Survey of the Literature December 2015

Testosterone/Androgens

Comment on: Comparative safety of testosterone dosage forms. JB Layton, CR Meier, JL Sharpless, T Sturmer, SS Jick, MA Brookhart. JAMA Intern Med 2015;175(7):1187–96.

Testosterone use continues to increase despite ongoing controversy regarding the potential cardiovascular risks of therapy, which was highlighted in a randomized trial of testosterone gels in older men that demonstrated increased cardiovascular events [1]. This possibility of increased cardiovascular risk with testosterone replacement therapy (TRT) has been a continued debate, where several manuscripts published in high impact factor journals demonstrated increased risk [2,3], and other studies have failed to demonstrate this risk as reality [4,5].

As each delivery mechanism posses varying pharmacokinetics, it is possible that one therapy may potentially carry a higher risk than the others. Injection therapy has been shown to cause a spike in testosterone level after administration, but the use of either a transdermal patch or gel imparts a more subtle increase [6]. In a new-user multicohort comparison study of the use of testosterone injection, gel, and patch, Layton and colleagues found that injection initiators had higher hazards of cardiovascular events when compared with testosterone gel use [7]. These analyses were conducted on three different cohorts of men, including a group of commercially insured men based in the U.S., a Medicare group from the U.S., and a compilation of general practitioner medical records from the U.K.. Patient databases were queried for outcomes to include myocardial infarction (MI), unstable angina, stroke, composite acute events (including MI, unstable angina, or stroke), all-cause hospitalization, mortality, and venous thromboembolism (VTE) that were recorded for up to 1 year after documented initiation of TRT. A total of 544,115 testosterone initiators were analyzed between the 3 cohorts where 55.8% of the patients received gel, 37.4% received injections, and 6.9% were on a patch. As expected, the reported incidence of cardiovascular events over 1 year was low among the younger privately insured US and UK populations when compared with the older aged Medicare sample. Injection initiators had higher hazards of cardiovascular events (ie, MI, unstable angina, and stroke) (1.26; 1.18–1.35), hospitalization (1.16; 1.13–1.19), and death (1.34;1.15–1.56) but not VTE (0.92; 0.76–1.11) when compared with gel initiators. Compared with gels, patches did not confer increased hazards of cardiovascular events (1.10; 0.94–1.29), hospitalization (1.04; 1.00–1.08), death (1.02; 0.77–1.33), or VTE (1.08; 0.79–1.47).

As the authors mentioned, this study is limited based on use of nonrandomized secondary healthcare data. Some of the data sets utilized also lacked to incorporate significant known risk factors of cardiovascular disease. More so, many patients that were included in the study were initiated on TRT without recorded serum testosterone tests or relevant diagnoses, thus, contaminating the population. Despite the possibility that cardiovascular risk may be increased relatively soon after TRT initiation [8], the 1 year follow up analyzed in this study is most likely too short to detect the long-term cardiovascular effects of testosterone via altering lipid levels. Based on the nature of the review, patients receiving in office injection therapy were more likely to be compliant with injections when compared with men who received prescriptions of a patch or gel, as the database

cannot account for what prescriptions were filled or used. This study provides good insight that high peaking serum levels of testosterone may potentially increase cardiovascular risks; however, randomized trials regarding the safety of testosterone among users compared with nonusers of the drug are needed.

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Comment on: Association between use of exogenous testosterone therapy (eTT) and risk of venous-thrombotic-events among eTT-treated and untreated men with hypogonadism. H Li, K Benoit, W Wang, S Motsko. J Urol 2015 Oct; Epub ahead of print.

A change in drug labeling of all approved testosterone products enforced by the Food and Drug Administration in 2014 required a general warning regarding the potential increased risk of venous thromboembolism (VTE) [1]. This prompted a study, funded by Eli Lilly and Company, that provided a retrospective cohort analysis of over 200,000 patients and a case-control analysis including 2,785 cases and 11,119 controls [2]. Retrospective cohort analysis revealed a HR of 1.08 for all eTT-treated patients (95% confidence interval [CI]: 0.91, 1.27; $P = 0.378$). Case-control analysis found an odds ratio [OR] = 1.02 (95% CI: 0.92, 1.13; $P = 0.702$) for current eTT exposure and 0.92 (95% CI: 0.82, 1.03; $P = 0.145$) for past eTT exposure. Thus, it was concluded there was no significant association between eTT and incidents of idiopathic VTE, as well as overall VTE in men with hypogonadism.

As mentioned by the authors, this study is limited due to being based on retrospective claims data. Certain comorbidities increasing risk for VTE were not available for inclusion in the analysis. Additionally, testosterone deficiency was not confirmed in the treated cohort prior to treatment; the need for treatment and levels of testosterone during treatment were not analyzed. Regarding the potential increased risk of VTE, one theorized mechanism is that testosterone induces polycythemia, which increases blood viscosity [3]. Interestingly, another recent nonrandomized single-center open-label registry study supports the possibility that longer duration testosterone replacement therapy (TRT) in testosterone deficient males may decrease the prevalence of anemia, improve lipid profiles, and may actually lower the overall risk for VTE [4]. When considering the effects of TRT administration, one must consider the overall need and goals of therapy, duration of treatment, and the patient's comorbidities. Much remains unclear regarding the mechanisms by which TRT may alter risk factors and who is at higher risk for these potentially morbid or fatal side effects. Recent data on the possible risks of TRT are insightful and thought provoking; however, further long term randomized control trials of properly selected patient groups are needed to determine if TRT does truly alter the risk of VTE.

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Female Basic Science

Comment on: Pelvic nerve injury negatively impacts female genital blood flow and induces vaginal fibrosis—implications for human nerve-sparing radical hysterectomy. F Castiglione, A Bergamini, M Albersen, JL Hannan, TJ Bivalacqua, A Bettiga, F Benigni, A Salonia, F Montorsi, P Hedlund. BJOG 2015;122:1457–65.

Since the development of the anatomic approach to radical prostatectomy (RP) by Dr. Patrick Walsh, nerve-sparing RP surgical techniques have been used to preserve urinary and sexual function in men with prostate cancer. Additionally, animal models of cavernous nerve injury have been well established and the mechanisms of nerve injury can be elucidated to preserve neuronal and erectile function. In women, cervical cancer is the second most common cancer and is most frequently treated by radical hysterectomy (RH). Similar to RP, women commonly suffer from bladder, anorectal, and sexual dysfunctions due to pelvic autonomic nerve damage following RH. More recently, a greater understanding of the neuroanatomy of the autonomic pelvic plexus that supplies the urogenital tract exists in women and nerve-sparing RH or individually tailored surgery to preserve nerve function is commonly performed. These refined surgical techniques have improved the quality of life of women undergoing RH; however, urogenital dysfunction persists in some patients. The mechanism of urogenital dysfunction in women following RH remains to be elucidated.

This study is the first to develop an animal model of female pelvic nerve injury to address the mechanisms of nerve-sparing RH on female genital blood flow. Authors performed two different types of unilateral pelvic nerve injury in young female rats: (1) a pelvic nerve crush (PNC) and (2) a clock-nerve crush (CNC) in which the pelvic, hypogastric, and vesicogenital branches of the pelvic plexus supplying the urinary bladder and vagina were crushed. Interestingly both PNC and CNC injuries resulted in similarly impaired nerve-mediated increases in clitoral and vaginal blood flow compared with stimulation of the uncrushed nerve at 3 and 10 days after injury. The histopathology in the animal model was comparable with that seen in patients following RH. The distal vagina appeared fibrotic as evidenced by the increased collagen types I and III and decreased alpha smooth muscle actin confirmed by immunofluorescence staining and Western blots. Neuronal nitric oxide synthase, which is responsible for the production of nerve-mediated release of nitric oxide (NO) during sexual responses, was decreased in vaginal tissue from injured rats while endothelial nitric oxide synthase remained unchanged.

This study is significant in that it is the first to describe a female model of pelvic nerve injury to evaluate impaired genital blood flow. Similar to the male animal model of RP, it appears that impaired vaginal blood flow is a result of decrease in the number of nitrergic nerves that are responsible for the release of NO. In the penis, impaired NO release leads to a hypoxic environment promoting the development of fibrosis and erectile dysfunction. The increased collagen deposition and impaired NO release in the vagina may lead to decreased smooth muscle compliance, decreased vaginal engorgement, and lubrication. This model provides some insight into the etiology of sexual dysfunction following RH and will help to discover novel therapeutic targets in the setting of neuropraxia-induced female sexual dysfunction.

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Comment on: The role of oxytocin in male and female reproductive behavior. JG Veening, TR deJong, MD Waldinger, SM Korte, B Olivier. Eur J Pharm 2015;208–28.

It has been known for decades that oxytocin is linked to various aspects of sexual and reproductive behavior. Oxytocin is released during orgasm

in men and women, and induces uterine contractions and lactation with a profound effect on maternal behavior. Over the past 20 years, the role for oxytocin has expanded to include social behaviors including enhancing trust and fear reduction. The mechanisms by which oxytocin modulates neural pathways to produce various physiological and psychological changes are still unclear, partly because of the difficulties in identifying and hence mapping the location of central receptors and how the central oxytocin system changes during development and in response to other hormones such as estrogen, progesterone, and prolactin.

In this review, Veening and colleagues provide an up to date summary of the role of oxytocin in female sexual and maternal behavior as well as its role in male sexual responses. A critical understanding of the function of oxytocin is explored based on the paraventricular hypothalamic nucleus (PVH), the supraoptic hypothalamic nucleus, and accessory hypothalamic neurons that produce oxytocin and their neuronal projections to the posterior pituitary where it is released into the general circulation. In addition, the neural projections of the PVH to the olfactory bulbs, limbic system, brainstem, and spinal cord regions that control various aspects of social and sexual behaviors are discussed in the context of emotional and sexual desire, copulatory responses, and orgasm in females and males as well as the interrelationship of aggressive behavior and parental care on social and sexual behaviors.

Another recent report [1] demonstrates how tyrosine hydroxylase containing neurons in the periventricular nucleus of the hypothalamus directly activates the release of oxytocin from neurons in the PVH to enhance maternal behavior in female mice and reduce aggressive behavior in male mice.

Therefore, basic research supports the general conclusion that oxytocin facilitates social behaviors by reducing associated anxiety and enhancing positive peripheral excitatory/genital feedback. The use of oxytocin as a treatment for various clinical CNS disorders has been challenging because oxytocin and its antagonists do not readily pass through the blood–brain barrier. However, studies in both animal models and humans recently acknowledged that intranasal administration of oxytocin modulates central nervous system (CNS) function, which provides a valuable tool for further understanding of the role of oxytocin in sexual behavior and provides treatments for CNS disorders such as depression and schizophrenia.

Oxytocin enhances social and sexual behaviors by direct action on peripheral target organs and brain regions and indirectly by activating neural networks that modulate the behaviors. Further understanding on the mechanisms by which the oxytocin system is regulated during development and the nature of environmental, hormonal, and genetic factors and their modulation of oxytocin production and release is required to more clearly understand the complex nature of oxytocin in reproductive and sexual behaviors.

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Comment on: Flibanserin treatment increases appetitive sexual motivation in the female rat. H Gelez, J Greggain-Mohr, JG Pfaus, KA Allers, F Giuliano. J Sex Med 2013;10:1231–9.

This preclinical study reports the findings from two separate laboratories that independently conducted research in female rats to assess the dose–response effects of acute and chronic flibanserin on female sexual behavior. This work demonstrated the first evidence that chronic, but not acute, flibanserin treatment augmented appetitive sexual behaviors in ovariectomized, hormonally primed female rats and provides evidence that solicitations in the female rat can be a predictive animal model of human female sexual desire. Additional studies performed in female marmoset monkeys suggested the drug increases social–sexual behavior [1,2]. Prior animal studies by Allers and colleagues demonstrated that flibanserin differentially modulates catecholaminergic and serotonergic activity in distinct brain areas to modulate sexual behavior [3,4]. In addition, Gelez et al. reported that flibanserin specifically activates neurons in brain regions, mesolimbic dopaminergic pathways and hypothalamic areas, involved with sexual motivation [5].

These studies provide basic science research supporting the use of flibanserin (Addyi™),

recently approved by the FDA for the treatment of premenopausal women with acquired, generalized hypoactive sexual desire disorder. Flibanserin (originally BIMT-17) is a mixed 5-HT1A agonist/5-HT2A antagonist that was originally developed for the treatment of major depressive disorder and had been tested extensively in animal models of depression and anxiety. Many clinical trials in women have shown that flibanserin helps improve low sexual desire. This comment references some of the animal studies that were performed and shows evidence of how animal studies can support clinical studies during drug development.

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Female Clinical Science

Comment on: Prevalence of sexual dysfunction after risk-reducing salpingo-oophorectomy. PE Tucker, MK Bulsara, SG Salfinger, JJ Tan, H Green, PA Cohen. Gynecol Oncol 2015 Nov 3. pii: S0090-8258(15)30174-8.

The authors conducted a cross sectional study of women who underwent a risk-reducing salpingo-oophorectomy (RRSO) to determine the prevalence of sexual problems and complaints in this postsurgical population. In addition, several factors were examined including hormonal profiles to discern which facets maybe associated with sexual health and wellness. The study population was in a tertiary gynecologic oncology unit, and subjects were obtained from January 2009 to October 2014. Detailed questionnaires that used validated sexual health indices and associated sexual distress were utilized. Relationship satisfaction, sexual self-image, body image, and quality of life considerations were also assessed. Patients had blood draws for serum testosterone and free androgen index. Fifty-eight percent or 119 out of 206 women participated in the study. The mean age of the participants was 52 years. Female sexual disorders were rather prevalent with hypoactive sexual desire disorder (HSDD) having an incidence of 73%. Other common complaints included changes in quality and quantity of vaginal lubrication, decline in overall sexual satisfaction, and painful intercourse. Twenty-five percent of the women who underwent a risk-reducing bilateral salpingo-oophorectomy (RRBSO) complained of change in orgasmic quality (intensity and/or latency).

Women who used minimally absorbed local vaginal estrogen products and those who had lowered body pain, as well as those who reported relationship fulfillment and contentment had a lowered likelihood of reporting sexual problems. Menopausal status, prior history of breast cancer, and removal of the uterus (hysterectomy) were not correlative with sexual dysfunction. Interestingly serum testosterone and free androgen index were not associated with sexual problems.

The data in this article are corroborated with other published articles, which demonstrate a linkage of RRBSO to sexual problems in the postoperative period that are linked to changes in quality of life.

With the increased popularity of Angelina Jolie's decision to undergo genetic testing, and subsequently undertake risk-reducing interventions, clinicians have seen an increase in both genetic testing and patient requests for prophylactic surgical interventions to potentially reduce cancer. Surgical intervention not only carries a risk during the operative period and during the recovery time but also has far reaching implications to the woman's overall quality of life and sexual vitality.

Women must be counseled accordingly regarding the sexual implications of RRBSO and inter-

ventions such as minimally absorbed local vaginal estrogen should be offered in anticipation of sexual problems. Perhaps the utility of a pre-operative sexual medicine consultation should be assessed. Given the high prevalence of sexual dysfunction after RRBSO, aggressive evaluation and diagnostics interventions should be implemented when clinical suspicion of sexual problems exists. Since sexual problems have far reaching implications on overall health and quality of life, assessment and referral for sexual health treatment from a specialist should be a part of the comprehensive management paradigm.

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Female Mental Health

Comment on: Sexual esteem in emerging adulthood: Associations with sexual behavior, contraception use, and romantic relationships. MK Mass, ES Lefkowitz. J Sex Behav 2015;52:795–806.

Sexual health practitioners/educators working with women can benefit from a better understanding of the emotional/mental side of sexual development. Understanding the development of sexual health behaviors and their associations with the romantic contexts of those behaviors and sexual esteem can inform sexual health education program designers to create educational programs that address not only risk reduction but promote consensual, emotionally fulfilling, and more pleasurable sex. This study aimed to explore these associations in an emerging adult population, which is when many people's sexual experiences seem to accelerate.

The researchers collected data using online surveys and the information gathered was part of a larger longitudinal study at a university in the United States. Data collection started in the students first year of college and the researchers followed the participants over 5 semesters. The final analytic sample consisted of 518 students, 56% of which were female, 97.7% of which were heterosexual, and with a mean age of 20.43 (SD = .41) years old. The researchers used two separate linear regression models with sexual esteem as the outcome.

The results of the study indicated that male and female participants who had oral sex more frequently, recently had more oral and penetrative sexual partners, and spent more time in romantic relationships tended to have higher sexual esteem than those who did not. Interestingly, sexually active male emerging adults who never used contraception during recent penetrative sex tended to have higher sexual esteem than those who did not use it, whereas female emerging adults who never used contraception tended to have lower sexual esteem than those did use it. This information can be very useful for sexual health practitioners wanting to promote safe, consensual, and pleasurable sex in women.

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Sexual Pain

Comment on: Depression and posttraumatic stress disorder among women with vulvodynia: Evidence from the population-based woman to woman health study. L Iglesias-Rios, SD Harlow, BD Reed. J Womens Health (Larchmt) 2015 Jul;24(7):557–62.

Vulvodynia, or idiopathic vulvar pain, may be exacerbated by psychological factors such as anxiety and fear of pain. However, most studies examining these factors are characterized by relatively small clinical samples, biased in terms of higher levels of distress. This multiethnic population-based study involving 1795 women corrected for this limitation and showed that those who screened positive for depression had a 53% higher prevalence of having vulvodynia, and those who screened positive for post-traumatic stress disorder (PTSD) had more than a twofold increase in the prevalence of having vulvodynia. Thus, depression and PTSD were independently associated with the prevalence of vulvodynia.

This is the first study to show that PTSD increases the odds of reporting vulvodynia. PTSD is a debilitating psychiatric disorder that may develop after unresolved trauma, such as childhood sexual abuse (CSA). It is characterized by intrusive re-experiencing of the traumatic event, avoidance behaviors, hypervigilance, and emotional numbing, as well as by activation in the physiological and neuroendocrine systems. A population-based study showed that women with vulvodynia had almost three times the odds of reporting experiences of severe childhood physi-

cal and sexual abuse when compared with women without vulvodynia [1]. PTSD is a common consequence of CSA. Although cross-sectional, findings of this study suggest that one of the pathways by which CSA may lead to the development of vulvodynia is through the modification of immunoinflammatory response mechanisms such as those involved in PTSD, as a growing body of evidence supports the role of inflammation in vulvodynia [2]. This study thus lends support to a biopsychosocial conceptualization of vulvodynia.

Findings also have implications for treatment. By providing strong support for the involvement of PTSD and depression in vulvodynia, results suggest that medical interventions may need to be combined with psychological approaches such as cognitive-behavioral therapy, in order to target the cognitive, affective, and behavioral correlates of vulvodynia, simultaneously with their neuroinflammatory counterpart, for optimal patient care.

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LGBT Studies

Comment on: Care of the transgender patient: A survey of gynecologists' current knowledge and practice. CA Unger. J Womens Health (Larchmt) 2015 Feb;24(2):114–8.

In general, clinicians are poorly equipped to meet the healthcare needs of transgender people. In an anonymous survey of US gynecologists' preferences and knowledge base with regard to transgender healthcare, Unger [1] sought to assess provider experience and practice environment, education about transgender health practices, personal experience with transgender patients, and knowledge base regarding current recommendations for the care of gender minority patients. Of the 141 gynecologists that responded (40.1% response rate), 80% had not received training in residency on the care of transgender patients and time in practice was not associated with having learned about transgender care. Only around one-third reported being comfortable caring for trans men (who may retain the internal genitalia of their birth) and trans women; around 60% did not know the recommendations for breast cancer screening for trans women.

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Comment on: Diagnosis of prolactinoma in two male-to-female transsexual subjects following high-dose cross-sex hormone therapy. FS Cunha, S Domenice, VL Camara, MH Sircili, LJ Gooren, BB Mendonca, EM Costa. Andrologia 2015 Aug;47(6):680–4.

Cunha et al. [1] report two new cases of prolactinoma in transwomen, aged 41 and 42 years. Both had very high serum prolactin levels and the diagnosis of prolactinoma was confirmed by imaging techniques; both responded well to treatment with cabergoline. This brings to five the total number of prolactinomas associated with supraphysiological doses of estrogens that are described in the literature.

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Comment on: Body image dissatisfaction and eating-related psychopathology in trans individuals: A matched control study. GL Witcomb, WP Bouman, N Brewin, C Richards, F Fernandez-Aranda, J Arcelus. Eur Eat Disord Rev 2015 Jul;23(4):287–93.

Witcomb et al. [1] explored the high levels of body dissatisfaction reported in the trans population and its association with eating disordered behaviors.

They assessed eating disorder risk by comparing 200 trans people, 200 people with eating disorders, and 200 control participants' scores on three subscales of the Eating Disorders Inventory-2 (EDI-2), and explored dissatisfaction among trans participants using the Hamburg Body Drawing Scale (HBDS). As might be expected, participants with eating disorders scored higher than trans or control groups on all EDI-2 measures; trans individuals had greater body dissatisfaction than control participants; and, importantly, trans men had comparable body dissatisfaction scores with eating-disordered men. Drive for thinness was greater in women (both natal and trans) compared with men. In relation to HBDS body dissatisfaction, both trans men and trans women reported greatest dissatisfaction, not only for gender-identifying body parts but also for body shape and weight. The authors conclude that trans males may be at particular risk for eating-disordered psychopathology and other body image-related behaviors.

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Comment on: Quality-of-life measurement: Assessing the WHOQOL-BREF scale in a sample of high-HIV-risk transgender women in San Francisco, California. HM Thompson, SL Reisner, N VanKim, H Fisher Raymond. Int J Transgenderism 2015;16(1):36–48.

Research in transgender healthcare is hampered by the lack of validated measures for use in these populations. In the *International Journal of Transgenderism*, Thompson et al. [1] assess the psychometric properties of the WHOQOL-BREF in a sample of HIV-positive trans women in San Francisco. This instrument consists of 24 items, encompassing four domains: physical health, psychological health, social relationships, and environmental conditions. It extends beyond assessment of health alone and captures important aspects of responders' daily social contexts. The authors conclude that it is an acceptable, reliable, and valid measure of quality of life for research with transgender women.

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