrity
- Cognition
- Behavior
- Fat metabolism
- Estrogens are ALSO implicated in numerous diseases, many of which occur after menopause and the absence of estrogen, including:
  - Various types of cancer: Breast, Ovarian, Colorectal, Prostate, Endometrial
  - Osteoporosis
  - Neuro-Degenerative Diseases: Stroke, Parkinson’s Disease, Alzheimer Disease
  - Insulin Resistance & Type 2 Diabetes
  - Lupus Erythematosus
  - Endometriosis
  - Obesity

**What are the Common Symptoms of Menopause?**

- **Vasomotor:**
  - Hot flashes
  - Perspiration and night sweats
  - Role of Blood Brain Barrier (See next page)
- **Physical:**
  - Palpitations
  - Vaginal dryness and irritation / dyspareunia
  - OAB symptoms & frequent UTI’s
  - Skin changes
  - Joint pain
  - Muscle pain
  - Dry eyes
  - Fatigue
- **Cerebral (Brain): \***
  - Irritability
  - Lethargy – lack of mental or physical energy
  - Anxiety



- Mood Swings
- Difficulty Concentrating
- Short-Term Memory Loss
- Insomnia
- Depression
- Decreased Libido \*\*

\* Estrogen deficiency may or may not be the only cause of any of these symptoms listed. Each woman is uniquely different and during the perimenopause her symptoms are often a moving target. I will discuss my approach to the management of the perimenopause later in this article (see Addendum II).

\*\* Comment: The issue of a decrease in *libido* or sex-drive during the peri-menopause or menopause is common and may be associated with declining levels of testosterone (which is also produced by the ovary). Additionally, a decrease in libido is often a reflection of less frequent intimacy in a marriage or relationship. It is often associated with a women's feeling that she has "insufficient time for herself" and of being "too tired" to even think about sex. A conversation regarding re-establishing "sex" as a priority and setting aside time for intimacy is very important for an emotionally healthy relationship. Intimacy does not always require the act of intercourse for a woman to feel fulfilled. A blood measurement of the testosterone level may suggest, if a trial of replacement therapy may improve libido.

## What are the Benefits of Estrogen Replacement in Women Who Experience Symptoms? Relief!!

- Vasomotor Symptoms – Hot Flashes & Night Sweating **gone**
- Sleep Disturbance (REM sleep **improved**)
- Anxiety/Depressive Symptoms (**improved**)
- Cognition & Short-Term Memory Loss (**improved**) "*Windex to My World*" = Mental Clarity
- Atrophic Genital/Vaginal Changes (**improved**)
- Lower Urinary Tract (bladder infections, incontinence, over-active bladder) (**improved**)

## Why Do Some Women Escape Symptoms of Menopause?

There is evidence that a "brain-estrogen threshold" may govern the presence or absence of symptoms. Women with a lower brain-estrogen threshold may not experience any symptoms, while a high brain-estrogen threshold (requiring higher blood estrogen levels to access the brain) is associated with early and severe symptoms. Further, symptoms may be increased by too much, as well as too little, estrogen, fluctuations in circulating estrogen levels or from side effects of progesterone. This is why hormone replacement therapy must be individualized for each patient. One size does not fit all women.

## What Does Long Term (>20 years) Estrogen Research Reveal About the Following:

- Cardio-Vascular Disease (CVD) / Heart Attacks – **Decreased by up to 40-50%** (Ref. #24)
- Stroke – **Neutral to slight Decrease** (Ref. WHI Study)
- Type II Diabetes – **Decreased** (Ref. WHI Study)
- Breast Cancer – **Decrease of 21- 40% with ERT** (Ref. #23)
- Colorectal Cancer – WHI: **Slight Decrease** (Ref. WHI Study)
- Endometrial Cancer – **Preventable** w/ progesterone or bazedoxifene (*Duavee*)
- Ovarian Cancer – WHI: **Neutral to slight Decrease** (Ref. WHI Study)
- Osteoporosis (Bone Loss & Fracture) - **Decrease** (Ref. WHI Study)
- Blood Clots– Increase only with oral estrogen; **None with transdermal estrogen** (Ref. WHI Study)
- Dementia & Alzheimer's - **40-50% Decrease** (Ref. #26 thru #35)
- All-Cause Mortality - **30-60% Decrease** (Ref. #23)

## What are the Contraindications to ERT or HRT?

- **Absolute contraindications** include any recent cardiovascular event, suspected pregnancy, or undiagnosed abnormal vaginal bleeding. The presence of thrombophlebitis, severe liver disease, active gall bladder disease, a history of deep vein blood clots or pulmonary emboli would require a non-oral route of administration of estrogen.
- **Relative contraindications** include a personal history of breast cancer or endometrial cancer, depending on the stage and status of the disease.

While these contraindications may be controversial, initiating ERT or HRT may be still be appropriate in selected patients. Physicians need to consider and treat the ‘whole woman’. If a woman on ERT or HRT develops any of these events, it is safe to temporarily discontinue her therapy, while considering the severity of any recurring menopausal symptoms. NOTE: The minimal increase in blood clots associated with oral administered hormones is not present with *non-oral* estrogen use; such as transdermal (skin) applications (patch, gel or cream), vaginal estrogen rings or tablets, pellet injection or by subcutaneous injection. Reason: The non-oral route of estrogen use bypasses the liver and therefore, does not trigger any small potential *genetic risk* for blood clots.

## In Summary:

### ➤ **Short Term Benefits:**

Menopausal hormone therapy (ET or EPT) is the only 100% effective treatment for vasomotor and atrophic symptoms due to ovarian failure during the post-menopausal phase of life. Symptoms frequently recur when ERT/HRT is stopped at any age.

### ➤ **Long Term (> 20 Years) Benefits:**

The current evidence testifying to the importance and safety of estrogen replacement therapy when a woman enters her perimenopausal years is irrefutable. “The 10-Year Window” maximal benefit theory is clear. Women should be completely reassured that making the decision to start and remain on ERT/HRT is truly in their best short-term and long-term health interests.

- Menopause is a natural phenomenon that occurs in all women when their ovaries cease functioning about the age of 51 years.
- Absence of ovarian function results in a loss of circulating estrogen, progesterone and testosterone that can cause physical, emotional and mental changes and symptoms. The absence of estrogen **will result** in certain reversible and irreversible physical changes and increased risks of multiple diseases and all-cause mortality, as discussed in this article.
- Estrogen is important to the emotional, mental and physical well-being of a woman’s life after menopause.
- ERT and HRT have statistically been shown to be safe and protective after 20 years of use.

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## ADDENDUMS:

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## ADDENDUM I

### When a Patient Considers HRT, What Do I Recommend?

#### Treating Menopausal Symptoms:

Estrogen is the only effective therapy for eliminating significant vasomotor symptoms (hot flashes, night sweats, palpitations), vaginal atrophy (thinning of the vaginal wall), painful intercourse, over-active bladder symptoms and frequent urinary tract infections. Estrogen may also improve many of the symptoms due to changes in the brain metabolism, including those listed on page 2, A. 3. If any of these symptoms are interfering with the quality of a woman's life, a trial of ERT should be strongly considered. Unless a woman has had a hysterectomy, estrogen should usually not be taken without progesterone to protect against uterine cancer.

#### What is a Patient's History Regarding?

- Prior Hysterectomy?
- Prior Cancers?
- BRAC 1 or 2 Carrier?
- Endometriosis
- Date of Last Menstrual Period
- Heart or Vascular Disease & Metabolic Risks (e.g. Diabetes)

#### Patient Creates Her Symptom List (from list reviewed in the main article).

List all symptoms under these three categories (pages 5-6), plus any other symptoms not listed.

- Vasomotor
- Physical
- Cerebral

\*After a trial of estrogen replacement and specific menopausal symptoms are controlled this list is used to separate estrogen from non-estrogen causes of her symptoms, if any remain.

#### Vulva-Vaginal Atrophy – Treatment Options:

- Vagifem – 10 mg. tab inserted vaginally
- Vaginal Estrogen Cream – Premarin, Estrace
- Estring – vaginal estradiol (2 mg) – replace every 3 months
- DHEA Ovules – Pasterone (Intrarosa) – converts to intra-cellular estradiol
- SERM - Ospemifene (Osphena) – 60 mg oral tab
- Lubricants: Replens, Sylk

#### Pharmaceutical (Prescription) Estrogen –Trial of Estradiol (E2) Options:

- Oral: Premarin (conjugated estrogen), Estrace (Estradiol),
- Trans-Dermal:
  - Patch: Alora, Climara, Estraderm, Estradiol Patch, Vivelle, Vivelle-Dot
  - Gel: Estragel pump
  - Spray mist: Evamist spray
    - Trans-Vaginal Ring: FemRing (0.05 & 0.1 mg), q 90 days
    - Injectable:
- Pellet: sub-Q insertion, local anesthesia, lasts 3-5 months
- Depo-Estradiol: lasts 3-4 weeks

#### Initial Dosage of Estrogen:

- Low dose transdermal estradiol (0.5 mg) is used initially
- Symptom improvement with 'List' highlighted - reviewed after 1 month



- Dosage is slowly adjusted higher until identified vasomotor symptoms are 100% controlled
- Brand vs Generic – is usually a matter of \$\$\$
- Continuous vs Cyclical dosing with progesterone – depends on if a woman is still menstruating

**Progesterone** (Usually required, if the uterus is present or the patient has history of endometriosis)

- Oral, Trans-dermal, Trans-vaginal gel or suppository, IUD (Mirena, Liletta, Skyla)
- Continuous vs cyclical dosing with estrogen
  - Brand vs Generic vs Compounded
- Dosage: Increased as level of estrogen dose is increased

**SERM's – Selective Estrogen Receptor Modulator**

- Agonist (positive) vs antagonist (negative) effects on estrogen receptors at cellular level of all the body organs and tissues.
- Bazedoxifene (Duavee) – FDA for HRT with intact uterus
- Tamoxifen – FDA approved for breast cancer
- Raloxifene (Evista) – FDA approved for osteoporosis

**Testosterone**

- FDA approved for men; NOT for women
- Compounded testosterone available for low blood levels of total and free testosterone

**Medications:**

- Anti-Depressants:
  - SSRI: paroxetine (Paxil)
  - SNRI: venlafaxine (Effexor)
- Gabapentin
- Clonidine (Catapres)

**List of Supplements (that may help with the milder symptoms only of menopause):**

- Isoflavones:
  - Phytoestrogens (Soy) (e.g. Estroven) - hot flashes, night sweats, vaginal dryness
  - Red Clover - hot flashes, night sweats
- Black Cohosh - hot flashes, night sweats
- St. John's Wort - mild depression

**Alternative Therapies for Menopausal (Vasomotor and Emotional) Symptoms**

For many women concerns about taking estrogen prompt them to rely on 'natural' alternative medicines to improve or control their symptoms. Estradiol is the primary estrogen produced during the reproductive-aged women. *Phytoestrogens* are naturally occurring in plant substrates and are functionally similar to a weak form of estradiol. It is important to recognize that all steroid hormones are derived from three major plant sources: soybeans, Chinese cactus needles and Mexican yams, with the exception of conjugated estrogens (Premarin). Therefore, these products are all natural. The issue with over-the-counter remedies is the absence of any quality or potency control. These 'natural' products are completely unregulated regarding their safety. Further, there are no reliable studies that have demonstrated that these alleged remedies for mild symptoms are giving any protection for the tissues and disease prevention discussed previously.

## Role of Compounding Pharmacies for HRT Therapy

The WHI study used an oral estrogen (Premarin), which has now been proven to be safe and protective. The progesterone (Provera) the study used was synthetic (not bio-identical) and was associated with a small increase in breast cancer risk. Bio-identical estrogen and bio-identical progesterone have a molecular structure that is *identical* to those produced by the ovary and has the same action at the receptor sites of the body's tissues. It is important to note that in this day of generic pharmaceutical drugs (obtained at local or web pharmacies) the purity and actual amount of a hormone may not always be what the label states, even though it is 'FDA approved'. There is a lack of regulation of FDA-approved bio-identical hormones prepared by compounding pharmacists. Currently, there are about 8000 pharmacies in the U.S. that compound medications. All 50 states have a Board of Pharmacy that licenses pharmacies within its State. While any pharmacy may compound non-sterile preparations of drugs the standards vary greatly and are generally unregulated. If a patient is going to use a compounding pharmacy for her medication, then I would recommend selecting a pharmacy accredited by the Pharmacy Compounding Accreditation Board (PCAB). The PCAB currently accredits about 200 pharmacies in the U.S. for quality assurance standards that ensure that medications (tablets, capsules, gels and creams) contain exactly what the label states. Web link: [www.pcab.org/consumers](http://www.pcab.org/consumers).

### In Summary:

- Compounding pharmacies are Not FDA regulated
- State Pharmacy Boards license and regulate pharmacies
- Licensing is required for sterile (injectable) products vs non-sterile (topical or oral) products
- Accreditation is voluntary:
  - United Credentialing and Accreditation Program (UCAP) is administered by the National Association of Boards of Pharmacy - NABP
  - Accreditation Commission for HealthCare (ACHC)
- Allows for individualization in hormones used and dosage variability
- Usually not covered by medical insurance companies
- Formulations:
  - **Estrogen:** Estradiol (20%) + Estriol (80%); cream or gel – referred to as 'Bi-Est'
  - **Progesterone:**
    - Oral: Micronized progesterone (Prometrium) passes via liver and metabolized to 4-allopregnanolone, a positive modulator at GABA receptor, which produces a sedative effect, improving sleep.
    - Trans-dermal: Not metabolized to 4-allopregnanolone and to benefit on sleep
  - **Pregnenolone:**
    - A neuro-steroid and is metabolized to progesterone;
    - Pregnenolone (25 mg) usually combined with DHEA (5-10 mg); oral admin.
    - Used as mood stabilizer and improve sleep and immune system; ? effect on anti-aging
  - **Testosterone:**
    - Women: Dosage – 1, 2, 4 mg; gel or cream
    - Indicated with a low total and free testosterone
  - **DHEA:**
    - Metabolizes to estradiol and testosterone
    - Role in anti-aging and immunity
    - Dosage: 5, 10, 25 mg. (higher doses may cause acne)

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## ADDENDUM II

### Additional Information on the Risks & Benefits of Estrogen Therapy

I continually engage and encourage my patients to take charge of their own health. My Longevity Program at [www.gettheearthhealthytoday.com](http://www.gettheearthhealthytoday.com) and Lifestyle Articles at [www.gordongunmd.com](http://www.gordongunmd.com) provides guidance to find the right combination of nutrition, exercise, meditation, sleep, prescription and targeted nutritional supplements to create a foundation for longevity, while improving mood, strength, energy, and sense well-being.

**April 2011:** The Journal of the American Medical Association (JAMA) published a follow-up study of the women in the WHI study who took estrogen alone and the incidence of breast cancer. (Ref. #3) The finding: a statistically significant reduction of 23%. Further, those women who did develop breast cancer were 63% less likely to die from their disease. There was NO increased risk for heart attack, stroke, blood clots, hip fracture and colon cancer.

**2012 Review of the WHI Study (Ref. #23):** Confirmed these finding and reported a 60% reduction in the mortality from *all-causes* of death. The North American Menopause Society (NAMS) has released a statement that supports these findings, stating, “combination hormone therapy (both estrogen and progesterone) initiated around the time of menopause is safe”.

**May 2013:** The British Menopause Society published their updated review and concluded (1) HRT should be individualized, (2) arbitrary limits should not be placed on the duration of usage, (3) HRT prescribed before the age of 60 years of age has a favorable benefit/risk profile, and (4) “It is imperative that women with premature menopause are encouraged to use HRT. (Ref. #25) This was re-enforced and published in 2014 in the ACOG Practice Bulletin No.141 (Ref. #33)

### Preventing Osteoporosis:

*Osteoporosis* is a disease in which the bones become extremely thin and porous and are subject to fracture, especially the spine, hip and forearm. *Osteopenia* is a less severe form of osteoporosis. According to the National Osteoporosis Foundation, osteoporosis is reaching epidemic proportions in the United States. An estimated 10 million Americans have osteoporosis and an additional 18 million have osteopenia. Bone mineral density (‘BMD’) decreases rapidly in women within 5 years of entering menopause and is measured by a simple DEXA screening of the spine and hips. This loss of bone density is directly due to estrogen deficiency, placing woman at an increased risk for osteoporosis and bone fracture. Numerous clinical research studies have demonstrated the benefits of ERT & HRT with a significant increase in BMD in both the hip and spine and a significant reduction in the incidence of fracture. The American College of Obstetrics and Gynecology has indicated that estrogen is the first-line therapy for the prevention of osteoporosis. When estrogen is contra-indicated, alternatives to estrogen can help prevent and treat bone loss (osteopenia and osteoporosis) of the spine, hip and total body. Refer to my article entitled **Osteoporosis** for further discussion and options for treatment.

### Cancer:

#### A. Breast Cancer

The majority of women still believe that breast cancer is the leading cause of death in the United States for women aged 65 years and older. In reality, it is responsible for less than 4% of deaths. The risk for invasive breast cancer increases with age and with a positive family history. For woman who have reached their 90’s, the incidence approaches 12%. Importantly, however, is that early detection of breast cancer has resulted in a cure rate of over 95% in women. The long-term follow-up of the women in the WHI study indicates an actual statistical decrease in the risk of breast cancer in those who were on ERT for over 20 years. Further, in those women who did develop breast cancer and used ERT there was a 63% higher survival rate than those women who had not used estrogen.

## B. Cancer of the Uterus (Endometrium):

The lifetime risk of cancer of the endometrium in a woman reaching the age of 85 and who is not taking estrogen is 2.7 percent. Studies have shown that women who take estrogen alone have up to a three-fold increased risk of developing endometrial cancer. If progesterone is combined with the estrogen, there is essentially no increased risk. Since patients who are on ERT or HRT are closely monitored by their physicians, any potential abnormality is usually found before it becomes an actual cancer. If a woman has had a hysterectomy, there is no risk. Further, studies have demonstrated that the use of birth control pills during the reproductive period of a woman's life decreases the risk of endometrial cancer by about 50% for 15 yrs. after stopping the pill.

## C. Cancer of the Ovary:

Cancer of the ovary is called the *silent killer*, because it produces no symptoms until it has reached an advanced stage. Every year, about 23,000 U.S. women are diagnosed with ovarian cancer and 14,000 women die from this disease. A woman's lifetime risk of developing ovarian cancer is 1.7 percent. This means that in a group of 100 women followed from birth to age 85, fewer than two would get ovarian cancer. In comparison, 12 women would get breast cancer, and 32 would develop osteoporosis. The WHI study did not find any increased risk in ovarian cancer. Studies do suggest that the use of birth control pills during the reproductive years decreases the risk of cancer of the ovary by 40-80%, and this decrease persists for at least 15 yrs. after discontinuance of the pill.

Currently, there are no specific screening tests for ovarian cancer. A blood test called a CA-125 is used as a tumor "marker" in a woman who has been previously treated for ovarian cancer. Ova-1 is a blood-screening test used in patients at risk for ovarian cancer. These are not *routine* screening tests. Neither are they specific for cancer, as the CA-125 may be elevated from other diseases, and it may be normal in the presence of early cancer of the ovary. Early detection of ovarian cancer is most frequently found by pelvic ultrasound.

## Blood Clots:

Blood clots in the veins are called *venous thrombosis*. If the clot becomes dislodged and travels to the lungs, the condition is called *venous thrombo-embolism* or VTE and can be fatal. The initial results of the WHI study showed a slight increased risk with estrogen alone and a slightly higher risk with progesterone. However, the follow-up review of the WHI did not show any increased risk in women who only used estrogen. Further, multiple studies have established that there is no increased risk of blood clots, when estrogen is given by a *non-oral route* described above.

## Heart Attack and Stroke

After menopause, the risk of heart disease and stroke slowly increases and by the age of 60 the risk equals that of men. This increasing risk is attributed to the loss of the beneficial effects of estrogen on cholesterol levels, distribution of body fat, blood coagulation, insulin sensitivity and a decrease of in the health of the arterial walls. This increased risk is not present in women who begin ERT in the early phase of their menopause. The initial and long-term follow-up results of the WHI study showed a decreased incidence of heart attack in the estrogen alone group. Women who took estrogen for at least 5 years had a 64% reduction in their coronary artery calcium score. Further, both the estrogen and the estrogen-progesterone studies reported a significant reduction in new cases of diabetes. More than 40 years of clinical trials and observational studies have reported on the cardiovascular protection from estrogen usage in post-menopausal women. The recent prospective study (Ref. #24) demonstrated a 50% reduction of cardiovascular disease events (heart attack, heart failure and stroke).

## Cognition, Dementia and Alzheimer's Disease

Cognitive decline is a nearly universal feature of aging. Starting at age 55, the hippocampus (the region in the brain critical to memory formation) shrinks 1 to 2 percent every year. It is estimated that 1 in 9 people age 65 and older has Alzheimer's disease. This number is expected to grow rapidly as the baby boom generation ages. The brain has remarkable neuroplasticity; that is, it can *remodel* and change itself in response to various experiences. Studies have demonstrated that memory training helps older subjects improve verbal reasoning. Further, physical exercise can also improve cognitive function and promote the creation and growth of neurons and new synaptic pathways for learning. A study was presented at the 2015 Alzheimer's Association International Conference held in Washington, D.C., which demonstrated that elderly patients with mild cognitive impairment (MCI) who completed a 12-week multidisciplinary brain

fitness program saw marked improvement in cognitive performance and enlargement in the size of the hippocampus. Key parts of this program included neuro-feedback, meditation, exercise, dietary changes and omega-3 fatty acids. The role of diet in being heart healthy is also going to be brain healthy.

Numerous studies have reported that estrogen therapy started early in the menopause period reduces short-term memory loss, improves cognitive thinking, and reduces the long-term risk of dementia and Alzheimer's disease, estrogen is started in women 15 years or more after menopause. A recent study from the University of Guelph, Ontario, Canada demonstrated that in female mouse brains infusion of estrogen caused an immediate increase in brain cell synapses (connections) located within the hippocampus. It further showed that these new connections remain silent unless they are used for learning. Learning tasks strengthened the connections, e.g. 'Use it or Lose it'. (Ref. #28-35)

Alzheimer Disease (AD) is the most common form of dementia, and it affects women more than men. One factor explaining this higher prevalence is that women have a longer life expectancy. A second factor may be the decline in estrogen that occurs with menopause. A recent prospective study published in 2017 showed a significant reduction in AD with hormone therapy. During a 20-year period, Finnish investigators sent questionnaires every 5 years to all women in their 40s and 50s who resided in a single province. National registry data was used to identify cases of AD. Among this cohort of over 8000 women, AD was diagnosed in 227 women. Although any use of hormone therapy (HT) was associated with a lower risk for AD compared with no use, this difference did not achieve statistical significance. However, **if** more than 10 years of HT was used, there was an associated statistically significant 40%-50% reduction in the incidence of AD. [Ref #34]

The findings of this Finnish population-based, prospective cohort study are congruent with those of a US study [Ref #35] that was conducted in a single county (Cache County) in Utah and used similar methodology. This study also reported that if initiated within 5 years of menopause and continued for more than 10 years, HT was associated with a reduced risk for AD.

The timing or 'critical window' hypothesis proposes that HRT exerts beneficial effects when initiated soon after menopause. Recent trials, including the Women's Health Initiative [Ref #36] and ELITE, [Ref #37] have provided evidence strongly supporting this timing hypothesis with respect to coronary heart disease and estrogen therapy. Importantly, these benefits cease when estrogen therapy is stopped.

## Longevity

Current evidence indicates that when estrogen therapy is started early and continued for over 20 years, women have a 60% overall lower mortality rate, primarily from a reduced incidence of heart attacks, stroke and complications from osteoporosis. Meta-analysis of the impact of HRT on longevity consistently indicates an additional 4 years.

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## ADDENDUM III

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