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Androgen Therapy in Women with Testosterone Insufficiency: Looking Back and Looking Ahead

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Abstract

In women, androgens not only serve as precursors for biosynthesis of estrogens but also exert a critical physiological role in sexual function, bone health, mood, behavior, and cognition. Despite research in the 1940s establishing the physiological role of testosterone (T) in women's health and the substantial benefits of T therapy (TTh) in women, the use of TTh in women today is rare, with little awareness of its value and safety within the medical community. We have identified several factors that have contributed to this situation, including: The rationale and use of androgens in women is not taught in medical schools; residual fear from the Women's Health Initiative study that sex hormones are associated with increased breast cancer risk; and absence of regulatory-approved T products for women in most parts of the world, except Australia. Although concerns regarding the efficacy and safety of TTh in women with sexual dysfunction have been appropriately addressed in randomized, placebo-controlled, studies TTh in women is prescribed by only a small percentage of physicians, and women who choose this treatment must use products intended for men as off-label treatment or find products via compounding pharmacies. Looking forward, we envision the possibility within the near future of symptomatic women with T insufficiency finding sympathetic health care providers who will recognize and appropriately treat their condition without negative judgment, allowing these women to experience the health and well-being associated with robust T levels. For this vision to occur, it will require education in medical school and postgraduate training, and broader acceptance of the science of TTh in women, noting its benefits and excellent safety profile.

Keywords: testosterone; testosterone deficiency; testosterone therapy; women sexual function; women's health

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Introduction

It is commonly believed that medical science moves forward inexorably, with researchers and clinicians constantly on the lookout for novel and useful treatments for various conditions afflicting humankind. Regrettably, our experience over many decades fails to support this notion. We have been dismayed by the failure of the medical community to recognize and embrace the use of testosterone (T) therapy (TTh) in women with T insufficiency and sexual dysfunction, despite remarkably powerful evidence of its benefits and safety dating back to the 1940s.

More than 80 years later, the use of TTh in women is rare, and there are no Food and Drug Administration (FDA)-approved T formulations indicated for use in women in the United States. Recently, a topical T formulation "Androphile" has been approved for use in women with hypoactive sexual desire disorder (HSDD) by the Australian Therapeutic Goods Administration and has been available in pharmacies across Australia since April 2021. We are not aware of any other testosterone products for women approved by regulatory agencies in any other countries.

Here, we provide a historical perspective and review key studies from the past demonstrating the importance of TTh in women, discuss events that have negatively impacted adoption of this valuable therapeutic treatment, and consider how greater awareness of the value of TTh in women will improve the health and well-being of women across the world.

An Historical Perspective on TTh in Women with Sexual Dysfunction

In 1947, Carter et al.[1] wrote: "For approximately a decade androgen have been utilized as therapeutic agents in women. The too rigid early concept of androgens as male hormones seemed at first to lend merely an academic interest to their application for women; but with the growing awareness that they were capable of profoundly altering the sexual physiology of women their potential value as therapeutic agents began to be appreciated. In the intervening decade they have been widely used in the management of a variety of derangements of female sex physiology and more recently for numerous metabolic disorders. The literature which has accumulated is now sufficiently extensive to permit a tentative evaluation of the present status of androgens as therapeutic agents in women."

This elegant and comprehensive review came on the heels of groundbreaking work by Shorr et al.,[2] Loeser,[3] Greenblatt and Wilcox,[4] Greenblatt et al.,[5] Salmon,[6] and Salmon and Geist,[7] who utilized T as a treatment for women with sexual dysfunction and various gynecological disorders. Loeser[3] published his early observations with TTh in women in 1940 and noted that "all patients acknowledge great feeling of wellbeing, more balanced moods and clear thinking; and some profess also a greater determination."

In the following years, a remarkable body of work on TTh in women was published by several renowned endocrinologists.[2–10] In a 1941 study of women receiving subcutaneous T pellets, Greenblatt and Wilcox reported, "increased sexual libido, and a sense of well-being was notably present in each patient after pellet implantation."[4] In one study of 38 women with lifelong histories of little or no sexual interest, androgen treatment produced a distinct increase in sexual interest in 30 women (79%), with 8 women reporting no changes.

In an additional 50 women who reported normal sexual interest, androgen treatment resulted in a distinct increase in sexual interest in 40 women (80%), with10 women reporting no change. Finally, in a group of 31 women who once had normal sexual interest and then lost it, 30 women (97%) reported an increase in sexual interest and only 1 woman reported no changes. It should be noted that the aforementioned findings were derived from various small studies[4–8] in which increased sexual interest in patients treated with T pellets were contrasted with those who did not receive treatment.

Sexual interest was based on patient "self-reporting" and not based on a validated questionnaire. The authors noted a distinct increase in sexual interest based on the number of women reporting an increased sexual desire.

Greenblatt et al.,[5] noted that the female libido was a result not just of hormonal imbalances but also, of "sentimental, psychologic, and anatomical factors.…" Interestingly, pellet implantation of 100 mg, compared with parenteral or oral administration, yielded a more consistent response in increasing libido.[5] Further, treatment of fibromyomas of the uterus with T also increased libido and improved the feeling of well-being in many patients.[4] This observation was further confirmed by Abel.[11]

Salmon et al.[6,7] reported similar results to those observed by Loeser[3] and noted clitoral enlargement in six of his patients and an increase in libido in response to

androgen treatment. Salmon observed that several young, married women who formerly considered themselves sexually "frigid" were able to experience "a marked increase in coital gratification, culminating in an orgasm" after T propionate injections and that "in the majority of these cases, the effects wore off within several weeks after the discontinuation of the injections."

Kennedy and Nathanson[12] found that the treatment of patients with breast cancer with androgens resulted in 37% of patients experiencing increased libido. Studd et al.[13] found that combining 100 mg of T and 50 mg of estradiol produced greater improvement in libido than estradiol treatment alone and that libido did not correlate with plasma levels of follicle stimulating hormone or luteinizing hormone, supporting earlier studies by Davis et al.,[14] on the role of T in women's sexual function.

The Era of Clinical Trials of TTh in Women with Sexual Dysfunction

Sherwin and Gelfand[15] reported that menopausal women who received androgens alone after hysterectomy and bilateral salpingo-oophorectomy reported fewer somatic and psychological symptoms than those who received estrogen alone or placebo and demonstrated that patients treated with combined androgen-estrogen or androgen alone had increased energy levels, well-being, and appetite compared with those who received estrogen alone or placebo.

The authors indicated that the androgen-treated group had superior functioning with increased plasma T levels during treatment, suggesting differential responses of physical and psychological symptoms to estrogens and androgens in surgically post-menopausal women. In another study, Sherwin et al.[16] compared the effects of androgen treatment on sexual function in patients treated with androgen alone, androgen plus estrogen, estrogen alone, or with placebo.

This study encompassed five groups. One group ($n=12$) was treated with estrogen combined with androgen, a second group ($n=11$) was treated with estrogen only, a third group ($n=10$) was treated with androgen only, a fourth group ($n=10$) comprised the placebo, and the fifth group ($n=10$) served as a control. The study evaluated the effects of such treatments on sexual desire, number of sexual fantasies, level of arousal attained during intercourse, and frequency of coitus and of orgasm.

It was reported that women treated with androgen-containing preparations had significantly higher scores on each parameter measured during each of the treatment than patients in the estrogen-only group or the placebo group. Interestingly, when the treatment was discontinued, during the intervening placebo month, sexual desire scores fell to levels below those of the control group.

In 1987, Sherwin and Gelfand[17] reported that in women who had undergone surgical menopause ($n=65$), TTh combined with estrogens improved sexual desire and sexual arousal compared with treatment with placebo or estrogens alone. Similarly, Davis et al.[14] reported that TTh together with estrogen supplementation in 34 women for up to 24 months improved sexual function in women. These improvements encompassed increased libido, sexual activity, satisfaction, pleasure, fantasy, and orgasm, which were not seen in women treated with estrogen alone.

Sarrel et al.[18] reported that TTh together with estrogen improved sexual function in women by improving sensation and desire. This effect was not observed in women treated with estrogen alone. In a randomized double-blind parallel group study of 218 women treated with T together with estradiol versus estradiol alone, Lobo et al.[19] reported significant changes in sexual interest score after 16 weeks of estradiol plus T treatment, as compared with those treated with estradiol alone.

Shifren et al.[20] conducted a placebo-controlled randomized clinical study in which the control group received placebo plus conjugated esterified estrogens, a second group received 150 μg of T plus conjugated esterified estrogens, and a third group received 300 μg T plus conjugated esterified estrogens. The composite score of the Brief Index of Sexual Functioning for Women was significantly increased in women only in women treated with the higher dose of T.[20] These observations suggest that there is considerable benefit of T treatment in ameliorating sexual dysfunction in women and this is independent of estradiol action.

The diagnosis of T insufficiency in women is controversial, but has generally been made based on having a characteristic constellation of symptoms, combined with low serum free T, and after excluding other medical conditions, most notably depression.[21] Reduced or absent libido is common among women, and the prevalence of loss of libido appears to increase with age or surgical oophorectomy.[22–24] Circulating androgen levels are believed to be a significant independent determinant of sexual behavior in women.[25–27]

As summarized in Table 1, a host of clinical studies have demonstrated significant benefits of TTh on improving sexual function and metabolism without serious safety concerns.[16,19,20,28–51]

Table 1. Clinical Studies of Testosterone Therapy in Women

References	Patients enrolled in the study	Study design	Duration of treatment	Treatment modality	Major findings
Sherwin and Gelfand[28] Sherwin et al.[16]	Women with surgical menopause ($n=53$).	Randomized, double-blind, placebo-controlled, crossover study.	3 months	Patients received estrogen only or TE 150 mg only or a combination of estrogen+TE 150 mg.	T treatment increased sexual desire, arousal, and fantasies.
Burger et al.[29]	Menopausal women ($n=20$).	Patients were randomized to two groups.		Patients were treated with either a single implant of E_2 40 mg or a combined implant of E_2 40 mg + T 50 mg.	T is believed to be beneficial in alleviating psychosexual symptoms.
Myers et al.[30]	Women with physiological menopause ($n=40$).	Randomized, double-blind, placebo-controlled, parallel study.	10 weeks	Patients received CEE 0.625 mg/day ($n=10$) or CEE+MPA 5 mg/day ($n=10$) or CEE+MPA and MT 5 mg/day ($n=10$) or placebo only ($n=10$)	T increased pleasure from masturbation, no changes in mood, sexual behavior, and sexual arousal.
Davis et al.[31]	Women with physiological menopause ($n=34$).	Randomized, single-blind, placebo-controlled, parallel study.	12 months	Patients received T implants 50 mg + E2 implants 50 mg or E2 implants only.	T improved bone mineral density as well as sexual activity, satisfaction, pleasure, and orgasm.
Watts et al.[32]	Women with surgical menopause ($n=66$).	Randomized, double-blind, placebo-controlled, parallel study.	24 months	Patients received CEE 0.625 mg/day or CEE 0.625 mg/day + MT 2.5 mg/day.	T improved bone mineral density and reduced HDL cholesterol and triglycerides.
Raisz et al.[33]	Women with physiological menopause ($n=28$).	Randomized, double-blind, placebo-controlled, parallel study.	9 weeks	Patients received CEE 1.25 mg + MT 2.5 mg/day ($n=13$) or CEE only ($n=15$).	T increased the markers of bone formation (osteocalcin, bone alkaline phosphatase, C-terminal procollagen peptide I) and reduced HDL and triglycerides.
Miller et al.[34]	Women with AIDS wasting syndrome ($n=53$) (37 ± 1 years).	Randomized, double-blind, placebo-controlled, parallel study.	12 weeks	Patients were treated with transdermal T patches (150 mg/day [$n=14$] or 300 mg/day [$n=18$] or placebo [$n=13$]).	T produced improvements in body weight and subjective health perception in the 300 mg dose group but there were no changes in lean body mass.
Shifren et al.[20]	Women with bilateral oophorectomy ($n=75$) (35–56 years).	Randomized, double-blind, placebo-controlled, crossover study.	12 weeks	Patients were treated with transdermal T patches containing CEE 0.625 mg+T 150 mg/day or CEE 0.625 mg+T 300 mg/day or CEE 0.625 mg+placebo	T increased sexual activity, pleasure, orgasm, fantasies, and self-perceived well-being in the 300 mg dose group.
Lobo et al.[19]	Postmenopausal women ($n=218$) on estrogen therapy with hypoactive sexual desire.	Double-blind randomized trial.	16 weeks	Patients received 0.625 mg of EE ($n=111$) or estrogen +1.25 mg of MT ($n=107$).	T increased sexual desire and responsiveness with significant improvement in sexual functioning in women.
Dobs et al.[35]	Women with physiological menopause ($n=36$).	Randomized, double-blind, placebo-controlled, parallel study.	16 weeks	Patients received estrogen 1.25 mg/day ($n=18$) or estrogens + MT 2.5 mg/day ($n=18$).	T increased sexual activity and pleasure.
Braunstein et al.[36]	Women with surgical menopause ($n=447$).	Randomized, double-blind, placebo-controlled, parallel study.	24 weeks	Patients were treated with transdermal T patches containing ERT + T 150 mg/day ($n=107$); or ERT + T 300 mg/day ($n=110$); or ERT + T 450 mg/day ($n=111$) or ERT+placebo ($n=119$).	T significantly increased frequency of satisfying sexual activity and sexual desire in the 300 and 450 μg dose groups.

(*continued*)

Table 1. (Continued)

References	Patients enrolled in the study	Study design	Duration of treatment	Treatment modality	Major findings
Buster et al.[37]	Women with surgical menopause ($n=447$).	Randomized, double-blind, placebo-controlled, parallel study.	24 weeks	Patients were treated with transdermal T patches containing ERT + T 300 mg/day or ERT+placebo.	T significantly increased frequency of satisfying sexual activity and sexual desire with no serious adverse events.
Simon et al.[38]	Women with surgical Menopause ($n=447$).	Randomized, double-blind, placebo-controlled, parallel study.	24 weeks	Patients were treated with transdermal T patches containing ERT + T 300 mg/day or ERT+placebo.	T significantly increased frequency of satisfying sexual activity and sexual desire with no serious adverse events.
Warnock et al.[39]	Women ranging in age from 32 to 61 years ($n=102$)	Randomized, double-blind study.	8 weeks	Patients received EEs (1.25 mg) with or without MT (2.5 mg).	Significant improvement in sexual functioning questionnaire (CSFQ-F-C) sexual desire/interest subscale score was noted in the T-treated group.
Shifren et al.[40]	Naturally menopausal women with HSDD ($n=549$).	A multicenter, randomized, double-blind, placebo-controlled, parallel-group trial.	24 weeks	Patients were treated with T 300 μg/day or placebo patches twice weekly, together with a stable dose of oral estrogen with or without progestin.	T increased the frequency of satisfying sexual activity and sexual desire, decreased personal distress.
Davis et al.[41]	Women with HSDD after oophorectomy.	Randomized, double-blind, placebo-controlled trial.	24 weeks	Patients were treated with placebo ($n=40$) or T 300μg/day ($n=37$) treatment.	TTh improved sexual desire and other sexual function domains.
Shah et al.[42]	Postmenopausal women ($n=76$).	A single-center, double-blind, randomized, placebo-controlled study.	8 weeks	Patients were treated with T 0.5% gel, daily with or without letrozole 2.5 mg/day or an identical placebo tablet.	It did not observe any effects of aromatase inhibition on cognition in healthy, estrogen-treated postmenopausal women treated with T.
Davis et al.[43]	Women with HSDD ($n=814$).	Randomized, double-blind, placebo-controlled trial.	52 weeks	Patients received a patch delivering 150 or 300 μg of T per day or placebo.	In postmenopausal women not treated with estrogen therapy, treatment with T (300 μg) produced a modest but meaningful improvement in sexual function.
Raghunandan et al.[44]	Postmenopausal women symptomatic for urogenital atrophy and sexual dysfunction ($n=75$).	Patients were randomly divided into two study groups and one control group.	12 weeks	Patients were treated with estrogen. Cream with or without T. The placebo group received nonhormonal lubricant KY gel.	T produced significant improvement in symptoms of urogenital atrophy and sexual dysfunction as compared with the control group. Improvement in sexuality score was greatest with combined estrogen–androgen therapy.
El-Hage et al.[45]	Menopausal healthy women ($n=36$).	A double-blind, randomized, placebo-controlled, crossover study	3 months	T Cream was utilized to raise T to physiological levels.	T significantly improved sexual desire, frequency of sex, receptivity, and initiation.
Flöter et al.[46]	Women ranging in age between 45 and 60 years old ($n=50$).	A double-blind design was chosen, with crossover to the other regimen for another 24 weeks of treatment.	24 weeks	Patients were treated with oral T undecanoate 40 mg+estradiol valerate 2 mg daily or placebo+estradiol valerate 2 mg daily.	T improved sexual function more than treatment with estrogen alone.

(*continued*)

Table 1. (Continued)

References	Patients enrolled in the study	Study design	Duration of treatment	Treatment modality	Major findings
Flöter et al.[47]	Women ranging in age between 45 and 60 years old, who had undergone a hysterectomy and bilateral salpingo-oophorectomy for benign disorders ($n=50$).	Patients were randomly assigned to oral treatment with T+E2.	24 weeks	Patients were treated with oral T undecanoate 40 mg+estradiol valerate 2 mg daily or placebo+estradiol valerate 2 mg daily.	T treatment had a positive effect on bone and no adverse effects were noted on body mass index, fat distribution, or blood pressure.
Nathorst-Böös et al.[48]	Postmenopausal women participated in this study ($n=53$).	Double-blind, randomized, crossover design.	3 months	10 mg of T gel (Testogel, Besins–Iscovesco) or placebo was administered to complement their already on-going HRT.	T had positive effects on several aspects of sexual life such as frequency of sexual activity, orgasm, arousal, fantasies, and sexual interest in postmenopausal women on HRT.
Tungmunsakulchai et al.[49]	Postmenopausal women with sexual complaints and FSFI ≤26.5 ($n=70$).	Participants were randomly assigned	8 weeks	Patients were treated with oral T undecanoate 40 mg or placebo twice weekly with daily oral E2.	T treatment was associated with a significant improvement in sexual function among postmenopausal women than the use of estrogen alone.
Davis et al.[50]	Postmenopausal women ($n=33$).	Randomized, controlled single-blind study in postmenopausal women.	2 years	Patients were treated with either 50 mg E2 alone or E2 50 mg + T 50 mg implants (E2+T) administered every 3 months for 2 years in conjunction with cyclic oral progestins.	T treatment with estrogens but not E alone resulted in increased FFM ($p<0.001$) and a reduced FM:FFM ratio ($p<0.05$). Both therapies were associated with sustained reductions in total cholesterol and LDL cholesterol.
Blümel et al.[51]	Healthy postmenopausal women aged 45–64 years ($n=47$).	Randomized, double-blind, double-dummy study with two parallel treatment arms.	3 months		Treatment with T together with hormone therapy improved quality of life and sexuality in post-menopausal women with sexual dysfunction. In the AHT group, the FSFI score improved significantly. FSFI was not modified in the placebo group.

CEE, conjugated equine estrogens; EE, esterified estrogen; ERT, estrogen replacement therapy; FFM, fat free mass; FM, fat mass; FSFI, female sexual function index; HDL, high-density lipoprotein; HRT, hormone replacement therapy; HSDD, hypoactive sexual desire disorder; LDL, low-density lipoprotein; MPA, medroxyprogesterone acetate; MT, methyltestosterone; T, testosterone; TE, testosterone enanthate; TTh, T therapy.

Effects of TTh on Other Metabolic Function in Women

Although the benefits of TTh in women with sexual dysfunction have been well recognized for many decades,[16,19,20,28–51] T treatment also improved bone mineral density, fat-free mass, and fat mass and improved metabolic function.[29,31–34,47,50–64] TTh was also shown to improve mood in women with anxiety and depression, and in women with anorexia nervosa.[56,57,59,63]

Safety of TTh in Women

Several adverse side effects of TTh in women have been anecdotally reported, which include body hair growth, acne, and voice changes. However, no medically serious adverse side effects have been reported in clinical studies[63–74] and findings in clinical trials reported in Table 1. Nevertheless, persistent concerns of serious adverse effects remain an obstacle for the use of TTh in women. Foremost among these has been the fear that androgen therapy could lead to an increased risk of breast cancer due to aromatization of T to estradiol.[75–79]

This alarming possibility has not been supported by the available data. Indeed, in the years since the first reports on T in women[1,2–7] to modern-day clinical trials,[16,19,20,28–51] no major safety concerns have arisen (Table 1). Regarding heart disease, Islam et al. concluded, "From a contemporary therapeutic perspective, there is no evidence that TTh, when used for the treatment of HSDD, is associated with adverse CV effects."[65]

As discussed by Traish and Gooren[71] and Traish et al.,[80,81] several lines of evidence argue against increased breast cancer risk with TTh. These include: (1) Data from breast tumor cell lines treated with androgens do not support the notion that T increases breast cancer risk.

On the contrary, androgens inhibit tumor cell growth, and thus they appear to be protective; (2) several epidemiological studies reporting an association between T and breast cancer failed to adjust for estrogen levels.[82–84] Studies that did adjust for estrogen levels have shown no association between T and breast cancer. (3) Clinical studies with TTh have not shown any increased incidence of breast cancer. (4) Women with polycystic ovary disease do not appear to be at an increased risk of breast cancer compared with the general population, despite higher serum androgen concentrations. (5) Female to male transsexuals, who receive supra-physiological doses of T for long time periods before surgical procedures, have not been shown to have an increased risk of breast cancer.[74]

(6) Finally, women with hormone responsive primary breast cancer were treated with aromatase inhibitors, which block conversion of androgens to estrogens, thus elevating androgen levels. These women do not experience increased incidence of contralateral breast cancer, nor do they experience increased tumor growth.

A recent report[85] suggested that a 10-year analysis of the Dayton study demonstrated reduced incidence of invasive breast cancer in T users by 39% compared with the "age-matched" population. Thus, the data in the contemporary literature suggest that TTh in women is unlikely associated with an increased risk of breast carcinoma.[10,12,43,71,74,78,81,84,86]

Events Negatively Impacting Adoption of TTh in Women

In our view, several key events have contributed to the failure of the medical community to recognize the importance of androgen insufficiency in women, and to adopt the treatment of affected women. These include (1) response to publication of findings from the Women's Health Initiative (WHI), (2) lack of approval for T formulations for women by the U.S. FDA, (3) the Endocrine Society Guidelines on TTh in women with T deficiency, and (4) lack of education and training of health care professionals (HCPs) in this field.

The WHI study

The publication in 2002 of initial results from the WHI concluded that hormone replacement therapy (HRT) in women was associated with several serious adverse health effects, including breast cancer.[87] A media frenzy ensued, reducing the use of HRT in the United States to a small fraction of previous levels. However, subsequent studies, including follow-up studies from the original WHI cohort, have failed to support those initial dire conclusions. Nonetheless, the belief that sex steroid use is risky for health, based on the 2002 WHI publication, has contributed mightily to the reluctance by clinicians to treat women with TTh.

Absence of FDA-approved T formulations for women

Regulatory-approved T products for women are not available throughout the world, except for Australia. In the United States, two topical formulations underwent review by the FDA and failed to gain approval.

One of these, a T patch, showed greater efficacy compared with placebo for the treatment of HSDD,

yet the FDA declined approval due to safety concerns. As noted by Parish et al., "Despite the lack of evidence for cardiovascular events or breast cancer in randomized, placebo-controlled clinical trials of T in postmenopausal women with HSDD, the regulators had concerns about these risks, given the results of the Women's Health Initiative."[88]

The absence of an FDA-approved T product for women means that clinicians have no choice but to prescribe T off-label, using T products approved for men but at a much lower dose appropriate for women, or use T topical agents or pellets produced by compounding pharmacies. This creates a prescribing hurdle to be overcome and contributes to the perception of TTh in women as "alternative medicine." It should be noted that there have been more than two dozen T formulations for men approved by the FDA.

There is an urgent need for an approved, safe T formulation for the treatment of women with HSDD. As lamented by Dr. Guay in 2005 after the FDA declined approval of a T product, "We have lost the opportunity of having a country and a regulatory agency validate the concept and diagnosis of androgen insufficiency in women. This could have facilitated requests for research funding in this area, and made androgen insufficiency a valid topic for evaluation, even though many doctors have been treating it off-label for decades."[89]

The Endocrine Society Guidelines on TTh in women

In 2006, the Endocrine Society published a Clinical Practice Guideline in which they concluded, "We recommend against making a diagnosis of androgen insufficiency in women at present because of the lack of a well-defined clinical syndrome and normative data on total or free T levels across the lifespan that can be used to define the disorder." This recommendation from a highly respected group was a major event that impeded the adoption of TTh in women.[90,91] Other experts strongly disagreed. Traish et al. commented, "We disagree with the therapeutic nihilism promoted by these Guidelines."[81] Braunstein commented, "The data from well-controlled trials support this approach (TTh) as being efficacious and safe."[92]

Lack of education regarding women's sexual health

The field of female sexual health is not taught in many medical schools or in residency programs in the United States.[93,94] This lack of education and training contributes to the reluctance of physicians to even consider the use of TTh in women.[95]

When Viagra was approved by the U.S. FDA in 1998 to treat male erectile dysfunction (ED), many middle-aged men sought out treatment for ED, and it also stimulated considerable research into the field. However, there has been no comparable set of circumstances for women and sexual dysfunction. In many Western cultures, women often avoid and/or are embarrassed to discuss their sexual health with their HCPs.

In addition, the lack of appropriate training, tools, time on the part of HCP, and the limited available treatment options all conspire to prevent affected women with T insufficiency from receiving beneficial treatment. The HCPs may avoid initiating conversation on sexual health because of a lack of confidence, personal discomfort, or a sense of discomfort on the part of the patient,[96,97] and the lack of education in this area compounds the problem. In addition, HCPs may assume that women's sexual function is less relevant after the reproductive years.[98,99] The absence of education regarding T insufficiency in women during medical school or residency creates an enormous hurdle for HCPs to consider taking on the evaluation and management of this problem in clinical practice.

Looking Ahead

The limited awareness of the importance of T insufficiency in women is an excellent example of how medical science fails to progress in a straight line from compelling research to clinical practice. Indeed, as reviewed earlier, much of the fundamental information regarding both the impact of T insufficiency and the benefits of treatment with TTh have been known for 80 years. And yet, the plight of affected women is that they are unlikely to be diagnosed, and even less likely to be treated. If they do receive treatment, it will be off-label via compounded medications since there are no regulatory-approved T products available through most of the world.

The impact of this is enormous, affecting millions of women in the United States alone, depriving them (and their partners) of satisfying sexual relations, strength, and vigor. How can this be rectified? Looking ahead, we see a number of steps that will be necessary to alter this course. First, the research must and will continue. We are confident this will occur, as an increasing number of investigators around the world have demonstrated interest in T and its effects on women.

Funding is likely to improve as the false fears generated by the WHI regarding sex hormones continue to fade. Of course, there is always the risk of another study being published that grabs headlines and sets back the field, but this becomes less likely as the foundational science becomes more established. Research alone will not be enough, however, as we have already seen.

Second, the lack of education regarding women's sexual dysfunction, and T insufficiency, needs to be addressed during medical education and training. Inclusion of this topic in formal curricula will go a long way to creating a sense among trainees that T insufficiency is a condition that merits serious attention, no less than the hundreds of other medical conditions taught in medical school.

Third, it will be helpful if professional organizations lend their support to the importance of diagnosing and treating women with T deficiency. Investigators and clinicians should consider promoting this concept within their own societies.

Fourth, it is to be hoped that one or more T products for women obtain regulatory approval in the United States and other countries. It is, of course, a business decision for pharmaceutical companies to decide whether to pursue the development of such a product, entailing considerable costs and efforts, which must be balanced against the likelihood of successful adoption of the treatment once approval is obtained.

We believe enough time has passed since the last FDA submission for a T product for women for there to be a more receptive attitude by regulatory agencies, which appear to have been spooked the last time by the firestorm caused by the WHI and rampant fears of serious adverse events with HRT, none of which have proven correct over the ensuing two decades. Although compounded T products are effective for women, the availability of an approved product by a regulatory agency such as the FDA would provide considerable comfort to prescribing HCPs and to patients alike and would go a long way toward making it easier for affected women to receive treatment.

Looking ahead, we are very encouraged by the recommendations and conclusions of the "The Global Consensus Position Statement" on the use of TTh for women.[100–103] This position statement is a valuable resource for all clinicians who are treating women complaining of HSDD. The recommendations of this Position Statement are evidence-based on data derived from randomized controlled clinical trials and meta-analyses. The panel recommended that the diagnosis of HSDD must involve a careful and complete clinical assessment and contributing factors to sexual dysfunction in women be determined and managed before commencing TTh.

The international panel was clear in its recommendations and conclusions that only evidence-based indication for TTh for women is for HSDD treatment, given that the contemporary available data provide a modest therapeutic benefit. The Position Statement provided clear and firm indication for TTh in women as well as the potential adverse effects of this therapy and highlighted knowledge gaps remaining to be bridged. Although meta-analyses of the available data showed no severe adverse events during physiological T use in women, caution needs be exercised.

Looking back, we are struck by the failure of science to effect meaningful change in clinical practice for women with T insufficiency over such a long period of time. Looking forward, we are encouraged by numerous developments in the field, perhaps especially by the growing calls to make women's health a priority. We can easily envision a time in the not-too-distant future when women with symptoms of T insufficiency are evaluated respectfully and without dismissing the importance of their symptoms, undergo prompt and thorough evaluation, and are offered effective treatment when appropriate. The consequences of this vision are not only improved health and well-being for those women, but also a happier existence for their families, friends, and society as a whole.

Acknowledgments

This article is dedicated to the memory of our friend, mentor, and colleague Andre T. Guay, MD, a genuine pioneer, a passionate physician, a fierce advocate for his patients, and a clinical researcher of the role of androgens in men's and women's health carried out with gravitas and integrity that is unsurpassed.

Disclaimer

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Abbreviations Used

CEE = conjugated equine estrogens
ED = erectile dysfunction
EE = esterified estrogen
ERT = estrogen replacement therapy
FDA = Food and Drug Administration
FFM = fat-free mass
FM = fat mass
FSFI = female sexual function index
HCPs = health care professionals
HDL = high-density lipoprotein
HRT = hormone replacement therapy
HSDD = hypoactive sexual desire disorder
LDL = low-density lipoprotein
MPA = medroxyprogesterone acetate
MT = methyltestosterone
T = testosterone
TE = testosterone enanthate
TTh = T therapy
WHI = Women's Health Initiative