



# AUA News

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## AUA

### 2008 ANNUAL MEETING HIGHLIGHTS

#### Testosterone Replacement Therapy

##### Course #43MC

Hypogonadism and Testosterone Replacement Therapy in Current Urologic Practice

##### Course #54PG

Urologic Diseases for the Allied Health Professional

##### Late Breaking Science Forum

Safety, Efficacy and Pharmacokinetics of Testosterone, Undecanoate Long-Acting Injection of Hypogonadism: Results of a Phase III Clinical Trial

#### Abstract Highlights

##### AUANews Editor

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ANNUAL MEETING  
17-22 may 2008  
orlando, florida usa

New Research.  
New Thinking.  
New Practices.

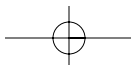
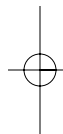
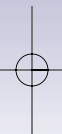
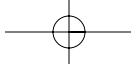


## ANNUAL MEETING HIGHLIGHTS

# Testosterone Replacement Therapy

This publication was supported by an educational grant from Indevus Pharmaceuticals, Inc.





## CME INFORMATION

## Highlights on Testosterone Replacement Therapy

(from Courses # 43MC and #54PG, 2008 AUA Annual Meeting)

### Medium and Method of Participation

This CME activity consists of a printed overview of the content presented at a live course at the 2008 AUA Annual Meeting and an evaluation. To receive CME credit, participants must read the overview of the course, complete the evaluation and claim credit. Visit <http://www.auanet.org/cme/TRT08> to complete the evaluation and claim credit for this activity.

Estimated Time to

Complete this Activity: 1.5 hours

Release Date: October 2008

Expiration Date: October 31, 2009

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or unapproved uses are discussed, these are also indicated.

### Course #43MC: Hypogonadism and Testosterone Replacement Therapy in Current Urologic Practice

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tor; *Auxilium*: Consultant/Advisor; *American Medical Systems*: Mentor; Investigator

#### Learning Objectives

At the conclusion of this educational activity, the participant should be able to:

- Review presentation, prevalence and diagnostic methods for male hypogonadism
- Appraise controversy regarding testosterone and prostate cancer
- Describe the shortcomings of current assay methodologies
- Devise a cost-effective treatment and followup algorithm for the hypogonadal male

### Course #54PG: Urologic Diseases for the Allied Health Professional

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Scientific Study/Trial; *Gen-Probe:* Consultant/Advisor; *Sanofi:* Consultant/Advisor, Investigator

**Learning Objectives**

At the conclusion of this educational activity, the participant should be able to:

- Describe the various types of male and female sexual dysfunction seen in the office setting
- Discuss the evaluation and treatment options for both male and female sexual dysfunction, including erectile dysfunction, hypogonadism and ejaculatory dysfunction in the male, and hypogonadism and hypoactive desire disorder in the female
- Review the physiology and pathophysiology of the male and female voiding system
- Characterize the abnormalities seen in the office with respect to OAB and incontinence in the male and female
- Delineate the algorithm for the treatment of the incontinent patient, including the role of urodynamics
- Detail the various surgical and non-surgical options for men and women with OAB and incontinence
- Review the AUA guidelines for BPH evaluation
- Describe the role of the urologist in the office evaluation of BPH
- Discuss the various treatment options for men with BPH, including medical and minimally-invasive surgical options

**Statement of Need**

Physicians and allied health professionals need an update on several areas of office urologic practice including sexual medicine, incontinence, BPH, overactive bladder focusing on the office evaluation of male and female with sexual problems, incontinence, overactive blad-

der and on men with BPH. Health-care providers also need to stay current with the presentation and management of hypogonadism and the controversy around testosterone and prostate bladder.

**Target Audience**

Urologists, urologists in training and allied health care professionals involved in urology

**Accreditation**

The American Urological Association (AUA) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

The American Urological Association takes responsibility for the content, quality and scientific integrity of this CME activity.

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As a provider of continuing medical education accredited by the ACCME, it is the policy of the AUA to review and certify that the content contained in this CME activity is based on acceptable scientific princi-

**CME Information**

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**COURSE 43MC**

## Importance of Hypogonadism and Testosterone Replacement Therapy in Current Urologic Practice

Wayne John G. Hellstrom, M.D., Course Director; Craig Donatucci, M.D., Faculty

**Introduction and Definition**

The hormone testosterone (T) is responsible for normal growth and development of male sex organs and maintenance of secondary sex characteristics. It is the primary androgenic hormone, and its production and secretion are the end products of a series of hormonal and enzymatic interactions and feedback regulatory mechanisms.

Testosterone deficiency results when the testes fail to produce normal levels of testosterone. Hypergonadotropic hypogonadism is called **primary** testicular failure. Testosterone levels are low and pituitary gonadotropins are elevated. In **secondary**, or hypogonadotropic hypogonadism, there is inadequate secretion of pituitary gonadotropins and, in addition to low serum testosterone level, luteinizing hormone (LH) and follicle-stimulating hormone levels are low or low normal (Appendix 1). While prepubertal hypogonadism is generally characterized by infantile genitalia and lack of virilization, the development of hypogonadism after puberty frequently results in clinical

complaints such as diminished libido, erectile dysfunction, infertility, gynecomastia, impaired masculinization, changes in body composition (muscle mass and fat-to-lean tissue ratio), reductions in body and facial hair, and osteoporosis/osteopenia. In addition to these complaints, mood inventory scores indicate that hypogonadal men report levels of anger, confusion, depression and fatigue that are significantly higher than those reported by men with normal testosterone levels.

**Age Related Declines in Serum Testosterone**

Although wide inter-individual variations exist, mean total and free T levels decline with age, whereas dihydrotestosterone (DHT) and estradiol levels tend to remain relatively constant. At age 75 years the mean total T level in the morning is about two-thirds of the mean level at ages 20 to 30 years, whereas the mean free T and bioactive T (free T plus albumin bound T) levels are only 40% of the mean levels in younger males. Furthermore, the circadian rhythm of

serum T levels is generally lost or attenuated in elderly men.

**Effects of Testosterone Deficiency on Male Sexual Function**

Sexual interest and activity, and erectile rigidity and duration decline in men as they age. Erectile dysfunction (ED) is seen with an age stratified incidence of 1.9% at 40 years and 25% or greater by age 65. The reported incidence of endocrinopathy as the etiology of erectile dysfunction is 1% to 35%. Interestingly, the prevalence of abnormally low serum T levels, even among men with ED, has historically been reported to be low (in urology approximately 6%). The majority of studies show that ED has a clear association with aging but no consistent correlation of total T with erectile function has been identified. The role T plays in human penile erectile physiology is unclear, and so far appears to be different from the effects in animal models. The physiology of erection depends on the integrity of corporal smooth muscle. In a variety of experimental conditions orchietomy has been associat-

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ed with decreased smooth muscle content and increased interstitial collagen in the penis. At the cellular level the absence of T reduces nitric oxide synthase and nitric oxide production. Recent clinical recommendations have been made regarding assessment of T levels in patients in whom phosphodiesterase type 5 inhibitor therapy fails. Although no direct link has been made to cavernosal muscular atrophy or penile neurological control, it may be that T not only affects sex behavior, but also subtly changes a number of physiological parameters directly regulating erectile activity.

**Diagnosis of Hypogonadism**

The diagnosis of hypogonadism requires the art and science of medicine. Subjective symptoms suggestive of androgen deficiency with characteristic signs on physical examination may lead one to suspect hypogonadism, which can then be confirmed by testing demonstrating low levels of serum testosterone.

The hallmark symptom of low testosterone is diminished libido which taken in conjunction with signs of testicular atrophy on physical examination is highly specific for hypogonadism when observed in patients with ED. However, focusing on these men alone may lead one to miss many men who are androgen deficient and who would be well served by testosterone replacement. Additional sexual symptoms due to low testosterone include erectile dysfunction, difficulty achieving orgasm, reduced intensity of orgasm, reduced ejaculatory volume and reduced sexual sensation in the genital region, particularly the penis. Nonsexual symptoms of hypogonadism include reduced sense of vitality or “energy,” increased fatigue, depressed mood, reduced motivation and decreased

muscle mass or strength. Note that these symptoms are not specific to androgen deficiency, and so a high index of suspicion should lead one to a diagnostic algorithm that would correctly diagnose the cause of these broad symptoms. Signs of androgen deficiency include testicular atrophy, anemia, reduced bone mineral density (osteopenia or osteoporosis) and changes in body composition (increased fat mass and reduced lean body mass). Low testosterone has also been associated with the metabolic syndrome, a set of risk factors for cardiovascular disease.

There has been a lack of consensus as to what blood levels of testosterone should be considered low and, thus, consistent with the diagnosis of hypogonadism. In the absence of a definition of low testosterone based on the best level of evidentiary medicine, we must rely on recommendations from expert panels. There have been a number of consensus panels published in the literature, most of which revolve around a level of testosterone of 300 ng/ml as normal. The recently published Endocrine Society Practice Guidelines recommend that total testosterone levels less than 300 ng/dl be considered diagnostic of hypogonadism, and that higher levels be considered normal. However, all attempts to identify a threshold that accurately distinguishes men with hypogonadism have been unsuccessful, and this threshold remains quite arbitrary. Other groups have suggested other thresholds, such as 354 ng/dl by the International Society for the Study of the Aging Male. Given the variability of individual sex hormone binding globulin (SHBG) levels, a therapeutic testosterone trial may be considered for symptomatic men with low levels of total testosterone or with levels in the low-normal range. This is known

as the “art” of medicine.

Total serum testosterone is composed of 3 components added together. Roughly half of testosterone is bound to the carrier molecule sex hormone binding globulin, almost all of the remainder is bound to albumin and approximately 1% to 2% is unbound or free. A key concept is that testosterone binds so tightly to SHBG that it is functionally unavailable to the cells. In contrast, albumin bound testosterone dissociates readily, meaning that this component and the free component are available to cells. The term “bioavailable testosterone” refers to a combination of the albumin bound and free portions. There are a variety of available laboratory tests of testosterone (total testosterone, free testosterone, bioavailable testosterone) that can be ordered as well as the laboratory methods used to determine the actual testosterone level (equilibrium dialysate method for determination of free testosterone being most accurate). Most laboratories will offer tests for total and free testosterone.

Since SHBG can vary considerably in men, total testosterone levels may be greatly affected. In some cases, relying on total testosterone as an indicator of the adequacy of circulating androgens available for physiological effects will lead to failure to discover hypogonadism. For example, SHBG increases with age, meaning that older men will tend to have normal levels of total testosterone even if they are truly hypogonadal, with low levels of free or bioavailable testosterone. Conversely, obesity is associated with low SHBG, which drives down total testosterone, even when the bioavailable fraction may be normal. The best way to obtain an accurate free testosterone is to use a laboratory offering the equilibrium dialysate method. Alternative-

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ly, an acceptable calculation based on total testosterone, SHBG and serum albumin levels is available.

Be aware that laboratory reference values for testosterone vary widely from one institution to another and, thus, are not particularly helpful. In 1 survey the reference value used to identify a value as low varied by 350% across 25 laboratories. Therefore, reference values provided by your local laboratory should be considered with this variance in mind. Despite the confusion about what a low testosterone level is, a symptomatic patient, with a low testosterone (or a low normal at my own institution) should be considered for androgen replacement therapy. Therefore, some clinical guidelines and recommendations can be made as a general rule of thumb. Men with total testosterone less than 200 ng/dl clearly are hypogonadal, men with total testosterone greater than 400 ng/dl are unlikely to be hypogonadal and men with total testosterone 200 to 400 ng/dl should be evaluated based on clinical presentation.

### **Treatment of Hypogonadism and Recognized Benefits**

Testosterone replacement therapy (TRT) is indicated for the treatment of testosterone deficiency in aging men with signs and symptoms of hypogonadism. The aims of such treatment are to restore body composition, bone density, libido and mood. However, the ideal dose is difficult to determine because the amounts of testosterone required for androgen dependent processes are unknown. Evidence suggests that there are different dose-response curves for different androgen dependent functions. Sexual function (libido) appears to be normalized by relatively low testosterone replacement levels, but it is not

known whether these levels can maintain bone and muscle homeostasis. Higher levels of testosterone are more likely to have adverse effects on behavior, lipid levels, insulin sensitivity and prostate growth. Available testosterone preparations are listed in Appendix 2.

### **Risks of Testosterone Therapy**

All medical therapies are associated with possible adverse effects, and TRT is no exception. The most common concern, particularly among urologists, is the possibility that TRT may also increase the subsequent risk of prostate cancer. The other major issue with TRT is there might be an increased risk of cardiac disease. Neither of these concerns appears to have a scientific basis.

Multiple studies have shown that the effect of TRT on the lipid profile is neutral. Transdermal therapy in particular has little to no effect on serum lipids in most studies and when present changes have generally demonstrated a balanced effect, for example a reduction in HDL (the “good” cholesterol) together with a decrease in the total testosterone or LDL (the “bad” cholesterol). For many years it was believed that TRT may increase the risk of heart disease, since men have a higher incidence of cardiovascular events than women. However, as newer evidence accumulates we find that the opposite may be true. Several studies suggest that higher levels of testosterone may actually confer a favorable effect on the risk of cardiovascular disease, and therapeutic reduction of androgens may lead to significant risks of cardiovascular incidents and even death.

For example, in the Rotterdam study men with testosterone levels in the highest third had a risk of atherosclerosis of the abdominal aorta that

was only 20% as high as men with testosterone in the lowest third of the population.<sup>1</sup> In a small study English et al reported that 22 men with chronic stable angina treated with transdermal TRT had greater angina-free exercise tolerance compared to 24 placebo treated controls.<sup>2</sup> Furthermore, direct injection of physiological levels of testosterone into the coronary arteries led to an increase in mean coronary artery diameter and blood flow compared to baseline. Studies of TRT have not demonstrated an increased incidence of cardiovascular disease or events such as myocardial infarction, stroke or angina episodes. A recent meta-analysis of 30 trials comprising 1,642 men revealed that TRT is not associated with important cardiovascular effects.

Although the available data appear reassuring, definitive assessment of the long-term consequences of TRT on cardiovascular health will require prospective, large-scale, placebo controlled studies. Interestingly, there is emerging evidence that low testosterone levels, such as those obtained with androgen suppression therapy (AST) for prostate cancer, may actually increase the risk of cardiovascular morbidity and mortality. D’Amico et al investigated the influence of androgen suppression therapy for prostate cancer on the frequency and timing of fatal myocardial infarctions (MI) and found an earlier onset of fatal MIs in men 65 years old or older on AST for 6 months or more.<sup>3</sup> Laughlin et al examined the association of endogenous testosterone levels on 794 older community-dwelling men followed for an average of 11.8 years.<sup>4</sup> They reported that testosterone deficiency in older men was associated with an increased risk of death during a 20-year period and that the increase in risk was independent of multiple car-

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diovascular risk factors or preexisting health conditions.

The greatest concern regarding TRT is the fear that higher testosterone levels will increase the risk of prostate cancer. Specifically, the concern is that small, undetected, inactive or incidental tumors will progress into clinically worrisome disease. This concern stems from the well-known fact that prostate cancer is androgen dependent. However, after age 65 years there remains no compelling evidence that this risk is real. Multiple studies have failed to show any association of higher testosterone and subsequent risk of prostate cancer. TRT in men at high risk for prostate cancer due to preexisting prostatic intraepithelial neoplasia did not demonstrate any increased risk of prostate cancer.

Marks et al provide a good explanation of why TRT does not appear to increase prostate cancer risk.<sup>5</sup> In a placebo controlled trial men received intramuscular testosterone every 2 weeks for 6 months. Tissue levels of testosterone and DHT were obtained by biopsy before TRT and at the end of the 6-month trial. Although serum levels of T and DHT increased substantially, there was no change in these androgens within the prostate itself.

Indeed, there is now some concern that men with low testosterone may be at increased risk of prostate cancer. Prostate biopsy in hypogonadal men with prostate specific antigen (PSA) less than 4.0 ng/ml revealed cancer in 15%, and men with more severe reductions in testosterone had a risk of cancer that was double the risk for those with milder reductions in testosterone. Low testosterone has been associated with worse prognosis, higher disease stage at presentation and higher grade cancers.

Another less significant risk to TRT

is preexisting benign prostatic hyperplasia. TRT causes a mild increase in prostate volume and PSA of approximately 15%, but does not appear to worsen voiding symptom scores, uroflow values or post-void residual volumes in this group. Another common adverse effect of TRT is erythrocytosis, representing an elevation in the hematocrit or hemoglobin. This is more likely to occur in men living at high altitude (Rocky Mountain states) or those who are on parenteral therapy. On average, TRT causes an increase in the hematocrit of approximately 3%. In a clinical trial of intramuscular testosterone, at least 1 episode of increased hematocrit occurred in 44% of men compared with 15% in men receiving testosterone via a transdermal patch. Proper monitoring and dose adjustment are necessary in men at risk for erythrocytosis with increased hemoglobin/hematocrit levels. Gynecomastia is an uncommon event associated with TRT, occurring via conversion of testosterone to estradiol, and acne may occur in a small percentage of men due to increased oiliness of the skin from higher testosterone levels. TRT has been associated with new onset or exacerbation of sleep apnea. The mechanism for this relationship remains unclear but men beginning therapy should be questioned for a preexisting diagnosis of sleep apnea.

Oral forms of testosterone have been associated with liver toxicity and are strongly discouraged, as none of the commonly used modes of therapy has been shown to cause any liver problems. Specifically, intramuscular injections, patches and gels appear safe with regard to the liver. There is no need to monitor liver function tests in men receiving these more standard modes of therapy.

Testicular atrophy and infertility are important effects of TRT. Exogenous

testosterone down-regulates release of LH and follicle-stimulating hormone. While serum levels may normalize, the interstitial environment with the testicle exhibits dramatically lower relative levels because the Leydig cells that are intimately associated with the spermatogenic epithelium are no longer producing testosterone, resulting in dramatic decreases in sperm production. Most men receiving TRT will be azoospermic or have severely depressed sperm concentrations, which usually return to baseline after cessation of TRT. Reduction in spermatogenesis may also result in reduced testicular size, which may be more noticeable and of greater importance to younger men. It is necessary to ask any man who is a candidate for TRT whether he desires children in the near future and, if so, he should not receive TRT. Some of these men may be successfully treated with agents that increase endogenous production of testosterone, such as clomiphene citrate and gonadotropins.

**Summary**

Testosterone is the primary androgenic hormone responsible for normal growth and development of male sex organs and maintenance of secondary sex characteristics. Evaluation of potential candidates for testosterone replacement therapy includes a complete medical history and hormonal screening. Total serum testosterone should be measured in the morning. When the serum testosterone level is low and LH is elevated, testosterone replacement therapy is warranted as this suggests **primary** (hypergonadotropic) hypogonadism. When serum levels are low, LH is normal or low and prolactin levels are elevated, an imaging study of the pituitary region is warranted and

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endocrinology consultation may be needed.

Testosterone replacement therapy should, in theory, approximate natural endogenous production of the hormone. The clinical rationale for treatment of testosterone deficiency may include stabilizing or increasing bone density, enhancing body composition by increasing muscle strength and reducing adipose tissue, improving energy and mood, and maintaining or restoring secondary sexual characteristics, libido and erectile function.

The physician prescribing TRT must evaluate for any changes in the clinical symptoms and signs of testos-

terone deficiency, and must monitor the patient regularly by performing digital rectal examination, and checking serum testosterone levels, PSA and hematocrit at baseline and at prescribed intervals (at 3 to 6 months and then annually) during treatment. Although testosterone replacement is contraindicated in men with carcinoma of the breast or known or suspected carcinoma of the prostate, in general therapy appears to be safe for the vast majority of hypogonadal men. There is no apparent association between testosterone replacement therapy and the development of prostate cancer. The administration of exogenous testosterone is not a

means of reversing the aging process in men with normal testosterone levels, but it may offer considerable benefit for those with hypogonadism. ♦

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2. English KM, Steeds RP, Jones TH et al: Low-dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina: a randomized, double-blind, placebo-controlled study. *Circulation* 2000; 102: 1906.
3. D'Amico AV, Denham JW, Crook J et al: Influence of androgen suppression therapy for prostate cancer on the frequency and timing of fatal myocardial infarctions. *J Clin Oncol* 2007; 25: 2420.
4. Laughlin GA, Barrett-Connor E and Bergstrom J: Low serum testosterone and mortality in older men. *J Clin Endocrinol Metab* 2008; 93: 68.
5. Marks LS, Mazer NA, Mostaghel E et al: Effect of testosterone replacement therapy on prostate tissue in men with late-onset hypogonadism: a randomized controlled trial. *JAMA* 2006; 296: 2351.

**APPENDIX 1: PRIMARY VS SECONDARY CAUSES OF HYPOGONADISM****Primary Hypogonadism**

(↓ T and ↑ LH)

- Klinefelter's syndrome
- Mumps orchitis
- Autoimmune orchitis
- Trauma
- Testicular irradiation or surgery

**Secondary Hypogonadism**

(↓T and ↑ ↔LH)

- Acquired idiopathic
- Pituitary tumors
- Uremia
- Systemic illness
- Cranial irradiation
- Hyperprolactinemia
- Hemochromatosis
- Cushing's syndrome
- Cirrhosis
- Morbid obesity
- Metabolic syndrome
- Diabetes mellitus

**APPENDIX 2: APPROVED TESTOSTERONE PREPARATIONS**

- Oral agents
- Pellet implants
- Scrotal patches
- Intramuscular preparations
  - Short acting
  - Long acting
- Transdermal patches
- Transdermal gels
- Buccal tablets

**COURSE 54PG****Urologic Diseases for the Allied Health Professional**

Allen D. Seftel, M.D., Course Director; Jeffrey Albaugh, Ph.D., Tamara Dickinson, R.N. C.U.R.N.,CCCN, Lindsey A. Kerr, M.D., Melissa Morrison, R.N. and John T. Wei, M.D., Faculty

This course for allied health professionals focused on several unique areas of office urological practice. Sexual medicine, incontinence, benign prostatic hyperplasia (BPH) and overactive bladder were reviewed and discussed by physicians and physician extenders, providing a var-

ied and well-rounded perspective on these topics. Emphasis centered on history, examination, ancillary studies, diagnosis, treatment and coding, which allowed for maximal benefit to the clinician interested in expanding or revamping office practice to meet the needs of patients with these varied

conditions.

Dr. Albaugh discussed female sexual dysfunction (FSD). Citing the study by Laumann et al,<sup>1</sup> we were reminded that the prevalence of FSD in 3,000 men and women 18 to 59 years old was 43% of the study population. The most common FSD was

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desire disorder. The alternative cycle of female sexual response was reviewed as described Basson,<sup>2,3</sup> with emphasis on the emotional component of female sexual desire. Basson suggests that it is a desire for increased emotional intimacy with the partner, rather than the “sexual hunger” posited in traditional models of sexual response, which predisposes a woman to engage in sexual activity. Once stimulated, she then moves from what was a state of sexual neutrality to one of sexual arousal. Basson also suggests that a large component of female sexual desire is responsive rather than spontaneous.

Female sexual dysfunction is categorized as sexual desire disorder, sexual arousal disorder, orgasmic disorder and sexual pain disorder.<sup>4</sup> Sexual desire disorder is defined as the persistent/recurring deficiency/absence of sexual fantasies or thoughts and the lack of receptivity to sexual activity which causes personal distress. This disorder is subclassified into hypoactive, which is the most prevalent type of FSD, and aversion, which is psychogenic/emotional.

Sexual arousal disorder is defined as the persistent or recurring inability to attain or maintain adequate sexual excitement which causes personal distress and decreased physical response.

Orgasmic disorder is defined as persistent/recurrent difficulty, delay or absence of attaining orgasm following sufficient sexual stimulation and arousal which causes personal distress.

Sexual pain disorder comprises dyspareunia and vaginismus. Dyspareunia is recurrent genital pain associated with sexual intercourse. Vaginismus is recurrent/persistent involuntary spasms of the musculature of the outer third of the vagina which inter-

fere with vaginal penetration and cause personal distress.

Treatment of these disorders include behavioral therapies, such as knowledge about sexuality, anatomy of the body and coital position; benefits of physical exercise; self-satisfaction options; lifestyle changes; and sensate focus. Pelvic floor physical therapy has been described for pain, arousal and orgasmic disorders. Eros and herbal therapies as well as ointments have also been prescribed for these disorders.

Dehydroepiandrosterone (DHEA), an androgenic hormone precursor to testosterone, has been evaluated in 2 studies.<sup>4,5</sup> In both studies women who received 25 to 50 mg DHEA daily experienced a statistically significant increase in sexual function including desire. Yams and the herb sarsaparilla are natural sources of DHEA. DHEA side effects included acne in 9% of the women, facial hair in 8%, weight gain in 4%, breast tenderness in 2% and hair loss in 5%. Ointments include Zestra, which is a topical oil that contains borage seed oil (starflower), evening primrose oil, extract of angelica, extract of coleus, antioxidants-ascorbic palmitate (vitamin C) and alpha-tocopherol (vitamin E). Ferguson et al performed a double-blind, placebo controlled, 2-way crossover study in 10 women with vs 10 without female sexual arousal disorder and Zestra improved desire and satisfaction in both groups.<sup>6</sup>

Dr. Seftel then discussed male sexual dysfunction in the office setting, including low libido-hypoactive sexual desire disorder, hypogonadism, organic and psychogenic erectile dysfunction, ejaculatory dysfunction, male orgasmic disorder and premature ejaculation.

Low libido is not fully synonymous

with hypogonadism. It is a broader term that may encompass hypogonadism among other factors. Low libido may also signal depression as well as relationship issues. Hypogonadism is defined by the Food and Drug Administration (FDA) as a total testosterone of less than 300 ng/dl. It may be suspected in a man with decreased energy, depressed mood, tiredness, loss of muscle mass, erection problems and a lack of stamina.

Erectile dysfunction is characterized by the inability to attain or maintain an erection for satisfactory sexual activity. Ejaculatory dysfunction may be divided into rapid ejaculation or delayed ejaculation, as the 2 most common areas seen clinically. Male orgasmic disorder is usually psychogenic in nature, although it can occur after radical prostatectomy.

Treatment of low libido may require psychological counseling in addition to testosterone replacement therapy, if low testosterone is detected on a blood test. Testosterone therapy is available as a gel, patch or intramuscular injection. A novel 3-month depot injection is not yet available in the United States but has received an approvable letter from the FDA.<sup>7</sup>

Treatment of erectile dysfunction includes oral phosphodiesterase inhibitors, sildenafil, vardenafil and tadalafil. Penile intracavernosal therapy remains a viable option as does the medicated urethral suppository (aprostadil), vacuum erection device therapy and penile prostheses. Treatment of premature ejaculation continues with off-label selective serotonin reuptake inhibitor as monotherapy or combined with counseling. Treatment of delayed ejaculation is still problematic.

Dr. Wei discussed office management of BPH. The Urologic Diseases in America Project indicated that

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**Course 54PG**

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approximately 6.3 million of the 27 million white males in the United States meet BPH diagnostic criteria.<sup>8</sup> BPH was the primary diagnosis for approximately 4.5 million doctor visits. A review of the AUA guidelines provides the paradigm for treatment of men with BPH.<sup>9</sup>

The office evaluation consists of history, physical examination, digital rectal examination, examination of the external genitalia and a focused neurological examination. Laboratory tests might include serum prostate specific antigen, fasting blood glucose, urinalysis and culture if indicated. Optional testing includes urinary flow test, completion of the AUA symptom score and more invasive urodynamics. Upper tract urological imaging studies are performed when indicated. Treatment options are patient specific and include watchful waiting, oral pharmacotherapy, phytotherapy and surgery.

Dr. Kerr, Ms. Morrison and Ms. Dickinson discussed the office elements of evaluation and treatment of bladder disorders. Incontinence in the female is a significant social and

public health problem that is distressing and disabling, affecting social, psychological, occupational, domestic, physical and sexual life. It is the leading cause of long-term care facility placement.

Furthermore a third of men and women 30 to 70 years old believe that urinary incontinence is a part of aging that must be accepted, and two-thirds of this population have never discussed bladder health with their doctor. One in 4 women older than 18 years experiences episodes of involuntary leaking. Only 1 in 8 Americans who have experienced urinary incontinence have been diagnosed, and two-thirds of this population does not use any treatment or product to manage their incontinence.

In 2002 and 2003 the International Continence Society published revised definitions of overactive bladder and other lower urinary tract symptoms. Overactive bladder is defined as “urgency with or without urge incontinence, usually with frequency and nocturia, in the absence of proven infection or other obvious pathology.” Treatment options

include behavioral therapy, biofeedback and pelvic floor exercise; anticholinergics (antimuscarinics); other neuro-regulating molecules; implantable or external stimulators; and botulinum toxin. ♦

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## LATE-BREAKING SCIENTIFIC FORUM

## Safety, Efficacy and Pharmacokinetics of Testosterone Undecanoate Long-Acting Injection in the Treatment of Hypogonadism: Results of a Phase III Clinical Trial

Abraham Morgentaler, Brookline, MA; Ronald S Swerdloff, Torrance, CA; Adrian S Dobs, Baltimore, MD; Joel Kaufman, Aurora, CO; Martin M Miner, Swansea, MA; Ridwan Shabsigh, Brooklyn, NY

**Introduction and Objective:** This study was conducted to assess the efficacy, safety, and pharmacokinetics (PK) of a novel, long-acting, testosterone undecanoate (TU) intramuscular injection administered at base-

line, week 4, and a dosing regimen of every 10 weeks thereafter, for the treatment of primary or secondary hypogonadism. Methods: N=130 males  $\geq$ 18 years of age meeting hypogonadism inclusion criteria (serum T <300

ng/dl) were enrolled in this multicenter, open-label, US-based study. Patients received TU 750 mg in castor oil solution injected at baseline, week 4, and week 14 of the study, and were followed for an additional 10 weeks.

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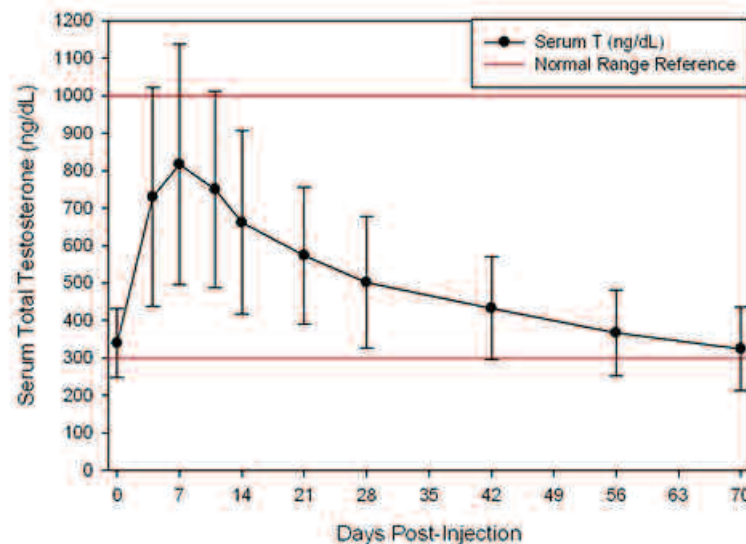
### Late-breaking Scientific Forum

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Serum T concentrations were measured at predetermined intervals during weeks 14-24 to assess PK outcomes. PK parameters included maximum concentration ( $C_{max}$ ), average concentration ( $C_{avg}$ ), and time to maximum concentration ( $T_{max}$ ). Adverse events (AEs), prostate-specific antigen (PSA), digital rectal examination (DRE), and safety laboratory testing were monitored at each injection visit. Results: 117 patients, with a mean age of 54.2 years ( $\pm$  10.3 standard deviation [SD]) were evaluable. Efficacy objectives were achieved, with patients reaching and maintaining eugonadal serum T levels. PK measurements indicated that 94% of subjects sustained  $C_{avg}$  serum T concentrations within the normal serum T range (300 to 1000 ng/dL) with a mean  $C_{avg}$  of 494.9 ng/dL during the 10-week dosing interval (Figure). AEs

judged as at least possibly related were reported in 24% of patients, with the most common AEs being acne and fatigue, each reported in 4.6% of patients. Conclusions: This 24-week study demonstrated that treatment with TU 750 mg injection

every 10 weeks is an effective and well-tolerated method with satisfactory PK, providing long-term, consistent, and reliable T replacement in men with hypogonadism. ♦



Mean serum T levels after 3rd injection of 750 mg TU (weeks 14 - 24)

## ABSTRACT HIGHLIGHTS

### Abstract 1244: Outcomes Analysis of Testosterone Supplementation in Hypogonadal Men Following Radical Prostatectomy

Omar Nabulsi, Raanan Tal, Geoff Gotto, Joseph Narus, Larry Goldenberg, John P Mulhall, Vancouver, BC, Canada and New York, NY

(Reprinted from *J Urol, suppl.*, 2008; 179: 426)

**Introduction and Objective:** The administration of exogenous testosterone (T) to men who have undergone radical prostatectomy (RP) for prostate cancer is highly controversial. Besides case series there are no long-term prospective studies assessing the safety or efficacy of this treatment in this population. Our approach has been to provide this as an option to men after a comprehensive discussion of the data and the

pros and cons of such a strategy. This prospective study was undertaken to define the safety of exogenous T supplementation in men post-RP.

**Methods:** Men with an early morning total T level in the hypogonadal (HG) range ( $<300$  ng/dl) or borderline T levels combined with symptoms of HG or abnormal bone densitometry were considered candidates for T supplementation. All men were started on transdermal T gel at 2.5g/d. Hormone levels were measured 2-4 weeks later. T dose was titrated to

achieve a serum level of 500 50 ng/dl. Patients had serum T and PSA levels checked every 6 months and 3 months respectively.

**Results:** A total of 22 patients have been prescribed T to date. Mean age and pre-RP PSA levels were 61 9 years and 5.9 3.5 ng/dl respectively. Baseline total and free T were 228 94 ng/dl and 51 34 ng/dl respectively. 58% had a Gleason Score (GS) of 6 or less, 32% had GS 7 disease. All but one patient had T2 disease. The mean 2, 5 and 7-year progression free

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**Abstract 1224**

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probabilities (PFP) were 99%, 98% and 97.5%, respectively. 75% of men had a 7-year PFP of 97%. Mean time post-RP before T supplementation was commenced was 26.35 (median 11 months; range 2.5-118) months. Mean transdermal T dose was 4.8.2.5 g/d. Post-treatment total T, free T and estradiol levels were 427.269, 92.108 ng/dl and 92.185, respectively. One

patient required intramuscular T to achieve physiological serum T levels. Mean duration on T supplementation at last follow-up was 24.16 (median 20; range 14-30) months equating to mean duration post-RP of 52.42 months. Only 1/22 (4.5%) patients had a PSA recurrence at 17 months post-RP. He had G8 disease, and was on transdermal T for 12 months at

time of PSA elevation.

**Conclusions:** In this prospective series, when patients are carefully selected (G 7, organ confined disease, at least 2 PSA levels undetectable, 7-year PFP 90%) the administration of exogenous T for the treatment of hypogonadal symptoms appears to be safe at 2 years post-T administration. ♦

## Abstract 1245: Correlation of Simultaneous PSA and Serum Testosterone Levels Among Hypogonadal Men Receiving Testosterone Replacement Therapy and Untreated Eugonadal Men

Ethan D Grober, Dolores J Lamb, Mohit Khara, Lata Murthy, Robert Hamilton, Larry I Lipshultz, Toronto, ON, Canada and Houston, TX

(Reprinted from *J Urol, suppl.*, 2008; 179: 427)

### **Introduction and Objective:**

Despite mounting evidence to contrary, patients and health care providers remain concerned that testosterone replacement therapy (TRT) may unmask sub-clinical prostate cancer. Recognizing that PSA remains the most sensitive screening test for the early detection of prostate cancer, the primary objective of the current study was to correlate and compare simultaneous measures of PSA and serum testosterone between hypogonadal men treated with TRT and untreated eugonadal men.

**Methods:** From 2001 to 2007, the records of our electronic laboratory database were reviewed to identify men who underwent simultaneously measurement of PSA and serum testosterone levels. The data was stratified based on two groups of men: Group 1 consisted of symptomatic hypogonadal men receiving TRT. Group 2 consisted of eugonadal men

evaluated for BPH, reproductive and sexual dysfunction. All laboratory samples were processed and analyzed by a single, experienced institution (Baylor College of Medicine-Laboratory for Male Reproductive Research Testing). Correlations were performed between PSA and total testosterone levels among the two groups of men.

**Results: Group 1: Untreated eugonadal men** (n = 884 patients). Among the eugonadal men, mean PSA and serum testosterone were 1.50 ng/ml (range: 0.1-22.7 ng/ml) and 432 ng/dL (range: 201-4823 ng/dL), respectively. There was no significant correlation between PSA and total serum testosterone levels ( $r = 0.003$ ,  $p = 0.9$ ). **Group 2: Hypogonadal men on TRT** (n = 373 patients and 978 individual samples analyzed). Prior to treatment, mean baseline PSA and total testosterone levels were 1.3 ng/ml and 265 ng/dL, respectively. Among the hypogonadal men treated with TRT, mean PSA and serum testosterone was, 1.51

ng/ml (range: 0.1 -13.7 ng/ml) and 566 ng/dL (range: 102-6855 ng/dL), respectively. There was no significant correlation between PSA and serum testosterone levels ( $r = -0.01$ ,  $p = 0.7$ ). Mean serum testosterone levels were significantly ( $p < 0.001$ ) greater among men treated with TRT (566 ng/dL) compared to the untreated eugonadal men (432 ng/dL). Mean PSA levels did not significantly differ between the two groups.

**Conclusions:** The current study found no meaningful correlation between simultaneous measures of PSA and serum testosterone among large samples of hypogonadal men receiving TRT and untreated eugonadal men. Further studies are indicated to validate the significance of these findings in relation to actual prostate cancer risk. ♦

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## Abstract 1910: Recovery of Spermatogenesis After Exogenous Testosterone Administration

Jesse N Mills, Ethan D Grober, Mohit Khera, David Fenig, Kumaran Sathymoorthy, Larry I Lipshultz, Toronto, ON, Canada and Houston, TX

(Reprinted from *J Urol, suppl.*, 2008; 179: 656)

**Introduction and Objective:** Exogenous testosterone (T) use among men of reproductive years is becoming increasingly common. An estimated 1% of men between the ages of 18 and 45 are on testosterone replacement therapy (TRT). Exogenous administration of T impairs or halts spermatogenesis. The two most common types of T administration in the United States are via injectable and transdermal (TD) gel routes. We investigated the impact of TRT on spermatogenesis and compared the difference in time course of testicular recovery between the two types of TRT.

**Methods:** In this retrospective study, 22 men aged 25 to 54, presented to one physician (LIL) for treatment for male-factor infertility on TRT. The duration of TRT, delivery system used, hormone levels (FSH, LH, T), semen volume and sperm density, and length of time to recov-

ery of sperm to the ejaculate were investigated. All men had azoospermia except one with a sperm density of 3 million/mL. All men were placed on the same regimen of HCG, 3000 units, IM, every other day and were concomitantly placed on an aromatase inhibitor to prevent gynecomastia. Semen and hormone analyses were performed after 4 weeks of treatment and every month thereafter until the semen quality became stable or a pregnancy was achieved.

**Results:** Since 2006, we have treated 22 men with non-obstructive azoospermia with a history of TRT. There were 10 men in the group using injectable T and 12 men in the group using TD T. Out of these 22 men, we have so far restored sperm to the ejaculate in 20. There was no significant difference in ages between the two groups. Men with a history of injectable testosterone administration had a mean recovery time of 3.2 months. Men in the TD group had a mean recovery time of 7.6 months.

This is a statistically significant difference (P value <0.04). No men discontinued therapy due to adverse effects of treatment.

**Conclusions:** TRT use is prevalent in males of reproductive age. Men using injectable TRT recover sperm sooner than men on TD TRT. This may be due to the reasons why these men initially used T. Men in the TD group were prescribed T for idiopathic hypogonadism and likely had impaired spermatogenesis at baseline. Men in the injectable group tended to be self-medicated and predictably had normal physiologic levels of T and normal spermatogenesis prior to treatment. An additional hypothesis is that injectable T causes fluctuating levels of serum T and therefore, at the T nadir, there may be intermittent increased gonadotropin release with some stimulation of spermatogenesis. ♦

