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Testosterone supplementation and the gender divide

Gary S. Donovitz MD, FACOG[1,2]

[1]Department of Obstetrics and Gynecology, Morehouse College School of Medicine, Atlanta, Georgia, USA

[2]BioTE Medical, Irving, Texas, USA

Correspondence
Gary S. Donovitz, MD, FACOG, BioTE Medical, LLC, 1875 West Walnut Hill Lane, Suite 100, Irving, TX 75038, USA.
Email: gary@donovitz.com

Abstract

Testosterone supplementation has proven benefits for women but unfortunately, to date, no Food and Drug Administration (FDA) approved product is available; while 31 different preparations of testosterone are FDA approved for men.

KEYWORDS

gender divide, hormone replacement therapy, testosterone supplementation

Testosterone (T) is the most abundant biologically active gonadal hormone throughout the female lifespan.[1] Yet, testosterone has always been perceived as being the "male" hormone. Ovaries in a woman of reproductive age produce approximately three to four times more testosterone than estrogen on a daily basis.[2] There is increasing data to support the use of testosterone supplementation for women who suffer from hypoactive sexual desire disorder (HSDD).[3] Supplemental testosterone in postmenopausal women has been shown in multiple large, randomized placebo controlled trials to improve sexual desire, arousal, orgasm and overall sexual satisfaction with minimal adverse events.[4–6] There are also multiple other studies supporting testosterone supplementation for brain health,[7] bone health,[8] cardiovascular protection[9] and breast cancer protection.[10] However, there remains lack of an Food and Drug Administration (FDA) approved testosterone product available to women. Rather, FDA approved testosterone products exist exclusively for men. Limiting access to testosterone for women creates a gender bias that negatively affects their general health, well-being, and quality of life.

Three prior attempts have been made to obtain an FDA approved testosterone product for women, all of which were denied. The first was Estratest, a combination of estrogen and testosterone initially available in the United States in 1965.[11] However, over time it was removed from the market even though safety and efficacy had been documented by multiple trials.[12] This was due to the FDA enacting the Drug Efficacy Study and Implementation regulation system. Given that Estratest was safe, the manufacturer would have had to prove that it is more efficacious than estrogen alone and for that reason it was taken off the market. Shortly thereafter, a testosterone patch called (Intrinsa) was also promoted for FDA approval in women.[13,14] The data on this product showed significant improvements over placebo and consequently held much promise for FDA approval. However, it was ultimately denied approval based on questionable theoretical concerns around androgen safety that stemmed from data related to estrogen and progesterone from the Women's Health Initiative Clinical Trial.[15] The most recent attempt was a product called Libigel,[16] a testosterone containing percutaneous gel. It did not meet FDA requirements based on theoretical concerns around long term safety. As with Intrinsa, the need for further research limited the manufacturers ability to meet the perceived FDA guidelines for approval.

On the other hand, there are 31 preparations of testosterone that are FDA approved for men. These products are indicated for those men who have low testosterone levels and other associated medical conditions. They have been approved by the FDA based on the manufacturer's ability to safely restore testosterone levels to the normal male range, often with a single pivotal open label clinical trial and with minimal safety data. Androgel was evaluated in one multicenter randomized parallel controlled trial of 180 days in 227 hypogonadal men. These studies are much less scientifically valid when compared to the larger studies performed in women.[17] This raises concerns that a double standard

has been applied by the FDA regarding evidence required for approval of testosterone products for men versus women. As a result, clinicians remain unguided regarding their ability to prescribe testosterone to women when it is clinically indicated. Their only choices are limited to off label FDA approved male product or utilize a compounding pharmacy to generate the appropriate testosterone preparation for their patient.

Additionally concerning is a recent effort by certain clinicians in conjunction with the FDA to limit and potentially regulate how physicians use compounded bioidentical hormones. In the summer of 2020 the National Academy of Science, Engineering and Medicine (NASEM), convened a consensus that more oversite and regulations on prescribers and pharmacies is needed. While certainly more data regarding the use of compounded hormone preparations is always beneficial the NASEM conclusions attempt to disrupt the current physician/patient relationship regarding use of compounded pharmacies.

These statements and conclusions from NASEM[18] were weighted more so on opinion rather than evidence. NASEM also displayed minimal knowledge on the current status of the various compounding pharmacies available to clinicians. After 2012, the FDA created a higher level of certification for compounding pharmacies known as the 503b outsource compound facility. They were required to meet specific and rigorous FDA standards. The 503b designation is an advanced certification granted by the FDA and must be registered for annually. They must follow strict CGMP (Current Good Manufacturing Practice) guidelines enforced by the FDA. In lay terms, CGMP assures proper monitoring and control of manufacturing processes and the facilities the compounded products are made in. The 503b outsource facility must report its compounding data twice a year and report adverse events to the FDA. These standards are similar to what is required by pharmaceutical manufacturers. Despite this, NASEM and its proponents appear unwilling to consider (i) the natural physiologic requirements of testosterone in women (ii) the evidence-based health benefits of replenishing testosterone in women (iii) the presence of compounding pharmacies already in place and following strict FDA standards to ensure safe and effective delivery of these treatments.

One cannot view television for even a relatively short length of time without seeing a commercial on erectile dysfunction. Similar advertisements are frequently on the internet as well. On the other hand, there remains widespread ignorance on the severe quality of life issues that women suffer from due to a lack of testosterone therapies. This unfortunate reality is due to the significant gender bias that exists with testosterone supplementation in women versus men. Clinicians are currently operating in a guidance vacuum regarding how best to manage HSDD as well as other symptoms and disease states that we know testosterone successfully treats. Hopefully future guidelines will account for and offer improved approaches for the use of testosterone in women.

CONFLICT OF INTERESTS

Gary Donovitz, MD, is the Founder, Chairman, and Chief Medical Officer of BioTE Medical, L.L.C. a training and marketing company for instruction in various HRT modalities.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

ORCID

Gary S. Donovitz https://orcid.org/0000-0002-8727-2388

REFERENCES

1. Dimitrakakis C, Zhou J, Bondy CA. Androgens and mammary growth and neoplasia. *Fertil Steril*. 2002;77:26-33.
2. Panay N, Fenton A. The role of testosterone in women. *Climacteric*. 2009;12(3):185-187.
3. Davis SR, Baber R, Panay N, et al. Global consensus position statement on the use of testosterone therapy for women. *Climacteric*. 2019;22:1-6.
4. Somboonporn W, Bell RJ, Davis SR. Testosterone for peri- and postmenopausal women. *Cochrane Database Syst Rev*. 2005: CD004509.
5. Abdallah RT, Simon JA. Testosterone therapy in women: its role in the management of hypoactive sexual desire disorder. *Int J Impot Res*. 2007;19:458-463.
6. Krapf JM, Simon JA. The role of testosterone in the management of hypoactive sexual desire disorder in postmenopausal women. *Maturitas*. 2009;63:213-219.
7. Friedman E. The new testosterone treatment: how you and your doctor can fight breast cancer, prostate cancer, and Alzheimer's. New York: Prometheus; 2013.
8. Studd J, Savvas M, Waston N, Garnett T, Fogelman I, Cooper D. The relationship between plasma estradiol and the increase in bone density in postmenopausal women after treatment with subcutaneous hormone implants. *Am J Obstet Gynecol*. 1990;163(5):1474-1479.
9. Islam RM, Bell RJ, Green S, Page MJ, Davis SR. Safety and efficacy of testosterone for women: a systematic review and meta-analysis of randomized controlled trial data. *Lancet Diabetes Endocrinol*. 2019;7:13-766.
10. Glaser R, York AE, Dimitrakakis C. Incidence of invasive breast cancer in women treated with testosterone implants: a prospective 10-year cohort study. *BMC Cancer*. 2019;19:271.
11. Lobo RA. Androgens in postmenopausal women: production, possible role, and replacement options. *Obstet Gynecol Surv*. 2001;56(6):361-376.

12. Suthers K. Estratest is not approved by the Food and Drug Administration. *Arch Intern Med*. 2007;167:205-206.
13. Simon J, Braunstein G, Nachtigall L, et al. Testosterone patch increases sexual activity and desire in surgically menopausal women with hypoactive sexual desire disorder. *J Clin Endocrinol Metab*. 2005;90:5226-5233.
14. Osborne V, Hazell L, Layton D, Shakir SAW. Drug utilization of Intrinsa (testosterone patch) in England: interim analysis of a prescription-event monitoring study to support risk management. *Drug Saf*. 2010;33(3):213-221.
15. Rossouw JE, Anderson GL, Prentice RL, et al, Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288:321-333.
16. White W. A cardiovascular safety study of LibiGel (testosterone gel) in postmenopausal women with elevated cardiovascular risk and hypoactive sexual desire disorder. *Am Heart J*. 2012;163(1):27–32.
17. Glaser R, York AE, Dimitrakakis C. Beneficial effects of testosterone therapy in women measured by the validated menopause rating scale (MRS). *Maturitas*. 2011;68:355-361.
18. www.nationalacademies.org/our-work/clinical-utility-of-treating-patients-with-compounded-bioidentical-hormone-replacement-therapy

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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