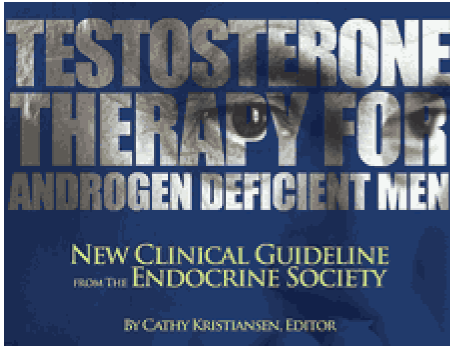

Endocrine News June 2006 Article:

TESTOSTERONE THERAPY FOR ANDROGEN DEFICIENT MEN
New Clinical Guideline from the Endocrine Society

By Cathy Kristiansen, Editor

Prescribing testosterone therapy for male patients can be a controversial issue that leaves many physicians unclear if they are indeed giving optimal treatment and whether they are treating the right patients. To help clarify best practices in this field and provide guidance for the evaluation and treatment of male androgen deficiency, The Endocrine Society has developed a guideline, Testosterone Therapy in Adult Men with Androgen Deficiency Syndromes, which was recently published in The Journal of Clinical Endocrinology & Metabolism.

Guideline for Testosterone Therapy for Androgen Deficiency Syndromes

Table 1A. Symptoms and signs suggestive of androgen deficiency in men

- Incomplete sexual development, eunuchoidism, aspermia
- Reduced sexual desire (libido) and activity
- Decreased spontaneous erections
- Breast discomfort, gynecomastia
- Loss of body (axillary and pubic) hair, reduced shaving
- Very small or shrinking testes (especially < 5 mL)
- Inability to father children, low or zero sperm counts
- Height loss, low trauma fracture, low bone mineral density (BMD)
- Reduced muscle bulk and strength
- Hot flushes, sweats

Table 1B. Other symptoms and signs associated with androgen deficiency that are less specific than those in Table 1A

- Decreased energy, motivation, initiative, aggressiveness, self-confidence
- Feeling sad or blue, depressed mood, dysthymia
- Poor concentration and memory
- Sleep disturbance, increased sleepiness
- Mild anemia (normochromic, normocytic, in the female range)
- Increased body fat, body mass index
- Diminished physical or work performance

"The document represents a conservative, well-thoughtout, evidence-based approach that practitioners will find useful," says Shalender Bhasin, M.D., chair of the androgen guideline task force. "The guideline may invite debate, yes. And that is quite reasonable, given that the field is so controversial."

Controversial Issues

Controversy arises because the available data are not sufficient to answer many key questions. "Because there is so much debate, one can infer that the data are not very good—and that is the case," Dr. Bhasin says. "What is striking is that most studies have been off-label trials, and they have not been randomized, clinical trials, because it's a relatively new field."

One confusing area involves accurate measurement of testosterone levels. Not only are numerous tests produced by different manufacturers, making standardization of results a challenge, but the assessment of normal levels has not been done in a scientifically sound way. "The normative ranges have been derived historically from very small samples, not random, population-based samples," Dr. Bhasin says. "If you don't have good normative ranges, then it becomes harder to define the lower level of normal with certainty."

Another area of confusion concerns the signs and symptoms of androgen deficiency. To date, no large population- based study has been done to yield standard information. For instance, no standard measurement

Potential Adverse Effects of Testosterone Replacement

A. 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

B. Uncommon Adverse Events for Which There Is Weak Evidence of Association with Testosterone Administration

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

C. 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 (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)
- Buccal T tablets
  - Alterations in taste
  - Irritation of gums

systems exist for both total and free testosterone, Dr. Bhasin notes.

Furthermore, treatment generates its own controversy. The media periodically highlight cases of illegal testosterone supplementation among athletes and recreational body builders. Also problematic is the off-label use of testosterone for indications for which testosterone has not been approved.

However, Dr. Bhasin says, “The major issue is whether people who have lower testosterone levels, whether because of age, chronic illness, or other reasons, should have testosterone therapy to raise their testosterone levels to normal. Although there are good data showing that testosterone declines with advancing age, we do not know the consequences of this decline, and there have not been randomized trials showing the risks or the benefits.” Such trials are under way, but will take another decade to complete. “That is why this document is so important,” Dr. Bhasin says. “It provides some guidance on what a reasonable practitioner might do until the data become available.”

Weighing the Facts

To develop a guideline that would earn the confidence of endocrinologists, The Endocrine Society established a rigorous review system. Furthermore, to avoid conflicts of interest in developing the guideline, the Society selffunded the work. All Society members involved in the process were selected for their expertise by the Clinical Guidelines Subcommittee, approved by the Society’s Council, and volunteered their time. “This was a very clean process, free of commercial interest,” Dr. Bhasin stresses.

To launch the process, the Society’s Clinical Guidelines Subcommittee selected a task force of six experts, a methodologist with expertise in evidence grading, and a medical writer. The task force systematically scrutinized reviews of available evidence—citing 109 papers in the references—held three group meetings and several conference calls, corresponded by email, and then compiled its key recommendations. Importantly, it used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to weigh the evidence, which takes into account the relative strengths and weaknesses of the best available evidence. GRADE, devised by the Knowledge and Encounter Research Unit in the Department of Medicine and Division of Endocrinology at the Mayo Clinic, shows the strength of the recommendation, with 1 being the strongest, and also judges the evidence on a scale of 1 to 5, with 5 indicating the highest quality. The judgment incorporates study design, study quality, consistency, and directness for each important outcome. “The GRADE system has more transparency,” Dr. Bhasin says. “This is valuable because guidelines by their nature are conservative, so they are driven not only by evidence, but also by safety needs.”

For example, he says, although evidence is very weak that testosterone accelerates the growth of prostate cancer, the guideline makes a strong recommendation. “The consequences of giving testosterone to men with prostate cancer would be so adverse, that in spite of the weak evidence, the recommendation is very strong that testosterone should not be given in such cases.”

The task force’s guideline drafts were reviewed successively by the Society’s Clinical Guidelines Subcommittee, its Clinical Affairs Committee, and Council. Once Council approved a draft, it was placed on The Endocrine Society’s Web site for member comment where it received more than 100 responses. At each stage of review, the panel received written comments and incorporated needed changes. “This document was almost 2 years in the making. There was a huge amount of anguish in our task force discussions,” Dr. Bhasin says. “What came out was truly reflective of the consensus of not just the task force but of members at multiple levels.”

Summary of Findings in the Guideline

The guideline reaches the following conclusion:

"We recommend making a diagnosis of androgen deficiency only in men with consistent symptoms and signs and unequivocally low serum testosterone levels. We suggest the measurement of morning total testosterone level by a reliable assay as the initial diagnostic test. We recommend 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 accurate assays. We recommend testosterone therapy for symptomatic men with androgen deficiency, 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. We recommend against starting testosterone therapy in patients with breast or prostate cancer, a palpable prostate nodule or induration or PSA > 3 ng/mL without further urological evaluation, erythrocytosis (hematocrit > 50%), hyperviscosity, untreated obstructive sleep apnea, severe lower urinary tract symptoms with IPSS symptom score > 19, or class III or IV heart failure. When testosterone therapy is instituted, we suggest aiming at achieving testosterone levels during treatment in the mid-normal range with any of the approved formulations, chosen on the basis of the patient's preference, consideration of pharmacokinetics, treatment burden, and cost. Men receiving testosterone therapy should be monitored using a standardized plan."

The guideline deals not only with diagnosis and treatment, but also advises about potential side effects from therapy (see box). Attributing some of these effects to the drugs has been controversial.

Future Review

Although newly completed, the guideline will be reviewed frequently over coming years to ensure it is as comprehensive as possible. "These are living documents, the field is moving," Dr. Bhasin notes. "This is an area for which there is strong public and scientific interest."

He cites the explosion in sales of testosterone drugs sales. In 1993, prescription sales totaled about $93 million and they are now at or above $500 million. "Even if you go by the conservative estimates, there has been very substantial growth," he says.

Dr. Bhasin hails the document for its thoroughness and predicted it would be valuable to many practitioners. "It has undergone intense scrutiny," he says. "It was like drafting the U.S. Constitution in some ways, only a shade less difficult, trying to get all the competing views accommodated. But it has been worthwhile." ■

For information on how to purchase a copy of the guideline, please contact Society Services at **societyservices@endo-society.org** or visit the Society's Web site at **www.endo-society.org/quickcontent/clinicalpractice/clinical-guidelines/GH_clinicalguideline.cfm**. For information on commercial reprints, contact Heather Edwards at **endoreprints@cadmus.com**.
For the order form for the guideline, visit: **http://www.endo-society.org/quickcontent/clinicalpractice/clinical-guidelines/CG_Androgen.cfm**

Members of the guideline's writing task force were: Shalender Bhasin, M.D. (chair), Glenn R. Cunningham, M.D., Frances J. Hayes, M.B., F.R.C.P.I., Alvin M. Matsumoto, M.D., Victor Montori, M.D., M.Sc., Peter J. Snyder, M.D., and Ronald S. Swerdloff, M.D.

Article reprinted with permission of the Endocrine Society
TESTOSTERONE THERAPY FOR ANDROGEN DEFICIENT MEN:
New Clinical Guideline from the Endocrine Society
By Cathy Kristiansen, Editor
Endocrine News June 2006, Vol. 31 No. 6, Pages 13-15
Endocrine News is a publication of The Endocrine Society
© The Endocrine Society, 2006