Complete Summary

GUIDELINE TITLE

Testosterone therapy in adult men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline.

BIBLIOGRAPHIC SOURCE(S)

Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, Montori VM. Testosterone therapy in adult men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2006 Jun;91(6):1995-2010. [109 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Adult androgen deficiency syndromes

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management
Screening
Treatment

CLINICAL SPECIALTY

Endocrinology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To provide guidelines for the evaluation and treatment of androgen deficiency syndromes in adult men

TARGET POPULATION

Adult men with androgen deficiency syndromes

INTERVENTIONS AND PRACTICES CONSIDERED

Screening/Evaluation/Diagnosis

1. History and physical examination
2. Morning total testosterone measurement
3. Confirmatory measurement of morning total testosterone
4. Screening for androgen deficiency in the general population (specifically not recommended)
5. Case detection in candidate groups

Treatment/Management

1. Selection of appropriate candidates for testosterone therapy
2. Dosing
    - Individualized vs. uniform therapy
    - Adjunctive therapy
    - Short-term therapy
    - Target serum testosterone levels
    - Selection of the optimal androgen delivery regimen
3. Monitoring
    - Hematocrit
    - Bone mineral density
    - Prostate specific antigen (PSA) and digital prostate examination
    - Specific side effects and complications

MAJOR OUTCOMES CONSIDERED

- Accuracy of the diagnosis of androgen deficiency syndrome
- Differentiation between primary vs. secondary androgen deficiency
- Appropriateness of testosterone therapy
- Response to testosterone therapy in terms of secondary sex characteristics, sexual function, sense of well-being, muscle mass and strength and bone mineral density in men with androgen deficiency syndromes

- Side effects and risks of testosterone therapy

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Evidence Grading

+OOO Denotes very low quality evidence

++OO Denotes low quality evidence

+++O Denotes moderate quality evidence

++++ Denotes high quality evidence

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Participants

The Task Force was composed of a chair, selected by the Clinical Guidelines Subcommittee of The Endocrine Society, five additional experts, a methodologist, and a professional writer. The Task Force received no corporate funding or remuneration.

Evidence

The Task Force used systematic reviews of available evidence to inform its key recommendations. The Task Force used consistent language and graphical descriptions of both the strength of recommendation and the quality of evidence, using the recommendations of the Grading of Recommendations, Assessment, Development, and Evaluation group.

Consensus Process

Consensus was guided by systematic review of evidence and discussion during three group meetings, several conference calls, and e-mail communications.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Strength of Recommendations

- The number 1 indicates a strong recommendation and is associated with the phrase "The Task Force recommends."
- The number 2 denotes a weak recommendation and is associated with the phrase "The Task Force suggests."

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The drafts prepared by the panelists with the help of a professional writer were reviewed successively by The Endocrine Society's Clinical Guidelines Subcommittee, Clinical Affairs Committee, and Council. The version approved by the Council was placed on The Endocrine Society's Web site for comments by members. At each stage of review, the Task Force received written comments and incorporated needed changes.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Definitions for the levels of evidence (+OOO, ++OO, +++O, and ++++); the strength of the recommendation (1 or 2); and for the difference between a "recommendation" and a "suggestion" are provided at the end of the "Major Recommendations" field.

Diagnosis

The Task Force recommends making a diagnosis of androgen deficiency only in men with consistent symptoms and signs and unequivocally low serum testosterone levels. (1 | +OOO)

The Task Force suggests the measurement of morning total testosterone level by a reliable assay as the initial test for the diagnosis of androgen deficiency in men. (2 | ++OO)

The Task Force recommends confirmation of the diagnosis by repeating the measurement of morning total testosterone and in some patients by measurement of free or bioavailable testosterone level, using an appropriate assay system. (1 | +OOO)

The Task Force recommends against screening for androgen deficiency in the general population. (1 |+ OOO)

The Task Force suggests that clinicians not use the available case-finding instruments for detection of androgen deficiency in men receiving health care for unrelated reasons. (2 | +OOO)

The Task Force suggests that clinicians consider case detection by measurement of total testosterone levels in men with certain clinical disorders, listed below, in which the prevalence of low testosterone levels is high or for whom testosterone therapy is suggested/recommended in the "Treatment" section.(2 | +OOO)

- Sellar mass, radiation to the sellar region, or other diseases of the sellar region
- Treatment with medications that affect testosterone production or metabolism, such as glucocorticoids, ketoconazole, and opioids
- Human immunodeficiency virus (HIV)-associated weight loss
- End-stage renal disease and maintenance hemodialysis
- Moderate to severe chronic obstructive lung disease
- Infertility
- Osteoporosis or low trauma fracture, especially in a young man
- Type 2 diabetes mellitus

Treatment

The Task Force recommends testosterone therapy for symptomatic men with the classical androgen deficiency syndromes who have low testosterone levels to induce and maintain secondary sex characteristics and to improve their sexual function, sense of well-being, muscle mass and strength, and bone mineral density. (1 | ++OO)

The Task Force suggests that clinicians offer testosterone therapy to men with low testosterone levels and low libido to improve libido (2 | ++OO) and to men with erectile dysfunction (ED) who have unequivocally low testosterone levels, after evaluation of underlying causes of ED and consideration of established therapies for ED. (2 | +OOO)

The Task Force recommends against a general clinical policy of offering testosterone therapy to all older men with low testosterone levels. (1 | +OOO)

The Task Force suggests that clinicians consider offering testosterone therapy on an individualized basis to older men with consistently low testosterone levels on more than one occasion and significant symptoms of androgen deficiency, after appropriate discussion of the uncertainties of the risks and benefits of testosterone therapy in older men. (2 | +OOO)

The Task Force suggests that clinicians consider short-term testosterone therapy as an adjunctive therapy in human immunodeficiency virus (HIV)-infected men with low testosterone levels and weight loss to promote weight maintenance and gains in lean body mass (LBM) and muscle strength. (2 | ++OO)

The Task Force suggests that clinicians offer short-term testosterone therapy to men receiving high doses of glucocorticoids who have low testosterone levels to promote preservation of LBM and bone mineral density. (2 | ++OO)

The Task Force recommends against starting testosterone therapy in patients with breast (1 | +OOO) or prostate cancer. (1 | +OOO)

The Task Force recommends against starting testosterone therapy in patients with a palpable prostate nodule or induration, or prostate-specific antigen (PSA) greater than 3 ng/mL without further urological evaluation. (1 | +OOO)

The Task Force recommends against starting testosterone therapy in patients with erythrocytosis (hematocrit 50%), hyperviscosity, untreated obstructive sleep apnea, severe untreated benign prostatic hypertrophy with International Prostate Symptom Score (IPSS) symptom score 19, or uncontrolled severe heart failure. (1 | +OOO)

Administration

When testosterone therapy is recommended, The Task Force suggests aiming at achieving serum testosterone levels during treatment in the mid-normal range with any of the following regimens, chosen on the basis of the patient's preference, consideration of pharmacokinetics, treatment burden, and cost: (2 | ++OO)

- 75 to 100 mg of testosterone enanthate or cypionate administered intramuscularly (im) weekly, or 150 to 200 mg administered every 2 weeks.
- One or two 5-mg nongenital, testosterone patches applied nightly over the skin of the back, thigh, or upper arm, away from pressure areas.
- 5 to 10 g of a testosterone gel applied daily over a covered area of nongenital skin (patients should wash hands after application).

- 30 mg of a bioadhesive buccal testosterone tablet applied to buccal mucosa every 12 hours.
- Oral testosterone undecanoate, injectable testosterone undecanoate, and testosterone pellets where available.

Monitoring Strategies and Schedule

The Task Force recommends evaluating the patient 3 months after treatment initiation and then annually to assess whether symptoms have responded to treatment and whether the patient is suffering any adverse effects. (1 | +OOO)

The Task Force suggests monitoring testosterone levels 3 months after initiation of testosterone therapy. (2 | ++OO)

- Therapy should restore serum testosterone levels to the mid-normal range.
- Testosterone cypionate or enanthate: measure serum testosterone levels midway between injections. If serum testosterone level is greater than 700 ng/dL (24.5 nmol/L) or less than 350 ng/dL (12.3 nmol/L), adjust dose or frequency.
- Transdermal patch: assess testosterone levels 3 to 12 hours after application of the patch.
- Buccal tablet: assess levels immediately before application of fresh system.
- Transdermal gel: assess testosterone level after patient has been on treatment for 1 to 2 weeks

The Task Force recommends determining hematocrit at baseline, at 3 months, and then annually. If hematocrit is greater than 54%, stop therapy until hematocrit decreases to a safe level, evaluate the patient for hypoxia and sleep apnea, and reinitiate therapy at a reduced dose. (1 | +OOO)

The Task Force suggests repeating bone mineral density of the lumbar spine, femoral neck, and hip after 1 to 2 yr of testosterone therapy in hypogonadal men with osteoporosis or low trauma fracture. (2 | +OOO)

The Task Force recommends digital examination of the prostate and PSA measurement before initiating treatment, at 3 months, and then in accordance with evidence-based guidelines for prostate cancer screening, depending on the age and race of the patient. (1 | +OOO)

The Task Force recommends that clinicians obtain urological consultation if there is: (1 | +OOO)

- Verified serum or plasma PSA concentration greater than 4.0 ng/mL.
- An increase in serum or plasma PSA concentration greater than 1.4 ng/mL within any 12-month period of testosterone treatment.
- A PSA velocity of more than 0.4 ng/mL per year using the PSA level after 6 months of testosterone administration as the reference. PSA velocity should be used only if there are longitudinal PSA data for more than 2 years.
- Detection of a prostatic abnormality on digital rectal examination.
- An American Urological Association (AUA) prostate symptom score of more than 19.

The Task Force recommends evaluation for symptoms and signs of formulation-specific adverse events at each visit: (1 | +OOO)

- Buccal testosterone tablets: inquire about alterations in taste and examine gums and oral mucosa for irritation.
- Injectable testosterone esters: inquire about fluctuations in mood or libido and evaluate hematocrit to detect excessive erythrocytosis, especially in older patients.
- Testosterone patch: look for signs of skin reaction at the application site.
- Testosterone gels: advise patients to cover the application site with clothing and wash the skin before having skin-to-skin contact, because gels leave a residue of testosterone on the skin that can be transferred to a woman or child who comes in close contact.

Definitions:

Strength of Recommendations

1 - Indicates a strong recommendation and is associated with the phrase "The Task Force recommends."

2 - Denotes a weak recommendation and is associated with the phrase "The Task Force suggests."

Evidence Grading

+OOO Denotes very low quality evidence

++OO Denotes low quality evidence

+++O Denotes moderate quality evidence

++++ Denotes high quality evidence

CLINICAL ALGORITHM(S)

An algorithm is provided in the original guideline document for "An approach for the diagnostic evaluation in adult men suspected of having androgen deficiency."

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The quality of the supporting evidence is identified and graded for each recommendation (see "Major Recommendations" field).

In the original guideline document, each *recommendation* is followed by a description of the *evidence*, *values* that panelists considered in making the recommendation, and in some instances *remarks*, a section in which panelists offer technical suggestions for dosing and monitoring. These technical comments

reflect the best available evidence applied to a typical patient. Often, this evidence comes from the unsystematic observations of the panelists and their values and preferences; therefore, these remarks should be considered suggestions.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Benefits of testosterone therapy for androgen deficiency syndrome in adult males have been found to include the induction and maintenance of secondary sex characteristics, and improvements in sexual function, sense of well-being, muscle mass and strength and bone mineral density. A full discussion of these benefits can be found in the original guideline document.

POTENTIAL HARMS

Potential Adverse Effects of Testosterone Replacement

Adverse events for which there is evidence of association with testosterone 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 testosterone administration:

- Gynecomastia
- Male pattern balding (familial)
- Worsening of benign prostatic hyperplasia (BPH) symptoms
- Growth of breast cancer
- Induction or worsening of obstructive sleep apnea

Formulation-specific adverse effects:

- Oral tablets
  - Effects on liver and cholesterol (methyltestosterone)
- Pellet implants
  - Infection, expulsion of pellet
- Intramuscular injections of testosterone enanthate or cypionate
  - Fluctuation in mood or libido
  - Pain at injection site
  - Excessive erythrocytosis (especially in older patients)
- Transdermal patches
  - Skin reactions at application site
- Transdermal gel
  - Potential risk for testosterone transference to partner
- Buccal testosterone tablets

- Alterations in taste
- Irritation of gums

CONTRAINDICATIONS

CONTRAINDICATIONS

Conditions in which testosterone administration is associated with a high risk of adverse outcome and in which testosterone should not be administered:

- Very high risk of serious adverse outcomes
  - Metastatic prostate cancer
  - Breast cancer
- Moderate to high risk of adverse outcomes
  - Undiagnosed prostate nodule or induration
  - Unexplained prostate specific antigen (PSA) elevation
  - Erythrocytosis (hematocrit > 50%)
  - Severe lower urinary tract symptoms associated with benign prostatic hypertrophy as indicated by American Urological Association-International Prostate Symptom Score (AUA/IPSS) > 19
  - Unstable severe congestive heart failure (class III or IV)

QUALIFYING STATEMENTS

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- Clinical Practice Guidelines are developed to be of assistance to endocrinologists by providing guidance and recommendations for particular areas of practice. The Guidelines should not be considered inclusive of all proper approaches or methods, or exclusive of others. The Guidelines cannot guarantee any specific outcome, nor do they establish a standard of care. The Guidelines are not intended to dictate the treatment of a particular patient. Treatment decisions must be made based on the independent judgment of health care providers and each patient's individual circumstances.
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IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Clinical Algorithm

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, Montori VM. Testosterone therapy in adult men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2006 Jun;91(6):1995-2010. [109 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2006 Jun

GUIDELINE DEVELOPER(S)

The Endocrine Society - Disease Specific Society

SOURCE(S) OF FUNDING

The Endocrine Society

GUIDELINE COMMITTEE

Androgen Deficiency Syndromes in Men Guideline Task Force

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Task Force Members: Shalender Bhasin; Glenn R. Cunningham; Frances J. Hayes; Alvin M. Matsumoto; Peter J. Snyder; Ronald S. Swerdloff; Victor M. Montori

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Shalender Bhasin, MD,—Consultation or Advisement: GTx, Pfizer, TAP; Grant or Other Research Support: Solvay, GSK; Honoraria: Solvay, Auxilium. Glenn R. Cunningham, MD,—Consultation or Advisement: Solvay Pharma; Columbia Lab, GSK; Grant or Other Research Support: Solvay Pharma, Columbia Lab, GSK; Speakers List: Solvay Pharma, Columbia Lab. Frances J. Hayes, MB, FRCPI,—Consultation or Advisement: Auxilium Pharma, GSK, New England Research Institute; Speakers Bureau for Solvay. Alvin M. Matsumoto, MD,—Consultation or Advisement: Solvay, GSK, Johnson & Johnson (J&J), Auxilium, GTx, TAP Pharmaceutical Products, Inc. (TAP), Threshold; Grant or Other Research Support: GSK, Columbia Labs, Solvay, Ascend. Peter J. Snyder, MD,—Consultation or Advisement: None Declared; Grant or Other Research Support: Solvay Pharma. Ronald S. Swerdloff, MD,—Consultation or Advisement: None Declared; Grant or Other Research Support: Actelion Pharma, ARYx Therapeutics, Inc., Auxilium, Bayer Corp., Besins/Ascend, BNS, Clarus, Columbia, Corcept, GSK, Eli Lilly & Co., MacroChem Corp., Organon, Schering AG, Solvay Pharma, Inc., Victor M. Montori, MD,—Consultation or Advisement: None Declared; Grant or Other Research Support: None Declared; Speakers List: None Declared

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from The Endocrine Society.

Print copies: Available from The Endocrine Society, c/o Bank of America, P.O. Box 630721, Baltimore, MD 21263-0736; Phone: (301) 941.0210; Fax: (301) 941-0257; Email: Societyservices@endo-society.org

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on Aug 1, 2006. The information was verified by the guideline developer on August 29, 2006.

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