Testosterone Update:

Bridging the Treatment Gaps in the Management of Hypogonadism

Co-Chairpersons

Glenn R. Cunningham, MD
Professor of Medicine and Molecular & Cellular Biology
Baylor College of Medicine
Medical Director, St. Luke's Episcopal Hospital-Baylor College of Medicine Diabetes Program
Houston, Texas

Ridwan Shabsigh, MD
Director, Division of Urology
Maimonides Medical Center
Brooklyn, New York
Professor of Urology
College of Physicians & Surgeons of Columbia University
New York, New York

Faculty

Shalender Bhasin, MD
Professor of Medicine
Chief, Division of Endocrinology, Metabolism and Molecular Medicine
Charles R. Drew University of Medicine and Science
Los Angeles, California

William J. Bremner, MD, PhD
Professor and Chairman
Department of Medicine
University of Washington School of Medicine
Seattle, Washington

Culley C. Carson III, MD
Rhodes Distinguished Professor and Chief of Urology
University of North Carolina at Chapel Hill
Chapel Hill, North Carolina

E. David Crawford, MD
Head, Urologic Oncology
University of Colorado Health Sciences Center
Associate Director
University of Colorado Comprehensive Cancer Center
Aurora, Colorado

Adrian S. Dobs, MD, MHS
Professor of Medicine and Oncology
Johns Hopkins University
Baltimore, Maryland

Andre T. Guay, MD
Director, Center for Sexual Function
Lahey Clinic Northshore
Peabody, Massachusetts
Clinical Assistant Professor of Medicine (Endocrinology)
Harvard Medical School
Boston, Massachusetts

Wayne J.G. Hellstrom, MD
Professor of Urology
Chief, Section of Andrology
Tulane University Medical Center
New Orleans, Louisiana

Joel M. Kaufman, MD
Medical Director
Urology Research Options
Aurora, Colorado

Kevin T. McVary, MD
Professor of Urology
Northwestern University Feinberg School of Medicine
Chicago, Illinois

Abraham Morgentaler, MD
Associate Clinical Professor
Urologic Surgery
Harvard Medical School
Boston, Massachusetts

Ajay Nehra, MD
Professor of Urology
Department of Urology
Mayo Medical School
Mayo Clinic
Rochester, Minnesota

Allen D. Seftel, MD
Professor of Urology and Reproductive Biology
Case Western Reserve University School of Medicine
Cleveland, Ohio

Ronald S. Swerdloff, MD
Associate Chair, Department of Medicine
Chief, Division of Endocrinology
Harbor-UCLA Medical Center
Torrance, California

Christina C. L. Wang, MD
Director, General Clinical Research Center
Harbor-UCLA Medical Center
Torrance, California
Professor of Medicine
UCLA David Geffen School of Medicine
Los Angeles, California

EDITORS' LETTER

Dear Colleague:

Hypogonadism affects several million men in the United States, and its prevalence increases with age. However, hypogonadism is generally underdiagnosed and undertreated, due in part to the paucity of evidence from large, long-term clinical trials to clearly delineate the best course of action. Understanding this situation does not, however, make the optimal treatment of patients with hypogonadism any clearer.

This paper was developed from the proceedings of the Testosterone Update: Collaborative for Improved Clinical Outcomes in Hypogonadism 2007 Distinguished Faculty Meeting held March 10, 2007, in Arlington, Virginia.

The faculty address issues facing physicians who manage hypogonadism, such as the assays used for measuring testosterone levels, and include considerations when evidence is lacking. They also offer suggestions to help physicians make more informed treatment decisions regarding their patients with hypogonadism.

This activity has been approved for 1.5 *AMA PRA Category 1 Credits™*.

We hope that you will find this paper useful for treating male hypogonadism.

Sincerely,

Glenn R. Cunningham, MD
Co-Chairperson
TU Collaborative

Ridwan Shabsigh, MD
Co-Chairperson
TU Collaborative

STATEMENT OF NEED

Hypogonadism affects several million men in the United States, its prevalence increases with age, and it is generally underdiagnosed and undertreated. Symptoms of low testosterone are often subtle and nonspecific. Not only has the definition of low testosterone been debated for years, but to further complicate matters, the measurement of testosterone levels has not been standardized, and a particular assay may be inaccurate. Few large, randomized clinical trials adequately address prostate safety during long-term testosterone therapy. Low testosterone has been associated with diabetes, insulin resistance, metabolic syndrome, and other comorbidities. Despite these controversies and the paucity of conclusive evidence, physicians must still address hypogonadism in their practices. This paper presents background information and current society recommendations to help physicians who treat patients with hypogonadism until definitive conclusions from future studies are available.

OBJECTIVES

After reading this paper, participants will be better able to

- Recognize that hypogonadism is prevalent and undertreated
- Understand the different definitions of hypogonadism and their clinical application
- Detail the issues regarding the measurement of testosterone levels
- Evaluate the evidence relating testosterone therapy and prostate health
- Describe the association of diabetes, insulin resistance, metabolic syndrome, and other comorbidities with low testosterone levels
- Review the advantages of available and investigational formulations of testosterone
- Apply current guidelines for the treatment of hypogonadism

INTRODUCTION

Hypogonadism in adult males is a deficiency in gonadal function that results in low testosterone levels and a variety of symptoms.[1] Declines in testosterone levels are a well-known occurrence in aging males and are associated with a number of common medical conditions, yet the clinical picture of hypogonadism is not well-defined and may be overlooked in the context of other problems. The paucity of large, long-term clinical trials poses challenges for physicians in making informed decisions about the efficacy and safety of lifelong testosterone therapy for their patients. These circumstances have created a treatment gap that may affect many men with hypogonadism.

In the meantime, however, new information is slowly emerging that may improve understanding of this common endocrinopathy. Symptoms of hypogonadism and the role of hypogonadism in many widespread medical conditions are becoming more generally recognized. Additionally, new data about prostate and cardiovascular safety during treatment may increase physicians' confidence in prescribing testosterone replacement therapy. Finally, options for testosterone administration have improved during the last 5 years, offering real choices for patients and physicians. This review provides an updated summary of significant clinical issues related to hypogonadism and testosterone therapy that clinicians might encounter in the primary care or specialist setting.

DEFINITIONS AND DIAGNOSIS OF HYPOGONADISM

The underdiagnosis of hypogonadism persists because several issues affect its definitions and diagnosis. Symptoms of low testosterone are often subtle and nonspecific and may increase so gradually over time that men and their physicians do not recognize them.[1,2] Men may not recognize their symptoms because they consider them to be merely a natural consequence of aging.[1] Potential findings in adult men with hypogonadism include the following[1,2]

- Progressive decrease in muscle mass
- Loss of libido
- Erectile dysfunction
- Oligospermia or azoospermia
- Menopausal-type hot flashes
- Poor ability to concentrate
- Loss in height
- Low bone mineral density
- Loss of body hair
- Decreased energy, motivation, self-confidence
- Sleep disturbance
- Mild anemia
- Increased body fat
- Diminished physical or work performance

Although there is general agreement that hypogonadism is characterized by both specific and nonspecific symptoms, as well as low testosterone levels, there is a lack of awareness about the proper diagnosis of hypogonadism. As a result, large population-based studies have used a variety of criteria to provide estimates of prevalence and incidence of hypogonadism in adult males (Table 1).[3,5] Experts disagree on how to define hypogonadism for clinical and epidemiologic purposes.[4,5] A statistical approach to defining hypogonadism relies on single-value cut-offs of testosterone levels, which may target patients with low testosterone levels but without significant symptomatology.[3,5] In addition, although several screening questionnaires for identifying hypogonadal symptoms have been used in clinical trials, none has proved satisfactory for screening and diagnostic purposes in clinical practice. Epidemiologic investigations that rely on these low sensitivity and specificity symptom questionnaires (resulting from the nonspecific nature of many symptoms of hypogonadism), combined with measurements of testosterone, can also be subject to measurement error. As a result, prevalence results and identification of risk factors for testosterone deficiency may vary significantly.[5]

Uncertainty in diagnosing hypogonadism also results from the variety of laboratory techniques used to measure free and total testosterone (Table 2).[6] Most current automated methods are sufficiently sensitive to be useful in adult males but are relatively inaccurate compared with liquid chromatography-tandem mass spectrometry.[6,7] A significant problem with the multiplicity of assays is that studies using different methods cannot be compared to each other or to clinical practice data. Although recent professional society guidelines recommend establishing a national testing standard for testosterone assays, physicians must still rely on local laboratory data to assess and compare patients in their own practices.[6]

Reference values for identifying low testosterone levels vary considerably among laboratories, even among laboratories using the same commercially available assay kits. Additionally, adjustments of reference values for age may or may not be used.[8] As a result of assay ambiguities and biological variations, no single level of testosterone separates hypogonadism from eugonadism.

Table 1. Operating Criteria for Hypogonadism in Observational Studies

Symptomatology	Testosterone Measurements
≥3 of 8 symptoms evaluated in the MMAS	TT <200 ng/dL (6.94 nmol/L)[5]
≥3 of 8 symptoms evaluated in the MMAS	TT 200-400 ng/dL (6.94-13.88 nmol/L) and FT <8.91 ng/dL (0.3092 nmol/L)[5]
	TT <11.3 nmol/L (325 ng/dL) or T/SHBG (FT index) <0.153 nmol/nmol[4]

FT=free testosterone; MMAS=Massachusetts Male Aging Study; SHBG=sex hormone-binding globulin; T=testosterone; TT=total testosterone.

Table 2. Testosterone Assays in General Use

Method	Strengths	Shortcomings
A. Methods for Measuring Total Testosterone		
Direct assay by RIA, ELISA, CLIA	Simple, rapid, and inexpensive High throughput and fast turnaround Can be automated	T concentration varies depending upon the assay, T can be overestimated Not standardized: results are method dependent Limited accuracy at T <300 ng/dL Reference intervals in different populations not well documented
RIA after extraction and chromatography	Extensively used, with well documented reference intervals in various populations Large serum samples can be used, increasing sensitivity T released from steroid-binding proteins during extraction	Labor-intensive, cumbersome, time-consuming, and expensive Requires high degree of technical expertise Imprecise; measurements must be corrected for recovery
MS after extraction and liquid or gas chromatography	Highly accurate when properly validated High throughput after extraction and chromatography	Relatively expensive Standardization is lacking but evolving Derivatization can introduce additional error
B. Methods for Measuring Free Testosterone, Unbound Testosterone, or Bio-T in Circulation		
Direct RIA	Simple, rapid, and inexpensive High throughput and fast turnaround Can be automated	T concentration can be overestimated Affected by serum SHBG concentration Not standardized: results are method-dependent Limited accuracy at T <300 ng/dL Reference intervals in different populations not well documented
Physical separation of protein-bound T from FT	Relatively accurate Relatively sensitive and reproducible	Relatively expensive Technically cumbersome and difficult Highly dependent on accuracy of total testosterone assay
Ammonium sulfate precipitation to measure bio-T	Technically simple	Labor intensive Cannot be automated Can be inaccurate
Calculation of free androgen index (T/SHBG)	Simple	Poor correlation with physical separation measures in men Highly dependent on accuracy of total T and SHBG assays
Calculation using algorithms based on law of mass action	Simple Excellent correlation with physical separation measures	Highly dependent on accuracy of total T and SHBG assays Assumptions and reference intervals not standardized Good correlation with equilibrium dialysis and with ammonium sulfate method for measuring bio-T
Calculation using empirical equations	Excellent correlation with physical separation measures Relatively sensitive	Hundreds to thousands of samples are needed to generate equations in individual laboratories Lack of transportability of the equations among laboratories

Bio-T=bioavailable testosterone; CLIA=chemiluminescent immunoassay; ELISA=enzyme-linked immunosorbent assay; FT=free testosterone; MS=mass spectrometry; RIA=radioimmunoassay; SHBG=sex hormone-binding globulin; T=testosterone.

Adapted with permission from Rosner W, Auchus RJ, Azziz R, Sluss PM, Raff H. Position statement: utility, limitations, and pitfalls in measuring testosterone: an Endocrine Society position statement. *J Clin Endocrinol Metab.* 2007;92:405-413.

To counter this uncertainty and correctly diagnose hypogonadism, physicians may want to carefully question patients about symptoms and their effects on daily life.[1] When physicians obtain a comprehensive patient history, they may want to include any history of reduced libido, sexual dysfunction, low-volume ejaculation, or erectile dysfunction, as well as a history of comorbidities and a record of past medications and other remedies.[1] It is beneficial for a physical examination to accompany the patient history, noting body mass index (BMI), waist circumference, amount and distribution of body hair, presence and degree of gynecomastia, and size of the testes and prostate.[1]

Physicians may also want to measure total testosterone (TT), free testosterone (FT), and calculated testosterone levels. Laboratory testing should be based on accurate, precise measurements of a known concentration of testosterone, not solely on agreement with measurements in other laboratories using the same method.[6] More than one serum sample should be obtained between 8:00 and 10:00 AM on different days.[6] Although the lower limit of normal TT remains undefined, TT >320 ng/dL is considered normal, whereas TT <200 ng/dL is generally indicative of hypogonadism.[6] Values between 200 and 320 ng/dL are equivocal and necessitate additional measurements to determine FT and bioavailable testosterone (bio-T).[6] Finally, clinical practice guidelines established by the Endocrine Society recommend confirming diagnosis by repeat measurements.[2]

PROSTATE CANCER RISK AND TESTOSTERONE THERAPY

Current or suspected prostate cancer is a contraindication for testosterone therapy and should be carefully ruled out before initiating therapy. However, there are few large, randomized clinical studies that adequately address prostate safety during long-term testosterone therapy in men who were initially without prostate cancer.[9] This deficiency may lead to uncertainty and reluctance to suggest testosterone therapy for men who are perceived to be at high or moderate risk for prostate cancer. Emerging evidence from observational studies and small clinical trials conducted over the last 5 years suggests that in many men, the risk of prostate cancer may not increase with testosterone therapy. These data may encourage initiation of the large, long-term studies that are needed to provide definitive answers about the relationship between testosterone therapy and prostate cancer risk.

Large-scale epidemiologic data suggest that high levels of circulating endogenous testosterone do not increase prostate cancer risk. In cohorts of more than 200,000 men in Nordic countries, a case-controlled investigation found no consistent pattern of increased prostate cancer risk associated with levels of TT, sex hormone-binding globulin (SHBG), and FT.[10]

In addition, some placebo-controlled, randomized clinical trials of several formulations of testosterone replacement therapy have been carried out for as long as 3 years (Table 3).[11-15] Overall, the incidence of new prostate cancer in patients who received testosterone in these trials does not indicate an increased risk of prostate cancer compared with the background prevalence. A large placebo-controlled testosterone trial is needed to determine the risk of clinical prostate cancer.

A recent analysis of biopsied prostate tissue in men receiving testosterone therapy for late-onset hypogonadism provides important evidence regarding prostate safety. In a randomized, double-blind, placebo-controlled study, 40 hypogonadal men received intramuscular injections of testosterone enanthate or placebo and had prostate biopsies at baseline and after 6 months of treatment. As levels in serum testosterone increased in the active treatment group, no corresponding increase of testosterone or dihydrotestosterone in prostate tissue was observed after 6 months. In addition, men who received testosterone therapy did not exhibit increases in tissue androgen receptors or in markers of cell proliferation or angiogenesis.[16] Prostate volume, voiding symptoms, and urinary flow rates were not significantly different between groups or from baseline to posttreatment, and no changes in known androgen-regulated genes were observed in the active treatment group compared with the placebo group.[16] Thus, exogenous testosterone that normalizes serum testosterone levels exerted little effect on the prostate gland during the 6-month period of this study.[16]

> "Testosterone therapy for hypogonadism may be safe, even in some patients at increased risk for prostate cancer."

Finally, in small case studies, hypogonadal men have been treated safely with testosterone therapy after curative treatment for prostate cancer. Seven patients who had undergone radical prostatectomy and 31 patients who had undergone brachytherapy received testosterone therapy for up to 12 and 8.5 years, respectively.[17,18] None of these patients developed new prostate cancer or recurrent disease.

In the absence of large, randomized, long-term clinical trials that adequately address prostate safety in men receiving testosterone therapy, these studies suggest that testosterone therapy for hypogonadism may be safe, even in some patients at increased risk for prostate cancer, provided that careful screening and monitoring of prostate health take place. Screening of all prospective recipients of testosterone therapy should include conducting digital rectal examination (DRE) and measuring prostate-specific antigen (PSA). Recommended monitoring includes follow-up every 3 to 4 months during the first year of therapy to assess efficacy and side effects, with adjustment of dose or formulation, as necessary. Afterward, PSA measurements, DRE, and assessment of prostate symptoms should occur every 6 to 12 months during therapy.[1,2] Urologic consultation is recommended under the following conditions: serum or plasma PSA >4.0 ng/mL, an increase in serum or plasma PSA >1.4 ng/mL within any 12-month period during treatment, subsequent PSA velocity >0.4 ng/mL/year, prostatic abnormality detected by DRE, or an American Urological Association (AUA) prostate symptom score >19.[1,2]

Table 3. Prostate Cancer Incidence in Testosterone Therapy Studies (Controlled)

Study Authors	Duration (months)	Patients Receiving T (n)	Age* (years)	PCa Cases (n)	Route of Administration
Kenny et al. (2001)[11]	12	24	76	0	Patch
Wang et al. (2000)[12]	6	227	19-68	1	Gel, Patch
Snyder et al. (1999)[13]	36	54	73	1	Patch
Dobs et al. (1999)[14]	6	66	44	3	Gel, IM (T enanthate)
Sih et al. (1997)[15]	12	17	66	0	IM (T cypionate)

*Mean or range.
PCa=prostate cancer; T=testosterone.

LOW TESTOSTERONE IN CHRONIC CONDITIONS

Recent observational studies indicate a strong association between hypogonadism, diabetes, and metabolic syndrome. However, the role of low testosterone in the cause or pathophysiology of these conditions is unknown, and large clinical trials have not been conducted to assess the potential benefits and risks associated with normalizing testosterone in hypogonadal men with these conditions.

Diabetes. Hypogonadal levels of FT and TT have been associated with diabetes in several types of clinical investigations.[19] The Third National Health and Nutrition Examination Survey (NHANES III) evaluated the prevalence of diabetes in 1,413 men with normal TT levels, including 101 men with diabetes. When estimated FT and bio-T levels were measured, diabetes was 4 times more prevalent in men in the lowest tertiles of estimated FT level and bio-T level than in the highest tertiles, even after adjusting for abnormal levels of low TT and known confounding factors, such as race/ethnicity and adiposity.[20] These observations suggest that low androgen levels may be a risk factor for development of diabetes in men.[20]

In a cross-sectional cohort study of elderly men (aged 50-86 years), diabetes was significantly more prevalent in men with TT levels below 10 nmol/L than in men with higher testosterone levels. This relationship was similar in the overall population and in nonobese men.[21]

Recent studies suggest some mechanisms responsible for the association between diabetes and low testosterone. In an evaluation of the hypothalamic-pituitary-gonadal axis in men with a spectrum of insulin sensitivity, insulin resistance was associated with a decrease in testosterone secretion by Leydig cells, as assessed by responsiveness to stimulation with human chorionic gonadotropin.[22] In contrast, no defect in pituitary or hypothalamus function was observed in men with low testosterone.[22] In another study, impaired mitochondrial function was observed in men with insulin resistance and low testosterone, suggesting a mechanism for the relationship between diabetes and low testosterone.[23]

The link between low testosterone levels and insulin resistance suggests that testosterone therapy may reduce insulin resistance in men with hypogonadism and diabetes. Recently, a small prospective study showed that men with hypogonadism and diabetes who were treated with testosterone experienced decreased insulin resistance and improved glycemic control.[24] Again, large prospective studies are needed to confirm these results and address safety concerns in this population.

Metabolic syndrome. Consistent with the observed correlations between insulin resistance and low testosterone, several studies have shown increased development of metabolic syndrome in men with hypogonadism. In the Massachusetts Male Aging Study (MMAS) cohort of 1,709 men, lower levels of TT and SHBG, as well as symptomatic testosterone deficiency, were predictive of metabolic syndrome, especially in nonobese men.[25] Similarly, significantly higher rates of metabolic syndrome were found in a cohort of men who were hypogonadal due to androgen-deprivation therapy for prostate cancer compared with age- and disease-matched eugonadal cohorts. Abdominal obesity and hyperglycemia were the greatest determinants of metabolic syndrome in men receiving androgen-deprivation therapy.[26,27]

Furthermore, a recent comprehensive review of clinical literature related to hypogonadism and metabolic syndrome suggests that hypogonadism is strongly associated with the presence and development of metabolic syndrome.[28] In fact, this study postulates that in time, the definition of metabolic syndrome may include hypogonadism as a diagnostic parameter.[28] The shared biochemical abnormalities and increased cardiovascular risk of both hypogonadism and metabolic syndrome suggest fundamental interrelationships among testosterone, adiposity, dyslipidemia, insulin resistance, and vascular disease in men.[29] These data indicate that hypogonadism may be an early warning sign of cardiovascular disease in men who would otherwise be considered at low risk for cardiovascular disease.[25,28]

Cardiovascular issues. Given the cardiovascular risk associated with hypogonadism, metabolic syndrome, and diabetes, the cardiovascular consequences of testosterone therapy are a subject of interest. Systematic reviews and meta-analyses to assess cardiovascular risk during testosterone therapy have suggested that cardiovascular effects of testosterone therapy are neutral to beneficial in men with hypogonadism.[30-33] Furthermore, there is no contraindication for testosterone therapy in men with hypogonadism and cardiovascular risk factors or overt cardiovascular disease.[30,34] Large clinical trials are needed to provide better information regarding cardiovascular risk during long-term testosterone therapy.

Given these interrelationships among hypogonadism, diabetes, metabolic syndrome, and cardiovascular disease, physicians should evaluate patients with metabolic syndrome or frank diabetes for hypogonadism. Conversely, physicians should evaluate patients with hypogonadism for signs of metabolic syndrome and diabetes.[28] Testosterone therapy aimed at restoring physiologic levels of testosterone in men with hypogonadism may contribute to a decreased risk of metabolic syndrome and cardiovascular disease.[29]

TESTOSTERONE FORMULATIONS

Several new formulations of testosterone therapy have become available in the past decade, providing a significant range of choices for patients and physicians. An ideal formulation would restore physiologic levels of testosterone for men with hypogonadism and have a favorable safety profile. In addition, a convenient dosing schedule and method of administration are important to maximize patient satisfaction and compliance with therapy.

Currently available testosterone preparations for adult male patients include the following[1]

- Oral agents
- Transdermal patches
- Transdermal gels
- Buccal mucosal tablets
- Implantable pellets
- Short-acting intramuscular preparations
- Long-acting intramuscular preparations

The choice of formulation for each patient depends on characteristics of efficacy (eg, restoration of serum testosterone to target physiologic levels), safety relative to the patient's medical profile, tolerability of the method of administration, cost and insurance coverage, and convenience for the patient's daily life.

Oral agents. Oral formulations of testosterone are not approved in the United States. Compounded oral methyltestosterone formulations are not recommended because of significant hepatotoxicity associated with their use. Capsules containing testosterone undecanoate in oil are available in Canada and Europe. The capsules must be taken 2 or 3 times per day, and serum testosterone levels are maintained in the target range for only part of the day.

Transdermal patches. The transdermal patch is applied daily and delivers 2.5 to 5.0 mg testosterone over 24 hours. Serum testosterone levels mimic normal circadian patterns when the patch is applied at night. Patches may produce itching and irritation at the application site.[35]

Transdermal gels. Transdermal gels deliver 5 to 10 mg of testosterone continuously over 24 hours. Caution must be used to avoid transferring testosterone to others via skin-to-skin contact. Application-site reactions are rare.[36,37]

Buccal mucosal tablets. An adhesive tablet is applied to gum tissue above the incisors twice daily and provides continuous systemic delivery of testosterone. Gum or mouth irritation and taste perversion were reported at low rates in clinical trials.[38]

Implantable pellets. Implantable testosterone pellets may be given in doses of 100 to 600 mg for men with hypogonadism. Implantation of 4 or 5 pellets under the skin approximately every 4 to 5 months, using local anesthesia, is typical. Extrusion of pellets may occur.[39]

Short-acting intramuscular injections. Either testosterone enanthate or testosterone cypionate is administered by deep intramuscular injection. The suggested dose is 50 to 400 mg every 2 to 4 weeks.[40] Serum testosterone may fluctuate from supraphysiologic levels immediately after the injection to below-normal levels before the next injection, causing ups and downs in vigor, mood, and sexual activity.[41]

Long-acting intramuscular injections. A formulation of testosterone undecanoate in castor oil, which is currently under clinical investigation in the United States and available in other countries, requires deep intramuscular injections of 1,000 mg every 10 to 14 weeks (after a loading dose at 6 weeks), maintaining serum testosterone within the normal range with only 4 injections per year.[41,42]

CONCLUSIONS

The clinical management of hypogonadism is evolving because of recent developments in diagnosis and testosterone therapy. Eventual standardization of diagnostic procedures, as well as emerging information concerning potential risks and benefits of testosterone therapy, should increase confidence for use of testosterone therapy. Additionally, the availability of several new testosterone formulations offers choices for patients and physicians that will optimize efficacy, safety, and tolerability of therapy.

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TU TestosteroneUpdate
Collaborative for Improved Clinical Outcomes in Hypogonadism
www.TestosteroneUpdate.org

TU c/o CogniMed Inc.
70 South Orange Avenue - Suite 200
Livingston, NJ 07039-4911

Intended Audience

This activity was developed for endocrinologists, urologists, and other clinicians who manage hypogonadism.

Accreditation and Certification

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the Annenberg Center for Health Sciences at Eisenhower and CogniMed Inc. The Annenberg Center is accredited by the ACCME to provide continuing medical education for physicians.

The Annenberg Center designates this educational activity for a maximum of 1.5 *AMA PRA Category 1 Credits*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

AAPA accepts Category 1 CME credit for the PRA from organizations accredited by ACCME.

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A maximum of 1.5 contact hours may be earned for successful completion of this activity.

Provider is approved by the California Board of Registered Nursing, Provider #13664, for 1.5 contact hours.

Course meets the qualifications for 1.5 hours of continuing education credit for MFTs and/or LCSWs as required by the California Board of Behavioral Sciences. Provider #PCE2048.

This program is co-sponsored by the Annenberg Center for Health Sciences at Eisenhower and CogniMed Inc. The Annenberg Center is approved by the American Psychological Association to sponsor continuing education for psychologists. The Annenberg Center maintains responsibility for this program and its content. This activity is approved for 1.5 hours of credit.

There is no charge for this activity. Statements of Credit will be provided by mail following activity participation and upon completion and return of the evaluation form to *TestosteroneUpdate*, c/o CogniMed Inc., 70 South Orange Avenue, Suite 200, Livingston, NJ 07039, or by fax to 877-403-5765. Please allow 4 to 6 weeks for the delivery of your statement.

This activity consists of a treatment gaps paper. Successful completion is achieved by reading the material, reflecting on its implications in your practice, and completing the assessment component or posttest.

The estimated time to complete the activity is 1.5 hours.

This activity was originally released July 30, 2007, and is eligible for credit through July 20, 2008.

This activity is supported by an independent educational grant from Indevus Pharmaceuticals, Inc.

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It is the policy of the Annenberg Center to ensure fair balance, independence, objectivity, and scientific rigor in all programming. All faculty and planners participating in sponsored programs are expected to identify and reference off-label product use and disclose any significant relationship with those supporting the activity or any others whose products or services are discussed.

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Glenn R. Cunningham, MD, reports that he has received speakers bureau honoraria from Merck & Co., Inc.; Novartis Pharmaceuticals Corporation; Pfizer Inc; and Solvay S.A.; consultant honoraria from Indevus Pharmaceuticals, Inc., and Solvay S.A.; advisor honoraria from Columbia Laboratories, Inc., and Indevus Pharmaceuticals, Inc.; and investigator grants from Ardana Bioscience; Ascend Therapeutics, Inc.; Columbia Laboratories, Inc.; Sanofi-Aventis; and Solvay S.A.

Dr. Cunningham has no identified conflicts of interest.

Ridwan Shabsigh, MD, reports that he has received speakers bureau honoraria from Lilly ICOS LLC, Pfizer Inc, and Solvay S.A., and consultant honoraria from American Medical Systems; Bayer Pharmaceuticals Corp.; GlaxoSmithKline; Indevus Pharmaceuticals, Inc.; Johnson & Johnson; Lilly ICOS LLC; and Schering-Plough Corporation.

Dr. Shabsigh has no identified conflicts of interest.

The faculty for this activity have disclosed that there will be discussion about the use of products for non-FDA approved indications.