



EDITORIAL

What is the position of testosterone in the care of women?

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In 1943, shortly after testosterone was synthesized from cholesterol in 1935 by Butenandt and Hanisch¹, Robert Greenblatt wrote that 'androgenic hormones are not peculiar to the male, for they are elaborated also by the female' and proposed that 'the employment of so-called "male" sex hormone in the treatment of certain gynecic disorders may appear paradoxical but it is not unphysiologic'².

Since that time, women have been treated with testosterone for diverse reasons. The most prominent clinical indication has been low sexual desire. Past proposed indications have also included fibrocystic breast disease³ and breast cancer^{4,5}. However, more recently women have reportedly been treated with testosterone for non-traditional indications including 'hot flushes, sweating, sleep disturbance, heart discomfort, depressive mood, irritability, anxiety, premenstrual syndrome, fatigue, memory loss, menstrual or migraine headaches, vaginal dryness, sexual problems, urinary symptoms including incontinence, musculoskeletal pain and bone loss'⁶. Whether any of these aforementioned clinical complaints justify treatment of women with testosterone has been contentious.

Although women all over the world are receiving testosterone therapy, no drug regulatory authority has approved a testosterone product for women. Consequently, most women who are treated with testosterone are either prescribed a male formulation and told to use a fraction of the male dose, or are given a prescription that includes testosterone to be compounded by a pharmacy. Both approaches are probably no better than a best guess in terms of dose and frequency of use as pharmacokinetic data for male formulations and compounded formulations for women are lacking. Women using such therapies are at risk of excessive androgen exposure.

So why does this situation exist if testosterone is an important hormone for women? One could argue that an approved formulation for women would protect women against the risks of unregulated dose estimation.

Although studies have shown clinical benefits for treatment of postmenopausal women with formulations that approximate blood concentrations in premenopausal women, in excess of placebo effects, there has been substantial debate as to the benefits and risks of testosterone therapy. Therefore, when given the opportunity to approve a testosterone product for women, regulators in the past have erred

on the side of caution and have denied approval. Since the last testosterone formulation was rejected by the US Food and Drug Administration in 2004, more studies have been published and more data have become available. But do the total available clinical trial data now support benefits above risks?

Achilli *et al.*⁷ conducted a systematic review and meta-analysis of the studies of transdermal testosterone patches for postmenopausal women presenting with low sexual desire associated with distress, also known as hypoactive sexual desire dysfunction/disorder (HSDD). They concluded that the available data supported short-term efficacy of transdermal testosterone patch therapy in postmenopausal women presenting with HSDD⁷. This year, a comprehensive review of all reported outcomes of randomized clinical trials of oral and non-oral testosterone in premenopausal and postmenopausal women was completed⁸. Islam *et al.*⁸ found that, compared with placebo or comparator therapy, testosterone improved female sexual function in trials of postmenopausal women, but data for premenopausal women were insufficient to be conclusive. They found no evidence for a benefit of testosterone for the treatment of any other symptoms or conditions such as well-being, depression, cognitive performance, and musculoskeletal health.

The synthesis of the available clinical trial data has been very informative, but the findings need to be translated to clinical care. To this end, the International Menopause Society convened an international expert panel to formulate a Position Statement on the use of testosterone for women, to guide current clinical practice and inform future research. The panel was comprised of delegates from leading international organizations with expertise in gynecology, endocrinology, epidemiology, psychology, and basic science. The goal for this Task Force was to develop a consensus document with global application. The Global Consensus Position Statement on the use of testosterone therapy for women is published in this edition of *Climacteric*. As the convener of this process, I sincerely thank and congratulate all of my co-authors. We met for a full day in Berlin on 17 May 2019. Available data were presented and, following in-depth discussion, consensus was reached for each key statement. The document draft was completed by the end of the day, and finalized by the end of the month. This was only possible

because of the knowledge, dedication, and timely responsiveness of all of the Task Force members.

The resultant Position Statement provides guidance for clinicians with respect to the measurement of testosterone in women, the limitations of the available methods, and the interpretation of biochemical results. It reviews the benefits and risks based on past meta-analyses^{7,8} and when and how a trial of testosterone is appropriate. Noteworthy points included in the Position Statement are that androgen deficiency is not diagnosed by a biochemical test; that the clinical meaning of free testosterone is uncertain; that presently the *only* indication for initiating a trial of testosterone therapy in a woman is a diagnosis of HSDD; and that compounded testosterone preparations cannot be recommended. Although testosterone therapy was found not to be associated with serious adverse events, the limitations of the safety data were highlighted.

By identifying the circumstances in which testosterone has proven benefit in women and those for which it is ineffective, inappropriate prescribing should be discouraged. Sharing of this information with consumers on World Menopause Day in multiple languages will empower women to make informed decisions about testosterone therapy.

In conclusion, I hope that this international Position Statement will draw the attention of policy-makers across the globe to the inequity in the lack of any approved product for the treatment of postmenopausal female sexual dysfunction and the need for an approved testosterone formulation for this purpose.

Potential conflict of interest Dr Davis reports having received honoraria from Besins Healthcare and Pfizer Australia, has been a consultant to Mayne Pharmaceuticals, Lawley Pharmaceuticals, and Que Oncology, and has received institutional grant funding for Que Oncology research.

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