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

Chiara Achilli, M.B.B.S.,[a] Jyotsna Pundir, M.D., M.R.C.O.G.,[a] Parimalam Ramanathan, M.D., M.R.C.O.G.,[a] Luca Sabatini, M.D., M.R.C.O.G.,[a] Haitham Hamoda, M.D., M.R.C.O.G.,[b] and Nick Panay, M.R.C.O.G.[c]

[a] Centre for Reproductive Medicine, St. Bartholomew's Hospital; [b] King's College Hospital; and [c] Queen Charlotte's and Chelsea Hospital, London, United Kingdom

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® 2016;■:■–■. ©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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Reprint requests: Jyotsna Pundir, M.D., M.R.C.O.G., Centre for Reproductive Medicine, St. Bartholomew's Hospital, West Smithfield, London EC1A 7BE, United Kingdom (E-mail: jyotsnapundir@yahoo.com).

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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