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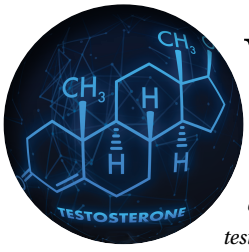
Society guidance on testosterone therapy for HSDD and approaches for evaluating and managing persistent genital arousal disorder, with expert commentary on the meaning for patient care

IN THIS ARTICLE

Many authors have commented on the lack of research into female sexual dysfunction, especially when compared with the hundreds of research publications related to male sexual health and dysfunction. Not surprisingly, very little has been published in the past year on the subject of female sexual health.

Recently, the International Society for the Study of Women's Sexual Health (ISSWSH) published 2 important papers: a guideline on the use of testosterone for hypoactive sexual desire disorder (HSDD) in women and a consensus document on the management of persistent genital arousal disorder (PGAD). The lack of funding and support for female sexual health leaves women's health professionals with little education or guidance on how to identify and treat conditions that are likely as common in women as erectile dysfunction is in men. While we would like to rely on randomized trials to inform our clinical care, the very limited literature on female sexual health makes this difficult. Bringing together experienced clinicians who focus their practices on sexual health, ISSWSH has provided some much-needed recommendations for the management of difficult conditions.

ISSWSH provides clinical guidance on testosterone therapy for women with HSDD



Parish S, Simon J, Davis S, et al. International Society for the Study of Women's Sexual Health clinical practice guideline for the use of systemic testosterone for hypoactive sexual desire disorder in women. J Sex Med. 2021;18:849-867.

For development of the ISSWSH clinical practice guideline on testosterone therapy for women with HSDD, 16 international researchers and clinicians were convened. A modified Delphi method was used to establish consensus at the meeting on

the recommended indications for testosterone treatment, formulations, and when measurement of testosterone levels is appropriate.

An extensive evidence-based literature review was performed, which included original research, meta-analyses, reviews, and clinical practice guidelines, to address the use of testosterone in women for management of HSDD. Notably, in 2019, representatives of 10 medical societies published a Global Consensus Position Statement on the Use of Testosterone Therapy for Women that reviewed the existing literature on testosterone's effects on sexual dysfunction, mood, cognition, musculoskeletal, cardiovascular, and breast health as well as androgenic side effects and adverse events.[1] Based on their review, the only evidence-based indication for testosterone use is for the treatment of HSDD.

Testosterone formulations, HSDD diagnosis, and sex steroid physiology

More than 10 years ago, the US Food and Drug Administration (FDA) reviewed an application for the use of a transdermal testosterone patch (Intrinsa) in women for the treatment of HSDD. Efficacy of treatment was clearly demonstrated, and no safety signals were found in the placebo-controlled trial. Based, however, on the opinions of regulators who were "concerned" about the *potential* for cardiovascular adverse outcomes and *worry* that the peripheral conversion of testosterone to estradiol *might* lead to an increase in breast cancer—worry generated from the findings of the Women's Health Initiative (which did not demonstrate an increase in breast cancer risk with estrogen alone but only when estrogen was combined with medroxyprogesterone acetate)—the FDA declined to approve the testosterone patch for women.

The *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (*DSM-IV*) defined HSDD as "persistent or recurrent deficiency or absence of sexual fantasies and desire for sexual activity with marked distress or interpersonal difficulty." The guideline authors noted that although the *DSM-5* edition merged female arousal disorder with desire disorder into a single diagnosis, they used the *DSM-IV* definition as it had been the basis for the studies and literature reviewed. HSDD is a prevalent condition worldwide that affects between 12% and 53% of peri- and postmenopausal women.

The consensus guideline authors extensively reviewed the physiology and mechanism of action of sex steroids in women, particularly their impact on sexual function and the biologic alterations that occur during peri- and postmenopause.

Consensus position and recommendations

The ISSWSH consensus guideline concluded that there is a moderate therapeutic benefit in adding testosterone therapy to achieve up to premenopausal levels in postmenopausal women with self-reported reduction in sexual desire that is causing distress as determined by a validated instrument.

The authors advise baseline hormone testing to rule out androgen excess and baseline renal, lipid, liver, and metabolic testing, even though transdermal testosterone therapy was not shown to alter these parameters in randomized trials of more than 3,000 women. Laboratory assays for both total and free testosterone are "highly unreliable" in the female range as they have been calibrated for male levels of hormone.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Transdermal testosterone is beneficial for the treatment of HSDD in postmenopausal women after other causes of decreased desire, such as dyspareunia, relationship issues, and other general medical conditions, have been ruled out. There is no diagnostic laboratory test to confirm HSDD or to use as a therapeutic target in treatment (for total or free testosterone, as these are highly unreliable laboratory values). Although large trials have identified no safety signals, they were generally limited to 6 months in duration. Prescribing one-tenth the dose indicated for male hypogonadism results in premenopausal testosterone levels for most women. If there is no benefit after 6 months of treatment, testosterone should be discontinued.

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FDA-approved testosterone treatments for men with hypogonadism include transdermal gels, patches, intramuscular injection, and an oral formulation. Dosing for women is approximately one-tenth the dosage for treatment of men. Patients should be informed that this treatment is off-label and that long-term studies to establish safety are not available. The authors advised against the use of compounded formulations based on the National Academies of Science, Engineering, and Medicine guidelines, but they went on to say that if compounded products are used, the pharmacy should adhere to Good Manufacturing Practice and Active Pharmaceutical Ingredients standards.

Rare, complex sexual function disorder requires integrated biopsychosocial approach, says ISSWSH

Goldstein I, Komisaruk BR, Pukall CF, et al. International Society for the Study of Women's Sexual Health (ISSWSH) review of epidemiology and pathophysiology, and a consensus nomenclature and process of care for the management of persistent genital arousal disorder/genito-pelvic dyesthesia (PGAD/GPD). J Sex Med. 2021;18:665-697.

FAST TRACK

PGAD/GPD negatively impacts sexual function, mental health, and ability to function in daily life

Persistent genital arousal disorder is a poorly understood and relatively rare sexual dysfunction in women. The American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin on Female Sexual Dysfunction does not mention this condition, leaving women's health practitioners with little guidance as to diagnosis or management.[2] Prevalence for the condition is estimated at 1% to 3%. The symptoms may be intermittent or continuous.

In a recent ISSWSH review, a consensus panel defined 5 criteria for this disorder: the perception of genital arousal that is involuntary, unrelated to sexual desire, without any identified cause, not relieved with orgasm, and distressing to the patient. The panel made a clear distinction between PGAD/genito-pelvic dysesthesia (GPD) and Compulsive Sexual Behavior Disorder (defined by the International Classification of Diseases revision 11 as "a persistent pattern of failure to control intense, repetitive sexual impulses or urges). Because there is considerable overlap with syndromes of genital dysesthesia—itching, burning, tingling, or pain—the consensus panel elected to expand the nomenclature to describe both persistent genital arousal and genito-pelvic dysesthesia as a single syndrome, namely, PGAD/GPD.

Negative impact of PGAD/GPD

The consensus panel identified several contributors to the overall morbidity of this complex disorder, including end organ pathology, peripheral nerve, spinal cord and central sensory processing malfunction, and significant psychological issues. PGAD/GPD also may be associated with spinal cysts, cauda equina pathology, and withdrawal from selective serotonin reuptake inhibitors (SSRIs). Functional magnetic resonance imaging has identified specific brain regions (for example, the paracentral lobule) that are active during clitoral stimulation and that also activate during patients' experience of persistent genital arousal.

PGAD/GPD negatively impacts sexual function, mental health, and ability to function in daily life. Of major importance is that a large proportion of people with this disorder have significant mental health disorders; in a survey, 54% of patients with PGAD reported suicidal ideation, compared with 25% of participants in a control group.

Evaluation and management recommendations

Diagnosis and management of PGAD/GPD are directed at the 5 areas of evaluation:

- end organ
- pelvis and perineum (assess for pelvic floor tension myalgia, pudendal neuropathy, pelvic congestion syndrome, or pelvic arteriovenous malformation)
- cauda equina (evaluate for neurologic deficits related to cysts compressing S2-S3 nerve roots)
- spinal cord (serotonin and norepinephrine pathways modulate nociceptive sensory activity; either SSRI/serotonin and norepinephrine reuptake inhibitor (SNRI) withdrawal or treatment could impact PGAD/GPD based on their actions in the spinal cord)
- brain.

The consensus panel recommends an integrated biopsychosocial model for evaluation and treatment of PGAD/GPD. Comorbid mental health conditions, such as depression and anxiety, are common. Small studies suggest that a history of sexual trauma may contribute to catastrophizing and the experience of distressing persistent genital sensations, either arousal or dyesthesia, with 46.7% to 52.6% of patients reporting childhood sexual abuse.[3]

WHAT THIS EVIDENCE MEANS FOR PRACTICE

PGAD/GPD is a poorly recognized source of major distress to a small but significant group of patients. Diagnosis and management require a multidisciplinary team to identify end organ, pharmacologic, neurologic, vascular, and emotional components that contribute to the syndrome. Treatment requires a biopsychosocial approach that addresses the various sources of aberrant sensory processing, including end organ disease, neuropathic signaling, spinal cord pathways, and brain signal processing. Recognizing the existence of, and approaches to, this disorder will help gynecologists understand the considerable distress and potential life-threatening consequences our patients with PGAD/GPD experience.

Future possibilities and current actualities for patient care

Research dollars and investment in female sexual dysfunction remain inadequate to address the considerable gaps that exist in evidence-based clinical guidelines. ISSWSH is working to help clinicians approach these evidence gaps with guidelines and consensus statements to help women's health professionals identify and manage our patients with sexual concerns and symptoms. An expert consensus guideline on the assessment and management of female orgasmic disorder is currently under development (personal communication, Dr. Sheryl Kingsberg). In addition, a phase 2b trial is underway to assess the impact of topical sildenafil cream for the treatment of female arousal disorder. Stay tuned for the results of these studies.

For now, women's health professionals have 2 FDA-approved treatment options for premenopausal women with arousal disorder, flibanserin (a daily oral medication that requires abstinence from alcohol) and bremelanotide (an injectable medication that can be used just prior to a sexual encounter). For postmenopausal women, there are no FDA-approved therapies; however, based on the ISSWSH guideline summarized above, transdermal testosterone may be offered to postmenopausal women with distressing loss of sexual desire in doses approximately one-tenth those used to treat men with androgen deficiency. These small doses are challenging to achieve consistently with the delivery systems available for FDA-approved products sold for men.

The National Academies of Science, Engineering, and Medicine advise against the use of compounded hormonal products due to the potential for inconsistency

FAST TRACK

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and lack of FDA oversight in the manufacturing/compounding process. I have found and used some compounding pharmacies that are dedicated to safety, quality control, and compliance; test their products; and provide consistent, reliable compounded drugs for my patients. Consideration of compounded testosterone should be discussed with patients, and they should be informed of the current professional association guidelines. Testosterone creams may be compounded to a 1% product—20 mg/mL. Researchers in Australia have demonstrated that 5 mg of transdermal testosterone cream (one-quarter of a mL) results in typical premenopausal testosterone levels.[4] When prescribing testosterone for postmenopausal women, check in with them after 6 weeks of treatment to assess impact and check blood levels to ensure that levels are not too high.

Testosterone pellets and intramuscular testosterone are not recommended and in fact should be actively avoided. These methods of administration are associated with extreme variation in hormone levels over time. There are typically supraphysiologic and quite high levels immediately after implantation or injection, followed by fairly significant drop-offs and rapid return of symptoms over time. This may lead to more and more frequent dosing and markedly elevated serum levels.

Management of PGAD/GPD is difficult, but knowing it exists as a valid syndrome will help clinicians validate patients' symptoms and begin to approach appropriate evaluation and workup targeted to the 5 domains suggested by the ISSWSH expert panel. It is useful to understand the possible relationship to initiation or withdrawal from SSRIs or SNRIs and how aberrant norepinephrine signaling along the sensory pathways may contribute to genital dysesthesia or chronic sensations of arousal. Nonpharmacologic therapies, such as cognitive-behavioral therapy and others, are essential components of the multifaceted approach to treatment. Finally, many complex problems, such as chronic pelvic pain, vestibulodynia, vulvodynia, and chronic fatigue syndrome, are associated with childhood adverse experiences and sexual trauma. Approaching these patients with trauma-informed care is important to create the trust and therapeutic environment they need for successful multidisciplinary care. ●

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