Testosterone in Men: A Review

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INTRODUCTION

You wake up one morning after another sleepless night. Who is that person in the mirror? He has less hair, wrinkles that you never noticed, and an enlarging mid-section. He does not feel like going to work or going to work out at the gym. His wife complains he is irritable all the time. Sex has become a chore with less of the great outcomes he remembered ten years ago. How old am I? Forty but I feel 50. Am I just getting old or could it be something else? My wife is on hormones. Do I need those? Could it be male menopause or andropause? My friends prefer to call it low T.

As men age, their blood levels of testosterone decrease. This decline after the age of 35 is gradual in most but can be accelerated in some men. The decline in testosterone is a cause of the clinical syndrome of testosterone insufficiency and is associated with many of the symptoms previously associated with aging. This clinical syndrome also can affect your general health and wellbeing, and without treatment you are at an increased risk for Alzheimer's disease, cardiovascular disease, prostate cancer, diabetes, osteoporosis, and sarcopenia.

Epidemiology of Testosterone Insufficiency

Testosterone levels decline 1-3 percent per year after age thirty.[i] This data reported from the Massachusetts Male Aging Study. The prevalence of low testosterone (total testosterone less than 300 ng/dl) is as high as 38.7 percent in males over 45 in out-patient primary care populations. This study obviously was based on a theoretical biochemical cut off value.[ii] The actual prevalence is much higher if one subscribes to the 2016 Consensus Paper by Abraham Morgentaler et al. whereupon testosterone insufficiency is defined as a clinical syndrome with a foundation based on symptoms and supported by a range of testosterone values not tied to single value threshold.[iii] Total serum testosterone is the most commonly used measurement of androgen activity, though it is a poor indicator of tissue activity.[iv] Based on this research, the fact that symptoms do not correlate with total testosterone, and the need to identify men at risk, health assessment questionnaires should be utilized for screening.

History

The history of testosterone is fascinating and unique.

In Greek mythology, castration was practiced early even within the first generation of gods. Gaea, mother earth, produced Uranos by parthenogenesis with whom she then generated the titan Chronos. When Uranos prevented Gaea from creating children with their son Chronos, she induced Chronos to castrate his father. Uranos' testes, thrown into the sea, caused the water to foam and out of these bubbles was born the goddess of love Aphrodite (Venus). Quite extraordinary events in terms of reproductive physiology! If you are ever in Florence, Italy, the painting by Giorgio Vasari (1511–1574) is in the Palazzo Vecchio.

Castration before puberty maintains the high voice of boys so that they remain soprano and alto voices even as adults. Such high-pitched voices were considered desirable especially at times when women were not allowed to sing in operas or in church. These castrated males performed in operas in the seventeenth and eighteenth centuries; in the Vatican choirs these voices could be heard until the early twentieth century. Strangely enough, while castration was forbidden in the Vatican state, which extended over most of middle Italy, it was not forbidden to employ castrated singers.

Prepubertal castration was thought to offer insight into the influence of testosterone on longevity. A retrospective comparison of the life expectancy of singers born between 1580 and 1858 and castrated before puberty, in order to preserve their high voices, to intact singers born at the same time did not reveal a significant difference between the lifespan of castrated intact singers (65.5 ± 13.8 vs. 64.4 ± 14.1, mean ± SD). This would imply that the presencevi or absence of normal male testosterone levels at the age of puberty, and beyond the age of puberty, has no influence on life expectancy. That's a rather huge misstatement and conclusion because it neglects the fact that 50 percent of males were dying by age 50 before they would have seen the long-term benefits.

If the history of castration transcends centuries, it should not be a surprise that the opposite of castration — using testes for medicinal support — also has its place in the annals of history. Roman Gaius Plinius Secundus (Pliny the Elder) recommended the consumption of animal testes to treat symptoms of testosterone deficiency. Slightly more refined was the prescription of testicular extracts for the same purpose in Arabic medicine, for example, by Mensue the Elder (777–837) in Baghdad. Albertus Magnus (1193–1280) in Cologne, better known as a philosopher, recommended powdered hog testes, but refined his recipe by offering the powder in wine.[vii]

However, the use of testicles grew exponentially towards the end of the nineteenth century when Charles E. Brown-Séquard (1817–1894) [viii], published his scientific paper on the results of his self-experiment in the Lancet. He gave himself 1-ml injections of a mixture of one-part testicular vein blood, one-part semen and one-part juice extracted from dog or guinea-pig testes, daily. Three weeks later he was astonished and purported that, 'A radical change took place in me. I had regained at least all the strength I possessed a good many years ago. I was able to make

experiments for several hours. My limbs, tested with a dynamometer, gained 6 to 7 kg in strength. The jet of urine and the power of defecation became stronger.' Oh, the power of suggestion and observation!

Nearly a half century later, two scientists, Leopold Ruzicka[ix] and Adolf Butenandt synthesized the hormone that would be the most important hormone for men and, as it turns out, also for women. Both scientists received The Nobel Prize for their findings. Initially testosterone was available for clinical use starting in the 1940s, but practitioners limited the therapy to those patients with the most severe cases of testosterone deficiency (TD) such as men with pituitary tumors or anorchia. It wasn't until the 1990s when physicians recognized a more expanded subset of patients who were symptomatic from low testosterone and would benefit from their symptoms being treated with testosterone replacement therapy (TRT).

Controversy

Testosterone has been controversial for many years, even before the hockey stick growth over the past 10 years. Journal articles claim no clinical consequences of the decline in serum testosterone with age are known with certainty, but several parallels between the effects of aging and those of hypogonadism due to pituitary or testicular disease suggest that the decline in serum testosterone might be a cause of several effects of aging. The data presented later in this chapter clearly dispels that myth.

Initially, there were concerns about testosterone and illicit performance enhancement in athletes and body builders[x] — the anabolic steroid craze.

Even before that physicians were convinced that testosterone "fueled the fire" of prostate cancer causing progression of, and increasing the severity of, the disease. A concern that does not have one shred of supporting evidence in the world literature.

In 2013, Vigen et al.[xi] reported an increase in heart attacks, strokes, and all-cause mortality in males taking testosterone. Just a few months later the Food and Drug Administration (FDA) announced an investigation into cardiovascular (CV) risk in males on testosterone products. Then came the black box warning on all testosterone products. Unfortunately, the Vigen study was flawed and the data actually showed testosterone was protective to the heart and there was less all-cause mortality in testosterone users. We are still awaiting a retraction of this misstated flawed study. The scientific research since has shown that CV risk is reduced on testosterone therapy.

Mechanisms of Testosterone Action

Testosterone has many different biologic effects, some occurring in its current molecule, which is testosterone. It can act directly by binding to the androgen receptor. It is here that many of the symptoms of testosterone deficiency (TD) are relieved. It can also be converted in tissues that express the enzyme 5-alpha-reductase, to dihydrotestosterone, which has a greater binding affinity for the androgen receptor than testosterone itself. This is necessary for secondary sex characteristics and sexual hair growth. Finally, it can act as an estrogen following conversion by aromatase to estradiol, which binds to the estrogen receptor. Without this important conversion men develop osteoporosis and have difficulty losing body fat.[xii]

Biologic Effects of Low Testosterone and the Benefits of TRT

In the introduction, I touched on some of the symptoms of low testosterone. These can include low energy level, insomnia, weight gain (especially around the midsection), brain fog, loss of muscle mass, decreased libido, decreased sexual performance (erectile dysfunction), joint pains, and mood disturbances including irritability and anxiety. Unfortunately, only 5 percent of males that suffer from testosterone insufficiency receive testosterone replacement therapy (TRT). Even fewer are receiving testosterone optimization therapy.

Why is this?

I believe it's because of inadequate screening and/or screening with biologic tests like serum or saliva rather than health assessment questionnaires which have a higher sensitivity in evaluating this clinical syndrome. Normal ranges vary widely between laboratories and bear little correlation to clinical findings.[xiii] Free testosterone measurements are equally inaccurate in the clinical setting.[xiv] Quality of life improvements were noted by the Aging Males' Syndrome questionnaire in somatic and sexual functioning in a study reported by Basaria.[xv] Similar results were seen using the St. Louis University ADAM questionnaire. Rather than medicate men with sleeping pills, diet pills, memory pills, and anxiolytics, hormone optimization guided by health questionnaires would widen our scope of males who would benefit from TRT.

We have looked at the short-term biologic effects of low testosterone, and now let us add in the long term effects which can affect the heart, brain, bones, and prostate.

Low testosterone is associated with:

- excess abdominal fat
- loss of insulin sensitivity,
- higher C-reactive protein, and
- atherosclerosis.[xvi]

Evidence from clinical studies[xvii] suggests that patients with low testosterone levels are at increased cardiovascular disease risk. Even though the exact mechanisms remain poorly understood, low plasma testosterone is associated with a pro-atherogenic lipid profile, insulin resistance, increased levels of pro-inflammatory mediators, and vascular dysfunction which is typically observed in patients with hypogonadism. Furthermore, recent evidence suggests that testosterone deficiency also has direct adverse effects on endothelium and nitric oxide bioavailability. Observations from studies in patients with hypogonadotropic hypogonadism (HH) imply that the mechanisms of endothelial dysfunction related with testosterone-deficiency may involve changes in asymmetric dimethylarginine (ADMA) levels, a known endogenous inhibitor of nitric oxide synthase. Evidence suggests that testosterone replacement therapy is not only a safe, but also an effective, means to reduce atherosclerotic risk and reverse endothelial dysfunction in patients with hypogonadotropic hypogonadism.

The damage to the endothelium can be repaired. There are endothelial progenitor cells that can repair the damage. These cells are activated by testosterone.[xviii] Without testosterone, there is accumulation of damage to the endothelium exacerbated by the pro-inflammatory cytokines and an increased risk of cardiovascular disease. In a study at The University of Texas at Galveston 6335 Men > 66 years of age, from 1997-2005, were followed retrospectively using injectable synthetic testosterone. The Highest Risk

Patients had reduction in myocardial infarctions (MI) HR .69 CI .53-.92.

With testosterone optimization:[xix]

- Testosterone reduces insulin resistance
- Testosterone reduces cholesterol
- Testosterone reduces visceral fat
- Testosterone reduces coronary artery disease (CAD)

Men given aromatize-able testosterone:[xx]

- Increase blood flow to the coronary arteries (even in patients with CAD)
- Decrease plaque in the coronary arteries
- Decrease inflammation in the coronary arteries

Multiple studies show low T is associated with high-grade prostate cancer (PCa) and a higher stage at presentation of their PCa.[xxi] If the age-old myth that testosterone "fueled the fire" of prostate cancer is not true, that begs the question: is the corollary true that optimal levels of testosterone are indeed protective to the prostate? A pooled prospective study of 3000 men in Finland, Norway, and Sweden had testosterone blood levels evaluated. 25 percent were diagnosed with PCa afterwards. There was a decreased risk of PCa in men with HIGHER testosterone levels.[xxii] For every 10ng/dL increment in annual reduction of testosterone, the risk of PCa increased by 14 percent. If more than 30 ng/dL reduction à 5X increase in PCa risk.

Osteoporosis is often thought of as a women's disease, as it is particularly common after menopause. The reality is, osteoporosis also affects men. In fact, twenty percent of those affected by osteoporosis are males. Overall, 1 in 5 men over the age of 50 will have an osteoporosis related fracture.[xxiii] This is greater than the likelihood of developing prostate cancer. Fractures from osteoporosis in males can be associated with higher rates of disability and death than in women. With the age of hypogonadism decreasing currently we need to be aware that one of the biologic effects of low T is the loss of bone mass. Testosterone increases bone density in men with low levels of this male hormone. In fact, studies have shown an 8.3 percent increase in bone mineral density (BMD) annually using TRT.

The number of Alzheimer's cases will triple by 2050 at a cost that will increase 500 percent, to $1.1 trillion per year. One of the biologic effects of low testosterone is an increase in cognitive decline, beginning in a man's mid-thirties, co-incidentally with his decline in testosterone. This can progress to a decrease in verbal memory and possibly dementia and Alzheimer's disease. Physiologically as T decreases, there is an increase in inflammatory cytokines in the brain, and this leads to more free radicals and oxidative stress. This causes damage to the endothelium, brain cells, and mitochondria. Both estrogen and testosterone have neuroprotective roles:[xxiv]

- Reducing apoptosis
- Increasing blood flow to the brain
- Decreasing Beta amyloid deposition in the brain
- Decreasing inflammatory cytokines

Evaluation for Possible Hypogonadism in Men

The clinical symptoms of male hypogonadism are well recognized and delineated earlier in this chapter. The causes both central and peripheral are sufficiently well known. Aging is one of the most common, and causes two important changes. One, the testosterone levels both total and free decrease. In addition, Sex Hormone Binding Globulin also increases, diminishing a male's free testosterone further. Health assessment questionnaires and test of the hypothalamic-pituitary-testicular axis are sufficiently accurate to permit the diagnosis in most patients. The patient has primary hypogonadism if the serum testosterone concentration is below normal and the serum luteinizing hormone (LH) and/or follicle-stimulating hormone (FSH) concentrations are above normal. The patient has secondary hypogonadism if the serum testosterone concentration is below normal and the serum LH and/or FSH concentrations are normal or low.[xxv]

Aside from aging, which the Endocrine Society and others have not recommended for screening, although the benefits are life changing as outlined above, Endocrine Society guidelines:[xxvi]

- Diseases of the Sella region
- Medications that affect testosterone production, such as high-dose glucocorticoids for a prolonged period and sustained-release opioids
- Human immunodeficiency virus (HIV)-associated weight loss
- End-stage kidney disease and maintenance hemodialysis
- Moderate to severe chronic obstructive lung disease
- Osteoporosis or low-trauma fracture, especially in a young man
- Infertility
- Type 2 diabetes

The initial test should be a serum total and free testosterone measurement early in the morning. If the result is low, the test should be repeated at least once, preferably twice. Testosterone should be measured in a laboratory that performs the assay by liquid chromatography or chemical luminescence.

If the hypogonadism is secondary and of moderate severity (e.g. <200 ng/dL) and/or associated with other hormonal deficiencies, a serum prolactin should be obtained and if elevated, a magnetic resonance imaging (MRI) of the Sella turcica area should be ordered.

A semen analysis is also part of the evaluation of testosterone insufficiency if the patient is pursuing fertility or has been diagnosed with infertility.

Once the diagnosis of hypogonadism is made, the patient should have his estradiol, thyroid profile, CBC, Vitamin D, CMP, and his HgA1C evaluated.

OPTIONS FOR TESTOSTERONE THERAPY

In Abraham Morgentaler MD's consensus report[xxvii] titled, "Fundamental Concepts Regarding Testosterone Deficiency and Treatment: International Expert Consensus Resolutions," it was unanimously decided that "TD is a well-established, clinically significant medical condition that negatively affects male sexuality, reproduction, general health, and quality of life." It was also unanimously decided that, "...symptoms and signs of TD occur as a result of low levels of T and may benefit from treatment regardless of whether there is an identified underlying etiology," and, that "there is no T concentration threshold that reliably distinguishes those who will respond to treatment from those who will not."

As reported, the starting concentration of testosterone predicts the magnitude and rapidity of response to treatment. The less hypogonadal the

subject, the larger the increase in circulating testosterone values must be for the effect to be 'perceived' by the subject, and the longer the duration of treatment to achieve an instrumentally.

The time-course of the spectrum of effects of testosterone shows considerable variation in the measurable difference in the desired outcome. The following are variables to be considered:

- Pharmacodynamics of the testosterone preparation
- Genomic and non-genomic effects
- Androgen receptor polymorphism
- Intracellular steroid metabolism

Many factors affect choice of regimen, including patient preference, cost, convenience, and insurance coverage. Let me try to break down some of the more common options.

There are many options for treating TD. First there are bio-identical options vs synthetic options. Bio-identical testosterone has the exact molecular structure of testosterone that the body produces. It tends to work synergistically with your hormone receptors. Bio-identical testosterone is usually made from soy or yams. Synthetic testosterone has a different molecular structure than what the body produces. Synthetic testosterone can cause many more side effects and interfere with proper hormone function. It is not plant based. It is usually administered as Testosterone cypionate, enanthate, undecanoate.

Route of delivery also has many variables that contribute to the benefits and side effects of TRT. Understanding the pharmacokinetics is important. There are no bio-identical testosterone preparations that are approved for oral administration. This is because absorption is variable and often poor. In addition, testosterone absorbed from the GI tract is rapidly metabolized in the liver and will give you sustainable levels. In the past, methyl testosterone was administered orally, however its absorption was poor and erratic and there were reports of liver toxicity.

There are bio-identical options for transdermal administration. This route of administration started in 1994 with the introduction of the scrotal patch (now no longer available). These would include Androgel®, Testim®, Axiron®, Fortesta®, and compounded testosterone cream. Most of these need to be administered twice a day and absorption is not predictable. In addition, it is often difficult to achieve optimal hormone levels in a majority of patients.

Injectable testosterone is usually synthetic (e.g. Testosterone cypionate, enanthate, undecanoate). The esterified molecule of testosterone and their oil base extend their period of efficacy. These products are in an oil base and time released. They are administered twice weekly to every 3 months depending on the product. Using testosterone undecanoate there have been reports of pulmonary oil micro embolism. The disadvantages are the need for deep Intra Muscular (IM) administration of an oily solution 50-100 times per year and fluctuations in the serum testosterone concentration, which result in fluctuations in symptom relief in many patients. Many patients have reported a "roller coaster" like feeling with hormone levels varying significantly between injections. On a positive note many insurance carriers will reimburse for these medications.

Finally, testosterone may be administered as a sub-cutaneous pellet (Testopel® or compounded) which is administered under the skin, usually in the gluteal region, and usually using bio-identical testosterone. The benefit of this method is more consistent testosterone hormone levels. This method, however, does require an insertion procedure with local anesthesia. The literature reports more consistent serum levels of testosterone with this method. Adverse events include pellet extrusion, infection, and fibrosis.

SIDE EFFECTS

There are some side effects to testosterone administration for the clinical syndrome of TD. These include:[xxviii]

- **Suppression of spermatogenesis** — This has been especially prevalent in men receiving parenteral testosterone or sub-cutaneous pellets because of the extreme suppression of FSH as part of the normal feedback loop. This side effect is usually reversible in men who want to resume fertility. It is a good idea to get a semen analysis in younger males with TD who may desire fertility in the future.
- **Erythrocytosis (an elevation of RBC mass)** — Testosterone stimulates erythropoiesis, so the hematocrit should be measured before initiating testosterone treatment for a baseline. Occasionally, you will need to have phlebotomy to correct this if symptomatic.
- **Obstructive sleep apnea (OSA)** — The estimated prevalence in North America is approximately 15 to 30 percent in males.xxix Testosterone therapy can worsen the symptoms of sleep apnea in approximately 1/3 of patients. Be alert if patient is African American, older male, obese, hypertensive, diabetic, hypothyroid, and/or a smoker.
- **Reduction in testicular size** — Occasionally there is a 10-15 percent reduction in the size of the testicle. This is thought to be due to a reduction in spermatogenesis in males on TRT. This side effect is reversible once therapy is stopped.
- **Liver Damage** — Non-oral testosterone preparations have not been shown to cause liver damage. Oral testosterone, particularly synthetic oral testosterone, has had reported cases. In the spirit of consistency, the FDA requires all testosterone preparations to carry this warning.
- **Fluid Retention** — A small percent of patients will experience fluid retention on TRT. This is secondary to the early increase in muscle mass which tends to hold onto water. This extracellular water weight usually resolves spontaneously.
- **Acne** — TRT can increase oil production in the glands of the skin. As such, some men will experience an increase in acne that usually responds well to systemic therapy.
- **Skin Rash** — Skin irritation can occur with any of the topical testosterone preparations.
- **Allergic Reaction** — There have been reported cases of allergic reactions to the cottonseed oil in parenteral preparations.
- **Breast Enlargement** — Many men will have breast enlargement (gynecomastia) with low testosterone levels. After TRT some men will develop gynecomastia from the aromatization of testosterone to estradiol causing proliferation of the breast tissue. This side effect and its predecessor, nipple sensitivity, are fortunately rare. Treatment usually involves a reduction in testosterone.

TAKEAWAYS

This chapter has focused on helping men who might have low testosterone recognize what symptoms make up the clinical syndrome of testosterone deficiency/insufficiency.

The short-term benefits including symptom relief were discussed. Clearly most men feel better with TRT. They have more energy, better sexual performance, improved cognition, sleep better, and have less anxiety/irritability. Testosterone optimization can be of paramount importance in avoiding the side effects of using multiple medications to treat the symptoms of TD.

In addition, the longterm benefits on the heart, brain, bones, and prostate were elucidated and expanded upon. TRT can reduce cardiovascular disease, diabetes, Alzheimer's disease, osteoporosis, and prostate cancer.

The type of hormone (synthetic vs bio-identical) MATTERS! The route of administration MATTERS! Physiologic HRT/TRT should mirror your hormone production when you felt your best in your 20's and 30's. It should be hassle free and be utilized with minimal side effects.

Longevity with your testosterone optimized as a male = Healthy Aging! Feeling your best as you age = A Pristine Quality of Life!

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Correspondence: Hormone Therapy for Postmenopausal Women

TO THE EDITOR:

In an assessment of therapies to treat the symptoms of menopause, Pinkerton (Jan. 30 issue)[1] dismisses compounded therapies (except for those used in patients with allergies or when there is a medical need for unusual dosing regimens), and she notes safety concerns. This blanket generalization overlooks the substantial Food and Drug Administration (FDA) oversight established by the 2013 Drug Quality and Security Act (DQSA).

Contrary to Pinkerton's assertion of "minimal government regulation and monitoring," the drug outsourcing facilities supervised under the DQSA must register with the FDA, be subject to regular unannounced inspections, comply with Current Good Manufacturing Practices, and use FDA regulated ingredients. Patients have depended on compounders and outsourcing facilities for decades to provide the customized formulations that work well for them, along with counseling on use of the compounded medication. I am extremely concerned about the potential consequences for women who use these therapies of disregarding this sector in its entirety owing to unfounded safety concerns.

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No potential conflict of interest relevant to this letter was reported.

1. Pinkerton JV. Hormone therapy for postmenopausal women. N Engl J Med 2020; 382: 446-55.

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TO THE EDITOR:

In her article on hormone therapy, Pinkerton focused on data from the Women's Health Initiative and did not mention the Danish Osteoporosis Prevention Study, which randomly assigned 1006 recently postmenopausal or perimenopausal women to estradiol or no estradiol for 11 years and followed them for 16 years. Women who received estradiol had significantly lower mortality (among 15 women vs. 26 women) and a significantly lower incidence of myocardial infarction (5 vs. 11) than women who did not receive estradiol, without an increase in the incidence of cancer (36 and 39, respectively), venous thromboembolism (2 and 1), or stroke (11 and 14).[1]

The article by Pinkerton also did not address sexual dysfunction[2] or menopause-related cognitive impairment,[3] which has been reported to be present in 60% of perimenopausal and postmenopausal women.[2-4] Subjective reports of symptoms are confirmed by objective evidence of decreases in measures of verbal memory, episodic memory, list learning, verbal fluency, or executive functioning.[2-4] Lack of awareness among physicians of this association between memory loss and menopause may have disastrous consequences for menopausal women, including the misdiagnosis of dementia in women with these symptoms.[3]

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THE AUTHOR REPLIES::

Schwartz notes concerns about the recommendation to avoid the use of compounded therapies except in special circumstances. The 2013 DQSA provides national licensure standards and FDA inspections for outsourcing wholesale distributors and third-party logistics providers who ship across state lines.[1] Compounding pharmacies that are not outsourcing providers are monitored by states, with wide variability in oversight.[1] The Pharmacy Compounding Accreditation Board assesses voluntary compliance with sterile and nonsterile pharmacy compounding processes. Major medical societies, including the American Medical Association, the American College of Obstetricians and Gynecologists, and the North American Menopause Society, recommend against compounded

hormone therapies owing to safety concerns regarding overdosing or underdosing, impurities, the lack of sterility, insufficient scientific efficacy and safety data, and the lack of labels providing information on dosing, ingredients, and risks.

FDA-approved bioidentical therapies include systemic and vaginal estrogen and progesterone and vaginal dehydroepiandrosterone. Medical indications for compounded hormone therapies should be documented.[1,2] For example, oral progesterone should not be used in patients with peanut allergy, preservative-free vaginal estrogen may be warranted, pellets with supraphysiologic levels of testosterone for sexual disorders are not recommended, and special dosing or formulations may be required. Federal and state oversight is needed for increased transparency about compounded product ingredients, financial conflicts of interest, and monitoring of adverse events.

With respect to the comments by Devi and colleagues: since the Danish Osteoporosis Prevention Study was open label, did not involve a placebo, and was much smaller than the Women's Health Initiative, the data are less robust. Devi et al. also call attention to the effects of menopause on sexual function and memory. Systemic and vaginal estrogen improve lubrication and blood flow and decrease the symptoms of genitourinary syndrome of menopause and painful sex, without effects on sexual interest, arousal, or orgasm beyond reduced vasomotor symptoms.[2] For women with low libido, transdermal estrogen is recommended because it has less effect on testosterone bioavailability than oral hormone therapy.

Memory problems during menopause (e.g., forgetfulness, losing keys, and difficulty concentrating or retrieving names) are usually not associated with clinically significant impairment. Treatment of depression, anxiety, and sleep disturbances, increased concentration to focus attention, and increased exercise may decrease memory problems.[3] Neuropsychological testing is recommended if cognitive symptoms interfere with daily life.3 Estrogen has been associated with improved cognition after early surgical menopause,[3] has neutral effects if used early in postmenopausal women,[4,5] and may worsen memory if initiated in patients older than 65 years of age.[2] Hormone therapy is not recommended to prevent or treat cognitive dysfunction or decline.

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