



EHS – POSITION STATEMENTS

Outlined below are statements that describe the official positions held by Evexias Health Solutions regarding numerous HRT-related topics. Each statement is followed by a list of citations from the medical literature. These citations, although not exhaustive, form the scientific foundation for each position. Complete references can be found in the alphabetical bibliography at the end of this document.

ARTICLE I. ESTROGEN:

SECTION 1.01 Estrogen – General Information

Edward Adelbert Doisy discovered the estrogens in 1923 and, soon thereafter, scientists learned to create similar, “look-a-like” molecules in the laboratory and synthetic hormones became prescription medications. Pharmaceutical companies bought up the patents and decades of controversy and confusion would soon follow.

- A. The conclusions drawn from the women’s health initiative trial have been generalized, misreported and mis-interpreted. Re-examination by an independent commission is justified and necessary.
 - 1) (Utian, 2012)
 - 2) (Brown, 2012)
 - 3) (Hersch AL, 2004)
 - 4) (Burger, 2003)

- B. New data accumulated in the USA and Europe indicate that, contrary to the data as it was published following the WHI trial, HRT regimens do not endanger the heart, but rather significantly reduce the incidence of cardiac related events and mortality. EHS teaches that estrogen has important cardiovascular functions including the regulation of vascular function, blood pressure and endothelial relaxation, and protection from hypertrophy and cardiac-related events.
 - 1) (Moskowitz, 2006)
 - 2) (Prentice, et al., 2013)
 - 3) (Sarrel, 2013)

SECTION 1.02 Estrogen and the Heart

The term heart disease refers to several types of heart conditions, including coronary artery disease and heart attack. Although heart disease is sometimes thought of as a man’s disease, almost as many women as men die each year of heart disease in the United States. One in five women will succumb to heart disease and it remains the number one killer in women.



- A. For women wishing to minimize their risk for heart disease and cardiovascular morbidity, EHS advocates the use of bio-identical estrogen replacement therapy to reverse atherosclerosis, decrease vascular inflammation and cardiovascular related death.
 - 1) (Spina, Bernacchi, Cecchi, Genazzani, & Simoncini, 2015)
 - 2) (Choi, Steinberg, Lee, & Naftolin, 2010)
 - 3) (Lobo R. P., 2016)
- B. The elite trial showed that post-menopausal women who started HRT within 3.4 years of reaching menopause versus 6 years from menopause had a 50% reduction in the rate of progression of atherosclerosis. EHS advocates for the start of HRT as close to menopause as possible to prevent and protect from progressive atherosclerotic CVD.
 - 1) (Hodis, et al., 2015)
 - 2) (Lobo R. , 2014)
- C. Women using HRT for a minimum of 10 years, have a decreased risk of cardiovascular, stroke and all-cause mortality. EHS advocates the use of HRT as a preventative strategy for bone loss, bone fractures, new onset type 2 diabetes and cardiovascular disease.
 - 1) (Tuomikoski, 2016)
 - 2) (Mikkola T. T., 2015)

SECTION 1.03 Estrogen and the Brain

In the United States, approximately 5.7 million people are living with dementia. Alzheimer's disease accounts for approximately 60%–70% of these cases, followed by vascular dementias. Similar to the global trends, these numbers are expected to rise as life expectancy increases. The number of adults living with dementia in the United States and other countries is expected to grow exponentially by 2050 (13.8 million).

- A. For women wishing to reduce their risk for age-related cognitive decline, memory loss and degenerative dementias, EHS advocates the use of BIHRT for prevention of amyloid deposition, inflammation and Alzheimer's disease.
 - 1) (Unfer, 2006)
 - 2) (Henderson, 2014)
 - 3) (Barron, 2006)
- B. HRT, particularly ERT, plays a protective role against neurodegenerative conditions such Alzheimer's disease and other forms of neurodegenerative decline. EHS advocates the use of ERT, especially within the first 5 years of menopause, for the prevention of cognitive decline.
 - 1) (Dye, Miller, Singer, & Levine, 2012)
 - 2) (Plamondon, Morin, & Charron, 2006)
- C. 17β -E2 acts locally and systemically as an immunomodulator and activates several neuroprotective pathways in the brain and inhibit pro-apoptotic peptides thereby offering protection from both ischemia and stroke. EHS endorses the use of 17β -E2 for neuroprotection in stroke and/or ischemia.
 - 1) (Sekhon & Agarwal, 2013)



2) (Petroni A. S., 2014)

D. The rapid discontinuation of post-menopausal estrogen therapy is associated with increased risk of cardiac and stroke death during the first-year post-treatment, especially in women less than 60 years. EHS endorses long-term use of HRT in post-menopausal women and judicious medical care in cases where HRT is stopped.

1) (Lee, et al., 2010)

2) (Rau, Dubal, Böttner, Gerhold, & Wise, 2003)

E. 17β -e2 offers long lasting effects on neuronal survival, learning and memory status ischemic and traumatic injury. EHS endorses the use of estrogen therapy for the prevention of and protection cognitive decline caused by ischemic neural damage.

1) (Hurn & Brass, 2003)

2) (Lebesgue, Chevalere, Zukin, & Etgen, 2009)

3) (Petroni A. R., 2015)

SECTION 1.04 Estrogen and Menopause

Menopause is a normal stage in a woman's life. A woman is considered postmenopausal once she has not menstruated for twelve consecutive months. As menopause nears, the ovaries gradually produce less estrogen, causing changes in the menstrual cycle and other physical changes. The most common symptoms of menopause are hot flashes, night sweats, emotional changes and changes in the vagina (dryness and atrophy or thinning of the vaginal walls).

A. The discontinuation of post-menopausal HRT in women increases the risk of cardiovascular disease, stroke and mortality. EHS advocates for long term use of post-menopausal estrogen therapy and cautions judicious follow up in patients where ERT is discontinued.

1) (Venetkoski, 2018)

2) (Salpeter, 2009)

3) (Cheung, 2010)

B. Post-menopausal women suffer from vasomotor, neuropsychiatric and genitourinary symptoms as a result of low estradiol levels. EHS advocates for estradiol replacement for the relief of symptoms related to the estradiol loss associated with menopause.

1) (Rivera-Woll, 2004)

2) (Woods, 2005)

3) (Pinkerton, 2017)

C. At menopause, ovarian production of estrogen ceases. Likewise, feedback inhibition of follicle stimulating hormone (FSH) ceases. FSH levels can be used to assess estrogen status in women. EHS advocates for the use of FSH levels (>20 = post-menopausal) to assess estrogen status in women.



SECTION 1.05 Estrogen and the Bones

Osteoporosis affects more women than men. Of the estimated 10 million Americans with osteoporosis, more than 8 million (or 80%) are women. Women lose more bone mass after menopause with very low levels of the hormone estrogen. Higher estrogen levels before menopause helps protect bone density. In the United States, osteoporosis affects one in four women 65 or older.

- A. Studies on bone mineral density (BMD) have demonstrated a 4-fold increase in BMD with estradiol pellet therapy versus oral estrogen therapy and a 2.5-fold increase in BMD with estradiol pellet therapy versus estrogen patch therapy. EHS advocates the use of estradiol pellet therapy in women (especially when combined with testosterone pellet therapy) for the prevention of osteoporosis and protection from age-related loss of BMD.
 - 1) (Studd, 1990)
 - 2) (Shea, 2015)
 - 3) (Greendale, 2003)

- B. Both natural and chemical suppression of estradiol results in the loss of bone. In contrast, estrogen therapy (especially when combined with exercise) provides significant protection from osteoporosis. EHS advocates the use of long-term estradiol replacement therapy in women for the prevention of osteoporosis and protection from age-related bone loss.
 - 1) (Chilibeck, 2007)
 - 2) (Gallagher, 2011)
 - 3) (Felson, 1993)
 - 4) (Saarelainen, 2016)

SECTION 1.06 Estrogen and the Breast

Except for skin cancer, breast cancer is the most common cancer in American women. Currently, the average risk of a woman in the United States developing breast cancer sometime in her life is about 12%. This means there is a 1 in 8 chance she will develop breast cancer.

- A. Numerous studies demonstrate the safety of 17β -estradiol even in breast cancer survivors. There is no evidence that it increases breast cancer recurrence or increases mortality from breast cancer. EHS believes that there is no evidence to support the universal withholding of estrogen in women who have survived low stage breast cancer.
 - 1) (Decker, 2003)
 - 2) (Levgur, 2004)
 - 3) (Natrajan & Soumakis, 1999)
 - 4) (Peters, 2001)
 - 5) (Natrajan P. G., 2002)

- B. Final analysis of the WHI trial implicates Progestins, and not CEE, in the increased risk for breast cancer. EHS sees no indication for the use of progestins in HRT.
 - 1) (Campagnoli, 2005)
 - 2) (Fournier, 2005)



3) (Wood, 2007)

ARTICLE II. TESTOSTERONE:

Section 2.01 Testosterone - General Information:

In 1939 the Nobel Prize for the synthesis of testosterone was presented to German scientist, Adolph Butenandt and Swiss scientist, Leopold Ruzicka. The earliest effective formulations came in the form of pellets and testosterone propionate (a daily injection). The medical journal, Endocrines, published the following by 1940:

“The drug testosterone is worthy of lengthy discussion, for when its use is indicated it is powerful and of considerable value. Indeed, in my experience this is one of the most potent drugs introduced to medicine.”

A. Testosterone is the most abundant active hormone in men and women. EHS recognizes testosterone replacement therapy as a safe and effective treatment for men and women.

1) (Gray, 1991)

B. Testosterone replacement therapy in men has been shown to improve erectile ability, build muscle mass, reduce anxiety and irritability, improve cognitive ability, reduce body fat, increase energy, lower cholesterol (increase HDL cholesterol), and offer protection of the heart, brain, bones and prostate. EHS recognizes that the etiology of androgen deficiency in men and women is multifactorial and likely consists of variable degrees of insufficient production, increase protein binding, reduced tissue responsiveness, decreased androgen receptor activity and impaired transcription and translation.

1) (Carruthers, 2008)

C. Androgen deficiency in men and women has been shown to be associated with increased risk of Alzheimer’s disease, cardiovascular disease, osteoporosis related fractures and diabetes type 2. EHS advocates the use of androgen replacement therapy for the long-term prevention of these ailments.

1) (Saad, et al., 2011)

2) (Buvat, 2013)

3) (Araujo A. E., 2007)

Section 2.02 Testosterone in Women

Most people think of testosterone as a male sex hormone, but everyone requires a certain amount. A woman’s testosterone levels naturally change throughout her life, her menstrual cycle, and even at different times of the day. A woman with low testosterone does not contain enough to help produce new blood cells, maintain sex drive, or boost levels of other reproductive hormones.



- A.** Female androgen insufficiency syndrome (FAIS) is a diagnosis made on the basis of symptoms of low libido, low sense of well-being and depressed mood in the setting of low free serum testosterone. EHS recognizes FAIS and advocates the replacement of bioidentical testosterone in these patients.
- 1) (Alexander, Dennerstein, Burger, & Graziottin, 2006)
 - 2) (Rivera-Woll, 2004)
 - 3) (Davison, 2005)
 - 4) (Davis S. T., 2001)
- B.** According to the Princeton consensus statement on FAIS, there is no established “normal” blood testosterone range. EHS teaches this fact and advocates for the use of testosterone replacement therapy in patients with symptoms of low testosterone in the setting of low free serum testosterone levels.
- 1) (Bachmann, 2002)
 - 2) (Davis S. D., 2005)
- C.** There is a positive association between low androgen levels in post-menopausal women and severe ICA atherosclerosis and higher androgen level have been shown to have a protective role. EHS advocates the use testosterone therapy in post-menopausal for the prevention of and protection from atherosclerotic CVD.
- 1) (Debing, 2007)

Section 2.03 Testosterone and the Bone

The most common sites of osteoporotic fracture are the wrist, spine, shoulder and hip. A hip fracture is one of the most serious consequences of falls in the elderly, with a mortality of 10% at one month and 30% at one year. There is also significant morbidity associated with hip fractures, with only 50% returning to their previous level of mobility and 10 to 20% of patients being discharged to a residential or nursing care placement. With hip fracture incidence rapidly rising, effective preventive therapies are needed.

- A.** There are androgen receptors in osteoblasts (cells key in bone formation), osteoclast (cells responsible for bone remodeling and resorption) and osteocytes (mature osteoblasts that lie within the matrix they laid down). Testosterone is known to play a key role in normal bone physiology. EHS advocates the use of testosterone replacement therapy as a component of good bone health and the prevention of osteoporosis.
- 1) (Notelovitz, 1987)
 - 2) (Tuck, 2009)
- B.** Studies demonstrate that estradiol, when combined with testosterone, has an additive effect on bone mineral density (BMD). EHS advocates the use of combined estradiol and testosterone pellet therapy in women for the prevention of osteoporosis and the protect from age-related decreases in BMD.
- 1) (Savvas, 1992)
 - 2) (Studd, 1990)
 - 3) (Fink, 2006)



Section 2.04 Testosterone and the Brain

Although both men and women can fall prey to depression, women are at greater risk for depression than men. Hormones and neurotransmitters share common pathways and receptor sites in areas of the brain linked to mood, particularly through the hypothalamic-pituitary-gonadal axis. It has been hypothesized that women presenting with episodes of depression associated with reproductive events (i.e., premenstrual, postpartum, menopausal transition) may be particularly prone to experiencing depression, in part because of a heightened sensitivity to intense hormonal fluctuations. (Journal of Psychiatry and Neuroscience).

- A. Testosterone therapy has been shown to promote myelin repair by reducing microglial activation, restoring synaptic protein expression and improving synaptic transmission. EHS recognizes the potential protection TRT may offer in demyelinating diseases.
 - 1) (Ghandour, 2014)
 - 2) (Hussain, 2013)

- B. Studies strongly support the positive effects of testosterone therapy in depression. Testosterone is believed to act directly through androgen receptors and via serotonergic transmission modulation. EHS endorses the use of testosterone therapy to improve well-being, mood and sleep.
 - 1) (Almeida, Yeap, Hankey, Jamrozik, & Flicker, 2008)
 - 2) (Booth, Johnson, & Granger, 1999)
 - 3) (Deneui, 2018)

Section 2.05 Testosterone and the Heart:

About 610,000 people die of heart disease in the United States every year—that's 1 in every 4 deaths. Heart disease is the leading cause of death for both men and women with Coronary Heart Disease (CHD) being the most common type of heart disease, killing over 370,000 people annually. As plaque builds up in the arteries of a person with heart disease, the inside of the arteries begins to narrow, which lessens or blocks the flow of blood. (CDC control and prevention).

- A. Low testosterone is associated with excess abdominal fat, loss of insulin sensitivity and atherosclerosis and is predictive of cardiovascular disease. EHS advocates the use of testosterone therapy in men and women for the prevention of and protection from cardiovascular disease.
 - 1) (Araujo A. D., 2011)
 - 2) (Ruige, 2011)
 - 3) (Malkin, C.J., Pugh, P.J., 2010)

- B. Low testosterone is an independent predictor of severity of coronary artery disease. Men given aromatiz-able testosterone show increased coronary artery blood flow, decreased coronary artery plaques and decreased coronary artery inflammation. EHS endorses the use of testosterone therapy for the prevention of and protection from coronary artery disease.
 - 1) (Gururani, 2016)
 - 2) (Jones, 2010)



- C. Baseline testosterone levels have been shown to be inversely related to cardiovascular, cancer and all-cause mortality. Testosterone therapy has been shown to reverse these risks. EHS endorses the use of testosterone therapy to reduce cardiovascular, stroke and all-cause mortality.
- 1) (Lucas-Herald, 2017)
- D. All-cause mortality, arterial stiffness is increased in men with low testosterone and type 2 diabetes. Testosterone therapy in these individuals has been associated with decreased obesity, fat mass, waist circumference, improved glycemic control and decreased mortality. EHS endorses testosterone therapy for the prevention of and protect from obesity, dm2 and metabolic syndrome.
- 1) (Brand, 2014)
- E. Low testosterone is independently associated with endothelial dysfunction. Androgens inhibit inflammatory activation of endothelial cells and the induction of their procoagulant and adhesive properties. EHS endorses the use of testosterone therapy for the prevention of and protection from endothelial dysfunction.
- 1) (Akishita, 2007) <https://doi.org/10.1291/hypres.30.1029>
 - 2) (Christiakov, 2018)
- F. Low testosterone is associated with increased insulin levels, fasting blood sugar levels, two-hour post-prandial glucose levels, triglycerides, total cholesterol and LDL cholesterol. EHS advocates testosterone therapy for prevention of and protection from cad, atherosclerosis, type 2 diabetes, metabolic syndrome and obesity.
- 1) (Pitteloud, et al., 2005)
 - 2) (Stanworth, 2009)
- G. In men with aromatase deficiency, low levels of HDL have been observed along with higher levels of LDL and triglycerides. Additionally, an association has been observed between elevated estradiol levels and a decreased risk of CVD in men. EHS advocates for very judicious use (if at all) of aromatase inhibitors in men.
- 1) (Tenover, 1992)
 - 2) (Fleta-Asin, 2007)
 - 3) (Kenney, 2002)
- H. Deficiencies of 25-hydroxy-vitamin D and/or free testosterone has been shown to increase both cardiovascular and all-cause mortality. EHS teaches that it is critical to test for and treat sub-optimal D3 levels.
- 1) (Nimptsch, 2012)

Section 2.06 Testosterone and the Breast

Testosterone is the most abundant biologically active hormone in women. Androgen receptors are located throughout the body including the breast. Testosterone's impact on overall health and quality of life, immune function, glycemic control, prevention of inflammation further support T (indirect) role in cancer prevention. Testosterone is essential for mental and physical health in women including breast cancer survivors. (Glaser, Dimitrakakis).

- A. Clinical and non-human primate studies suggest that androgens inhibit mammary cell proliferation and breast growth. This data suggests that androgens are breast protective. EHS endorses the use of testosterone plus anastrozole in breast cancer survivors.



- 1) (Dimitrakakis, 2009)
- 2) (Glaser, 2015)
- 3) (Hickey, 2012)

Section 2.07 Testosterone and the Prostate

“It took a generation to disabuse our simplistic notions about testosterone and prostate cancer. We have rediscovered the obvious. This provides a new opportunity to access the true potential of treatment of men with testosterone deficiency. Testosterone deficiency is common, important, and treatment provides benefits critical to men.”

- Abraham Morgentaler

A. High levels of circulating testosterone have not been associated with an increased occurrence of prostate cancer in patients with prostate cancer or in the general population. EHS teaches that testosterone therapy in men does not increase their risk of prostate cancer.

- 1) (Rhoden, 2004)

B. Multiple studies have shown an increased risk of high-grade prostate cancer in men with low testosterone. It is EHS' position that testosterone therapy does not increase the risk of prostate cancer and that patients with stable PSA level >2 years post treatment are eligible for testosterone therapy.

- 1) (Khera, 2014)
- 2) (Morgentaler, 2011)
- 3) (Pastuzak, 2013)

Section 2.08 Testosterone and Inflammation

According to the American Pain Foundation, 40 to 50 million Americans suffer from chronic pain. Low-grade chronic inflammation is now known to be a driver of most of our chronic degenerative diseases. Likewise, low-grade chronic inflammation, not associated with a known injury, is known to be the driver of much of our chronic pain. Low-grade chronic inflammation manifests itself both locally and systemically by releasing a variety of inflammatory mediators. Anti-inflammatory treatments are now recognized as safe and effective options for the treatment of chronic pain.

A. Decreased testosterone levels are linked to high risk of inflamed nociceptors and resultant chronic pain. EHS advocates the use of testosterone as a mandatory component in the treatment protocol for chronic pain.

- 1) (Koelling, 2010)
- 2) (Melchior, 2016)
- 3) (Tennant, 2010)

B. Deficient levels of testosterone have been linked to several chronic pain conditions such as PTSD, fibromyalgia and CPD. Testosterone therapy downregulates pain signaling and has shown to be an effective treatment option for chronic pain states.

- 1) (White, 2015)
- 2) (Aloisi, 2006) <https://doi.org/10.1016/j.yhbeh.2005.12.002>



ARTICLE III. PROGESTERONE:

Section 3.01 Progesterone – General Information

The modern history of progesterone begins in 1929 when Nobel Prize winner, Adolf Butenandt (who would later be a co-discoverer of testosterone), isolated a crystalline material with “high progestational activity” from the corpus luteum of laboratory animals. In 1930, W. M. Allen was able to demonstrate that this corpus luteal extract was key for the maintenance of pregnancy. Finally, in 1934, Butenandt would determine the pure crystalline form of progesterone by extracting it from several thousand liters of urine.

- A. Progesterone is a steroid hormone made by the human body. It is distinct from all other synthetic “progestins”. EHS advocates the use of progesterone replacement therapy as a safe and effective treatment in women.
 - 1) (Campagnoli, 2005)
 - 2) (Fournier, 2005)
 - 3) (Wood, 2007)
 - 4) (Holtorf, 2015)

- B. Progesterone (with or without estradiol) decreases the proliferation of breast tissue and cancer cells. “Progestins”, however, stimulate the proliferation of breast tissue and cancer cells. EHS endorses the use of progesterone as a breast protective therapy.
 - 1) (Gizard, 2005)
 - 2) (Foidart, 1998)
 - 3) (Asi, 2016)

ARTICLE IV. SPECIALIZED TOPICS:

Section 4.01 Specialized topics – General Information

Bio-identical hormone preparations are available in patches, creams, gels, rapidly disintegrating tablets, striants, pills, intra-muscular injections, sub-cutaneous injections and sub-cutaneous implants. The paucity of head-to-head comparison studies have made comparing the various modalities difficult. Likewise, “loose definitions” of hormones by investigators mandate careful interpretation of the literature.

- A. The steroid hormones, testosterone, estradiol and progesterone, have been shown in scientific studies to positively affect the brain, bone, heart, breast, prostate, pain and inflammation. EHS recognizes that these studies are limited by lack of consistent HRT modality studied, extrapolations are made across modalities, lack of comparison studies and experiential outcome data.



SECTION 4.02 Specialized Topics – Aromatase Inhibition

Aromatase is the rate-limiting enzyme involved in the biosynthesis of estrogens. It acts by catalyzing the conversion of testosterone (an androgen) to estradiol (an estrogen). Aromatase can be found in estrogen-producing cells in the adrenal glands, ovaries, placenta, testicles, adipose (fat) tissue, and brain.

- A. The aromatization of testosterone to estradiol in men is associated with an improvement of verbal memory. EHS advocates for extremely judicious use of aromatization blockade.
 - 1) (Cherrier, 2005)
- B. The aromatization of testosterone to estradiol in men is associated with an improvement of sexual function, libido and quality of life. EHS advocates for extremely judicious use of aromatization blockade.
 - 1) (Overmyer, 2014)
- C. Aromatase inhibition in men has been shown to decrease vascular reactivity, HDL cholesterol and to increase LDL cholesterol, triglycerides and cardiovascular risk. EHS advocates for extremely judicious use of aromatization blockade.
 - 1) (Fleta-Asin, 2007)
 - 2) (Bagatell, 1994)
- D. Aromatase inhibition in men has been shown to decrease bone mineral density, insulin sensitivity and increase abdominal fat. EHS advocates for extremely judicious use of aromatization blockade.
 - 1) (Burnett-Bowie, 2009)
 - 2) (Gibb, 2016)

SECTION 4.03 Specialized Topics – Erythrocytosis

Erythrocytosis is sometimes referred to as polycythemia, however, the conditions are distinct. From a purely technical point of view, Erythrocytosis is an increase in RBCs relative to the volume of blood. Polycythemia is an increase in both RBC concentration and hemoglobin, the protein in red blood cells that carries oxygen to the body's tissues.

- A. Erythrocytosis literally means erythro-: red, cy-: cell, -tosis: many – “too many red cells”. Polycythemia literally means poly-: many, cy-: cell, -themia: blood – “too many blood cells”. Polycythemia Vera is a blood dyscrasia associated with red blood cells that grow and mature independent of the hormone erythropoietin. Erythrocytosis (too many red cells) is a feature of the disease of Polycythemia Vera (sometimes called primary erythrocytosis) and, when present, is often treated with phlebotomy. The erythrocytosis seen with testosterone replacement (also known as secondary erythrocytosis) is associated with an increase in erythropoietin levels and rarely requires phlebotomy. EHS recommends basing the decision on whether to phlebotomize a patient on testosterone replacement therapy with an elevated hematocrit on both clinical and laboratory data. Patients that may benefit from phlebotomy may complain of weakness, tiredness, light-headedness, headache or shortness of breath.
 - 1) (Liesveld, 2018)
 - 2) (Spivak, 2002)



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