Received: 17 August 2018 | Revised: 15 November 2018 | Accepted: 22 November 2018

DOI: 10.1111/cen.13906

REVIEW ARTICLE

WILEY

A systematic review of randomized controlled trials investigating the efficacy and safety of testosterone therapy for female sexual dysfunction in postmenopausal women

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Funding information
MRC; BBSRC; NIHR

Summary

The clinical sequelae of oestrogen deficiency during menopause are undoubted. However, the pathophysiological role of testosterone during the menopause is less clear. Several randomized, placebo-controlled clinical trials suggest that testosterone therapy improves sexual function in postmenopausal women. Some studies suggest that testosterone therapy has additional effects, which include increased bone mineral density and decreased serum high-density lipoprotein (HDL) cholesterol. Furthermore, the long-term safety profile of testosterone therapy in postmenopausal women is not clear. This article will provide a concise and critical summary of the literature, to guide clinicians treating postmenopausal women.

KEYWORDS

androgen, libido, menopause, safety, sexual dysfunction, testosterone, women

1 | INTRODUCTION

Menopause is the cessation of menstruation and reproductive function, due to reduced ovarian activity. Menopause typically occurs between 45 and 55 years of age.[1]

Reduced circulating levels of oestrogen during menopause transition or perimenopause may cause hot flushes, low mood and symptoms of vulvovaginal atrophy.[2] The hallmark symptoms of menopausal transition/perimenopause are hot flushes and irregular periods, whereas amenorrhoea is required for menopause itself. Women may experience vaginal atrophy and vaginal dryness mostly in the late menopausal transition and even beyond.[2-4] Some women also experience decreased libido, receptivity and responsiveness, and reduced frequency of sexual thoughts and fantasies during menopause transition and postmenopause. It is estimated that 50%-60% of all postmenopausal women suffer from symptoms of urogenital and sexual dysfunction.[5,6]

Androgens are natural steroid hormones regulating the development and maintenance of classically male characteristics. However, women also depend on the physiological action of androgens which are thought to include regulation of libido and sexual arousal.[7] Androgens are synthesized in the testes, ovaries and adrenal glands.[8]

It is over 60 years since testosterone therapy was first reported in postmenopausal women.[9] There is currently growing interest in the role of testosterone therapy for the treatment of sexual dysfunction in postmenopausal women; however, prescribing behaviour is highly variable across the UK, which reflects uncertainty about the safety and effectiveness of therapy. This article aims to provide an objective summary of the evidence to date investigating the effectiveness and safety of testosterone replacement for sexual dysfunction in postmenopausal women.

2 | MATERIALS AND METHODS

2.1 | Search and selection

A search of the electronic databases CENTRAL, EMBASE, MEDLINE and PubMed was conducted in accordance with the

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Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement during July 2018[10] (See Table S1). All studies identified using search terms up until July 2018 were considered for inclusion to the study. Databases were searched using the following terms: "female OR females OR women OR woman," AND "postmenopausal OR postmenopausal OR postmenopause OR postmenopause OR perimenopausal OR peri-menopausal OR perimenopause OR peri-menopause OR climacteric" AND "testosterone" AND "placebo OR placebos OR random OR randomised OR randomized OR randomly OR randomly allocated." Identified studies were excluded if the abstracts were not in the English language, or included purely pharmacokinetic outcomes. For studies to be included, subjects were required to be perimenopausal or postmenopausal women presenting with symptoms of sexual dysfunction, dyslipidaemia, impaired memory, decreased bone mineral density or breast symptoms. One study was excluded because all subjects had rheumatoid arthritis.[11]

2.2 | Data extraction

Study titles and abstracts were initially screened before full-text review was completed in duplicate by two study investigators (CSL and CNJ). Discrepancies were dealt with by consensus. A total of 69 studies fulfilled the criteria for inclusion to this systematic review (Figure 1). Data identified for all studies were as follows: date of publication; intervention administered; blinding; randomization; treatment duration; allocation; route of administration and treatment dosage; number of subject participants; design of the study, study references and source of funding.

3 | ANDROGENS AND THEIR ROLE IN SEXUAL FUNCTION

Oestrogens are the dominant sex hormones required for female reproductive maturation and activity. However, androgens also play a biological role in women. Further, in premenopausal women, circulating T and E2 have similar picomolar concentrations. The major androgens in the serum of normal cycling women are dehydroepiandrosterone sulphate (DHEAS), dehydroepiandrosterone (DHEA), androstenedione, testosterone and dihydrotestosterone (DHT). Though abundant in the circulation, DHEAS, DHEA and androstenedione may be considered pro-hormones, requiring conversion to testosterone or DHT to express their androgenic effects.[12] As testosterone requires conversion to E2 or DHT to express its biological effects, it too can be considered a pro-hormone in males and females.

The ovaries and the adrenal glands are the major sources of androgen synthesis in women. Testosterone is the major ovarian androgen, and dehydroepiandrosterone (DHEA) is the major adrenal androgen.[13] Androgen hormones circulate in the blood stream bound to carrier proteins such as sex hormone binding globulin (SHBG) and albumin and corticosteroid binding globulin. Circulating testosterone is highly bound to plasma proteins, with about 66% bound to SHBG and 33% to albumin. SHBG weakly binds DHEA but not DHEAS.[14-16] Androgens exert biological effects by activating androgen receptors (AR), and indirectly by conversion to oestrogen via aromatization. Androgen receptors are located in several organs of the body, including breast, brain, ovaries, bone, muscle, fat, liver and skin.[17] Moreover, testosterone is known to have multiple anabolic

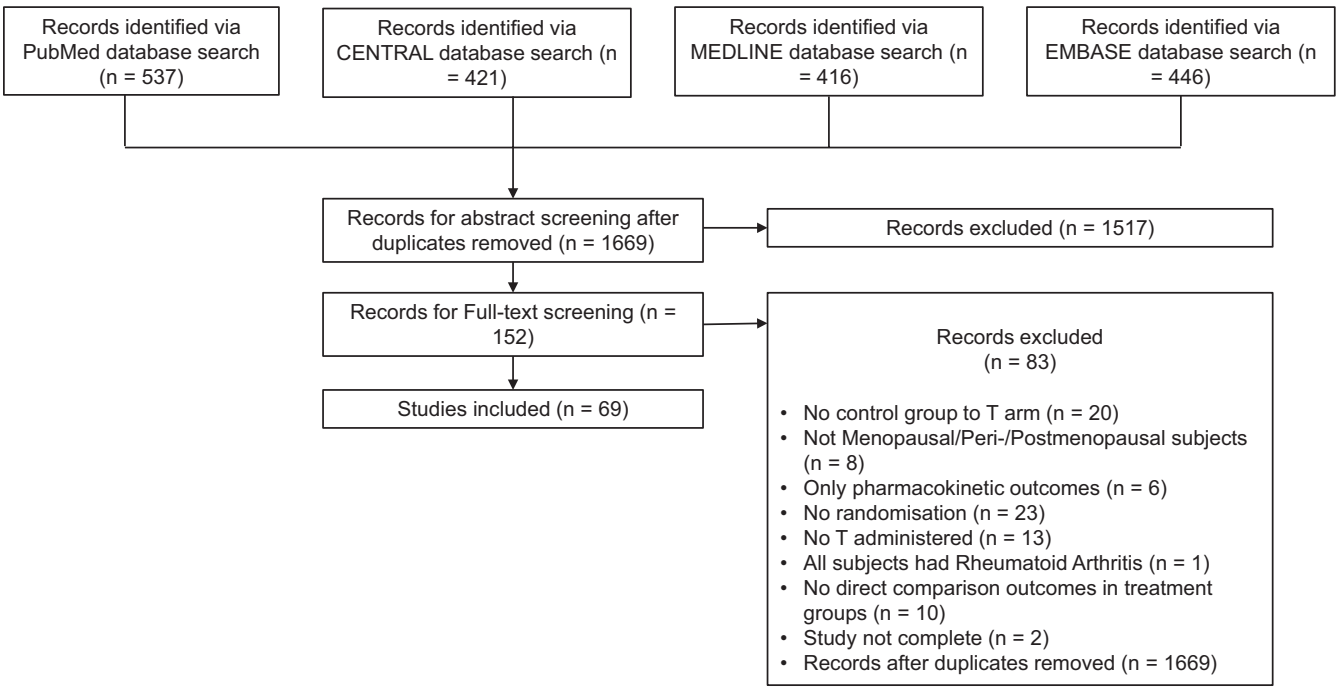

FIGURE 1 PRISMA chart summarising search strategy for the systematic review

effects on muscles, body fat and bone mineral content in women.[18] Androgens are likely to influence behaviour through organizational or activational effects on the brain, which may be either directly, or indirectly mediated through aromatization to oestrogen.[19] It is also important to recognize that effects of sex hormones on sexual function, sexual thoughts and behaviour may be (at least partially) mediated indirectly through improved vaginal lubrication.[20] Of relevance in men, penile injury following intercourse reduces libido, and circumcision to prevent future penile injury is associated with recovery of libido.[21]

A cross-sectional study of 1423 women between the ages of 18 and 75 suggested total testosterone measured via radioimmunoassay, calculated free testosterone, dehydroepiandrosterone sulphate and androstenedione declined steeply in the early reproductive years and do not vary as a consequence of natural menopause, and the postmenopausal ovary seems to be an ongoing site of testosterone production.[22,23] It is however important to highlight that there are many limitations using immunoassays to measure testosterone in women; this is due to limited accuracy and sensitivity at low concentrations of total testosterone when compared with mass spectrometry.[24]

Some studies measuring serum androgen levels in premenopausal and menopausal women (whether natural or surgically induced) have failed to demonstrate any consistent relationship between low androgen concentrations and low sexual function. However, other studies have shown associations between androgens and sexual function in women. Davis SR et al reported the results of a community-based study of 1021 randomly recruited healthy women observed a direct association between an endogenous level of DHEAS below the tenth percentile and low sexual responsiveness in women aged 45 years or older. In women aged 18-44 years, concentrations of DHEAS below the tenth percentile were directly associated with low libido, arousal and responsiveness. No associations with androstenedione or total and free testosterone were seen. Wahlin-Jacobsen et al reported that the serum level of free testosterone and androstenedione was statistically significantly correlated with libido in the total cohort of women including 560 healthy women aged 19-65 years. Moreover, a prospective longitudinal study of 3266 women aged 42-52 years reported by Randolph JF et al demonstrated that endogenous testosterone was associated with masturbation frequency, libido and arousal, and DHEAS was positively associated with masturbation frequency and desire.[22,25-27] Data correlating androgen levels with specific signs or symptoms are unavailable. Consequently, the American Endocrine Society[28] recommends against making the diagnosis of androgen deficiency in women. In summary, it is accepted that androgens may influence sexual behaviour, but it is unclear whether a reduction in endogenous androgen production contributes to sexual dysfunction during the postmenopause.

The 11-ketotestosterone (11 KT) and 11-ketodihydrotestosterone (11KDHT) are androgen derivatives of the adrenal steroid precursor, 11β-hydroxyandrostenedione (11OHA4). Both 11 KT and 11KDHT are potent agonists of the human androgen receptor (AR). Studies are required to investigate whether levels of 11 KT and 11KDHT are significantly related to sexual function in women during menopause transition.[29]

4 | THE DIAGNOSIS AND PREVALENCE OF SEXUAL DYSFUNCTION IN MENOPAUSAL WOMEN

A number of previous studies have investigated the prevalence of sexual dysfunction in menopausal women using structured questionnaires. A prospective observational community-based study of Australian born women aged 45-55 observed that the prevalence of sexual dysfunction using the McCoy Female Sexuality Questionnaire rose from 42% at early menopause to 88% at late menopause defined by hormone testing.[30] Furthermore, cross-sectional studies using the Female Sexual Function Index (FSFI) in postmenopausal, sexually active Malaysian and Thai women suggest that the prevalence of sexual dysfunction is 89.0% and 82%, respectively.[31,32] The American Psychiatric Associations Diagnostic and Statistical Manual of Mental Disorders (DSM) provides a strict set of diagnostic criteria for sexual dysfunction. The previous edition (DSM-4) classified reduced libido in men or women as a form of hypoactive sexual desire disorder (HSDD). However, the newer DSM-5 classification has split HSDD into gender-specific diagnoses; female sexual interest/arousal disorder is defined as symptoms including absent or significantly reduced interest in sexual activity, sexual thoughts or fantasies, and reduced initiation of sexual activity absent arousal from external sexual/erotic cues.[33] These symptoms need to have persisted for a minimum duration of 6 months, be significant enough to cause distress to the individual, and not be attributable to other mental or physical health conditions. The Women's International Study of Health and Sexuality (WISHeS) analysed the prevalence of sexual symptoms associated with distress in over 3500 women aged 20-70 years in the United States; the prevalence of HSDD was reported as 12%-19% in the United States and 6%-13% in Europe.[34] Therefore, the prevalence of HSDD defined using strict DSM-5 criteria is much lower than the prevalence of sexual dysfunction estimated using the structured questionnaire tools. However, there has been criticism of the DSM-V criteria among experts (McCabe 2016). An alternative classification system for female sexual dysfunction has been produced by the International Society of Sexual Medicine (McCabe 2016) and is summarized in Table 1.[35]

5 | EFFECTS OF TESTOSTERONE SUPPLEMENTATION ON SEXUAL FUNCTION

Greenblatt et al in 1950 conducted the first randomized study of testosterone therapy (alone or in combination with oestrogen) in postmenopausal women. Since then, several randomized controlled trials have investigated the effects of testosterone therapy

TABLE 1 Definitions of female sexual dysfunction recommended by International Society of Sexual medicine (ISSM)[35] and DSM-V Criteria for comparison[33]

Sexual dysfunctions	ISSM Definitions	DSM-V Criteria
Hypoactive sexual desire dysfunction	Persistent or recurrent deficiency or absence of sexual or erotic thoughts or fantasies and desire for sexual activity	Split into diagnoses below
Female sexual arousal dysfunction	Persistent or recurrent inability to attain or maintain arousal until completion of the sexual activity, an adequate subjective assessment of her genital response	Lack of or significantly reduced sexual interest/arousal, as manifested by at least three of the following: (a) absent/reduced interest in sexual activity; (b) absent/reduced sexual/erotic thoughts or fantasies; (c) no/reduced initiation of sexual activity and typically unreceptive to partner's attempts to initiate; (d) absent/reduced sexual excitement/pleasure during sexual activity in almost all sexual encounters; (e) absent/reduced sexual interest/arousal in response to any internal or external sexual/erotic cues; (f) absent/reduced genital or nongenital sensations during sexual activity in almost all sexual encounters
Female orgasmic dysfunction	(a) Marked delay in, marked frequency of, or absence of orgasm and/or (b) markedly decreased intensity of orgasmic sensation	Presence of either of following symptoms and experienced on almost all or all occasions of sexual activity: (a) marked delay in, marked infrequency of, or absence of orgasm; (b) markedly reduced intensity of orgasmic sensations
Female genital-pelvic pain dysfunction	Persistent or recurrent difficulties with at least one of the following: (a) vaginal penetration during intercourse; (b) marked vulvovaginal or pelvic pain during genital contact; (c) marked fear or anxiety about vulvovaginal or pelvic pain in anticipation of, during, or as a result of genital contact; or (d) marked hypertonicity or overactivity of pelvic floor muscles with or without genital contact	Persistent or recurrent difficulties with one (or more) of the following: (a) vaginal penetration during intercourse; (b) marked vulvovaginal or pelvic pain during vaginal intercourse or penetration attempts; (c) marked fear or anxiety about vulvovaginal or pelvic pain in anticipation of, during, or as result of vaginal penetration; (d) marked tensing or tightening of pelvic floor muscles during attempted vaginal penetration
Persistent genital arousal disorder	Spontaneous, intrusive and unwanted genital arousal (ie, tingling, throbbing, pulsating) in the absence of sexual interest and desire. Any awareness of subjective arousal is typically, but not invariably, unpleasant. The arousal is unrelieved by at least one orgasm and the feeling of arousal persists for hours or days	No DSM-V diagnostic criteria
Postcoital syndrome (Postorgasmic illness syndrome)	Negative feelings, experiences and/or physical symptoms such as headache, malaise, fatigue and other symptoms after sexual activity	No DSM-V diagnostic criteria
Hypohedonic orgasm	Lifelong or acquired decreased or low level of sexual pleasure with orgasm	No DSM-V diagnostic criteria
Painful orgasm	The occurrence of genital and/or pelvic pain during or shortly after orgasm	No DSM-V diagnostic criteria

in postmenopausal women with symptoms of sexual dysfunction (Table 2). These trials have utilized different dosing regimens and routes of administration. Some trials have used testosterone replacement alone, whereas others have studied the effects of testosterone therapy during oestrogen replacement. Some studies have included women with age-associated ("natural") menopause, whereas others have included women with surgically induced menopause. All studies excluded women with psychological or medical conditions that could impact on their sexual function in keeping with the DSM-4 and DSM-5 diagnostic criteria. Furthermore, most studies were restricted to participants with long-term partners.

Most trials measured sexual function using validated symptom scores. Some authors[6,36,37] have used the modified McCoy's sex scale[38] which covers sexual experience and responsiveness during the last 30 days and contains seven items (eg, "Are you satisfied with your present frequency of sexual activity?" "How enjoyable is sex for you?" and "How often do you have an orgasm during sex?"). Some studies[39,40] used the female sexual function index (FSFI), which is a standardized questionnaire used to assess sexual function among postmenopausal women, and is an anonymous patient-based self-reported instrument.[41] Other authors[42-48] have used the following validated scales: Sexual Activity Log; Profile of Female Sexual Function; Personal Distress Scale. The result of testosterone administration

in postmenopausal women has also been summarized in a recent Cochrane review.[49]

5.1 | Transdermal testosterone administration

Several placebo-controlled double-blind studies have investigated whether testosterone improves sexual function in postmenopausal women taking oestrogen with or without progestin therapy. Most studies have investigated the effects of transdermal testosterone therapy. Three of the largest published studies randomized postmenopausal women with surgically induced menopause to daily dermal patch administration of placebo or 300 μg testosterone for 24 weeks of duration.[42,44,45] All women included in these trials had received oestrogen supplementation for at least 3 months before randomization. Simon et al[44] observed that in 562 women, testosterone administration significantly increased the frequency of total satisfying sexual activity (as measured by the SAL) from 2.82 to 4.92 episodes per 4 weeks, when compared with an increase from 2.94 to 3.92 episodes per 4 weeks in the placebo group ($P = 0.0003$). Libido was also increased significantly during testosterone supplementation when compared with placebo. Buster et al[42] observed in 533 women that testosterone increased total satisfying sexual activity when compared with placebo (1.56 episodes vs with 0.73 episodes per 4 weeks), and improved libido. Braunstein et al[45] randomized 447 women to one of 3 different daily doses of testosterone supplementation (150, 300 or 450 μg) or placebo; subjects receiving the 300 μg testosterone dose reached total serum testosterone levels of 91 ng/dL by week 24 and experienced a statistically significant increase in libido from baseline when compared with placebo (67% vs 48%; $P = 0.05$) and in frequency of satisfying sexual activity (79% vs 43%; $P = 0.049$); these results are concordant with similar smaller studies.[46,50] However, it is important to note the placebo response was substantial. No significant changes in libido or satisfying sexual activity were observed during 150-μg/d or 450-μg/d testosterone supplementation reaching total serum testosterone concentrations of 44.5 and 122.5 ng/dL, respectively, when compared with placebo in postmenopausal women. Shifren et al[47] studied the effects of testosterone patch in 549 women with natural menopause who were taking a stable dose of oral oestrogen (with or without progestin). Participants were randomized to placebo or transdermal testosterone patch (300 μg/d) twice weekly for 24 weeks. They were then followed up to measure a change from baseline in the number of satisfying sexual events using the SAL. Women allocated to testosterone reported a significantly greater increase in sexual events measured using SAL during testosterone when compared with placebo (placebo, 0.5 ± 0.23; testosterone, 2.1 ± 0.28, $P < 0.0001$ vs placebo). The largest RCT performed to date randomized 814 women with menopause (natural or surgical) and HSDD to placebo or testosterone patch at the doses 150 μg or 300 μg per day over a 24-week period.[48] Participants randomized to the 300 μg group, but not the 150 μg group reported significantly greater Satisfying Sexual Events (SSEs) over a 4-week period when compared with participants in the placebo group (episodes per 4 weeks: placebo, 0.7; 150 μg testosterone, 1.2, $P = 0.11$ vs placebo; 300 μg testosterone, 2.1, $P < 0.001$ vs placebo). Though not reported, it would be interesting to determine whether the effects of testosterone differed between women with a natural or surgical menopause.

Panay et al[43] conducted a 6-month placebo-controlled, double-blind trial (the ADORE study). They randomized 272 women to transdermal testosterone patch (TTP; 300 μg/d) or placebo, and used the SAL to measure satisfying sexual episodes as their primary end-point. Increases in Significant Sexual Events (SSEs; $P = 0.0089$), libido $P = 0.0007$ and reduced personal distress ($P = 0.0024$) were observed following 6 months of TTP administration when compared with placebo in menopausal women. In summary, several studies suggest transdermal testosterone increase sexual activity. Collectively, these multiple randomized placebo-controlled studies suggest that testosterone therapy significantly improves symptoms of sexual dysfunction in women with natural or surgical menopause. These conclusions are in keeping with two recent systematic reviews of the literature.[18,49] However, it is important to consider that symptoms of sexual dysfunction do not have a clear relationship with low level of circulating testosterone. Therefore, questions remain as to whether testosterone administration in postmenopausal women exerts pharmacological or physiological actions. It is also important to consider to what extent any effects of androgens on sexual function are attributable to aromatization to oestrogens. For instance in men, aromatase inhibition prevents testosterone administration from improving libido in GnRH agonist-induced hypogonadism.[51] Finally, it would be helpful to specifically investigate whether the testosterone therapy improves sexual function in postmenopausal women whose serum oestradiol levels are replete (eg, serum E2 levels 300-600 pmol/L) during HRT; this would suggest that testosterone is not simply acting to supplement bodily oestrogen exposure (via aromatization).

5.2 | Other routes of testosterone administration

Recent clinical trials have investigated the administration of non-transdermal application of testosterone in postmenopausal women. Urogenital topical application was investigated in 75 menopausal women (natural or surgical), who were randomized to placebo, oestrogen only or oestrogen with testosterone over a 12-week period.[6] McCoy Sexuality scores increased in all treatment groups, but were highest in the oestrogen with testosterone group (Percentage improvement in McCoy Sexuality score: placebo, 18.6; oestrogen only, 42.4, $P < 0.05$ vs placebo; oestrogen with testosterone, 147, $P < 0.01$ vs placebo). This implies that effects of sex hormones on sexual function may be partially mediated indirectly through improved vaginal lubrication.[20] Studies are needed to delineate the relative importance of vulvovaginal vs cerebral effects of sex steroids in sexual function in postmenopausal women. Similar increase in McCoy Sexuality score was observed in a 2002 study of 50 surgically menopausal women[52]; enjoyment of sex, satisfaction with frequency of sexual activity, interest in sex and total score all increased significantly with testosterone compared to placebo, as well as studies in 2006[36] and 2007.[37]

TABLE 2 Summary of systematic review of testosterone therapy in peri- and postmenopausal women

Author and date	Number of subjects	Study design	Findings	Industry funding
Raghunandan C, 2010[6]	75	RCT Postmenopausal 3 study arms: Twice weekly—Topical. E; E + T (1 mg); Placebo (KY Jelly) 12 wk	McCoy improvement: E: 42% E + T: 147% Placebo: 18.6% $P < 0.01$	None stated
Nathorst-Boos J, 2006[36]	53	RCT, crossover study Postmenopausal aged 50-65 EP + 10 mg testosterone gel EP + placebo gel 3 mo	McCoy Questionnaire: "significantly improved ($P < 0.001$) for testosterone vs placebo"	Yes
De Paula FJF, 2007[37]	85	RCT. Postmenopausal aged 49-63 4 study arms: EP + Placebo; EP + MT 2.5 mg (4 m); EP + placebo (2 m) then MT (2 m); 4 EP + MT (2 m) then placebo (2 m) 4 mo in total	McCoy's: EP + MT 2.5 mg groups, showed a statistically significant increase compared to baseline and placebo 2.5 ± 0.4 ($P < 0.05$)	None stated
Fernandes T, 2014[39]	80	RCT Postmenopausal aged 40-70 4 arms: Dermal oestrogen; testosterone (300 μg); Polyacrylic acid (moisturizer); Oil lubricant (placebo). 3 times a week for 12 wk	FSFI: No treatment groups showed improvements in arousal and orgasm compared with the placebo lubricant group	None stated
Tungmunsakuchai R, 2015[40]	70	RCT Postmenopausal aged 40-60 E + Placebo E + T (40 mg) Twice weekly doses 8 wk	FSFI: T 28.6 ± 3.6 Placebo 25.3 ± 6.7 ($P = 0.04$)	None stated
Buster JE, 2005[42]	533	RCT Surgically menopausal women Twice weekly E + TTP (300 μg); E + P 24 wk	SAL: SSE Testosterone: increase of 1.56 Placebo: 0.73 increase ($P = 0.001$)	Yes
Panay N, 2010[43]	272	RCT Menopausal aged 40-70 E + TTP (300 μg); E + Placebo 6 mo	SAL: SSE/4 wk increase from baseline T: 1.69; P: 0.53 ($P = 0.0089$)	Yes
Simon J, 2005[44]	562	RCT Surgically menopausal women aged 26-70 E + TTP (300 μg); E + Placebo 24 wk	SAL: SSE/4 wk increase from baseline T: 2.10 P: 0.98 ($P = 0.0003$)	Yes
Braunstein GD, 2005[45]	447	RCT Surgically menopausal women aged 24-70 received 4 arms Placebo; twice weekly transdermal TTP 150 μg; TTP 300 μg; TTP 450 μg 24 wk	PFSF: TTP 300 μg increases libido vs placebo (67% vs 48%; $P = 0.05$), and frequency of satisfying sexual activity vs placebo (79% vs 43%; $P = 0.049$). 150-μg/d and 450-μg/d not different from placebo.	Yes

(Continues)

TABLE 2 (Continued)

Author and date	Number of subjects	Study design	Findings	Industry funding
Davis SR, 2006[46]	61	Randomized, double-blind, placebo-controlled trial (PHARMACEUTICAL) Surgically menopausal women aged 20-70 received TTP (300 μg/d); Placebo patch 24 wk	Significant increase in PFSF with T compared to placebo (P = 0.02) 43% increase in weekly frequency of SSE at 24 wk for T vs placebo (P = 0.06) Significant reduction in PDS with T vs placebo (P = 0.003) Significant increase in sexual arousal (P = 0.02), orgasm (P = 0.03), sexual responsiveness (P = 0.005), sexual self-image (P = 0.04), lessening of sexual concerns (P = 0.003) and increase in PGWB (P = 0.04) with T vs placebo. Adverse events mostly mild (59%) or moderate (37%) severity. Significant increase in total hirsutism score for T vs placebo, but no significant difference from baseline	Yes
Shifren JL, 2006[47]	549	RCT Menopausal aged 40-70 E ± P + Placebo E ± P + Testosterone (300 μg) Twice weekly. 24 wk	SAL: SSEs average increase from baseline T 2.1 ± 0.28 Placebo 0.5 ± 0.23 (P < 0.0001)	Yes
Davis SR, 2008[48]	814	RCT Surgically menopausal women aged 40-70 received 3 arms: Daily Placebo; TTP 150 μg; TTP 300 μg 24 wk	SAL: SSE/4wk increase from baseline TTP 300 μg 2.1 Placebo 0.7 (P < 0.001) TTP 150 μg 1.2 episodes, (P = 0.11) Not significant	Yes
Shifren JL, 2000[50]	75	RCT Surgically menopausal women aged 31-56 received 2 placebo patch; 1 placebo + 1TTP (150 μg/d); 2TTP (total 300 μg/d) 2 times a week for 4 wk	3 women with adverse effects in placebo, 1 with 1TTP and 2 with 2TTP. 2TTP significantly increased score for frequency of sexual activity and pleasure-orgasm compared with placebo (P = 0.03)	Yes
Floter A, 2002[52]	50	Randomized, double-blind, crossover, placebo-controlled trial. Surgically menopausal women aged 45-60 received Oral: E (2 mg/d) + T (40 mg/d); E (2 mg/d) + Placebo 24 wk	McCoy Questionnaire total score increased with T: enjoyment of sex, satisfaction with frequency of sexual activity, interest in sex and total score. No change in full blood count or liver enzymes. Acne seen in 3 women with T and 1 with placebo, defined as mild to moderate. 5 women reported mild body swelling with T, but no weight gain. All side-effects reversible.	Yes

(Continues)

TABLE 2 (Continued)

Author and date	Number of subjects	Study design	Findings	Industry funding
Lobo 2003[53]	221	Double-blind randomized trial Naturally or surgically menopausal women aged 40-65 received 0.625 mg of esterified oestrogens (n = 111) or the combination of 0.625 mg of esterified oestrogens and 1.25 mg of methyltestosterone (n = 107) 4 mo Change in level of sexual interest or desire as rated on the Sexual Interest Questionnaire	Increased circulating levels of unbound testosterone and suppression of SHBG provide a plausible hormonal explanation for the significantly improved sexual functioning in women receiving the combination of esterified oestrogen and methyltestosterone	None stated
Sherwin,1985[54]	53	RCT 10 premenopausal 43 Surgical menopause Oestradiol 8.5 mg_testosterone 150 mg or oestradiol 8.5 mg or testosterone 150 mg or placebo 1 mol/L 8 mo	Increase in libido Increase in sexual arousal	Not stated
Watts, 1995[55]	66	Randomized, double-blind Trial 96 wk Surgically menopausal women received oral esterified oestrogens (1.25 mg), or esterified oestrogens (1.25 mg) and methyltestosterone (2.5 mg) daily For 2 y	Both treatment regimens prevented bone loss at spine and hip; combined EE + MT associated with significant increase in spinal bone mineral density compared with baseline (n = 24; mean score ±standard error 3.4 ± 1.2%, $P < 0.01$) In EE group, HDL cholesterol increased significantly and LDL cholesterol decreased significantly. Cholesterol, HDL and triglycerides decreased significantly in EE + MT group. Menopausal symptoms of somatic origin (hot flushes, vaginal dryness and insomnia) improved significantly by both treatments	None stated
Huang G, 2014[56]	71	RCT Surgically menopausal women aged 21-60 received 5 arms. E + Placebo E + T 3 mg E + T 6.25 mg E + T 12.5 mg E + T 25 mg Via IM injection. 24 wk	BISF-W: Changes only statistically significant in the T 25 mg group when compared to placebo ($P < 0.05$).	Yes

(Continues)

TABLE 2 (Continued)

Author and date	Number of subjects	Study design	Findings	Industry funding
Dobs AS, 2002[57]	40	RCT double-blind Naturally and surgically menopausal aged 41-76 Tablet: EE (1.25 mg); EE (1.25 mg) + MT (2.5 mg) 4 mo	Significant increase in lean body mass of legs, arms and trunk with EE + MT ($P = 0.007$) Significant decrease in %fat tissue with MT ($P = 0.002$) but not significant for fat tissue ($P = 0.077$) Upper body press increased significantly from 20 kg to 23 kg ($P < 0.036$) and leg press increased significantly from 107 to 130 kg ($P < 0.0024$) Significant increase in lower body strength only with MT Significant decrease in total cholesterol, HDL and triglyceride with MT, but no change in LDL. Significant decrease in LDL with EE only. BISF-W significantly increased for frequency/psychosexual ($P = 0.05$) and pleasure/orgasm ($P = 0.041$) with MT SRS and SIQ increased significantly for interest in sex with MT at 10 wk ($P = 0.031$) and 16 ($P = 0.014$) Significant improvement in somatic symptoms, sexual functioning and vasomotor symptoms with MT 2 patients experienced mild hirsutism	Yes
Dow MGT, 1983[58]	40	RCT Postmenopausal aged 49-54 E2 (50 mg) implant; E2 (50 mg) + T (100 mg) implant	No significant difference between treatment groups for menopausal symptoms (Psychology, Somatic and Vasomotor) as well as frequency of sexual interest, general sexual satisfaction and frequency of orgasm.	None stated
Davis SR 1995[13]	34	RCT single-blind Postmenopausal E2 (50 mg) implant; E2 (50 mg) + T (50 mg) implant Every 3 mo for 2 y	Significant increase in BMD for total body ($P < 0.008$), vertebral L1-L4 ($P < 0.001$) and trochanteric BMD ($P < 0.05$) with T compared to E2 alone. E2 + T greater increase in sexuality: activity ($P < 0.03$), pleasure ($P < 0.01$), orgasm ($P < 0.035$) and relevancy ($P < 0.05$) compared to E2 alone	Yes
Heard-Davison A, 2007[59]	10	Randomized, double-blind, crossover, placebo-controlled trial Postmenopausal aged 50-62 MT (5 mg) single dose; Placebo single dose 2 visits	Significant difference in VPA between T and placebo ($P = 0.03$) 4.5 h post single dose. No significant difference in subjective sexual arousal, scores of mental and physical sexual arousal between treatment groups. Significant ($P < 0.001$) positive correlations between VPA difference scores and mental sexual arousal ($r = 0.60$) and physical sexual arousal scales ($r = 0.62$)	None stated

(Continues)

TABLE 2 (Continued)

Author and date	Number of subjects	Study design	Findings	Industry funding
Myers LS, 1990[60]	40	RCT Postmenopausal mean age 58 Capsules: E (0.625 mg); E (0.625 mg) + MP (5 mg); E (0.625 mg) + MT (5 mg); Placebo 10 wk	No significant difference between groups for energy, euphoria, irritability or anxiety. E + MT group highest frequency, orgasm and pleasure from masturbation compared to other groups.	None stated
Penotti M, 2001[61]	40	RCT Postmenopausal Transdermal HRT + Oral T (40 mg/d); Transdermal HRT 8 mo	2 cases major hair loss, 1 hirsutism Significant difference between groups in PI of MCA at T2 ($P < 0.05$) with T increased from 0.780 to 0.822 ($P < 0.01$) but not ICA. No difference observed in libido and satisfaction.	None stated
Guerrieri GM, 2014[63]	128	RCT Postmenopausal with Primary Ovarian Insufficiency aged 18-42 Transdermal EPT (100 μg/d Oestradiol + 10 mg/d MP) + Placebo; Transdermal EPT (100 μg/d) Oestradiol + 10 mg/d MP) + T (150 μg/d) 12 mo	No significant difference in Q-Les-Q, Rosenberg Self-Esteem Scale Scores, CES-D or HAM-D scores between groups. 2 women given T reported skin irritation or rash. Androgenic effects reported by several women, but infrequent and no significant difference between groups.	Yes
James L, 2011[64]	1288	RCT (PHARMACEUTICAL) Menopausal Tablet: EE (0.15 mg/d); EE (0.3 mg/d); EE (0.45 mg/d); EE (0.15 mg/d) + MT (0.15 mg/d); EE (0.15 mg/d) + MT (0.3 mg/d); EE (0.3 mg/d) + MT (0.3 mg/d); EE (0.3 mg/d) + MT (0.6 mg/d); MT (0.6 mg/d); Placebo 12 wk	No beneficial effects with T for hot flash frequency and severity. Adverse effects with at least 2% greater incidence than placebo included: Acne, Genital Pruritus, weight increase, Upper Respiratory Tract Infection, Hirsutism and Vaginal bleeding. Vaginal bleeding and breast pain not judged as severe.	Yes
Hickok LR, 1993[65]	26	RCT double-blind Postmenopausal aged 40-60 Tablet: EE (0.625 mg) + MT (1.25 mg) + placebo; EE (0.625 mg) + placebo 6 mo	No significant difference in Endometrial cells between groups. Significant reduction in cholesterol, HDL, HDL2, HDL3 and Apolipoproteins A1 and A2 seen with MT, but not EE alone. 5 reports of acne and 2 facial hair with MT.	None stated

(Continues)

TABLE 2 (Continued)

Author and date	Number of subjects	Study design	Findings	Industry funding
Barton DL, 2007[66]	150	Randomized, placebo-controlled, crossover trial Postmenopausal female cancer survivors T cream (10.4 mg); Placebo 4 wk	No significant difference in combined desire subscales, CSFQ, total mood disturbance on Profile of Mood States or Vitality subscale between treatment groups. Mean bioavailable T significantly increased in T group compared to placebo ($P < 0.001$) No significant difference between groups for Acne, voice deepening, abnormal hair loss or abnormal hair growth, as well as negative mood swings, peripheral oedema, headache or overall quality of life. No change in libido	None stated
Barrett-Connor E, 1999[67]	311	RCT, double-blind Surgically menopausal women aged 21-65 received Oral: CEE (0.625 mg); CEE (1.25 mg); EE (0.625 mg) + MT (1.25 mg) EE (1.25 mg) + MT (2.5 mg) Daily for 2 y	BMD increased significantly more with MT at lumbar spine ($P = 0.014$) and hip ($P = 0.009$) compared with nonMT groups No significant difference in menopausal symptoms (hot flushes, sweats and vaginal dryness) between treatment groups. No significant difference in hirsutism between treatment groups. Significant decrease in HDL, total cholesterol and triglycerides with T ($P < 0.05$) compared with EE alone. No significant difference in LDL between treatment groups.	None stated
Davis SR, 2009[70]	279	RCT Menopausal aged 40-70 3 arms: Placebo; TTP 150 μg; TTP 300 μg 52 wk	Percentage Density change from baseline for: placebo 0.05 ± 0.16 TTP 150 μg 0.06 ± 0.19 TTP 300 μg 0.21 ± 0.17 were not significantly different ($P = 0.942$)	Yes
Hofling M, 2007[71]	99	Randomized, double-blind, placebo-controlled trial Postmenopausal aged 45-65 E2 (2 mg) daily + NA (1 mg) daily + TTP (300 μg/d); E2 (2 mg) daily + NA (1 mg) daily + Placebo 6 mo	No significant difference in breast symptoms, mammographic density or % dense mammographic area.	Yes
Hofling M, 2007[72]	99	Randomized, double-blind, crossover, placebo-controlled trial Menopausal aged 45-65 Oral: E (2 mg/d) + T (40 mg/d); E (2 mg/d) + Placebo FNA of breast cells 48 wk	Placebo group more than fivefold increase in total breast cell proliferation from median value of 1.1%-6.2% at 6 mo ($P < 0.001$) as well as epithelial and stromal cell proliferation. No significant increase in proliferative activity in T group.	None stated

(Continues)

TABLE 2 (Continued)

Author and date	Number of subjects	Study design	Findings	Industry funding
Duarte MPC, 2006[73]	37	RCT Postmenopausal aged 42-62 E2 gel (1 mg/d) + MT tablet (1.25 mg); E2 gel (1 mg/d) + Placebo tablet 12 mo	17% decrease in HDL with MT vs placebo, but no change in total cholesterol, LDL or triglycerides. No change in BMI between groups, but visceral fat increased 11% with T vs placebo, but no change in glucose, insulin or HOMA.	None stated
Floter A, 2004[74]	50	Randomized, double-blind, crossover, placebo-controlled trial. Surgically menopausal women aged 45-60 received Oral: E (2 mg/d) + T (40 mg/d); E (2 mg/d) + Placebo 24 wk	No significant difference in total or LDL cholesterol, but 11% reduction in HDL vs placebo with T ($P < 0.001$)	Yes
Chiuve SE, 2004[75]	79	RCT double-blind Surgically menopausal women received Tablet: MT (2.5 mg) + EE (1.25 mg); EE (1.25 mg) 10 wk	MT significantly decreased plasma total triglycerides (11%), total cholesterol (10%), HDL cholesterol (24%), apoCI (13%), apoCII (14%), apoCIII (14%) and apoE (13%) ($P = 0.06$) No significant effect of MT on apoB APOCIII reduced significantly in VLDL (62%), LDL (35%) and HDL (17%)	Yes
Basaria S, 2002[76]	40	RCT double-blind Naturally and surgically menopausal aged 21+ Tablet: EE (1.25 mg); EE (1.25 mg) + MT (2.5 mg) 16 wk	Plasma viscosity significantly reduced in MT group ($P = 0.04$) Significant increase in fibrinogen levels in MT group ($P = 0.006$) Significant decrease in LDL with E ($P = 0.03$) Significant decrease in total cholesterol ($P = 0.009$), HDL ($P < 0.001$) and triglyceride ($P = 0.001$) with MT No change in LDL levels 2 women developed mild hirsutism with MT	None stated
Zang H, 2006[77]	63	RCT Postmenopausal 44-64 Oral: T (40 mg/2 d); E (2 mg/d); T (40 mg/2 d) + E (2 mg/d) 3 mo	No differences reported in Insulin sensitivity, lipid profile and body mass between treatment groups.	None stated
Fernandes T, 2018[78]	60	RCT Postmenopausal aged 40-70 Topical cream: T (300 μg); E (0.625 mg); Glycerine lubricant placebo 3 times weekly or 12 wk	No significant difference in serum metabolic levels (total cholesterol, HDL, LDL, triglycerides and liver function) between treatment groups. No significant difference in endometrial thickness between treatment groups.	None stated

(Continues)

TABLE 2 (Continued)

Author and date	Number of subjects	Study design	Findings	Industry funding
Davis SR, 2000[79]	34	RCT, single-blind Postmenopausal Implant: E2 (50 mg); E2 (50 mg) + T (50 mg) Every 3 mo for 2 y	No significant difference in mean body weight, fat mass or lipid profile between treatment groups.	Yes
Garnett T, 1992[81]	50	RCT Postmenopausal E2 (75 mg) implant; E2 (75 mg) + T (100 mg) implant Every 6 mo for 1 y	No significant difference in bone density at any measured sites between treatment groups.	None stated
Miller BE, 2000[82]	57	RCT, double-blind Naturally and surgically postmenopausal women Sublingual tablet: If hysterectomized: microionized E2 (0.5 mg); microionized E2 (0.5 mg) + microionized T (1.25 mg) If intact Uteri: microionized D2 (0.5 mg) + microionized P4 (100 mg); microionized E2 (0.5 mg) + microionized P4 (100 mg) + microionized T (1.25 mg) 1 y	No difference between treatment groups in bone biochemical markers (Ntx, Dpd or BSAP) by 1 y BMD of hip increased significantly ($P < 0.01$) with T compared to HRT alone No difference in BMD at lumbar spine but significantly higher with T ($P = 0.026$) compared to HRT alone	Yes
Floter A, 2005[83]	50	RCT, crossover Surgically menopausal women aged 45-60 received Oral: E2 (2 mg/d) + T (40 mg/d); E2 (2 mg/d) + Placebo 24 wk	Total lean body mass significantly increased only with T treatment. No difference in BMI, total body fat, systolic and diastolic blood pressure or Liver Enzymes between treatment groups. Markers of bone formation (IGF-1 and P1CP) were significantly higher in T group.	Yes
Kocoska-Maras L, 2009[98]	50	Randomized, double-blind, crossover, placebo-controlled trial Surgically menopausal women aged 45-60 received Oral: E (2 mg/d) + T (40 mg/d); E (2 mg/d) + Placebo 48 wk	T counteracts E induced rise in hs-CRP, but no effects on other inflammatory markers of Cardiovascular disease (IL-6, TNF-A and Homocysteine)	Yes
Huang G, 2014[99]	71	RCT, double-blind Surgically menopausal women aged 21-60 received IM injection: Placebo; T (3 mg); T (6.25 mg); T (12.5 mg); T (25 mg) Once weekly for 24 wk	No significant difference in fasting glucose, insulin concentration, adiponectin or hs-CRP levels between groups. No significant difference in systolic or diastolic blood pressure, abdominal or visceral fat volumes between groups.	None stated

(Continues)

TABLE 2 (Continued)

Author and date	Number of subjects	Study design	Findings	Industry funding
Friebely JS, 2001[100]	34	RCT double-blind crossover Menopausal aged <66 Oral: EE (0.625 mg); EE (0.625 mg) + MT (1.25 mg) 8 wk	No difference in cognitive performance testing between MT and EE alone	None stated
Krug R, 2003[101]	12	RCT crossover Postmenopausal aged 47-65 TTP (6 mg/d); Placebo 3 d	T significantly increased divergent thinking (fantasies and fluency of speech) compared to placebo ($P < 0.07$) No change in subjective mood or other aspects of cognitive function	Yes
Huang G, 2016[102]	71	RCT, double-blind Surgically menopausal women aged 41-62 received IM injection: Placebo; T (3 mg); T (6.25 mg); T (12.5 mg); T (25 mg) Once weekly for 24 wk	No significant difference in measures of cognition (spatial ability, verbal fluency, verbal memory, executive function or attention) between treatment groups	Yes
Kocoska-Maras L, 2011[103]	200	RCT, double-blind Postmenopausal aged 5-65 Oral: T (40 mg/d); E2 (2 mg/d); Placebo 4 wk	No significant difference in verbal fluency, memory or spatial ability between treatment groups ($P > 0.05$)	None stated
Davis SR, 2014[104]	92	Randomized, double-blind, placebo-controlled trial Postmenopausal aged 55-65 T gel (300 μg/d); Placebo Daily for 26 wk	No significant difference seen at week 12 between treatment groups. Cogstate ISLT scores significantly increased at 26 wk with T compared to Placebo Difference 1.57units ($P = 0.03$) No difference in PGWB between treatments. 1 woman given T had perceived temporal hair thinning.	Yes
Moller MC, 2010[105]	50	Randomized, double-blind, crossover, placebo-controlled trial Surgically menopausal women aged 45-60 received Tablet: E (2 mg/d) + T (40 mg/d); E (2 mg/d) + Placebo 48 wk	Immediate verbal memory impaired at 24 wk, but delayed verbal memory not impaired and no other aspects of memory function affected.	Yes
Wisniewski AB, 2002[106]	26	RCT, double-blind Naturally and surgically postmenopausal aged 46-77 Oral: EE (1.25 mg); EE (1.25 mg) + MT (2.50 mg) Daily for 4 mo	Significantly higher building memory score on T vs placebo ($P < 0.05$) No difference in other aspects of cognitive function: cube comparison, shape memory or identical pictures	Yes

(Continues)

TABLE 2 (Continued)

Author and date	Number of subjects	Study design	Findings	Industry funding
Sherwin BB, 1984[107]	49	RCT, double-blind, crossover Surgically menopausal women IM injection: T (150 mg); T (150 mg) + E (10 mg) 3 mo	No effect on suppression of hot flushes when compared with E alone.	None stated
Penteado SRL, 2008[109]	60	RCT Postmenopausal aged 42-60 oestrogen- progesterone + placebo; oestrogen-progesterone + 2.0 mg oral daily testosterone 12 mo	Perceived difference in sexual energy level ("complete relief of all problems"): 34.5% testosterone group 11.1% placebo (P = 0.028)	Yes
El-Hage G, 2007[110]	36	RCT crossover study Surgically menopausal women mean age 54 E + 10 mg T cream;E + placebo 3 mo	BISF-W T: +8.8 vs Placebo (P = 0.000)	Yes
Davis SR, 2006[111]	60	RCT Surgically menopausal women E + T (400 μL) gel + Letrozole (2.5 mg); E + T (400 μL) gel + Placebo. 16 wk	No difference in SSSS between groups.	None stated
DeRogatis LR, 2009[112] & Kingsberg S, 2007[113]	132	Sample of 132 women who were enrolled in 2 RCTs (n = 1094). Surgically menopausal women received Placebo; TTP (300 μg/d) 6 mo	*Responder rate* was significantly higher (P < 0.001) in T vs placebo Desire 50% vs 34%; SSA, 44% vs 30%; Distress 51% vs 39%	Yes
Fernandes T, 2016[109]	80	RCT Postmenopausal aged 40-70 Vaginal cream (3 g) Polyacrylic acid; Vaginal cream testosterone propionate (330 μg); Vaginal cream conjugated oestrogens (0.625 mg); Lubricant glycerine gel (3 g) (placebo) 3 times a week for 12 wk	Women with Vaginal PH ≤5 significantly increased when treated with E (P < 0.05) and T (P < 0.005) compared with Placebo. Vaginal health score significantly increased when treated with T (P < 0.05) and E (P < 0.005) compared with Placebo. Significant increase of Lactobacilli in Vagina with T and E (P < 0.05) compared with Placebo.	None stated
Moller MC, 2013[110]	50	RCT crossover study. Surgically induced menopausal women aged 45-60 received E + T (40 mg) tablet; E + Placebo. 24 wk	No statistical significant correlations between cognitive function or PGWB scores.	Yes
Warnock JK, 2005[111]	102	RCT. Surgically menopausal women aged 32-61 received 2 arms. EE + Placebo EE + MT (2.5 mg) tablet daily. 8 wk	CSFQ-F-C: Significant differences between treatments not seen.	Yes

(Continues)

TABLE 2 (Continued)

Author and date	Number of subjects	Study design	Findings	Industry funding
Blumel JE, 2008[112]	47	RCT Postmenopausal aged 45-64 EP + MT (1.25 mg); EP + Placebo 3 mo	FSFI: T group baseline 17.3 ± 6.2 to 26.5 ± 5.3 ($P < 0.001$). (no change in placebo) T group: 68.7% no longer sexually dysfunctional	None stated
Zang H, 2012[113]	60	RCT Postmenopausal aged 44-64 Oral: T (40 mg/2 d); E2 (2 mg/d); T (40 mg/2 d) + E2 (2 mg/d) 3 mo	Insulin-induced glucose disposal decreased by 20% with T ($P < 0.01$) and lesser extent with T + E2 ($P < 0.05$) but not with E2 alone.	Yes
Burger H, 1987[114]	20	RCT single-blind Natural and surgically postmenopausal women received E2 (40 mg) implant; E2 (40 mg) + T (50 mg) implant 6 wk	Significant increase in libido with T ($P < 0.01$)	Yes
Zang H, 2007[115]	63	RCT Postmenopausal aged 44-64 Oral: T (40 mg/2 d); E (2 mg/d); T (40 mg/2 d) + E (2 mg/d) 3 mo	Endometrial proliferation (Ki-67 expression) significantly lower with E + T vs E alone.	Yes
Zang H, 2008[116]	31	RCT Postmenopausal aged 44-64 Oral: T (40 mg/2 d); E (2 mg/d); T (40 mg/2 d) + E (2 mg/d) 3 mo	Expression of AR and ER-B stronger in glands of endometrium after T compared to placebo.	None stated
Sarrel PM, 1997[117]	20	Randomized, double-blind, placebo-controlled trial Postmenopausal Oral: EE (1.25 mg/d); EE (1.25 mg/d) + MT (2.5 mg/d) 8 wk	No significant difference in vaginal blood flow rate and AUC of fingertip postocclusion blood between treatments.	None stated
Zethraeus N, 2009[118]	200	Randomized, double-blind, placebo-controlled trial Postmenopausal 50-65 Oral: E (2 mg/d); T (40 mg/d); Placebo 4 wk	No significant difference in economic behaviour (risk attitudes, altruism and reciprocal fairness) between treatment groups ($P > 0.05$)	Yes
Huang G, 2015[119]	71	Double-blind randomized placebo-controlled trial Surgically menopausal women aged 41-62 received IM injection Placebo; IM injection T Enanthate (3, 6.25, 12.5 or 25 mg) 1 time a week for 24 wk	Sustained "Ah" Test: Significant decrease in voice pitch in 12.5 and 25 mg T groups compared to Placebo ($P < 0.05$) related to increase in serum free T concentration. Sentence Test: Significant decrease in voice pitch at 25 mg T compared with Placebo ($P < 0.05$)	Yes

(Continues)

TABLE 2 (Continued)

Author and date	Number of subjects	Study design	Findings	Industry funding
Davis SR 2000[79]	33	RCT single-blind Postmenopausal women E2 (50 mg) implant; E2 (50 mg + T (50 mg) implant Every 3 mo for 2 y	FFM increased significantly ($P < 0.01$), whereas FM:FFM ratio declined ($P < 0.05$) with T, but not with E2 alone. Significant decrease in hip and abdominal circumference ($P < 0.01$, $P < 0.05$ respectively) with E2 alone.	Yes

For studies to be included, subjects were required to be perimenopausal or postmenopausal women presenting with symptoms of sexual dysfunction, dyslipidaemia, impaired memory, decreased bone mineral density or breast symptoms.
BISF-W, brief index of sexual functioning for women; CSFQ-F-C, changes in sexual functioning questionnaire; FSFI, female sexual function index; McCoy, McCoy female sexuality questionnaire; PFSF, profile of female sexual function; PGWB, psychological general well-being scale; SAL, sexual activity log; SSEs, satisfying sexual episodes; SSSS, Sabbatsberg sexual self-rating scale; WHQ, women's health questionnaire.
Drugs: APO, apoprotein; AR, androgen receptor; AUC, area under curve; BISF-W, brief index of sexual functioning for women; BMD, bone mineral density; BMI, body mass index; CEE, conjugated equine oestrogens; CES-D, centre for epidemiological studies depression scale; CSFQ, changes of sexual functioning questionnaire; DHEA, dehydroepiandrostenedione; E, oestrogen; E2, oestradiol; EE, esterified oestrogens; EP, oestrogen-progestogen; EPT, oestrogen-progestin therapy; ER, oestrogen receptor; FAI, free androgen index; FFM, free fat mass; FM, Total body fat mass; FNA, fine needle aspirate; HAM-D, Hamilton rating for depression; HDL, high-density lipoprotein; HOMA, homeostatic model assessment; hs-CRP, high-sensitivity C-reactive protein; ICA, internal carotid artery; IGFBG-1, insulin-like growth factor binding globulin-1; IL, interleukin; IM, intra-muscular; ISLT, international shopping list test; LDL, low-density lipoprotein; LPA, lipoprotein A; MCA, middle cerebral artery; MP, medroxyprogesterone acetate; MT, methyltestosterone; NA, norethisterone acetate; P, progesterone; PGWB, psychological general well-being index; PI, pulsatility index; PR, progesterone receptor; Q-Les-Q, quality of life enjoyment and satisfaction questionnaire; RBMT, Rivermead behavioural memory test; SIQ, sexual interest questionnaire; SRS, Sabbatsberg revised sexual self-rating scale; T, testosterone; TFS, tape/film scale; TNF-A, tumour necrosis factor-A; TTP, transdermal testosterone patch; VCAM-1, vascular cell adhesion molecule-1; VPA, vaginal pulse amplitude; WAIS-R, wechsler adult intelligence scale-revised.

Tungmunsakulchai et al[40] investigated the effects of twice weekly administration of either oral placebo or testosterone undecanoate 40 mg in combination with oral oestrogen in a randomized double-blind study. Sexual function was significantly higher in the testosterone group when compared with placebo (FSFI scores: placebo, 28.6 ± 3.6; testosterone, 25.3 ± 6.7, $P = 0.04$ vs placebo).

Lobo et al[53] performed a double-blind randomized trial of 221 postmenopausal women receiving either oral combined esterified oestrogens/methyltestosterone or oral esterified oestrogens alone; changes in levels of sexual interest or desire as rated on the Sexual Interest Questionnaire were investigated. Treatment with the combination of esterified oestrogens and methyltestosterone significantly increased the concentration of bioavailable testosterone and suppressed SHBG. Scores measuring sexual interest or desire and frequency of desire increased from baseline with combination treatment and were significantly greater than those achieved with esterified oestrogens alone. Treatment with the combination was well tolerated.

Sherwin et al studied 10 premenopausal 43 surgical menopause who received either oestradiol 8.5 mg and testosterone 150 mg, oestradiol 8.5 mg, testosterone 150 mg or placebo 1 mol/L in a randomized control trial. They concluded that a combined oestrogen androgen therapy can enhance the quality of life for both naturally and surgically postmenopausal women and increase sexual arousal and libido. A randomized double-blind trial by Watts et al investigated 66 surgically menopausal women received either oral esterified oestrogens (1.25 mg), or esterified oestrogens (1.25 mg) combined with methyltestosterone (2.5 mg) daily for 2 years. Menopausal symptoms of somatic origin (hot flushes, vaginal dryness and insomnia) were improved significantly by both treatments. Also, both treatment regimens prevented bone loss at the spine and hip.[53-55] However, there was no significant difference in somatic symptoms between the treatment groups.

In another double-blinded randomized study by Huang et al,[56] 71 menopausal women who previously underwent hysterectomy with or without oophorectomy received a standardized transdermal oestrogen regimen during the 12-week run-in period, and were then randomized to receive weekly IM injections of placebo, or 3, 6.25, 12.5 or 25 mg testosterone enanthate for 24 weeks. Dose-dependent improvements in several domains of sexual function, lean body mass, chest-press power and loaded stair-climb power were observed, with the greatest improvements at the highest dose. Furthermore, a double-blind randomized study by Dobs and colleagues, with 40 naturally and surgically menopausal women, observed significant increases in upper and lower body strength with testosterone compared to placebo.[57] Whilst the majority of studies observed testosterone significantly increased sexual arousal/interest,[39,42,52,57,58] frequency of orgasms[13,39,57] and frequency of sexual activity[13,47,52] when compared to placebo, some suggest no significant difference between the treatment groups.[39,58-61] In conclusion, most but not all studies suggest that testosterone improves symptoms of sexual dysfunction regardless of the route of administration. Further studies are required to investigate whether the observed effects of testosterone administration on sexual function are truly dose dependent.

6 | NONSEXUAL EFFECTS OF TESTOSTERONE THERAPY

Testosterone therapy is anticipated to cause symptoms of androgen excess such as excess body hair (hirsutism) and acne. Accordingly, clinical trials reported that the most common adverse effects associated with testosterone therapy were skin reactions, unwanted hair growth, acne and vaginal bleeding; however, most were mild and rarely resulted in withdrawal from the study.[18,44,46,50,52,57,62-65] Furthermore, two published studies observed no significant difference in adverse effects between treatment groups.[66,67]

6.1 | Breast cancer risk

Exogenous sex steroids may stimulate the growth of sex-hormone dependent tissues, most notably breast tissue in women,[68,69] so it is relevant to consider whether testosterone therapy increases the risk of breast cancer. The only published long-term investigation of testosterone therapy in postmenopausal women has been conducted by the product's manufacturer.[62] They performed an open-label, uncontrolled safety and tolerability trial of transdermal testosterone (daily dose, 300 μg) in over 900 women with surgical menopause and HSDD, for up to 4 years of duration. Three cases of invasive breast cancer during 4 years of TTP administration; however, the authors concluded that this was not inconsistent with background rates for women in the same age-group. The randomized controlled trial by Davis et al[48] over 24 weeks observed 4 cases of breast cancer in the testosterone group when compared with no cases in the placebo group. However, the same authors performed a follow-up study suggesting that 1 year of TTP therapy had no significant effect on digitally quantified absolute or per cent dense mammographic area in postmenopausal women when compared with placebo[70]; these data are concordant with results of a study by Hofling et al of 6 months TTP administration in 99 postmenopausal women.[71] Furthermore, Hofling et al also observed no significant increase in breast cell proliferative activity with testosterone compared to placebo.[72]

6.2 | Endometrial effects

Testosterone promotes endometrial atrophy when given without concomitant oestrogen. Davis et al[48] investigated endometrial findings in 814 women randomly assigned to receive a patch delivering 150 or 300 μg of testosterone per day or placebo. They observed that endometrial bleeding was reported more frequently on the 300 g/d dose testosterone (10.6%) compared with 150 g/d testosterone (2.7%) or placebo (2.6%). Endometrial bleeding was accompanied at the highest dose by endometrial atrophy.[48] It is therefore important to provide concurrent continuous or cyclic progestin therapy to nonhysterectomized women administered combined oestrogen and testosterone treatment as per normal practice.

6.3 | Dyslipidaemia

Whilst many studies have suggested that testosterone administration may cause lipid disarrangements such as reduced high-density lipoprotein (HDL)[18,49,55,57,65,73-76] and an increase in low-density lipoprotein (LDL),[18,49] some indicate no change in LDL,[73,74,76] a decrease in LDL[75] or no significant change in lipid profile at all with testosterone.[77-79] Studies seem inconsistent regarding total cholesterol with some observing no change with testosterone compared to placebo,[73,74,78] whilst others observed a decrease.[55,57,75,76] A similar pattern of inconsistency in the literature is observed with the effects of testosterone on triglycerides; some studies observe a decrease,[55,57,75,76] whereas others observe no change with testosterone.[78] The authors of a 2011 study failed to observe any significant increase in haematocrit, or adverse changes in glycemic markers or lipid profile following up to 4 years of TTP therapy.[62] Further, long-term studies are required to investigate the potential effects of testosterone supplementation on risks of malignancy and cardiovascular disease in postmenopausal women. However, the available evidence allows us to speculate that any effects of testosterone therapy on serum lipids are likely to be minor, which is of relevance when discussing therapeutic options with patients.

6.4 | Bone mineral density

The Women's Health Initiative Observational Study of 93 676 postmenopausal women aged 50-79 years investigated hip fracture risk in relation to the circulating level of testosterone. They observed higher circulating levels of serum SHBG is associated with an increased risk of subsequent hip fracture and high endogenous testosterone with a decreased risk, independent of each other, serum oestradiol concentration and other recognized risk factors.[80]

The reported effects of testosterone on bone of naturally postmenopausal women are heterogeneous. Elraiyah et al[18] conducted a systematic review and meta-analysis, which included 35 randomized trials, four of which reported on bone densitometry during combined testosterone and oestrogen therapy, and compared it to oestrogen alone. They concluded that testosterone had no significant effect on bone mineral density (BMD) in any tested site concordant with a study by Garnett et al in 1992.[81] However, Miller et al[82] observed BMD of the hip increased significantly with testosterone compared to HRT alone, whilst a study by Barrett-Connor et al[67] observed an increase in BMD both at the hip and lumbar spine with testosterone treatment when compared to placebo. Further, a 1995 study by Davis et al[13] on 34 postmenopausal women with oestradiol alone, or oestradiol plus testosterone implants observed BMD increased significantly for total body, at vertebrae L1-L4 and the trochanter with testosterone compared to oestradiol alone. In addition, whilst Miller et al[82] observed no difference in bone biochemical markers (Ntx, Dpd or BSAP) between treatment groups, another observed markers of bone formation (IGF-1 and P1CP) were significantly higher with testosterone compared to placebo.[83] No trials have reported long-term fracture rates during testosterone therapy in postmenopausal

women. In summary, early data suggest that testosterone may have some beneficial effects of increasing BMD at specific locations in the body, but further longer-term studies are required to provide more conclusive evidence.

6.5 | Cardiovascular effects

Exogenous testosterone increases haematocrit, so it is important to consider if the risk of thromboembolic and cardiovascular disease is altered during therapy.[84] Some recent studies have shown an increased risk of cardiovascular events in men treated with testosterone.[85-87] However, other studies data did not provide any evidence of an association between testosterone and cardiovascular events.[88-90] Testosterone-containing medicines are licensed in the European Union (EU) for the treatment of male hypogonadism. There is limited experience on the safety and efficacy of the use of these medicines in patients over 65 years of age, and the use of testosterone to boost these levels in healthy older men is not authorized in the EU. In the United States (US), the US Food and Drug Administration (FDA) cautions that prescription testosterone are approved only for men who have low testosterone levels caused by certain medical conditions. The safety and benefit of these medications have not been established for the treatment of low testosterone levels due to ageing.[91,92] There is no specific evidence about the cardiovascular effect in women treated with testosterone. The randomized control trials comparing testosterone therapy in women with placebo have not observed any significant differences in event rates for any cardiovascular disease outcomes, including venous thromboembolic events in short-term trials. Furthermore, adverse cardio-metabolic changes have not been frequent during short-term observations (12-24 months) in women treated with testosterone.[28] Data suggest that the testosterone transdermal patch improves exercise tolerance, muscle strength and insulin resistance without side effects in elderly female patients with stable chronic heart failure. In a double-blind, randomized, placebo-controlled study in women with heart failure, testosterone therapy (the TTP releasing 300 μg/d) was associated with significant functional improvements assessed by peak oxygen consumption, distance walked over the 6-minute walking test, muscle strength and insulin resistance compared with placebo. Moreover, a systematic review of testosterone therapy on cardiovascular outcomes in postmenopausal women was conducted by Spoletini et al 2014; they observed a favourable effect of testosterone therapy in postmenopausal women, such as high-density lipoprotein cholesterol, total cholesterol, body fat mass and triglycerides.[93-97] In addition, a study by Kocoska-Maras et al in 2009[98] observed testosterone counteracts the oestrogen induced rise in high-sensitivity C-Reactive Protein (hs-CRP) but had no effects on other inflammatory markers of cardiovascular disease, such as Interleukin-6, Tumour Necrosis Factor-Alpha and Homocysteine. In contrast, a 2014 study[99] observed no significant difference in hs-CRP levels between testosterone and placebo treatments. Studies appear to agree that testosterone has no significant effect on systolic and diastolic blood pressure compared to placebo.[83,99] Testosterone has also been observed to significantly increase fibrinogen levels with testosterone compared to placebo.[76] In summary, despite many studies being conducted on this topic, the long-term cardiovascular consequences of testosterone therapy remain unclear.[28]

6.6 | Anthropometric measurements

Studies seem to agree that testosterone has no significant effect on BMI compared to placebo,[73,83] but are inconclusive when it comes to body composition. A 2006 study by Zang et al on 63 postmenopausal women[77] observed no significant difference in body fat with testosterone compared to other treatment groups, similar with a study by Davis et al,[79] whilst a 2005 study[83] observed lean body mass significantly increased, consistent with another study[57] indicating significant increases in lean body mass of the legs, arms and trunk. A study by Duarte et al[73] observed visceral fat significantly increased with testosterone by 11% vs placebo, in direct contrast with a 2014 study stating no difference in both abdominal and visceral fat volumes between treatment groups.[99] One study observed free fat mass increased[100] when given testosterone vs placebo, but others observed no change in fat mass[73,77] with one indicating a decrease in % fat tissue with testosterone.[57] Overall, whilst studies agree that testosterone has no effect on BMI, there is no consensus on its effects on fat mass in the absence of long-term large scale trials.

6.7 | Cognitive function

The effects of steroid hormones on human cognition are of considerable interest, particularly during the menopause. A study by Krug et al on 12 postmenopausal women observed testosterone significantly increased divergent thinking, (fantasies and fluency of speech) compared to placebo,[101] but no other aspects of cognitive function were affected. This is in direct contrast to many other studies indicating no change in verbal fluency, or any other measures of cognitive function.[102-104] A 2014 study observed testosterone therapy had no effect on cognition after 12 weeks of treatment compared to placebo, but at 26 weeks, the Cogstate International Shopping List Test (ISLT) score significantly increased by 1.57 units vs placebo.[104] One study observed immediate verbal memory to be impaired with testosterone, but no other memory functions were affected.[105] A 2002 study by Wisniewski et al on 26 naturally and surgically postmenopausal women discovered testosterone significantly increased building memory score compared to placebo, despite no other aspects of cognitive function being affected (cube comparison, shape memory or identical pictures).[106] In summary, studies published to date have observed a variety of effects on cognition following testosterone therapy; it is therefore difficult to draw conclusions on the predicted effects of testosterone in postmenopausal women.

6.8 | Physical symptoms

A 2002 study by Dobs and colleagues gave esterified oestrogens with or without methyltestosterone to 40 naturally and surgically menopausal women and observed testosterone significantly improved both somatic and vasomotor symptoms compared to oestrogen alone.[57] However, the majority of studies seem to agree testosterone therapy has no significant beneficial effect on suppressing hot flash frequency and severity.[58,64,67,107] A further study observed no significant improvement in somatic or psychological symptoms with testosterone compared to placebo[58] whilst another observed no significant difference in sweating and vaginal dryness between treatment groups.[67] In summary, most studies suggest that testosterone does not affect menopausal hot flushes and it remains to be determined whether somatic symptoms or vaginal dryness is altered during testosterone therapy.

7 | LIMITATIONS OF DATA

Currently, there is limited long-term data evaluating whether testosterone replacement increases the risks of cardiovascular disease, or breast cancer. In view of the controversy regarding the safety of testosterone therapy in older men (albeit when administered at much higher doses),[108] a similarly cautious approach might be appropriate for postmenopausal women with risk factors for cardiovascular disease or breast cancer. It is also important to consider that many of the clinical trials performed to date have been industry funded. It is plausible that reporter bias might have skewed the published literature towards studies supporting the usage of testosterone in postmenopausal women; future, academic-sponsored studies are needed to address this concern. Finally, to fulfil the criteria for HSDD or Female sexual dysfunction, selected study participants were screened to exclude disease comorbidities. It is, therefore, not known whether postmenopausal women with disease comorbidities would also benefit from testosterone therapy. This limits the extent to which published data may reflect everyday clinical practice.

8 | CONCLUSION

Sexual dysfunction is a common problem in postmenopausal women, which may profoundly affect quality of life. Endogenous testosterone may influence sexual behaviour in women. However, there is a lack of evidence implicating deficient endogenous testosterone in the evolution of sexual dysfunction in women. Furthermore, there is considerable variation in the prevalence of menopause-related sexual dysfunction, depending on the criteria employed. Several randomized, placebo-controlled clinical trials suggest that testosterone therapy significantly improves sexual function assessed using validated questionnaires, in postmenopausal women with sexual dysfunction or hypoactive sexual desire disorder. The effect size is modest, with approximately one additional satisfactory sexual activity per month. In the short-term, testosterone therapy is generally well tolerated and safe adverse effects predominantly consist of localized skin reactions and cosmetic effects of hyperandrogenaemia. Possible impacts on lipid metabolism, cardiovascular and cancer risk warrant further detailed investigations, although no major safety concerns have been raised to date. In line with the US Endocrine Society Clinical Practice Guidelines, there is currently insufficient evidence regarding general recommendations for testosterone therapy in women.[28] There are also no licensed products in the UK for female administration of testosterone; testosterone preparations designed to administer much higher doses (to men) must therefore be used. If clinicians are considering offering this treatment to postmenopausal women, it is necessary to provide full counselling on the risks and benefits, particularly the limited effect of testosterone and the lack of long-term safety data. However with these caveats, there is sufficient evidence to recommend testosterone therapy for the minority of postmenopausal women for whom other management strategies have failed.

ACKNOWLEDGEMENTS

The Section of Investigative Medicine is funded by grants from the MRC, BBSRC and is supported by the NIHR Imperial Biomedical Research Centre Funding Scheme. FMA is funded by the Abu Dhabi Health Services company (SEHA). CNJ is funded by an NIHR PostDoctoral Fellowship. WSD is funded by an NIHR Professorship. The views expressed are those of the authors and not necessarily those of the above-mentioned funders, the NHS, the NIHR or the Department of Health.

CONFLICT OF INTEREST

Nothing to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Jayasena CN, Alkaabi FM, Liebers CS, Handley T, Franks S, Dhillo WS. A systematic review of randomized controlled trials investigating the efficacy and safety of testosterone therapy for female sexual dysfunction in postmenopausal women. *Clin Endocrinol (Oxf)*. 2019;90:391–414. https://doi.org/10.1111/cen.13906