Testosterone Therapies

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KEYWORDS

• Testosterone • Therapies • Formulations • Gels • Androgens

KEY POINTS

- There are numerous testosterone formulations now available, and patients and clinicians should take into account the "4 Cs": cost, compliance, convenience, and concentration levels.
- Testosterone is a natural contraceptive and should not be used in men trying to achieve a pregnancy.
- All testosterone gels and solutions have an increased risk of transference, and there should be increased caution when in contact with children and pregnant women.

INTRODUCTION

Over the past decade, there has been exponential growth in sales of testosterone therapies and their utilization. In 2012, testosterone was one of the fastest growing medications in the United States. Much of the increased sales and utilization of testosterone can be attributed to an aging US population, decreased concern that testosterone can cause prostate cancer, increased awareness of the beneficial effects of testosterone, and direct to consumer advertising and marketing. There has been expansive growth in "testosterone centers" throughout the United States, signifying an increase in patient demand to seek treatment for this condition. Although in 2006 there were only 2 topical gels in the testosterone market, just a decade later there are now 6 topical formulations, new long-acting testosterone pellets and injections, and promising oral formulations on the horizon. Although there are many testosterone therapies available, patients and clinicians must decide the optimal formulation specifically for each patient.

HISTORY

The beneficial effects of testosterone have been known for thousands of years. Throughout history, numerous attempts have been made to use testosterone extracts to treat sexual dysfunction and reverse the aging process.[1] For example, in 2000 BC, the ancient Indian manuscripts described the ingestion of testicular tissue for the treatment of erectile dysfunction. The ancient Egyptians also described the medicinal powers of the testis. In1889, a prominent French physiologist, Charles Brown-Sequard, injected himself with an extract of crushed canine and guinea pig testes and reported improvements in his urinary stream, intellect, and erectile function. Testicular transplants first began in 1912. In 1920, Serge Vornoff completed the first testicular tissue transplant from chimpanzee to human.[2] Testosterone therapy (TTh) officially started in 1935 when Enrest Lacquer isolated testosterone from bull testes, and in 1939 when Butenandt and Ruzicka first described the synthesis of testosterone. In the 1940s, the first subdermal testosterone implants were introduced, and 10 years later was the development of the first testosterone esters. These esters are the basis of the intramuscular (IM) injections that are used today. In the 1970s, testosterone undecanoate (TU; Andriol Testocaps, Organon) became available outside the United States. Currently, TU has recently been made available in the United States as a long-acting testosterone injection formulation. In1994, the first transdermal testosterone was introduced as a patch, known as Testoderm (Alza Corporation), and in 2000, the first topical testosterone gel became available. Finally, in 2008, subdermal

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testosterone implants, and in 2014, nasal testosterone gels were the first to be US Food and Drug Administration (FDA) approved.

PRETREATMENT CONSIDERATIONS

In March 2015, the FDA issued a drug safety communication cautioning about the use of testosterone products for low testosterone due to aging. The manufacturers of testosterone products were also required by the FDA to amend the drug labels to also include warnings for possible increased risk of myocardial infarction and stroke. Revisions to all the testosterone labeling were completed in May 2015 and now include the following[3]:

Testosterone is indicated for replacement therapy in adult men for conditions associated with a deficiency or absence of endogenous testosterone.

Primary hypogonadism (congenital or acquired): testicular failure due to conditions such as crypotorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (follicle-stimulating hormone, FSH; luteinizing hormone, LH) higher than the normal range.

Hypogonadotropic hypogonadism (congenital or acquired): gonadotropin or LH-releasing hormone deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum concentrations, but gonadotropins in the normal or low range.

Safety and efficacy of testosterone in men with "age-related hypogonadism" (also referred to as "late-onset hypogonadism") have not been established.

Epidemiologic studies and randomized controlled trials have been inconclusive for determining the risk of major adverse cardiovascular events (MACE), such as nonfatal myocardial infarction, nonfatal stroke, and cardiovascular deaths, with the use of testosterone compared with nonuse. Some after-marketing studies, but not all, have reported increased risk of MACE in association with use of testosterone replacement therapy in men.

Before initiating TTh, several factors have to be taken into consideration. The "4 Cs" can help clinicians and patients determine which formation is most suitable. The "4 Cs" include cost, compliance, convenience, and concentration. Cost has become a major barrier for many patients trying to obtain access to TTh because many insurance carriers now have much more stringent criteria for which patients can receive coverage for TTh. A concern for many of the topical agents is their ability to penetrate the skin and obtain therapeutic serum testosterone levels. Not all gels are equally effective in all men, and at times, patients are required to switch to a different gel that may offer better serum testosterone concentration levels.[4] Some patients are not compliant with daily applications of testosterone, and in these patients, a long-acting testosterone formulation may be more appropriate. Other considerations before initiating TTh are the risk of transference and concerns for future fertility. Exogenous testosterone is a natural contraceptive and thus should not be used in men trying to achieve a pregnancy. In these men, methods to increase endogenous testosterone should be implored.

CONTRAINDICATIONS TO TESTOSTERONE THERAPY

The 2010 American Endocrine Guidelines state that TTh is contraindicated in patients with the following conditions[5]:

- Metastatic prostate cancer
- Breast cancer
- Unevaluated prostate nodule or induration
- Prostate-specific antigen (PSA) >4 ng/mL (>3 ng/mL in high-risk individuals)
- Hematocrit >50%
- Severe lower urinary tract symptoms associated with benign prostatic hypertrophy (BPH) as indicated by American Urological Association/International Prostate Symptom Score (IPSS) score >19
- Uncontrolled or poorly controlled congestive heart failure

The Endocrine Society recommends Urologic consultation for patients with a prostate nodule, elevated PSA greater than 4 ng/mL (>3 ng/mL in high-risk individuals), and IPSS scores greater than 19 before starting TTh. Urologists should use their own judgment in assessing prostate cancer and BPH risk on the basis of their clinical experience because TTh can be safely initiated in many of these patients if they are monitored carefully.

TREATMENT OPTIONS

Currently, most TTh users in the United States are receiving some form of transdermal gel therapy. In