Testosterone replacement in menopause

Is testosterone a female hormone?
Yes - premenopausal women produce both testosterone and estrogen physiologically. Androgens, including testosterone, are essential for development and maintenance of female sexual anatomy and physiology, and modulation of sexual behaviour.

What happens to testosterone levels with age?
The decline in testosterone levels appears to be age related at least partly due to loss of ovarian function, but can also occur more profoundly due to iatrogenic menopause which may be medical or surgical.

Should testosterone be replaced just because levels are low?
No. Many women with low systemic testosterone levels do not complain of distressing low libido or other symptoms, even on direct questioning.

Why do systemic testosterone levels not always correlate directly with Hypoactive Sexual Desire Disorder (American Psychiatric Association's definition of distressing low libido)?
The intracrinological metabolism of testosterone may be more important than the circulating levels. This may be particularly important in the central nervous system where DHEA is converted to testosterone in the brain.

Who should be offered testosterone?
Testosterone supplementation should only be considered in women who complain of low sexual desire after a biopsychosocial approach has excluded other causes such as relationship, psychological and medication related HSDD e.g. SSRIs/SNRIs. However, combined hormonal and psychosexual approaches may be beneficial in cases with mixed aetiologies.

Should testosterone be prescribed on its own or with HRT?
The NICE Menopause Guideline (NG23) and the BMS recommend that a trial of conventional HRT is given before testosterone supplementation is considered.

Oral estrogens, especially conjugated estrogens, can reduce the effectiveness of testosterone by increasing sex hormone binding globulin levels. Switching women with HSDD from oral to transdermal estrogen can be beneficial as this can increase the proportion of circulating free testosterone without requiring exogenous testosterone.

It is important that any symptoms of vulvovaginal atrophy are also adequately treated if testosterone is being considered for HSDD. Although studies have shown that testosterone can be beneficial in women not using concomitant estrogen containing hormone therapy, the incidence of adverse androgenic effects such as acne and excess hair growth is higher; this strategy is therefore not usually recommended in routine clinical practice.

What about the potential wider benefits of testosterone?
Randomised clinical trials of testosterone to date have not demonstrated the beneficial effects of testosterone therapy for cognition, mood, energy and musculoskeletal health. Further better designed studies are required with these health issues as primary outcome measures as some individuals report improvement of these symptoms. Until these data are available, the primary indication for testosterone should therefore be for HSDD following a biopsychosocial approach.

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Are there side effects and risks?

Adverse effects of testosterone in women are uncommon if levels are maintained within the female physiological range. The commonest are excess hair growth, acne and weight gain which are usually reversible with reduction in dosage or discontinuation. Alopecia, deepening of voice and clitoral enlargement are rare with physiological testosterone replacement.

More data are required for the long term effects on cardiovascular and breast outcomes but the short term data from a recent meta-analysis are reassuring.

Why is it not licensed for women except in one country?

Although there is a lack of long term safety data for cardiovascular and breast outcomes, an equally important factor is the reluctance of the pharmaceutical industry to finance further clinical studies thus far to achieve licensing of female androgenic products.

The recent licensing of 1% testosterone cream in Australia is an encouraging development; it is hoped that regulators in other countries may be encouraged by this enlightened approach by the Australian regulators who recognised the unmet need and the large body of evidence already available for testosterone in women.

How long should testosterone be prescribed for?

It may take 3-6 months to fully evaluate the efficacy of treatment. There should be at least an annual re-evaluation of ongoing usage based on the same criteria that would be used for standard hormone therapy i.e. carefully weighing up the pros and cons of long term usage.

Monitoring?

It is recommended that **total testosterone levels** are checked before treatment to establish a baseline for future monitoring and to ensure that levels are not in the upper range before treatment is commenced.

Ideally total testosterone should be measured by liquid/gas chromatography and tandem mass spectrometry although direct assays can also be used in clinical practice to exclude high baseline concentrations and supraphysiological concentrations during treatment.

Free testosterone assays are not recommended in this context as correlation with biological activity of testosterone has not been confirmed. Clinical assessment of potential adverse effects is equally important as some women are more sensitive to physiological levels of androgens

It is also recommended by some guidelines that testosterone levels are reassessed at 3-6 weeks after treatment is commenced, but given that most national health service clinics review their patients after 2-3 months it is recognised that this is an aspirational goal and that testing should be performed as close to this timeline as possible.

It is important that monitoring continues every 6-12 months to ensure that levels remain within the female physiological range in order to minimise adverse effects.

What are the available treatment options?

Most testosterone products are off label/license for female usage and may not always be available. The regulatory advice regarding use of compounded medications advises against their use unless an equivalent alternative is not available. In most countries and settings there are licensed male testosterone preparations that can be down titrated to female doses (typically 1/10th).

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However, where these are absent, compounded varieties may need to be considered. If a compounded product is used, the compounding pharmacy should meet industry standards for purity of Active Pharmaceutical Ingredients and Good Manufacturing Practice.

In some countries, oral DHEA is more commonly used than testosterone; however further research is required before this product can be recommended as clinical trials and meta analyses have not definitively proven the benefits for sexual function in women with normal adrenal function.

This list is an example of some of the more commonly used products in clinical practice:

- **Testim gel** [Endo Ventures Ltd] 1% testosterone gel in 5ml tubes: Starting dose 0.5ml (5mg) per day making each tube last for 10 days.
- **Tostran** [Kyowa Kirin Ltd] (2% testosterone gel in a canister containing 60g) : Starting dose 1 metered pump of 0.5g = 10mg on alternate days – each canister should last 240 days.
- **Testogel** [Besins Healthcare UK] (2.5g sachets containing 40.5mg testosterone): Starting dose 1/8 of a sachet/day = approx. 5mg/day i.e. each sachet should last 8 days. *(new formulation)*
- **AndroFeme cream** [Lawley Pharma] (1% testosterone cream in 50ml tubes with screw cap): Starting dose 0.5ml/day = 5mg /day i.e. each tube should last 100 days.
- **Testosterone Implants** [Smartway Pharma] (100mg implanted pellets) – imported from USA

Prescribing Notes:

1. Androfeme is licensed in Australia for female usage and imported to the UK for private use under special MHRA license.
2. Testosterone implants are currently unlicensed in the UK and can only be used privately or through agreement of the local formulary committee with appropriate monitoring of hormone levels and adverse effects. Designed for female usage.
3. Tibolone is weakly androgenic, progestogenic and estrogenic – although it is an oral option for women with low sexual desire it is not sufficiently androgenic nor estrogenic in many women. The progestogenic effect is not required in hysterectomised women and may cause unnecessary adverse effects.
4. Compounded bioidentical testosterone preparations are not recommended by the regulatory authorities or the menopause societies
5. When treating low sexual desire /arousal it is also important that urogenital tissues are adequately estrogenised in women with vulvovaginal atrophy / genitourinary syndrome of the menopause e.g. through use of vaginal estrogen, to avoid dyspareunia
6. This factsheet refers to testosterone replacement in menopause, both natural and surgical. There are very few data for testosterone replacement in premenopausal women which remains a controversial area requiring more research.
7. Oral androgens are not recommended as they are difficult to monitor, and oral testosterone can lead to adverse lipid effects.
8. It is hoped that with support from this prescribing tool, the off label prescribing of testosterone can take place in primary care, with support from secondary care / menopause specialists where required through management care pathways.

How should testosterone gel/cream be used?

The testosterone gel/cream should be to applied to clean dry skin (lower abdomen/upper thighs) and allowed to dry before dressing. 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.

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When should testosterone be avoided or used with caution?

- During pregnancy or breastfeeding
- Active liver disease
- History of hormone sensitive breast cancer – off label 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
- Women with upper normal or high baseline testosterone levels / FAI

Audit and research

In order to achieve global licensing of testosterone use in women more long term data are not only desirable, but are essential. In the absence of long term prospective randomised controlled trials the best way to gather these data are through service evaluation and prospective quality data collection through registries.

Next research steps in special populations

More data are particularly required in:

- Women with Premature Ovarian Insufficiency
- Women with Hypothalamic Amenorrhoea
- Premenopausal women especially those on SSRIs and combined hormonal contraception
- Women with hormone sensitive malignancy e.g. breast cancer

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NICE: Menopause Diagnosis and Management: https://www.nice.org.uk/guidance/ng23

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Further reading

GMC: Good practice in prescribing and managing medicines and devices. *https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/prescribing-and-managing-medicines-and-devices/prescribing-unlicensed-medicines*

MHRA: Off-label or unlicensed use of medicines: prescribers' responsibilities. *https://www.gov.uk/drug-safety-update/off-label-or-unlicensed-use-of-medicines-prescribers-responsibilities*

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WE HAVE ALSO PUBLISHED A FACTSHEET AIMED AT WOMEN, WHICH IS AVAILABLE TO DOWNLOAD ON THE WHC WEBSITE:

https://www.womens-health-concern.org/help-and-advice/factsheets/testosterone-for-women/

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