BIO-IDENTICAL HORMONE THERAPY

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This booklet contains numerous ideas to stimulate discussions regarding hormone therapy. We work together with other health care professionals and their patients to customize medications which meet each individual's specific needs.

Your questions are always welcome!

RETHINKING HORMONE THERAPY FOR WOMEN

The North American Menopause Society (NAMS) released its 2017 Hormone Therapy Position Statement, which has been endorsed by 52 agencies including the American Association of Clinical Endocrinologists, the American Women's Medical Association, and the Society of Obstetricians and Gynaecologists of Canada, and supported as an educational tool by the American College of Obstetricians and Gynecologists (ACOG). To quote the statement: "**Hormone therapy (HT) remains the most effective treatment for vasomotor symptoms (VMS) and the genitourinary syndrome of menopause (GSM) and has been shown to prevent bone loss and fracture.** ***The risks of HT differ depending on type, dose, duration of use, route of administration, timing of initiation, and whether a progestogen is used. Treatment should be individualized to identify the most appropriate HT type, dose, formulation, route of administration, and duration of use, using the best available evidence to maximize benefits and minimize risks*****, with periodic reevaluation of the benefits and risks of continuing or discontinuing HT. For women aged younger than 60 years or who are within 10 years of menopause onset and have no contraindications, the benefit-risk ratio is most favorable for treatment of bothersome VMS and for those at elevated risk for bone loss or fracture. For women who initiate HT more than 10 or 20 years from menopause onset or are aged 60 years or older, the benefit-risk ratio appears less favorable because of the greater absolute risks of coronary heart disease, stroke, venous thromboembolism, and dementia. Longer durations of therapy should be for documented indications such as persistent VMS or bone loss, with shared decision making and periodic reevaluation. For bothersome GSM symptoms not relieved with over-the-counter therapies and without indications for use of systemic HT, low-dose vaginal estrogen therapy or other therapies are recommended**."

Menopause. 2017 Jul;24(7):728-753.
The 2017 hormone therapy position statement of The North American Menopause Society.
https://www.ncbi.nlm.nih.gov/pubmed/28650869

In September, 2017, Manson *et al.* published an observational follow-up of approximately 98% of the 27,347 postmenopausal women aged 50-79 who were enrolled in two WHI randomized clinical trials between 1993 and 1998 and followed up through 2014. They concluded that among postmenopausal women, hormone therapy with estrogen plus progestin for a median of 5.6 years or with estrogen alone for a median of 7.2 years was not associated with risk of all-cause, cardiovascular, or cancer mortality during a cumulative follow-up of 18 years.

JAMA. 2017 Sep 12;318(10):927-938.

Arefa Cassoobhoy, MD, MPH, a senior medical correspondent for Medscape, interviewed JoAnn Manson, MD, professor of medicine at Harvard Medical School and Brigham and Women's Hospital in Boston, and lead author of the WHI. Dr. Manson shared the following perspectives:

- For women (below age 60) and closer proximity to onset of menopause (within 10 years), the absolute risks of heart disease, stroke, deep venous thrombosis (DVT), and breast cancer, related to hormone therapy, are lower.
- Women who are at greater risk for and have a higher frequency of hot flashes and night sweats are more likely to derive quality-of-life benefits from hormone therapy. Thus, the benefit-risk ratio becomes much better because of the lower absolute risk and the greater likelihood of deriving quality-of-life benefits.
- Transdermal hormone therapy has the advantage of avoiding first-pass liver metabolism, and therefore it's less likely to increase clotting protein or triglyceride levels and avoids some of the other concerns associated with the oral route of administration. The observational studies suggest that the risks for DVT, pulmonary embolism, and possibly even stroke are lower with the transdermal than the oral route. As of yet, there are no large-scale randomized trials doing direct head-to-head comparisons.
- The risk for cardiovascular events, both heart disease and stroke, will be greater in older women. If you are going to use hormone therapy in women who are more distant from the onset of menopause or who have significant risk factors such as diabetes or hypertension, it is preferable to go with the low-dose transdermal formulation rather than oral hormone therapy.
- In contrast to the vasomotor symptoms (hot flashes and night sweats), genitourinary symptoms actually progress over time. About 50% of women are seriously affected by these symptoms in terms of decreased quality of life, poor sexual health, and discomfort with sexual activity. Genitourinary conditions and also are associated with urinary tract infections and physical health. These symptoms are undertreated and under-recognized, and clinicians should ask about them because many women are very uncomfortable bringing up the subject. Low-dose vaginal estrogen is the most effective treatment and does not increase the blood level of estrogen above the usual postmenopausal range. In terms of the evidence base and the clinical trial data, there is no evidence of an increased risk for heart disease, stroke, DVT, dementia, or breast cancer with low-dose vaginal estrogen.
- Women with early menopause (either premature ovarian insufficiency or early surgical menopause)—who have an increased risk for heart disease, cognitive decline, bone loss, and osteoporosis - are particularly good candidates for hormone therapy.
- The WHI observational follow-up urges caution when considering initiating hormone therapy at an older age in women with diabetes, as these women are at the greatest risk for cognitive decline.

NAMS' New Hormone Therapy Position Statement: Clinical Takeaways
http://www.medscape.com/viewarticle/88408

The mortality toll of estrogen avoidance: an analysis of excess deaths among hysterectomized women aged 50 to 59 years.

Findings from the Women's Health Initiative (WHI) published in 2002 indicated a greater risk of breast cancer and coronary heart disease among women who used a combination of estrogen and progestin as menopausal hormone replacement therapy. In the WHI study arm that investigated the use of estrogen alone (no progestin in women who had hysterectomies), there was a decrease in the risk of breast cancer and heart disease, and a lower rate of mortality in comparison with women who received a placebo.

The backlash from widely publicized findings frightened many women and some physicians, and the use of hormone replacement therapy precipitously declined. Sarrel et al. of the Yale University School of Medicine, Yale University School of Public Health and University of Florence (Italy) Department of Public Health examined the effect of estrogen avoidance on mortality rates. They derived a formula to relate the excess mortality among hysterectomized women aged 50 to 59 years assigned to placebo in the WHI randomized controlled trial to the entire population of comparable women in the United States, incorporating the decline in estrogen use observed between 2002 and 2011. They calculated that **a minimum of 18,601 and as many as 91,610 postmenopausal women died prematurely because of the avoidance of estrogen therapy**. "Sadly, the media, women, and health care providers did not appreciate the difference between the two kinds of hormone therapy," commented lead researcher Philip Sarrel, MD. "As a result, the use of all forms of FDA-approved menopausal hormone therapy declined precipitously." He concluded that informed discussion between the women and their health care providers about the effects of hormone therapy is a matter of considerable urgency. “Essentially, estradiol inhibits the development of atherosclerosis and helps maintain normal arterial blood flow.”

Am J Public Health. 2013 Sep;103(9):1583-8.

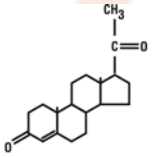
There are significant differences between hormones that are natural to humans (sometimes referred to as bio-identical) and synthetic (including horse) hormones that are not produced naturally by humans.

Side chains are added to a natural substance to create a synthetic product that can be patented by a manufacturer. A patented drug can be profitable to mass produce, and therefore a drug company can afford to fund research as to the medication’s use and effectiveness. Structural differences that exist between human, synthetic, and animal hormones may be responsible for side effects that are experienced when non-bio-identical hormones are used for replacement therapy.

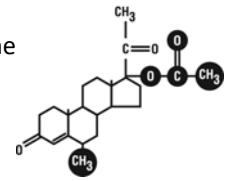
The term “bio-identical” does not indicate the source of the hormone, but rather indicates that the chemical structure of the replacement hormone is identical to that of the hormone naturally found in the human body. In order for a replacement hormone to fully replicate the function of hormones which were originally naturally produced and present in the human body, the chemical structure must exactly match the original. Bio-identical hormones are able to follow normal metabolic pathways so that essential active metabolites are formed in response to hormone replacement therapy. Examples of natural or bio-identical hormones include estradiol (E2), estriol (E3), progesterone, testosterone, dehydroepiandrosterone (DHEA), and pregnenolone.

The difference in chemical structure is obvious...

Progesterone USP (natural)



Medroxyprogesterone Acetate (synthetic)



Clarifying Confusing Reports

Hormone therapy can be a hot topic of discussion in women’s groups and among healthcare professionals. Unfortunately, many commentaries erroneously report the drugs which were used in various studies, failing to differentiate manufactured products from compounded hormones.

In response to a prescription from a licensed practitioner, compounding pharmacists prepare customized dosage forms containing the prescribed hormones in the precise dose for administration by the most appropriate route for a specific patient, using pharmaceutical grade chemicals from FDA-inspected facilities with certificates of analysis to verify purity.

The Women’s Health Initiative (WHI) study was designed to identify the potential risks and benefits of HRT, but evaluated only NON-bio-identical synthetic hormones. For women taking conjugated equine estrogen (CEE) alone, the WHI reported a slightly increased risk of stroke. For women taking the CEE+progestin (medroxyprogesterone acetate) combination, researchers found an increased risk of heart disease, breast cancer, stroke, blood clots, and dementia. Benefits of HRT noted in the WHI study include a decreased risk of osteoporosis -related hip fractures and colorectal cancer. The WHI's study population consisted of older postmenopausal women. Participants were an

average age of 63 at the start of the trial. A more complete analysis of data from the WHI suggested that there is a reduced risk of heart disease if women begin estrogen early in their postmenopausal years. The data analysis revealed participants age 50 to 59 who took estrogen experienced fewer heart attacks and deaths from coronary artery disease than study participants who took a placebo.

Progesterone was not investigated in the WHI study, which studied the progesterone analogue or "progestin" medroxyprogesterone acetate (MPA). MPA and progesterone both protect the uterus from the proliferative effects of estrogen, but their benefit and side effect profiles are quite different. Unfortunately, the terms "progesterone" and "progestin" are incorrectly used interchangeably, not only in the lay press but also by reputable medical journals and professionals, resulting in confusion.

Medical evidence ***does*** indicate that therapeutic benefits and side effects vary based on whether a hormone is administered orally or transdermally, and that "bio-identical hormones" may offer therapeutic advantages over non-bio-identical synthetic hormones. Studies have shown that synthetic progestins such as medroxyprogesterone acetate partially negate the beneficial effects on cholesterol levels that result from taking estrogen, while progesterone maintains the benefits of estrogen on lipid and cholesterol profiles and minimizes the side effects associated with MPA. Additional studies report that progesterone may enhance the beneficial effect of estrogen on exercise-induced myocardial ischemia in postmenopausal women (in contrast to MPA). On the other hand, clinical trials have reported that the risk of breast cancer is increased by long-term exposure to conjugated equine estrogens, and further increases when synthetic MPA is added to the regimen.

A decision about HRT is best made taking a broad, long term view of health goals, symptoms, and lifestyle. Smoking cessation, weight management, and exercise should be employed to reduce risk factors (such as high cholesterol and blood pressure) for heart attack or stroke. The decision to use any form of HRT should only be made following a thorough medical examination and evaluation of baseline hormone levels, and women receiving HRT should be regularly monitored to allow practitioners to use the lowest dose of hormones that will provide therapeutic benefit, thereby minimizing the risk of side effects.

When a physiologic balance is restored using bio-identical hormones such as estriol, estradiol, progesterone, and testosterone, many symptoms attributed to hormone decline can be eliminated. Based on results of laboratory tests, symptoms, and response to therapy, doses of individual hormones can be adjusted and administered in the most appropriate dosage form to meet each woman's specific needs, while minimizing the risk of side effects.

Customized Hormone Therapy for Women

Hormone related symptoms or problems occur throughout the feminine life cycle.

- Dysmenorrhea (cramps)
- Premenstrual Syndrome (PMS)
- Infertility/Endometriosis
- Irregular menstrual periods
- Fibrocystic breasts
- Premenopausal symptoms
- Weight gain
- Mood swings
- Reduced libido
- Vaginal thinning/Dryness
- Painful intercourse
- Hot flashes
- Night sweats
- Depression
- Poor concentration/Memory lapses
- Insomnia/Disturbed sleep
- Heart disease/Arteriosclerosis
- Osteoporosis

Goals of Hormone Therapy

- Alleviate the symptoms caused by the natural decrease in production of hormones by the body
- Restore the protective benefits which were originally provided by naturally occurring hormones
- Re-establish a hormonal balance

The three types of hormones typically prescribed for natural hormone therapy (HT) are estrogens, progesterone, and androgens. The precise components of each woman's therapy need to be determined after physical examination, medical history, and laboratory testing are considered. Close monitoring is essential to ensure that appropriate dosage adjustments are made.

Estrogens:

- estradiol (E2), and estriol (E3) are often prescribed in combination to re-establish a normal physiologic balance.
- relieve menopausal symptoms, including vaginal thinning and dryness.
- may increase HDL "good" cholesterol and decrease LDL "bad" cholesterol.
- help to decrease blood pressure and reduce plaque formation on the arterial walls.
- reduce the risk of colorectal cancer.

- may improve mood, energy levels, and sleep patterns.
- may reduce the risk of developing or the severity of type 2 diabetes.
- may improve memory and cognitive function.
- reduce bone loss.

The term "estrogen" actually refers to a group of related hormones, each with a unique profile of activity. Under normal circumstances, a woman's circulating estrogen levels fluctuate based on her menstrual cycle. For Hormone Replacement Therapy, these hormones are often prescribed in combination to re-establish a normal physiologic balance. The three main estrogens produced in female humans are:

- Estrone -E1- (10-20% of circulating estrogens) is the primary estrogen produced after menopause
- Estradiol -E2- (10-30% of circulating estrogens) is the most potent and major secretory product of the ovary, and the predominant estrogen produced before menopause. Estradiol is the primary estrogen of ovarian origin and the major form of estrogen in pre-menopausal women.
- Estriol -E3- (60-80% of circulating estrogens) is thought to be protective against breast cancer. Estriol causes little or no buildup of the endometrium (uterine lining), and is very effective in alleviating vaginal and urinary symptoms in postmenopausal women. Estriol has been shown to be clinically effective for the treatment of menopausal symptoms as well as postmenopausal problems including vaginal atrophy, dryness, vaginal infections, painful intercourse, and various conditions of the urinary tract. Estriol is produced in very large amounts during pregnancy and may be protective against breast cancer. High levels of estriol are found in vegetarians and Asian women, who have a much lower incidence of breast cancer.

Since women are living longer, on average 20-40 years after the end of the reproductive years, osteoporosis and heart disease may become more of a reality, not just a risk. One in two American women is at risk of fracture due to osteoporosis, and one in three women after the age of 65 develops heart disease. Risk factors include, but are not limited to, a decline in estrogen and progesterone levels, diet, genetics, and level of activity.

Heart disease is the most common cause of death in women in nearly all industrialized countries. It is believed that this is because the protective effect of naturally-occurring estrogens is lost in post-menopausal women, raising their cardiovascular risk to that of men. Estrogens appear to be cardioprotective, increasing HDL "good" cholesterol and decreasing LDL "bad" cholesterol. Estrogen has a relaxing factor in the smooth muscle cells which regulate the body's blood flow. This allows the arterial walls to remain flexible. The hormone also has the ability to inactivate nitric oxide (a substance present in the human body) which may help to decrease blood pressure and reduce plaque formation on the arterial walls.

Upon initiation of natural hormone replacement therapy, many women experience a significant improvement in energy levels, sleep patterns, memory and libido.

A study in the *Journal of the American Medical Association* found that post-menopausal women who take estrogen replacement therapy (ERT) have increased brain function and memory retrieval patterns. The activity that was observed is similar to that seen in the brains of younger women. While women were receiving ERT, magnetic resonance imaging (MRI) of their brains was obtained as they performed verbal and nonverbal memory tasks. The parts of the brain where increased activity was observed are associated with types of memory function that are required many times each day, such as recalling telephone numbers.

Reports suggest that ERT may reduce the risk of developing type 2 diabetes or may reduce the severity of the disease. A study of over 14,000 women of various ethnic backgrounds found that hyperglycemia was more often controlled by diet alone (no hypoglycemic medication) in women using ERT versus non-users. A survey of 418 postmenopausal women suggested that women who had never used ERT were nearly five times more likely to develop type 2 diabetes. Another report discussed the effect of ERT on the beta cells of the pancreas - where insulin is made. The beta cells appear to function more effectively in patients receiving ERT. It is quite important that diabetic patients receiving ERT have lipids monitored routinely, as ERT may raise plasma triglycerides.

Oral versus Transdermal Estrogen: Contrasting Effects on C-Reactive Protein

C-reactive protein (CRP) is one of the main independent predictors of cardiovascular events. Oral post-menopausal estrogen replacement therapy (ERT) increases CRP levels by a first-pass hepatic effect. These elevated levels of CRP may be responsible for the early increased cardiovascular risk that has been reported shortly after women begin oral combined hormone replacement therapy (HRT) *using NON bio-identical synthetic hormones*. However, transdermal 17beta-estradiol has shown no significant effect on CRP in either short-term or long-term use.

The incidence of ischemic heart disease shows a sharp rise after menopause. However, the effects of HRT on cardiovascular disease are still controversial. Kawano *et al.* compared the effects of HRT on endothelial function, cellular antioxidant system and inflammation between oral and transdermal administration in mild hypercholesterolemic postmenopausal women. Transdermal *bio-identical* estradiol replacement was administrated to 12 patients for 12 weeks, and oral conjugated equine estrogen was administrated to 12 patients for 12 weeks. The vasodilation of the brachial artery increased with HRT, and thioredoxin levels (a marker of the cytoprotective antioxidant system) decreased with HRT. CRP levels increased with oral HRT while transdermal HRT did not elicit any changes. Both oral and transdermal HRT improved endothelial function and decreased oxidative stress through affecting the cellular redox state.

Abbas *et al.* of the University of Texas, found that synthetic oral conjugated estrogens significantly increased levels of serum amyloid A (SAA), HDL, and HDL-SAA, whereas transdermal estradiol reduced both SAA and HDL-SAA but had no effect on HDL in the same women. They concluded that the effect was due to first-pass hepatic mechanism on oral estrogens.

The risk of venous thromboembolism (VTE) and cardiovascular disease (CVD) complications were evaluated and healthcare costs were assessed in menopausal women using an estradiol transdermal system versus oral estrogen therapy (ET). It was determined that transdermal ET users incurred lower adjusted all-cause and VTE/CVD-related healthcare costs relative to oral ET users and transdermal users also incurred lower healthcare costs.

At the University of Connecticut Health Center, a randomized, double-blind, placebo-controlled study evaluated the effect of 3 doses (0.25 mg/day, 0.5 mg/day, and 1 mg/day) of micronized 17beta-estradiol (E2) on CRP, interleukin-6, and lipids, compared with placebo, in healthy older women participating in an osteoporosis study, and found that after 12 weeks of treatment, CRP decreased 59% in the 0.25 mg/day E2 group and increased 65% in the 1 mg/day E2 group, compared with placebo. The CRP level continued to be elevated 12 weeks after treatment was discontinued in the 1 mg/day E2 group. HDL and HDL2 cholesterol increased and LDL cholesterol decreased at 12 weeks in the 1 mg/day E2 group, with a significant dose-response effect. Therefore, low-dose E2 decreased CRP, but did not affect lipid parameters, whereas the highest dose increased CRP and had a beneficial effect on lipid parameters. This study indicates that estradiol dose should be considered when risk:benefit ratios are evaluated for individual women before ERT is initiated.

A Finnish study reported that oral but not transdermal estradiol combined with cyclic NETA (synthetic progestin) increased hs-CRP levels. A placebo-controlled study of 27 healthy postmenopausal women showed that 12 weeks of oral but not transdermal estradiol (unopposed by progestin) was associated with an increase in CRP.

In another placebo-controlled study in healthy women using oral conjugated equine estrogens and transdermal estradiol (both with oral sequential medroxyprogesterone acetate), only oral treatment with *NON-bio-identical hormones* increased CRP during 6 and 12 months of therapy.

No published studies describe the effects on CRP produced by bio-identical estriol or a balanced ratio of bio-identical hormones. In conclusion, our review underscores the importance of customized HRT, using the hormones and route of administration that are most appropriate for each patient, while considering medical history and treatment goals.

Menopause. 2016 Jun;23(6):600-10.
Arterioscler Thromb Vasc Biol. 2004 Oct;24(10):e164-7
Maturitas. 2003 Dec 10;46(4):245-53
Thromb Haemost. 2003 Jul;90(1):124-31
Thromb Haemost. 2001 Apr;85(4):619-25
Int J Clin Pharmacol Ther. 2003 Aug;41(8):346-53
Hum Reprod. 2003 Apr;18(4):866-70
Am J Cardiol. 2003 Jul 15;92(2):212-4

Progesterone:

- is commonly prescribed for perimenopausal women to counteract “estrogen dominance.”
- alone, or combined with estrogen, may improve Bone Mineral Density.
- minimizes the risk of endometrial cancer in women who are receiving estrogen.
- is preferred by women who had previously taken synthetic progestins, according to one Mayo Clinic study.
- may enhance the beneficial effect of estrogen on lipid and cholesterol profiles and exercise-induced myocardial ischemia in postmenopausal women (in contrast to medroxyprogesterone acetate).

Progesterone vs. Progestins

Progesterone is a term that is incorrectly used interchangeably to describe both natural progesterone and synthetic substitutes. Synthetic progestins (also called progestogens or progestational agents) are analogues of bio-identical progesterone, and were developed because they are longer-lasting, more potent, and patentable. Medroxyprogesterone acetate, previously the most commonly used synthetic progestin, was shown in a large study to cause significant lowering of HDL cholesterol, thereby decreasing the cardioprotective benefit of estrogen therapy. Bio-identical progesterone has never been shown to have any serious side effects. However, progestins can have significant and serious side effects at typical doses, including migraine headache, weight gain, mood swings, depression, irritability, acne, menstrual irregularities, and fluid retention. These side effects are a frequent cause for discontinuation of HRT. Only about 20% of women who start synthetic HRT remain on it two years later.

Progesterone is commonly prescribed for perimenopausal women to counteract “estrogen dominance.” Perimenopause is the time between the onset of changes in hormonal secretions and menopause, and is characterized by fluctuating hormones. Estrogen dominance occurs when a woman produces smaller amounts of progesterone than normal relative to estrogen levels.

Progesterone therapy is not only needed by women who have an “intact uterus”, but is also valuable for women who have had a hysterectomy. Progesterone builds bone density, promotes glucose utilization, and improves sleep patterns and libido.

Both natural progesterone and synthetic progestins are members of a class of drugs known as progestogens. Progestins are derivatives which were developed prior to the availability of micronized progesterone to provide an oral preparation that could be patented, and therefore profitable to manufacture. Progesterone and progestins exert an antiproliferative effect on uterine endometrium in women who are receiving estrogen replacement. However, progesterone therapy is also valuable for women who have had a hysterectomy, as there are progesterone receptors throughout the body. Studies at Wake Forest University School of Medicine have concluded that bio-identical progesterone protects against vasospasm. In contrast, synthetic progestins partially negate the beneficial effects on cholesterol levels that result from taking estrogen, increase the progression of coronary artery atherosclerosis and the potential for development of clots and atherosclerotic plaques, promote insulin resistance and consequent hyperglycemia, and can significantly lower high density lipoproteins.

Since commercially-available progesterone capsules contain peanut oil, it poses a problem for individuals who are allergic to peanuts. Compounding pharmacies can prepare capsules that are free of peanut oil; however, oral progesterone is not well tolerated by some women, with side effects that include nausea, breast swelling, dizziness, drowsiness, and depression. Oral progesterone also undergoes a substantial amount of first-pass gut and liver metabolism, and metabolites such as allopregnanolone and deoxycorticosterone may be responsible for the side effects.

Transdermal progesterone cream has been widely prescribed as an alternative to oral progesterone and progestins.

Nature Medicine, 3(3): 324-7
J Am Coll Cardio March 1, 1997: 671-5
Br J Obstet Gynaecol 1984;91:1111-1119

Progesterone can be compounded using a micronized powder into an oral capsule, a lozenge or troche, transdermal cream or gel, vaginal or rectal suppository, or intramuscular injection. All of these dosage forms are available by prescription through our compounding pharmacy. There are a number of commercial progesterone creams available over the counter (without a prescription); however, these products vary considerably as to their actual progesterone content.

Natural Progesterone Can Slow Breast Cancer Growth

A large team of scientists have determined that unlike synthetic progestins which increase breast cancer risks, **natural progesterone has the potential to slow the growth of many breast cancer tumors or even *shrink* them**.

It has long been known that tumors with estrogen receptors (ER) and progesterone receptors (PR) (ER/PR double positive) have the best clinical outcome, but the interplay between the two proteins has remained elusive. Both are transcription factors, which means they are both involved in switching genes on and off. In a study published in Nature, July 2015, researchers from prestigious institutions including the Cancer Research UK Cambridge Institute; University of Adelaide, Australia; University of Texas, Southwestern Medical Center at Dallas; and University of North Carolina at Chapel Hill explain why double positive breast cancer patients have the best chance of survival. The finding could benefit up to half of all breast cancer patients.

Scientists know that when activated by most forms of estrogen – especially estradiol and its metabolites, estrogen receptors turn on genes within cancerous cells that program those cells to multiply rapidly and stay alive rather than die off as normal, healthy cells do. When activated by progesterone, progesterone receptors attach themselves to estrogen receptors. Once this happens, estrogen receptors stop turning on genes that promote the growth of the cancer cells. Instead, they turn on genes that promote the death of cancer cells (apoptosis) and stimulate the growth of healthy, normal cells.

Jason Carroll and colleagues of Cancer Research UK's Cambridge Research Institute grew breast cancer cells that displayed both ER and PR in the laboratory, and made sure the cells had enough estrogen and progesterone to bind to the receptors. They found that the receptor bound to different regions of DNA depending on whether progesterone was present. In other words, the PR (that had bound to progesterone) was changing the genes that the ER was switching on or off. In addition, the researchers saw that progesterone was associated with slowing cancer cell growth.

Following *in vitro* testing, the researchers ran tests on breast cancer tumors in live mice. After embedding ER positive/PR positive breast tumors in a number of mice, they exposed some of the mice to estrogen only, others to both estrogen and progesterone, and others to no hormones at all. After 25 days, the team found that while the tumors in the mice that received only estrogen grew, the tumors in the mice that received both estrogen and progesterone *decreased* in size.

Progesterone inhibited estrogen-mediated growth of $ERα^+$ cell line xenografts and primary $ERα^+$ breast tumor explants, and had increased anti-proliferative effects when coupled with an ERα antagonist. These findings indicate that PR functions as a molecular rheostat to control ERα chromatin binding and transcriptional activity, which has important implications for prognosis and therapeutic interventions.

The researchers pointed out that only natural, bio-identical progesterone slows the growth of breast cancer. Conversely, synthetic progestins (molecularly altered forms of progesterone) have been shown to increase rather than decrease breast cancer risks.

This is exciting news for women who are diagnosed with ER/PR positive breast cancers. If such women have healthy progesterone levels, or when progesterone levels are increased through natural progesterone supplementation, treatment outcomes may improve significantly. In their book *What Your Doctor May Not Tell You About Breast Cancer*, John R. Lee, M.D. and David Zava, Ph.D. noted that **women with progesterone levels that are low relative to estrogen levels are more likely to get breast cancer and have poorer treatment outcomes.** They concluded that estrogen dominance causes estrogen receptors to activate genes such as Bcl-2 that are known to promote the rapid growth of cancer cells. They theorized that chronic states of estrogen dominance contribute to high rates of breast cancer, and their theory has been validated with this latest research.

Hormonal imbalances have reached epidemic proportions in most developed countries over the last several decades. Due to poor diets, lack of exercise, a rise in obesity levels, the widespread use of hormone-altering chemicals, and other factors, many women suffer from chronically higher than normal estrogen levels and much lower than normal progesterone levels.

Ask our compounding pharmacist for more information about natural progesterone and the benefits of topical therapy. We work together with physicians and other practitioners and their patients to customize medications in the proper dosage to meet each patient's specific needs.

Nature. 2015 Jul 16; 523(7560): 313–317.
Pharmaceutical Journal, 2015 Jul 17; 14:53.

Estradiol and Natural Progesterone for Menopausal Hormone Therapy

Estradiol and progesterone are molecularly identical to endogenous hormones and are an option for women who prefer natural (bioidentical) hormones for the reduction of moderate to severe vasomotor symptom frequency and severity. Several formulations combining estrogens and progestogens for hormone therapy (HT) have been approved worldwide for the treatment of menopausal symptoms, yet recent data indicate a decline in their use and an increase in compounded bioidentical HT. Women with a uterus who take exogenous estrogen are prescribed a progestogen to prevent endometrial cancer. Progestogens such as micronized progesterone have been shown to inhibit endometrial hyperplasia related to unopposed estrogen stimulation. Published data suggest that estradiol and natural progesterone have a safer profile when compared to conjugated equine estrogens (CEE) and progestins such as medroxyprogesterone acetate (MPA).

Studies have shown that HT containing estrogen plus progesterone is better tolerated than HT containing MPA in terms of spotting/bleeding and quality of life. In a randomized 9-month study of women taking CEE plus either micronized progesterone or MPA, the progesterone group experienced fewer days of bleeding (4.3 vs 6.2 days) and less blood flow than the MPA group. This better bleeding profile observed with progesterone may be related to the effect of progestogens on several angiogenic factors in the glandular endometrium. *In vitro* studies in endometrial epithelial cells demonstrated that progestins, but not progesterone, may alter the balance between angiogenic promoters and inhibitors. These alterations with progestins could induce a unique pro-angiogenic activity in the endometrial capillary plexus, with consequent aberrant vasculogenesis, which may result in irregular endometrial bleeding.

In a cross-sectional study of 176 women who had previously switched from HT containing MPA to HT containing micronized progesterone, 71% had switched because of the better side effect profile, 35% because they believed the long-term risks would be fewer, and 23% because of intolerance to MPA. When evaluated at 1 to 6 months after switching, the women experienced significantly better quality of life, including less depression and anxiety, than with MPA. Patient satisfaction questionnaires also indicated that women preferred micronized progesterone over their previous regimen for better symptom control and fewer adverse effects. Sleep was significantly improved with no decreases in time spent awake after 6 months of CEE plus micronized progesterone but not with CEE plus MPA in a randomized study of 21 postmenopausal women tested in a sleep laboratory.

The type of progestogen can also influence the incidence of breast cancer. Observational studies have reported that oral estrogens plus micronized progesterone is less likely to increase breast cancer risk than oral estrogens with various synthetic progestins. A more detailed analysis of the E3N study showed estrogens plus dydrogesterone significantly increased lobular breast cancer and that estrogens plus other progestins significantly increased ductal, lobular, pure lobular and mixed ductal/lobular cancer, but that estrogens plus progesterone did not increase any of these breast cancer subtypes.

One reason for the use of synthetic progestins in the past was that effective absorption of oral natural progesterone was difficult to achieve. Studies have clarified that absorption is influenced by the vehicle used and progesterone particle size. Now, micronized progesterone which is well absorbed is readily available and can be compounded into various dosage forms to meet each woman's specific needs. Commercially available progesterone capsules contain peanut oil, a common allergen. Our pharmacy can compound hormones and other medications without allergens and other problem-causing excipients.

No single product combining natural estradiol and progesterone has been approved by the US Food and Drug Administration (FDA) or the European Medicines Agency (EMA) and therefore, these combinations must be compounded.

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Absorption and Efficacy of Combination of Hormones in a Vaginal Cream

Is a combination hormone-containing cream absorbed when applied vaginally for local and systemic symptom relief? A pilot study examined the extent of absorption of a single cream containing micronized estriol USP, micronized estradiol USP, micronized progesterone USP, micronized DHEA, and micronized testosterone propionate USP. A combination cream was administered to postmenopausal women in two differing doses over two independent time periods.

In the first arm of the study, patients were instructed to apply 0.25ml of cream to the mucous membranes of the labia and vagina each morning using their index finger, supplying a daily dose of estriol 0.5mg, estradiol 0.125mg, progesterone 25mg, DHEA 1.25mg, and testosterone 0.25mg. In the second arm of the study, patients applied 0.5ml of a cream containing estriol 0.5mg, estradiol 0.5mg, progesterone 50mg, DHEA 50mg, and testosterone 0.5mg. Following therapy for 28 days (arm 1), some women continued therapy for 14 additional days (arm 2) with higher doses. During arm 2, saliva was collected 6 hours after the cream was applied vs. 24 hours after application in arm 1, with documented absorption of all hormones in arm 2. Throughout the study, these parameters were measured: hormones in saliva and blood, symptom relief, patient tolerability, and health-related quality of life (HRQoL).

“Patients found the once daily, single cream, mucous membrane/vaginal method convenient and easy to use… Vaginal delivery of hormones provided relief of systemic symptoms along with relief of vaginal and urinary symptoms; 87% of patients in this study had genital urinary symptoms before therapy and all patients had relief of genital urinary symptoms with therapy at day 28.” In the second arm of the trial, one woman had complaints consistent with androgen excess and “the 50mg dose of DHEA was felt to be excessive”.

This study is the first documenting systemic absorption of multiple hormones by both saliva and blood as well as improvement of HRQoL. This therapy was generally well-tolerated with only 2 patients experiencing minor irritation. Additional studies in larger numbers of patients will provide better knowledge for clinicians wanting to provide similar therapy at the lowest effective dose.

Gynecol Obstet Invest. 2008;66(2):111-8.

Vaginal Estriol to Alleviate Symptoms of Urogenital Atrophy and Recurrent UTI

Recurrent urinary tract infections are a problem for many postmenopausal women. Estrogen replacement restores atrophic mucosa, lowers vaginal pH, and may prevent urinary tract infections. Ninety-three postmenopausal women with a history of recurrent urinary tract infections participated in a randomized, double-blind, placebo-controlled trial of a topically applied intravaginal estriol cream. The incidence of urinary tract infection in the group given estriol was significantly reduced as compared with that in the group given placebo (0.5 vs. 5.9 episodes per patient-year). Lactobacilli were absent in all vaginal cultures before treatment and reappeared after one month in 22 of 36 estriol-treated women (61%) but in none of the 24 placebo recipients. With estriol, the mean vaginal pH declined from 5.5 to 3.8.

To assess the efficacy and safety of intravaginal estriol administration on urinary incontinence, urogenital atrophy, and recurrent urinary tract infections in postmenopausal women, 88 postmenopausal women with urogenital aging symptoms were enrolled in this prospective, randomized, placebo-controlled study. Women in the treatment group received intravaginal estriol 1 mg once daily for 2 weeks and then 2 mg once weekly for a total of 6 months as maintenance therapy. After therapy, the symptoms and signs of urogenital atrophy significantly improved in the treatment group. Physicians observed significant improvements of colposcopic findings, and there were statistically significant increases in mean maximum urethral pressure, and in mean urethral closure pressure as well as in the abdominal pressure transmission ratio to the proximal urethra.

At Copenhagen University, Denmark, 251 postmenopausal women, with a mean age of 66 years, reporting at least one bothersome lower urinary tract symptom were treated with either an estradiol-releasing ring for 24 weeks; or estriol pessaries 0.5 mg every second day for 24 weeks. The two treatments were equally efficacious in alleviating urinary urgency (51% vs 56%), urge incontinence (58% vs 58%), stress incontinence (53% vs 59%) and nocturia (51% vs 54%). The practicing gynecologists concluded that vaginally administered estradiol and estriol are equally efficacious in alleviating lower urinary tract symptoms which appear after menopause.

Younger women taking oral contraceptives can suffer from similar symptoms. Thirty women (mean age 22.7 years) with a longstanding history of recurrent urinary tract infections received vaginal estrogen therapy consisting of 1mg estriol (E3) daily for two weeks and twice a week for two additional weeks. In the follow-up period of 11 months after treatment, 24/30 patients reported no symptoms of cystitis and used no additional medication. Normal bladder epithelium in control cystoscopy after estriol therapy was seen in all patients. Responsiveness to local estriol may correspond to improved cystoscopic findings as a consequence of increased bladder perfusion.

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Androgens, such as testosterone and DHEA:

- enhance libido
- enhance bone building (increase calcium retention)
- provide cardiovascular protection (lower cholesterol)
- improve energy level and mental alertness

Androgens are hormones that are important to the integrity of skin, muscle, and bone in both males and females, and have an important role in maintaining libido. DHEA (dehydroepiandrosterone) is an androgen precursor from which the body can derive testosterone. After menopause, a woman's ovaries continue to produce androgens; however, the majority of the androgens produced in the female body, even before menopause, come from peripheral conversion of DHEA. As the body ages, production of DHEA declines so that by the time a woman goes through menopause, the production of DHEA is often inadequate.

The addition of the androgens to a woman's HRT regimen can alleviate recalcitrant menopausal symptoms and further protect against osteoporosis, loss of immune function, obesity, and diabetes. Declines in serum testosterone are associated with hysterectomy, menopause, and age-related gender-independent decreases in DHEA and DHEA-sulfate. Additionally, ERT may cause relative ovarian and adrenal androgen deficiency, creating a rationale for concurrent physiologic androgen replacement.

The diagnosis of female androgen insufficiency syndrome (FAIS) is made on the basis of clinical signs and symptoms and low levels of bioavailable testosterone. Clinical symptoms of FAIS may include decreased libido and sexual pleasure; a diminished sense of well being; dysphoric mood and loss of motivation; and persistent unexplained fatigue. Signs include bone loss, decreased muscle mass and strength, and adipose tissue redistribution. Although FAIS remains formally undefined, there is evidence of potentially therapeutic effects of androgen replacement on overall well being, mood, sexual function and bone health in women with low testosterone levels.

The androgens found in women in descending order of their concentrations include dehydroepiandrosterone sulfate (DHEAS), dehydroepiandrosterone (DHEA), androstenedione, testosterone (T), and dihydrotestosterone (DHT). Both the ovaries and adrenal glands produce androgens, and levels are at least partially regulated by pituitary hormones. Precursor hormones are also converted peripherally. Because androgens affect many organs including the musculoskeletal and central nervous systems, androgen replacement therapy can have numerous beneficial effects. There is a need for formulations of testosterone therapy specifically designed for use in women, along with clear guidelines regarding optimal therapeutic doses and long-term safety data.

In women, serum androgen levels decline about 50% between the ages of 20 and 40 years, due to the gradual reduction in adrenal androgen production and the loss of cyclical ovarian androgen. Unlike estrogen levels, testosterone levels do not change significantly at menopause, but decrease at a gradual rate throughout a woman's lifetime. Only 1% to 2% of total circulating testosterone is free and biologically active. The rest is bound by sex hormone-binding globulin (SHBG) and albumin. Women with pituitary or adrenal insufficiency or premature ovarian failure, or those who have a surgically induced menopause also have reduced androgen production. Various drugs - such as corticosteroids, thyroid hormone, and oral estrogens—may decrease circulating androgen levels. Increasing levels of estradiol increase SHBG and decrease testosterone levels, exacerbating testosterone deficiency syndromes. Conditions that have been associated with androgen insufficiency include anorexia nervosa, rheumatoid arthritis, SLE, or HIV infection.

Estrogen therapy in menopausal women improves vasomotor symptoms, vaginal dryness and general well being, but has little or no benefit for low libido. However, in women suffering from dyspareunia secondary to atrophic vaginitis, estrogen replacement may improve libido secondary to relieving vaginal symptoms. Testosterone has vasomotor effects, enhancing vaginal blood flow and lubrication.

Androgen therapy should be combined with estrogen therapy since estrogen up-regulates androgen receptors, thus facilitating androgen expression; estrogen may also modulate the adverse effects of androgens. The optimal replacement dose of estrogen that should be given with androgen treatment is difficult to predetermine. This may depend on the amount of endogenous estrogen produced in a given individual and will differ between surgically and naturally menopausal women, as the ovaries continue to be an important source of androgen after menopause. Also, in older and obese postmenopausal women, there is an increased peripheral aromatization of androgen to estrogen.

Androgens also play an important role in bone physiology. Aromatization of androgens within bone to estrogen is important for maintenance of bone mineralization. In postmenopausal women, androgen levels are positively correlated with bone mineral density (BMD), and low bioavailable testosterone is associated with vertebral osteoporosis.

It is essential that women have adequate estrogen levels prior to androgen replacement in order to avoid the unwanted side effects of unopposed androgens. Therefore, a woman must be premenopausal with a regular menstrual cycle, or postmenopausal and receiving estrogen, prior to commencing T therapy. If circulating levels of free T are kept within the normal physiological range, masculinizing effects are very unlikely. Contraindication to testosterone therapy include pregnancy and lactation, androgen-dependent neoplasia, severe acne, hirsutism, androgenic alopecia, and a history of polycystic ovary syndrome.

The safety and efficacy of testosterone therapy depend on the dose and type of androgen used in the formulation, duration of treatment, and route of administration, all of which significantly affect the blood levels that are attained. In general, injectable testosterone is not recommended because of the associated peaks and valleys and potential for steroid accumulation. Currently available commercial preparations of oral micronized testosterone are poorly absorbed. Hepatic side effects of androgen therapy in women are predominantly associated with the use of high doses of oral methyltestosterone (MT) and other 17-alkylated derivatives. Oral androgens decrease HDL cholesterol concentrations significantly, whereas transdermal or implanted androgens appear to be lipid neutral. However, testosterone implants often result in supraphysiological dosing in women, increasing the risk of adverse effects. Transdermal testosterone formulations have become well accepted in the treatment of testosterone deficiency in men and are currently being developed in appropriate strengths for women. Both oral and parenteral administration of androgens appear to have extremely different effects on markers of cardiovascular risk.

Hormones sold over-the-counter (OTC) as dietary supplements vary widely in actual content from the strength stated on the label. Because the pharmacokinetics and pharmacodynamics of both estrogen and androgens vary with their formulation, ***women should only use hormones from a trusted source. Our compounding pharmacy prepares hormones in prescription strength exactly as ordered, using an analytical balance to measure each drug.***

Women who choose to receive androgen therapy should be aware that data on safety and efficacy are limited, and that the success of therapy will depend not only on the preparation, but the knowledge and experience of the health care team. Quoting Morris Notelovitz, MD, Ph.D., MB BCh, FRCOG, ***"the skill and art of medical practice is to know when and how to apply validated scientific observations to the needs of the individual patient."***

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HORMONE REPLACEMENT FOR MEN

Knowledge and attitudes regarding the existence of and treatments for andropause - the "male menopause" - have recently undergone a revolutionary change. Andropause may consist of a variety of signs and symptoms, including:

- weakness
- fatigue
- reduced libido
- osteoporosis
- heart disease
- atherosclerosis
- irritability
- insomnia

Hypogonadism is a clinical condition in which low levels of serum testosterone are found in association with specific signs and symptoms, including diminished libido and sense of vitality, erectile dysfunction, depression, anemia, reduced muscle mass and bone density, increased fat mass, frailty, osteopenia, and osteoporosis. When hypogonadism occurs in an older man, the condition is often called andropause, or Androgen Deficiency of the Aging Male (ADAM). Epidemiological studies associate increased morbidity and mortality with low testosterone states in aging males.

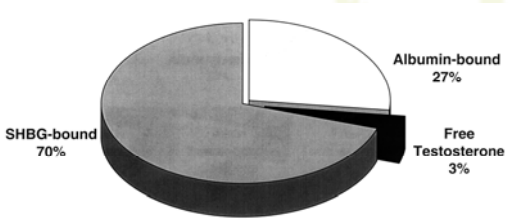
Increasing lifespan has resulted in a steady rise in the proportion of older men. The number of men in the United States ≥ 65 years of age is projected to increase from 14.5 million in 2000 to 31.3 million in 2030. Some men may actually go through a rather sudden change in testosterone levels that might correlate with the hormonal changes that women experience at menopause. However, most men have a more slow and subtle hormonal decline, experiencing the same symptoms over a period of time. On the average, a man's testosterone levels begin to decline at a rate of 1% per year after age 40. Approximately 5% of men 40 to 50 years of age, 30% of men 60-70 years of age, and 70% of men 70-80 years of age have low free or bioavailable testosterone levels.

Testosterone levels decline for a variety of reasons:

- Testosterone-producing Leydig cells begin to die off.
- SHBG (Sex Hormone Binding Globulin) increases with age, binding more hormone and decreasing the amount of bioavailable testosterone (the portion that can be used by the body).
- There is more estradiol but less LH (luteinizing hormone) reaching the testes, so less testosterone is produced.

Clinical symptoms of androgen deficiency should be verified by laboratory studies. Total serum testosterone levels quantify testosterone that is both bound and unbound (free). Blood or saliva testing is necessary to determine an individual's testosterone levels and to establish the need for testosterone replacement therapy. Testosterone replacement therapy is only recommended for men whose testosterone levels are low. Screening for parameters related to potential risks of androgen therapy should be performed prior to the initiation of treatment. Evaluation should include a history of or potential for sleep apnea, arrhythmias, significant symptoms of benign prostatic hypertrophy (BPH) or personal or family history of prostate carcinoma, a physical exam and laboratory testing including PSA.

When ordering serum testosterone levels, clinicians should be aware that the results can be influenced by obesity, serum albumin, serum sex-hormone binding globulin (SHBG), interacting drugs and diurnal variations. Because serum levels of SHBG increase with age and obesity, the decline in levels of non-SHBG-bound testosterone (bioavailable testosterone) is often much greater than the decline in total testosterone levels. Testosterone (T) that is bound to SHBG is not necessarily active, so although total serum T may appear normal, the amount of active T may be low. Therefore, it is important to measure free or "Bioavailable Testosterone" (BT), which represents testosterone that is physiologically active.



TOTAL VS. BIOAVAILABLE TESTOSTERONE

Bioavailable Testosterone = Free + Albumin-Bound

Hypogonadism is defined as **bioavailable testosterone** less than 60 ng/dl. Concentrations of total and free testosterone decrease in aging men, with a larger decline in available free testosterone in tissues. A man may be considered hypogonadal at any age if **total testosterone** is less than 200 ng/dl. If only Total Testosterone is studied, about 5% of men are hypogonadal. Because serum levels of SHBG increase with aging, the decline in levels of non-SHBG-bound testosterone (bioavailable testosterone) is often much greater than the decline in total testosterone levels. Basaria and Dobs of Johns Hopkins University recommend that elderly men with symptoms of hypogonadism and a total testosterone level <300ng/dl should be started on hormone replacement. When hormones are replaced or restored back to physiologic levels considered normal for younger males, men may experience a dramatic reversal of many of the changes caused by aging.

The diagnosis of hypogonadism is made based on the presence of signs or symptoms and confirmed by laboratory testing, which should include:

- Total testosterone
- Bioavailable testosterone (Free plus Albumin Bound)
- Estradiol
- Cholesterol

Goals of Testosterone Replacement Therapy in Adult Hypogonadal Men (≥50 years)

- Improvement in psychological well-being and mood
- Improvement in erectile dysfunction
- Improvement in libido
- Increased muscle mass
- Increased strength and stature
- Preservation of bone mass
- Possible decrease in cardiovascular risk

Natural Testosterone Replacement is Central to the Treatment of All Facets of Andropause.

The term "testosterone" is often used generically when referring to numerous synthetic derivatives, as well as natural bio-identical testosterone. The confusion surrounding testosterone transcends the lay person; it is responsible for conflicting data in the medical literature about the benefits and risks of testosterone therapy. Studies must be reviewed carefully to determine the form of testosterone that was used. Natural testosterone must not be confused with synthetic derivatives or "anabolic steroids," which when used by athletes and body builders have caused disastrous effects, even resulting in heart problems and cancer. For example, administration of synthetic

non-aromatizable androgens, like stanozolol or methyltestosterone, causes profound decreases in HDL-C ("good cholesterol") and significant increases in LDL-C ("bad cholesterol"). Yet, hormone replacement with aromatizable androgens, such as testosterone, results in lower total cholesterol and LDL cholesterol levels while having little to no impact on serum HDL cholesterol levels.

Proper monitoring of laboratory values and clinical response are essential when prescribing testosterone replacement therapy.

Information from the medical literature indicates that testosterone therapy may reduce the risk of:

Osteoporosis - According to the National Osteoporosis Foundation, approximately 2 million men in the U.S. have osteoporosis, and another 3 million are at risk. Osteoporosis-related fractures occur in 12% of all men older than 50. Twenty-five percent of all hip fractures occur in men, and 33% of these patients die within one year of fracture. **Gradual loss of testosterone is one of the major causes of osteoporosis in elderly men.** In one study, 59% of men with hip fracture had low testosterone, compared with 18% of controls. Fracture occurs at a later age in men than women because men's bones are denser at baseline. Androgens are important to the attainment of peak bone mass and in bone mass maintenance in adult men. Testosterone receptors are present in osteoblasts, and testosterone is an important factor in bone and calcium metabolism. Several studies have reported beneficial effects of testosterone therapy on bone in older men, showing an increase in BMD (bone mineral density) and slowing of bone degeneration.

Cardiovascular disease - Risk is decreased with higher serum total testosterone levels, according to most reports. A number of studies have demonstrated that testosterone minimizes several important risk factors for heart attack, including:

- reducing cholesterol and triglycerides
- reducing blood glucose levels
- decreasing visceral fat mass
- normalizing blood clotting

The degree of atherosclerotic disease, as measured by the mean percent coronary artery occlusion, increased significantly with declining levels of free testosterone. Visceral fat accumulation is connected with increased vascular risk, and studies have shown that androgen administration can decrease this fat accumulation. ***The use of anabolic steroids including methyltestosterone, but not natural testosterone, has been associated with serious heart disease.***

Frailty - The age-related testosterone decline appears to place the older man at risk for developing frailty. In fact, low bioavailable testosterone levels have been found to predict frailty in inner-city African-American males. In addition to the physical aspects (i.e. generalized weakness, impaired mobility and balance, and poor endurance), it is clear that frailty can also be related to a decline in cognitive function.

Alzheimer's Disease -Two interventional studies have supported the concept that testosterone can improve cognitive function in older men. Testosterone may play an integral role in the age-related cognitive impairment that occurs in males and low testosterone levels may play a permissive role in the pathogenesis of Alzheimer's disease.

Gandy et al. measured plasma levels of testosterone, 17 ß-estradiol, and amyloid-peptide (which is the main neurotoxic component of cerebral amyloid found in Alzheimer's Disease) in 6 men aged 44 to 83 years who underwent hormonal suppressive therapy for adenocarcinoma of the prostate. Samples were obtained 1 week prior to the first treatment and on weeks 4, 12, and 24. Plasma levels of testosterone and 17 ß-estradiol declined precipitously and then stabilized at low detectable levels during the first 2 months of therapy in all 6 patients. Plasma amyloid-peptide concentrations increased in a parallel manner by about 2-fold and then stabilized for at least 6 months. These data support the hypothesis that levels of circulating amyloid-peptide may be under the control of gonadal hormones and suggest that androgen replacement therapy might prevent or delay AD in postandropausal men.

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Depression - Standardized measurements of depression are higher when levels of bioavailable testosterone are low; perhaps because an associated decrease in sexual function results in depression, irritability, and mood swings. In the Rancho Bernardo Study which examined the association between levels of sex hormones and depressed mood in 856 men ages 50-89, bioavailable testosterone levels were 17% lower for depressed men. The results suggested that testosterone treatment might improve depressed mood in older men who have lower levels of bioavailable testosterone.

Symptoms of testosterone deficiency are often attributed to other problems, denied by the patient, and unrecognized by the

physician. Testosterone is necessary for spontaneous erections, normal libido, and ejaculation. The Massachusetts Male Aging Study reported that hypogonadism is the sole cause of erectile dysfunction (ED, formerly termed impotence) in 10% of cases. Unfortunately, many of these men and their physicians will not be aware of the cause and the option of treatment using natural testosterone, as ED is often still erroneously considered a psychological problem. They may instead resort to other forms of therapy with the potential for side effects, rather than experience the many benefits of natural hormone replacement.

What is the Optimal Form of Testosterone for Replacement Therapy?

Testosterone USP is natural "bio-identical" testosterone that has been approved by the United States Pharmacopoeia and is available as a bulk chemical. Upon a prescription order, compounding pharmacists can use Testosterone USP to prepare numerous dosage forms. The information that follows should be considered as prescriber, patient, and pharmacist work together to meet the specific needs of each patient.

A healthy adult male secretes 8-15mg/day of testosterone. This "physiologic dose" should be considered when prescribing replacement therapy. High serum levels of testosterone can result in a greater conversion to estradiol (and side-effects resulting from abnormally high estradiol levels), because the body can not effectively store excess testosterone. This may be a reason to administer testosterone on a daily basis, rather than using depot injections. An additional advantage of transdermal testosterone replacement is that it delivers testosterone at a controlled rate into the systemic circulation.

Testosterone is converted into dihydrotestosterone (DHT) by 5a-reductase or into estradiol by aromatase. Significant obesity can result in high serum estrogen levels, as estrogen stores are greater in fat. Aromatase activity is higher in overweight individuals, resulting in increased conversion of testosterone to estradiol. There is good reason to believe that what is important to a man's health is not necessarily the absolute amount of each hormone but rather the testosterone to estradiol ratio. Maintaining a proper body weight may produce a more desirable hormonal balance. It may be possible to maintain sufficient testosterone levels if the conversion to estradiol and dihydrotestosterone can be slowed by inhibiting the enzymes aromatase and 5-alpha reductase. Supplementation with vitamin C may reduce aromatase activity and decrease estradiol production.

There are many issues related to the appropriate use of testosterone and related therapies, and considerations in andropause treatment should include:

- the role of dihydrotestosterone (DHT) and its relationship with benign prostatic hypertrophy (BPH), levels of DHT, and even DHT supplementation.
- the use of 5-alpha reductase inhibitors and aromatase inhibitors to modify the amount of the metabolites DHT and estradiol that are produced when testosterone is broken down by the body.
- DHEA (dehydroepiandrosterone) and its role as an "anti-aging" supplement and in the treatment of symptoms of andropause.

Testosterone replacement therapy (TRT) is well tolerated, and long term TRT appears to be a safe and effective means of treating hypogonadal elderly males, provided that frequent follow-up blood tests and examinations are performed. Studies on TRT have not shown any increased incidence of stroke, angina, or myocardial infarction, and effects on the clotting system are probably neutral. Testosterone also may have beneficial vasodilatory properties. English et al. concluded that low-dose supplemental testosterone treatment in men with chronic stable angina reduces exercise-induced myocardial ischemia.

The general consensus (supported by at least 16 studies) is that TRT does not cause obstructive BPH. Tan and Salazar of Baylor College of Medicine and University of Texas note that current evidence suggests no causal relationship between prostate cancer and physiological dosing of testosterone, especially with careful selection and monitoring of patients. However, guidelines recommend that TRT should not be initiated in older men with PSA serum levels above the normal range. Due to the potential of testosterone to cause erythrocytosis, therapy is contraindicated in men with a hematocrit > 52%. During TRT, hemoglobin should be followed and appropriate measures should be taken if marked erythrocytosis occurs. Side effects of testosterone therapy can include emotional lability, leg swelling, skin reactions, acne, alopecia, gynecomastia, and infertility (which is usually reversible with cessation of T therapy).

In the past, oral testosterone, particularly the 17-alkylated derivatives, caused hepatotoxicity due to high first-pass metabolism. Due to the increasing recognition of hypogonadism in aging males and the introduction of newer, bioavailable topical preparations, testosterone prescriptions have increased 500% in the past 10 years. TRT has relieved symptoms and improved the quality of life for many men. Testosterone is well-absorbed from transdermal creams, gels, and lotions which avoid first pass metabolism. A satisfactory response can be achieved with BID dosing. Compounded preparations can be very advantageous because the exact amount of medication needed by a particular patient can be applied as a single dose. There is no need to shave the scrotum to apply one or more patches, and there is no skin irritation from patch adhesive. Tar and Salazar report that hepatotoxicity has not been reported following T administration using transdermal gels in physiologic doses.

The only absolute contraindication to androgen replacement therapy is the presence of prostate or breast cancer. Although it is known that the clinical course of prostate cancer is accelerated by testosterone, its incidence is not increased by testosterone administration. There is no clear evidence that testosterone replacement accelerates the development of BPH.

The testosterone controversy stems largely from poorly designed clinical studies in which patients were subjected to testosterone replacement therapy without having their estradiol and dihydrotestosterone levels properly controlled.

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Healthy Lifestyle

A healthy lifestyle has been shown to be associated with higher hormone levels, and higher hormone levels seem to induce a more active, healthier lifestyle, according to andropause expert Eugene Shippen, M.D. When hormone levels decline, we become less active and gain weight. As we gain weight, hormones are stored in fat and become unavailable to meet the body's demands. Lack of exercise, excessive alcohol use, and many diseases can reduce bioavailable hormone levels. For optimal results, it is vital that hormone replacement therapy be combined with adequate exercise, proper nutrition, and appropriate use of natural supplements.

Thyroid Hormone Replacement Therapy for Men and Women

Symptoms of hypothyroidism (low levels of thyroid hormone) include fatigue, cold and heat intolerance, hypotension, fluid retention, dry skin and/or hair, constipation, headaches, low sexual desire, infertility, irregular menstrual periods, aching muscles and joints, depression, anxiety, slowed metabolism and decreased heart rate, memory impairment, enlarged tongue, deep voice, swollen neck, PMS, weight gain, hypoglycemia, and high cholesterol and triglycerides. Yet, more than half of all people with thyroid disease are unaware of their condition.

Although both T4 (thyroxine, an inactive form that is converted to T3 in other areas of the body) and T3 (triiodothyronine, the active form) are secreted by the normal thyroid gland, many hypothyroid patients are treated only with levothyroxine (synthetic T4). Some hypothyroid patients remain symptomatic, and T3 may also be required for optimal thyroid replacement therapy. However, the only commercially available form of T3 is synthetic liothyronine sodium in an immediate release formulation which is rapidly absorbed, and may result in higher than normal T3 concentrations throughout the body causing serious side effects, including heart palpitations. Research indicates there is a need for *sustained-release* T3 preparations in order to avoid adverse effects.

A randomized, double-blind, crossover study found inclusion of T3 in thyroid hormone replacement improved cognitive performance, mood, physical status, and neuropsychological function in hypothyroid patients. Two-thirds of patients preferred T4 plus T3, and tended to be less depressed than after treatment with T4 alone. Patients and their physicians may wish to consider the use of sustained-release T3 in the treatment of hypothyroidism, particularly when the response to levothyroxine (T4) has not been complete.

J Endocrinol Invest. 2002 Feb; 25(2):106-9
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Adrenal Dysfunction

The adrenal glands secrete hormones such as cortisol, estrogen, and testosterone that are essential to health and vitality and significantly affect total body function. After mid-life, the adrenal glands gradually become the major endogenous source of sex hormones in both men and women. Intense or prolonged physical or emotional stress commonly associated with modern lifestyles or chronic illness can lead to Adrenal Fatigue, which is an important contributing factor in health conditions ranging from allergies to obesity.

Anti-inflammatory and anti-oxidant adrenal hormones like cortisol help to minimize allergic and negative reactions, such as cancer and autoimmune disorders. These hormones closely affect the utilization of carbohydrates and fats, the conversion of fats and proteins into energy, and cardiovascular and gastrointestinal function. Proper adrenal support is essential to complete the hormonal pathway to optimal health, and includes proper nutrition, getting plenty of sleep, regular moderate exercise, stress management, slowing down to regain a proper perspective on life, and replacement of deficient hormones.

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JAMA. 2017 Sep 12;318(10):927-938.
Menopausal Hormone Therapy and Long-term All-Cause and Cause-Specific Mortality: The Women's Health Initiative Randomized Trials.
Manson JE, Aragaki AK, Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Chlebowski RT, Howard BV, Thomson CA, Margolis KL, Lewis CE, Stefanick ML, Jackson RD, Johnson KC, Martin LW, Shumaker SA, Espeland MA, Wactawski-Wende J1; WHI Investigators.

Health outcomes from the Women's Health Initiative Estrogen Plus Progestin and Estrogen-Alone Trials have been reported, but previous publications have generally not focused on all-cause and cause-specific mortality. To examine total and cause-specific cumulative mortality, including during the intervention and extended postintervention follow-up, of the 2 Women's Health Initiative hormone therapy trials. Observational follow-up of US multiethnic postmenopausal women aged 50 to 79 years enrolled in 2 randomized clinical trials between 1993 and 1998 and followed up through December 31, 2014. Conjugated equine estrogens (CEE, 0.625 mg/d) plus medroxyprogesterone acetate (MPA, 2.5 mg/d) (n = 8506) vs placebo (n = 8102) for 5.6 years (median) or CEE alone (n = 5310) vs placebo (n = 5429) for 7.2 years (median). All-cause mortality (primary outcome) and cause-specific mortality (cardiovascular disease mortality, cancer mortality, and other major causes of mortality) in the 2 trials pooled and in each trial individually, with prespecified analyses by 10-year age group based on age at time of randomization. Among 27 347 women who were randomized (baseline mean [SD] age, 63.4 [7.2] years; 80.6% white), mortality follow-up was available for more than 98%. During the cumulative 18-year follow-up, 7489 deaths occurred (1088 deaths during the intervention phase and 6401 deaths during postintervention follow-up). All-cause mortality was 27.1% in the hormone therapy group vs 27.6% in the placebo group (hazard ratio [HR], 0.99 [95% CI, 0.94-1.03]) in the overall pooled cohort; with CEE plus MPA, the HR was 1.02 (95% CI, 0.96-1.08); and with CEE alone, the HR was 0.94 (95% CI, 0.88-1.01). In the pooled cohort for cardiovascular mortality, the HR was 1.00 (95% CI, 0.92-1.08 [8.9 % with hormone therapy vs 9.0% with placebo]); for total cancer mortality, the HR was 1.03 (95% CI, 0.95-1.12 [8.2 % with hormone therapy vs 8.0% with placebo]); and for other causes, the HR was 0.95 (95% CI, 0.88-1.02 [10.0% with hormone therapy vs 10.7% with placebo]), and results did not differ significantly between trials. When examined by 10-year age groups comparing younger women (aged 50-59 years) to older women (aged 70-79 years) in the pooled cohort, the ratio of nominal HRs for all-cause mortality was 0.61 (95% CI, 0.43-0.87) during the intervention phase and the ratio was 0.87 (95% CI, 0.76-1.00) during cumulative 18-year follow-up, without significant heterogeneity between trials.
CONCLUSIONS AND RELEVANCE:
Among postmenopausal women, hormone therapy with CEE plus MPA for a median of 5.6 years or with CEE alone for a median of 7.2 years was not associated with risk of all-cause, cardiovascular, or cancer mortality during a cumulative follow-up of 18 years.
PMID: 28898378

Am J Public Health. 2013 Sep;103(9):1583-8.
The mortality toll of estrogen avoidance: an analysis of excess deaths among hysterectomized women aged 50 to 59 years.
https://www.ncbi.nlm.nih.gov/pubmed/23865654

Nature. 2015 Jul 16; 523(7560): 313–317.
Progesterone receptor modulates estrogen receptor-α action in breast cancer.

Progesterone receptor (PR) expression is employed as a biomarker of estrogen receptor-α (ERα) function and breast cancer prognosis. We now show that PR is not merely an ERα-induced gene target, but is also an ERα-associated protein that modulates its behaviour. In the presence of agonist ligands, PR associates with ERα to direct ERα chromatin binding events within breast cancer cells, resulting in a unique gene expression programme that is associated with good clinical outcome. Progesterone inhibited estrogen-mediated growth of ERα+ cell line xenografts and primary ERα+ breast tumour explants and had increased anti-proliferative effects when coupled with an ERα antagonist. Copy number loss of *PgR* is a common feature in ERα+ breast cancers, explaining lower PR levels in a subset of cases. Our findings indicate that PR functions as a molecular rheostat to control ERα chromatin binding and transcriptional activity, which has important implications for prognosis and therapeutic interventions.

Click here to access the full article: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4650274/

Pharmaceutical Journal. 2015 Jul 17; 14:53.
Progesterone receptor could slow breast cancer growth
Full article, accessed October, 2017:
http://www.pharmaceutical-journal.com/news-and-analysis/news/progesterone-receptor-could-slow-breast-cancer-growth/20068984.article

JAMA. 1995 Jan 18;273(3):199-208.
Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial.

OBJECTIVE--To assess pairwise differences between placebo, unopposed estrogen, and each of three estrogen/progestin regimens on selected heart disease risk factors in healthy postmenopausal women. DESIGN--A 3-year, multicenter, randomized, double-blind, placebo-controlled trial. PARTICIPANTS--A total of 875 healthy postmenopausal women aged 45 to 64 years who had no known contraindication to hormone therapy. INTERVENTION--Participants were randomly assigned in equal numbers to the following groups: (1) placebo; (2) conjugated equine estrogen (CEE), 0.625 mg/d; (3) CEE, 0.625 mg/d plus cyclic medroxyprogesterone acetate (MPA), 10 mg/d for 12 d/mo; (4) CEE, 0.625 mg/d plus consecutive MPA, 2.5 mg/d; or (5) CEE, 0.625 mg/d plus cyclic micronized progesterone (MP), 200 mg/d for 12 d/mo. PRIMARY ENDPOINTS--Four endpoints were chosen to represent four biological systems related to the risk of cardiovascular disease: (1) high-density lipoprotein cholesterol (HDL-C), (2) systolic blood pressure, (3) serum insulin, and (4) fibrinogen. ANALYSIS--Analyses presented are by intention to treat. P values for primary endpoints are adjusted for multiple comparisons; 95% confidence intervals around estimated effects were calculated without this adjustment. RESULTS--Mean changes in HDL-C segregated treatment regimens into three statistically distinct groups: (1) placebo (decrease of 0.03 mmol/L [1.2 mg/dL]); (2) MPA regimens (increases of 0.03 to 0.04 mmol/L [1.2 to 1.6 mg/dL]); and (3) CEE with cyclic MP (increase of 0.11 mmol/L [4.1 mg/dL]) and CEE alone (increase of 0.14 mmol/L [5.6 mg/dL]). Active treatments decreased mean low-density lipoprotein cholesterol (0.37 to 0.46 mmol/L [14.5 to 17.7 mg/dL]) and increased mean triglyceride (0.13 to 0.15 mmol/L [11.4 to 13.7 mg/dL]) compared with placebo. Placebo was associated with a significantly greater increase in mean fibrinogen than any active treatment (0.10 g/L compared with -0.02 to 0.06 g/L); differences among active treatments were not significant. Systolic blood pressure inreased and postchallenge insulin levels decreased during the trial, but neither varied significantly by treatment assignment. Compared with other active treatments, unopposed estrogen was associated with a significantly increased risk of adenomatous or atypical hyperplasia (34% vs 1%) and of hysterectomy (6% vs 1%). No other adverse effect differed by treatment assignment or hysterectomy status. CONCLUSIONS--Estrogen alone or in combination with a progestin improves lipoproteins and lowers fibrinogen levels without detectable effects on postchallenge insulin or blood pressure. Unopposed estrogen is the optimal regimen for elevation of HDL-C, but the high rate of endometrial hyperplasia restricts use to women without a uterus. In women with a uterus, CEE with cyclic MP has the most favorable effect on HDL-C and no excess risk of endometrial hyperplasia.
PMID: 7807658

Gynecol Obstet Invest. 2008;66(2):111-8.
Pilot study: absorption and efficacy of multiple hormones delivered in a single cream applied to the mucous membranes of the labia and vagina.
Glaser RL, Zava DT, Wurtzbacher D.

There is a lack of evidence in the literature supporting vaginal application of a combination hormone-containing cream for local and systemic symptom relief. This pilot study examined the extent of absorption of a single cream containing estriol, estradiol, progesterone, DHEA, and testosterone. A combination cream was administered to 12 postmenopausal women in two differing doses over two independent time periods. Following 28 days (arm 1) and an additional 14 days (arm 2), measurement of hormones in saliva and blood and measurements of symptom relief, patient tolerability, and health-related quality of life (HRQoL) were obtained. The dosage and time of evaluation for study arm 1 was not ideal for providing documented increases in hormone levels. HRQoL measurements supported measured improvement in this arm. The second arm did document absorption of the various hormones when given vaginally. This study is the first documenting systemic absorption of multiple hormones by both saliva and blood as well as improvement of HRQoL. This therapy was generally well-tolerated with only 2 patients experiencing minor irritation, not necessitating discontinuation. Additional studies in larger numbers of patients will provide better knowledge for clinicians wanting to provide similar therapy at the lowest effective dose. PMID: 18446040

ENDO 2015: The Endocrine Society Annual Meeting. Abstract FRI-125, presented March 6, 2015.

A systematic review and meta-analysis of 43 randomized clinical trials concluded there were no significant associations between use of menopausal hormone-replacement therapy and all-cause mortality. No significant associations were found between hormone use and mortality due to myocardial infarction, breast cancer, or stroke. When analyzed separately, there were also no associations with risks for death from cancers of the lung, ovary, or colon/rectum. Results were similar for estrogen-only therapy and for combined estrogen-progesterone therapy.

Climacteric. 2013 Apr;16(2):203-4.
Global consensus statement on menopausal hormone therapy.

Menopausal hormone therapy is the most effective treatment for symptoms related to the hormonal changes of menopause, such as hot flushes and sleep deprivation. Hormone therapy is also beneficial for bone health and may decrease mortality and cardiovascular disease. Risks associated with menopausal hormone therapy are acknowledged, but benefits derived will generally outweigh the risks for women under 60, or within 10 years of the menopause. Taking menopausal hormone therapy is a decision which needs to be individualized, according to a woman's symptoms, and her individual health history. This decision should be made under the advisement of a qualified physician.

BMJ 2012;345:e6409
Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomised trial

After 10 years of treatment, women receiving hormone replacement therapy soon after menopause had a significantly reduced risk of mortality, heart failure, or myocardial infarction, without any apparent increase in risk of cancer, venous thromboembolism, or stroke.

Int J Pharm Compd. 2013 Jan-Feb;17(1):74-85.
The effects of compounded transdermal hormone therapy on hemostatic, inflammatory, immune factors; cardiovascular biomarkers; quality-of-life measures; and health outcomes in perimenopausal and postmenopausal women.

The study examined the long-term effects of compounded natural transdermal hormones on cardiovascular biomarkers, hemostatic, inflammatory, immune signaling factors; quality of life measures; and health outcomes in peri/postmenopausal women within the context of a hormone restoration model of care. This model of care warrants consideration for peri/postmenopausal women especially in populations with high perceived stress and a history of stressful life events prior to, or during the menopausal transition.

Maturitas. 2013 Mar;74(3):230-4.
Testosterone therapy in women: Myths and misconceptions.

Testosterone (T) therapy is being increasingly used to treat symptoms of hormone deficiency in pre and postmenopausal women. T is essential for physical and mental health in women. A source of confusion concerning the safety of T therapy in both men and women is the extrapolation of adverse events from high doses of oral and injectable anabolic-androgenic steroids to T therapy, despite a lack of evidence. Testosterone is not masculinizing and does not increase aggression or cause hoarseness. Testosterone increases scalp hair growth, is mood stabilizing, and is cardiac and breast protective. "Abandoning myths, misconceptions and unfounded concerns about T and T therapy in women will enable physicians to provide evidenced based recommendations and appropriate therapy."

Clin Ther. 2001 Jul;23(7):1099-115.
Quality of life and costs associated with micronized progesterone and medroxyprogesterone acetate in hormone replacement therapy for nonhysterectomized, postmenopausal women.
Ryan N, Rosner A.

Because natural progesterone is poorly absorbed and rapidly metabolized, synthetic derivatives of progesterone, such as medroxyprogesterone acetate (MPA), are used in combination with estrogen in hormone replacement therapy. A micronized form of natural progesterone is available that is readily absorbed and reaches peak serum concentrations from 1 to 4 hours after administration.

The purpose of this study was to compare the quality of life (QOL), menopausal symptoms, and costs associated with a natural micronized progesterone (MP) formulation versus MPA as add-on therapy to estrogen in hormone replacement for post-menopausal women.

This prospective, multicenter, randomized, fixed-dose, open-label, parallel-group study enrolled postmenopausal, otherwise healthy, nonhysterectomized women 45 to 65 years of age who had been amenorrheic for > or =6 months and exhibited symptoms of estrogen deficiency. All women received 0.625 mg conjugated equine estrogens on days 1 to 25 of a 30-day cycle; on days 12 to 25, women were randomized to receive either MP 200 mg or MPA 5 mg; patients were followed for 9 months. QOL, the primary end point, was measured at baseline and months 3, 6, and 9 using the 36-Item Short-Form Health Survey (SF-36), the Nottingham Health Profile (NHP), and the condition-specific Women's Health Questionnaire (WHQ). Bleeding pattern, compliance, menopausal symptoms, and cost were evaluated as secondary end points. Costs (in 1997 Canadian dollars) were assessed from the societal perspective and included costs of study medication, hormone therapy monitoring, concomitant medication, outpatient resources, out-of-pocket expenses, and patient and caregiver time loss.

A total of 182 women were enrolled; 89 received MP and 93 received MPA. Improvements in climacteric symptoms were observed from baseline to month 9 for both treatments. Mean scores on all domains of the SF-36 at month 9 were greater than scores at baseline in both treatment groups but the increases were not statistically significant. All domains within the NHP and WHQ improved significantly over this period for both groups (P < or = 0.008). Only patients receiving MP showed specific improvements in the menstrual problems and cognitive domains of the WHQ.
PMID: 11519773

J Womens Health Gend Based Med. 2000 May;9(4):381-7.
Comparison of regimens containing oral micronized progesterone or medroxyprogesterone acetate on quality of life in postmenopausal women: a cross-sectional survey.
Fitzpatrick LA1, Pace C, Wiita B.
Mayo Clinic and Mayo Foundation, Rochester, Minnesota 55905, USA.

A cross-sectional survey was conducted to examine quality of life (QOL) related to physiological, somatic, and vasomotor effects of changing progestogen treatment from medroxyprogesterone acetate (MPA) to micronized progesterone in postmenopausal women. Eligible women (n = 176) were currently using hormone replacement therapy (HRT) containing micronized progesterone for 1-6 months and had previously received HRT containing MPA. QOL was assessed via telephone interview using the Greene Climacteric Scale and the Women's Health Questionnaire. When compared with the MPA-containing regimen, women using micronized progesterone-containing HRT experienced significant improvement in vasomotor symptoms, somatic complaints, and anxiety and depressive symptoms. Women reported improved perceptions of their patterns of vaginal bleeding and control of menopausal symptoms while on the micronized progesterone-containing regimen. Approximately 80% of women reported overall satisfaction with the micronized progesterone-containing regimen. A micronized progesterone-containing HRT regimen offers the potential for improved QOL as measured by improvement of menopause-associated symptoms.
PMID: 10868610

Menopause. 2016 Jun;23(6):600-10.
Venous thromboembolism and cardiovascular disease complications in menopausal women using transdermal versus oral estrogen therapy
Simon JA, Laliberté F, Duh MS, Pilon D, Kahler KH, Nyirady J, Davis PJ, Lefebvre P.
The George Washington University School of Medicine, The Women's Health & Research Consultants, Washington, DC; Groupe d'analyse, Ltée, Montréal, Quebec, Canada; Analysis Group, Inc, Boston, MA; Novartis Pharmaceuticals Corporation, East Hanover, NJ.

To evaluate the risk of venous thromboembolism (VTE) and cardiovascular disease (CVD) complications, and assess healthcare costs in menopausal women using an estradiol transdermal system versus oral estrogen therapy (ET). Health insurance claims from 60 self-insured US companies from 1999 to 2011 were analyzed. Women at least 50 years of age, newly initiated on transdermal or oral ET, were included. Cohorts were matched 1:1 based on exact factors and propensity score-matching methods. The incidence rate ratios (IRRs) of CVD complications, as well as VTE and other CVD events separately, were assessed through conditional Poisson models. Cohorts were also compared for healthcare costs using linear regression models to assess per-patient per-month cost differences. Confidence intervals (CIs) and P values were determined using a nonparametric method for cost outcomes. From each cohort, 2,551 users were matched to form the study population. A total of 274 transdermal ET users developed CVD complications compared with 316 women in the oral ET cohort (adjusted IRR 0.81; 95% CI, 0.67-0.99). Transdermal ET users also incurred lower adjusted all-cause and VTE/CVD-related healthcare costs relative to oral ET users (all-cause per-patient per-month cost difference [95% CI] = $41 [-34; 137], P = 0.342). This large matched-cohort study based on real-world data suggests that women receiving transdermal ET have significantly lower incidences of CVD events compared with those receiving oral ET, and that they also incur lower healthcare costs.
PMID: 26953655

Menopause. 2001 Jan-Feb;8(1):10-6.
Sleep in menopause: differential effects of two forms of hormone replacement therapy.
Montplaisir J, Lorrain J, Denesle R, Petit D.
Centre d'étude du sommeil, H pital du Sacré-Coeur de Montréal and Department of Psychiary, Université de Montréal, Québec, Canada.

The aim of the present study was to evaluate differences between two regimens of estrogen/progestogen replacement therapy on nocturnal sleep in postmenopausal women. Twenty-one (21) postmenopausal women were studied. They were randomized into two treatment groups: (1) estrogen (Premarin 0.625 mg) and medroxyprogesterone acetate (Provera 5 mg) (n = 11) or (2) estrogen (Premarin 0.625 mg) and oral micronized progesterone (Prometrium 200 mg) (n = 10). Postmenopausal women were recorded for two consecutive nights in the sleep laboratory at baseline and again after 6 months of treatment in a randomized trial. The women also had to fill out

evening and morning sleep and vigilance questionnaires for 7 days before baseline recordings and for 23 days before month 6 recordings. Sleep efficiency was found to be significantly improved in the micronized progesterone group. It increased by 8% (p = 0.014) with no such increase observed in the medroxyprogesterone acetate group. Time spent awake after sleep onset was also significantly improved in the micronized progesterone group but not in the medroxyprogesterone acetate group. On the other hand, menopausal symptoms and subjective measures of sleep (questionnaires) improved in both groups after treatment. This study suggests that medroxyprogesterone acetate and micronized progesterone are both effective for treating menopausal symptoms but that the latter might better improve the quality of sleep in postmenopausal women taking estrogen.
PMID: 11201509

PLoS ONE 2013;8:e78016.
Risk of Breast Cancer by Type of Menopausal Hormone Therapy: a Case-Control Study among Post-Menopausal Women in France
Click below to view the article (accessed October 2017)
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0078016

Breast Cancer Res Treat 2008;107:103–11.
Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study.
Fournier A, Berrino F, Clavel-Chapelon F.

Erratum in
Breast Cancer Res Treat. 2008 Jan;107(2):307-8. This article has been corrected.

Large numbers of hormone replacement therapies (HRTs) are available for the treatment of menopausal symptoms. It is still unclear whether some are more deleterious than others regarding breast cancer risk. The goal of this study was to assess and compare the association between different HRTs and breast cancer risk, using data from the French E3N cohort study. Invasive breast cancer cases were identified through biennial self-administered questionnaires completed from 1990 to 2002. During follow-up (mean duration 8.1 postmenopausal years), 2,354 cases of invasive breast cancer occurred among 80,377 postmenopausal women. Compared with HRT never-use, use of estrogen alone was associated with a significant 1.29-fold increased risk (95% confidence interval 1.02–1.65). The association of estrogen-progestagen combinations with breast cancer risk varied significantly according to the type of progestagen: the relative risk was 1.00 (0.83–1.22) for estrogen–progesterone, 1.16 (0.94–1.43) for estrogen–dydrogesterone, and 1.69 (1.50–1.91) for estrogen combined with other progestagens. This latter category involves progestins with different physiologic activities (androgenic, nonandrogenic, antiandrogenic), but their associations with breast cancer risk did not differ significantly from one another. This study found no evidence of an association with risk according to the route of estrogen administration (oral or transdermal/percutaneous). These findings suggest that the choice of the progestagen component in combined HRT is of importance regarding breast cancer risk; it could be preferable to use progesterone or dydrogesterone.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2211383/

J Clin Oncol. 2008 Mar 10;26(8):1260-8.
Use of different postmenopausal hormone therapies and risk of histology- and hormone receptor-defined invasive breast cancer.
Fournier A, Fabre A, Mesrine S, Boutron-Ruault MC, Berrino F, Clavel-Chapelon F.

We previously found that the risk of invasive breast cancer varied according to the progestagen component of combined postmenopausal hormone therapy (CHT): progesterone, dydrogesterone, or other progestagens. We conducted the present study to assess how these CHTs were associated with histology- and hormone receptor-defined breast cancer. We used data from the French E3N cohort study, with 80,391 postmenopausal women followed for a mean duration of 8.1 years; 2,265 histologically confirmed invasive breast cancers were identified through biennial self-administered questionnaires completed from 1990 to 2002. The relative risks (RRs) were estimated using Cox proportional hazards models. Compared with postmenopausal hormone therapy (HT) never-use, ever-use of estrogen+progesterone was not significantly associated with the risk of any breast cancer subtype, but increasing duration of estrogen+progesterone was associated with increasing risks of lobular (P = .06) and estrogen receptor-positive/progesterone receptor-negative (ER+/PR-; P = .02). Estrogen+dydrogesterone was associated with a significant increase in risk of lobular carcinoma (RR, 1.7; 95% CI, 1.1 to 2.6). Estrogen+other progestagens was associated with significant increases in risk of ductal and lobular carcinomas (RR, 1.6; 95% CI, 1.3 to 1.8; and 2.0; 95% CI, 1.5 to 2.7, respectively), of ER+/PR+ and ER+/PR- carcinomas (RR, 1.8; 95% CI, 1.5 to 2.1; and 2.6; 95% CI, 1.9 to 3.5, respectively), but not of ER-/PR+ or ER-/PR- carcinomas (RR, 1.0; 95% CI, 0.5 to 2.1; and 1.4; 95% CI, 0.9 to 2.0, respectively).
CONCLUSION:
The increase in risk of breast cancer observed with the use of CHTs other than estrogen+progesterone and estrogen+dydrogesterone seems to apply preferentially to ER+ carcinomas, especially those ER+/PR-, and to affect both ductal and lobular carcinomas.
PMID: 18323549

Postgrad Med. 2009 Jan;121(1):73-85.

The bioidentical hormone debate: are bioidentical hormones (estradiol, estriol, and progesterone) safer or more efficacious than commonly used synthetic versions in hormone replacement therapy?

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BACKGROUND: The use of bioidentical hormones, including progesterone, estradiol, and estriol, in hormone replacement therapy (HRT) has sparked intense debate. Of special concern is their relative safety compared with traditional synthetic and animal-derived versions, such as conjugated equine estrogens (CEE), medroxyprogesterone acetate (MPA), and other synthetic progestins. Proponents for bioidentical hormones claim that they are safer than comparable synthetic and nonhuman versions of HRT. Yet according to the US Food and Drug Administration and The Endocrine Society, there is little or no evidence to support claims that bioidentical hormones are safer or more effective. OBJECTIVE: This paper aimed to evaluate the evidence comparing bioidentical hormones, including progesterone, estradiol, and estriol, with the commonly used nonbioidentical versions of HRT for clinical efficacy, physiologic actions on breast tissue, and risks for breast cancer and cardiovascular disease. METHODS: Published papers were identified from PubMed/MEDLINE, Google Scholar, and Cochrane databases, which included keywords associated with bioidentical hormones, synthetic hormones, and HRT. Papers that compared the effects of bioidentical and synthetic hormones, including clinical outcomes and in vitro results, were selected. RESULTS: Patients report greater satisfaction with HRTs that contain progesterone compared with those that contain a synthetic progestin. Bioidentical hormones have some distinctly different, potentially opposite, physiological effects compared with their synthetic counterparts, which have different chemical structures. Both physiological and clinical data have indicated that progesterone is associated with a diminished risk for breast cancer, compared with the increased risk associated with synthetic progestins. Estriol has some unique physiological effects, which differentiate it from estradiol, estrone, and CEE. Estriol would be expected to carry less risk for breast cancer, although no randomized controlled trials have been documented. Synthetic progestins have a variety of negative cardiovascular effects, which may be avoided with progesterone. CONCLUSION: Physiological data and clinical outcomes demonstrate that bioidentical hormones are associated with lower risks, including the risk of breast cancer and cardiovascular disease, and are more efficacious than their synthetic and animal-derived counterparts. Until evidence is found to the contrary, bioidentical hormones remain the preferred method of HRT. Further randomized controlled trials are needed to delineate these differences more clearly.
PMID: 19179815

Endocrine. 2004 Aug;24(3):211-6

Postmenopausal hormone therapy and breast cancer: a clinician's message for patients.

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The Women's Health Initiative agrees with some but not all case-control and cohort studies that current use of postmenopausal estrogen -progestin therapy is associated with a small increase in the risk of breast cancer. It is not known whether this is because of new tumor growth or an effect of hormonal therapy on preexisting tumors. Many studies indicate that women who develop breast cancer while using postmenopausal hormone therapy have a reduced risk of dying from breast cancer; this is consistent with an effect on preexisting tumors so that tumors appear at a less virulent and aggressive stage.
PMID: 15542887

Int J Fertil Womens Med. 2004 Nov-Dec;49(6):252-67

A clinician's review of the WHI-related literature.

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When the monitoring board of the Women's Health Initiative (WHI) canceled the estrogen-progestin arm of the study in July 2002, the effect was immediate and dramatic, as several million postmenopausal women with the full agreement of their physicians ceased taking combined hormone therapy. Soon thereafter the manufacturers of conjugated equine estrogens felt compelled to publicize a drastic restriction of the indications for their product. Little notice, except in the medical literature, was given to the continuation of the other treatment arms of the WHI, nor did the rather small (however significant) increases in risk of cardiovascular disease and breast cancer resulting from combined therapy receive widespread serious analysis. In this article, special attention is given to the population sampling involved in setting up the WHI, arm by arm, with full discussion of how these samplings compare with those in other studies--HERS, ERA, WEST, etc. All studies are scrutinized in terms of treatment regimens, follow-up, confounding factors, particularly statins and aspirin, and high drop-out rates in order to discover possible reasons for the results in the WHI for primary and secondary prevention of cardiovascular disease in the combined-therapy arm and slightly disappointing results for breast cancer. Each of the two main sections of the article, Cardiovascular Disease and Breast Cancer, concludes with a detailed summation of points derived from the often contrasting results of the various studies, which can be used in counseling patients.
PMID: 15751264

JAMA. 2007 Apr 4;297
Erratum in: JAMA. 2008 Mar 26;299(12):1426. The correction has been made to the results section below.
Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause.
Rossouw JE, **Prentice RL**, **Manson JE**, **Wu L**, **Barad D**, **Barnabei VM**, **Ko M**, **LaCroix AZ**, **Margolis KL**, **Stefanick ML**.
Women's Health Initiative Branch, National Heart, Lung, and Blood Institute, Bethesda, Md 20892, USA.

The timing of initiation of hormone therapy may influence its effect on cardiovascular disease. To explore whether the effects of hormone therapy on risk of cardiovascular disease vary by age or years since menopause began. Secondary analysis of the Women's Health Initiative (WHI) randomized controlled trials of hormone therapy in which 10,739 postmenopausal women who had undergone a hysterectomy were randomized to conjugated equine estrogens (CEE) or placebo and 16,608 postmenopausal women who had not had a hysterectomy were randomized to CEE plus medroxyprogesterone acetate (CEE + MPA) or placebo. Women aged 50 to 79 years were recruited to the study from 40 US clinical centers between September 1993 and October 1998. Statistical test for trend of the effect of hormone therapy on coronary heart disease (CHD) and stroke across categories of age and years since menopause in the combined trials. RESULTS: In the combined trials, there were 396 cases of CHD and 327 cases of stroke in the hormone therapy group vs 370 [corrected] cases of CHD and 239 cases of stroke in the placebo group. For women with less than 10 years since menopause began, the hazard ratio (HR) for CHD was 0.76 (95% confidence interval [CI], 0.50-1.16); 10 to 19 years, 1.10 (95% CI, 0.84-1.45); and 20 or more years, 1.28 (95% CI, 1.03-1.58) (P for trend = .02). The estimated absolute excess risk for CHD for women within 10 years of menopause was -6 per 10,000 person-years; for women 10 to 19 years since menopause began, 4 per 10,000 person-years; and for women 20 or more years from menopause onset, 17 per 10,000 person-years. For the age group of 50 to 59 years, the HR for CHD was 0.93 (95% CI, 0.65-1.33) and the absolute excess risk was -2 per 10,000 person-years; 60 to 69 years, 0.98 (95% CI, 0.79-1.21) and -1 per 10,000 person-years; and 70 to 79 years, 1.26 (95% CI, 1.00-1.59) and 19 per 10,000 person-years (P for trend = .16). Hormone therapy increased the risk of stroke (HR, 1.32; 95% CI, 1.12-1.56). Risk did not vary significantly by age or time since menopause. There was a nonsignificant tendency for the effects of hormone therapy on total mortality to be more favorable in younger than older women (HR of 0.70 for 50-59 years; 1.05 for 60-69 years, and 1.14 for 70-79 years; P for trend = .06).
CONCLUSIONS: Women who initiated hormone therapy closer to menopause tended to have reduced CHD risk compared with the increase in CHD risk among women more distant from menopause, but this trend test did not meet our criterion for statistical significance. A similar nonsignificant trend was observed for total mortality but the risk of stroke was elevated regardless of years since menopause. These data should be considered in regard to the short-term treatment of menopausal symptoms.
PMID: 17405972

Climacteric. 2006 Apr;9(2):108-18
Comment in: Climacteric. 2006 Apr;9(2):73-4.
The long-term impact of 2-3 years of hormone replacement therapy on cardiovascular mortality and atherosclerosis in healthy women.
Alexandersen P, Tanko LB, Bagger YZ, Qin G, Christiansen C.
Center for Clinical and Basic Research, Ballerup, Denmark.

OBJECTIVE: The effect of hormone replacement therapy (HRT) on cardiovascular risk is intensely debated. The aim of this study was to investigate the long-term effects of HRT given for a few years on all-cause and cardiovascular mortality and the severity of atherosclerosis. METHODS: This analysis was based on a cohort of 1,458 postmenopausal women (55.8 +/- 6.1 years old) who previously participated in a number of randomized, placebo-controlled, clinical trials assessing the efficacy of 2-3 years of therapy with various estrogen plus progestin combinations for preventing bone loss. Women were followed on average for 9.8 years and came for a follow-up visit. Outcome variables were all-cause and cardiovascular mortality and the severity of atherosclerosis, as estimated by semi-quantitative scoring of vascular calcification in the lumbar aorta on lateral radiographs. RESULTS: A total of 174 women died during the observation period. All-cause mortality was decreased by 30% in the HRT+ group compared with the HRT- group (hazard ratio (HR) 0.70; 95% confidence interval (CI) 0.50-0.97) after adjusting for age, body mass index and smoking. Under the same conditions, similar results characterized mortality from cardiovascular disease (n = 61 deaths; 35.1% of all deaths) and coronary heart disease (n = 39 deaths; 22.4% of all deaths), which were decreased by 46% and 53%, respectively. Furthermore, the mean severity score of aortic calcification at follow-up was significantly lower in hormone-treated compared to non-treated women ($p < 0.0001$). CONCLUSION: Women who receive 2-3 years of HRT after menopause do not have increased all-cause mortality, and results of the present study suggest relative cardiovascular benefits compared to those who had not used hormones.
PMID: 16698657

Altern Med Rev. 2006 Sept;11(3):208-223
Complete article is available FREE at http://www.thorne.com/altmedrev/.fulltext/11/3/208.pdf
A comprehensive review of the safety and efficacy of bioidentical hormones for the management of menopause and related health risks

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Numerous forms of estrogens and progestins are utilized for the treatment of menopausal complaints and associated conditions that occur temporally. Although known to be different with respect to molecular structure, receptor affinity, metabolism, and other physiological traits, most have been treated as if they were clinically identical. The majority of these hormone preparations, commonly referred to as hormone replacement therapy (HRT), should perhaps be more aptly referred to as hormone substitution therapy, as most of the therapies utilized do not exactly match those produced in the body. Research indicates these synthetic hormones vary clinically in safety and efficacy. As such, women and their physicians have, in increasing numbers, been opting for the use of bioidentical hormones; i.e., those that match the structure and function of hormones produced in the body. With greater utilization and research surrounding bioidentical hormones, the differences can now begin to be fully assessed and appreciated. This article reviews the disparities between synthetic and bioidentical estrogens and progestins/progesterone with respect to safety and efficacy; special attention is devoted to clinical outcomes in the breast, endometrium, bone, cardiovascular system, and brain. The studies reviewed suggest bioidentical progesterone does not have a negative effect on blood lipids or vasculature as do many synthetic progestins, and may carry less risk with respect to breast cancer incidence. Studies of both bioidentical estrogens and progesterone suggest a reduced risk of blood clots compared to non-bioidentical preparations. Bioidentical hormone preparations have demonstrated effectiveness in addressing menopausal symptoms. The author advocates for continued research on bioidentical hormones and concludes there is currently sufficient evidence to support their preferred use over that of their synthetic cousins.
PMID: 17217322

Menopause. 2006 May-Jun;13(3):442-50
Efficacy of a new, oral estradiol acetate formulation for relief of menopause symptoms
Speroff L, **Haney AF**, **Gilbert RD**, **Ellman H**;
Estradiol Acetate Investigator Group. Department of Obstetrics and Gynecology, Oregon Health & Science University, Portland, OR

OBJECTIVE: To determine the efficacy of three doses of a new, oral formulation of estradiol acetate (EA) for alleviation of vasomotor and urogenital symptoms in postmenopausal women. DESIGN: Two separate 12-week studies were undertaken in postmenopausal women with moderate to severe vasomotor symptoms. In the first study, women were randomly assigned to EA 0.9 mg/day, EA 1.8 mg/day, or placebo (study 1; N = 293), and in the second study to oral EA 0.45 mg/day or placebo (study 2; N = 259). Women recorded the frequency and severity of vasomotor symptoms daily and urogenital symptoms weekly on diary cards. Investigators assessed signs of vaginal atrophy. RESULTS: Frequency of moderate to severe vasomotor symptoms decreased significantly versus placebo, starting at week 2 in the EA 1.8-mg group ($P = 0.005$), week 3 in the EA 0.9-mg group ($P = 0.003$), and week 6 in the EA 0.45-mg group ($P < 0.05$). At week 12, mean percent reduction from baseline in vasomotor-symptom frequency was 91%, 78%, and 61%, respectively. Vasomotor-symptom severity decreased significantly versus placebo, starting at weeks 2 and 3 with EA 1.8 mg and 0.9 mg, respectively, and at week 5 with EA 0.45 mg. Vaginal pH and maturation index improved significantly in all EA groups versus placebo, and some signs and symptoms of vaginal atrophy improved at the EA 0.9- and 1.8-mg doses. Side effects were mild to moderate and consistent with estrogen therapy. CONCLUSIONS: Oral EA at all doses was well tolerated and significantly reduced the frequency and severity of postmenopause symptoms versus placebo.
PMID: 16735941

Maturitas. 2005 May 16;51(1):4-7
Comment in: Maturitas. 2005 May 16;51(1):1-3.
Practical guidelines for postmenopausal hormone therapy.
Speroff L, **Kenemans P**, **Burger HG**.
Oregon Health & Science University, Portland, OR 97239, USA.

The fourth Amsterdam Menopause Symposium (2-4 October 2004) was dedicated to practical recommendations to guide clinicians after the confusion, concerns, and controversies generated by study results over the previous several years. Those recommendations are summarized in this deliberately concise and user-friendly document, always recognizing that each clinician must help women with their decision-making according to individual needs, desires, and understanding of benefits and risks.
PMID: 15883102

Maturitas 2001 Dec 14;40(3):195-201
Hormone replacement therapy: the benefits in tailoring the regimen and dose.
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Despite the clear benefits of long-term hormone replacement therapy (HRT), the majority of patients tend to undergo short-term treatment. The cyclical bleedings induced by the sequential progestogen administration are often unacceptable namely in the elderly postmenopausal women. At the standard doses HRT preparations can also induce annoying hormone-related side effects, both in sequential and continuous combined regimens. Lower HRT schedules are reported to be highly effective in the relief of climacteric symptoms, inducing minimal endometrial stimulation with high rates of amenorrhea. Continuous administration of low doses of progestins is safe for endometrium protection and minimizes progestin-related side effects. Indeed, it has been demonstrated that low dose HRT can prevent the increase in bone turnover and the consequent bone loss in postmenopausal women. The choice of lower HRT dosages can also be useful for the number of potential disadvantages of standard HRT doses, mainly for long-term treatments Low dose regimens should be considered as a starting dose to minimize the occurrence of side effects, improving compliance and, therefore, HRT effects on the prevention of long-term consequences of estrogen deprivation.

Chem Res Toxicol. 1998 Feb;11(2):94-101.
Alkylation of 2'-deoxynucleosides and DNA by the Premarin metabolite 4-hydroxyequilenin semiquinone radical.
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Department of Medicinal Chemistry and Pharmacognosy (M/C 781), College of Pharmacy, University of Illinois at Chicago

Premarin (Wyeth-Ayerst) is the estrogen replacement treatment of choice and continues to be one of the most widely dispensed prescriptions in the United States. In addition to endogenous estrogens, Premarin contains unsaturated estrogens including equilenin. We synthesized the catechol metabolite of equilenin, 4-hydroxyequilenin (4-OHEN), and found that the semiquinone radical of 4-OHEN reacted with 2'-deoxynucleosides generating very unusual adducts. 2'-Deoxyguanosine (dG), 2'-deoxyadenosine (dA), or 2'-deoxycytosine (dC) all gave four isomers, but no product was observed for thymidine under similar physiological conditions. The structures of these adducts were determined by electrospray mass spectrometry and NMR experiments including 1H, 13C, DQF-COSY, ROESY, HOHAHA, HMQC, and HMBC. The spectral data show that dG forms a cyclic adduct with the 4-OHEN producing 2-N1,3-N2-deoxyguanosyl-1,3-dihydroxy-5,7,9(10)-estratriene-4,17-d ione. Similarly, reaction with dA produced 1-N6,3-C2-deoxyadenosyl-2,3-dihydroxy-5,7,9(10)-estratriene-4,17-d ione, and incubations with dC resulted in 1-N3,3-N4-deoxycytosyl-2,3-dihydroxy-5,7,9(10)-estratriene-4,17-di one. We found that care needed to be taken during the isolation of the dA adducts in particular, as any exposure to acidic environments caused hydrolysis of the sugar moiety leaving alkylated adenine. In mixtures of the deoxynucleosides treated with 4-OHEN, reaction occurred primarily with dG followed by dC and dA. With DNA significant apurinic sites were produced as 4-OHEN-adenine adducts were detected in the ethanol wash prior to hydrolysis. When the DNA was hydrolyzed to deoxynucleosides and analyzed by electrospray mass spectrometry, only one isomer of 4-OHEN-dG and one isomer of 4-OHEN-dC were observed. Our data suggest that several different types of DNA lesions could be expected from 4-OHEN including apurinic sites and bulky stable adducts, in addition to the published oxidized damage to DNA caused by 4-OHEN. The production of these semiquinone radical-derived DNA adducts could play a role in the carcinogenic effects of Premarin estrogens.
PMID: 9511900

In addition to containing estrone in a disproportionately high ratio to that found in humans and 17 ß-estradiol in a lower ratio, conjugated estrogens also contain a number of estrogens that are natural to horses, but not to humans, including unsaturated horse estrogens such as equilenin. Shen et al. of the University of Illinois at Chicago synthesized the catechol metabolite of equilenin, 4-hydroxyequilenin (4-OHEN) and found that the semiquinone radical of 4-OHEN reacted with 2'-deoxynucleosides generating highly unusual adducts with DNA. "Our data suggest that several different types of DNA lesions could be expected including apurinic sites and bulky stable adducts, in addition to the published oxidized damage to DNA caused by 4-OHEN. If similar adducts are formed *in vivo* which are not repaired efficiently, mutations could result leading to initiation of the carcinogenic process in the endometrium or breast. Finally, it should be noted that equilenin or 17ß-dehydroequilenin are the major urinary and biliary metabolites of equilin [another horse estrogen which comprises an estimated 6 to 15% of the conjugated estrogen dose], and it is quite possible that 4-OHEN-semiquinone radicals are formed from these estrogens as well. The implication of these adducts to the biological effects of Premarin[®] is not known; however, given the direct link between long-term estrogen replacement therapy and the enhanced risk of breast cancer, the potential for formation of redox -active/electrophilic metabolites from all of the estrogens in estrogen replacement formulations needs to be explored."

Chem Res Toxicol 1998 Sep;11(9):1105-11
The equine estrogen metabolite 4-hydroxyequilenin causes DNA single-strand breaks and oxidation of DNA bases in vitro.
Chen Y, Shen L, Zhang F, Lau SS, van Breemen RB, Nikolic D, Bolton JL
Department of Medicinal Chemistry and Pharmacognosy (M/C 781), College of Pharmacy, The University of Illinois at Chicago, IL, USA.

Premarin (Wyeth-Ayerst) is the estrogen replacement treatment of choice and continues to be one of the most widely dispensed prescriptions in North America. In addition to endogenous estrogens, Premarin contains unsaturated equine estrogens, including equilenin [1,3,5(10),6,8-estrapentaen-3-ol-17-one]. In previous work, we showed that the equilenin metabolite 4-hydroxyequilenin (4-OHEN) can be autoxidized to 4-OHEN-o-quinone which readily entered into a redox couple with the semiquinone radical catalyzed by NAD(P)H, P450 reductase, or quinone reductase, resulting in generation of reactive oxygen species [Shen, L., Pisha, E., Huang, Z., Pezzuto, J. M., Krol, E., Alam, Z., van Breemen, R. B., and Bolton, J. L. (1997) Carcinogenesis 18, 1093-1101]. As oxidative damage to DNA by reactive oxygen species generated by redox active compounds has been proposed to lead to tumor formation, we investigated whether 4-OHEN could cause DNA damage. We treated lambda phage DNA with 4-OHEN and found that extensive single-strad breaks could be obtained with increasing concentrations of 4-OHEN as well as increasing incubation times. If scavengers of reactive oxygen species are included in the incubations, DNA could be completely protected from 4-OHEN-mediated damage. In contrast, NADH and CuCl2 enhanced the ability of 4-OHEN to cause DNA single-strand breaks presumably due to redox cycling between 4-OHEN and the semiquinone radical generating hydrogen peroxide and ultimately copper peroxide complexes. We also confirmed that 4-OHEN could oxidize DNA bases since hydrolysis of 4-OHEN-treated calf thymus DNA and HPLC separation with electrospray MS detection revealed oxidized deoxynucleosides, including 8-oxodeoxyguanosine and 8-oxodeoxyadenosine. Our data suggest that DNA single-strand breaks and oxidation of DNA bases by 4-OHEN could contribute to the carcinogenic mechanism(s) of equine estrogens.

Climacteric. 2017 Aug;20(4):321-330.

The efficacy and safety of estriol to treat vulvovaginal atrophy in postmenopausal women: a systematic literature review.

Rueda C, Osorio AM, Avellaneda AC, Pinzón CE, Restrepo OI.

To evaluate the efficacy and safety of estriol for the treatment of vulvovaginal atrophy in postmenopausal women. A systematic literature review was performed. We searched the following electronic databases: Medline, Cochrane, Embase, Lilacs, CINHAL and Google Scholar. The studies selected included controlled clinical trials and quasi-experimental studies. Selections were made in pairs and independently, first by title and abstract and then complete texts. We identified 188 studies, 22 of which met the inclusion criteria; 13 were controlled clinical trials and nine were quasi-experimental, and 1217 women were included. These studies confirmed the efficacy of local estrogens to treat symptoms of vulvovaginal atrophy with few adverse effects reported. Following treatment, serum estriol levels rose, peaking at 1 h. At the 6-month follow-up, there was no increase in serum estriol in treated women.
CONCLUSIONS:
The available evidence (of low and moderate quality) shows that, when administered vaginally, estriol preparations appear to be safe for women who have risk factors related to systemic estrogen therapy.
PMID: 28622049

Menopause. 2017 Sep;24(9):1081-1085.

Estriol: emerging clinical benefits.

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Department of Internal Medicine, School of Medicine, Section of Endocrinology, Texas Tech University Health Science Center, Lubbock, TX.

Estriol is the main estrogen in pregnancy, but has received less attention outside gestation. It is well known that pregnancy has an immunosuppressive effect on many autoimmune diseases such as multiple sclerosis, psoriasis, thyroiditis, uveitis, and rheumatoid arthritis. Emerging evidence indicates that estriol has potential immunomodulatory benefits for many disease states including autoimmune, inflammatory, and neurodegenerative conditions. In this review, we discuss emerging roles for estriol in the treatment of menopausal symptoms, osteoporosis, cancer, hyperlipidemia, vascular disease, and multiple sclerosis. Estriol appears to offer a potentially cost-effective approach to a variety of conditions and may offer a wide range of health benefits. We reviewed the English language MEDLINE literature with estriol in the title with emphasis on publications including nonpregnant females between January 1974 and August 2016. Approximately 393 such articles were considered and 72 articles have been referenced in this review.
RESULTS:
Estriol offers considerable benefits for postmenopausal women with reduced risks that are normally associated with traditional hormone therapies. These benefits include improved control of menopausal symptoms and better urogenital health. Moreover, the immunomodulatory role of estriol in reducing proinflammatory cytokines may be an important new therapeutic option for chronic autoimmune and neurodegenerative illnesses. Since it is a relatively weak estrogen, there is potential for use in men for conditions such as multiple sclerosis.
CONCLUSIONS:
We conclude transvaginal estriol potentially offers a suitable physiologic delivery and cost-effective alternative to currently available estrogen regimens in selected patients. Additional studies on mode of delivery, safety, and efficacy merit further investigation.
PMID: 28375935

Altern Med Rev 1998 Apr;3(2):101-13
Estriol: safety and efficacy.
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While conventional hormone replacement therapy provides certain benefits, it is not without significant risks. Estriol has been found to provide some of the protection without the risks associated with stronger estrogens. Depending upon the situation, estriol may exert either agonistic or antagonistic effects on estrogen. Estriol appears to be effective at controlling symptoms of menopause, including hot flashes, insomnia, vaginal dryness, and frequent urinary tract infections. Results of research on its bone-density-maintaining effects have been contradictory, with the most promising results coming from Japanese studies. Estriol's effect on cardiac risk factors has also been somewhat equivocal; however, unlike conventional estrogen prescriptions, it does not seem to contribute to hypertension. Although estriol appears to be much safer than estrone or estradiol, its continuous use in high doses may have a stimulatory effect on both breast and endometrial tissue.

Maturitas 2001 Sep 28;39(3):253-7
Short term oral estriol treatment restores normal premenopausal vaginal flora to elderly women.
Yoshimura T, Okamura H.
Department of Obstetrics and Gynecology, Kumamoto University School of Medicine, Honjo 1-1-1, 860-8556, Kumamoto, Japan.

OBJECTIVE: Estriol is an estrogen with considerably weaker stimulatory effects on endometrial proliferation than estradiol. A study was conducted to determine the effects of oral estriol on vaginal flora and endometrial thickness. METHODS: Fifty-nine postmenopausal women (50-75 years of age), complaining of pruritus or vaginal discharge, participated in the study. Vaginal flora and endometrial thickness were evaluated before treatment and after receiving oral estriol (2 mg/day) for 14 days. RESULTS: Prior to treatment, lactobacilli were found in vaginal cultures from only six of the 59 study participants, whereas after treatment, the vaginal flora of 27 women showed a presence of lactobacilli ($P<0.0001$). Endometrial thickness exceeded 5 mm in only five cases. No side effects were reported. CONCLUSION: Estriol, which has little effect on the endometrium, has the potential to be highly useful for the treatment of atrophic vaginitis.
PMID: 11574185

J Reprod Med 2000 Mar;45(3 Suppl):245-58
Rationale for hormone replacement therapy in atherosclerosis prevention.
Wagner JD
Comparative Medicine Clinical Research Center, Wake Forest University School of Medicine, Winston-Salem, NC

Progestogens are clearly useful to balance the proliferative effects of estrogens on the endometrium; however, some progestogens have been shown to attenuate the cardiovascular benefits of estrogen, and this has been the subject of considerable debate. Accumulating evidence confirms the deleterious effects of medroxyprogesterone acetate on estrogen's cardioprotective effects and provides new and compelling evidence that not all progestogens are alike in this regard. Maintaining estrogen's cardioprotective effects is strongly dependent upon the type of progestogen and route and method of administration. Numerous periclinical studies conducted on nonhuman primates and other models have demonstrated that certain progestogens, such as micronized progesterone, can be administered concurrently with estrogen replacement therapy, providing protection against endometrial hyperplasia without significantly affecting the beneficial effects of estrogen on lipid profiles, atherosclerosis and vascular reactivity.

Menopause 2001 Sep-Oct;8(5):347-52
Comparison of transdermal and oral estrogen-progestin replacement therapy: effects on cardiovascular risk factors.
Chen FP, Lee N, Soong YK, Huang KE.
Department of Obstetrics and Gynecology, Keelung Chang Gung Memorial Hospital, Keelung, Taiwan, Republic of China.

To determine the effects of oral and transdermal hormone replacement therapy on lipid profile and hemostatic factors in postmenopausal women. Twenty subjects were treated with oral E2 valerate (2 mg) combined with cyproterone acetate (1 mg) (group I) and 21 with transdermal E2 (1.5 mg) plus oral medroxyprogesterone acetate (5 mg) (group II). The effects on lipid profile and hemostatic parameters were evaluated at baseline and after 3, 6, and 12 months of treatment. RESULTS: Group I showed a stronger increase of high-density lipoprotein (HDL) cholesterol levels (2-8%) and stronger reduction of atherogenic indices (total cholesterol/HDL cholesterol and low-density lipoprotein/HDL cholesterol) than group II. Group II showed a more pronounced reduction of triglyceride (21-31%) and factor VII (6-10%) levels than group I. Both groups showed reduced concentrations of total cholesterol, low-density lipoprotein cholesterol, tissue plasminogen activator, plasminogen activator inhibitor-1, antithrombin III, and protein S, whereas protein C was increased after 12

months of treatment. CONCLUSIONS: The cardioprotective effects of hormone replacement therapy are demonstrated by favorable effects on lipid profile and fibrinolytic activity. Oral hormone replacement therapy showed a more prominent effect on lipoprotein metabolism than did transdermal administration, but transdermal medication had a stronger effect on triglyceride and coagulation factors. However, it needs to be considered that there is an increased risk of venous thrombotic events in the first year of treatment.

Maturitas 1996 May;24(1-2):43-50
Transdermal estrogen replacement therapy: beneficial effects on hemostatic risk factors for cardiovascular disease.
Lindoff C, Peterson F, Lecander I, Martinsson G, Astedt B.
Department of Obstetrics and Gynecology, University Hospital, Lund, Sweden.

OBJECTIVES: To assess the effect of estrogen replacement therapy on hemostatic risk factors for cardiovascular disease (CVD) in postmenopausal women during 2 years of treatment. METHODS: In an open prospective study, patients (n = 42) were investigated before and during 2 years of treatment, and compared to an untreated postmenopausal control group (n = 18) followed during the same period, healthy premenopausal women (n = 20) being included as a reference group for premenopausal values. The patients underwent treatment with transdermal 17 beta-estradiol (E2) (50 micrograms/24 h), oral medroxyprogesterone acetate (5 mg/day) being added for 12 days every second month. RESULTS: After 2 years of treatment there was a significant increase in t-PA antigen (P = 0.01) and a significant decrease in F VII antigen (P = 0.01). PAI-1 antigen concentrations decreased slightly. Fibrinogen concentrations were already significantly decreased at 3-month follow-up (P = 0.01), and were still low after 2 years. By contrast, at 2 year follow-up the postmenopausal control group manifested significant increases in F VII and PAI-1 antigen and slight increases in fibrinogen, which resulted in significant differences between patients and controls. Regression analysis showed the increase in the serum estradiol concentrations to be inversely correlated to the decreases in the plasma concen-trations of F VII antigen (r = -0.34, P = 0.001) and fibrinogen (r = -0.35, P = 0.001). There were no changes in AT III or protein C in any group. CONCLUSIONS: The increase in serum estradiol concentrations due to replacement therapy did not adversely affect the studied components of the fibrinolytic and protein C defense system against thrombosis, and resulted in beneficial decreases in F VII antigen and fibrinogen. These findings may help to explain the beneficial effects of estrogen replacement therapy in terms of protection from cardiovascular disease.

J Neurosci. 2003 Dec 10;23(36):11420-6
Estradiol attenuates programmed cell death after stroke-like injury.
Rau SW, Dubal DB, Bottner M, Gerhold LM, Wise PM.
Department of Physiology, University of Kentucky College of Medicine, Lexington, Kentucky 40536, USA.

Estradiol is a known neurotrophic and neuroprotective factor. Our previous work demonstrated that replacement with physiological concentrations of estradiol protects the cortex against middle cerebral artery occlusion (MCAO)-induced cell death. The cerebral cortex exhibits caspase-dependent programmed cell death (PCD) in many models of focal cerebral ischemia. We hypothesized that estradiol attenuates PCD during stroke injury. The current study explored the temporospatial pattern of markers of PCD, their relationship to the evolution of injury, and their modulation by estradiol. Rats were ovariectomized and treated with either estradiol or vehicle. One week later, rats underwent MCAO, and brains were collected at 1, 4, 8, 16, and 24 hr. We assessed the temporospatial evolution of infarction volume, DNA fragmentation, and levels of spectrin cleavage products in ischemic cortex. Estradiol led to a delay and attenuation of injury-mediated DNA fragmentation as early as 8 hr after MCAO. Estradiol also dramaticall reduced the level of the 120 kDa caspase-mediated spectrin breakdown product (SBDP120) at 4 hr but not at 8 or 16 hr. The SBDP150, produced by caspase and calpain, showed peak levels at 16 hr but was not altered by estradiol. These results strongly suggest that estradiol protects the ischemic cortex by attenuating PCD, thereby reducing caspase activity, DNA fragmentation, and subsequently, overall cell death. These studies deepen our understanding of the mechanisms underlying estrogen-mediated neuroprotection.
PMID: 14673006

Endocrinology 2001 Mar 1;142(3):969-973
Minireview: Neuroprotective Effects of Estrogen-New Insights into Mechanisms of Action.
Wise PM, Dubal DB, Wilson ME, Rau SW, Bottner M
Department of Physiology, College of Medicine, University of Kentucky, Lexington, Kentucky 40536.

An accumulating body of evidence clearly establishes that estradiol is a potent neuroprotective and neurotrophic factor in the adult: it influences memory and cognition, decreases the risk and delays the onset of neurological diseases such as Alzheimer's disease, and attenuates the extent of cell death that results from brain injuries such as cerebrovascular stroke and neurotrauma. Thus, estradiol appears to act at two levels: 1) it decreases the risk of disease or injury; and/or 2) it decreases the extent of injury incurred by suppressing the neurotoxic stimulus itself or increasing the resilience of the brain to a given injury. During the past century, the average life span of women has increased dramatically, whereas the time of the menopause has remained essentially constant. Thus, more women will live a larger fraction of their lives in a postmenopausal, hypoestrogenic state than ever before. Clearly, it is critical for us

understand the circumstances under which estradiol exerts protective actions and he cellular and molecular mechanisms that underlie these novel, nonreproductive actions. "Our analysis strongly suggests estrogen replacement therapy can help reduce the risk of colorectal cancer, which is the second leading cause of cancer deaths in the United States after lung cancer," said Stampfer, professor of Epidemiology and Nutrition at the Harvard School of Public Health. While researchers are not certain how estrogen affects the colon, it is possible that estrogen affects the production of bile acids that aid digestion in the colon and seem to be important for colorectal cancer. Additionally, estrogen interacts with estrogen-specific receptors that line the colon and could suppress the growth of abnormal cells. Both Drs. Burt and Stampfer agree that further studies are needed to determine why estrogen may protect postmenopausal women against colorectal cancer, and to shed light on how physicians might prevent the disease in the future. The American Gastroenterological Association recommends colorectal cancer screening for all women over the age of 50, unless there is a family history of colon cancer, which may make screening at an earlier age necessary. In addition, women should talk with their physicians about how a healthy lifestyle and proper diet may reduce their risk for this disease.

J Neuroendocrinol. 2007 Jan;19(1):1-6
Oestrogen, cognition and the maturing female brain
Craig MC, **Murphy DG**.
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Many women complain of memory and other cognitive difficulties at times that are associated with changes in ovarian steroid levels. However, the biological mechanisms through which ovarian steroids exert these effects remains poorly understood. Furthermore, the effect of hormone therapy, especially oestrogen therapy, on cognition and brain function in healthy women, and its role in the prevention of Alzheimer's disease, remains controversial. Here, we review the evidence that, in healthy women, ovarian steroids/oestrogen affects brain regions crucial to higher cognitive function at the macroscopic, microscopic, functional and neurotransmitter levels.
PMID: 17184480

Hum Reprod Update. 2006 Nov 29; [Epub ahead of print]
Estrogen, cognition and female ageing
Genazzani AR, Pluchino N, Luisi S, Luisi M.
Department of Reproductive Medicine and Child Development, Division of Obstetrics and Gynecology, University of Pisa, Pisa.

Starting from fetal life, estrogens are crucial in determining central gender dimorphism, and an estrogen-induced synaptic plasticity is well evident during puberty and seasonal changes as well as during the ovarian cycle. Estrogens act on the central nervous system (CNS) both through genomic mechanisms, modulating synthesis, release and metabolism of neurotransmitters, neuropeptides and neurosteroids, and through non-genomic mechanisms, influencing electrical excitability, synaptic function and morphological features. Therefore, estrogen's neuroactive effects are multifaceted and encompass a system that ranges from the chemical to the biochemical to the genomic mechanisms, protecting against a wide range of neurotoxic insults. Clinical evidences show that, during the climacteric period, estrogen withdrawal in the limbic system gives rise to modifications in mood, behaviour and cognition and that estrogen administration is able to improve mood and cognitive efficiency in post-menopause. Many biological mechanisms support the hypothesis that estrogens might protect against Alzheimer's disease (AD) by influencing neurotransmission, increasing cerebral blood flow, modulating growth proteins associated with axonal elongation and blunting the neurotoxic effects of beta-amyloid. On the contrary, clinical studies of estrogen replacement therapy (ERT) and cognitive function have reported controversial results, indicating a lack of efficacy of estrogens on cognition in post-menopausal women aged >/=65 years. These findings suggest the presence of a critical period for HRT-related neuroprotection and underlie the potential importance of early initiation of therapy for cognitive benefit. In this review, we shall first describe the multiple effects of steroids in the nervous system, which may be significant in the ageing process. A critical update of HRT use in women and a discussion of possible prospectives for steroid use are subsequently proposed.
PMID: 17135285

BMC Neurosci. 2006 Nov 3;7:74 (Full text article free online)
Estrogen protects neuronal cells from amyloid beta-induced apoptosis via regulation of mitochondrial proteins and function.
Nilsen J, **Chen S**, **Irwin RW**, **Iwamoto S**, **Brinton RD**.
Department of Pharmacology and Pharmaceutical Sciences, School of Pharmacy, University of Southern California, Los Angeles, California 90033, USA.

BACKGROUND: Neurodegeneration in Alzheimer's disease is associated with increased apoptosis and parallels increased levels of amyloid beta, which can induce neuronal apoptosis. Estrogen exposure prior to neurotoxic insult of hippocampal neurons promotes neuronal defence and survival against neurodegenerative insults including amyloid beta. Although all underlying molecular mechanisms of amyloid beta neurotoxicity remain undetermined, mitochondrial dysfunction, including altered calcium homeostasis and Bcl-2 expression, are involved in neurodegenerative vulnerability. RESULTS: In this study, we investigated the mechanism of 17beta-estradiol-induced

prevention of amyloid beta-induced apoptosis of rat hippocampal neuronal cultures. Estradiol treatment prior to amyloid beta exposure significantly reduced the number of apoptotic neurons and the associated rise in resting intracellular calcium levels. Amyloid beta exposure provoked down regulation of a key antiapoptotic protein, Bcl-2, and resulted in mitochondrial translocation of Bax, a protein known to promote cell death, and subsequent release of cytochrome c. E2 pretreatment inhibited the amyloid beta-induced decrease in Bcl-2 expression, translocation of Bax to the mitochondria and subsequent release of cytochrome c. Further implicating the mitochondria as a target of estradiol action, in vivo estradiol treatment enhanced the respiratory function of whole brain mitochondria. In addition, estradiol pretreatment protected isolated mitochondria against calcium-induced loss of respiratory function. CONCLUSION: Therefore, we propose that estradiol pretreatment protects against amyloid beta neurotoxicity by limiting mitochondrial dysfunction via activation of antiapoptotic mechanisms.
PMID: 17083736

Lancet 1996 Aug 17;348(9025):429-32
Effect of oestrogen during menopause on risk and age at onset of Alzheimer's disease.
Tang MX, Jacobs D, Stern Y, Marder K, Schofield P, Gurland B, Andrews H, Mayeux R
Gertrude H Serglevsky Center, Columbia University, New York, NY 10032, USA.

BACKGROUND: Oestrogen use by postmenopausal women has many health benefits, but findings on the effect of oestrogen in Alzheimer's disease are conflicting. Oestrogen promotes the growth and survival of cholinergic neurons and could decrease cerebral amyloid deposition, both of which may delay the onset or prevent Alzheimer's disease. To investigate whether use of oestrogen during the postmenopausal period affects the risk of Alzheimer's disease, we studied 1124 elderly women who were initially free of Alzheimer's disease, Parkinson's disease, and stroke, and who were taking part in a longitudinal study of aging and health in a New York City community. METHODS: Relative risks and age-at-onset distributions were calculated from simple and adjusted Cox proportional hazards models. Standard annual clinical assessments and criterion-based diagnoses were used in follow-up (range 1-5 years). FINDINGS: Overall, 156 (12.5%) women reported taking oestrogen after onset of menopause. The age at onset of Alzheimer's disease was significantly later in women who had taken oestrogen than in those who did not and the relative risk of the disease was significantly reduced (9/156 [5.8%] oestrogen users vs 158/968 [16.3%] nonusers; 0.40 [95% Cl 0.22-0.85], $p < 0.01$), even after adjustment for differences in education, ethnic origin, and apolipoprotein-E genotype. Women who had used oestrogen for longer than 1 year had a greater reduction in risk; none of 23 women who were taking oestrogen at study enrollment has developed Alzheimer's disease. INTERPRETATION: Oestrogen use in postmenopausal women may delay the onset and decrease the risk of Alzheimer's disease. Prospective studies are needed to establish the dose and duration of oestrogen required to provide this benefit and to assess its safety in elderly postmenopausal women.

Ophthalmic Epidemiol. 2005 Feb;12(1):37-45
Hormone replacement therapy, reproductive factors, and age-related macular degeneration: the Salisbury Eye Evaluation Project
Freeman EE, **Munoz B**, **Bressler SB**, **West SK**.
Dana Center for Preventive Ophthalmology, Wilmer Eye Institute, Johns Hopkins Hospital, Baltimore, MD 21287

PURPOSE: To evaluate a potential relationship between hormone replacement therapy (HRT), reproductive factors and age-related macular degeneration (AMD). METHODS: 1,458 female participants (age 65-84) from the Salisbury Eye Evaluation study were available for this cross-sectional analysis. AMD outcomes were identified by reading center assessment of fundus photographs. RESULTS: Women who currently used HRT had a lower adjusted odds of large drusen (> 125 microm). Use of HRT was not statistically significantly associated with the prevalence of early AMD or advanced AMD, although the odds ratios were all much less than 1. Women who had had an increased number of births had a greater prevalence of large drusen (test of linear trend, $p = 0.03$). CONCLUSIONS: Current use of HRT was associated with a lower odds of large drusen, which may be predictive of advanced AMD. No statistically significant correlations were found between HRT or reproductive factors and early or advanced AMD.
PMID: 15848919

Arch Ophthalmol. 2006 Jul;124(7):988-92
Hormone therapy and age-related macular degeneration: the Women's Health Initiative Sight Exam Study
Haan MN, **Klein R**, **Klein BE**, **Deng Y**, **Blythe LK**, **Seddon JM**, **Musch DC**, **Kuller LH**, **Hyman LG**, **Wallace RB**.
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OBJECTIVE: To determine the effectiveness of treatment with conjugated equine estrogens (CEE) or with CEE combined with progestin (CEE + P) on age-related macular degeneration (AMD). METHODS: In an ancillary study to the Women's Health Initiative clinical trial of hormone therapy, 4262 women 65 years and older underwent fundus photography for the determination of AMD. Participants were recruited from April 2000 to June 2002 at 21 clinical sites an average of 5 years after randomization. Participants were randomized to treatment with CEE, CEE + P, or placebo. Participants had been treated for an average of 5 years at the ophthalmic evaluation for AMD. RESULTS: The overall prevalence of any AMD was 21.0%. No association was found between CEE + P and early-stage AMD. The CEE + P

was associated with a reduced risk of soft drusen after adjustment for covariates and with a reduced risk of neovascular AMD. CONCLUSIONS: Treatment with CEE alone or CEE + P does not affect early- or late-stage AMD. Treatment with CEE + P may reduce the risk of soft drusen or neovascular AMD.
PMID: 16832022

Funct Neurol 2000;15 Suppl 3:143-53
Migraine associated with menstruation.
MacGregor A.
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Many women report increased frequency of migraine in association with menstruation. The term 'menstrual' migraine is often used despite lack of an agreed definition. The International Headache Society has classified most headaches but not 'menstrual' migraine. A proposed definition is based on the finding that the prevalence of migraine increases on day 1 +/- 2 of the menstrual cycle. Attacks occurring at this time of the cycle are typically without aura. Effective acute therapy is the mainstay of management for menstrual and non-menstrual attacks although there is some evidence that attacks linked to menstruation are less responsive to treatment compared with migraine at other times of the cycle. If several attacks occur throughout the cycle, standard prophylactic agents should be used. Women with exclusive 'menstrual' migraine may benefit from perimenstrual prophylaxis but this should only be instigated once the association between migraine and menstruation has been confirmed with prospective records kept or a minimum of three cycles. NSAIDs are the treatment of choice in reducing migraine associated with menorrhagia and/or dysmenorrhea, otherwise perimenstrual oestrogen supplements using percutaneous or transdermal oestrogens are recommended. Combined oral contraceptives are useful for women requiring contraception although there is a tendency for attacks to occur during the pill-free interval. If these are contraindicated, depot progestogen is an alternative as it also inhibits ovulation and can improve migraine, provided amenorrhea is achieved. Oral progestogen-only contraception has little place in the management of 'menstrual' migraine as it does not inhibit ovulation and is often associated with a disrupted menstrual cycle. Some women consulting with menstrual migraine are menopausal and may be considering hormone replacement therapy. Studies suggest that non-oral routes of delivery of oestrogen, which provide stable levels, are more likely to improve migraine than oral oestrogens, which produce variable day-to-day levels. Too low a dose of oestrogen is ineffective at controlling symptoms but too high a dose, particularly if coupled with surges of endogenous oestrogen, can trigger migraine aura. Once the route and dose has been optimized, continuous oestrogens can control migraine as well as menopausal symptoms. Additional progestogen, necessary for unhysterectomised women, can exacerbate migraine. To minimize this, progesterone derivatives or non-oral routes of delivery are recommended, with continuous regimens used where possible.

Obstet Gynecol. 2004 Mar;103(3):440-6
Rapid loss of hip fracture protection after estrogen cessation: evidence from the National Osteoporosis Risk Assessment.
Yates J, Barrett-Connor E, Barlas S, Chen YT, Miller PD, Siris ES.
Merck and Company, Inc., Upper Gwynedd, Pennsylvania, USA

OBJECTIVE: Since the findings from the Women's Health Initiative became available in July 2002, millions of women have discontinued postmenopausal hormone therapy (HT). The objective of this study was to evaluate the association between HT cessation and hip fracture risk. METHODS: Women who participated in the National Osteoporosis Risk Assessment and completed the 12-month follow-up survey were studied. All participants were aged at least 50 years, were postmenopausal, and had no previous diagnosis of osteoporosis. Baseline and 12-month follow-up questionnaires assessed use of HT and incident fractures. Of the 140,584 women in this study, 269 reported an incident hip fracture. A logistic regression model was used to assess association between HT use and incident hip fracture, controlling for potential confounders. RESULTS: Consistent with the Women's Health Initiative, women in National Osteoporosis Risk Assessment who were currently on HT had a 40% lower incidence of hip fractures compared with those who nver used HT. Women who stopped using HT more than 5 years earlier had similar hip fracture risk to never users, as expected. However, surprisingly, women who had discontinued HT within the previous 5 years had an increased hip fracture odds ratio of 1.65 (95% confidence interval 1.05, 2.59) relative to never users of HT. CONCLUSION: Postmenopausal women who have discontinued HT within the past 5 years have a risk for hip fracture that is at least as high as that in women who have never used HT.

Menopause. 2003 Sep-Oct;10(5):390-8
Comment in: Menopause. 2003 Sep-Oct;10(5):383-4.
Transdermal testosterone therapy improves well-being, mood, and sexual function in premenopausal women.
Goldstat R, Briganti E, Tran J, Wolfe R, Davis SR.
Jean Hailes Foundation Research Unit, Clayton, Victoria, Australia.

OBJECTIVE: Circulating testosterone in women declines during the late reproductive years such that otherwise healthy women in their

40s have approximately half the testosterone level as women in their 20s. Despite this, research showing the benefits of androgen replacement has been limited to the postmenopausal years. In view of the known premenopausal physiological decline in testosterone, we have evaluated the efficacy of transdermal testosterone therapy on mood, well-being, and sexual function in eugonadal, premenopausal women presenting with low libido. DESIGN: Premenopausal women with low libido participated in a randomized, placebo-controlled, crossover, efficacy study of testosterone cream (10 mg/day) with two double-blind, 12-week, treatment periods separated by a single-blind, 4-week, washout period. RESULTS: Thirty-four women completed the study per protocol, with 31 women (mean age 39.7 +/- 4.2 years; serum testosterone 1.07 + 0.50 nmol/L) providing complete data. Testosterone therapy resulted in statistically significant improvements in the composite scores of the Psychological General Well-Being Index [+12.9 (95% CI, +4.6 to +21.2), P = 0.003] and the Sabbatsberg Sexual Self-Rating Scale [+15.7 (95% CI, +6.5 to +25.0), P = 0.001] compared with placebo. A mean decrease in the Beck Depression Inventory score approached significance [-2.8 (95% CI, -5.7 to +0.1), P = 0.06]. Mean total testosterone levels during treatment were at the high end of the normal range, and estradiol was unchanged. No adverse effects were reported. CONCLUSIONS: Testosterone therapy improves well-being, mood, and sexual function in premenopausal women with low libido and low testosterone. As a substantial number of women experience diminished sexual interest and well-being during their late reproductive years, further research is warranted to evaluate the benefits and safety of longer-term intervention.
PMID: 14501599

Mayo Clin Proc. 2004 Apr;79(4 Suppl):S19-24
The role of androgens in female sexual dysfunction.
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There are many treatment options for female sexual dysfunction (FSD), with the optimal therapy depending on the etiology of the problem. The cause of sexual dysfunction is multifactorial and may include psychological problems such as depression or anxiety disorders, conflict within the relationship, partner performance and technique, issues relating to prior abuse, medical illness, medications, fatigue, stress, or gynecological problems that make sexual activity uncomfortable. The role of low androgen concentrations in FSD is gaining increasing attention. Available therapeutic options include adjusting medications, counseling, treating depression or anxiety, reducing stress and fatigue, sex therapy, devices, estrogen therapy for genitourinary atrophy, and possibly vasoactive substances. Although no androgen therapies are currently approved by the Food and Drug Administration for FSD, they are being used in clinical practice, and early clinical trial results suggest that they may be both effective and safe in the treatment of FSD, specifically low libido. Androgen therapy should be considered primarily in women who have a physiological reason for reduced androgen concentrations, including aging, hypopituitarism, oophorectomy, or adrenal insufficiency... Possible risks include hirsutism, acne, liver dysfunction, lowering of the voice, adverse lipid changes, virilization of a female fetus, and, as androgens are aromatized to estrogens, potentially the risks of estrogen therapy.

N Engl J Med. 2000 Sep 7;343(10):682-8
Comment in: Curr Psychiatry Rep. 2001 Jun;3(3):179-80, N Engl J Med. 2000 Sep 7;343(10):730-1.
Transdermal testosterone treatment in women with impaired sexual function after oophorectomy.
Shifren JL, Braunstein GD, Simon JA, Casson PR, Buster JE, Redmond GP, Burki RE, Ginsburg ES, Rosen RC, Leiblum SR, Caramelli KE, Mazer NA.
Department of Obstetrics and Gynecology, Massachusetts General Hospital, Boston 02114, USA.

BACKGROUND: The ovaries provide approximately half the circulating testosterone in premenopausal women. After bilateral oophorectomy, many women report impaired sexual functioning despite estrogen replacement. We evaluated the effects of transdermal testosterone in women who had impaired sexual function after surgically induced menopause. METHODS: Seventy-five women, 31 to 56 years old, who had undergone oophorectomy and hysterectomy received conjugated equine estrogens (at least 0.625 mg per day orally) and, in random order, placebo, 150 microg of testosterone, and 300 microg of testosterone per day transdermally for 12 weeks each. Outcome measures included scores on the Brief Index of Sexual Functioning for Women, the Psychological General Well-Being Index, and a sexual-function diary completed over the telephone. RESULTS: The mean (+/-SD) serum free testosterone concentration increased from 1.2+/-0.8 pg per milliliter (4.2+/-2.8 pmol per liter) during placebo treatment to 3.9+/-2.4 pg per milliliter (13.5+/-8.3 pmol per liter) and 5.9+/-4.8 pg per milliliter (20.5+/-16.6 pmol per liter) during treatment with 150 and 300 microg of testosterone per day, respectively (normal range, 1.3 to 6.8 pg per milliliter [4.5 to 23.6 pmol per liter]). Despite an appreciable placebo response, the higher testosterone dose resulted in further increases in scores for frequency of sexual activity and pleasure-orgasm in the Brief index of Sexual Functioning for Women (P=0.03 for both comparisons with placebo). At the higher dose the percentages of women who had sexual fantasies, masturbated, or engaged in sexual intercourse at least once a week increased two to three times from base line. The positive-well-being, depressed-mood, and composite scores of the Psychological General Well-Being Index also improved at the higher dose (P=0.04, P=0.03,

and P=0.04, respectively, for the comparison with placebo), but the scores on the telephone-based diary did not increase significantly. CONCLUSIONS: In women who have undergone oophorectomy and hysterectomy, transdermal testosterone improves sexual function and psychological well-being.
PMID: 10974131

Endocr Res. 2000 Nov;26(4):505-11
DHEA replacement in women with adrenal insufficiency--pharmacokinetics, bioconversion and clinical effects on well-being, sexuality and cognition.
Arlt W, Callies F, Allolio B.
Department of Internal Medicine, University of Wurzburg, Germany.

Standard replacement for adrenal insufficiency (AI) consists of glucocorticoids and mineralocorticoids while DHEA deficiency is routinely ignored. Thus, AI represents the ideal pathophysiological model of isolated DHEA deficiency. We investigated the effects of DHEA replacement in 24 women with primary and secondary AI employing a double blind, placebo-controlled, randomized crossover design. A DHEA dose of 50 mg/d was chosen based on preceding single-dose pharmacokinetics and bioconversion studies. Each patient received four months of treatment with DHEA and four months placebo, with a one-month washout period. Measurements included serum steroid hormones, somatotropic parameters and psychometric assessment of well-being, mood, cognition and sexuality. Treatment with DHEA raised the initially low serum concentrations of DHEA, DHEAS, androstenedione, and testosterone into the normal range. DHEA induced a slight increase in serum IGF-I, but only in patients with primary AI, suggesting a growth hormone-mediated effect. DHEA treatment significantly improved overall wellbeing as well as scores for depression, anxiety, and their physical correlates. Furthermore, DHEA significantly increased both sexual interest and the level of satisfaction with sex. DHEA replacement had no influence on the cognitive performance, which was already on a high level at baseline. In conclusion, DHEA replacement improves well-being and sexuality in women with adrenal insufficiency. If this is due to a direct effect of DHEA on the brain, an indirect effect via increased androgen synthesis, or both, remains to be elucidated. Long-term studies in patients of both sexes are needed to further define the role of DHEA in standard replacement for adrenal insufficiency.
PMID: 11196420

N Engl J Med 1999 Feb 11;340(6):424-9
Effects of Thyroxine as Compared with Thyroxine plus Triiodothyronine in Patients with Hypothyroidism
Robertas Buneviius, M.D., Ph.D., Gintautas Kaanaviius, M.D., Ph.D., Rimas alinkeviius, M.D., and Arthur J. Prange, M.D.

Background Patients with hypothyroidism are usually treated with thyroxine (levothyroxine) only, although both thyroxine and triiodothyronine are secreted by the normal thyroid gland. Whether thyroid secretion of triiodothyronine is physiologically important is unknown. *Methods* We compared the effects of thyroxine alone with those of thyroxine plus triiodothyronine (liothyronine) in 33 patients with hypothyroidism. Each patient was studied for two five-week periods. During one period, the patient received his or her usual dose of thyroxine. During the other, the patient received a regimen in which 50 µg of the usual dose of thyroxine was replaced by 12.5 µg of triiodothyronine. The order in which each patient received the two treatments was randomized. Biochemical, physiologic, and psychological tests were performed at the end of each treatment period. *Results* The patients had lower serum free and total thyroxine concentrations and higher serum total triiodothyronine concentrations after treatment with thyroxine plus triiodothyronine than after thyroxine alone, whereas the serum thyrotropin concentrations were similar after both treatments. Among 17 scores on tests of cognitive performance and assessments of mood, 6 were better or closer to normal after treatment with thyroxine plus triiodothyronine. Similarly, among 15 visual-analogue scales used to indicate mood and physical status, the results for 10 were significantly better after treatment with thyroxine plus triiodothyronine. The pulse rate and serum sex hormone–binding globulin concentrations were slightly higher after treatment with thyroxine plus triiodothyronine, but blood pressure, serum lipid concentrations, and the results of neurophysiologic tests were similar after the two treatments. *Conclusions* In patients with hypothyroidism, partial substitution of triiodothyronine for thyroxine may improve mood and neuropsychological function; this finding suggests a specific effect of the triiodothyronine normally secreted by the thyroid gland.

J Endocrinol Invest. 2002 Feb;25(2):106-9
Levothyroxine therapy and serum free thyroxine and free triiodothyronine concentrations.
Woeber KA.
Department of Medicine, University of California, San Francisco/Mount Zion, San Francisco 94143-1640, USA.

Although the normal thyroid gland secretes both levothyroxine (L-T4) and levotriiodothyronine (L-T3), normalization of serum TSH with L-T4-replacement therapy alone in hypothyroidism is generally believed to result in a normal serum L-T3 and to reflect a euthyroid state. However several recent studies suggest that this may not be the case. Accordingly, the relationship between serum free L-T4 and free L-

T3 was examined in 20 normal individuals (group A) and in 53 patients with chronic autoimmune thyroiditis, 18 with normal TSH on no L-T4-replacement (group B), and 35 with normal TSH on L-T4-replacement therapy for hypothyroidism (group C). Data were analyzed by applying a one-way analysis of variance with correction for multiple comparisons. Serum TSH values were very similar among the 3 groups. In groups A and B, mean serum free T4 and free T3 were very similar. In group C, the mean free T4 (16+/-2 pmol/l) was significantly higher than the values in groups A (14+/-1) and B (14+/-2) ($p<0.001$) and the mean free T3 lower (4.0+/-0.5 pmol/l vs 4.2+/-0.5, NS and 4.4+/-0.5, $p<0.02$). Consequently, the mean molar ratio of free T4 to free T3 was significantly higher in group C than the ratios in groups A and B ($p<0.0001$), despite very similar TSH values. These findings indicate that in hypothyroid patients L-T4-replacement, that is sufficient to maintain a normal serum TSH, is accompanied by a serum free T4 that is higher than that in untreated euthyroid patients or normal individuals and may not result in an appropriately normal serum free T3 concentration.
PMID: 11929079

Supporting Literature: Hormone Therapy for Men

Asian J Androl. 2016 Jan-Feb;18(1):25-34.
Effects of long-term androgen replacement therapy on the physical and mental statuses of aging males with late-onset hypogonadism: a multicenter randomized controlled trial in Japan (EARTH Study).
Konaka H, Sugimoto K, Orikasa H, Iwamoto T, Takamura T, Takeda Y, Shigehara K, Iijima M, Koh E, Namiki M; EARTH study group.
Department of Integrative Cancer Therapy and Urology, Kanazawa University Graduate School of Medical Science, Kanazawa, Ishikawa, Japan.

Androgen replacement therapy was associated with significant decreases in waist circumstance and serum triglycerides; with significant increases in whole-body and leg muscle mass volumes, serum hemoglobin, IPSS voiding subscore, and a positive effect on erectile function. There was no significant difference between the groups in terms of severe adverse events.
PMID: 25761833

Korean J Urol. 2015 Apr;56(4):310-7.
Elderly men over 65 years of age with late-onset hypogonadism benefit as much from testosterone treatment as do younger men.
Saad F, Yassin A, Haider A, Doros G, Gooren L

To investigate the potential benefits of testosterone administration to elderly men (>65 years) with late-onset hypogonadism (LOH) in comparison with younger men and to assess the safety of testosterone administration to elderly men. A total of 561 hypogonadal men from two registry studies were divided into age groups of ≤65 years (group Y, n=450; range, 32-65 years) and >65 years (group O, n=111; range, 66-84 years). Following an initial 6-week interval, all men were treated with 3-month injections of parenteral testosterone undecanoate for up to 6 years. Over the 6 years, there was a progressive decrease of body weight and waist circumference. Beneficial effects on lipids and other metabolic factors and on psychological and sexual functioning progressed over the first 24 to 42 months and were sustained. Rather than a deterioration, there was an improvement of urinary parameters. Prostate volume and prostate-specific antigen increased moderately. Hematocrit levels increased but remained within safe margins. **The benefits of restoring serum testosterone in men with LOH were not significantly different between men older than 65 years of age and younger men. There were no indications that side effects were more severe in elderly men. The effects on prostate and urinary function and hematocrit were within safe margins. Age itself need not be a contraindication to testosterone treatment of elderly men with LOH.**
PMID: 25874045

Curr Atheroscler Rep. 2015 Mar;17(3):490.
The role of testosterone therapy in cardiovascular mortality: culprit or innocent bystander?
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Testosterone therapy is recommended for men with symptomatic androgen deficiency and unequivocally low testosterone levels. Although the prevalence of hypogonadism seems relatively constant, studies of prescribing patterns in both the United States and the United Kingdom show a dramatic increase in testosterone prescription in recent years, possibly due to increased marketing and inappropriate therapy. Concurrent with this, there has been growing concern regarding the potential adverse effects of testosterone therapy, particularly its cardiovascular risks. In this review, we present our current understanding of the implications of testosterone deficiency, as well as the conflicting evidence surrounding the cardiovascular effects of testosterone replacement therapy. Although there is a lack of adequate data, based on the current evidence, we conclude that testosterone therapy can be safely considered in men

with appropriately diagnosed clinical androgen deficiency and increased cardiovascular risk after a thorough discussion of potential risks and with guideline recommended safety monitoring.
PMID: 25687258

Horm Mol Biol Clin Investig. 2015 Jun;22(3):111-7.
Testosterone therapy in men with Crohn's disease improves the clinical course of the disease: data from long-term observational registry study.
Nasser M, Haider A, Saad F, Kurtz W, Doros G, Fijak M, Vignozzi L, Gooren L.

Crohn's disease is an inflammatory chronic bowel disease characterized by an imbalanced production of pro-inflammatory mediators (tumor necrosis factor-α) and an increased recruitment of leukocytes to the site of inflammation. Low serum testosterone is associated with an increase in inflammatory factors, while testosterone administration reduces them. There is evidence for an immunomodulatory effect of testosterone on differentiation of regulatory T cells. The research was carried out in clinics in Germany and Syria. The study was a cumulative, prospective, registry study with an increasing number of men over time receiving testosterone. While men diagnosed with Crohn's disease received appropriate treatment for Crohn's disease, they were tested for testosterone deficiency (cut-off point ≤12.1 nmol/L). In total, 92 men received parenteral testosterone undecanoate 1000 mg/12 weeks for up to 7 years. Fourteen men opted not to receive testosterone and served as a comparison group. In men receiving testosterone, the Crohn's Disease Activity Index declined from 239.36±36.96 to 71.67±3.26 at 84 months (p<0.0001 vs. baseline). C-reactive protein levels decreased from 12.89±8.64 to 1.78±1.37 mg/L at 84 months (p<0.0001 vs. baseline). Leukocyte count decreased from 11.93±2.85 to 6.21±1.01×109/L (p<0.0001 at 84 months vs. baseline). No changes were observed in the comparison group. There were no significant side effects of testosterone.
CONCLUSION: Normalizing serum testosterone in hypogonadal men with Crohn's disease had a positive effect on the clinical course, also evidenced by biochemical parameters. Testosterone administration appeared safe.
PMID: 26020563

Int J Pharm Compd. 2015 May-Jun;19(3):195-203.
Compounded Testosterone Troches TO OPTIMIZE HEALTH AND THE TESTOSTERONE CONTROVERSY.
Guth MA.

As men age, testosterone levels progressively fall and inflammatory biomarkers increase. The gradual decline in testosterone production with aging, known as andropause, is common and may have deleterious effects on men including decreased overall well-being, increased sarcopenia, increased risk of cardiovascular disease, reduced sexual function, and bone loss. Therefore, it comes as no surprise that an increasing number of men worldwide have begun requesting testosterone replacement therapy from their physicians. Occasionally, physicians discourage male patients from getting testosterone replacement therapy based on a few recent studies indicating the therapy causes cardiovascular events, including myocardial infarctions. Yet, an extensive review of the testosterone replacement therapy literature reveals that the majority of clinical studies show that properly administered testosterone replacement therapy, in which estradiol and dihydrotestosterone levels are also controlled, has no adverse effects on myocardial infarction risk. The current state-of-the-art in testosterone replacement therapy comprises compounded testosterone troches; an aromatase inhibitor, such as generic Anastrazole, to control estradiol levels; and a 5α-reductase inhibitor, such as beneric Dutasteride or Finasteride, to control dihydrotestosterone. Compounded testosterone troches easily raise serum testosterone levels to the optimal range, are highly cost effective at $82 for a 180-day supply, and provide affordable access to testosterone replacement therapy to millions of men requesting it. Yet, the Blue Cross Blue Shield-associated firms have largely denied requests for coverage of compounded medications, including testosterone troches. Despite data demonstrating strong links between testosterone deficiency and significant comorbid conditions (including Type 2 diabetes and other metabolic syndrome diseases) as well as the health benefits of testosterone replacement therapy, some physian have been swayed against prescribing testosterone replacement therapy to their aging male patients. The testosterone controversy stems largely from poorly designed clinical studies in which patients were subjected to testosterone replacement therapy without having their estradiol and dihydrotestosterone levels properly controlled.
PMID: 26714360

Cancer. 2006 Dec 20;109(3):536-541 [Epub ahead of print]
Testosterone replacement for hypogonadism after treatment of early prostate cancer with brachytherapy
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South Texas Urology and Urologic Oncology, San Antonio, Texas.

BACKGROUND: Controversy and a notable paucity of published clinical data best characterize the current knowledge of testosterone-replacement therapy (TRT) for hypogonadism after treatment for early, localized prostate cancer. The objective of this study was to assess the risk of biochemical failure with TRT after treatment of early prostate cancer with permanent transperineal brachytherapy with

or without external beam therapy in patients with low serum levels of testosterone and clinical symptoms of hypogonadism. METHODS: Patients who underwent prostate brachytherapy from 1996 to 2004 and received subsequent TRT for symptomatic hypogonadism were reviewed to detail cancer characteristics and treatment as well as pre- and post-TRT serum testosterone and prostate-specific antigen (PSA) values. RESULTS: Thirty-one men received TRT after prostate brachytherapy for 0.5 to 8.5 years (median, 4.5 years), with a follow-up that ranged from 1.5 years to 9.0 years (median, 5.0 years) postbrachytherapy. TRT was started from 0.5 years to 4.5 years (median, 2.0 years) after brachytherapy. Serum total testosterone levels ranged from 30 ng/dL to 255 ng/dL (median, 188 ng/dL) before TRT and rose to 365 ng/dL to 1373 ng/dL (median, 498 ng/dL) on TRT. Transient rises in PSA were observed in 1 patient. The most recent PSA level was <0.1 ng/mL in 23 patients (74.2%), <0.5 ng/mL in 30 patients (96.7%), and <1 ng/mL in 31 patients (100%). No patients stopped TRT because of cancer recurrence or documented cancer progression. CONCLUSIONS: For patients with low serum testosterone levels and symptoms of hypogonadism, TRT may be used with caution and close follow-up after prostate brachytherapy.
PMID: 17183557

Aging Male. 2006 Dec;9(4):201-6
Testosterone and erectile physiology
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The role of testosterone deficiency in sexual dysfunction is an important aspect of aging, because it affects such a large proportion of men over 50 years old. A number of age-related factors can cause sexual dysfunction (in particular erectile dysfunction) and testosterone deficiency, such as chronic illness and multiple medications, and the causative link between hypogonadism and erectile dysfunction is still debated. However, studies in castrated animals have proven that addition of testosterone, and its conversion to dihydrotestosterone, can restore erectile function. It appears that testosterone achieves this by peripheral mechanisms (endothelial dependent and independent) and central mechanisms. Testosterone replacement therapy is therefore effective for erectile dysfunction in men with hypogonadism, with success rates of 35-40%. Testosterone supplementation is also important in men who fail on phosphodiesterase type-5 inhibitors, because a minimum plasma concentration of testosterone is required for the successful restoration of erectile function with these agents. Testosterone gels are now the preferred formulation for testosterone supplementation and they can be highly beneficial in a proportion of men with erectile dysfunction.
PMID: 17178555

Int J Clin Pract. 2006 Sep;60(9):1087-92
The evolving role of testosterone in the treatment of erectile dysfunction
Shabsigh R, **Rajfer J**, **Aversa A**, **Traish AM**, **Yassin A**, **Kalinchenko SY**, **Buvat J**.
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Hypogonadism may play a significant role in the pathophysiology of erectile dysfunction (ED). A threshold level of testosterone may be necessary for normal erectile function. Testosterone replacement therapy is indicated in hypogonadal patients and is beneficial in patients with ED and hypogonadism. Monotherapy with testosterone for ED is of limited effectiveness and may be most promising in young patients with hypogonadism and without vascular risk factors for ED. A number of laboratory and human studies have shown the combination of testosterone and other ED treatments, such as phosphodiesterase type 5 (PDE5) inhibitors, to be beneficial in patients with ED and hypogonadism, who fail PDE5 inhibitor therapy alone. There is increasing evidence that combination therapy is effective in treating the symptoms of ED in patients for whom treatment failed with testosterone or PDE5 inhibitors alone. Testosterone replacement therapy has potentially evolved from a monotherapy for ED in cases of low testosterone, to a combination therapy with PDE5 inhibitors. Screening for hypogonadism may be useful in men with ED who fail prior PDE5 inhibitors, especially in populations at risk for hypogonadism such as type 2 diabetes and the metabolic syndrome.
PMID: 16939550

J Sex Med. 2005 Nov;2(6):785-92
Testosterone therapy in erectile dysfunction and hypogonadism
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INTRODUCTION: Laboratory experiments indicate that the nitric oxide erectile pathway is testosterone-dependent. Castration induces erectile dysfunction (ED) and reduction in nitric oxide synthase and in phosphodiesterase type 5 (PDE5) in the erectile tissue. Furthermore, castration causes apoptosis adversely affecting smooth muscle content and penile hemodynamics leading to veno-occlusive dysfunction. Testosterone therapy reverses these structural, biochemical, and physiological changes. In humans, testosterone therapy improves erectile function in men with hypogonadism. However, the efficacy of testosterone monotherapy may not be adequate

because of the multifactorial nature of the pathophysiology of ED. METHODS: Preliminary data from a number of studies have been reviewed. RESULTS: There are emerging evidence-based benefits to using the combination of testoterone and PDE5 inhibitors. A recently published multicenter, randomized, placebo-controlled study evaluated the safety and efficacy of testosterone gel 1% plus sildenafil vs. placebo gel plus sildenafil, in producing an erectile response in hypogonadal men who had failed prior sildenafil alone for ED. Screening yielded a prevalence of hypogonadism in ED patients who failed prior sildenafil. Following randomization, the double-blinded treatment phase was 12 weeks. Testosterone therapy with testosterone gel significantly improved erectile function in response to sildenafil. In addition, it significantly improved orgasmic function and patient satisfaction. CONCLUSION: It is important to screen all men with ED for hypogonadism, especially those with a history of inadequate response to prior PDE5 inhibitors. The combination of testosterone plus PDE5 inhibitors may be considered for the treatment of ED in men with low to low-normal testosterone levels, who had inadequate response to prior treatment with PDE5 inhibitors alone.
PMID: 16422803

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Association of testosterone and estradiol deficiency with osteoporosis and rapid bone loss in older men
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CONTEXT: The clinical value of measuring testosterone and estradiol in older men with osteoporosis and of measuring bone mineral density (BMD) in older men with testosterone or estradiol deficiency is uncertain. OBJECTIVE: The objective of the study was to examine the association of testosterone and estradiol deficiency with osteoporosis and rapid bone loss in older men. DESIGN: This study was a cross-sectional and longitudinal analysis. Setting: The study was conducted at six U.S. centers of the Osteoporotic Fractures in Men study. PARTICIPANTS: The study population consisted of 2447 community-dwelling men aged 65 yr or older. MAIN OUTCOME MEASURES: Total testosterone deficiency was defined as less than 200 ng/dl. Total estradiol deficiency was defined as less than 10 pg/ml. Osteoporosis was defined as femoral neck or total hip BMD T-score of -2.5 or less. Rapid bone loss was defined as 3%/yr or more. RESULTS: Prevalence of osteoporosis in men with deficient and normal total testosterone was 12.3 and 6.0% (P = 0.003) and 15.4 and 2.8% (P < 0.0001) in those with deficient and normal total estradiol. Among osteoporotic men and those with normal BMD, prevalence of total testosterone deficiency was 6.9 and 3.2% (P = 0.01), and prevalence of total estradiol deficiency was 9.2 and 2.4% (P = 0.0001). Incidence of rapid hip bone loss in men with deficient and normal total testosterone was 22.5 and 8.6% (p = 0.007) and in those with deficient and normal total estradiol was 14.3 and 6.3% (p = 0.08). CONCLUSIONS: Older men with total testosterone or estradiol deficiency were more likely to be osteoporotic. Those with osteoporosis were more likely to be total testosterone or estradiol deficient. Rapid hip bone loss was more likely in men with total testosterone deficiency. BMD testing of older men with sex steroid deficiency may be clinically warranted.
PMID: 16849417

Aging Male. 2006 Dec;9(4):195-9
Testosterone and the brain
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Gender differences in spatial recognition, and age-related declines in cognition and mood, point towards testosterone as an important modulator of cerebral functions. Testosterone appears to activate a distributed cortical network, the ventral processing stream, during spatial cognition tasks, and addition of testosterone improves spatial cognition in younger and older hypogonadal men. In addition, reduced testosterone is associated with depressive disorders. The relationship between depression and testosterone appears to partly depend upon the androgen receptor genotype of the patient, and in appropriate patients with low testosterone levels, testosterone substitution can increase positive mood and decrease negative mood. The much publicized link between testosterone and aggression is probably only of importance in athletes who supplement their testosterone levels to excessively high levels, whereas in hypogonadal men, testosterone supplementation only enhances the positive aspects of aggression such as vigour and energy. Current data suggest that testosterone supplementation in hypogonadal men of all ages will enhance many aspects of mood and cognition.
PMID: 17178554

Diabetes Care 2000 Apr;23(4):490-4
Testosterone, sex hormone-binding globulin, and the development of type 2 diabetes in middle-aged men: prospective results from the Massachusetts male aging study.
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OBJECTIVE: The objective was to examine prospectively the association between low testosterone and sex hormone-binding globulin (SHBG) levels and the subsequent development of type 2 diabetes in men. RESEARCH DESIGN AND METHODS: Analyses were conducted on the cohort of the Massachusetts Male Aging Study, a population-based random sample of men aged 40-70. Of the 1,709 men enrolled in 1987-1989 (T1), 1,156 were followed up 7-10 years later (T2). Testosterone and SHBG levels at T1 were used to predict new cases of diabetes between T1 and T2. RESULTS: After controlling for potential confounders, diabetes at follow-up was predicted jointly and independently by lower baseline levels of free testosterone and SHBG. The odds ratio for future diabetes was 1.58 for a decrease of 1SD in free testosterone (4 ng/dl) and 1.89 for a 1SD decrease in SHBG (16 nmol/l), both significant at $P < 0.02$. CONCLUSIONS: Our prospective findings are consistent with previous, mainly cross-sectional reports, suggesting that low levels of testosterone and SHBG play some role in the development of insulin resistance and subsequent type 2 diabetes.

Urology 2000 May;55(5):755-8
Serum dehydroepiandrosterone sulfate concentrations in men with erectile dysfunction.
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OBJECTIVES: In 1994, the Massachusetts Male Aging Study presented the finding of an inverse correlation of the serum levels of dehydroepiandrosterone sulfate (DHEAS) and the incidence of erectile dysfunction (ED). Prompted by the positive results of a pilot study on the treatment of ED with dehydroepiandrosterone (DHEA), we performed a detailed investigation on the serum DHEAS levels in men with ED according to age category. METHODS: Inclusion criteria included a history of ED for more than 6 months, a body mass index less than 30, and a state of good general health. Serum DHEAS concentrations were determined in 309 patients with ED and 133 healthy volunteers. All participants were carefully screened to assess medical factors known or suspected to alter endocrine function. Questions 3 and 4 of the International Index of Erectile Function were used to evaluate erectile function. RESULTS: The mean serum levels of DHEAS in patients with ED were lower than in healthy volunteers until 60 years of age. The shape o the curve of the patients with ED indicated a quadratic decrease of DHEAS with age in contrast to a more linear decrease of DHEAS with age in the control group. CONCLUSIONS: Our results suggest that until the age of 60 years, the mean serum level of DHEAS is lower in patients with ED than in healthy volunteers.

Arthritis Res. 2001;3(3):183-8. Epub 2001 Feb 21
Hyposecretion of the adrenal androgen dehydroepiandrosterone sulfate and its relation to clinical variables in inflammatory arthritis.
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Hypothalamic-pituitary-adrenal underactivity has been reported in rheumatoid arthritis (RA). This phenomenon has implications with regard to the pathogenesis and treatment of the disease. The present study was designed to evaluate the secretion of the adrenal androgen dehydroepiandrosterone sulfate (DHEAS) and its relation to clinical variables in RA, spondyloarthropathy (Spa), and undifferentiated inflammatory arthritis (UIA). Eighty-seven patients (38 with RA, 29 with Spa, and 20 with UIA) were studied, of whom 54 were women. Only 12 patients (14%) had taken glucocorticoids previously. Age-matched, healthy women (134) and men (149) served as controls. Fasting blood samples were taken for determination of the erythrocyte sedimentation rate (ESR), serum DHEAS and insulin, and plasma glucose. Insulin resistance was estimated by the homeostasis-model assessment (HOMAIR). DHEAS concentrations were significantly decreased in both women and men with inflammatory arthritis (IA) ($P < 0.001$). In 24 patients (28%), DHEAS levels were below the lower extreme ranges found for controls. Multiple intergroup comparisons revealed similarly decreased concentrations in each disease subset in both women and men. After the ESR, previous glucocorticoid usage, current treatment with nonsteroidal anti-inflammatory drugs, duration of disease and HOMAIR were controlled for, the differences in DHEAS levels between patients and controls were markedly attenuated in women ($P = 0.050$) and were no longer present in men ($P = 0.133$). We concluded that low DHEAS concentrations are commonly encountered in IA and, in women, this may not be fully explainable by disease-related parameters. The role of hypoadrenalism in the pathophysiology of IA deserves further elucidation. DHEA replacement may be indicated in many patients with IA, even in those not taking glucocorticoids.
PMID: 11299059

Our compounding professionals work together with patients and practitioners to provide customized hormone therapy in the most appropriate strength and dosage form to meet each man or woman's specific needs. Hormone therapy should be initiated carefully after a complete medical and family history have been reviewed. Every person is unique and will respond to therapy in his or her own way; therefore the selection of hormone(s), dose, dosage form, and route of administration should be specific to each patient. Close monitoring and medication adjustments are important to minimize the risk of side effects.

NOTES:

- Before initiating hormone therapy, it's important to check baseline levels, and to monitor levels during therapy. Convenient, inexpensive home testing is available. Blood spot or saliva testing can be recommended based on the hormones being checked, and if oral or transdermal therapy is used.
- Our compounding pharmacy puts patient safety first by adhering to current regulations and compounding medications using pure ingredients from FDA-inspected facilities.

REASONS FOR CHOOSING COMPOUNDED MEDICATIONS INCLUDE:

- Patient allergies or failure to respond to commercial products
- Adverse reactions to commercial preparations; i.e., if a patient has a reaction to an adhesive on a patch, we can compound the needed medication as a transdermal cream.
- Need for a dose or dosage form that is not commercially available. For example, transdermal and vaginal creams may offer potential advantages because non-oral administration bypasses first-pass hepatic metabolism.