NHS
Pan Mersey
Area Prescribing Committee

Testosterone gel for testosterone deficiency in women. Guidance for prescribing in Primary and Secondary Care.

GUIDELINE

AR **Amber recommended**

Background

Testosterone levels naturally decline throughout a woman's lifespan. Loss of testosterone is particularly profound after iatrogenic i.e. surgical and medical menopause and premature ovarian insufficiency when testosterone production decreases by more than 50%. [1]

Symptoms and referral by GP

Testosterone deficiency can lead to several distressing sexual symptoms such as low sexual desire, arousal and orgasm. Testosterone deficiency can also contribute to a reduction in general quality of life, tiredness, depression, headaches, cognitive problems, osteoporosis and sarcopenia.[1,2]

- British Menopause Society guidance on testosterone replacement therapy advises that testosterone contributes to libido, sexual arousal and orgasm by increasing dopamine levels in the central nervous system. Testosterone also maintains normal metabolic function, muscle and bone strength, urogenital health, mood and cognitive function.[1,2]

- NICE Guideline (NG23) Menopause Diagnosis and Management 2015 advises that clinicians consider testosterone supplementation for menopausal women with low sexual desire if HRT alone is not effective.[2]

- Clinical Knowledge Summary on Menopause advises primary care clinicians to refer women who have persistent altered sexual function and where hormonal and/or non-hormonal, or non-drug treatments are ineffective to seek specialist advice regarding the use of testosterone supplementation (off-label use).[3]

Specialist Care

When treating low sexual desire / arousal it is also important that urogenital tissues are adequately oestrogenised in women with vulvovaginal atrophy / genitourinary syndrome of the menopause e.g. through use of vaginal oestrogen, to avoid dyspareunia. Although the NICE guideline recommends that systemic HRT should be prescribed before a trial of testosterone,[2] there is trial data in women with hyposexual sexual desire disorder (HSDD) which indicate that testosterone used without systemic oestrogen, is equally effective and safe.[3]

Specialist clinicians will initiate/optimise HRT if this has not already been done. The patient is then reviewed in 3 to 4 months' time at which stage, dependent on response to HRT, testosterone replacement therapy may be considered. If the patient has already been on HRT for 3 to 4 months but demonstrates symptoms of testosterone deficiency, then testosterone replacement may be started immediately. Routine testosterone levels are not required as the dose does not increase.

Note: Patients who are not eligible for treatment under this statement may be considered on an individual basis where their GP or consultant believes exceptional circumstances exist that warrant deviation from the rule of this policy. In this situation, follow locally defined processes.

Testosterone levels

The assessment and interpretation of testosterone levels is problematic, particularly as the majority of testosterone is protein bound. Free testosterone assays are the gold standard but are rarely available, particularly in the public sector. Total testosterone can be measured, but for greater accuracy sex hormone binding globulin (SHBG) levels should be considered using the following calculation to work out the Free Androgen Index = Total Testosterone x 100 / SHBG.[2]

Although it is not mandatory to perform testosterone level estimation prior to or for monitoring treatment, it can be useful in some cases. A low FAI < 1.0% in women with symptoms of low sexual desire and arousal, supports the use of testosterone supplementation. Repeat estimation at the 2-3 month follow up visit can be performed to demonstrate if there has been an increase in levels, though clinical response is of paramount importance. It is also useful to demonstrate that values are being maintained within the female physiological range, typically < 5%, thus making androgenic side effects less likely.[3]

Response to testosterone therapy and duration of use

The loss of sexual desire is complex and may have hormonal, medical, psychosexual and psychosocial aetiologies. In clinical trials of women with HSDD, approximately 2/3 of women responded positively to testosterone therapy (compared to 1/3 using placebo). The trials demonstrated that response may not be immediate, taking 8-12 weeks in some instances for the effect to become clinically significant. It is therefore advised that treatment should be trialled for a minimum of 3 months and maximally for 6 months before being discontinued due to lack of efficacy. Duration of use should be individualised and evaluated at least on an annual basis, weighing up pros and cons according to benefits and risks, as per HRT advice from all menopause societies.[1]

Transfer of information to the GP for initiation and length of treatment

Prior to transferral to the GP the specialist will optimise HRT and then recommend initiation of testosterone therapy by the GP with a letter. For the GP to prescribe testosterone, a letter from the specialist must be sent to the GP to explain that the patient is to be started on testosterone gel in accordance with this guideline. The letter will detail the dose and frequency to be prescribed. The duration of treatment will be for as long as an improvement in symptoms is achieved or until the patient is post-menopausal and HRT is stopped.

GP Monitoring

Testosterone replacement therapy does not require any formal monitoring, clinical improvement of symptoms is more beneficial than aiming for a specific testosterone level.[4] No levels will be required in line with this guidance.

Treatments, dosage and directions for use

Testosterone gel should be applied to clean dry skin (inner forearm) and allowed to dry before getting dressed. Skin contact with partners or children should be avoided until dry and hands should be washed immediately after application. The area of application should not be washed for 2-3 hours after application.
The products and doses which may be prescribed as part of this guideline are;

- 1st Line; Tostran 2% gel: Dose - 1 metered pump (0.5g of gel is equivalent to 10mg testosterone) on alternate days – each canister should last 240 days. £28.63/60g[5]
- 2nd Line *; Testim single dose containers 50mg/5ml: Dose - 1/10 of a container/day (a 'baked bean' sized amount) daily = 5mg/day i.e. each container should last 10 days. £31.11/30 containers[6]

*Testim single dose containers only to be used if Tostran pump is unavailable

Any variation from the (standard) (above) dose will result in the patients' care being retained under specialist prescribing. Testosterone is a schedule 4 (part 2) Controlled Drug. Use in women is currently off-label.

<u>Adverse effects of testosterone therapy</u>

Response to testosterone with regards to efficacy and adverse effects is highly variable. This is most likely due to varying absorption, metabolism and sensitivity to testosterone. Not uncommonly, adverse effects occur because healthcare professionals and their patients are confused about the appropriate preparation and dose which should be used in women, due to the lack of specific female preparations and information sheets. Clinical trials have demonstrated that as long as appropriate female physiological doses are prescribed adverse androgenic effects are not problematic and virilising problems do not occur.[1]

Reported adverse effects are shown below. Occurrence of side-effects, particularly those that are rare should raise the possibility with the prescriber that incorrect quantities are being used by the patient; if thought to be linked, the dosage should be reduced, or treatment stopped and referral made to specialist.

- Increased body hair at site of application (occasional problem) – spread more thinly, vary site of application, reduce dosage.
- Generalised Hirsutism (uncommon)
- Alopecia, male pattern hair loss (uncommon)
- Acne and greasy skin (uncommon)
- Deepening of voice (rare)
- Enlarged clitoris (rare)

Randomised controlled trials and meta-analyses have not shown an increased risk of cardiovascular disease or breast cancer although longer term trials would be desirable.

Testosterone be avoided; [1]

- During pregnancy or breastfeeding
- Active liver disease
- Women with known upper normal or high baseline testosterone levels / FAI.

Testosterone be used in caution (these patients will remain under specialist care);

- History of hormone sensitive breast cancer – exceptions to this may be agreed in fully informed women with intractable symptoms not responding to alternatives
- Competitive athletes – care must be taken to maintain levels well within the female physiological range

For further information about testosterone consult the BNF and the product SPC. [6,4,5]

References

1. British Menopause Society guidance on testosterone replacement 2019. Mr Nick Panay, Consultant Gynaecologist, Imperial College Healthcare & Chelsea and Westminster Hospitals, London; Trustee and Past Chairman – British Menopause Society; General Secretary, International Menopause Society and former Editor-in Chief Climacteric, The Journal of the IMS, in collaboration with the medical advisory council of the British Menopause Society. Accessed on 11/03/2022
2. National Institute of Clinical Effectiveness (NICE). Menopause diagnosis and management 2015 (NG23). Available via National Institute of Clinical Effectiveness (NICE). Menopause diagnosis and management 2015 (NG23). Accessed on 11/03/2022
3. NICE Clinical Knowledge Summaries (CKS) ; Menopause. November 2020. Available via Clinical Knowledge Summary on Menopause accessed on 11/03/2022
4. Electronic Medicines Compendium (EMC). Summary of Product Characteristics, Tostran [Kyowa Kirin Ltd]. Available via www.medicines.org.uk/emc/ on 11/03/2022
5. Electronic Medicines Compendium (EMC). Summary of Product Characteristics, Testim [Endo Venutres Ltd]. Available via www.medicines.org.uk/emc/ on 11/03/2022
6. National Institute of Clinical Effectiveness (NICE). BNF. Testosterone. Indications and Dose. Available via https://bnf.nice.org.uk/drug/testosterone.html on 11/03/2022

Further reading

- Should we be prescribing testosterone to perimenopausal and menopausal women? A guide to prescribing testosterone for women in primary care. Alice Scott and Louise Newson. British Journal of General Practice 2020; 70 (693): 203-204.

- Achilli C, Pundir J, Ramanathan P, Sabatini L, Hamoda H, Panay N. Efficacy and safety of transdermal testosterone in postmenopausal women with hypoactive sexual desire disorder: a systematic review and meta-analysis. Fertil Steril. 2017; 107(2):475-482.

- Maclaran K, Panay N. The safety of postmenopausal testosterone therapy. Women's Health (Lond Engl). 2012 8(3):263-75.

- Guys & St Thomas NHS Foundation Trust. Hormone Replacement therapy. Patient Leaflet.