## Successful Aging

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# CLINICS IN GERIATRIC MEDICINE

November 2011 • Volume 27 • Number 4

# Hormone Replacement Therapy in the Geriatric Patient: Current State of the Evidence and Questions for the Future. Estrogen, Progesterone, Testosterone, and Thyroid Hormone Augmentation in Geriatric Clinical Practice: Part 1

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Geriatric medicine historically has been the domain of sick, frail, old, and aging populations of patients. Therapies for aging patients focus primarily on prolonging life, often at very high emotional and financial cost with little focus on the quality of life the patient experiences. As the proportion of aging people continues to rise, reducing the burden of age-related conditions becomes increasingly important in geriatric care. In addition, as the life expectancy of the population increases, years of disability follow unless comprehensive prevention and treatment of age-related diseases and frailty are addressed.

With the transition of the baby boomers into the geriatric population, a significant movement away from the disease-centric model and toward prevention and wellness maintenance and enhancement is taking place. The goal of this article is to present an up-to-date review of the literature on hormone augmentation in the elderly to help primary care physicians better evaluate and utilize hormone replacement and optimization strategies to benefit their patients. The scientific literature suggests that hormone supplementation with estrogen, progesterone, testosterone, growth hormone, and

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thyroid hormone has the potential to improve quality of life and to prevent, or reverse, the many symptoms and conditions associated with aging, including fatigue, depression, weight gain, frailty, osteoporosis, loss of libido, and heart disease. Much hesitation surrounds the possible long-term side effects of hormone therapies, including the potential increased risk of cancers. When attempting to find the ideal balance for the individual patient, physicians should be concerned not only with improving their patients' life spans, but also their health spans—the duration of time a person experiences a high-quality, vigorous, and enjoyable life. Toward that end, this article hopes to help clarify the often confusing area of anti-aging medicine. We believe, if properly examined, the literature in this area can provide much help and support to the aging patient.

## ESTROGEN AND PROGESTERONE

By the year 2025, there will be 1.1 billion women older than the age of 50 in the world.[1] The magnitude and significance of this number must be addressed from the perspective of the primary care practitioner who is now faced with an exploding number of aging women seeking to maintain, and even improve, their health. In these authors' opinions, women who are menopausal and postmenopausal should no longer accept a pat on the back and an antidepressant as a best therapy for postmenopausal symptoms often caused by aging and its attendant loss of hormones. We as physicians need to expand our knowledge and expertise to be able to provide aging women with safe and effective approaches to aging—to provide them with sound information to help them make the best decisions for their individual situation.

### The Women's Health Initiative

The widely accepted "gold standard" information on estrogen and progestogens in menopausal women stems overwhelmingly from the Women's Health Initiative (WHI).[2] This large-scale (>16,000 women) placebo-controlled study that started in 1991 evaluated the long-term effects of conjugated equine estrogens alone or in conjunction with medroxyprogesterone acetate (MPA) versus placebo. The study aimed to prove that Premarin (brand name for conjugated equine estrogens) and Provera (brand name for medroxyprogesterone acetate) would protect aging women from heart disease (the number one killer of menopausal and postmenopausal women), osteoporosis, and Alzheimer's disease.

The study was planned for 8.5 years but was abruptly halted 3 years before its projected termination in July of 2002 owing to a significant increase in statistical relative risk of breast cancer (1.4), myocardial infarctions, and cerebrovascular accident in the group taking active hormones.[2] The abrupt termination of the study was a very public affair, resulting in discontinuation of hormone replacement therapy (HRT) in millions of women by physicians who became fearful of using any type of hormone therapy. Due consideration was given to potential harm to the patient, possible legal ramifications, and general lack of educational support for continuation of hormone therapies in general.

The results of the study have been reviewed and reevaluated over more than 10 years. A major criticism has been that the women in the study were, on average, more than 10 years post-menopause, averaging 63 years of age at the initiation of therapy, which is usually considered old for women to start on hormone replacement, and had preexisting conditions that negatively affected outcome.[3] As recently as October 2010, further analysis of the WHI study determined that long-term (11 years) use of

conjugated estrogens and MPA is associated with more aggressive and deadlier breast cancers in the women who took the drugs.[4]

At the same time, another long-term survey in the United Kingdom, The Million Women Study, found that women started on a combination therapy of estrogen and progestin immediately post-menopause were also at higher risk of breast cancer than those who started the hormone therapies more than 5 years after menopause.[5]

Current users (but not past users) of HRT were found to be at increased risk of breast cancer, and the risk increased with increasing length of use. The implications of this survey are quite serious but have been strongly criticized because of possibly significant selection bias. The women in this survey were enrolled in the study only when they presented for routine mammography.[6] The bias exists because women going in for mammograms are not representative of the general population because they may be more likely to be part of specific socioeconomic strata and geographic locations, have concerns about breast cancer, and may have increased risk factors (eg, previous lumps, family or genetic history).

A follow-up of more than 1 million women in the Million Women Study 7 years after the initial survey found that women using an ongoing combination of estrogen and *synthetic* progestin were more likely to develop breast cancer than those who were not using HRT.[7]

The effects were similar for all types and doses of estrogen and progestagen; for oral, transdermal, and implanted HRT; and for continuous and sequential patterns of use. Current users of estrogen–progestagen HRT had a 2.0 increased risk of developing breast cancer and current users of estrogen-only HRT had a 1.3 risk. In the United Kingdom, use of HRT by women aged 50 to 64 years who had mammograms in the decade from 1993 to 2003 resulted in an estimated 20,000 extra breast cancer cases.[7]

### Making a Decision

Until recently, no distinction has been made between bioidentical and synthetic hormones, thus leaving a deficit in the public and physicians' knowledge and understanding of hormones in general.[4] With the lack of distinction between types of hormones, we have been left with treatment recommendations based solely on the information obtained from studies on *synthetic* hormones. This has led to recommendations of continued, but shorter-term, use of synthetic hormone replacement combinations.[2,8] According to an article on the American College of Obstetricians and Gynecologists (ACOG) website: "Again, there are no good studies to tell us precisely what constitutes safe short-term use. In the past, hormone therapy of five years or less was believed to be associated with little or no risk. However, the WHI study[2] found an increase in the incidence of blood clots and stroke during the first year of use, and a rise in the diagnosis of breast cancer after four years, suggesting that even the first four years of use may not be risk-free (Million Women Study). The estrogen-only arm of the WHI study did *not* show an increased risk for breast cancer after nearly seven years, but did find similar small increases in blood clots and stroke after just one or two years' use."

### Current Recommendations

The patient, working with a well-informed physician, should decide whether the benefits of using synthetic hormone replacement for relief of menopause symptoms are worth the risks that have been identified. Starting with a thorough medical evaluation and working with the patient to educate her as much as possible about the available options in hormone formulations, the physician can provide much needed

support for menopausal and postmenopausal patients. As physicians become better informed about the available options of hormone therapies, the choices patients make will become truly informed and ultimately tailored to their individual needs.

If patients choose HRT, the US Preventive Services Task Force recommends that they use the smallest effective dose for the shortest possible time and that the patient see her doctor at least once a year to discuss whether she should stop and what new information may be available that might influence the patient's decision to stop or continue using hormones.[9] (An important note: As research continues, recommendations may change.) Of course, the patient may wish to continue regular breast cancer screenings, including annual physician breast exams and periodic mammograms. (ACOG recommends mammograms every 1–2 years during the 40s, and annually thereafter while the US Preventative Services Task Force recommends testing every 2 years starting only at the age of 50.)

As with most issues concerning health, the decision to use hormones is a personal one that ultimately must be made by the patient. It is the physician's role to help the patient make sure the decision is a well informed one with which the patient feels comfortable. The more knowledgeable and informed the physician is regarding the different types of hormone therapies available and the evidence supporting them, the more information he or she can provide for the patient. Before making a decision about HRT, women should consult with their physicians for individualized advice that takes into account types of hormone therapies available, recommendations of medical societies and governmental agencies, personal needs, and medical and family history.[2,10,11]

To help physicians better understand the state of the information as it relates to WHI and the conjugated equine estrogens and MPA, the findings of the WHI are recapped here. The results of the WHI indicated that if 10,000 women were given 0.625 mg of conjugated estrogen and 2.5 mg of medroxyprogesterone and followed for 5 years, there would be eight additional cases of breast cancer, seven additional coronary events, eight additional strokes, and eight additional cases of pulmonary embolism than in those women not receiving HRT. The major question, however, is: Would the results be different if different forms (synthetic vs. bioidentical) of HRT were used?

## BIOIDENTICAL HORMONES

The WHI study did not evaluate other types of HRT; specifically, bioidentical or natural hormones. These are a class of hormones including estradiol, progesterone, and testosterone that are pharmaceutically indistinguishable from the same hormones naturally produced by the human body (as opposed to equine estrogens, which are the source of conjugated estrogens and are not a natural hormone combination for humans). Bioidentical or natural hormones have been used for decades in Europe and since the 1990s in the United States.[12–30]

### Bioidentical Versus Synthetic

The molecular differences between bioidentical and nonhuman identical hormone preparations[31] are illustrated in **Fig. 1**.

### State of the Evidence of Various Hormone Preparations in Women

The differences in action between conjugated equine estrogens, synthetic progestins, and bioidentical hormones have been described and studied extensively in the scientific literature over a period of 40 years.[32–35] Early small studies in the 1970s and
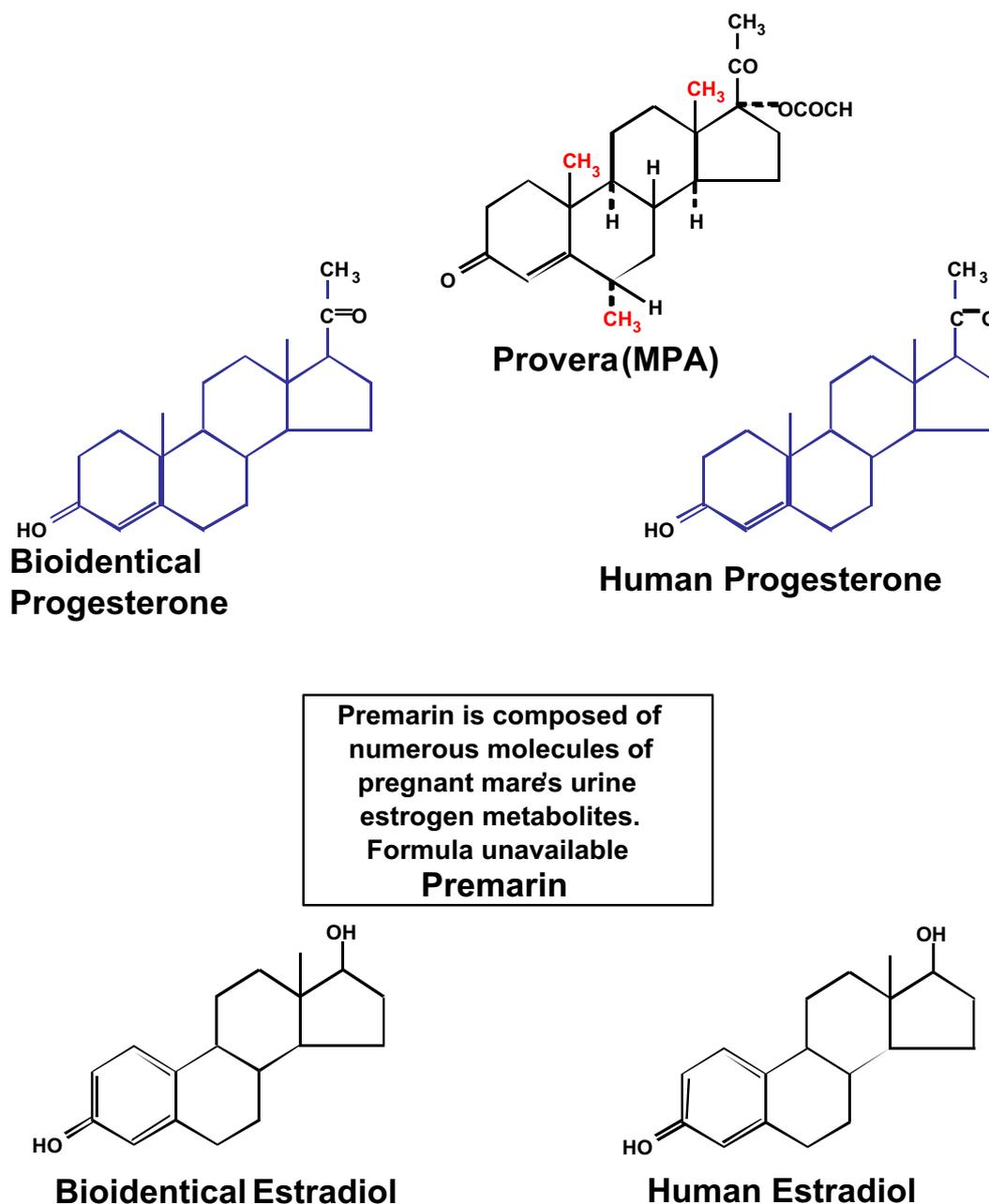
**Fig. 1.** The molecular formulas of various types of progestagens and estrogens. (*Adapted from* Schwartz E, Holtorf K. Prim Care Clin Office Pract 2008;35:669–705; with permission.)

1980s suggested the safety of bioidentical hormones, although the studies were too small to reach statistical significance.

As early as 1975, the safety of bioidentical estradiol appeared in the conventional medical literature.[20] Studies and reports of increased risk of endometrial and breast carcinoma among users of synthetic conjugated estrogens (the type of hormone preparations studied by the WHI) also appeared in the scientific literature in the 1970s.[19,36–38] By January 1978, the *Journal of the American Geriatrics Society* addressed the growing concern that treatment with exogenous synthetic estrogen could cause cancer and recommended the addition of a synthetically manufactured progestogen as a working solution.[39] Adding small doses of a progestogen (MPA) to either estradiol or conjugated estrogen (CEE) in a cycled manner was determined to be a safe solution to the carcinogenicity concern associated with the use of conjugated estrogens.[40]. It is noteworthy that in 1983, the options for treatment

studied and reported in the major medical journals included both the bioidentical 17-beta estradiol along with conjugated (synthetic) estrogens and MPA.[39,41]

An article in the *British Medical Journal* in March 1980 by Whitehead and Townsend stated that bioidentical "oral progesterone *may be* of value when synthetic progestogens have caused adverse symptoms that necessitate stopping treatment." Such symptoms include acne, breast tenderness, depression, hypertension, and adverse changes in high-density lipoprotein cholesterol. In the article, no such side effects were reported with the use of bioidentical progesterone. "Naturally occurring progesterone may not alter blood lipids and it is stable for two years and cheaper . . . and useful in treating menopause."[41(p827)]

In the 1980s and early 1990s, research scientists expressed concern that (synthetic) MPA used in hormone therapy could increase the risk of breast cancer.[42,43] At the same time, the literature contained reports of numerous small in vitro and in vivo studies hinting at the possibility of greater safety with the use of bioidentical/"natural" hormones.[19–22,32-35,38,44–49] These studies show that replacing a synthetic progestin with bioidentical progesterone results in improved efficacy, fewer side effects, improved quality of life, and greater patient satisfaction.[50–54]

For instance, Fitzpatrick and colleagues compared patient satisfaction and quality of life, as well as anxiety, depression, sleep problems, menstrual bleeding, vasomotor symptoms, cognitive difficulties, attractiveness to others, and sexual functioning in 176 menopausal women on HRT.[50] In this cross-sectional study, all women were currently on bioidentical progesterone HRT (micronized progesterone for 1–6 months) and previously had been on synthetic HRT (MPA). Patient telephone surveys found significant differences in all psychological, somatic, and vasomotor symptoms, except for attraction, when the use of bioidentical progesterone was compared to synthetic MPA ($P<.001$). Compared to MPA, bioidentical progesterone was associated with a 30% reduction in sleep problems, 50% reduction in anxiety, 60% reduction in depression, 30% reduction in somatic symptoms, 25% reduction in menstrual bleeding, 40% reduction in cognitive difficulties, and 30% improvement in sexual function. Overall, 65% of women thought that HRT consisting of estrogens combined with bioidentical progesterone was better than HRT consisting of estrogen combined with synthetic MPA.[50] Such cross-sectional data are far from conclusive, but do point out the perception of improved results among women taking natural hormones. The risk of breast cancer and heart disease could not be addressed in this telephone survey.

## RISKS AND BENEFITS
### *Physiologic Effects: Bioidentical Progesterone Versus Synthetic Progestins*

Scientific reviews of the pharmacology and action of progestins[55–61] demonstrate that all progestins and progestogens are not equal. Their actions vary significantly according to their molecular structures.[45,55–60,62–88] Although bioidentical progesterone and synthetic progestins have similar effects on endometrial tissue, they have contrasting effects on breast tissue.

### *Breast Cancer: Bioidentical Progesterone Versus Synthetic Progestins*

Synthetic progestins are shown, in vitro, to increase estrogen-stimulated breast cell mitotic activity and proliferation,[56,62–75] which increases the risk of breast cancer.

In contrast, bioidentical progesterone has an opposite effect on in vitro breast tissue, inhibiting estrogen-stimulated breast epithelial cells[56–58,71–79] down-regulating estrogen receptors in the breast,[58,59,78] and diminishing breast cell mitotic activity.[45,56,58,62,76–81]

The demonstration of increased risk of breast cancer with the use of the synthetic progestin MPA in the WHI study was not surprising because, despite significant variability in the design, significance, and size of previous studies, synthetic progestins have consistently been associated with increased risk of breast cancer.[2,3,5,25,27,55,61–63,89–111]

In contrast, the use of bioidentical progesterone has shown *no* association with increased risk of breast cancer; in fact, it repeatedly has been proven to decrease its risk.[45,57,76,112–121] However, until recently, no large-scale randomized trials had been conducted with bioidentical hormones establishing beyond doubt that bioidenticals posed no increased risk of cancer.

### Large-Scale Studies Inclusive of Bioidentical Hormones

Large-scale studies[26,89,121,122] have been conducted in Europe, where bioidentical HRT is the main type of hormone therapy in menopausal women. The most significant study is the E3N or Epic cohort study that followed 80,000 postmenopausal women on various types of hormones including bioidentical hormones for more than 8 years, with 56,666 having used some form of HRT and 23,723 having never used any form of HRT.

The results demonstrated there was no significant increased risk of breast cancer in those who used estrogen-only therapy (98.7% used bioidentical estradiol and only 1.3% used conjugated equine estrogen), but the use of a synthetic progestin increased the risk to 1.69 times that of control subjects ($P = .01$).[26]

To evaluate the risk of breast cancer associated with the combination of (bioidentical) estradiol and progesterone, the most commonly prescribed hormone combination in France, De Ligniere led a study of a cohort including 3175 postmenopausal women followed for a mean of 8.9 years (28,367 women/year).[122] Eighty-three percent of the participating women were receiving exclusively or primarily a combination of transdermal (bioidentical) estradiol gel and progesterone. About 105 cases of breast cancer occurred during the follow-up period, corresponding to a mean of 37 new cases per 10,000 women per year. Using multivariate analysis the authors were *unable* to detect an increase in the relative risk (RR) of breast cancer (RR 0.98, 95% confidence interval [CI]; 0.65–1.5) in the HRT users. The authors concluded that their results, "do not justify early interruption of such type of HRT, which is beneficial for quality of life, prevention of bone loss and cardiovascular risk profile, without the activation of coagulation and inflammatory protein synthesis measured in users of oral estrogens."[122(p339)]

An analysis by Fournier and colleagues of more than 50,000 postmenopausal women followed for an average of 5.8 years found the use of a synthetic progestin associated with a significantly increased risk of breast cancer (RR = 1.4) whereas the use of bioidentical progesterone was associated with a decreased risk of breast cancer (RR = 0.9) ($P = .001$) over the same study period.[89]

In a final corroborating study, Bakken and colleagues investigated the relationship between various forms of HRT and cancer in more than 30,000 Norwegian women in a 7- to 12-year retrospective study.[123] In this study, the use of (synthetic) estrogen-only HRT (1542 women) *did* increase the risk of breast cancer compared with that in nonusers (RR = 1.8). Interestingly, the risk was eliminated if the HRT was used for more than 5 years. Those who used a synthetic progestin (7714 women) had a 2.5-fold increased breast cancer risk (RR = 2.5) that increased with increasing duration of use (RR = 2.8 with >5 years of use). The use of preparations that contained the bioidentical estrogen estriol (592 women) was not associated with an increased risk of breast cancer compared to those who never used HRT (RR = −1.0).

Because the risks of synthetic progestins are now well established, further comparison studies between synthetic and bioidenticals would be unethical. Future research should be focused on bioidentical hormones versus placebo.

### Cardiovascular: Bioidentical Progesterone Versus Synthetic Progestins

The only long-term study on myocardial infarction (MI) and stroke to date is the WHI, which did not address the effects of bioidentical hormones on cardiovascular events. In contrast, numerous studies including the WHI have found the use of a synthetic progestin will result in an increase in cardiovascular risk factors, including worsening of lipid profiles,[124-139] prevention of normal vasodilation and promotion of coronary artery vasospasm,[126,127,130,134,139] increasing hypercoagulability,[13,140,141] worsening insulin resistance,[132,142–144] and promotion of cardiovascular plaque formation.[131,135,137,138,145–147]

In addition, synthetic progestin is proven to increase the actual incidence of myocardial infarction and stroke.[2,139] Conversely, bioidentical progesterone has been shown *not* to have negative effects on the aforementioned cardiac risk factors in the short term in small studies. Unfortunately, these studies cannot be compared in scope and duration to the WHI study, leaving the question of whether bioidentical progesterone can actually protect from myocardial infarction or stroke in need of a more definitive answer.[23,124,129,133,136,148]

### Cardiovascular Risk and Estrogen

The WHI Estrogen Alone trial differed from the better known WHI trial of estrogen plus progestin in that it enrolled women who did not have a uterus and did not need the progestin hormone supplementation to protect their endometrium from the well documented negative effects of conjugated equine estrogens. In the Estrogen Alone trial, 10,739 women with prior hysterectomy, aged 50 to 79 years, were assigned to take conjugated estrogens (Premarin) 0.625 mg daily or to placebo. The study was stopped ahead of schedule in February 2004 by the National Institutes of Health (NIH) because of increased stroke risk and a possible but not categorical increase incidence of myocardial infarction during the 7 years of follow-up. In addition, the conjugated estrogen studied in this arm of the WHI study did not prove to offer *any* overall protection against heart attack or coronary death in the hormone therapies studied.[149]

In conclusion, our extensive review of the literature finds that all hormones are not equal. Bioidentical and synthetic hormones have differing and often opposite effects. This is important because physicians are often exposed to confusing information about hormone replacement in general and have to help patients make safe and intelligent individual decisions.

Bioidentical hormones have been associated with patient satisfaction, symptom relief, improved cardiovascular risk factors, and reduced risk of breast cancer compared to their synthetic counterparts. Although more randomized control trials are needed to cement and clarify further the extent of the differences between bioidentical and synthetic hormones, the present authors believe that the current state of the evidence demonstrates that bioidentical hormones should be the preferred method of therapy when HRT is chosen. Further, physicians must become familiar and comfortable with the differences in the preparations of hormones available and adapt their prescribing practices accordingly.

### TESTOSTERONE FOR WOMEN

Testosterone production in women derives from three sources: the ovaries, the adrenal glands, and from peripheral conversion from other circulating androgens.

Testosterone levels decrease with age, with levels in the fifth decade averaging about half of the level seen in women in their third decade.[150] This decline is due to a combination of factors: androgen production from the adrenal glands progressively declines with age and, although testosterone production from the ovaries remains relatively intact after menopause, the adrenal secretion of androstenedione declines by 50%.[150] The lower androstenedione levels result in a significant reduction in the peripheral conversion to testosterone at menopause. In addition, women who have undergone bilateral oophorectomy experience a 50% further reduction in testosterone levels.

Signs and symptoms of androgen insufficiency include loss of libido, fatigue, reduced sense of well-being, decreased lean body mass, and reduced bone density.[151]

Most commercial assays for the measurement of free and total testosterone levels were developed to measure the much higher levels in men. Consequently, assays in general lack the sensitivity and precision required to measure the normal low levels seen in women. Thus there is no real basis for most of the reference ranges used for testosterone measurements in women.[152,153] Also, serum levels have not been found to correlate with the presence or absence of symptoms (normal levels do not mean testosterone replacement will not be effective). Thus, if a normal testosterone level is found, it should not be used to rule out a deficiency in women or become the sole determinant when making the decision to treat or trying to make the connection between testosterone levels and symptomatology.

Although there is currently no FDA-approved testosterone preparation for the treatment of "testosterone insufficiency" in women, androgen replacement has been used off-label for more than 70 years.[154] Testosterone therapy in postmenopausal women has been shown to improve sexual desire and responsiveness,[155–158] sense of well-being,[159–162] and body composition[163,164] and to increase bone density.[157,165,166] All the studies reviewed in the preceding text are small with statistically significant results. However, more randomized control trials need to be performed to determine efficacy, optimal dosing, and risks.

### Risks of Testosterone Treatment in Women

Several side effects are potentially associated with testosterone therapy in women, including potential adverse effects on the cardiovascular system, hirsutism, acne, and breast cancer.[167] The main concern with testosterone replacement in women is its potential negative effect on lipids. The use of testosterone has been shown in some studies to have significant adverse effect on lipid levels.[167,168] The findings include slight lowering of high-density lipoprotein but no appreciable effect on low-density lipoprotein.[168–170]

No randomized trials of sufficient size or duration have been reported to assess the breast cancer risk with testosterone replacement. Although no study reports significant increase in risk, we found two studies that in fact provide support for its use. A retrospective study by Dimitrakakis and colleagues in *Menopause* in 2004 found no increase in risk of breast cancer when adding testosterone to 508 women receiving conventional HRT, conventional synthetic HRT that were followed for an average of 5.8 years.[171] and the study by Hubayter and colleagues in *Climacteric* in 2008 showing positive results with testosterone usage for improvement of sexual dysfunction in postmenopausal women.[172]

Unwanted cosmetic effects, such as acne and hirsutism, are possible side effects associated with large doses of testosterone supplementation, especially in women with a history of such problems. If testosterone is given at an appropriate dose and closely monitored, these side effects tend to be minimal and resolve with a reduction in dose or discontinuation of therapy.[172]

### Treatment

Because, as stated previously, free or total testosterone levels do not accurately reflect deficiency states in women, the decision to initiate replacement therapy should be based on a case-by-case evaluation of *symptoms and signs* rather than laboratory assessments alone. Replacement may be initiated after ruling out other potential causes (eg, hypothyroidism, chronic illness, other hormone deficiency, adrenal syndrome) for the symptoms (eg, fatigue, loss of libido). Testosterone should be used with caution in patients with a history of hirsutism, hair loss, and acne, and in those with untreated estrogen deficiency because they may be more prone to side effects with the use of testosterone alone.

In our opinion, it is reasonable to initiate a therapeutic trial of testosterone for 3 months in those considered to be good candidates. Effective dosing can range from 0.5 mg to 1.0 mg per day given sublingually or via a transdermal gel or cream.[173,174] Oral testosterone absorption may be erratic and should not be entertained. Intramuscular and subcutaneous pellets are also available, but research findings on their effectiveness and safety are lacking and thus we do not recommend their usage based on the present state of the evidence.

## SUMMARY

In summary, based on the literature reviewed and the state of the evidence in our clinical experiences that span decades and include tens of thousands of women, the authors believe that aging women should not be deprived of hormone therapies based on the findings of the WHI.

Many studies and practical clinical experience demonstrate on an ongoing basis the safety and efficacy of bioidentical hormones and supplemental testosterone therapies for improved well-being, elimination of symptoms of menopause, and even prevention of chronic conditions such as osteoporosis, hyperlipidemia, clotting disorders, and atherosclerosis.

More studies are needed to evaluate and further clarify the specific differences between bioidentical and synthetic hormones but ethical reasons prevent researchers from undertaking these studies given the results of the WHI and the many other study results on synthetic hormones. As such, we recommend studies be undertaken that evaluate the effects of bioidentical hormones and testosterone versus placebo.

Until such studies are completed, we also recommend the individual physician become well versed in the scientific literature presented in this article and work with each patient individually to provide her with the best possible care.

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