

Andropause and why pelleted testosterone is the best choice for men.

Bruce Dorr, MD and Ross W. McQuivey, MD

The hormonal transition of menopause doesn't just occur in females. Andropause or male menopause, noted as a decline in sex hormones, also occurs in men. This phenomenon has also been termed testosterone deficiency, androgen deficiency, and late-onset hypogonadism. The medical community is debating whether men really go through a well-defined menopause as their testosterone levels decline, which can have a big impact physically and psychologically. Whatever term that is used, andropause involves a decline in testosterone in men of about 1-2% per year starting around age 30.¹ The accompanying signs and symptoms such as sexual dysfunction, fatigue, weakness, and depression may become noticeable, and in some incapacitating. Testosterone deficiency (TD) is associated with decreased bone mineral density, impaired cognition, increased adverse cardiovascular outcomes, and prostate disease.²

In men with testosterone deficiency, sexual complaints are the most common symptoms. According to the American Urological Association (AUA), reduced libido, erectile dysfunction, decreased spontaneous and morning erections are defining diagnostic factors.³ Fortunately, these symptoms are the most reliable and are very responsive to testosterone therapy. When it comes to maintaining therapy and compliance in men, sexual function is an important driver. Both the ideal serum levels as well as sustained delivery are necessary, in most men, to restore normal nerve and vascular function.⁴ Unlike women, men have a number of FDA approved choices when it comes to testosterone therapy. (See Figure 1).

Figure 1. FDA Approved Testosterone Products

Brand	Dosage Form	Company
Androderm (testosterone)	Transdermal (patch)	Allergan plc
AndroGel (testosterone)	Transdermal (gel)	AbbVie Inc.
Aveed (testosterone undecanoate)	Intramuscular Injection	Endo Pharmaceuticals, Inc.
Depo-Testosterone (testosterone cypionate)	Intramuscular Injection	Pharmacia and Upjohn Company LLC
Fortesta (testosterone)	Transdermal (gel)	Endo Pharmaceuticals, Inc.
Jatenzo (testosterone undecanoate)	Oral	Clarus Therapeutics, Inc.
Kyzatrex (testosterone undecanoate)	Oral	Marius Pharmaceuticals
Natesto (testosterone)	Nasal (gel)	Aytu BioSciences, Inc.
Testim (testosterone)	Transdermal (gel)	Endo Pharmaceuticals, Inc.
Testopel (testosterone)	Pellet (implant)	Endo Pharmaceuticals, Inc.
Tlando (testosterone undecanoate)	Oral	Anateres Pharma, Inc.
Vogelxo (testosterone)	Transdermal (gel)	Upsher-Smith Laboratories, LLC
Xyosted (testosterone enanthate)	Subcutaneous Injection	Antares Pharma, Inc.

According to a 2022 Allied Market research report, the global male hypogonadism market size was \$3.1 billion in 2020 and is projected to reach \$5.1 billion by 2030, expanding at a compounded annual growth rate of 5.1% from 2021 to 2030.⁵ The largest segment of that market are the synthetic hormone therapies like testosterone undecanoate and IM injections which carry known risks of high blood pressure, arterial and venous blood clots, heart attacks, and pulmonary emboli.⁶

In addition to the FDA approved products, men have compounded product options like testosterone injections, topical creams, scrotal/atrevis creams, troches, BLA testosterone injections, human chorionic gonadotropin injections, and gonadorelin injections/troches. It is important to emphasize that when it comes to hormones and testosterone therapy, similar is not the same. Iso-molecular (bioidentical) testosterone is the same—synthetics are similar but behave differently in the body. Though cheaper, the modified injectable testosterone forms, for example testosterone cypionate (Depo-Testosterone), propionate (Testoviron), undecanoate (Aveed), or enanthate (Xyosted) have been reported to increase platelet aggregation and thromboxane A₂—potentiating the risk of thrombosis or clotting.⁷ These also are metabolized by the liver, possibly increasing liver function tests, while increasing SHBG, which can diminish the effectiveness of therapy, because SHBG binds free testosterone making it unavailable to the tissues.

So why choose testosterone pellet therapy?

Testosterone cannot be orally absorbed through the GI tract, so oral testosterone formulations, i.e., methyl testosterone or testosterone undecanoate, are modified for absorption directly into the lymphatic system. When a methyl group (one carbon and 3 hydrogen molecules) is added to the testosterone molecule, it makes it bioavailable and absorbable by the GI tract. This methylated synthetic modification may cause unwanted outcomes, for example, increased clotting risks.

Transdermal testosterone, which includes patches, gels and creams are the fastest growing market due to their convenience.⁵ However, they may be poorly absorbed causing the total testosterone levels to only increase by 100-200ng/dL or super-absorbed and lead to supraphysiologic levels and unwanted side effects.⁸ Gels and creams also pose the risk of transference to close contacts, which is a significant risk that cannot be ignored.

Injections are currently the most commonly prescribed TRT. This form is less expensive than pellets, but involves risks of pain, bruising or injection site reactions. It also spikes the testosterone due to the nature of the oil delivery. It is normally dosed every 2 weeks, but most men will only feel good for 2-3 days. To decrease this roller-coaster effect, injections are recommended weekly or even better, 2x/week or 104 shots/year! The injection amount is typically .25 cc or about \$7/shot. This is about half of the cost of pellets—but a lot more needles and risk of injury, bruising and infection. Testosterone levels may be good—or even too high—on days 1-2, but not much longer afterwards.⁹ The needles and alcohol swabs can be hard to take on trips and levels don't increase after exercise providing muscle recovery, growth or development. The synthetic injections are more stressful on the liver, with increased erythrocytosis and acne—peak levels can be 2000 plus.¹⁰

Natesto is a newer iso-molecular nasal testosterone gel. Because of its short acting half-life, it has been promoted as a testosterone formulation that may preserve fertility. However, its short half-life also requires that it be administered 3 times a day, which may be prohibitive for many patients. It has also been reported to cause nasal irritation, epistaxis, bronchitis, and nasal drainage.

Subcutaneous pellets require a minor in-office surgical procedure and thus carry the rare risk of infection or pellet extrusion. However, once placed, testosterone pellets most represent the normal physiology of hormone distribution. Testosterone is made available to the body via cardiac output, like when endogenous testosterone is made available from the testicles. This physiologic delivery increases the likelihood receptor function returns to normal with improvement to erectile function¹¹ as well as more consistent levels in the brain, bone, and muscle.¹² When dosed appropriately, common side effects like erythrocytosis, elevated estradiol from increased aromatization, and increased DHT conversion associated with prostate issues, acne, or hair loss/growth may be lessened.

Of note, in March of 2023 Biote held a Men's Health Consortium that involved non-Biote academic urologists which included the former President of the AUA. The consensus of this group for their preferred mode of administration as it relates to replacing testosterone was subcutaneous pellets. They highlighted consistency of delivery and absorption, patient compliance along with more consistent serum levels as a few of their reasons for this preference.

The other advantage of pellets is you, the Biote provider! Many men are acquiring testosterone supplements and testosterone therapy online without a physical exam or consultation with an expert in hormone therapy assessing the individual's potential benefits and risks. These pop-up shops and on-line distributors frequently provide testosterone with minimal workup. This is in direct contrast to Biote's individualized and personalized comprehensive approach, incorporating all aspects of therapy—from testosterone to thyroid to nutraceuticals and lifestyle interventions, which allow for an overall improved quality of life. Often patients revel in the attention that is paid to them and their health concerns provided by Biote providers, which motivate them to remain engaged in their journey to better health and wellness.

In conclusion, endogenous testosterone levels diminish with each decade, and low testosterone in adult men can be diagnosed and treated effectively with pellet therapy. Testosterone therapy, as demonstrated by clinical trials, can increase total testosterone levels into the optimal range, improve body composition, muscle strength, bone mineral density; enhance sexual function and activity; decrease adverse cardiovascular events and may improve cognition. These improvements should result in an enhanced quality of life and overall health and wellness.

-
- ¹ Feldman HA, Longcope C, Derby CA, et al. Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts Male Aging Study. *J Clin Endocrinol Metab.* 2002; 87:589-598.
 - ² Low serum testosterone levels are predictive of prostate cancer. Mearini L, Zucchi A, et al. *World J Urol* 2011 09 Nov, 31(2):247-252.
 - ³ Mulhall JP, Trost LW, Brannigan RE et al: Evaluation and management of testosterone deficiency: AUA guideline. *J Urol* 2018; 200: 423.
 - ⁴ Onyeji IC, Clavijo RI. Testosterone replacement therapy and erectile dysfunction. *Int J Impot Res.* 2022 Nov;34(7):698-703.
 - ⁵ AlliedMarketResearch.com. Male Hypogonadism Market by Drug Delivery (Topical Gels, Injectables, Transdermal Patches, Others), by Therapy (Testosterone Replacement Therapy, Gonadotropin and Gonadotropin Releasing Hormone Therapy), by Type (Klinefelters Syndrome, Kallmann Syndrome, Pituitary Disorders, Others): Global Opportunity Analysis and Industry Forecast, 2020-2030.
 - ⁶ JATENZO [prescribing information]. Northbrook, IL: Clarus Therapeutics, Inc.; 2019. Data on file. Clinical Study Report: CLAR-15012. Clarus Therapeutics, Inc. (per FDA Guidance).
 - ⁷ Ajayi AA, Halushka MR. Testosterone increases human platelet thromboxane A2 receptor density and aggregation responses. *Circulation.* 1995 Jun 1;91(11):2742-7.
 - ⁸ Grober ED, Khera M, Soni SD, Espinoza MG, Lipshultz LI. Efficacy of changing testosterone gel preparations (AndroGel or Testim) among suboptimally responsive hypogonadal men. *Int J Impot Res.* 2008 Mar-Apr;20(2):213-7.
 - ⁹ Yassin AA, Haffejee M. Testosterone depot injection in male hypogonadism: a critical appraisal. *Clin Interv Aging.* 2007;2(4):577-90.
 - ¹⁰ Wang C, Swerdloff RS. Practical aspects of testosterone substitution. *J Endocrinol Invest.* 2005;28(3 Suppl):109-11.
 - ¹¹ Onyeji IC, Clavijo RI. Testosterone replacement therapy and erectile dysfunction. *Int J Impot Res.* 2022 Nov;34(7):698-703.
 - ¹² Armagan A, Kim NN, Goldstein I, Traish AM. Dose-response relationship between testosterone and erectile function: evidence for the existence of a critical threshold. *J Androl.* 2006 Jul-Aug;27(4):517-26.