

From The Medical Letter on Drugs and Therapeutics

Safety of Testosterone Replacement Therapy

Three coordinated double-blind, placebo-controlled clinical trials have evaluated the efficacy of one year of testosterone replacement therapy (Table) in improving sexual function, physical function, and vitality in a total of 790 men ≥ 65 years old with moderately low serum testosterone concentrations and symptoms suggesting hypoandrogenism. Sexual function improved modestly, and there appeared to be marginal benefits in some areas of physical function and vitality as well. The trials were not designed to evaluate the safety of testosterone replacement therapy.¹

Adverse Effects

Testosterone administration has been associated with development of acne, gynecomastia, peripheral edema, and polycythemia. Injections of testosterone undecanoate rarely have caused pulmonary oil microembolism (POME) and anaphylactic

reactions. The main concern with testosterone replacement therapy, however, has been the possibility that it could increase the risk of prostate cancer and cardiovascular disease.

Prostate Cancer

Testosterone replacement therapy has been associated with increases in serum prostate-specific antigen (PSA) concentrations. In the coordinated trials, which excluded men at high risk for prostate cancer, a PSA increase of ≥ 1.0 ng/mL occurred in 23 men treated with testosterone and 8 treated with placebo. Four men developed prostate cancer during the trials or in the subsequent year; three were in the testosterone group. Large randomized controlled trials are lacking, but recent reviews have found no convincing evidence that higher testosterone levels increase the risk of prostate cancer.^{2,3}

Table. Some Testosterone Replacement Products

Drug	Some Available Formulations	Usual Adult Dosage	Cost ^a
Injectable			
Testosterone cypionate - generic Depo-Testosterone (Pfizer)	1, 10 mL vial (100 mg/mL, 200 mg/mL) ^b	50-400 mg IM q2-4 wks	\$45.30 73.50
Testosterone enanthate - generic Delatestryl (Endo)	5 mL vial (200 mg/mL)	50-400 mg IM q2-4 wks	68.00 82.80
Testosterone undecanoate - Aveed (Endo)	3 mL vial (250 mg/mL)	750 mg IM at 0 and 4 wks, then q10 wks	850.00
Transdermal			
Androderm (Actavis)	2, 4 mg/d patch	4 mg once nightly	471.30
Testosterone 1% gel packet - generic ^c	2.5 g gel packet (25 mg test); 5 g gel packet (50 mg test); 75 g MDP (12.5 mg test in 1.25 g gel/act)	50 mg once/d	374.30
AndroGel 1.62% (Abbvie)	1.25 g gel packet (20.25 mg test); 2.5 g gel packet (40.5 mg test); 75 g MDP (20.25 mg test in 1.25 g gel/act)	40.5 mg once/d	489.00
Axiron (Lilly)	90 mL MDP (30 mg test in 1.5 mL soln/act)	60 mg once/d ^d	521.80
Testosterone 2% gel - generic Fortesta (Endo)	60 g MDP (10 mg test in 0.5 g gel/act)	40 mg once/d	341.30 383.50
Testosterone 1% gel - generic	5 g tube of gel (50 mg test); 5 g gel packet (50 mg test) ^e ;	50 mg once/d	309.60
Vogelxo (Upsher Smith)	88 g MDP (12.5 mg test in 1.25 g gel/act)		445.50
Testim (Auxilium/Endo)	5 g tube of gel (50 mg test)		490.20
Intranasal			
Natesto (Trimel/Endo)	11 g MDP (5.5 mg test in 0.122 g gel/act)	11 mg tid ^f	650.70
Buccal			
Striant (Auxilium/Endo)	30 mg buccal tablet	30 mg bid	545.50

Abbreviations: act, actuation; MDP, metered-dose pump; test, testosterone.

^a Approximate wholesale acquisition cost (WAC) for one 10-mL vial (100 mg/mL) of testosterone cypionate, one 5-mL vial of testosterone enanthate, one 3-mL vial of Aveed, or a 30-day supply of transdermal, intranasal, or buccal formulations at the usual adult dosage. WAC = wholesaler acquisition cost or manufacturer's published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly, February 5, 2016. Reprinted with permission by First Databank, Inc. All rights reserved. ©2016. www.fdbhealth.com/policies/drug-pricing-policy. Cost of administration is not included.

^b The 100 mg/mL formulation is only available in a 10-mL vial.

^c AndroGel 1%, the reference product for these formulations, is no longer manufactured.

^d Should be administered as 1 pump actuation (30 mg) to each axilla.

^e Tubes and packets are therapeutically equivalent to Testim.

^f Should be administered as 1 pump actuation (5.5 mg) in each nostril.

Cardiovascular Disease

Some studies have found an association between testosterone replacement therapy and cardiovascular events. In the coordinated trials, 7 men in each treatment group had a major cardiovascular event.

In an earlier 6-month randomized trial in 209 men ≥ 65 years old with a high prevalence of cardiac risk factors, 23 treated with testosterone gel had cardiovascular-related adverse events, compared to 5 who received placebo (HR 2.4; $p = 0.05$).⁴ A meta-analysis of randomized, placebo-controlled trials also found an increased risk of cardiovascular-related adverse events in men treated with testosterone (OR 1.54; 95% CI 1.09-2.18); an analysis by funding source found that the risk was greater in

trials not sponsored by the pharmaceutical industry (OR 2.06 vs 0.89).⁵

Other studies have not found an association between testosterone replacement therapy and cardiovascular risk, and some have found a reduced incidence of myocardial infarction and mortality in men treated with testosterone.⁶⁻⁸

Conclusion

The safety of testosterone replacement therapy remains unclear. There is no convincing evidence to date that it increases the risk of prostate cancer. Some studies have found an increased incidence of cardiovascular events in men treated with testosterone, but others have not.

ARTICLE INFORMATION

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