CLINICAL INVESTIGATION

Safety and efficacy of transdermal testosterone for treatment of hypoactive sexual desire disorder

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Hypoactive sexual desire disorder is a significant life-stressor prevalent among women of all ages worldwide. Androgens have been shown to maintain healthy female sexual function and testosterone supplementation has been used as an off-label treatment modality in the USA via oral, intramuscular, pellet or transdermal routes of delivery. It is hypothesized that transdermal testosterone delivery may be safer than other regimens because it bypasses first-pass hepatic metabolism. This article examines the current research on efficacy and safety of transdermal testosterone for the treatment of hypoactive sexual desire disorder. Although multiple randomized-controlled clinical trials have demonstrated that transdermal testosterone improves female sexual function with minimal side effects, long-term safety data is still needed, specifically to elucidate the possible long-term risks of breast cancer and cardiovascular disease.

Keywords: androgens • bioavailable testosterone • free testosterone • sex-hormone-binding globulin • total testosterone

Hypoactive sexual desire disorder (HSDD) is defined as a persistent or recurring deficiency or absence of sexual thoughts and desire for or receptivity to sexual activity that causes personal distress [1–2]. This disorder may be the result of a medical, substance-related or psychiatric disease. Risk factors include psychological and sociological factors that may affect sexual desire, aging, menopause, the presence of co-morbidities, and certain medications [3]. The pathophysiology of HSDD is hypothesized to be related to the interplay between sexual hormones and neurotransmitters in the CNS. Dopamine, estrogen, progesterone and testosterone (T) play an excitatory role in sexual desire. Serotonin, prolactin and opioids are thought to play an inhibitory role. It is theorized that HSDD may be caused by decreased excitatory activity, increased inhibitory activity, or both [4].

A women's relationship with her sexual partner seems to be one of the most important psychosocial variables that influence desire. One study found that prior function and relationship factors are more important than hormonal determinants of sexual function [5]. Low sexual desire has been correlated with low levels of arousal, orgasm and pleasure [6–8]. HSDD has been associated with poor relationship satisfaction as well as negative emotional states [9]. The effect of HSDD on quality of life is profound, comparable to that of other chronic conditions such as diabetes and back pain [10].

Approximately 4 million US women over the age of 50 experience distress associated with low sexual desire [11]. In a study polling 31,000 women, 12% self-reported sexually related personal distress, with highest prevalence found between the ages of 45–64 years [12]. A smaller study found the prevalence of HSDD to be 12–19% in the USA and 6–13% in Europe, with no significant change with age [13]. Worldwide it is estimated that between 5–10% of women have frequent low

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libido and 25–40% lack sexual interest; the highest prevalence being in Asia and the Middle East [14].

Role of androgens in HSDD

Due to the high prevalence of HSDD in states of endocrine disruption that result in decreased androgen levels, it is believed that diminished androgens are a prime causal factor of HSDD. Some, but not all studies have correlated low libido with low T [15,16], and low T levels have been uniformly found in women participating in the transdermal T-patch treatment trials for HSDD [17–21]. In addition, HSDD is found in such medical conditions as bilateral oophorectomy, adrenal insufficiency, corticosteroid adrenal suppression and hypopituitarism [22,23]. All of these conditions result in low T levels. Oophorectomy results in a 50% reduction in circulating T levels and over a half of oophorectomized women report decreased libido [23,24]. Women on oral estrogen therapy (ET), either hormone therapy (HT) or oral contraceptive pills, also may experience HSDD due to the increase in T binding to sex-hormone-binding globulin, resulting in lower circulating free T levels [7,8].

Animal data has demonstrated that sexual behavior is mediated by the preoptic area of the brain [25] and androgen receptors are found in this area as well as in the hypothalamus [26]. Androgens have been shown to maintain healthy female sexual function by stimulating libido and maintaining desire [27] dating back to the initial double-blinded, placebo-controlled crossover trial with 102 ovariectomized women carried out by Greenblatt *et al.* in 1950, which demonstrated that exogenous oral T enhances sexual desire [28,29].

The Princeton Consensus Conference defined female androgen insufficiency as having clinical symptoms including decreased libido and sexual pleasure, in the presence of decreased bioavailable T and normal estrogen levels, where other pathologic etiologies of low libido have been excluded [30]. A pooled Cochrane analysis of T treatment, also demonstrated that the addition of T to HT regimens improved postmenopausal female sexual function scores and number of total satisfying sexual episodes (SSEs) [31].

T regimens

There are multiple T-delivery regimens used, such as oral, intramuscular, pellet and transdermal. Oral regimens undergo first-pass hepatic metabolism with potential risk of hepatotoxicity and adverse lipid effects including a decrease in high-density lipoprotein (HDL) [32]. Injectable T requires less frequent dosing (2–4 weeks) but does not result in steady serum levels of T, often resulting in extreme peaks and troughs, as well as patient discomfort at the injection site [33]. Tachyphylaxis and suboptimal clinical effect may also occur with the injectable formulation [34]. Pellet T implants are slowly metabolized and may result in supraphysiologic T levels with potential side effects including virilization and infection from the implantation procedure [34].

The challenge has been to formulate an androgen delivery system that results in physiologic and stable levels of androgen that restore sexual desire without virilization or other adverse events (AEs) [22]. Transdermal formulations including a matrix patch, gel and spray have been studied in short-term trials, and benefits of this route of delivery include ease of use, maintenance of steady serum-T concentrations, and the advantage of bypassing hepatic first-pass metabolism [33,35].

Data on the efficacy of transdermal T

In 2000, the first randomized controlled trial (RCT) was conducted on the transdermal T patch (TTP) at the dose of 150 and 300 µg/day administered with concomitant oral ET in oophorectomized women with HSDD. The results found a 12-week dose–response improvement in sexual function (increase from mean ± SD) composite score of 52 ± 27% at baseline to 72 ± 38% during placebo, 74 ± 37% during treatment with 150 µg T and 81 ± 37% during treatment with 300 µg/day T ($p = 0.05$ for comparison with placebo); and well-being mean composite score 78 ± 15 at baseline increased by 1 ± 14 during treatment with placebo, 2 ± 14 during treatment with 150 µg/day T, and 5 ± 14 with 300 µg T ($p = 0.04$ for comparison with placebo) [35]. A larger RCT was next performed over 24 weeks to study the comparative efficacy and safety of 150, 300 and 450 µg/day TTP versus placebo in oophorectomized women on concomitant oral ET [17]. Results of this trial found that the 300 µg/day patch had the greatest increase of sexual desire compared with placebo (67 vs 48%; $p = 0.05$) and frequency of satisfying sexual activity (79 vs 43%; $p = 0.49$). The 150 µg/day group showed no treatment effect for increase in sexual desire or satisfying sexual activity and the 450 µg/day group was not statistically different from the 300 µg/day versus placebo. AEs were mild and similar in all groups except for a higher incidence of unwanted hair growth reported in all TTP groups [17].

Further research using the 300 µg/day TTP then followed, demonstrating effectiveness in improving sexual function with a short-term favorable safety profile in surgically menopausal women with HSDD. The Intimate SM1 was a 6-month study of the effects of a biweekly 300 µg/day TTP in surgically menopausal women with HSDD receiving concomitant

oral ET [36]. There was a significant increase from baseline in the frequency of total SSEs in those treated with TTP versus placebo (2.18 vs 0.98 SSEs/4 weeks, respectively; p = 0.0003). The TTP users also demonstrated a significant improvement in sexual desire and a decrease in distress. All seven domains of sexual function were measured by the Profile of Female Sexual Function (PFSF) including desire, pleasure, arousal, orgasm, concerns, responsiveness and self-image, and were significantly improved in those receiving TTP [36]. AEs were similar and mild in the TTP and placebo groups, with application-site reaction being the most commonly reported AE. Baseline free- and total-serum-T levels were low in these patients suggesting that baseline T measurements are not necessary in oophorectomized women with HSDD being considered for T treatment [36].

The Intimate SM2 Phase III study showed similar results to the Intimate SM1. In this study, total SSEs and sexual desire improved with the 300 µg/day TTP group compared with placebo (1.56 vs 0.73 episodes/4 weeks, respectively; p = 0.001) and personal distress significantly decreased [18]. As in Intimate SM1, all seven domains of the PFSF significantly improved in those receiving TTP with the maximal effect observed by week 12. AEs were mostly mild and similar in both groups. No effect on total estrogen levels was seen, suggesting that this dose of T does not cause appreciable increases in peripheral androgen aromatization. In both the Intimate SM1 and SM2 trials, the placebo group also had improvement in sexual function, suggesting that awareness and help in seeking treatment influences treatment response [18].

A 4-year open-label extension of the Intimate SM1 and SM2 continued to evaluate safety of the 300 µg/day TTP group. This was the first large long-term safety assessment of oophorectomized women with HSDD on concomitant ET. There was no increase seen in the rate of new occurrences or severity of AEs, serious AEs or withdrawal due to AEs over time [37]. Again, the most common AEs were mild, and included application-site reactions and minimal unwanted hair growth. Four patients on TTP exhibited clitoral enlargement: one patient had resolution of symptoms after study withdrawal, two cases resolved during active treatment, and the last patient was lost to follow-up. Two cases of angina were reported and no myocardial infarctions occurred. No clinically significant serum laboratory changes were seen with up to 4 years of therapy. Serum-free, bioavailable and total T and dihydrotestosterone increased from baseline but did not continue to increase over time. Small increases in systolic and diastolic blood pressure (≤3 mmHg), and weight was seen in patients after 3 years of active treatment; however, these changes are likely attributed to normal population aging.

Overall, the safety profile of TTP in follow-up was deemed to be favorable and reassuring; however, the causal relationship between TTP use and breast cancer remained uncertain [37]. Three cases of invasive breast cancer were reported, which was consistent with an age-appropriate expected rate. There were also three cases of ductal carcinoma *in situ* reported with an additional case diagnosed 1 year after discontinuing therapy. The study size was considered too small to evaluate subtle changes in cancer growth rate. One patient on concomitant 1.25 mg conjugated equine estrogen experienced an ischemic stroke after 2 years of treatment. No deaths occurred during the 4 years of treatment [37].

The Intimate NM1 study was the first large RCT of TTP using the 300 µg/day patch or placebo in 549 women with HSDD who underwent natural menopause, on oral estrogen with or without progesterone [21]. Women randomized to TTP had a significantly greater increase in total SSEs (mean change from baseline in TTP group: 1.9 ± 0.26 vs placebo: 0.5 ± 0.21 episodes/4 weeks; p < 0.0001 in intent-to-treat population) and an increase in all other domains of the PFSF scale as well as diminished distress compared with placebo. A similar number of women randomized to each treatment group withdrew due to AEs (22 women for TTP and 19 women for placebo), which were mild or moderate in severity including application-site reactions, upper respiratory infections and hirsutism. Treatment efficacy was noted in patients after 4–16 weeks. Median-free and bioavailable T levels were predictable and steady with TTP and remained within the reference range of premenopausal women. Similar to the preceding Intimate studies, women in the placebo group also showed improvement in sexual function, again suggesting that perhaps awareness and the act of seeking treatment influences treatment response.

In 2006 a RCT examined the efficacy and safety of TTP 300 µg/day in oophorectomized women receiving concomitant transdermal estrogen [19]. This trial also spanned 6 months and, unlike previous trials completed in North America, was carried out in European and Australian women. The TTP group showed a significantly greater improvement from baseline in scores for sexual desire compared with placebo (change from baseline: 16.43 vs 5.98, respectively; p = 0.02). Scores for arousal, orgasm, decreased sexual concerns, decreased distress and responsiveness, also increased from baseline compared with placebo [19]. The frequency of SSEs increased but was

not statistically different between treatment groups (0.77 ± 0.15 vs 0.28 + 0.15 increase in events per week for treatment arms and placebo, respectively; p = 0.06). AEs were similar in both groups and were mild, including application-site reaction, breast pain, mild hirsutism and mild acne. Unlike prior studies, the women exhibited much lower placebo-response rates, perhaps reflecting a cultural difference.

The APHRODITE Phase III trial studied 150 µg/day and 300 µg/day of TTP versus placebo in naturally and surgically postmenopausal women with HSDD not taking ET or estrogen and progestogen therapy (EPT) [38]. Efficacy was measured for 24 weeks and safety measured for 52 weeks. By 24 weeks, women treated with TTP 300 µg/day reported an increase in frequency of SSEs per month compared with placebo (2.1 vs 0.7, respectively; p < 0.001). Sexual desire increased and distress diminished for both doses of TTP, with those in the 300 µg/day group showing a significant treatment effect compared with placebo. It took 8 weeks for efficacy to manifest and treatment effects were similar in women who had undergone natural versus surgical menopause. The 300 µg/day T group reported significantly higher scores for sexual desire and lower scores for personal distress compared with the Intimate SM studies.

The incidence of adverse androgenic events was consistent with results of the Intimate studies in women taking HT, with a higher incidence of hair growth reported. Mild clitoromegaly occurred in one woman receiving 150 µg/day of T and in three women in the 300 µg/day T group. In naturally menopausal women there was an increased report of mild vaginal bleeding, with two women showing proliferative endometrium by subsequent biopsy, although no cases of endometrial hyperplasia or carcinoma were diagnosed. This was hypothesized to be the result of the atrophic effect of T on the endometrium [39]. No adverse metabolic effects were observed and free T levels remained within the reference range for premenopausal women. Most concerning in this study was the finding of four cases of breast cancer in women treated with T. Two of the cancers were likely to have been pre-existing [38].

The ADORE trial studied efficacy and safety of TTP in naturally menopausal women, most of whom were not using HT [40]. Participants received 300 µg/day T patch twice weekly or placebo, for 6 months. The TTP group had significant improvements in SSEs (p = 0.0089), sexual desire (p = 0.0007) and reduced personal distress (p = 0.0024) versus placebo for both the subgroup not using HT and the subgroup using HT. A higher percentage of those in the TTP group experienced androgenic side effects, including acne and increased hair growth. Alopecia and voice deepening were similarly reported in both the TTP and placebo groups. The percentage of patients with breast tenderness was slightly higher in the TTP group. There was no increased incidence of application-site reactions in this group. No serum lipid, renal or liver function changes were noted. Serum-free and -total-T levels increased from baseline, with free T levels remaining within the normal range. Maximum treatment effect was noted between weeks 13–16. The results of this study were similar to those seen in surgically menopausal women [40].

Other studies have looked at alternative forms of transdermal T including cream, gel and spray. T gel has been shown to be well absorbed and effective for treatment of hypogonadal men [41]. A RCT using daily transdermal T gel (10 mg) in premenopausal women with HSDD showed significant improvement in psychological general well-being (p = 0.003) and sexual self-rating (p = 0.001) compared with placebo. No AEs were reported. Baseline levels of total T increased from 0.87 ± 0.52 to 1.09 ± 0.44 nmol/l in the placebo group, whereas in the T-treated group baseline total T increased from 1.04 ± 0.59 to 2.58 ± 1.22 nmol/l. Free androgen index, a predictor of free T, increased from 1.6 ± 1.1 to 2.0 ± 1.3 in the placebo group compared with an increase in the T group from 1.9 ± 1.3 to 5.5 ± 4.1, crossing the upper limit of normal [42]. The same regimen was looked at in 53 postmenopausal women on HT over 3 months, and significant improvement was noted in several dimensions of sexual function with no AEs. Total T levels increased more than tenfold during treatment and dihydrotestosterone levels were doubled. The authors suggest that decreased dose and continued monitoring of serum-T levels be utilized in future studies [23].

Initial results from two completed Phase III efficacy trials, BLOOM 1 and BLOOM 2, demonstrated that T gel (300 µg/day) is well tolerated with a safety profile comparable with placebo. However, no significant improvement was seen compared with placebo in the primary end points of number of days with SSEs and increase in mean sexual desire. BLOOM 1 demonstrated an increase of 1.47 days with SSEs in the T group versus 1.26 days with SSEs in the placebo group (p = 0.463), and an increase in mean sexual desire of 0.03 over placebo (p = 0.672). BLOOM 2 resulted in an increase of 1.00 day with SSEs in the T group versus 1.28 days with SSEs in the placebo group (p = 0.214), and an increase in mean sexual desire of 0.03 compared with placebo (p = 0.48). In both trials, a decrease in sexual distress was seen in the treatment group [101]. A 5-year safety trial for this gel is ongoing.

A small RCT completed in Australia examined the

effects of 1% T cream (10 mg T) versus placebo on sexual desire in postmenopausal hysterectomized women on transdermal estrogen [43]. The cream was shown to significantly improve libido and sexual frequency. Ease of use was noted and no side effects were reported over a 3-month period. Significant yet mild increases in total-serum T occurred. Little placebo effect was seen, and no beneficial effect on mood or energy was demonstrated in the T group.

It is hypothesized that a 'pulse' of T could have beneficial effects on sexual desire or arousal. A controlled pilot study looked at an 'as needed' application of transdermal T gel for premenopausal women with HSDD, 4–8 h prior to intercourse. Results showed that the T-gel group had a small but significant improvement in sexual arousal compared with placebo ($p = 0.03$). Reported side effects were tingling after administration and mild hirsutism. Larger clinical trials are needed to define optimal dosage and time schedule of as needed T application [44].

Barton *et al.* studied the efficacy of T cream versus placebo in treating decreased sexual desire in postmenopausal women with a history of cancer in a randomized, placebo-controlled crossover trial ($n = 150$). Although women treated with T cream demonstrated higher levels of bioavailable T, this did not translate into increased libido in the treatment arm. The authors concluded that these results may be attributed to estrogen depletion at baseline [45].

Davis *et al.* looked at safety and efficacy of a T metered-dose transdermal spray for treating premenopausal women with HSDD in Australia [46]. Three different doses of T-metered dose spray were evaluated for 16 weeks versus placebo. The frequency of SSEs was statistically significant for women treated with the intermediate dose of T therapy (90 µl spray) than for women treated with placebo (2.48 vs 1.70, respectively, $p = 0.04$). There was no difference from placebo in frequency of SSEs in women treated with low (56-µl spray) and high (two 90-µl sprays) doses of T. After 4 months, most of those treated with the 90-µl dose had free T levels less than the upper limit of the normal for women. The most frequently reported AE was hypertrichosis at the application site, which was dose-related. Other AEs included headache, nausea, acne and dysmenorrhea. No significant changes were seen in blood test values, serum biochemical variables or vital signs. The placebo effect was also noted to be strong in this study [46]. As in prior studies, there was no dose–response relationship noted, possibly because there may be no further benefit with higher doses, or because the increase in AEs seen with higher doses may overshadow perceived benefit in treated women [17]. With the T-spray delivery, less application-site reactions were noted compared with prior studies on TTP [17,18,21]. The importance of using concomitant contraception in the premenopausal population was noted [46].

Summary of placebo-controlled trials of transdermal T in women with HSDD can be found in Supplementary Table 1.

Safety of T therapy

Supraphysiologic doses of T are rare with low dose therapy, but when present, are known to cause virilizing side effects such as voice deepening and clitoromegaly [47]. High levels of exogenous T also cause anger and hostility; however, these effects have not been reported with transdermal T [48–50]. Androgenic effects such as acne, hirsutism and androgenic alopecia are uncommon with oral as well as transdermal androgen preparations that result in free or total-serum-T levels that are at, or slightly above, physiologic levels [20]. In women who experience mild hirsutism, hair patterns regress to normal after cessation of therapy [20,51].

T acts as a prohormone for estradiol via aromatization, thus the question arises whether peripheral conversion of T to estrogen places a woman at an increased risk for endometrial cancer, breast cancer and/or cardiovascular disease [52]. *In vitro* studies have demonstrated that androgens exert an inhibitory effect on endometrial proliferation [53]. Similarly, exogenous T does not appear to stimulate endometrial proliferation [39].

In vitro data and animal models indicate that androgens exhibit apoptotic and antiproliferative effects on breast tissue, possibly limiting the mitogenic and cancer-promoting effects of estrogen and exerting a protective effect on breast tissue [54–56]. However, results from epidemiological studies in breast cancer patients are mixed, with some studies showing an increased risk of breast cancer in those with low androgen levels and others demonstrating an increased risk of breast cancer in those with high androgen levels [55,57,58]. One prospective study evaluated breast cell proliferation in postmenopausal women on EPT plus transdermal T versus EPT with placebo patch. No increased breast cell proliferation was found in those randomized to a TTP, while women on placebo exhibited a fivefold increase in breast cell proliferation [59]. An observational study showed that patients on EPT plus T therapy had lower rates of breast cancer, similar to national averages of women not on hormones [54]. Davis *et al.* conducted a placebo-controlled RCT on natural and surgical postmenopausal women not on concomitant ET, using transdermal T 150 or 300 µg/day. Results showed no significant effect of either dose

of T on mammographic breast density compared with placebo [60]. In an immunohistochemical study of breast tissue from transgender individuals, long-term exogenous T therapy did not appear to have a significant effect on breast tissue [61]. However, there have been reports of breast cancer in female-to-male transgender individuals who received supraphysiologic doses of T [62]. As mentioned above, in the recent APHRODITE RCT of transdermal T versus placebo in women not on ET, four cases of breast cancer were diagnosed in the T group. One of these patients had nipple discharge prior to study initiation, another was diagnosed after only 4 months of therapy, and another had prior treatment with HT for 25 years and family history of breast cancer, leading the authors to speculate that perhaps these cancers were unrelated to T therapy. The fourth cancer was diagnosed after 24 months of treatment and a causal relation could not be definitively excluded [46]. The observational Nurses Health Study found that combined estrogen–T therapy was associated with a 17.2% higher risk of breast cancer than estrogen-only treatment per year of use [63]. However, this study had a number of methodological issues and did not show a duration effect, which would have been expected if T is a risk factor for cancer.

Although there is concern regarding T and the risk of breast cancer, most data do not support a causal link between T supplementation and increased risk of breast cancer, and may even suggest that T antagonizes estrogenic effects on breast tissue, thereby reducing the risk of breast cancer [32]. To date, no RCTs have been large enough or of sufficient duration to provide meaningful data on breast cancer risk.

Numerous studies have looked at the effects of T on cardiovascular disease risk. Oral T has been shown to decrease levels of HDL and triglycerides, an effect mediated by first-pass liver metabolism. No effect on low-density lipoprotein has been found [51,64]. Transdermal T has the advantage of bypassing hepatic first-pass metabolism and unlike oral T, appears to have no attenuation of HDL [35]. Oral T has been shown to cause mild insulin resistance [65]; however, transdermal T has not been found to cause adverse changes in fasting glucose or insulin levels [17,32]. No studies have demonstrated that T therapy has an AE on blood pressure, blood viscosity or coagulation factors [32,66,67]. T implants have been shown to improve endothelial-dependent and -independent vasodilation in women on concomitant ET [68]. No trials have reported significant liver dysfunction from transdermal T replacement in women with or without concomitant ET, however, liver abnormalities have been reported with the use of high oral T doses [32].

It is important to consider that long-term safety data on T therapy is sparse and there is still a need for long-term RCTs, such as the one that is currently ongoing with T gel, to safely determine risks of therapy.

The decision to initiate T therapy

The US FDA has not approved T formulations for HSDD in women; however, transdermal T is approved in Europe as a treatment for HSDD in oophorectomized women on concomitant ET. In 2004, an FDA Advisory Committee did not recommend approval of the female T patch due to lack of long-term safety data, although they accepted that the modest increase in sexual desire was evidence of efficacy [102]. The Endocrine Society concluded that despite evidence for short-term efficacy of T in certain populations, they do not recommend generalized use of T due to inadequate indications for treatment and lack of long-term safety data in women [69].

In contrast, the North American Menopause Society (NAMS) issued a position statement advising that T therapy may be an option for postmenopausal women on concomitant ET in whom pathologic causes of HSDD have been ruled out [70]. Patients should be appropriately counseled regarding risks and benefits. Transdermal regimens are preferred, as they bypass first-pass hepatic metabolism and should be administered at the lowest dose for the shortest time consistent with treatment goals.

The discrepancy in these two guidelines may be related to the inaccuracy of T assays in women and the dearth of age-matched normative data, making androgen measurement a poor diagnostic tool of HSDD [71,72]. For the Endocrine Society, this problem along with the lack of a well-defined clinical syndrome, serves as an impediment to generalized T treatment recommendations. There is no reliable, commercially available free T assay available, and the rapid fluctuation of endogenous T concentrations often precludes accurate T measurement. The NAMS approach highlights the importance of clinical HSDD presentation as opposed to serum-hormone levels. Additionally, quality of life is the primary benefit of T treatment in women with HSDD, while long-term risks are as yet unknown. The risk–benefit analysis for T treatment of a condition that does not result in severe morbidity or mortality is another source of controversy between the two guidelines [32].

Despite the lack of consensus, there is prevalent 'off-label' use of T in women using either compounded T formulations or T regimens intended for men that are FDA approved. In 2003, according to the National Disease and Therapeutic Index, over 20% of the total

prescriptions for male T products were used in women and, during that same year, 1.3 million prescriptions were written for compounded T in women. Both formulations result in inconsistent dosing for women and dubious safety profiles, supporting the need for FDA approved and regulated medical therapies [22]. The NAMS warns that, unlike government-approved therapies, custom-compounded T formulations do not undergo quality regulation nor are they assessed for safety and efficacy in large clinical trials [70].

Prior to consideration of off-label treatment it is important to consider that HSDD may be associated with comorbidities including diabetes, hypothyroidism, congestive heart failure, hyperprolactinemia, Addison's disease, Cushings' disease, temporal lobe lesions, and medications such as chemotherapy, selective-serotonin reuptake inhibitors, steroids, and antihypertensives [34]. Additionally, women should be evaluated for psychological and social etiologies of sexual dysfunction including depression, eating disorders, unresolved sexuality and relationship problems. Physical factors such as vestibulitis, vulvodynia, pelvic inflammatory disease, endometriosis and vaginal atrophy in postmenopausal women should also be assessed [34]. Treatment is contraindicated in women with breast or uterine cancer or in those with cardiovascular or liver disease [73]. Optimal treatment of HSDD should include both pharmacological therapy as well as individualized psychosocial therapies with attention to the myriad of physiological, psychological and social factors involved in the development of HSDD [74].

Future perspective

Short-term data on safety and efficacy of transdermal T appears reassuring, and current data suggests that transdermal T may be safer than oral T delivery with a favorable short-term side effect profile. However, there is still a need for further longitudinal research on breast and cardiovascular safety. Additionally, most of the studies have examined the safety of exogenous T therapy in patients taking concomitant HT. More studies are needed to examine efficacy and safety in women who receive T alone, without other exogenous hormones.

T therapy for the treatment of HSDD in women has

Executive summary

Background

- The multifactorial nature of hypoactive sexual desire disorder (HSDD) requires a detailed patient assessment taking into account contributing psychosocial variables and medical comorbidities. Relationship satisfaction is an important contributing factor to HSDD and a therapeutic approach will likely include hormonal and non-hormonal treatments, such as cognitive behavioral therapy.

Role of androgens in HSDD

- Androgens have been shown to play a key role in maintaining healthy female sexual function by stimulating libido and maintaining desires.

Testosterone regimens

- There are multiple testosterone (T)-delivery regimens used, such as oral, intramuscular, pellet and transdermal; the challenge has been to formulate an androgen delivery system that results in physiologic and stable levels of androgen that restore sexual desire without virilization or other adverse events.

Data on the efficacy of transdermal T

- Transdermal T therapy has been shown in some studies to be an effective treatment option for women with HSDD.

Safety of T therapy

- Supraphysiologic doses of T therapy have been shown to cause virilizing side effects and optimally T therapy should maintain serum T levels within the normal range for a reproductive aged women.
- Randomized controlled trials have demonstrated that short-term use of transdermal T appears to be safe and effective, yet long-term outcomes on breast cancer and cardiovascular disease remain uncertain. T therapy is contraindicated in women with breast or uterine cancer or in those with cardiovascular or liver disease.

The decision to initiate T therapy

- There is currently no US FDA-approved T therapy available for women in the USA. An individual risk benefit analysis should be carefully considered before initiating off-label T use, with continued risk–benefit assessment after 3 months of therapy. Patients should be aware of off-label use and that treatment effects are usually only seen after three months of therapy.
- Androgenic side effects for transdermal therapy should be assessed including hirsutism and acne. Serum-free T index should be checked after 2 or 3 months of therapy. Monitoring should also include subjective patient assessments of sexual response.

Future perspective

- Continued longitudinal research is needed regarding safety of transdermal T on breast and cardiovascular health, to provide a safe and effective option for treating HSDD.

yet to be approved by the FDA. A long-term Phase III safety trial is underway, looking at 3000 women in a RCT to compare rate of cardiovascular disease and breast cancer in women using T gel versus placebo. The active double-blinded, placebo-controlled treatment phase is 5 years. This study will provide the largest database of T safety in women [75]. Hopefully, continued research and long-term RCTs will support the results of short-term trials to provide a safe and effective option for this prevalent condition that effects quality of life in so many women.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.future-science.com/doi/full/10.4155/CLI.12.18

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