Efficacy and safety of transdermal testosterone in postmenopausal women with hypoactive sexual desire disorder: a systematic review and meta-analysis

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Objective: To systematically review and summarize the existing evidence related to the efficacy and safety of transdermal T in postmenopausal women for the treatment of hypoactive sexual desire disorder (HSDD).
Design: Systematic reviews and meta-analysis.
Setting: Not applicable.
Patient(s): Seven randomized controlled trials enrolled 3,035 participants; 1,350 women were randomized to treatment with T patch, and 1,379 women were randomized to placebo.
Intervention(s): None.
Main Outcome Measure(s): Primary outcome: satisfying sexual episodes. Secondary outcomes: sexual activity, orgasm, Profile of Female Sexual Function domains (desire), personal distress score, adverse events, acne, increased hair growth, facial hair, alopecia, voice deepening, urinary symptoms, breast pain, headache, site reaction, total adverse events, serious adverse events, withdrawal from study, and follow-up rate.
Result(s): The T group had significantly more satisfying sexual episodes, sexual activity, orgasms, desire, significant change in Personal Distress Scale score, androgenic adverse events, acne, and hair growth compared with the placebo group. There was no significant difference between the two groups in increase in facial hair, alopecia, voice deepening, urinary symptoms, breast pain, headache, site reaction to the patch, total adverse events, serious adverse events, reasons for withdrawal from the study, and the number of women who completed the study.
Conclusion(s): The short-term efficacy in terms of improvement of sexual function and safety of transdermal T in naturally and surgically menopausal women affected by HSDD either on or not on estrogen progestin hormone therapy is evident from this systematic review. The use of transdermal T is associated with increase in androgenic adverse events such as acne but is not associated with any serious adverse events. (Fertil Steril® 2017;107:475–82. ©2016 by American Society for Reproductive Medicine.)
Key Words: Transdermal testosterone, postmenopausal, HSDD, hypoactive sexual desire disorder

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Hypoactive sexual desire disorder (HSDD) is a sexual disorder characterized by distress related to loss or decline in sexual interest. It is estimated to affect approximately one in 10 women (1). HSDD is defined as a persistent or recurrent deficiency or absence of sexual fantasies and desire for sexual activity that causes marked distress or interpersonal difficulty (2, 3). Female sexual dysfunction might be evaluated in

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different domains including sexual interest, arousal, orgasm, and pain (4). Low sexual desire has been associated with emotional or psychological distress (5), low self-esteem (6), and depression (7). Women with low desire are also more likely to experience problems with sexual arousal, pleasure, and orgasmic difficulties and have dissatisfaction with their sex life and partner relationship (6). HSDD, as a consequence, also results in a significant decrease in the quality of life (8).

Menopausal status has a significant impact on the prevalence of HSDD, with several studies showing that the prevalence of HSDD is greatest in younger surgically menopausal women (16%–26%), compared with naturally premenopausal women (7%–14%) (5, 6, 9).

Although sexual function declines throughout the menopause transition (10, 11), it is unclear whether this is caused by low estrogen levels, aging, or both (12, 13). Reviews on postmenopausal estrogen replacement have demonstrated the benefits of both local and systemic therapy on sexual function (14).

Together with the decline in E_2 levels, women also exhibit progressively lower androgen levels as they age (15). Even though there is no abrupt perimenopausal decline, the total serum T concentrations observed among women after the age of 50 are approximately half those of women in their 20s (16). For this reason, exogenous T has also been recognized to play a role in improving sexual desire. Although older studies demonstrated a benefit from T along with estrogen replacement in postmenopausal women, these studies generally involved oral and IM T preparations administered in supraphysiological doses (17, 18). However, with the oral and IM T preparations, there are concerns over adverse effects on lipid profiles due to their first-pass hepatic metabolism. More recent research has concentrated on T replacement via the transdermal route with reported serum levels of T closer to the physiological range.

The systematic reviews on this subject have included all types and different routes of administration of T and have provided limited information on the outcomes specific to the transdermal route of administration (19, 20). There are also limited details on the analysis of side effect profile and reasons for withdrawal from these studies.

Since recent research and practice have been on the use of the transdermal route for T replacement in women with HSDD, we sought to systematically review and summarize the existing evidence related to the efficacy and safety of transdermal T in naturally and surgically postmenopausal women for the treatment of HSDD to further guide clinical practice.

MATERIALS AND METHODS

Literature Search Methodology

We searched MEDLINE (1950 to October 2014) and EMBASE (1980 to October 2014). The search also included International Statistical Institute conference proceedings as well as databases for registration of ongoing and archived randomized controlled trials (RCTs), namely, International Standard Randomized Controlled Trial Number, register and meta-register for RCTs (http://www.controlled-trials.com), World Health Organisation trials search portal (apps.who.int/trialsearch/Trial), and the Cochrane Library. A combination of medical subject headings and text words were used to generate two subsets of citations, one including studies of "testosterone" ("testosterone"; "methyl testosterone") and the second "hypoactive sexual desire disorder" ("hypoactive sexual desire"; "sexual desire"; "sexual function"; "sexual dysfunction"; "sexual activity"; "libido"; "HSDD"). These subsets were combined using "AND" to generate a subset of citations relevant to our research question. The reference lists of all known primary and review articles were examined to identify cited articles not captured by the electronic searches. No language restrictions were placed on any of our searches. The searches were conducted independently by J.P. and P.R. Institutional Review Board approval was not required.

Study Selection

Study protocol for the review in terms of PICOS was followed. Studies were selected if the target population (P) were postmenopausal women who were either on estrogen ± P hormone therapy (HT) or not on HT (both surgically and naturally postmenopausal women) with HSDD who were given T patch or gel (I) and were compared with either placebo or no treatment (C). Postmenopausal women were defined as women with surgically induced menopause (bilateral oophorectomy) or natural menopause (12 consecutive months of spontaneous amenorrhea with no obvious pathologic cause). We excluded studies where the population was premenopausal women with HSDD. The T preparation used was T patch or gel. Some studies used three doses of T patch (150, 300, and 450 μg); we included the 300 μg group as most of the studies reported on this dose of T replacement. We excluded all studies which used oral, IM, SC, or vaginal routes of T or used dehydroepiandrostenedione (DHEA). The primary outcome measure was satisfying sexual episodes (SSE). Secondary outcomes were sexual activity, orgasm, Profile of Female Sexual Function (PFSF) domains (desire, arousal, orgasm, pleasure, decreased concerns, responsiveness, and self-image), personal distress scores, adverse events, follow-up rate, reasons for withdrawal from the study, and the laboratory profile.

Only RCTs were included in this systematic review. Studies were selected in a two-stage process. First, the titles and abstracts from the electronic searches were scrutinized by two reviewers independently (P.R. and C.A.), and full manuscripts of all citations that were likely to meet the predefined selection criteria were obtained. Second, final inclusion or exclusion decisions were made on examination of the full manuscripts. Any disagreements about inclusion were resolved by consensus or arbitration by a third reviewer (J.P.). We wrote to the corresponding authors for details in cases where data were not clear.

Assessment of Methodological Quality and Data Extraction

The selected studies were independently assessed by two review authors (C.A., P.R.) for methodological quality and

data extraction. The assessment of methodological quality for risk of bias was based on Cochrane risk of bias assessment tool (www.cochrane-handbook.org) to assess allocation (random sequence generation and allocation concealment), blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting, and other bias. We presented the conclusions for risk of bias in Supplemental Table 3 and Supplemental Figures 2 and 3. Any disagreements were resolved by discussion or by a third review author (J.P.).

Statistical Analysis

For continuous estimates, we calculated the mean difference (MD) and for continuous data, measured on different scales across studies, and we calculated the standardized MD using the inverse-variance method. For dichotomous data, we used the numbers of events in the control and intervention groups of each study to calculate the Mantel-Haenszel risk ratio (RR). $P<.05$ was considered statistically significant. The results from individual studies were pooled using either a fixed effects or random effects model as appropriate. Heterogeneity of the exposure effects was evaluated statistically using the I^2 statistic. If the I^2 value was >50%, showing significant heterogeneity, a random effects model was used. A χ^2 test for heterogeneity was also performed, and the P values are presented. Exploration of causes of heterogeneity was planned using variations in features of population, exposure, and study quality. We presented 95% confidence intervals (CI) for all outcomes. When studies reported sufficient detail to calculate MD but gave no information on the associated SD, the outcome was assumed to have an SD equal to the highest SD from other studies using the same assessment scale. We included both data reported as final mean scores in each group and mean change scores from baseline in each group. Where studies reported both values, we preferentially included mean change scores from baseline. We treated ordinal data (for example, quality-of-life scores) as continuous data. We adhered to published guidance for conducting systematic reviews, that is, the Cochrane Handbook throughout. Statistical analyses were performed using RevMan 5.2.7 software (Cochrane Collaboration, Oxford, UK) and StatsDirect.

RESULTS

Literature Search

The process of literature identification and selection is summarized in Supplemental Figure 1. Of the 1,190 publications identified by the search, 36 were selected during the initial screening. After examination of the full manuscripts, 29 were excluded (Supplemental Table 1), while the remaining seven studies satisfied the selection criteria and were included in this review (21–27).

Study Characteristics

The seven included studies enrolled 3,035 participants. The sample size per study varied across the trials and ranged from 76 to 814 participants. In total, 1,350 women were randomized to treatment with T patch and 1,379 women were randomized to placebo. No RCTs have reported on the use of T gel. The characteristics and methodological quality of the included trials are summarized in Supplemental Table 2 and Supplemental Table 3, respectively. Our judgments about each risk of bias item, presented as percentages across all included studies, are shown in Supplemental Figure 2 and for each risk of bias item for each included study in Supplemental Figure 3.

In four studies, women had undergone hysterectomy and bilateral salpingo-oophorectomy, therefore they were in surgically induced menopause at least 1 year before entering the studies (21–23, 27); in two studies, the patients were naturally menopausal women from at least 1 year before entering the studies (25, 26); in one study, both patients with surgically induced menopause and naturally menopausal women were included (24). The patients had been receiving a stable dose of oral or transdermal estrogen for at least 3 months in four studies (21– 23, 27); in one study, progestin was added if the uterus was present (26), and in one study patients did not receive concomitant estrogen therapy (24). In another study, naturally menopausal women received systemic transdermal estrogen, oral nonconjugated equine estrogen, or no estrogen therapy (with or without continuous oral or transdermal progestogen) (25).

Some studies reported on both 150 and 300 μg T in the treatment arm (21, 24). We included the data from 300 μg T group to maintain the homogeneity across the studies as most of the studies reported on this dose of T. HSDD symptoms were assessed with the same instruments (Sexual Activity Log [SAL], PFSF, and PDS) in all seven studies.

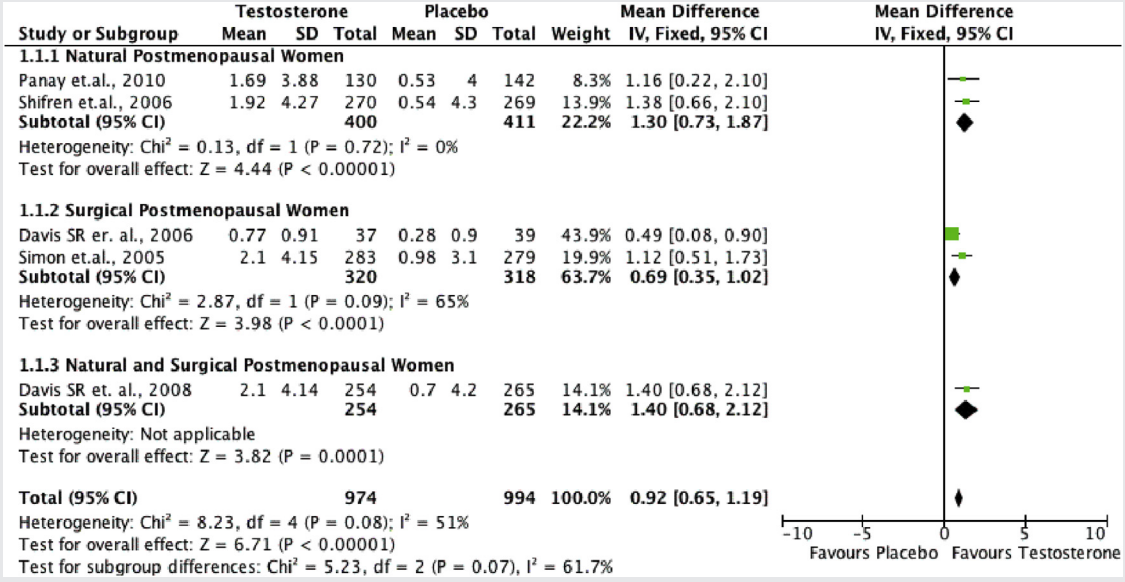
Primary Outcome Measure: SSE

Five studies reported on the MD change in SSE (23–27). Pooling the results of these studies showed that the T group had significantly more SSE compared with the placebo group (MD, 0.92; 95% CI, 0.65, 1.19; $P<.00001$; Fig. 1).

We performed a subgroup analysis to see the effect of T patches in naturally and surgically postmenopausal women. Two studies reported on naturally postmenopausal women (25, 26). Pooling the results from these studies showed that the T group had significantly more SSE compared with the placebo group (MD, 1.30; 95% CI, 0.73, 1.87; $P<.00001$; Fig. 1). Two studies reported on surgically postmenopausal women (23, 27). Pooling the results of these studies showed that the T group had significantly more SSE compared with the placebo group (MD, 0.69; 95% CI, 0.35, 1.02; $P<.00001$, Fig. 1). One study reported on both naturally and surgically postmenopausal women (24). The results from this study showed that the T group had significantly more SSEs compared with the placebo group (MD, 1.40; 95% CI, 0.68, 2.12; $P=.0001$, Fig. 1).

We performed subgroup analysis to see the effect of T patches in women who are on concomitant estrogen ± P HT or not. Four studies reported on postmenopausal women who were on estrogen ± P HT (23, 25–27). Pooling the results from these studies showed that the T group had significantly more SSE compared with the placebo group (MD, 0.96; 95% CI, 0.50, 1.42; $P<.0001$; Fig. 2). One

FIGURE 1



Forest plot of comparison. T versus placebo. Outcome: SSE. Subgroup analysis: naturally or surgically menopausal women.

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study reported on postmenopausal women who were not on any estrogen ± P HT (23). The results of this study showed that the T group had significantly more SSE compared with the placebo group (MD, 1.40; 95% CI, 0.68, 2.12; P=.0001, Fig. 2).

Secondary Outcome Measures

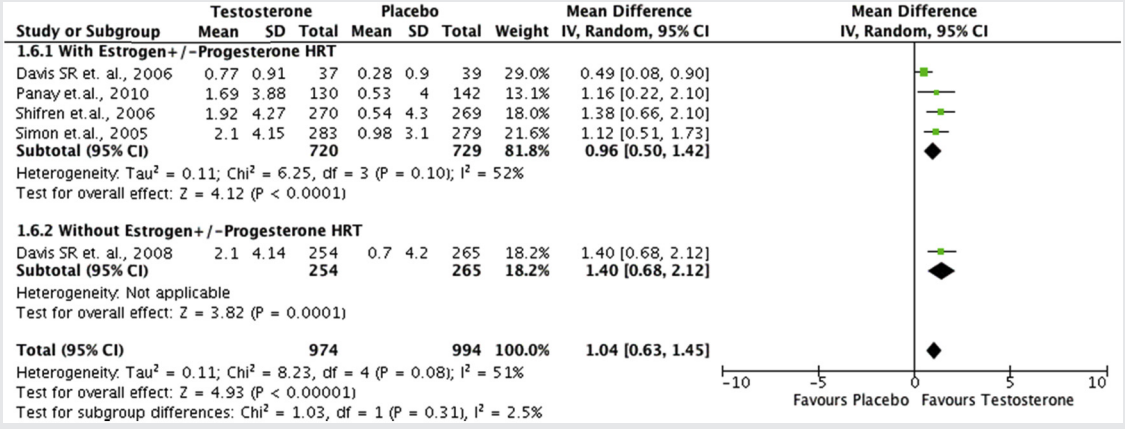
Sexual activity. Two studies reported on the mean change in sexual activity (26, 27). Pooling the results of these studies showed that the T group had significantly more sexual activity compared with the placebo group (MD, 0.96; 95% CI, 0.51, 1.41; P<.0001, Supplemental Fig. 4A).

Orgasm. Two studies reported mean change in orgasms experienced (26, 27). Pooling the results of these studies showed that the T group had significantly more orgasms compared with the placebo group (MD, 1.16; 95% CI, 0.68, 1.65; P<.00001, Supplemental Fig. 4B).

PFSF domains: desire. Six studies reported mean change in sexual desire experienced by women (21–23, 25–27). Pooling the results of these studies showed that the T group had experienced significantly more desire compared with the placebo group (MD, 6.09; 95% CI, 4.51, 7.68; P<.00001, Supplemental Fig. 5).

We performed subgroup analysis to see the effect of T patches on the naturally and surgically postmenopausal

FIGURE 2



Forest plot of comparison: T versus placebo. outcome: SSE. Subgroup analysis: on estrogen ± P HT or not.

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women. Two studies reported on naturally postmenopausal women (25, 26). Pooling the results of these studies showed that T group had experienced significantly greater improvement in desire compared with the placebo group (MD, 6.37; 95% CI, 3.92, 8.82; $P<.00001$, Supplemental Fig. 5). Four studies reported on surgically postmenopausal women (21–23, 27). Pooling the results of these studies showed that the T group had experienced significantly more desire compared with the placebo group (MD, 5.89; 95% CI, 3.80, 7.98; $P<.00001$, Supplemental Fig. 5).

Personal distress score. Four studies reported mean change in personal distress score experienced (22, 25–27). Pooling the results of these studies showed that the T group had more significant change in PDS score compared with the placebo group (MD, −8.15; 95% CI, −10.60, −5.70; $P<.00001$, Fig. 3).

We performed subgroup analysis to see the effect of T patches on the naturally and surgically postmenopausal women. Two studies reported on naturally postmenopausal women (25, 26). Pooling the results of these studies showed that T group had more significant change in PDS score compared with the placebo group (MD, −9.76; 95% CI, −13.78, −5.74; $P<.00001$, Fig. 3). Two studies reported on surgically postmenopausal women (22, 27). Pooling the results of these studies showed that the T group had more significant change in PDS score compared with the placebo group (MD, −7.20; 95% CI, −10.29, −4.11; $P<.00001$, Fig. 3).

Adverse events. Pooling the results of three studies (24–26) showed that the T group had significantly more total androgenic adverse events compared with the placebo group (RR, 1.37; 95% CI, 1.12, 1.69; $P=.002$). Pooling the data from seven studies (21–27) showed that the T group had significantly more acne compared with the placebo group (RR, 1.41; 95% CI, 1.05, 1.88; $P=.02$). Pooling data from five studies (21, 23–25, 28) showed that the T group had significantly more hair growth compared with the placebo group (RR, 1.56; 95% CI, 1.17, 2.09; $P=.003$). Pooling the data from five studies (21–23, 26, 27) showed that there was no significant difference between the two groups in increase in facial hair (RR, 1.07; 95 % CI, 0.86, 1.33; $P=.54$). Pooling the results from five studies (22, 24–27) showed that there was no significant difference between the two groups in alopecia (RR, 1.02; 95% CI, 0.71, 1.47; $P=.90$) or voice deepening (RR, 1.12; 95% CI, 0.74, 1.67; $P=.60$; Supplemental Fig. 6).

Pooling the results from all seven studies (21–27) showed that there was no significant difference in total adverse events (RR, 1.01; 95% CI, 0.97, 1.05; $P=.77$; Fig. 4); severe adverse events (RR, 1.02; 95% CI, 0.62, 1.68; $P=.94$; Supplemental Fig. 7); withdrawal rate from the study (RR, 0.91; 95% CI, 0.76, 1.10; $P=.33$); or the follow-up rate (RR, 1.03; 95% CI, 0.99; 1.08; $P=.14$; Supplemental Fig. 8) between the T and the placebo group.

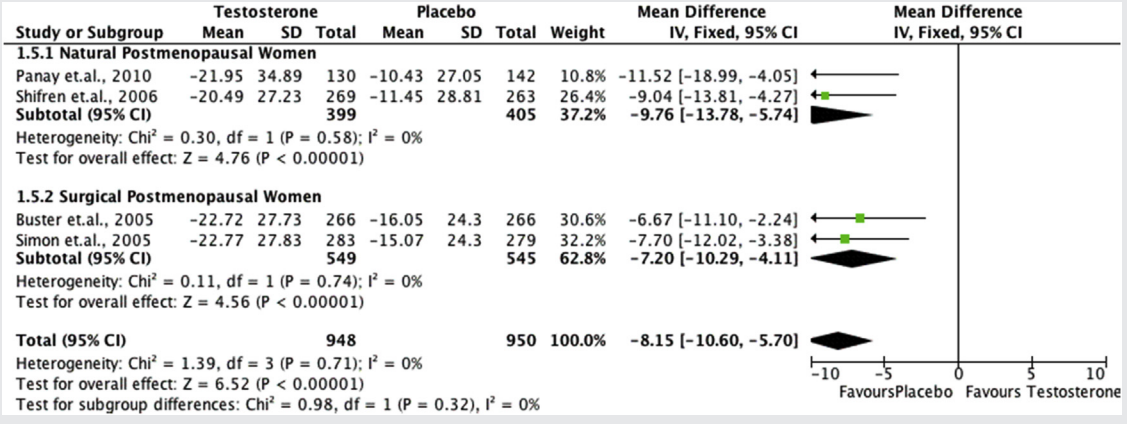
Analysis of laboratory data: Liver function tests, lipids, and blood counts. Serum lipid profiles, carbohydrate metabolism, and renal and liver function as assessed by serum chemistry and hematology indices were reported to be similar among the treatment and the control groups in all seven studies (21–27), and no clinically relevant changes from baseline were observed for any vital signs and body weight during the 24-week study.

DISCUSSION

Summary of Main Results

This systematic review and meta-analysis shows that postmenopausal women with HSDD noted significant improvement in sexual function in several domains including the number of SSE, sexual activity, number of orgasms, and sexual desire along with a significant reduction in personal distress scores with transdermal T replacement. There was no significant difference between the two groups in terms of total adverse events and serious adverse events. Even though it is associated with a significantly increased incidence of acne and increased hair growth, there was no increase in the incidence of facial hair, alopecia, deepening of

FIGURE 3



Forest plot of comparison: T versus placebo. Outcome: personal distress score.

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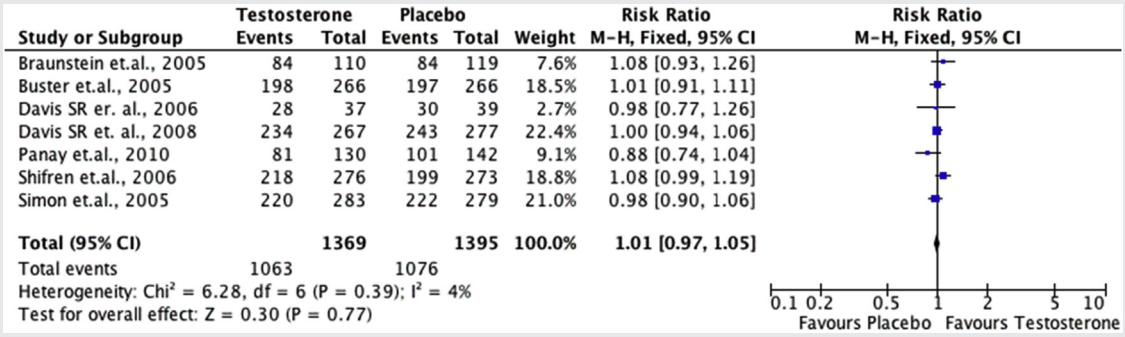
FIGURE 4



Forest plot of comparison: T versus placebo. Outcome: total adverse events.

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voice, urinary symptoms, breast pain, headaches, or patch site reactions. Moreover, none of the androgenic adverse effects were rated as severe. There was no significant difference in the number of discontinuations from the T group compared with placebo, thereby providing further reassurance regarding the side effects associated with the use of T.

Serum lipid profiles, carbohydrate metabolism, and renal and liver function as assessed by serum chemistry and hematology indices were reported to be similar among the treatment and the control groups in all seven studies, and no clinically relevant changes from baseline were observed for any vital signs and body weight during the 24-week study. These data further support the safety of transdermal T.

Strengths and Limitations

We made an extensive electronic and manual search and carefully evaluated the studies for eligibility. There was a predetermined strategy for study selection and quality assessment of included studies, conducted by two independent assessors; when there were any disagreements about inclusion or exclusion, these were resolved by consensus or arbitration by a third reviewer. We excluded all studies that included premenopausal women with HSDD; women who used oral, IM, vaginal, or sublingual T preparation; or women who used DHEA as androgen replacement. Furthermore, among the studies that used different doses of T, we included data only from one regimen in the analysis (300 μg of T, twice weekly). There was also homogeneity in the length of the treatment in all seven studies (24 weeks), and the same instruments (SAL, PFSF, PDS) were used to assess HSDD symptoms across these studies.

Limitations of this review are that not all studies provided data on all outcome measures and therefore were not suitable for meta-analyses for some outcomes. There is also a lack of data on sense of well-being, bone health, cognition, menopausal symptoms, mood alteration, breast cancer, and cardiovascular disease. Progestin was a cointervention in two of the included trials. This could potentially obscure the treatment effects of T on sexual function, body composition, and lipid profiles. Long-term safety data are not available from any of these studies.

Some of the studies included were overseen by the same the researchers and had the same sponsor group. The researchers described in their published manuscripts what measures they undertook to minimize bias. However, this needs to be taken into consideration when interpreting the results.

Agreements and Disagreements with Other Studies or Reviews

In support of the effects of HT on sexual function, a Cochrane review reported that HT treatment with estrogen alone or in combination with progestogen was associated with a small to moderate improvement in sexual function, when used in women with menopausal symptoms or in early postmenopause (within 5 years of amenorrhea) but not in unselected postmenopausal women (28). This study also reported that there is no significant benefit with tibolone or selective estrogen receptor modulators alone or in combination with estrogens on sexual function.

Even with adequate estrogen and P replacement, many women experience a persistent decrease in libido (29). Several studies have indicated that the addition of T to estrogen therapy improves sexual well-being in postmenopausal women (30–33). A Cochrane review compared systemic T plus HT versus HT alone (19) and reported that adding T to HT has a beneficial effect on sexual function in postmenopausal women. A subgroup analysis showed that high-density lipoprotein levels were noted to be markedly lower in postmenopausal women who were treated with oral T compared with transdermal T patches.

A recent systematic review on this subject by Elraiyah et al. (20) included 35 RCTs using any form of T and irrespective of the route of administration. The investigators concluded that T use was associated with statistically significant improvement in various domains of sexual function and personal distress in postmenopausal women. They carried out subgroup analysis on the oral and nonoral routes of T administration, but the data and information from this subgroup analysis were very limited. Our review looked at the use of 300 μg T patch only and thereby provided information on the use of T patches. We also looked at all side effects experienced and reasons for withdrawal from these studies to

provide safety information to further inform clinical practice. A subgroup analysis in the study of Elraiyah et al. (20) showed the reduction in total cholesterol was found to be more noticeable with methyltestosterone and oral T and that triglyceride reduction was found to be significantly less with the oral T compared with the nonoral route. Our review showed that the change in serum lipid profiles, carbohydrate metabolism, renal, liver function, and blood cell indices were similar among the treatment and the control groups. Contrary to Elraiyah et al. (20), who reported that surgically menopausal women achieved significantly higher scores in sexual pleasure and enjoyment on sexual function scales than those who had natural menopause, our subgroup analysis found that naturally postmenopausal women had similar or more improvement in SSE, desire, and PDS scores compared with surgically postmenopausal women with the use of T patch.

Interpretation

Based on the evidence provided by our review, an indication for adding transdermal T to estrogen and progestin HT is to enhance sexual function in postmenopausal women. Adding transdermal T to HT in the form of estrogen ± P HT or giving transdermal T alone in the absence of estrogen ± P improves the number of satisfying sexual events number, sexual activity, number of orgasms, desire, and personal distress compared with placebo. Close surveillance for androgenic adverse events, acne, and other side effects is necessary. The incidence of androgenic adverse events such as acne and hair growth is clearly increased by addition of T, but there is no significant increase in total adverse events and serious adverse events.

Unfortunately, evidence for long-term effects on breast cancer and coronary heart disease and other outcomes like sense of well-being, bone health, cognition, menopausal symptoms, and mood alteration is lacking. Information is also lacking on how long transdermal T can be used safely by women for relief of symptoms. Further RCTs are needed to verify the duration of safe long-term use and adverse events associated with it.

Previous systematic reviews (19, 20) have included T and DHEA from different routes of administration. Since transdermal preparation is currently in practice, we focused on this route of administration to guide our practice. This paper summarizes not only the benefits but also the side effect profile with the use of transdermal T preparation in this cohort of women. This information was not available from any of the previous reviews in the literature. Therefore, this paper will bring more information on the efficacy and safety profile of transdermal T preparation.

Conclusion

The short-term efficacy in terms of improvement of sexual function and safety of transdermal T in naturally and surgically menopausal women affected by HSDD either on or not on estrogen ± progestin HT is evident from this systematic review. The use of transdermal T is associated with an increase in androgenic adverse events such as acne but is not associated with any serious adverse events. Data on long-term safety outcomes are lacking, and further studies are needed to assess long-term outcomes such as cardiovascular and breast safety.

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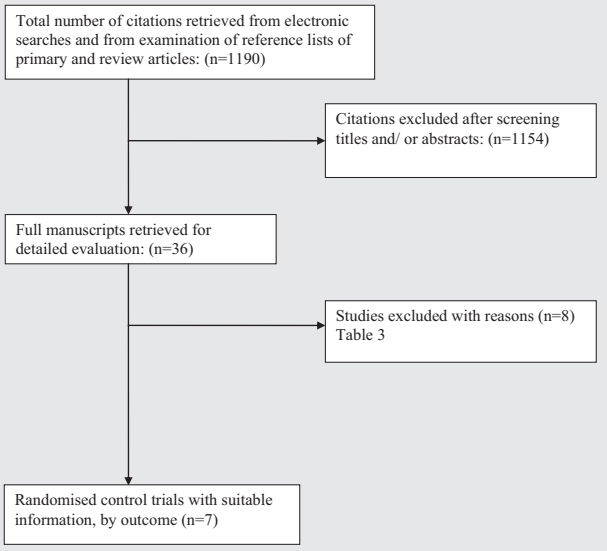
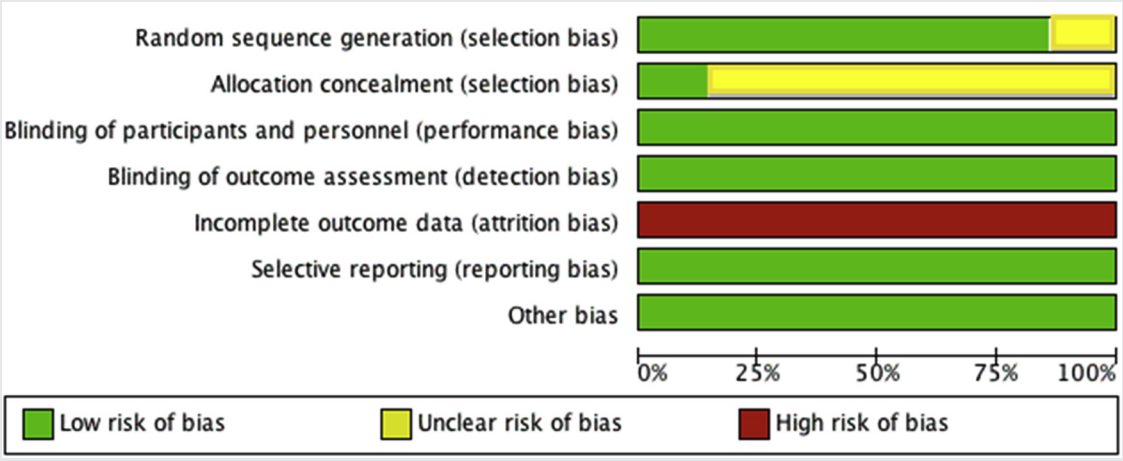
SUPPLEMENTAL FIGURE 1



Study selection process for the systematic review of the efficacy and safety of transdermal T in postmenopausal women with HSDD.

Achilli. Transdermal T and HSDD. Fertil Steril 2016.

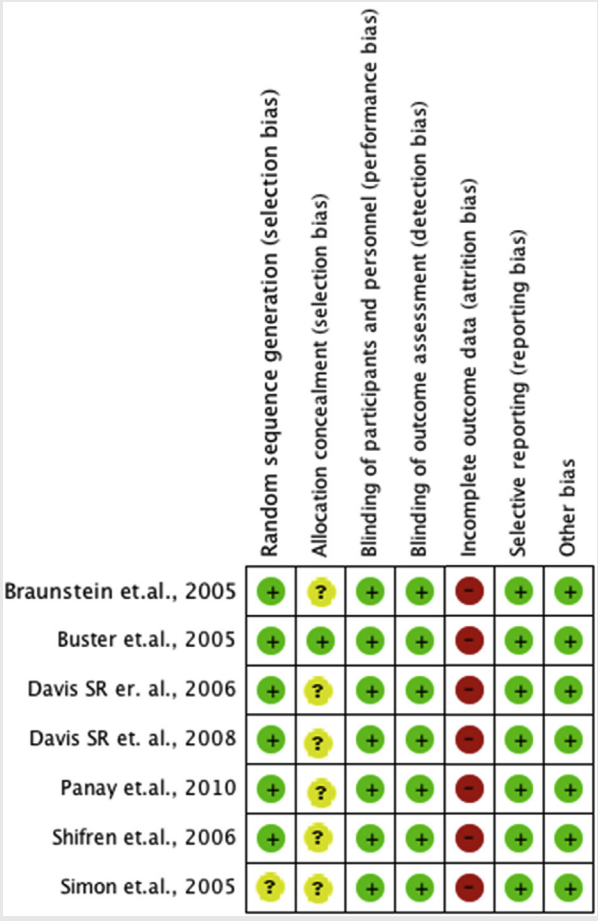
SUPPLEMENTAL FIGURE 2



Risk of bias graph for studies included in the systematic review of the efficacy and safety of transdermal T in postmenopausal women with HSDD.

Achilli. Transdermal T and HSDD. Fertil Steril 2016.

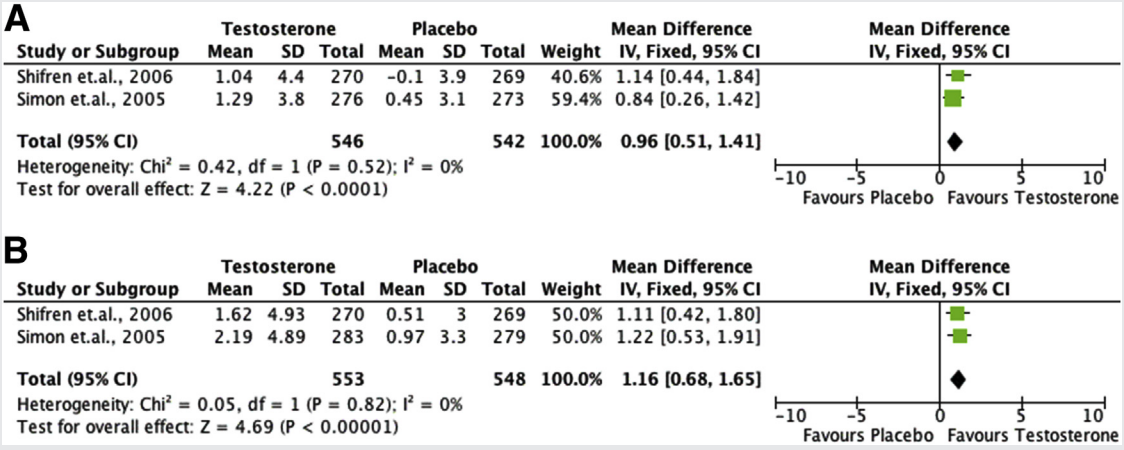
SUPPLEMENTAL FIGURE 3



Risk of bias summary graph for studies included in the systematic review of the efficacy and safety of transdermal T in postmenopausal women with HSDD.

Achilli. Transdermal T and HSDD. Fertil Steril 2016.

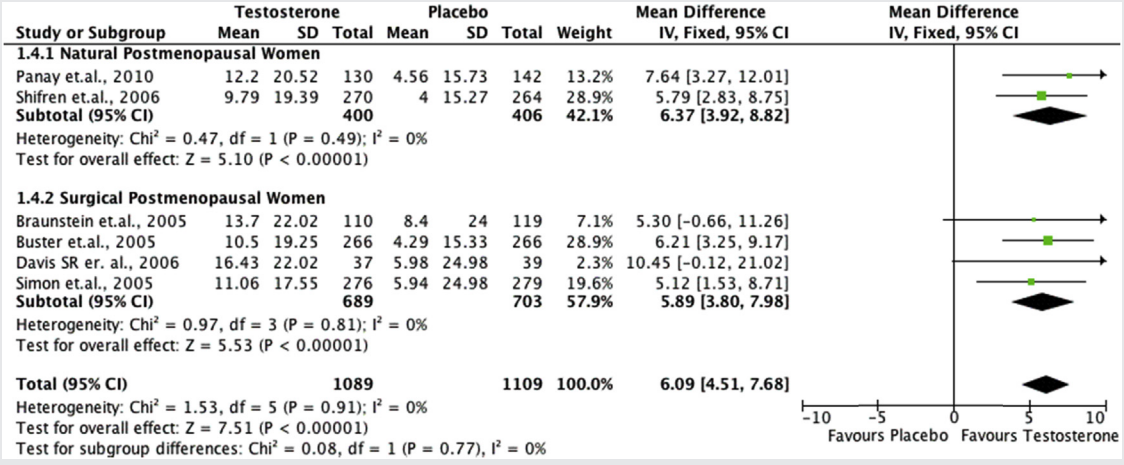
SUPPLEMENTAL FIGURE 4



Forest plot of comparison: T versus placebo. Outcome: sexual activity (**A**) and orgasm (**B**).

Achilli. Transdermal T and HSDD. Fertil Steril 2016.

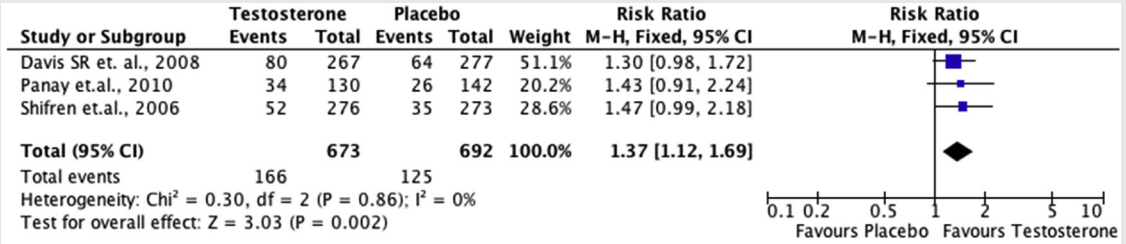
SUPPLEMENTAL FIGURE 5



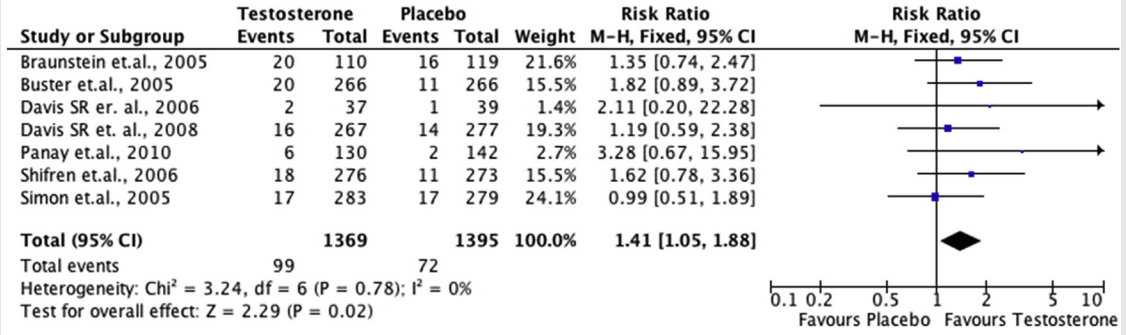
Forest plot of comparison: T versus placebo. Outcome: desire. Subgroup analysis: naturally or surgically menopausal women.

Achilli. Transdermal T and HSDD. Fertil Steril 2016.

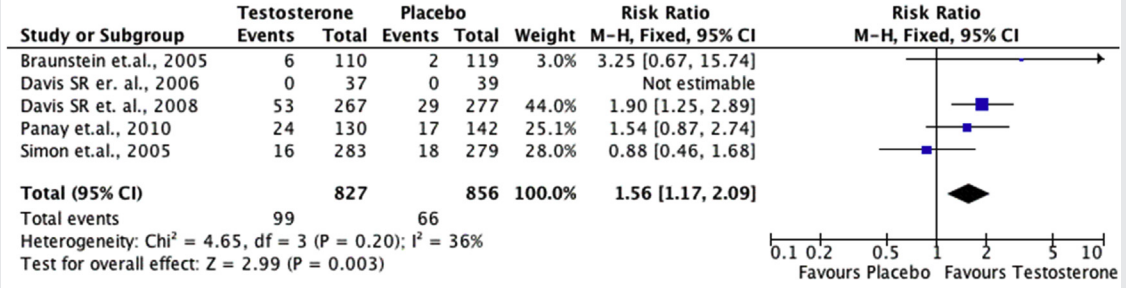
SUPPLEMENTAL FIGURE 6



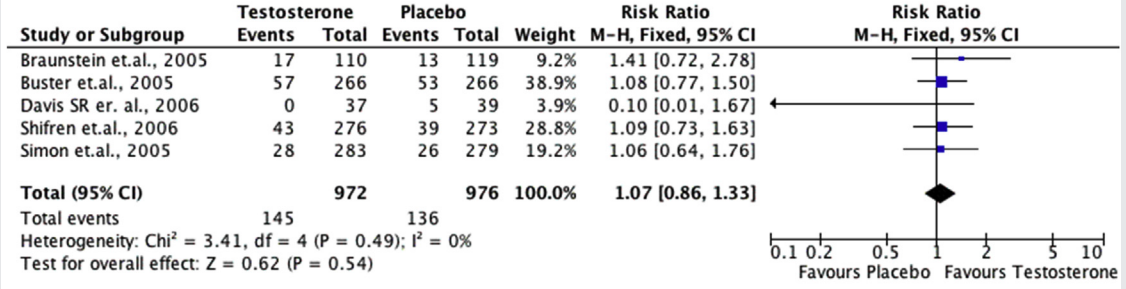
Total androgenic adverse events



Acne



Hair growth



Facial hair

Forest plot of comparison: T versus placebo. Outcome: total androgenic adverse events, acne, increased hair growth, facial hair, alopecia, and voice deepening.

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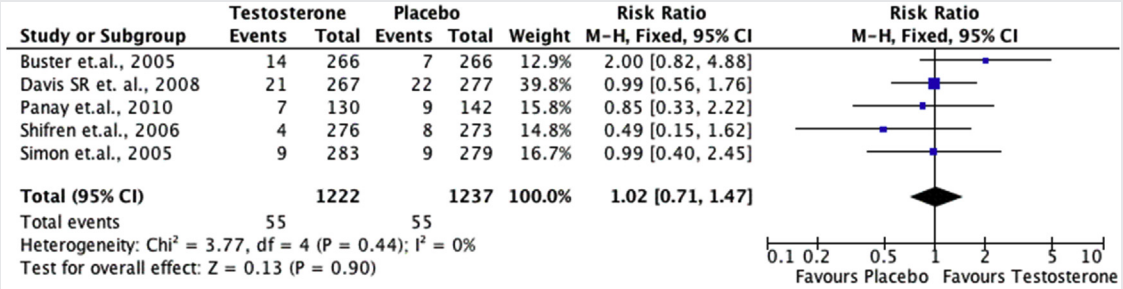
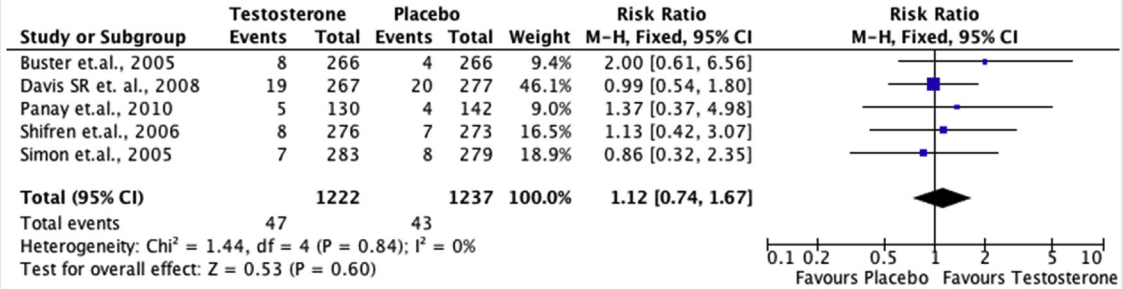
SUPPLEMENTAL FIGURE 6 Continued



Alopecia



Voice deepening

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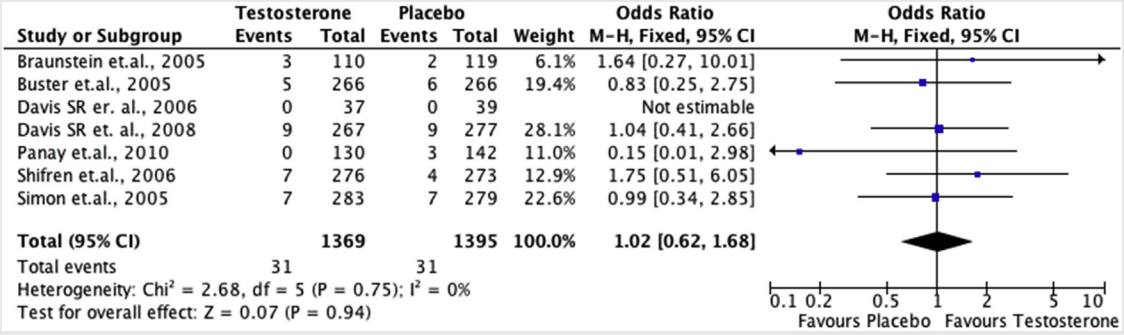
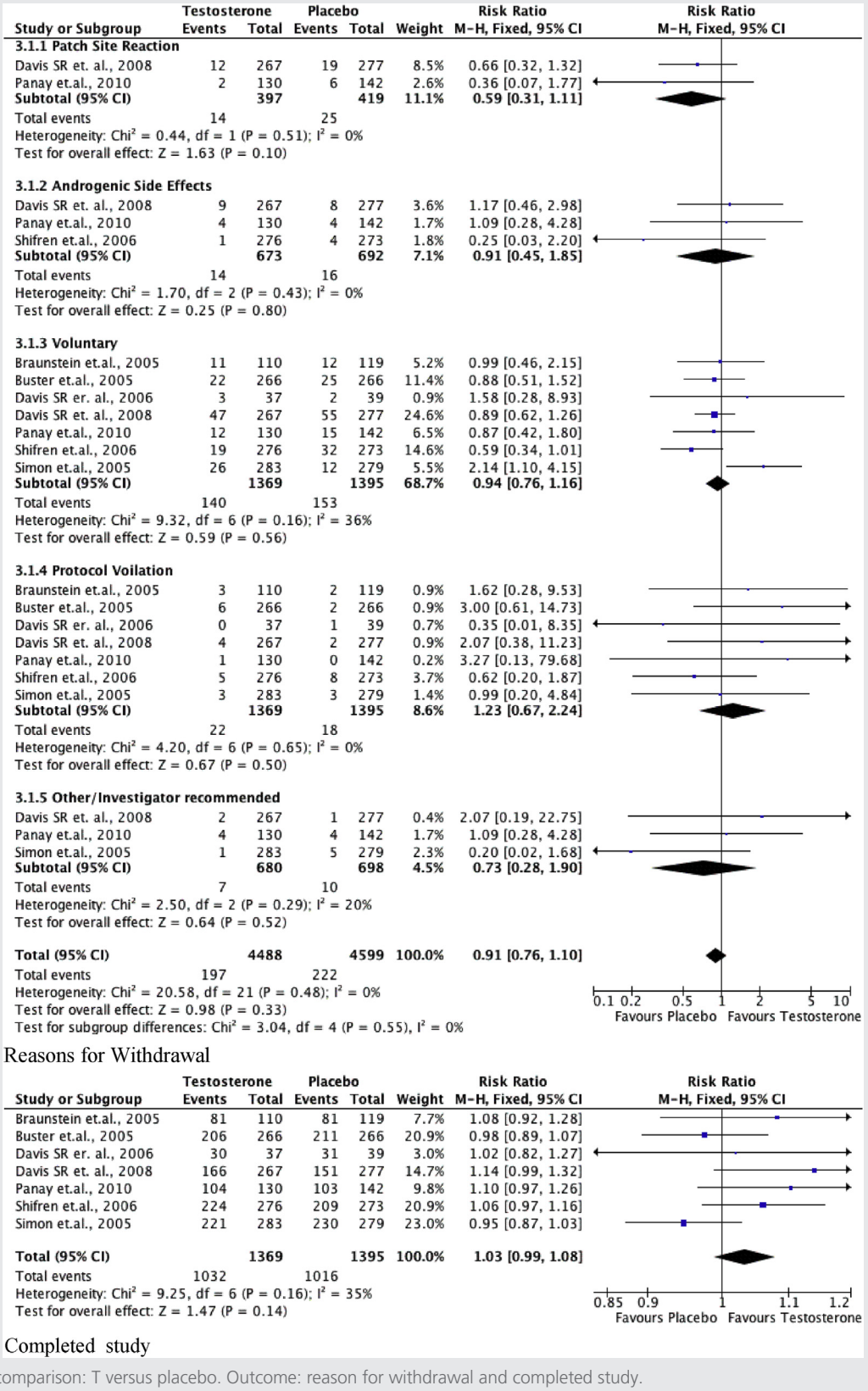
SUPPLEMENTAL FIGURE 7



Forest plot of comparison: T versus placebo. Outcome: severe adverse events.

Achilli. Transdermal T and HSDD. Fertil Steril 2016.

SUPPLEMENTAL FIGURE 8



Forest plot of comparison: T versus placebo. Outcome: reason for withdrawal and completed study.

Achilli. Transdermal T and HSDD. Fertil Steril 2016.

SUPPLEMENTAL TABLE 1

Reason for exclusion of studies in the systematic review of the efficacy and safety of transdermal T in postmenopausal women with HSDD.

Study	Reason for exclusion
Barton et al. 2007 (34)	Oncology patients
Basaria et al. 2002 (35)	Oral methyltestosterone
Blümel et al. 2008 (36)	Oral methyltestosterone
Chudakov et al. 2007 (37)	Premenopausal women with HSSD
Davis et al. 1995 (32)	Implant
Davis et al. 2008 (38)	Premenopausal patients
Davis et al. 2009 (39)	Outcome: mammographic density
De Paula et al. 2007 (40)	Oral methyltestosterone
DeRogatis et al. 2009 (41)	Follow-up study from a previous study
El-Hage et al. 2007 (42)	Crossover study
Fernandes et al. 2014 (43)	Vaginal T
Flöter et al. 2002 (17)	Oral T
Goldstat et al. 2003 (44)	Premenopausal women with low libido
Kingsberg et al. 2007 (45)	Two RCTs, Buster and Simon
Lobo et al. 2003 (18)	Oral T
Mathews et al. 1983 (46)	Sublingual T
Nathorst-Böös et al. 2005 (47)	Nonrandomized study
Raghunandan et al. 2010 (48)	Quasi-randomization study
Shifren et al. 2000 (33)	Crossover study
Warnock et al. 2005 (49)	Oral T
White et al. 2012 (50)	Outcome: CV events

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SUPPLEMENTAL TABLE 2

Characteristics of the studies included in the systematic review of the efficacy and safety of transdermal T in postmenopausal women with HSDD.

Author/no. of cases	Inclusion criteria	Exclusion criteria	Route of T	Cases	Controls	Method of assessment	Outcomes reported
Braunstein et al. 2005 (21) (n = 447)	Ages 24–70 y; bilateral oophorectomy at least 1 y before; on oral estrogen at a stable dose for at least 12 wk; in a sexual relationship for at least a year; have an affirmative response to the set questionnaire and absence of other conditions that could cause HSDD.	Androgen therapy; moderate or severe hirsutism (a score of ≥6 on the Lorenzo scale of 15); hyperlipidemia; psychiatric illness (including a score of ≥14 on the Beck Depression Inventory II16); dyspareunia; physical limitations that interfered with sexual function; history of breast or gynecologic cancer; on medications likely to interfere with sexual function.	Patch twice weekly	150 μg/d (n = 107); 300 μg/d (n = 110); 450 μg/d (n = 111)	Placebo (n = 119)	PFSF, PDS	Sexual desire, satisfying sexual activity, adverse event, acne, hirsutism, monthly facial depilation rate. Laboratory: total T, free T, SHBG, percentage of free DHT, bioavailable T, total E_2, estrone.
Buster et al. 2005 (22) (n = 533)	Women who had undergone hysterectomy and bilateral oophorectomy at least 6 mo before and had been receiving a stable dose of oral or transdermal estrogen for at least 3 mo; women who could plan intercourse with their partner.	Women who have received oral, sublingual, topical, or transdermal androgens during the past 3 mo; injectable or implantable androgen during the past 7 mo; medications known to impair sexual function in the past 12 wk such as selective serotonin reuptake inhibitors, tricyclic antidepressants, antiandrogens, progestins, and beta-blockers. Dyspareunia, severe dermatologic problems, history of sexual trauma, breast cancer, estrogen-dependent neoplasia, relationship disturbances, significant psychiatric disorders, alcohol or drug dependency, diabetes, cerebrovascular disease, or other serious medical conditions.	Patch twice weekly for 24 wk	300 μg/d (n = 211)	Placebo (n = 206)	SAL, PFSF, PDS. Hair was evaluated using the facial portion of the Lorenzo pictorial rating scale. Acne was evaluated using a scale by Palatsi et al.[a]	Changes in sexual desire, frequency of total SSE. Laboratory: hormone levels. Adverse events.

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SUPPLEMENTAL TABLE 2

Continued.

Author/no. of cases	Inclusion criteria	Exclusion criteria	Route of T	Cases	Controls	Method of assessment	Outcomes reported
Davis et al. 2006 (23) (n = 77)	Women ages 20–70 y who had undergone hysterectomy and bilateral oophorectomy at least 1 y before; on transdermal E_2 for at least 12 wk; serum-free T concentration <3.5 pg/mL (12.1 pmol/L); in a stable sexual relationship for at least 1 y; body mass index, 18–30 kg/m^2. Reported HSDD if they were asked. Normal screening mammogram.	Women who had received oral, topical, or vaginal androgens in the previous 3 mo, or T implants in the previous 7 mo. Women with >15 moderate to severe hot flushes per week; moderate or severe hirsutism (score of >6 on Lorenzo scale); hyperlipidemia, psychiatric illness (score of ≥14 on the Beck Depression Inventory-II), dyspareunia, or physical limitations that interfered with normal sexual function; taking medication known to affect sexual function such as chronic glucocorticosteroids, sex steroids other than E_2, antidepressants, or some antihypertensives.	Patch twice weekly for 24 wk; had an additional 8-wk pretreatment period.	300 μg/d (n = 37)	Placebo (n = 40)	PFSF, SAL	PFSF, changes in sexual desire; SAL, frequency of SSE.
Davis et al. 2008 (24) (n = 814)	Women with surgically induced menopause, ages 20–70 and postmenopausal for at least 12 mo. Women with natural menopause ages 40–70 and postmenopausal for at least 2 y. Normal screening on mammogram and Pap smear, no evidence of endometrial cancer or hyperplasia. SHBG level >12 nmol/L; stable monogamous relationship with a sexually functional partner for at least 1 y. Reported HSDD if they were asked.	Use of systemic estrogen or estrogen plus progestin during the previous 3 mo; any androgen therapy during the previous 3 mo (7 mo for implantable T); any serious medical condition; a psychiatric disorder; dyspareunia, a history of breast or gynecologic cancer or physical limitations. Use of nutritional supplements or medications that were likely to affect sexual function such as antidepressants. Any other systemic HT.	Patch twice weekly for 24 wk	150 μg/d (n = 267); 300 μg/d (n = 267)	Placebo (n = 277)	SAL, PFSF, PDS	Frequency of SSE, changes in sexual desire.

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SUPPLEMENTAL TABLE 2

Continued.

Author/no. of cases	Inclusion criteria	Exclusion criteria	Route of T	Cases	Controls	Method of assessment	Outcomes reported
Panay et al. 2010 (25) (n = 272)	Naturally menopausal women; predominantly not using HT; 40–70 y of age; at least 12 mo postmenopause and have a normal mammogram and Pap smear. In a stable monogamous relationship with a sexually functional partner for at least 1 y. Reported HSDD if they were asked.	Women on any androgen therapy during the previous 3 mo (7 mo for implantable T); serious medical conditions, psychiatric disorders, dyspareunia, a history of breast or gynecological cancer, physical limitations, or the use of nutritional supplements or medications, such as antidepressants likely to affect sexual function.	Patch twice weekly for 24 wk; women were stratified based on hormonal regimen: non-HT; estrogen; or estrogen and progestin therapy.	300 μg/d (n =130)	Placebo (n = 142)	SAL, PDS	SAL, 4-wk frequency of SSE; PFSF, sexual desire, adverse events. Laboratory: parameters for hormone levels.
Shifren et al. 2006 (26) (n = 549)	Healthy menopausal women, ages 40–70 y receiving a stable dose of oral estrogen with or without progestin (if the uterus was present). Posthysterectomy women with at least one ovary and a screening FSH level > 30 IU/L. In a stable monogamous relationship; answered yes to five questions enquiring about their sex life including level of desire and amount of sexual activity before and after menopause (as set by the research group).	Women on any androgen therapy during the previous 3 mo (7 mo for implantable T therapy); serious medical condition, psychiatric disorder, dyspareunia, history of breast or gynecological cancer, physical limitations; taking nutritional supplements or drugs that were likely to affect sexual function, such as antidepressants.	Patch twice weekly for 24 wk	300 μg/d (n = 276)	Placebo (n = 273)	SAL, PFSF, PDS. Adverse event facial portion of the Ferriman-Gallwey/Lorenzo scoring system scale developed by Palatsi et al.[a]	Primary: change from baseline in frequency of total SSE. Laboratory: free, total, and bioavailable T; SHBG; free and total E_2; and estrone. Adverse events: lip or chin hair, acne, scalp hair, voice.
Simon et al. 2005 (27) (n = 562)	Women who had hysterectomy and bilateral oophorectomy at least 6 mo before; 20–70 y of age with a normal mammogram and Pap smear; have no physical impediment to sexual function. On stable dose of estrogen therapy (oral or transdermal patch) for at least 3 mo before	Women who have other conditions that could impact sexual function, including dyspareunia; major life change interfering with sexual function; a psychiatric disorder, including depression (Beck Depression Inventory II score ≥14); drug or alcohol dependency;	Patch twice weekly for 24 wk stratified by route of concomitant estrogen therapy (transdermal or oral)	300 μg/d (n = 283)	Placebo (n = 279)	SAL, weekly diary PFSF, PDS. Adverse event facial portion of the Ferriman-Gallwey/Lorenzo scoring system scale developed by Palatsi et al.[a]	Primary: SAL change in the frequency of total SSE. Secondary: PFSF, PDS. Adverse event: lip or chin hair, acne, scalp hair, voice. Serum chemistry, hematology, lipid profile, carbohydrate metabolism, renal and liver

Achilli. Transdermal T and HSDD. Fertil Steril 2016.

SUPPLEMENTAL TABLE 2

Continued.

Author/no. of cases	Inclusion criteria	Exclusion criteria	Route of T	Cases	Controls	Method of assessment	Outcomes reported
	screening and in a stable monogamous relationship with a partner who was sexually functional. Women had a satisfying sex life before oophorectomy and a meaningful loss of sexual desire and decrease in sexual activity after surgery and are bothered by that.	taking medications known to affect sexual function including androgens, phytoestrogens, selective serotonin reuptake inhibitors, systemic beta blockers, raloxifene, tamoxifen, and sildenafil. Any history of breast cancer or estrogen-dependent neoplasia; significant organic disease that could affect the outcome of the study; active gall bladder disease, diabetes, history of cerebrovascular disease or thromboembolic disorders; or abnormal levels of TSH, serum creatinine, or liver enzymes.					function and coagulation parameters

Note: DHT = dihydrotestosterone; SHBG = sex hormone–binding globulin.

[a] Palatsi R, Hirvensalo E, Liukko P, Malmiharju T, Mattila L, Riihiluoma P, et al. Serum total and unbound testosterone and sex hormone binding globulin (SHBG) in female acne patients treated with two different oral contraceptives. Acta Derm Venereol 1984;64:517–23.

Achilli. Transdermal T and HSDD. Fertil Steril 2016.

SUPPLEMENTAL TABLE 3

Quality of studies included in the systematic review of the efficacy and safety of transdermal T in postmenopausal women with HSDD.

Author	Method of randomization	Allocation concealment	Follow-up rate, %	Design
Braunstein et al. 2005 (21)	Randomly assigned	ND	71	Randomized, parallel-group design
Buster et al. 2005 (22)	Random permuted blocks	The random allocation sequence was implemented using a central telephone system.	78	Randomized, parallel-group design
Davis et al. 2006 (23)	Random permuted block	ND	79	Randomized, parallel-group design
Davis et al. 2008 (24)	Random permuted blocks	ND	71	Randomized, parallel-group design
Panay et al. 2010 (25)	Random permuted blocks	ND	76	Multicenter, randomized
Shifren et al. 2006 (26)	Random permuted blocks	ND	88	Multicenter, randomized, placebo controlled
Simon et al. 2005 (27)	ND	ND	80	Multicenter, randomized, Placebo controlled

Note: Control groups were all placebo controlled. All blinding was double. An intent to treat analysis was used in all cases. ND = not documented.

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