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Pharmacological Therapy for Female Sexual Dysfunction

Has Progress Been Made?

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Abstract

The investigation of female sexual dysfunction (FSD) is an evolving area in which definitions and models for female sexual functioning are being continually reviewed and revised. The lack of consensus amongst experts in the field and regulating authorities regarding appropriate inclusion and exclusion criteria for FSD trials, and main outcome measures appropriate for the evaluation of drug interventions has somewhat hampered progression in this area. Nonetheless, there is evidence from randomized controlled trials that androgen therapy improves the quality of the sexual experience for postmenopausal women with low libido, and preliminary data that this may also apply to premenopausal women.

The study of female sexual dysfunction (FSD) has lagged behind research into male sexual health, resulting in very slow progress in the development of pharmacological therapy for FSD. Historically, the problem was that researchers tried to approach FSD from a male perspective, which has increasingly been acknowledged as inappropriate. The next limitation to emerge was the lack of a definition for 'normal female sexual function' and the continuous evolution of the definition of FSD. Furthermore, there is no gold standard self-assessment instrument for the evaluation of female sexual function and thus data of sexual behaviour across the adult female lifespan are lacking.

Available data indicate the most commonly reported sexual problems in women relate to desire, arousal, pleasure and global satisfaction. It has been proposed that each of these present different diagnoses and should be researched and treated differently.[1] However, for most women these problems are part of a continuum of the sexual experience and are inextricably related.

Population-based studies indicate that the prevalence of sexual problems among women ranges from 9% to 43%.[2-5] However, the validity and reliability of these data is uncertain as epidemiological studies on female sexual function are constrained by the limited response rate, the limited use of validated instruments, and the lack of information

about the duration and context of sexual problems.[6] The US FDA's 2000 draft guidance document for FSD clinical trials recommends the use of the change in the frequency of successful satisfactory sexual events recorded in a daily diary as the primary endpoint and self-administered questionnaires as secondary endpoints.[7] Although this approach remains controversial,[6] it has been the primary approach adopted by the pharmaceutical industry investigating new therapies for FSD in order to meet the requirements set down by the FDA in 2000. Furthermore, inclusion and exclusion criteria for recruitment to the large randomized control trials (RCTs) of pharmacological agents for FSD indicate acknowledgement of the multi-factorial nature of FSD. Thus, in general, women with poor relationships, depression, ill health and other identifiable factors that may underpin their FSD have been excluded. Therefore, the positive findings from the published data are specific to the populations that have been studied and cannot be extrapolated to women with FSD complicated by other conditions.

1. Potential Approaches for Treating Female Sexual Dysfunction (FSD)

Early research suggested some benefits of testosterone therapy for women[8,9] and these findings formed the basis of *ad hoc* administration of testosterone to women by individual practitioners. Subsequently, research approaches to the treatment of FSD have included primarily selective phosphodiesterase (PDE) inhibitors and androgen therapy, specifically testosterone. PDE_5 inhibitors are effective in the treatment of male erectile dysfunction. Studies of the PDE_5 inhibitor sildenafil in the treatment of symptoms of FSD suggest that this therapy may be useful for some women with genital arousal disorder rather than the larger group of women with low desire and subjective arousal.[10,11] Other subsets of women, such as women with type 1 diabetes mellitus, may also benefit.[12] However, large studies of PDE_5 inhibitors in the general population have been disappointing.[13] Similarly, studies of other agents, such as apomorphine and bupropion, have not as yet provided evidence of significant benefit and have been reviewed elsewhere.[13]

2. Tibolone for FSD

Tibolone is a selective tissue estrogenic activity regulator. It is metabolized in the gastrointestinal tract to the 3α and 3β metabolites, which then circulate predominantly in their sulfated inactive forms. These metabolites become estrogenically active when desulfated in target tissues, such that tibolone is effective in the treatment of estrogen deficiency symptoms. Thus, the global effect of tibolone would be expected to be estrogenic. There are some data to suggest that tibolone may improve sexual function, particularly sexual desire and arousal, to a greater extent than traditional estrogen-progestogen therapy in healthy postmenopausal women. These effects have been attributed to (i) the intrinsic capacity of a tissue metabolite of tibolone (the Δ4-isomer) to activate the androgen receptor;[14] and (ii) the reduction in sex hormone binding globulin (SHBG) and hence the increase in bioavailable testosterone.

Whether tibolone is more likely to restore sexual well-being than conventional or transdermal estrogen-progestogen therapy in postmenopausal women presenting with FSD was explored in a multicentre RCT. In this study, after exclusion of major study violators, sexual function improved in the tibolone group when compared with transdermal estrogen-progestogen therapy.[15] These data suggest that for postmenopausal women with FSD, a trial of tibolone therapy should precede initiation of testosterone with or without estrogen therapy.

Over the last decade, a number of large RCTs have evaluated the use of testosterone therapy for postmenopausal women and, as a result, transdermal testosterone has been approved for the treatment of

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estrogen-treated surgically menopausal women with hypoactive sexual desire disorder (HSDD) in Europe. Therefore, the remainder of this review focuses on the evidence for the use of testosterone in women.

3. Testosterone for the Treatment of Hypoactive Sexual Desire Disorder

A Cochrane review of the earlier studies of the use of testosterone in postmenopausal women for low libido concluded that there are benefits in terms of improved sexual function with the addition of testosterone to standard postmenopausal hormone therapy.[16] Subsequent large RCTs in both surgically menopausal[17-19] and naturally menopausal women[20] for which the frequency of satisfactory sexual events was the primary endpoint, demonstrate that treatment with a transdermal testosterone patch, which delivers 300 μg of testosterone per day (but not a patch delivering 450 μg/day), significantly increased the number of self-reported sexually satisfying events per month when compared with placebo. These studies also demonstrated significant improvements in desire, arousal, responsiveness, orgasm, pleasure and satisfaction.

An analysis of data from a number of these studies indicates that women with a SHBG level >160 nmol/L or who are taking concurrent conjugated equine estrogen (CEE) are unlikely to benefit from testosterone therapy.[21] The former is because testosterone binds to SHBG with high affinity; therefore, having an elevated SHBG results in a very low level of free or bioavailable testosterone. The interaction between CEE therapy and exogenous testosterone is unclear, but it may be that a component of CEE interferes with the binding of testosterone to the androgen receptor in addition to increasing SHBG.

There is a paucity of data pertaining to the use of testosterone in premenopausal women. Testosterone levels decline in women prior to menopause and do not appear to change across menopause; hence, women in their late reproductive years are just as likely to have low testosterone levels as women in their early menopausal years.[22,23] A small pilot, randomized, cross-over trial showed that premenopausal women treated with testosterone had significant improvements in sexual functioning and in well-being compared with placebo.[24] Subsequently, a larger RCT compared three different doses of transdermal testosterone with placebo and reported an increase in the frequency of the number of satisfactory sexual events in women treated with the middle dose of testosterone versus placebo.[25] The links between postmenopausal estrogen-progestogen use and both breast cancer and cardiovascular disease, have created a level of concern regarding any form of hormone use in women.[26] Testosterone has been widely used by women as an unapproved therapy for decades. There is no evidence from studies of premenopausal women or postmenopausal women using systemic estrogen treated with testosterone for up to 24 months, or studies of women with chronic androgen excess due to polycystic ovarian syndrome, that elevated testosterone levels, even above what is considered physiologically normal, are associated with altered breast cancer risk.[27,28] Primate and human studies suggest that testosterone may in fact protect the breast from estrogen-induced breast cell proliferation.[29-31] However, this is an area of considerable controversy that needs to be addressed in post-marketing surveillance research. There is also no evidence that in women without insulin resistance, testosterone adversely affects cardiovascular disease risk. We recently demonstrated that endogenous testosterone and the adrenal pre-androgens *per se* are not significant independent determinants of circulating cardiovascular disease risk markers (C-reactive protein and lipoprotein lipids).[32] However, uncertainty as to the consequences of restoring testosterone levels to those of premenopausal women in those

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who are many years past menopause remains. Now that the testosterone patch has been approved for surgically menopausal women with HSDD despite estrogen therapy (other than CEEs) in Europe, these data will eventually be forthcoming from post-marketing-surveillance studies of women in the community.

4. Who to Treat

A pragmatic concern is which women are candidates for pharmacotherapy for FSD? To date, no clinically applicable diagnostic algorithm has achieved acceptance. A low serum testosterone level is not predictive of a diagnosis of low libido nor does it predict likelihood of therapeutic response.[33] The assessment of a woman presenting with low sexual well-being requires a comprehensive clinical evaluation with a full history and physical examination. One must ascertain whether the woman has experienced a decline in sexual function from a previously satisfactory situation. Women who have never experienced satisfactory sexual function need to be assessed differently. Then, relationship issues, partner health, depression, personal social issues (e.g. children and work pressures) and adverse effects of other psychoactive therapies need to be considered. Menstrual and menopausal status must be evaluated and other potentially contributing conditions sought and, if identified, treated. These include estrogen deficiency, vaginismus, dyspareunia, thyroid disease and other systemic illnesses. If no clearly identifiable factor can be found in an otherwise healthy woman, whether she be premenopausal or postmenopausal, a trial of testosterone therapy might be considered. Women who have undergone premature ovarian failure or surgical menopause, or who have adrenal insufficiency or hypopituitarism, are known to have loss of androgen production and also merit consideration for treatment if they exhibit symptoms of sexual dysfunction.

5. Current Therapeutic Choices

As oral estrogen therapy tends to result in an increase in SHBG and hence lower free testosterone,[34] it would be worth while initially changing women from oral estrogen to transdermal therapy and reviewing after at least 3 months to evaluate whether this has resulted in an improvement in sexual interest. This approach seems to be least effective for women who have a low endogenous testosterone level prior to changing formulations. For postmenopausal women, tibolone, where available, should be considered as first-line therapy. As part of the efficacy of tibolone may reside in the reduction of SHBG and hence increase in free testosterone, it may be that women with very low testosterone levels, such as those who have had a surgical menopause, will benefit less. However, there is no clinical data to support this hypothesis. Tibolone should not be used by premenopausal women. Safety issues regarding tibolone and the breast have been raised in a large observational study.[35] However, strong treatment bias in this study make the findings uncertain.

Transdermal testosterone patch therapy has only been approved in Europe for women who have undergone surgical menopause. Further large studies of testosterone in naturally menopausal women are currently underway and it is highly likely that the approval will eventually be extended to naturally menopausal women.

There has been considerable clinical experience with the administration of testosterone implants in postmenopausal women and these are approved for use in women in the UK. These implants are fused crystalline implants, 4–5 mm in diameter, containing testosterone BP (British Pharmacopoeia) as the active ingredient. A dose of 50 mg is effective[36] and does not cause virilizing adverse effects. This dose can be obtained by bisecting a 100-mg implant under sterile conditions. The implant is inserted subcutaneously (under local anaesthesia), usually

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into the lower anterior abdominal wall, using a trocar and cannula. This therapy provides a slow release of testosterone with an approximate duration of effect of 3–6 months for a 50-mg implant. There is marked individual variation in this period; therefore, testosterone levels must be carefully monitored, with a testosterone level measured prior to the administration of each subsequent implant.

Other modes of delivery of testosterone, including transdermal gel, skin spray and nasal spray, are currently in the research pipeline.

6. Conclusions

FSD remains a complex, controversial and under-researched clinical issue. Women experiencing FSD have the right to treatment with effective and safe therapeutic options. Progress in this field has been slow, such that testosterone remains the only treatment specifically approved for the treatment indication of FSD, and this approval is limited oophorectomised women and to European countries. However, there is widespread off-label use by women of testosterone products approved for men and extensive prescription of compounded testosterone products for women in clinical practice. One might conclude that an uncontrolled clinical trial of the safety of testosterone is ongoing in the community.

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