THIS YEAR IN: GONADS

Conflitti di interesse

Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiaro che negli ultimi 2 anni ho avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

This year in … Male Gonads 2018

Roma, 8-11 novembre 2018

ITALIAN CHAPTER

Sono quasi le sette di sera e vorrei tanto andare a prepararmi per il party di questa sera e non ho alcuna voglia di sentire Francesco Romanelli, per fortuna c'è Maurizio Merico che mi darà aggiornamenti importanti di andrologia nel 2018…..

CLINICAL PRACTICE GUIDELINE

Testosterone Therapy in Men With Hypogonadism: An Endocrine Society* Clinical Practice Guideline

Shalender Bhasin,[1] Juan P. Brito,[2] Glenn R. Cunningham,[3] Frances J. Hayes,[4] Howard N. Hodis,[5] Alvin M. Matsumoto,[6] Peter J. Snyder,[7] Ronald S. Swerdloff,[8] Frederick C. Wu,[9] and Maria A. Yialamas[10]

[1]Brigham and Women's Hospital, Boston, Massachusetts 02115; [2]Mayo Clinic, Rochester, Minnesota 55905; [3]Baylor College of Medicine, Houston, Texas 77030; [4]Massachusetts General Hospital, Boston, Massachusetts 02114; [5]Keck School of Medicine, University of Southern California, Los Angeles, California 90033; [6]Veterans Affairs Puget Sound Health Care System, Seattle, Washington 98108; [7]Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania 19104; [8]Harbor–UCLA Medical Center, Torrance, California 90502; [9]University of Manchester, Manchester M13 9PL, United Kingdom; and [10]Brigham and Women's Hospital, Boston, Massachusetts 02115

*Cosponsoring Organizations: European Society of Endocrinology.

*Endorsing Organizations: European Academy of Andrology.

Evaluation and Management of Testosterone Deficiency: AUA Guideline

John P. Mulhall, Landon W. Trost, Robert E. Brannigan, Emily G. Kurtz, J. Bruce Redmon, Kelly A. Chiles, Deborah J. Lightner, Martin M. Miner, M. Hassan Murad, Christian J. Nelson, Elizabeth A. Platz, Lakshmi V. Ramanathan and Ronald W. Lewis

From the American Urological Association Education and Research, Inc., Linthicum, Maryland

Purpose: There has been a marked increase in testosterone prescriptions in the past decade resulting in a growing need to give practicing clinicians proper guidance on the evaluation and management of the testosterone deficient patient.

Materials and Methods: A systematic review utilized research from the Mayo Clinic Evidence Based Practice Center and additional supplementation by the authors. Evidence-based statements were based on body of evidence strength Grade A, B, or C and were designated as Strong, Moderate, and Conditional Recommendations with additional statements presented in the form of Clinical Principles or Expert Opinions (table 1 in supplementary unabridged guideline, http://jurology.com/).

Results: This guideline was developed by a multi-disciplinary panel to inform clinicians on the proper assessment of patients with testosterone deficiency and the safe and effective management of men on testosterone therapy. Additional statements were developed to guide the clinician on the appropriate care of patients who are at risk for or have cardiovascular disease or prostate cancer as well as patients who are interested in preserving fertility.

Conclusion: The care of testosterone deficient patients should focus on accurate assessment of total testosterone levels, symptoms, and signs as well as proper on-treatment monitoring to ensure therapeutic testosterone levels are reached and symptoms are ameliorated. Future longitudinal observational studies and clinical trials of significant duration in this space will improve diagnostic techniques and treatment of men with testosterone deficiency as well as provide more data on the adverse events that may be associated with testosterone therapy.

Abbreviations and Acronyms

AUA = American Urological Association
ASCVD = atherosclerotic cardiovascular disease
FDA = U.S. Food and Drug Administration
LH = luteinizing hormone
Hct = hematocrit
hCG = human chorionic gonadotropin
MACE = major adverse cardiac event
RT = radiation therapy
RCTs = randomized controlled trials
VTE = venous thromboembolic event

Accepted for publication March 22, 2018.

The complete unabridged version of the guideline is available at http://jurology.com/. This document is being printed as submitted

BSSM guidelines on testosterone deficiency: a summary

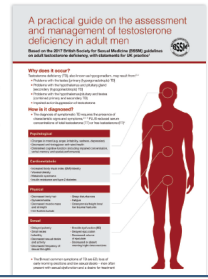
Geoff Hackett, Consultant in Urology and Andrology, Good Hope Hospital, Sutton Coldfield, Birmingham; Mike Kirby, GP and Visiting Professor, University of Hertfordshire and the Prostate Centre, London

The British Society for Sexual Medicine (BSSM) 2018 guideline on adult testosterone deficiency was developed to help address the widespread media and scientific concerns over the appropriate treatment of testosterone deficiency with testosterone therapy. In this article the authors provide an overview of the guideline.

The British Society for Sexual Medicine (BSSM) 2018 guideline (available to download from the BSSM website; Figure 1) on the management of adult testosterone deficiency is based on evidence gathered and graded between 2005–2017.[1]

Epidemiology of TD

There is wide variation in the estimated prevalence of TD. The European Male Aging study evaluated more than 3000 men between 40–79 years of age according to biochemistry and symptoms, defining the syndrome of TD as the presence of three or more sexual symptoms associated with a total testosterone (TT) level less than 11 nmol/L, and a free testosterone (FT) level less than 0.22 nmol/L. There was an overall prevalence of 2.1% in men aged 40–79 years and rates increased from 0.1% in men in their 40s, to 0.6% in men in their 50s, to 3.2% in men in their 60s and to 5.1% in men in their 70s.[2] The prevalence of primary TD was 2%, secondary TD 11.8%, and compensated/subclinical TD (worthy of observation but not treatment with testosterone) 9.5%.[3]



J Clin Endocrinol Metab, May 2018, 103(5):1–30

Testosterone Therapy in Men With Hypogonadism: An Endocrine Society* Clinical Practice Guideline

Shalender Bhasin,[1] Juan P. Brito,[2] Glenn R. Cunningham,[3] Frances J. Hayes,[4] Howard N. Hodis,[5] Alvin M. Matsumoto,[6] Peter J. Snyder,[7] Ronald S. Swerdloff,[8] Frederick C. Wu,[9] and Maria A. Yialamas[10]

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*Cosponsoring Organizations: European Society of Endocrinology.

*Endorsing Organizations: European Academy of Andrology.

Diagnosis of men with suspected hypogonadism

1.1 We recommend diagnosing hypogonadism in men with symptoms and signs of testosterone deficiency and unequivocally and consistently low serum total testosterone and/or free testosterone concentrations (when indicated). (1|⊕⊕⊕O)

Screening and case detection for hypogonadism

1.2 We recommend against routine screening of men in the general population for hypogonadism. (1|⊕⊕OO)

Distinguishing between primary or secondary hypogonadism

1.3 In men who have hypogonadism, we recommend distinguishing between primary (testicular) and secondary (pituitary–hypothalamic) hypogonadism by measuring serum luteinizing hormone and follicle-stimulating hormone concentrations. (1|⊕⊕⊕O)

Evaluation for determining the etiology of hypogonadism

1.4 In men with hypogonadism, we suggest further evaluation to identify the etiology of hypothalamic, pituitary, and/or testicular dysfunction. (2|⊕⊕OO)

Table 1. Classification of Hypogonadism and Causes of Primary and Secondary Hypogonadism

Primary Hypogonadism	Secondary Hypogonadism
ORGANIC	
KS	Hypothalamic/pituitary tumor
Cryptorchidism, myotonic dystrophy, anorchia	Iron overload syndromes
Some types of cancer chemotherapy, testicular irradiation/damage, orchidectomy	Infiltrative/destructive disease of hypothalamus/pituitary
Orchitis	Idiopathic hypogonadotropic hypogonadism
Testicular trauma, torsion	
Advanced age	

Table 1. Classification of Hypogonadism and Causes of Primary and Secondary Hypogonadism

FUNCTIONAL

Medications (androgen synthesis inhibitors)
End-stage renal disease[a]

Hyperprolactinemia
Opioids, anabolic steroid use, glucocorticoids
Alcohol and marijuana abuse[a]
Systemic illness[a]
Nutritional deficiency/excessive exercise
Severe obesity, some sleep disorders
Organ failure (liver, heart, and lung)[a]
Comorbid illness associated with aging[a]

Table 2. Conditions in Which Measurement of FT Concentration Is Recommended

1. Conditions that are associated with decreased SHBG concentrations
Obesity
Diabetes mellitus
Use of glucocorticoids, some progestins, and androgenic steroids
Nephrotic syndrome
Hypothyroidism
Acromegaly
Polymorphisms in the SHBG gene
2. Conditions associated with increased SHBG concentrations
Aging
HIV disease
Cirrhosis and hepatitis
Hyperthyroidism
Use of some anticonvulsants
Use of estrogens
Polymorphisms in the SHBG gene
3. Total testosterone concentrations in the borderline zone around the lower limit of the normal range (*e.g.*, 200-400 ng/dL)

Table 3. Symptoms and Signs Suggestive of T Deficiency in Men

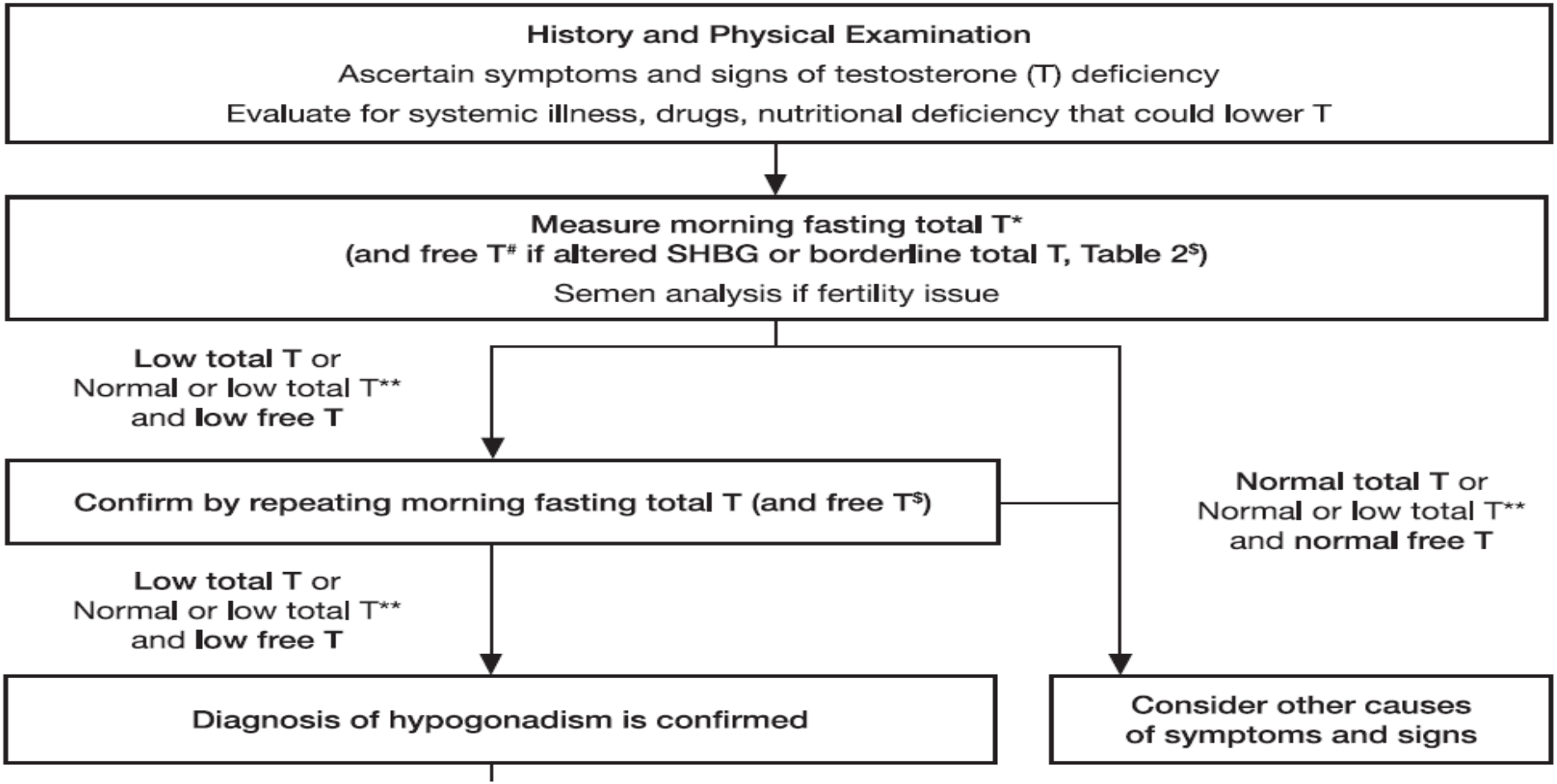
Specific symptoms and signs
Incomplete or delayed sexual development
Loss of body (axillary and pubic) hair
Very small testes (<6 mL)
Suggestive symptoms and signs
Reduced sexual desire (libido) and activity
Decreased spontaneous erections, erectile dysfunction
Breast discomfort, gynecomastia
Eunuchoidal body proportions
Inability to father children, low sperm count
Height loss, low-trauma fracture, low BMD
Hot flushes, sweats

Table 3. Symptoms and Signs Suggestive of T Deficiency in Men

Nonspecific symptoms and signs associated with testosterone deficiency
Decreased energy, motivation, initiative, and self-confidence
Feeling sad or blue, depressed mood, persistent low-grade depressive disorder
Poor concentration and memory
Sleep disturbance, increased sleepiness
Mild unexplained anemia (normochromic, normocytic)
Reduced muscle bulk and strength
Increased body fat, body mass index

Table 4. Conditions in Which There Is a High prevalence of Low T Concentrations and for Which We Suggest Measurement of Serum T Concentrations

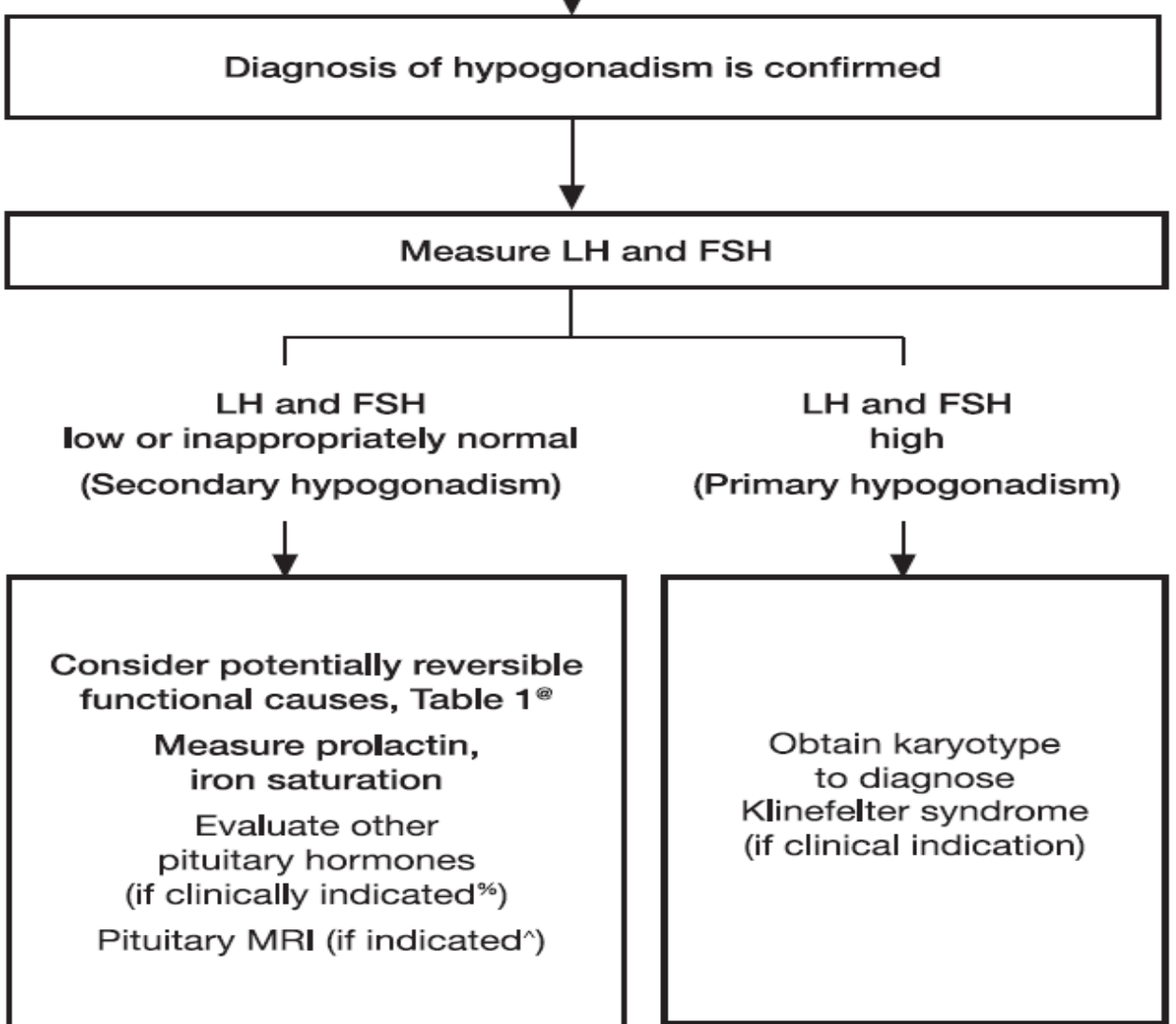
Pituitary mass, radiation to the pituitary region, or other diseases of the sellar region
Treatment with medications that affect T production or metabolism, such as opioids and glucocorticoids
Withdrawal from long-term AAS use
HIV-associated weight loss
Infertility
Osteoporosis or low trauma fracture
Low libido or erectile dysfunction


History and Physical Examination
Ascertain symptoms and signs of testosterone (T) deficiency
Evaluate for systemic illness, drugs, nutritional deficiency that could lower T
Measure morning fasting total T*
(and free T# if altered SHBG or borderline total T, Table 2$)
Semen analysis if fertility issue
Low total T or
Normal or low total T**
and low free T
Confirm by repeating morning fasting total T (and free T$)
Normal total T or
Normal or low total T**
and normal free T
Low total T or
Normal or low total T**
and low free T
Diagnosis of hypogonadism is confirmed
Consider other causes
of symptoms and signs

CDC-standardized measurements (31). The harmonized reference range for TT in healthy, *nonobese* young men (aged 19 to 39 years) was 264 to 916 ng/dL (9.2 to 31.8 nmol/L) using the 2.5th and 97.5th percentile, and 303 to 852 ng/dL (10.5 to 29.5 nmol/L) using the 5th and 95th percentile (31). Clinicians can use this range for all CDC-certified TT assays.

A major difficulty in interpreting FT concentrations is the lack of standardization regarding FT assays, resulting in variability in the lower limit of the reference ranges quoted by different laboratories. Given the uncertainties

Clinicians should also measure FT in men whose serum TT concentration is modestly above or below the lower limit of normal (e.g. 200 to 400 ng/dL)


Diagnosis of hypogonadism is confirmed
Measure LH and FSH
LH and FSH
low or inappropriately normal
(Secondary hypogonadism)
LH and FSH
high
(Primary hypogonadism)
Consider potentially reversible functional causes, Table 1@
Measure prolactin, iron saturation
Evaluate other pituitary hormones (if clinically indicated%)
Pituitary MRI (if indicated^)
Obtain karyotype to diagnose Klinefelter syndrome (if clinical indication)

2.1 We recommend testosterone therapy in hypogonadal men to induce and maintain secondary sex characteristics and correct symptoms of testosterone deficiency. (1|⊕⊕⊕O)

2.2 We recommend against testosterone therapy in men planning fertility in the near term or in men with breast or prostate cancer, a palpable prostate nodule or induration, a prostate-specific antigen level > 4 ng/mL, a prostate-specific antigen level > 3 ng/mL combined with a high risk of prostate cancer (without further urological evaluation), elevated hematocrit, untreated severe obstructive sleep apnea, severe lower urinary tract symptoms, uncontrolled heart failure, myocardial infarction or stroke within the last 6 months, or thrombophilia. (1|⊕⊕OO)

2.3 In hypogonadal men 55 to 69 years old, who are being considered for testosterone therapy and have a life expectancy > 10 years, we suggest discussing the potential benefits and risks of evaluating prostate cancer risk and prostate monitoring and engaging the patient in shared decision making regarding prostate cancer monitoring. For patients who choose monitoring, clinicians should assess prostate cancer risk before starting testosterone treatment and 3 to 12 months after starting testosterone (2|⊕OOO). In hypogonadal men being considered for testosterone therapy who are 40 to 69 years old and at increased risk of prostate cancer (*e.g.*, African Americans and men with a first-degree relative with diagnosed prostate cancer), we suggest discussing prostate cancer risk with the patient and offering monitoring options. (2|⊕OOO)

2.4 We suggest against routinely prescribing testosterone therapy to all men 65 years or older with low testosterone concentrations (1|⊕⊕OO). In men >65 years who have symptoms or conditions suggestive of testosterone deficiency (such as low libido or unexplained anemia) and consistently and unequivocally low morning testosterone concentrations, we suggest that clinicians offer testosterone therapy on an individualized basis after explicit discussion of the potential risks and benefits. (2|⊕⊕OO)

HIV-infected men with weight loss

2.5 We suggest that clinicians consider short-term testosterone therapy in HIV-infected men with low testosterone concentrations and weight loss (when other causes of weight loss have been excluded) to induce and maintain body weight and lean mass gain. (2|⊕⊕OO)

Men with type 2 diabetes mellitus

2.6 In men with type 2 diabetes mellitus who have low testosterone concentrations, we recommend against testosterone therapy as a means of improving glycemic control. (1|⊕⊕OO)

3.1 In hypogonadal men who have started testosterone therapy, we recommend evaluating the patient after treatment initiation to assess whether the patient has responded to treatment, is suffering any adverse effects, and is complying with the treatment regimen. (Ungraded Good Practice Statement)

3.2 We recommend a urological consultation for hypogonadal men receiving testosterone treatment if during the first 12 months of testosterone treatment there is a confirmed increase in prostate-specific antigen concentration > 1.4 ng/mL above baseline, a confirmed prostate-specific antigen > 4.0 ng/mL, or a prostatic abnormality detected on digital rectal examination. After 1 year, prostate monitoring should conform to standard guidelines for prostate cancer screening based on the race and age of the patient. (2|⊕⊕OO)

Table 5. Clinical Pharmacology of T Formulations Approved in the United States and Europe

Formulation	Typical Starting Doses	Pharmacokinetic Profile	Advantages	Disadvantages
T enanthate or cypionate	150–200 mg IM every 2 wk or 75–100 mg/wk	After a single IM injection, serum T concentrations rise into the supraphysiological range, then decline gradually into the hypogonadal range by the end of the dosing interval	Relatively inexpensive, if self-administered; flexibility of dosing	Requires IM injection; peaks and valleys in serum T concentrations that may be associated with fluctuations in symptoms
T transdermal gels: 1%, 1.62%, or 2%	50–100 mg of 1% transdermal gel; 20.25–81 mg of 1.62% gel or 40–70 mg of 2% transdermal gel applied to skin; check package insert for application site and instructions	With appropriate dose, restores serum T and E2 concentrations to the physiological male range; less fluctuation of T concentrations than T enanthate or cypionate	Provides flexibility of dosing, ease of application, good skin tolerability; less erythrocytosis than injectable T	Potential of transfer to a female partner or child by direct skin-to-skin contact; T concentrations may be variable from application to application; skin irritation in a small proportion of treated men; moderately high DHT concentrations (of unknown significance)
T Axillary Solution	60 mg of T solution applied in the axillae	Restores serum T and E2 concentrations to the physiological male range	Provides, good skin tolerability	Potential of transfer to a female partner or child by direct skin-to-skin contact; T concentrations may be variable from application to application; skin irritation in a small proportion of treated men; moderately high DHT concentrations (of unknown significance)
Transdermal T patch	One or two patches, designed to nominally deliver 2–4 mg of T during 24 h applied every day on nonpressure areas	Restores serum T, DHT, and E2 concentrations to the physiological male range	Ease of application	Serum T concentrations in some T-deficient men may be in the low-normal range; these men may need applications of two patches daily; skin irritation at the application site occurs frequently in many patients

Formulation	Typical Starting Doses	Pharmacokinetic Profile	Advantages	Disadvantages
Nasal T gel	11 mg two or three times daily	Serum T concentrations are maintained in the normal range in most treated men	Rapid absorption and avoidance of first pass metabolism	Multiple daily intranasal dosing required; local nasal side effects, not appropriate for men with nasal disorders
Buccal, bioadhesive T tablets	30-mg controlled release, bioadhesive tablets twice daily	Restores serum T, DHT, and E2 concentrations to the physiological male range; absorbed from the buccal mucosa	Convenience and discreet	Gum-related adverse events in 16% of treated men
T pellets	Pellets containing 600–1200 mg T implanted SC; the number of pellets and the regimen may vary with formulation	Serum T peaks at 1 month and then is sustained in normal range for 3–6 mo, depending on formulation	Requires infrequent administration	Requires surgical incision for insertions; pellets may extrude spontaneously; rarely, local hematoma and infection may occur
Injectable long-acting T undecanoate in oil	United States regimen: 750 mg IM, followed by 750 mg at 4 wk, and 750 mg every 10 wk	When administered at a dose of 750 mg IM, serum T concentrations are maintained in the normal range in most treated men	Requires infrequent administration	Requires IM injection of a large volume (3 or 4 mL); coughing episode reported immediately after injection in a small number of men

Formulation	Regimen	Pharmacokinetic profile	Advantages	Disadvantages
Oral T undecanoate	40–80 mg oral, two or three times daily with meals	When administered in castor oil, T undecanoate is absorbed hrough the lymphatics, bypassing the portal system; considerable variability in the same individual on different days and among individuals	Convenience of oral administration	Variable clinical responses; administration with fatty meal is required; fat content of meals affects bioavailability; variable serum T concentrations, high DHT:T ratio
T-in-adhesive matrix patch	Two 60-cm^2 patches delivering ~4.8 mg	Restores serum T, DHT, and E2 to the physiological range	Lasts 2 d	Some skin irritation

Table 7. Conditions in Which T Administration Is Associated With a High Risk of Adverse Outcomes and for Which We Recommend Against Using T

Very high risk of serious adverse outcomes
Metastatic prostate cancer
Breast cancer
Moderate to high risk of adverse outcomes
Unevaluated prostate nodule or induration
Unevaluated PSA > 4 ng/mL (>3 ng/mL in individuals at high risk for prostate cancer, such as African Americans or men with first-degree relatives who have prostate cancer)
Hematocrit > 48% (>50% for men living at high altitude)
Severe LUTS associated with benign prostatic hypertrophy as indicated by AUA/IPSS > 19
Uncontrolled or poorly controlled congestive heart failure
Desire for fertility in the near term

Table 8. Potential Adverse Effects of T Replacement

Adverse events for which there is evidence of association with T administration
Erythrocytosis
Acne and oily skin
Detection of subclinical prostate cancer
Growth of metastatic prostate cancer
Reduced sperm production and fertility
Uncommon adverse events for which there is weak evidence of association with T administration
Gynecomastia
Male pattern balding (familial)
Growth of breast cancer
Induction or worsening of obstructive sleep apnea

Formulation-specific adverse effects

Intramuscular injections of T enanthate, cypionate, or undecanoate
- Fluctuation in mood or libido
- Pain at injection site
- Coughing episodes immediately after the intramuscular injection[a]

Transdermal patches
- Frequent skin reactions at application site

Transdermal gels and solutions
- Potential risk for T transfer to partner or another person who is in close contact (need to remind patient to cover application sites with clothing and to wash skin and hands with soap before having skin-to-skin contact with another person)
- Skin irritation and odor at application site
- Stickiness, slow drying, dripping

Buccal T tablets
- Alterations in taste
- Irritation of gums

Pellet implants
- Infection, expulsion of pellet

T nasal gel
- Rhinorrhea, epistaxis, nasal discomfort, nasal congestion, parosmia

Oral tablets (methylT)—not recommended
- Effects on liver and cholesterol[b]

Table 9. Monitoring Men Receiving T Therapy

Explain the potential benefits and risks of monitoring for prostate cancer and engage the patient in shared decision making regarding the prostate monitoring plan.

Evaluate the patient at 3–12 mo after treatment initiation and then annually to assess whether symptoms have responded to treatment and whether the patient is suffering from any adverse effects

Monitor T concentrations 3–6 mo after initiation of T therapy:

Therapy should aim to raise serum T concentrations into the mid-normal range.

- Injectable T enanthate or cypionate: measure serum T concentrations midway between injections. If mid-interval T is >600 ng/dL (24.5 nmol/L) or <350 ng/dL (14.1 nmol/L), adjust dose or frequency.
- Transdermal gels: assess T concentrations 2–8 h following the gel application, after the patient has been on treatment for at least 1 wk; adjust dose to achieve serum T concentrations in the mid-normal range.
- Transdermal patches: assess T concentrations 3–12 h after application; adjust dose to achieve T concentration in the mid-normal range.
- Buccal T bioadhesive tablet: assess concentrations immediately before or after application of fresh system.
- T pellets: measure T concentrations at the end of the dosing interval. Adjust the number of pellets and/or the dosing interval to maintain serum T concentrations in the mid-normal range.
- Oral T undecanoate[a]: monitor serum T concentrations 3–5 h after ingestion with a fat-containing meal.
- Injectable T undecanoate: measure serum T levels at the end of the dosing interval just prior to the next injection and aim to achieve nadir levels in low-mid range.

Table 9. Monitoring Men Receiving T Therapy

Check hematocrit at baseline, 3–6 mo after starting treatment, and then annually. If hematocrit is >54%, stop therapy until hematocrit decreases to a safe level; evaluate the patient for hypoxia and sleep apnea; reinitiate therapy with a reduced dose.
Measure BMD of lumbar spine and/or femoral neck after 1–2 y of T therapy in hypogonadal men with osteoporosis, consistent with regional standard of care.
For men 55–69 years of age and for men 40–69 years of age who are at increased risk for prostate cancer who choose prostate monitoring, perform digital rectal examination and check PSA level before initiating treatment; check PSA and perform digital rectal examination 3–12 mo after initiating T treatment, and then in accordance with guidelines for prostate cancer screening depending on the age and race of the patient.
Obtain urological consultation if there is:
An increase in serum PSA concentration >1.4 ng/mL within 12 mo of initiating T treatment
A confirmed PSA > 4 ng/mL at any time
Detection of a prostatic abnormality on DRE
Substantial worsening of LUTS
Evaluate formulation-specific adverse effects at each visit as per Table 5.

Table 5. Clinical Pharmacology of T Formulations Approved in the United States and Europe

Formulation	Typical Starting Doses	Pharmacokinetic Profile	Advantages	Disadvantages
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T Axillary Solution	60 mg of T solution applied in the axillae	Restores serum T and E2 concentrations to the physiological male range	Provides, good skin tolerability	Potential of transfer to a female partner or child by direct skin-to-skin contact; T concentrations may be variable from application to application; skin irritation in a small proportion of treated men; moderately high DHT concentrations (of unknown significance)
Transdermal T patch	One or two patches, designed to nominally deliver 2–4 mg of T during 24 h applied every day on nonpressure areas	Restores serum T, DHT, and E2 concentrations to the physiological male range	Ease of application	Serum T concentrations in some T-deficient men may be in the low-normal range; these men may need applications of two patches daily; skin irritation at the application site occurs frequently in many patients

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Buccal, bioadhesive T tablets	30-mg controlled release, bioadhesive tablets twice daily	Restores serum T, DHT, and E2 concentrations to the physiological male range; absorbed from the buccal mucosa	Convenience and discreet	Gum-related adverse events in 16% of treated men
T pellets	Pellets containing 600–1200 mg T implanted SC; the number of pellets and the regimen may vary with formulation	Serum T peaks at 1 month and then is sustained in normal range for 3–6 mo, depending on formulation	Requires infrequent administration	Requires surgical incision for insertions; pellets may extrude spontaneously; rarely, local hematoma and infection may occur
Injectable long-acting T undecanoate in oil	United States regimen: 750 mg IM, followed by 750 mg at 4 wk, and 750 mg every 10 wk	When administered at a dose of 750 mg IM, serum T concentrations are maintained in the normal range in most treated men	Requires infrequent administration	Requires IM injection of a large volume (3 or 4 mL); coughing episode reported immediately after injection in a small number of men
Nasal T gel	11 mg two or three times daily	Serum T concentrations are maintained in the normal range in most treated men	Rapid absorption and avoidance of first pass metabolism	Multiple daily intranasal dosing required; local nasal side effects, not appropriate for men with nasal disorders

Table 6. Testosterone Formulations Available Outside the United States, but Not Approved by the FDA

Formulation	Regimen	Pharmacokinetic profile	Advantages	Disadvantages
Oral T undecanoate	40–80 mg oral, two or three times daily with meals	When administered in castor oil, T undecanoate is absorbed hrough the lymphatics, bypassing the portal system; considerable variability in the same individual on different days and among individuals	Convenience of oral administration	Variable clinical responses; administration with fatty meal is required; fat content of meals affects bioavailability; variable serum T concentrations, high DHT:T ratio
T-in-adhesive matrix patch	Two 60-cm^2 patches delivering ~4.8 mg	Restores serum T, DHT, and E2 to the physiological range	Lasts 2 d	Some skin irritation

The Efficacy and Adverse Events of Testosterone Replacement Therapy in Hypogonadal Men: A Systematic Review and Meta-Analysis of Randomized, Placebo-Controlled Trials

Ponce et al

J Clin Endocrinol Metab, May 2018, 103(5):1745–1754

Study Selection: Randomized clinical trials assessing the efficacy and adverse events of TRT of at least 12 weeks compared with placebo in adult men with hypogonadism, defined by morning total testosterone ≤300 ng/dL and at least one symptom or sign of hypogonadism.

Data Extraction: Reviewers working independently and in duplicate assessed the quality of RCTs and collected data on patient characteristics, interventions, and outcomes.

Results: We found four RCTs (including 1779 patients) at low risk of bias. Compared with placebo, TRT was associated with a small but significant increase in sexual desire or libido [standardized mean difference (SMD): 0.17; 95% confidence interval (CI), 0.01, 0.34; n = 1383], erectile function (SMD: 0.16; 95% CI, 0.06, 0.27; n = 1344), and sexual satisfaction (SMD: 0.16; 95% CI, 0.01, 0.31; n = 676) but had no effect on energy or mood. TRT was associated with an increased risk of developing erythrocytosis (relative risk: 8.14; 95% CI, 1.87, 35.40; n = 1579) compared with placebo but had no significant effect on lower urinary tract symptoms.

Conclusion: In hypogonadal men, TRT improves sexual desire, erectile function and sexual satisfaction; however, it increases the risk of erythrocytosis. (*J Clin Endocrinol Metab* 103: 1745–1754, 2018)

Lessons From the Testosterone Trials

Endocrine Reviews, June 2018, 39(3):369–386

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ESSENTIAL POINTS

- Testosterone treatment of 1 year for older men with low testosterone improved all aspects of sexual function
- Testosterone treatment of 1 year for older men with low testosterone improved walking distance by a small amount
- Testosterone treatment of 1 year for older men with low testosterone did not improve vitality but slightly improved mood and depressive symptoms
- Testosterone treatment of 1 year for older men with low testosterone improved hemoglobin and corrected mild to moderate anemia
- Testosterone treatment of 1 year for older men with low testosterone markedly increased the volumetric bone mineral density and estimated bone strength
- Testosterone treatment of 1 year for older men with low testosterone increased the coronary artery plaque volume
- Testosterone treatment of 1 year for older men with low testosterone was not associated with more cardiovascular or prostate adverse events; however, the number of men and the duration of treatment were not sufficient to draw definitive conclusions about the risks of this treatment

Benefits and Health Implications of Testosterone Therapy in Men With Testosterone Deficiency

Abdulmaged M. Traish, PhD, MBA

ABSTRACT

Introduction: Testosterone (T) deficiency (TD; hypogonadism) has deleterious effects on men's health; negatively affects glycometabolic and cardiometabolic functions, body composition, and bone mineral density; contributes to anemia and sexual dysfunction; and lowers quality of life. T therapy (TTh) has been used for the past 8 decades to treat TD, with positive effects on signs and symptoms of TD.

Aim: To summarize the health benefits of TTh in men with TD.

Methods: A comprehensive literature search was carried out using PubMed, articles relevant to TTh were accessed and evaluated, and a comprehensive summary was synthesized.

Main Outcome Measures: Improvements in signs and symptoms of TD reported in observational studies, registries, clinical trials, and meta-analyses were reviewed and summarized.

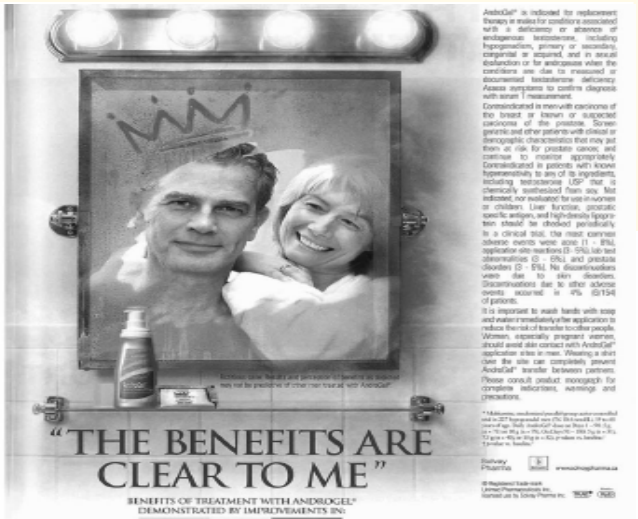
Results: A large body of evidence provides significant valuable information pertaining to the therapeutic value of TTh in men with TD. TTh in men with TD provides real health benefits for bone mineral density, anemia, sexual function, glycometabolic and cardiometabolic function, and improvements in body composition, anthropometric parameters, and quality of life.

Conclusion: TTh in the physiologic range for men with TD is a safe and effective therapeutic modality and imparts great benefits on men's health and quality of life. **Traish AM. Benefits and Health Implications of Testosterone Therapy in Men With Testosterone Deficiency. Sex Med Rev 2018;6:86–105.**

The marketing of testosterone treatments for age-related low testosterone or 'Low T'

Barbara Mintzes **Curr Opin Endocrinol Diabetes Obes** 2018, 25:224–230

- The key focus of marketing of testosterone from the early 2000s to 2018 has been on age-related testosterone loss or 'Low T', an off-label use for which there is limited efficacy evidence.
- Unbranded DTCA for 'Low T' has been a key promotional strategy internationally and has been largely unregulated, as manufacturers do not mention specific brand names in these campaigns.



- Unbranded DTCA was associated with the strongest effects on testing and treatment in a US analysis comparing exposure levels with health insurance claims; overall, per monthly advertising exposure, there was a relative 0.6% increase in testosterone testing, 0.7% increase in treatment initiation, and a 0.8% increase in treatment initiation without prior testing.
- Promotional strategies targeting health professionals have included sponsored CME and ghostwriting that frame 'Low T' as a serious condition requiring treatment.
- In late 2014, the US FDA changed testosterone labeling to emphasize the restriction of the indication to pathological causes, leading all manufacturers to stop testosterone advertising.

Evaluation and Management of Testosterone Deficiency: AUA Guideline

John P. Mulhall, Landon W. Trost, Robert E. Brannigan, Emily G. Kurtz, J. Bruce Redmon, Kelly A. Chiles, Deborah J. Lightner, Martin M. Miner, M. Hassan Murad, Christian J. Nelson, Elizabeth A. Platz, Lakshmi V. Ramanathan and Ronald W. Lewis

From the American Urological Association Education and Research, Inc., Linthicum, Maryland

THE JOURNAL OF UROLOGY®
Vol. 200, 1-10, August 2018

Purpose: There has been a marked increase in testosterone prescriptions in the past decade resulting in a growing need to give practicing clinicians proper guidance on the evaluation and management of the testosterone deficient patient.

Materials and Methods: A systematic review utilized research from the Mayo Clinic Evidence Based Practice Center and additional supplementation by the authors. Evidence-based statements were based on body of evidence strength Grade A, B, or C and were designated as Strong, Moderate, and Conditional Recommendations with additional statements presented in the form of Clinical Principles or Expert Opinions (table 1 in supplementary unabridged guideline, http://jurology.com/).

Results: This guideline was developed by a multi-disciplinary panel to inform clinicians on the proper assessment of patients with testosterone deficiency and the safe and effective management of men on testosterone therapy. Additional statements were developed to guide the clinician on the appropriate care of patients who are at risk for or have cardiovascular disease or prostate cancer as well as patients who are interested in preserving fertility.

Conclusion: The care of testosterone deficient patients should focus on accurate assessment of total testosterone levels, symptoms, and signs as well as proper on-treatment monitoring to ensure therapeutic testosterone levels are reached and symptoms are ameliorated. Future longitudinal observational studies and clinical trials of significant duration in this space will improve diagnostic techniques and treatment of men with testosterone deficiency as well as provide more data on the adverse events that may be associated with testosterone therapy.

Abbreviations and Acronyms

AUA = American Urological Association

ASCVD = atherosclerotic cardiovascular disease

FDA = U.S. Food and Drug Administration

LH = luteinizing hormone

Hct = hematocrit

hCG = human chorionic gonadotropin

MACE = major adverse cardiac event

RT = radiation therapy

RCTs = randomized controlled trials

VTE = venous thromboembolic event

Accepted for publication March 22, 2018.

The complete unabridged version of the guideline is available at http://jurology.com/.

This document is being printed as submitted

THE JOURNAL OF UROLOGY® John P. Mulhall Vol. 200, 1-10, August 2018

Diagnosis of Testosterone Deficiency

1. Clinicians should use a total testosterone level below 300 ng/dL as a reasonable cut-off in support of the diagnosis of low testosterone. (Moderate Recommendation; Evidence Level: Grade B)

2. The diagnosis of low testosterone should be made only after two total testosterone measurements are taken on separate occasions with both conducted in an early morning fashion. (Strong Recommendation; Evidence Level: Grade A)

3. The clinical diagnosis of testosterone deficiency is only made when patients have low total testosterone levels combined with symptoms and/or signs. (Moderate Recommendation; Evidence Level: Grade B)

Testosterone totale (ng/dl)

> 350

230 - 350

< 230

2008 European Academy of Andrology • *International Journal of Andrology* **32,** 1–10

Investigation, treatment and monitoring of late-onset hypogonadism in males C. Wang

4. **Clinicians should consider measuring total testosterone in patients with a history of unexplained anemia, bone density loss, diabetes, exposure to chemotherapy, exposure to testicular radiation, HIV/AIDS, chronic narcotic use, male infertility, pituitary dysfunction, and chronic corticosteroid use even in the absence of symptoms or signs associated with testosterone deficiency. (Moderate Recommendation; Evidence Level: Grade B)**

5. **The use of validated questionnaires is not currently recommended to either define which patients are candidates for testosterone therapy or monitor symptom response in patients on testosterone therapy. (Conditional Recommendation; Evidence Level: Grade C)**

Adjunctive Testing

6. **In patients with low testosterone, clinicians should measure serum luteinizing hormone levels. (Strong Recommendation; Evidence Level: Grade A)**

7. **Serum prolactin levels should be measured in patients with low testosterone levels combined with low or low/normal luteinizing hormone levels. (Strong Recommendation; Evidence Level: Grade A)**

8. **Patients with persistently high prolactin levels of unknown etiology should undergo evaluation for endocrine disorders. (Strong Recommendation; Evidence Level: Grade A)**

9. Serum estradiol should be measured in testosterone deficient patients who present with breast symptoms or gynecomastia prior to the commencement of testosterone therapy. (Expert Opinion)

10. Men with testosterone deficiency who are interested in fertility should have a reproductive health evaluation performed prior to treatment. (Moderate Recommendation; Evidence Level: Grade B)

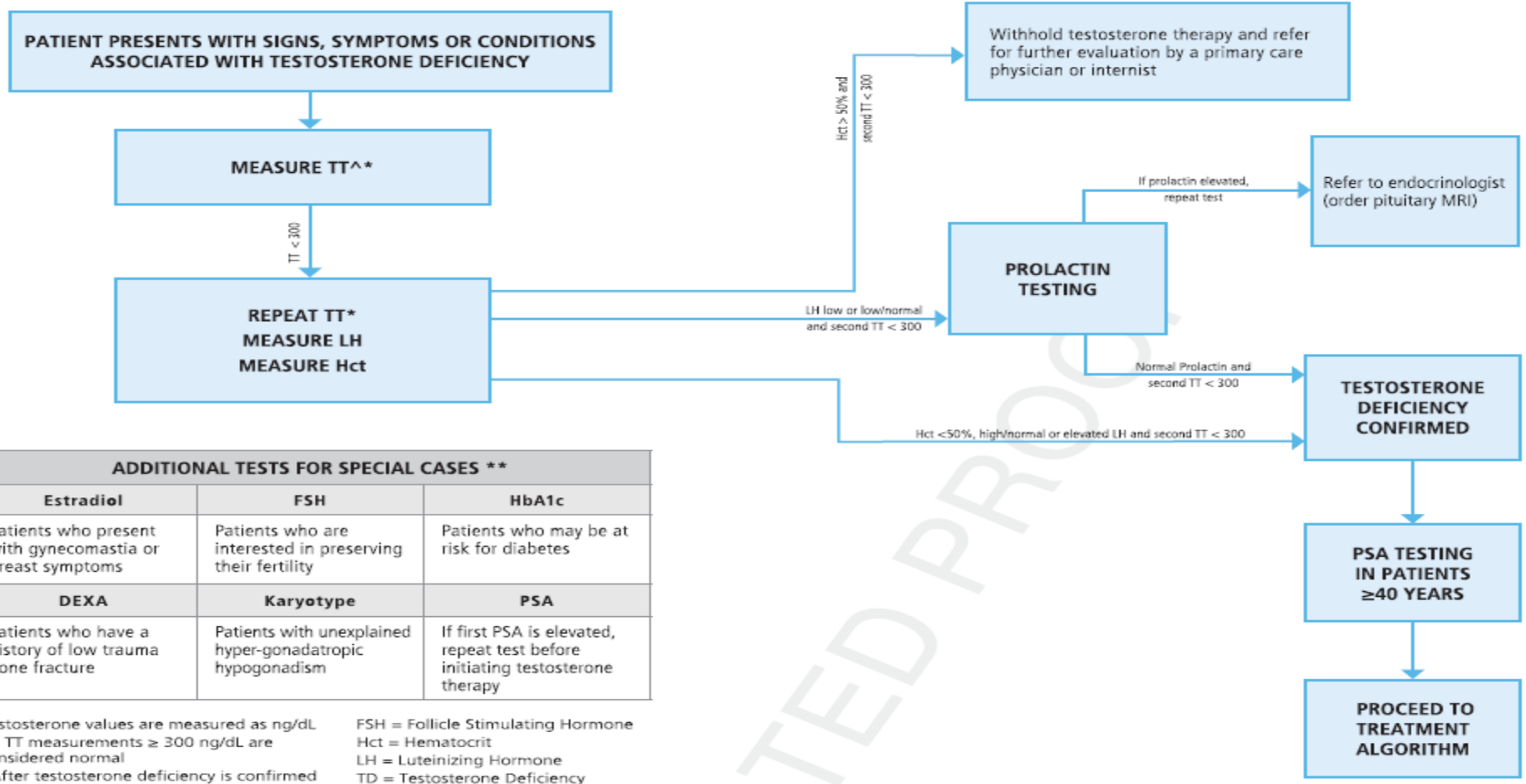
11. Prior to offering testosterone therapy, clinicians should measure hemoglobin and hematocrit and inform patients regarding the increased risk of polycythemia. (Strong Recommendation; Evidence Level: Grade A)

12. **PSA should be measured in men over 40 years of age prior to commencement of testosterone therapy to exclude a prostate cancer diagnosis. (Clinical Principle)**

13. **Clinicians should inform testosterone deficient patients that low testosterone is a risk factor for cardiovascular disease. (Strong Recommendation; Evidence Level: Grade B)**

14. **Patients should be informed that testosterone therapy may result in improvements in erectile function, low sex drive, anemia, bone mineral density, lean body mass, and/or depressive symptoms. (Moderate Recommendation; Evidence Level: Grade B)**

EVALUATION AND MANAGEMENT OF TESTOSTERONE DEFICIENCY: DIAGNOSTIC ALGORITHM



ADDITIONAL TESTS FOR SPECIAL CASES **		
Estradiol	**FSH**	**HbA1c**
Patients who present with gynecomastia or breast symptoms	Patients who are interested in preserving their fertility	Patients who may be at risk for diabetes
DEXA	**Karyotype**	**PSA**
Patients who have a history of low trauma bone fracture	Patients with unexplained hyper-gonadatropic hypogonadism	If first PSA is elevated, repeat test before initiating testosterone therapy

^Testosterone values are measured as ng/dL
*All TT measurements ≥ 300 ng/dL are considered normal
**After testosterone deficiency is confirmed additional tests may be considered for special cases

FSH = Follicle Stimulating Hormone
Hct = Hematocrit
LH = Luteinizing Hormone
TD = Testosterone Deficiency
TT = Total Testosterone

MERICO MAURIZIO

COGNOME E NOME DELL'ASSISTITO *(O INIZIALI OVE PRESCRITTO DALLA LEGGE)*

INDIRIZZO *(OVE PRESCRITTO DALLA LEGGE)*

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PRESCRIZIONE

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Testosterone
Emocromo
SHBG
Prolattina
FSH
PSA
Albuminemia

Sospetto ipogonadismo

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NUMERO CONFEZIONI / PRESTAZIONI

TIPO DI RICETTA

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Prof. Francesco ROMANELLI
Dirigente Medico
Policlinico Umberto I

TIMBRO E FIRMA DEL MEDICO

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NUMERO PROGRESSIVO

IMPORTI

TICKET

GALEN. DIR. CHIAM. ALTRO

I.P.Z.S. - ROMA

fare di più
non significa fare meglio
Choosing Wisely Italy

1. Non richiedere di *routine* l'ecografia tiroidea nei soggetti senza segni e/o sintomi di patologie tiroidee e non appartenenti a gruppi a rischio per carcinoma tiroideo.
2. La ripetizione dell'indagine densitometrica ossea è raramente giustificata a intervalli minori di due anni.
3. Non richiedere il dosaggio del testosterone libero nel sospetto diagnostico di ipogonadismo e di iperandrogenismo.
4. Non richiedere di routine il dosaggio di FT3 nei pazienti con patologia tiroidea.
5. Non trattare con L-tiroxina i pazienti con gozzo nodulare se non in casi selezionati.

15. Patients should be informed that the evidence is inconclusive whether testosterone therapy improves cognitive function, measures of diabetes, energy, fatigue, lipid profiles, and quality of life measures. (Moderate Recommendation; Evidence Level: Grade B)

16. The long-term impact of exogenous testosterone on spermatogenesis should be discussed with patients who are interested in future fertility. (Strong Recommendation; Evidence Level: Grade A)

17. Clinicians should inform patients of the absence of evidence linking testosterone therapy to the development of prostate cancer. (Strong Recommendation; Evidence Level: Grade B)

18. **Patients with testosterone deficiency and a history of prostate cancer should be informed that there is inadequate evidence to quantify the risk-benefit ratio of testosterone therapy. (Expert Opinion)**

19. **Patients should be informed that there is no definitive evidence linking testosterone therapy to a higher incidence of venothrombotic events. (Moderate Recommendation; Evidence Level: Grade C)**

20. **Prior to initiating treatment, clinicians should counsel patients that, at this time, it cannot be stated definitively whether testosterone therapy increases or decreases the risk of cardiovascular events (e.g., myocardial infarction, stroke, cardiovascular-related death, all-cause mortality). (Moderate Recommendation; Evidence Level: Grade B)**

21. All men with testosterone deficiency should be counseled regarding lifestyle modifications as a treatment strategy. (Conditional Recommendation; Evidence Level: Grade B)

22. Clinicians should adjust testosterone therapy dosing to achieve a total testosterone level in the middle tertile of the normal reference range. (Conditional Recommendation; Evidence Level: Grade C)

23. Exogenous testosterone therapy should not be prescribed to men who are currently trying to conceive. (Strong Recommendation; Evidence Level: Grade A)

24. Testosterone therapy should not be commenced for a period of three to six months in patients with a history of cardiovascular events. (Expert Opinion)

25. Clinicians should not prescribe alkylated oral testosterone. (Moderate Recommendation; Evidence Level: Grade B)

26. Clinicians should discuss the risk of transference with patients using testosterone gels/creams. (Strong Recommendation; Evidence Level: Grade A)

27. Clinicians may use aromatase inhibitors, human chorionic gonadotropin, selective estrogen receptor modulators, or a combination thereof in men with testosterone deficiency desiring to maintain fertility. (Conditional Recommendation; Evidence Level: Grade C)

28. Commercially manufactured testosterone products should be prescribed rather than compounded testosterone, when possible. (Conditional Recommendation; Evidence Level: Grade C)

TESTOSTERONE

INIETTIVO

CAPSULE ORALI

CEROTTO SCROTALE TRANSDERMICO

CEROTTO TRANSDERMICO

GEL TRANSDERMICO

IMPIANTO SOTTOCUTANEO

SISTEMA BUCCALE MUCOADESIVO

GEL ASCELLARE

GEL NASALE

Androgen Replacement Therapy
Present and Future

Louis J.G. Gooren and *Mathijs C.M. Bunck*

Drugs 2004; 64 (17): 1861-1891

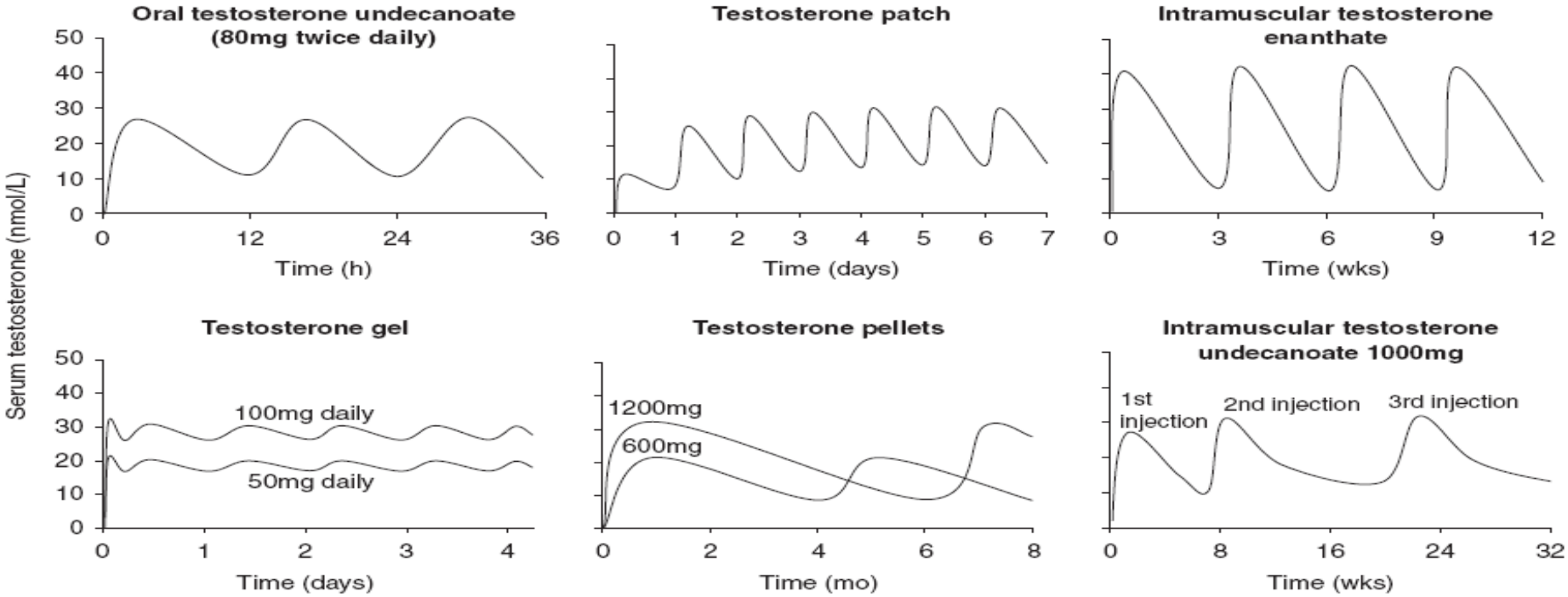


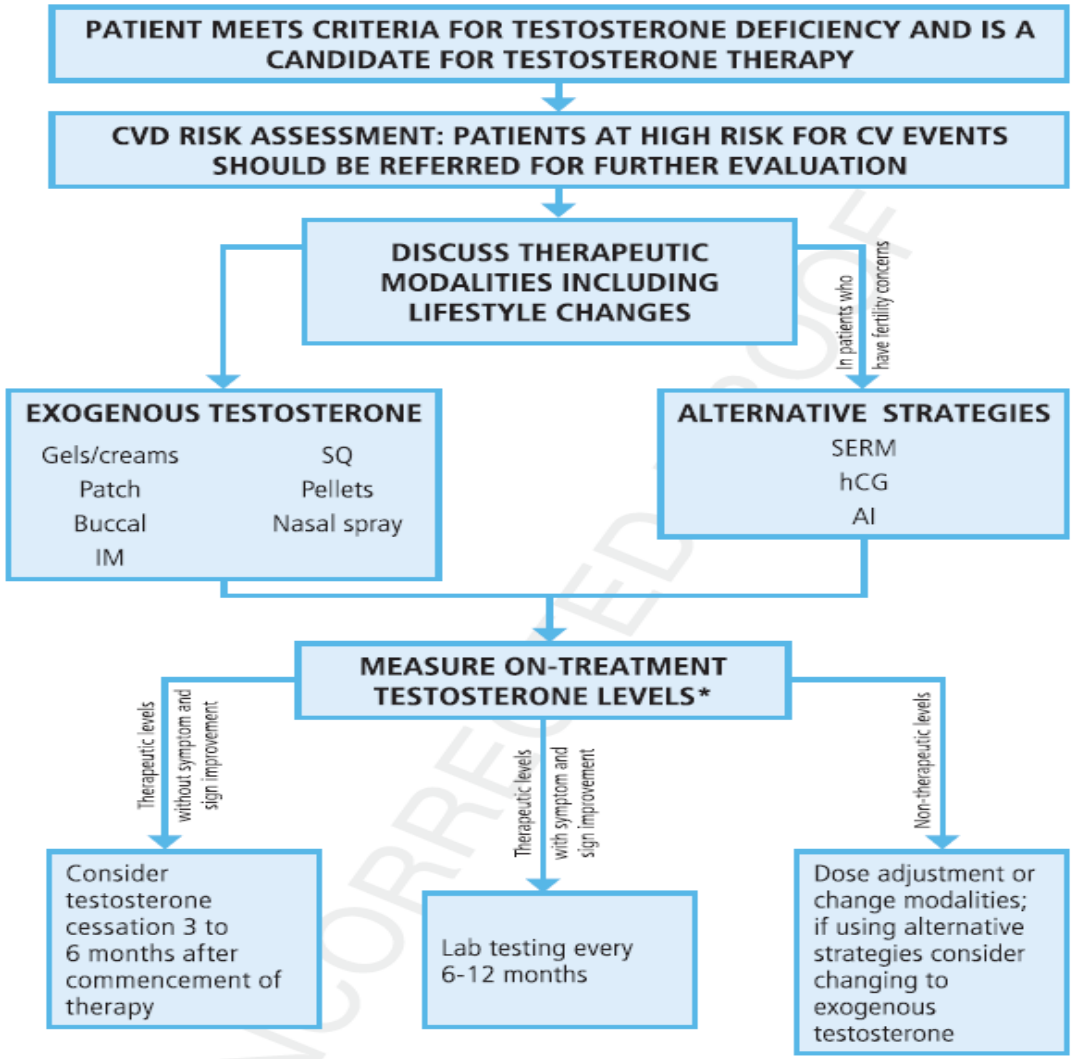
Fig. 1. Serum testosterone levels in different forms of testosterone application (time scales are adjusted per preparation).

Follow-up of Men on Testosterone Therapy

29. **Clinicians should measure an initial follow-up total testosterone level after an appropriate interval to ensure that target testosterone levels have been achieved. (Expert Opinion)**

30. **Testosterone levels should be measured every 6-12 months while on testosterone therapy. (Expert Opinion)**

31. **Clinicians should discuss the cessation of testosterone therapy three to six months after commencement of treatment in patients who experience normalization of total testosterone levels but fail to achieve symptom or sign improvement. (Clinical Principle)**


PATIENT MEETS CRITERIA FOR TESTOSTERONE DEFICIENCY AND IS A CANDIDATE FOR TESTOSTERONE THERAPY
CVD RISK ASSESSMENT: PATIENTS AT HIGH RISK FOR CV EVENTS SHOULD BE REFERRED FOR FURTHER EVALUATION
DISCUSS THERAPEUTIC MODALITIES INCLUDING LIFESTYLE CHANGES
In patients who have fertility concerns
EXOGENOUS TESTOSTERONE
Gels/creams
Patch
Buccal
IM
SQ
Pellets
Nasal spray
ALTERNATIVE STRATEGIES
SERM
hCG
AI
MEASURE ON-TREATMENT TESTOSTERONE LEVELS*
Therapeutic levels without symptom and sign improvement
Therapeutic levels with symptom and sign improvement
Non-therapeutic levels
Consider testosterone cessation 3 to 6 months after commencement of therapy
Lab testing every 6-12 months
Dose adjustment or change modalities; if using alternative strategies consider changing to exogenous testosterone

BSSM guidelines on testosterone deficiency: a summary

Trends in Urology & Men's Health | May/June 2018

Geoff Hackett

Box 3. A summary of BSSM recommendations for the management of testosterone deficiency[1]

Screening for testosterone deficiency (TD)

Screen for TD in:

- All adult men with consistent and multiple signs of TD (LoE 3, Grade C)
- All men presenting with ED, loss of spontaneous erections or low sexual desire (LoE 1, Grade A)
- All men with type 2 diabetes, BMI >30 kg/m^2 or waist circumference > 102 cm (LoE 2, Grade A)
- All men on long-term opiate, antipsychotic or anticonvulsant medication (LoE 2, Grade B)

Diagnosing testosterone deficiency

- Restrict diagnosis to men with persistent symptoms suggesting TD and confirmed low testosterone levels (LoE 3, Grade C)
- Measure fasting testosterone levels before 11am in the morning, remembering that in normal life non-fasting levels may be up to 30% lower (LoE 2, Grade A)
- Repeat total testosterone (TT) assessment on at least two separate occasions with a reliable method, and measure free testosterone (FT) in men with testosterone levels close to the lower normal range (8–12 nmol/L) or those with suspected or known abnormal sex hormone-binding globulin levels (LoE 1, Grade A)
- Measure luteinising hormone (LH) levels to differentiate primary from secondary TD (LoE 2, Grade A)
- Base therapy decisions on published action levels rather than laboratory reference ranges (LoE 4, Grade B)

Initiating testosterone therapy

- Perform cardiovascular, prostate, breast and haematologic assessments prior to starting treatment (LoE 1a, Grade A)
- Offer testosterone therapy to men with symptomatic TD syndrome for treated localised low-risk prostate cancer (Gleason score <8, stages 1–2, pre-operative prostate-specific antigen (PSA) level <10 ng/mL, and not starting before one year of follow-up) and without evidence of active disease (via measurable PSA level, digital rectal examination (DRE) result and evidence of metastatic disease) (LoE 3, Grade B)
- Assess cardiovascular risk factors before starting testosterone therapy and optimise secondary prevention in men with established disease (LoE 1a, Grade A)

The benefits and risks of testosterone therapy

- Beyond six months there is evidence that testosterone therapy benefits body composition, bone mineralisation and features of metabolic syndrome (LoE 3, Grade A)

BSSM guidelines on testosterone deficiency: a summary

Trends in Urology & Men's Health | May/June 2018

Geoff Hackett

Box 3. A summary of BSSM recommendations for the management of testosterone deficiency (cont.)[1]

- Testosterone therapy improves sexual desire, erectile function and sexual satisfaction (LoE 1, Grade A)
- Reduced BMI and waist circumference, and improved glycaemic control and lipid profile, are observed in hypogonadal men receiving testosterone therapy (LoE 2, Grade A)
- Trials of testosterone therapy should last at least six months and maximal benefit is often seen beyond 12 months (LoE 2, Grade A)
- The patient should be fully informed about the expected benefits and side-effects of therapy to facilitate a joint decision by an informed patient and physician (LoE 3, Grade A)
- Fully discuss the adverse effects of testosterone therapy and reversibility on future fertility with each patient and his partner, and offer alternative treatment as necessary (LoE 1b, Grade B)
- When prescribing testosterone therapy to men with adult-onset TD, offer weight loss and lifestyle advice as standard management (LoE 2, Grade A)
- In severely symptomatic patients with TT levels <8 nmol/L, lifestyle and dietary advice alone is unlikely to produce meaningful clinical improvement within a relevant clinical period (LoE = 2, Grade B)

Follow-up

- Assess the response to therapy at three, six and 12 months, and every 12 months thereafter (LoE 4, Grade C)
- Aim for a target TT level of 15–30 nmol/L to achieve an optimal response (LoE 4, Grade C)
- Monitor haematocrit before starting treatment, at three to six months, 12 months, and every 12 months thereafter. Decrease the dose or switch the preparation if haematocrit is >0.54. If haematocrit remains high, consider stopping and reintroduce at a lower dose (LoE 4, Grade C)
- Assess prostate health via PSA and DRE before starting testosterone therapy, followed by PSA at three to six months, 12 months, and every 12 months thereafter (LoE 4, Grade C)
- Assess cardiovascular risk before starting testosterone therapy and monitor cardiovascular risk factors throughout therapy (LoE 1b, Grade A)

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THE JOURNAL OF SEXUAL MEDICINE

J Sex Med 2018;■:1–9

ORIGINAL RESEARCH

Summative Usability Evaluation of the SCTE-AI Device: A Novel Prefilled Autoinjector for Subcutaneous Testosterone Administration

Samir Arora, MD,[1] Betsy Moclair, RN, CRCC,[2] Kyle Murphy,[1] Jonathan S. Jaffe, MD,[3] and Jed C. Kaminetsky, MD[2]

ABSTRACT

Background: The subcutaneous testosterone enanthate (TE) autoinjector (SCTE-AI) is a single-use, pre-filled, disposable autoinjector intended for testosterone (T) self-administration in adult males with T deficiency.

Aim: To evaluate the usability of the market configuration of the SCTE-AI, including packaging and instructions for use (IFU), in order to identify and mitigate any preventable patterns of use errors that could result in harm.

Methods: 4 groups of participants (injection-naïve or injection-experienced patients or caregivers) were randomized to 1 of 3 doses (50, 75, and 100 mg) of TE and either trained (ie, reviewed the IFU and shown how to properly inject) or not trained (only given the IFU). After simulated at-home use, participants were asked questions regarding the comprehensibility of the IFU and the intuitiveness/usability of the device. All tasks were measured as success, use error, or close call (participant initiated an error but recovered in time).

Main Outcome Measure: Usability (success rates, errors, and close calls) of the drug/device combination by adult males with T deficiency or their caregivers.

Results: 65 patients received 1 dose of TE, and 59 patients received 2 doses. Overall, 99 of 123 (80.5%) attempted injections resulted in administration of 1 full dose. Injection success rates were high and comparable among the various user groups. The most common use error (21 of 24) was due to not holding the autoinjector on the abdomen long enough (at least 8 seconds). Few critical drug delivery and safety errors or close calls were observed. No unmitigated use errors by patients or caregivers were apparent that could result in harm or have a negative impact on treatment. SCTE-AI was well tolerated.

Clinical Implications: The SCTE-AI development process resulted in a subcutaneous, TE autoinjection device that is intuitive to use, with clear labeling and packaging and an easy-to-understand IFU, providing an option for T-deficient adult males to self-inject subcutaneously at home.

This year in...Male Gonads 2018

Effect of testosterone replacement on measures of mobility in older men with mobility limitation and low testosterone concentrations: secondary analyses of the Testosterone Trials

www.thelancet.com/diabetes-endocrinology Vol 6 November 2018

Shalender Bhasin, Susan S Ellenberg, Thomas W Storer, Shehzad Basaria, Marco Pahor, Alisa J Stephens-Shields, Jane A Cauley, Kristine E Ensrud, John T Farrar, David Cella, Alvin M Matsumoto, Glenn R Cunningham, Ronald S Swerdloff, Christina Wang, Cora E Lewis, Mark E Molitch, Elizabeth Barrett-Connor, Jill P Crandall, Xiaoling Hou, Peter Preston, Denise Cifelli, Peter J Snyder, Thomas M Gill**

Interpretation Testosterone therapy consistently improved self-reported walking ability, modestly improved 6MWT distance (across all TTtrials participants), but did not affect falls. The effect of testosterone on mobility measures were related to baseline gait speed and self-reported mobility limitation, and changes in testosterone and haemoglobin concentrations.

This year in...Male Gonads 2018

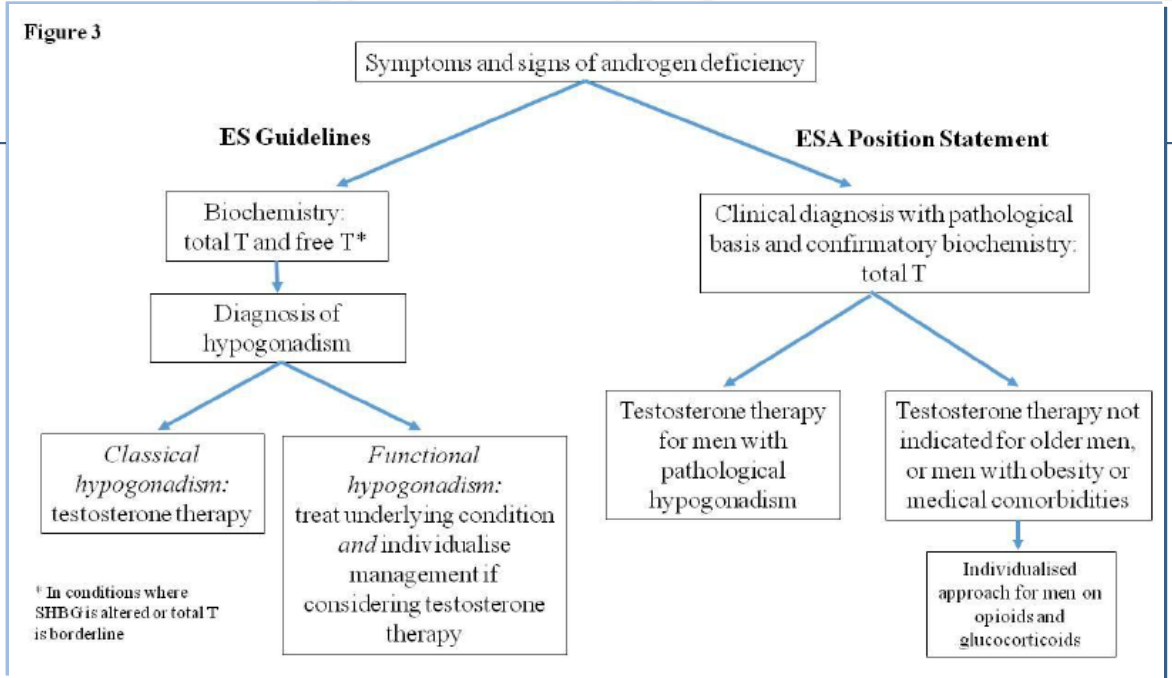
This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/cen.13888

Title Bu B. Yeap

Frederick C.W. Wu

Clinical practice update on testosterone therapy for male hypogonadism: contrasting perspectives to optimise care

Figure 3



Testosterone Therapy: Do American and European Clinicians Have Different Approaches?

Landon Trost, MD,[1] and Michael Zitzmann, MD, PhD[2]

J Sex Med 2018;15:1373–1377

Table 1. Comparisons of testosterone prescribing practices and attitudes between the United States and Europe

	Europe	United States
General opinions		
Opinions on testosterone	Divided opinions with pro-testosterone clinicians and backlash against testosterone clinics that provide supplementation without appropriate diagnosis and oversight	Similar to Europe
Opinions on treating men with "classical" hypogonadism*	Nearly universally supported	Nearly universally supported
Opinions on treating men with age-associated declines in testosterone/ "functional" hypogonadism (eg, testosterone deficiency secondary to obesity)	Support for age-associated and combined therapy with testosterone and comorbid condition management for functional hypogonadism	Dichotomous opinions: guidelines support, FDA suggests off-label
Guidelines and policies		
Region-specific guidelines	European Association of Urology, Male Hypogonadism (2012; updated 2018)[6] and Investigation, Treatment and Monitoring of Late-onset Hypogonadism in Males: ISA, ISSAM, EAU, EAA and ASA Recommendations[7]	American Urological Association, Evaluation and Management of Testosterone Deficiency: AUA Guideline[10]
Government restrictions on physician payments	Strict regulation of industry payment to physicians, including easily searchable monetary payments to physicians	Strict regulation of industry payment to physicians, including easily searchable monetary payments to physicians
Manufacturing regulations	European Medicines Agency and country-specific agencies regulate sale/distribution of commercial products; pharmacies selling testosterone products are regulated by national or regional institutions and are only allowed to sell the product when it is prescribed	FDA regulates sale/distribution of commercial products; state pharmacies regulate compounded preparations
Insurance coverage		
Coverage for testosterone	Varies by country, individual, and therapy; patient costs may range from minimal to up to the equivalent of $200/mo for prescriptions	Varies significantly by region, individual, and therapy; patient costs may range from minimal to $300–$400/mo for prescriptions
Coverage for clinical visits	Covered by nearly all insurance plans	Covered by nearly all insurance plans
Market		
Market for testosterone	Includes traditional indications (low testosterone + symptoms) and the "anti-aging" market	Similar to Europe
Advertising	Any form of advertising pharmaceutical products that require prescription is prohibited, including testosterone preparations	Direct-to-consumer advertising permitted
Rate of prescriptions	UK: 90% increase from 2001 to 2010[2]	359% increase from 2001 to 2011[1,3]

CONCLUDING REMARKS

Testosterone therapy is an increasingly complex and politically charged topic that brings together groups of varying motivations and desires. It should be highlighted that despite several differences in the landscape between Europe and the United States, there are significant similarities as well, including universal guideline recommendations that only men with low testosterone and associated signs and symptoms are appropriate candidates for treatment. Regulatory bodies such as the FDA emphasize a need for clinical efficacy and safety of approved therapies; guideline panels emphasize best practices based on published literature and expert opinions; testosterone manufacturers emphasize creating therapies that improve quality and quantity of life while maintaining a financially viable model; insurance companies sustain a business that balances patient and physician desires with the realities of limited resources. These factors ultimately leave practitioners with the challenging task of navigating an increasingly complex landscape where competing interests often intersect. It is no wonder then in this period of fluctuating agendas and dialogues that there is significant divergence and fragmentation of clinical practice, research interests, public policy, and opinions. However, as is often the case in medicine, confusion and divisions may aid in the discovery process and result in an optimal outcome.

Successful Aging and Changes in Sexual Interest and Enjoyment Among Older European Men and Women

Aleksandar Štulhofer, PhD,[1] Sharron Hinchliff, PhD,[2] Tanja Jurin, PhD,[3] Gert Martin Hald, PhD,[4] and Bente Træen, PhD[5]

J Sex Med 2018;15:1393–1402

ABSTRACT

Introduction: Despite the popularity and analytical relevance of the concept of successful aging, little efforts have been made to address its relationship to sexuality in older individuals.

Aim: To explore the relationship between successful aging and the (retrospectively assessed) change in sexual interest and enjoyment in the past 10 years, using a new multidimensional model of successful aging.

Methods: The data for this study was collected in 2016 using national probability-based surveys in four European countries (Norway, Denmark, Belgium and Portugal). In total, information from 2,461 sexually active and inactive participants aged 60–75 years was used for analyses. Multigroup structural equation analysis was employed to address the associations between key constructs.

Main Outcome Measure: The dependent variable was a composite (two-item) indicator of change in sexual interest and enjoyment in the past 10 years; a multifaceted model of successful aging predicted the change by country and gender.

Results: Tested cross-culturally, the proposed model of successful aging demonstrated a good fit to the data. Furthermore, its metric characteristics enabled direct comparisons across gender and national cultures. Controlling for sociodemographic characteristics, higher successful aging scores were consistently related to lower reduction in sexual interest/enjoyment among men and women across the 4 countries.

Clinical Implications: Given an increased life-expectancy and focus on healthy aging in many countries, the findings about the associations between sexual expression, quality of life and aging well are valuable to professionals working in the area of healthy sexual aging.

WORLD ANTI-DOPING AGENCY
play true

The official text of the *Prohibited List* shall be maintained by *WADA* and shall be published in English and French. In the event of any conflict between the English and French versions, the English version shall prevail.

This List shall come into effect on 1 January 2018

b. Endogenous** AAS when administered exogenously:

19-Norandrostenediol (estr-4-ene-3,17-diol);
19-Norandrostenedione (estr-4-ene-3,17-dione);
Androstanolone (5α-dihydrotestosterone, 17β-hydroxy-5α-androstan-3-one);
Androstenediol (androst-5-ene-3β,17β-diol);
Androstenedione (androst-4-ene-3,17-dione);
Boldenone;
Boldione (androsta-1,4-diene-3,17-dione);
Nandrolone (19-nortestosterone);
Prasterone (dehydroepiandrosterone, DHEA, 3β-hydroxyandrost-5-en-17-one);
Testosterone;

Athlete Name: .....

Therapeutic Use Exemption (TUE) Application

Please complete all sections in capital letters or typing.
Illegible or incomplete forms will be returned immediately.
Athlete to complete sections 1, 5, 6 and 7; physician to complete sections 2, 3 and 4.

1. Athlete Information

Surname: ..... Given Names: .....

Female ❑ Male ❑ Date of Birth (dd/mm/yyyy): .....

Address: : .....

City..... Country: ..... Postcode:.....

Tel.: ..... E-mail: .....
(with international code)

Sport: ..... Discipline/ Position: .....

International or National Sporting Organization: .....

If you are an Athlete with an impairment, please indicate the impairment: .....

.....

2. Medical Information

Diagnosis:

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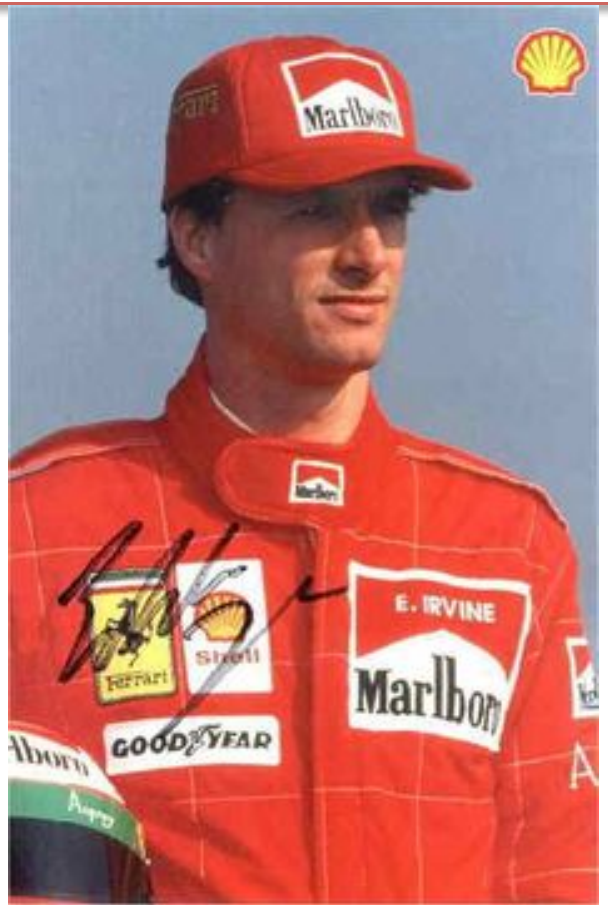

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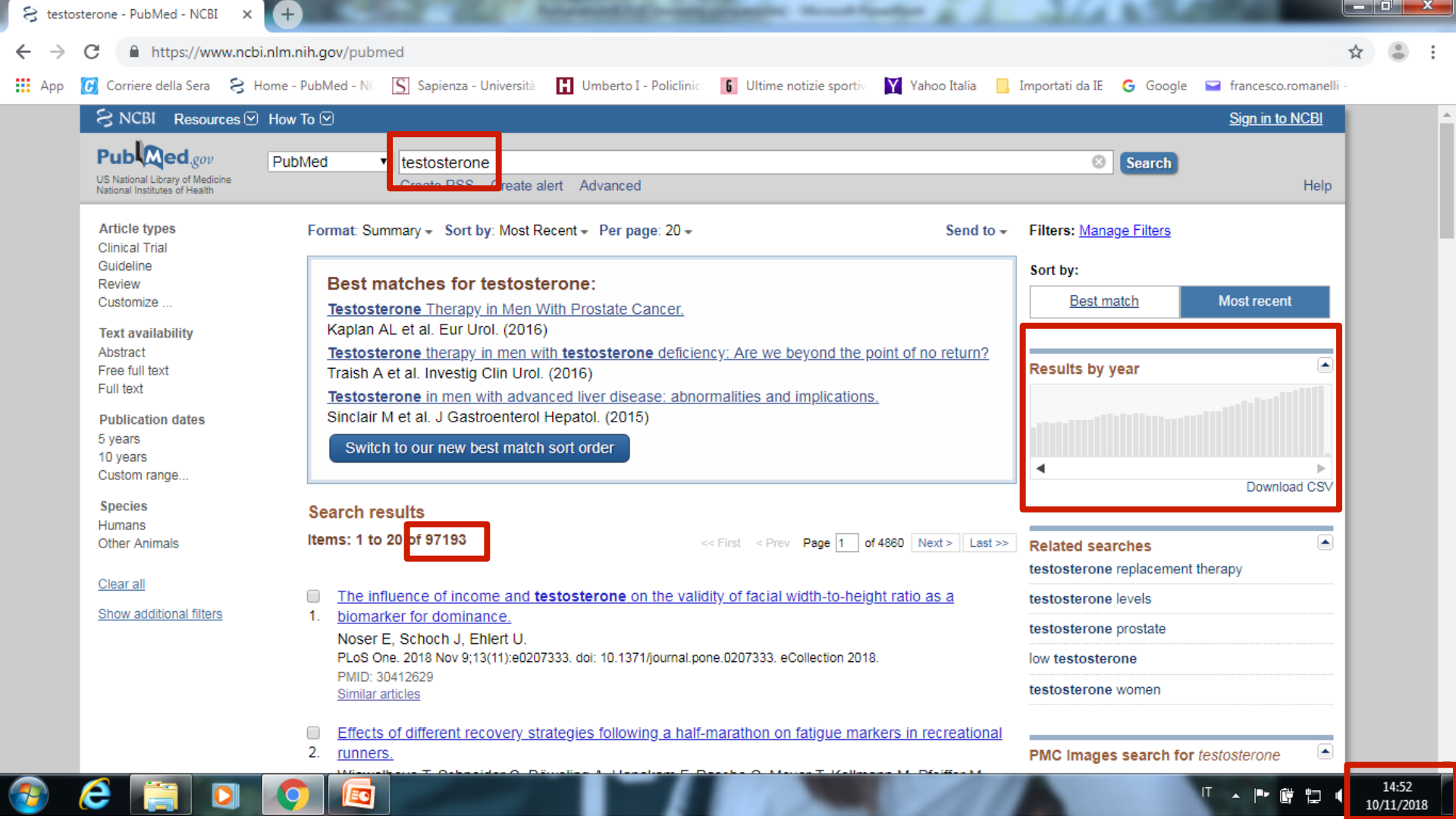
Grazie per la Vostra pazienza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Human Reproduction, Vol.32, No.4 pp. 719–724, 2017

Andrea Busnelli[1,2,*], Edgardo Somigliana[1,2], and Paolo Vercellini[2,3]

“Essere giovani vuol dire tenere aperto l’oblò della speranza, anche quando il mare è cattivo e il cielo si è stancato di essere azzurro”

“Ogni umana attività è indotta dal desiderio”

Bertrand Russell