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Alexandra Dimit  
*Ohio Northern University*

Joelle Farano  
*Ohio Northern University*

Haley Armstrong  
*Ohio Northern University*

Michelle Musser  
*Ohio Northern University, m-musser@onu.edu*

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## Testosterone Replacement Therapy in Aging Males

Alexandra Dimit, fifth-year pharmacy student from North Canton, Ohio; Joelle Farano, fourth-year pharmacy student from Darien, Ill.; Haley Armstrong, fifth-year pharmacy student from Sylvania, Ohio; Michelle Musser, PharmD, assistant professor of pharmacy practice

### Abstract

The U.S. Food and Drug Administration (FDA) cautions health care providers and patients regarding the use of testosterone replacement therapy products for the aging process, including a decrease in muscle strength, muscle mass, and lack of energy or sexual desire, due to an increased risk of heart attacks and strokes. Testosterone replacement therapy products are indicated for genetic defects, chemotherapy damage, or damage to the hypothalamus or pituitary gland, where testosterone is produced. A patient and his team of health care professionals must seriously consider the risks and benefits when using these products for other indications. Use of testosterone replacement therapy products for low testosterone due to natural aging has been on the rise due to disease state awareness, pharmaceutical marketing and media attention. Pharmacists can make a difference in patients' lives by conducting patient education and counseling for these products.

### Key Terms

Hormone; Hormone Replacement Therapy; Aging; Testosterone; Androgen

### Introduction

Testosterone replacement therapy (TRT) has received recent attention in the scientific community as the U.S. Food and Drug Administration (FDA) has communicated that caution should be advised when using testosterone products for the aging process, including for symptoms such as declining muscle mass, muscle strength and libido. In September 2014, the FDA used input from an advisory committee of experts to conclude that there may be an increased cardiovascular risk with testosterone use.<sup>1</sup> With a March 2015 update, the FDA states that testosterone products are now required to include labels indicating increased risk of heart attacks and strokes. Health care providers are encouraged to inform their patients of these risks.<sup>1</sup>

Testosterone replacement therapy products are indicated in male patients who have genetic defects causing lack of testosterone production by the testes, damage from chemotherapy to the testes or damage to the hypothalamus or pituitary gland. However, many males who receive testosterone products have been diagnosed with idiopathic hypogonadism, which is a low level of testosterone due to no other determined reason except for aging. Within the past six years, there has been a significant increase in the use of TRT products; 1.3 million patients received TRT prescriptions in 2009 compared to 2.3 million in 2013, with 70 percent of those patients between the ages of 40 and 64 years.<sup>2</sup> The increase in use of TRT may be due to confounding factors including the rise in the baby boomer generation, pharmaceutical marketing or media attention for low testosterone. Moreover,

with the use of TRT nearly doubling in recent years, ongoing investigational research studying the potentially harmful, long-term effects of TRT is invaluable. Patients obtain medical advice from numerous outlets, many of them unreliable. Thus, it is important that health care professionals are aware of current research to provide appropriate and trustworthy clinical advice and counseling to all patients.

### Hypogonadism and Testosterone Replacement Therapy Recommendations

Hypogonadism is the manifestation of testosterone deficiency or infertility in males, the symptoms of which vary depending on age. Symptoms in males before puberty include small testes, phallus and prostate, decreased growth of pubic hair, delayed epiphyseal closure resulting in disproportionately long limbs, gynecomastia, high-pitched voice and loss of testicular function. Older patients with lower levels of testosterone may experience fatigue, decreased libido, impotence, decreased sperm production, loss of lean muscle mass, hot flashes and osteoporosis.<sup>3</sup>

Testosterone replacement therapy may be prescribed to patients with low testosterone levels to reduce the severity of these symptoms and improve the patient's overall quality of life. Short-term studies have shown an increase in lean body mass and production of blood cells and a decrease in low-density lipoprotein (LDL) levels in patients using hormone replacement. Libido has also been shown to improve in older men.<sup>3</sup>

The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology protocol for standardized production of clinical guidelines recommend the use of testosterone replacement for the following indications:

- Management of congenital or acquired primary hypogonadism resulting from orchiectomy (surgical removal of one or both testes) or testicular failure.
- Management of congenital or acquired primary hypogonadism resulting from idiopathic gonadotropin/gonadotropin-releasing hormone deficiency or from pituitary-hypothalamic injury caused by tumors, trauma or radiation.
- Androgen deficiency and acquired immune deficiency syndrome (AIDS) wasting in human immunodeficiency virus (HIV)-infected men.
- Low serum testosterone concentrations (less than 300 ng/dL) in patients receiving long-term corticosteroid therapy.
- Improvement of body composition, strength, bone density, frailty, cognitive function, mood, sexual function, quality of life and to induce secondary sex

characteristics in men with symptomatic androgen deficiency when the benefits outweigh potential risks.<sup>4,5</sup>

The Endocrine Society has recommended that a patient be diagnosed with androgen deficiency only when displaying consistent symptoms of low serum testosterone levels diagnosed by measuring morning total testosterone levels by a reliable assay. Measurement of total testosterone levels should be repeated for confirmation. The panel of experts disagreed on the exact level of serum testosterone. Some panelists saw the benefits of treating patients with serum testosterone levels of 280 to 300 ng/dL, which is the lower limit of normal for a healthy adult male. Clinical trial data indicates a level of 200 ng/dL or less would be appropriate for diagnosis and initiation of replacement therapy. Goal testosterone levels, once replacement therapy has been initiated, should be mid-normal levels (normal range 300 to 1,050 ng/dL) and consistently monitored.<sup>6,7</sup>

The Endocrine Society has recommended against the use of TRT in patients with breast or prostate cancer or a palpable prostate nodule. It is also not recommended to use TRT in patients with levels of prostate-specific antigen (PSA), a glycoprotein enzyme that can serve as a biomarker for prostate disorders, above 4 ng/dL or in men at high risk for prostate cancer.<sup>6</sup> It is the general consensus of both the FDA and Endocrine Society that TRT should not be generally offered to all older male patients with low testosterone levels.<sup>1,6</sup> Before testosterone therapy is recommended, physicians should discuss the potential risks and benefits with their patients.<sup>6</sup> Use of TRT for erectile dysfunction is currently not an FDA labeled use in men with normal serum testosterone levels, although it has been prescribed for this indication.<sup>1,6</sup> Because men presenting with hypogonadism tend to have increased likelihood of mood disturbances including depression, low self-esteem and learning problems, it is recommended that TRT be combined with psychiatric counseling for the most beneficial results.<sup>3</sup>

Testosterone replacement therapy seems to have a positive effect on patients' symptoms and quality of life in short-term follow-up. However, research evaluating the long-term effects of TRT is scarce. Studies assessing the potential cardiovascular complications and cancerous associations with TRT have shown conflicting results. Ongoing long-term research and increased awareness of the potential risks will only help improve patient care.<sup>3</sup>

#### Increased use of TRT in Men and Performance Enhancement

Idiopathic hypogonadism associated with aging has been shown to affect between 5 percent and 40 percent of males between the ages of 40 and 79 years. Lower testosterone levels manifest in ways that can deeply affect a patient's quality of life, but may not warrant immediate action from a physician. However, in recent years, there has been increased awareness of this disorder which has resulted in increased prescribing for testosterone replacement. Largely due to media attention and pharmaceutical marketing, patients have begun to seek treatment for hypogonadism. This can be evidenced by the 500 percent increase in prescrip-

tions since 1993.<sup>7</sup> Most likely stemming from a desire to retain the level of wellness and physical activity one had at a younger age, consumer spending on testosterone therapies has exponentially increased. In 2011, \$1.6 billion was spent on TRT prescriptions, almost tripling what was spent in 2006.<sup>8</sup>

Also contributing to the surge of TRT prescriptions is use of testosterone for enhancement of physique and increased muscle mass used most significantly by athletes and bodybuilders. According to the New England Journal of Medicine, androgen therapy for the purpose of performance enhancement began in the 1940s and has since skyrocketed. Doses of TRT for performance enhancement are 100 times larger than those used for appropriate indications and require significant periods of time off therapy in order to allow the body to recover from adverse reactions caused by such large doses.<sup>9</sup>

As the baby boomer generation ages and direct-to-consumer advertising becomes more popular, TRT prescriptions are projected to increase. Without readily available research of long-term TRT or the proper awareness of potential complications of TRT, concern for patient safety should be of the utmost importance.<sup>10</sup>

#### Risks Associated with Testosterone Replacement Therapy

It is currently agreed upon that there may be some long-term risks involving TRT. The AACE published a comprehensive report on treating men with hypogonadism, reporting on TRT as a treatment option and the identification of potential side effects that might accompany treatment.<sup>3</sup> One potential adverse event is cardiovascular morbidity. However, a consensus has not been reached as to how TRT and testosterone levels in the aging male body affect cardiovascular health. There is a large body of literature suggesting that testosterone therapy may increase the risk of certain adverse cardiovascular events, including nonfatal myocardial infarction and stroke in older men (due to testosterone's tendency to increase platelet aggregation), and in young men with preexisting heart conditions.<sup>3,10,11</sup>

In 2010, Malkin and colleagues published a paper suggesting that low serum testosterone (i.e., endogenous) levels correlate with increased mortality in men with coronary heart disease.<sup>12</sup> Other work by Malkin and his colleagues has demonstrated that testosterone therapy improves functional capacity and reduces symptom severity in men with moderate severity heart failure.<sup>13</sup> The important distinction to make between the conflicting evidence is that low *endogenous* testosterone levels were related to adverse cardiovascular effects, whereas TRT, by definition, introduces *exogenous* testosterone to the endocrine system. This does, however, raise questions as to whether it is worth the risk to utilize TRT as a treatment for hypogonadism in male patients with preexisting cardiovascular risks.

In addition to the adverse effects that TRT may have on cardiovascular health, the AACE report also emphasizes the need to evaluate elevated risks of prostate cancer that may or may not be associated with TRT.<sup>3</sup> It has already been es-

established that patients with prostate cancer are not recommended to receive TRT.<sup>3,4</sup> However, it is less clear as to whether there is a direct relationship between TRT and increased risk of prostate cancer in cancer-free patients at baseline. A 2005 paper from the Brady Urological Institute at Johns Hopkins Hospital showed a correlation between high levels of free serum testosterone with higher incidences of prostate cancer, leading the authors to directly call into question the safety of TRT as it relates to elevated risk of prostate cancer.<sup>14</sup> Information regarding adverse effects and formulation-specific adverse effects of TRT are presented below in Table 1 and Table 2.

In the opposing camp, Rhoden and Morgentaler (2003) concluded that TRT is not an ill-advised treatment option in hypogonadic patients, even in those who have prostatic intraepithelial neoplasia (PIN), a precancerous prostatic lesion that often leads to the development of prostate cancer.<sup>15</sup> In a later 2010 study, Morgentaler and colleagues further concluded that testosterone therapy in men with untreated prostate cancer was not associated with progression of the disease in the first three to 12 months. They recommended that the discouraged use of testosterone therapy in men with less severe prostate cancer or treated prostate cancer should be reconsidered.<sup>14</sup> Recently, TRT is being consid-

### Potential Adverse Side Effects and Various Types of Testosterone Replacement Therapy.<sup>5</sup>

**Table 1. General Testosterone Administration Adverse Effects.**

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) Growth of breast cancer Induction or worsening of obstructive sleep apnea

**Table 2. Formulations and Formulation Specific Adverse Effects.**

Formulation	Specific Adverse Effects
Intramuscular injections of testosterone ethanate, cypionate or undecanoate	Fluctuation in mood or libido Pain at injection site Excessive erythrocytosis (especially in older patients) Coughing episodes immediately after the intramuscular injection*
Transdermal patches	Frequent skin reactions at application site
Transdermal gel	Potential risk for testosterone 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
Buccal testosterone tablets	Alterations in taste Irritation of gums
Pellet Implants	Infection, expulsion of pellet
Oral tablets	Effects on liver and cholesterol (methyltestosterone)†

\*The mechanism of cough, which has been reported rarely after intramuscular injections of testosterone undecanoate and even more rarely after testosterone enanthate and cypionate, is unknown, but it has been attributed to oil embolization.

†Liver toxicity has been reported mostly with oral 17-alpha alkylated androgens. The frequency of skin reactions is higher with the testosterone patch than with the transdermal gels.

ered in patients with hypogonadism associated with prostate cancer comorbidities in some cases, although consistent monitoring is strictly encouraged.<sup>15</sup>

### Monitoring Parameters

Treatment monitoring is important to ensure the patient safety remains at the center of all individualized therapy regimens. Testosterone and its byproducts stimulate the growth of the prostate gland and seminal vesicles. While current research has failed to definitively prove a direct correlation between TRT and increased PSA levels or abnormal prostate growth, monitoring of these parameters is still essential. Follow-up appointments every three to four months is crucial for all patients receiving TRT during the first year of therapy.<sup>13</sup> Patients receiving injected testosterone should have their serum testosterone measured at the midpoint between injections; the level should be within a mid-normal range.<sup>3</sup>

Digital rectal exams (DRE) are recommended every six to 12 months and PSA levels should be measured annually in older males. If PSA levels are determined to be abnormally high (greater than 4 ng/dL), TRT should be discontinued and the patient may need to be referred for urologic consult. In patients concurrently receiving finasteride, further evaluation may be warranted if PSA levels show a significant increase.<sup>3</sup>

Because testosterone increases production of blood cells by the bone marrow, hematocrit should also be routinely monitored every six to 12 months so that coagulation does not result. TRT should be discontinued if hematocrit rises above 50 percent. Other side effects reported with testosterone therapy include gynecomastia resulting from the chemical change testosterone undergoes in the body to produce estrogen and an increased risk of alopecia. This should be considered when assessing the risk versus benefit analysis for each patient.<sup>14</sup>

### How Can Pharmacists Help?

As with any prescription, counseling from a pharmacist is highly recommended. Considering the added risks of hormone therapy, patient education of TRT is a necessity. Testosterone therapy is available in a wide range of formulations including injection, transdermal patches and topical gels, each with their own set of precautions and specific directions for application. Successful and safe utilization of therapy for each patient requires thorough comprehension of their TRT prescriptions.

It is also important that a patient be equipped with all the relevant information regarding the risks of initiating TRT at the point of prescribing. Physicians should attempt to present accurate information to each patient, especially in a society where faulty information is only a click away, and help the patients make the best possible decision in accordance with their own individual health and wellness.

### Conclusion

Testosterone therapies are a rapidly-growing option for aging men that will continue to expand with the aging of the baby boomer generation, due to a higher incidence of hy-

pogonadism in the aging population. Increased use of TRT coupled with its high potential for abuse make counseling and education an essential step for pharmacists at the time of dispensing. The growing demand for testosterone replacement in conjunction with the FDA requirement to label the increased risk of heart attacks and strokes on testosterone products necessitates that health care providers utilize caution when prescribing these therapies and share their awareness of the potential risks and benefits associated with using these products with patients.<sup>1</sup>

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