

Survey of Literature

Androgens/Female Clinical/Female Basic Science

Screening and monitoring in men prescribed testosterone therapy in the U.S., 2001–2010.

J Baillargeon, RJ Urban, YF Kuo, HM Holmes, MA Raji, A Morgentaler, BT Howrey, YL Lin, KJ Ottenbacher. *Public Health Rep* 2015;130:143–52.

Editorial Comment: Testosterone therapy for late-onset hypogonadism is a controversial practice. What is not controversial is the need for appropriate patient selection and careful monitoring for treatment emergency adverse events in those patients who do choose to initiate testosterone therapy. While individual practitioners may vary in the details of their follow-up protocols, all experts agree that patients should be followed. This follow-up must include physical examination and routine laboratory testing.

This insurance claims database makes clear a distressing reality; there exist a substantial number of U.S. men being treated with testosterone without proper testing before initiation of therapy and/or absence of follow-up serum after therapy has been initiated. As would be expected, clinicians with particular expertise in hypogonadism were more likely to adhere to established guidelines.

The issue of PSA screening is itself controversial, and hence, some providers may opt to defer this testing altogether. While deferral of PSA testing may be appropriate in properly counseled patients, it is counter-intuitive, and perhaps medico-legally risky, to avoid PSA testing in a patient receiving a therapy that has been associated with PSA changes and prostate cancer. Setting aside the issue of PSA, it is clearly inappropriate not to test serum testosterone level before starting treatment and/or after therapy has been initiated. While there is controversy about appropriate cutoff levels for “low testosterone,” very few studies support any benefit from supplementation in men with total serum testosterone levels greater than 400 ng/dL; indeed, most studies recommend a much lower cut

point around 300 ng/dL. Supplementing men who may have serum levels greater than these cutoffs is potentially risky and of unclear clinical benefit.

Unfortunately, providers who are not knowledgeable about established cut-offs are likely less prone to read literature such as this paper. It behooves medical practices and regulatory agencies to ensure that their practitioners adhere to the best available evidence-based guidelines; at a minimum, this should mean pretreatment assessment of serum testosterone levels and follow-up to ensure appropriate supplementation is achieved.

Alan W. Shindel, MD, MAS

Hypogonadal symptoms are associated with different serum testosterone thresholds in middle-aged and elderly men.

R Ramasamy, N Wilken, JM Scovell, JR Kovac, LI Lipshultz. *Urology* 2014;84:1378–82.

Editorial Comment: There exists substantial controversy about serum testosterone levels; what constitutes “low T”? Reference ranges vary widely between labs, and assays themselves are prone to marked variation. Aside from issues with testosterone itself, there is a growing body of evidence to suggest that variations in the androgen receptor may modulate the potency of serum testosterone in vivo. When coupled with the generally vague nature of “low T” symptoms, proper patient selection can be challenging.

Most organizations to date have favored a cutoff range around 300 ng/dL serum testosterone for “low testosterone.” This interesting study suggests that a “one-size-fits-all” approach to serum testosterone testing may not be appropriate and that some men with higher testosterone levels may still have significant symptom burden. Interestingly, decreased libido, one of the more common low T complaints, became increasingly prevalent in men with serum levels less than 375 ng/dL, well above

the more standard cut off of 300 ng/dL. Progressively lower levels (still over 300 ng/dL) corresponded with increasing prevalence of the physical symptoms of low testosterone (decreased ability with sports, loss of strength, etc). Wu et al. [1] reported that certain symptoms of testosterone deficiency become more prevalent with progressively lower serum levels, so this paper adds to this prior work.

The study is limited in its use of the nonspecific ADAM questionnaire. It does however give credence to the notion that clinicians should use their own judgment and carefully counsel patients who have symptoms of low T and borderline levels. Supplementation may be of benefit in such men, but careful discussion and informed consent of the patient are essential.

Alan W. Shindel, MD, MAS

Reference

- 1 Wu FC, Tajar A, Beynon JM, Pye SR, Silman AJ, Finn JD, O'Neill TW, Bartfai G, Casanueva FF, Forti G, Giwercman A, Han TS, Kula K, Lean ME, Pendleton N, Punab M, Boonen S, Vanderschueren D, Labrie F, Huhtaniemi IT; EMAS Group. Identification of late-onset hypogonadism in middle-aged and elderly men. *N Engl J Med* 2010;363:123–35.

Female Clinical Science

Mechanism of action of Flibanserin, a multifunctional serotonin agonist and antagonist (MSAA), in hypoactive sexual desire disorder. SM Stahl. *CNS Spectr* 2015;20:1–6.

Editorial Comment: For decades, the field of sexual medicine has been bombarded by scientific breakthroughs when it comes to pathophysiological understanding of the endocrinological aspects of male sexual function and dysfunction. We have noticed a significant lag in the understanding when it pertains to female sexual health and wellness. This article takes a deep dive into the female brain and hormonal regulation of female sexual interest and desire. We now can glean from the presented evidences that sexual desire is regulated not only by sex hormones (e.g., testosterone, estrogen, and progesterone) but also by brain neurotransmitters. Principle among these are dopamine and norepinephrine, which work in concert to enhance sexual interest and desire. Serotonin levels are also critical as they appear to act directly to inhibit sexual interest and desire.

Brain circuitry involved in connecting the prefrontal cortex with emotional/limbic pleasure

centers may be integrally involved in mediating personal and sexual motivation, interest, and desire. One may consider that dysregulation in these circuits will result in abnormal and/or deficient information processing; this may result in disorders of sexual interest and desire. Flibanserin, a novel medication which has recently been resubmitted to the Food and Drug administration for approval for female HSDD, is a multifunctional serotonergic agent with both 1A agonist and a serotonin 2A antagonist properties.

Flibanserin's most likely mechanism of action is by boosting pathways involved in the release of dopamine and norepinephrine while concurrently reducing serotonin release. By these mechanisms, the drug facilitates an improvement in sexual functioning with associated decrease in sex-related distress. Flibanserin is a novel multifunctional serotonin agonist and antagonist that has demonstrated improved sexual functioning in premenopausal women who suffer from reduced sexual interest and desire. This review is a must read!

Michael Krychman, MD

Bariatric surgery: Impact on sexuality of the obese person *Cirurgia bariátrica: Repercussões na sexualidade da pessoa obesa.* ML Lobato Mariano, MA Boccardo de Paula, D Germano Bassi, P Roberto de Paula. *Rev Col Bras Cir* 2014;41:412–20.

Editorial Comment: Obesity is running rampant both globally and within the United States. We have long recognized some of the medical and physical ramifications from increased body mass index (BMI) and have now labeled obesity a medical illness which warrants intervention to decrease morbidity and mortality. Obesity is considered grade I when the BMI is less than 30 kg/m², grade II when the BMI is equal to or greater than 35 kg/m², and grade III when the BMI is equal to or greater than 40 kg/m². Sexual problems and dysfunction have long been associated with changes in weight, and it has been demonstrated that severe obesity is a contributing facet to poor overall sexual functioning.

Many patients are now opting for aggressive surgical treatment for obesity. While treatment is effective in managing weight issues, there are limited data on sexual function outcomes in these patients. Increased attention to postoperative sexuality issues is an important component of

overall quality of life assessment in patients who have undergone bariatric surgery.

Obese people may experience a variety of medical and psychological ramifications from their increased weight including (but not limited to) discrimination, body image disorders, anxiety, depression, low self-esteem, isolation, hypertension, metabolic syndrome, and diabetes. Morbid obesity may directly impact sexuality by fatigue, decreased physical stamina/mobility, lower sexual self-esteem, and/or guilt and shame. There are positive outcomes of physical and emotional domains after the surgical treatment of obesity, favoring the improved quality of life, including sexuality.

This small yet significant qualitative/quantitative research study followed a nonrandom sample of 30 patients who had undergone Fobi-Capella Roux-Y gastric bypass. Data collection occurred through individual interviews and questionnaires between May and June 2011. The mean age of the patients was 44 ± 12 years. The majority of participants (24, 80%) were female. Seventy-seven percent were married. Almost all (96%) had hypertension, whereas only eight (33%) had diabetes. The average weight loss postoperatively was 44 ± 13.8 kg for women and 47 ± 16.3 kg for men. Mean weight loss as a percentage was 36% for both genders.

Postoperatively, 63% of participants reported that sexual frequency was changed: 16 (53%) reported increased sex frequency, one (3%) reported a decrease in frequency, one (3%) completely stopped having intercourse, and one (3%) did not report on sex frequency; 37% of individuals reported no change in intercourse frequency.

Data such as these support the notion that sexual health improves with management of obesity. As the population ages, and as obesity and morbid obesity become more prevalent, it is critical for us to examine our own preconceived notions on obesity and recognize that bariatric surgery may provide a new start toward improved sexual function, desire, and sexual capacity.

Michael Krychman, MD

The use of magnetic resonance imaging for studying female sexual function: A review. CM Vaccaro. *Clin Anat* 2015;28:324–30.

Editorial Comment: With recent advances in the peripheral neurological and endocrine understanding of female sexual functioning, a logical

next step is further investigation of the sexual organs and brain via advanced imaging technology. Noninvasive magnetic resonance imaging (MRI) is useful in sex research in order to better discern the underlying mechanisms of female sexual health.

MRI is more sensitive than ultrasound and computed tomography for examining small differences in tissue properties. This capability has made MRI useful in investigation of both mental and physical factors involved in female sexual function. For instance, Arnov et al. demonstrated differential brain activation and deactivation in those with hypoactive sexual desire disorder and those without this disorder [1]. Functional MRI (fMRI) has also been used in the clinical setting to reveal central sexual excitation. FMRI is able to detect even slight changes in blood flow; this property has enabled the discovery that with normative sexual response, there is deactivation of the frontal lobe and activation of the instinctual limbic system of the midbrain.

MRI has also been instrumental in assessment and documentation of the complete clitoral complex. Careful imaging studies have demonstrated the distinct nature of the clitoral glans and the paired clitoral corpora, crura, and bulbs. Important discoveries have included documentation of the average clitoral sizes and its associated structures as well as the distances between the clitoral complex and other pelvic structures.

Interestingly, MRI-based anatomical measurements have been associated with variation in female sexual function. For instance, increased distance between the clitoral complex and the vaginal lumen correlates with poorer sexual function. Genital and subjective arousal are only weakly correlated in women; however, physiological engorgement is beneficial for many aspects of female sexual arousal. Indeed, it is the opinion of many sexual medicine specialists that arousal disorder is likely to be due to a combination of inadequate desire, deficient central activation, and poor peripheral vascular engorgement.

Unfortunately, MRI is expensive in the US (less so in other countries), lacks portability, is both time-consuming, and may be difficult in patients who are claustrophobic or sensitive to noise. Furthermore, MRI is contraindicated in patients with metal implants. Despite these limitations, MRI technology is an increasingly vital adjunct in clinical research for female sexuality. It is conceivable that in the near future, MRI may have direct clinical

cal applications in the diagnosis and management of female sexual concerns.

Michael Krychman, MD

Reference

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Female Mental Health

Sensual, erotic, and sexual behaviors of women from the “kink” community. JE Rehor. *Arch Sex Behav* 2015;44:825–36.

Editorial Comment: Individuals who engage in unconventional sensual, erotic, and sexual behaviors (sometimes referred to as “kink”) have routinely been understudied. Women who engage in these behaviors have been particularly marginalized, with previous studies on kink behavior focused on clinical or criminal samples. There is a dearth of information regarding women who consensually engage in kink behaviors and what types of behaviors they engage in.

In this study, a nonclinical/noncriminal sample of 1,580 female participants were recruited through kink community events and online forums. Participants were invited to fill out an online questionnaire asking about the types of kink activities these women have participated in and the type of participation (doing to, having done to, observing). The questionnaire asked about 126 sensual, erotic, and sexual behaviors among these women including 62 BDSM-related behaviors, 10 role-play scenarios, five forms of exhibitionistic behaviors, eight forms of erotica, five broad categories of fetishistic behaviors, 24 overt sexual activities, and 12 miscellaneous erotic activities.

The researchers determined that women in the kink community willingly engage in a much wider variety of erotic activities than has previously been documented in the literature. Of interest, 85% percent of the sample indicated using bondage toys, 82% indicated that they have observed some type of erotica, and 56% indicated engaging in some type of exhibitionistic activity (e.g., showing bare breasts, engaging in public sex, posing or sharing images, etc.) for their own sensual or erotic pleasure.

The results of this study provide educators, counselors, therapists, and medical professionals a

much better understanding of the depth and breadth of activities women willingly engage in the kink community. It also adds to the literature by providing data on kink behaviors in women from a nonpathologizing perspective.

Rose Hartzell-Cushmanick, PhD, EdS, CHES, LMFT

Women’s motivations to have sex in casual and committed relationships with male and female partner. HL Armstrong, ED Reissing. *Arch Sex Behav* 2015;44:921–34.

Editorial Comment: Women are motivated to engage in sexual activity for a variety of reasons, and these motivations may change from one context to another. A better understanding of how these sexual motives work in women can help sex therapists, educators, and physicians more effectively work with women with low sexual desire or those engaging in risky sexual behavior.

In this study, the authors explored how relationship type, sexual attraction, and the gender of one’s partner interact and affect sexual motivation. Women were recruited at a large university through online advertising and by word-of-mouth. A total of 510 women completed the YSEX? Questionnaire. This survey posed questions about motivations for sex in the past and/or what would motivate them to engage in sexual activity in the future. Examples of potential enticements to sex included wanting to achieve an orgasm, being “horny,” and/or the potential partner’s physical appearance “turning them on.”

The authors report that the type of relationship (casual vs. committed) affected the women’s reported motivation for sex. For causal sex, physical reasons were most frequently endorsed as motivations, whereas for committed relationships, women more frequently motivated by emotional needs/desires. These results were consistent regardless of the gender of their partner (i.e., if their potential partner was another woman or a man).

This study is an important contribution to the literature and can benefit sexual health practitioners/therapists working with women by providing them with more insight into women’s sexual motivations (e.g., in working with women reporting symptoms of low sexual desire). In addition, the similarity in sexual motivation for women, regardless of sexual orientation or gender of partner, is also noteworthy.

Rose Hartzell-Cushmanick, PhD, EdS, CHES, LMFT

Sexual Pain

Prevalence of symptoms consistent with a diagnosis of vulvodynia: Population-based estimates from 2 geographic regions. BL Harlow, CG Kunitz, RH Nguyen, SA Rydell, RM Turner, RF MacLehose. *Am J Obstet Gynecol* 2014;210:40.e1–8. doi:10.1016/j.ajog.2013.09.033.

Editorial Comment: Vulvodynia, or idiopathic vulvar pain, is a frequent cause of sexual pain, now classified as genito-pelvic pain in the DSM-5 [1]. Vulvodynia adversely impacts women's sexual health, psychological well-being, and quality of life. Unfortunately, most studies in the area, both biomedical and psychosocial, are characterized by relatively small clinical samples. This significant limitation introduces a selection bias associated with clinically referred participants, who typically show higher levels of symptomatology. The field is in dire need of large-scale community-based studies; such data will inform scientists and health care providers about population prevalence, help-seeking behaviors and attitudes, and risk factors for the development of this neglected women's sexual health issue.

One such important study was recently published [2]. Bernard Harlow and his team gathered epidemiologic data from 5,440 premenopausal women from three ethnically diverse neighborhoods and two west suburban communities of the Boston metropolitan area (BMA) between 2001 and 2005, and 13,681 from all geographic locations within the Minneapolis/St Paul metropolitan area (MSP) between 2010 and 2012. Participants completed the self-report measures concerning their history of vulvar pain that interfered with vaginal intercourse and that lasted more than 3 months. Participants from BMA were systematically sampled from census-based directories, and those from MSP stemmed from an administrative database of women who were seen for any reason at one of several outpatient community clinics within that defined geographic region.

Although boasting large representative samples, community-based studies have the inevitable disadvantage of needing to forego more in-depth assessment of study participants. In the case of vulvodynia, this may mean that women cannot take part in a gynecological examination to confirm their diagnosis. To circumvent this

caveat, Harlow and colleagues first developed a vulvar pain questionnaire which has shown 83% sensitivity and 94% specificity for meeting a medical diagnosis of vulvodynia, based on the cotton swab test and other elements of clinical examination to rule out potential known causes of vulvar pain [3].

To determine age-specific cumulative incidence in the present study, the authors defined vulvodynia as pain on contact in the last 6 months that limited or prevented intercourse. Results indicate that for both samples, the rate of first onset of vulvodynia was highest prior to the age of 25 years, decreased during the late 20s and early 30s, and then increased in participants' late 30s. These results are similar to what is often observed clinically when speaking to women with sexual pain. Interestingly, women of Hispanic ethnicity were at an increased risk of developing vulvodynia.

Overall, 7–8% of women in this study reported symptoms consistent with vulvodynia by age 40. Among women with vulvodynia, between 30% and 48% never sought treatment; unfortunately, over 50% of those who sought care never received a diagnosis. Those with primary vulvodynia (i.e., pain on genital contact/intercourse since the first vaginal intercourse attempt) were more likely to have sought treatment compared with women with secondary vulvodynia (i.e., pain after a period of pain-free intercourse).

Two significant conclusions can be drawn from this study. First, vulvodynia is a highly prevalent condition that is often neglected by many health care professionals. Potential explanations for failure to address the issue in practice include ignorance, lack of training, discomfort discussing sexuality, and feelings of helplessness in the face of a persistent yet private pain condition that is challenging to treat. Second, almost half of women with vulvodynia do not seek treatment; even those women who do seek treatment are frequently frustrated by failure to receive a diagnosis. One may glean from this that existing studies on vulvodynia based on clinical samples represent a self-selected, limited, and biased group of women. Given that the best available data may be based on a biased population, it may be inferred that accurate knowledge on vulvodynia is less than accurate, even among sexual medicine specialists.

Sophie Bergeron, PhD

References

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- 3 Harlow BL, Vazquez G, MacLehose RF, Erickson DJ, Oakes JM, Duval SJ. Self-reported vulvar pain characteristics and their association with clinically confirmed vestibulodynia. *J Womens Health* 2009;18:1333–9.

Basic Science

Impact of prolapse meshes on the metabolism of vaginal extracellular matrix in rhesus macaque. R Liang, W Zong, S Palcsey, S Abramowitch, PA Moalli. *Am J Obstet Gynecol* 2015;212:174e1–e7.

Editorial Comment: Surgery for pelvic organ prolapse has increased since 2004 when the FDA approved the first mesh kits required to aid insertion of synthetic vaginal grafts during reconstruction. As a consequence, the use of the polypropylene mesh has improved surgical outcomes; however, mesh-related complications, such as pain, infection, and erosion may still occur. As a result, the FDA has issued public health notifications warning of complications related to mesh used for prolapse surgery and requested that additional research be conducted. Preclinical studies examining the mechanisms and outcomes of vaginal reconstruction are limited, as are comparisons between various mesh properties. In vivo studies are required to evaluate various types of mesh as their properties change in situ.

In this study, Liang et al. evaluated collagen and elastin metabolism after implantation of meshes that varied in weight, stiffness, and porosity. Rhesus macaques were divided into five groups in which hysterectomy was performed and each group was implanted with one of the following mesh types: Gynemesh PS®; UltraPro Perpendicular®; UltraPro Parallel®; or Restorelle®. A control group received no mesh. Twelve weeks later, tissue was harvested for analysis. Western blot techniques were used to measure precursors, degradation enzymes and products of collagen and elastin. While subtle differences in the various materials were detected, implantation with heavier, stiffer, and/or less porous mesh (e.g. Gynemesh PS), was associated with increased catabolism of collagen

and elastin in the vagina, increased matrix degradation, and an increase in matrix metalloproteinase (MMPs) enzymes (interstitial collagenase and fibroblast collagenase). The lighter, more porous, and less stiff meshes (e.g. UltraPro® and Restorelle®) had less of a negative impact on the remodeling of the elastin and collagen in the vagina.

The authors propose that further studies on the mechanisms by which the body activates MMPs in response to various mesh properties might help provide superior materials with less adverse effects.

Lesley Marson, PhD

Paced mating behavior is affected by clitoral–vaginocervical lidocaine application in combination with sexual experience. SH Meerts, HK Strnad, RS Schairer. *Physiol & Behav* 2015;140:222–9.

Editorial Comment: Rodents are the primary species used to study sexual behavior. Genitosensory information received during sexual behavior modulates the intensity of subsequent lordosis responsiveness, proceptive behavior, and contact return latencies in females. Recent studies have examined the effects of local anesthesia of the genital organs on the female sexual response. However, differences in methodology between studies have led to inconclusive results. Furthermore, the role of clitoral stimulation in female rat sexual behavior has not been well documented.

This study examined the effect of vaginocervical anesthesia and clitoral–vaginocervical anesthesia on sexual experience during paced sexual behavior in female rats. Rats were surgically ovariectomized and treated with estrogens to modulate estrous cycles; their sexual behavior was examined under paced mating conditions with different males to avoid development of conditioned partner preference. The timing of entries and exits to the males' compartment, as well as type of stimuli received by the male and the intensity of lordosis, were recorded over five weekly trials. Lidocaine treatment was balanced with vehicle controls that received the same type of stimuli during drug application; each group was compared with the appropriate control group. Females with anesthesia of the vaginocervical area had reduced contact return latencies to intromissions that were related to sexual experience. Females with anesthesia of the clitoris–vaginocervical area spent significantly

more time with the males and returned to them more quickly after an ejaculation compared with the vehicle-treated controls. Local anesthesia of the clitoris–vaginocervical area in sexually experienced females did not alter any aspect of female sexual behavior.

The authors explain that under normal paced conditions, the female rat is attracted toward the male through various sensory cues. Particular cues include genital sensory input received from the male during a mount, intromission, or ejaculation that induce a reward signal. Under normal conditions, males require several intromissions before ejaculation can occur. The positive feedback of this genitally evoked reward strengthens the approach behavior by the female to allow subsequent mating interactions to occur; this sets the stage for the male to be able to ejaculate. Females withdraw

from the males for a short time after genital stimulation because the stimuli they receive is temporarily aversive.

These data suggest that anesthesia of the clitoris area reduces the intensity of the sensory input for the female rat after an ejaculation during copulation. No significant changes in contact return latencies were seen with anesthesia of the vaginocervical area alone. Paced mating behavior in sexually experienced females did not a change with a single application of lidocaine to the clitoral–vaginocervical area. Taken together, the authors conclude that the complex pattern of female-paced behavior emerges with sexual experience and that the sensory information received during these sessions modulates the behavioral patterns that emerge.

Lesley Marson, PhD