REVIEW ARTICLE

Current Hypogonadism Treatment Options

Steven H. Barag, DO, FACOFP[1]; Talin Meshefedjian, OMS[2]; Jay Yim, OMS[2]; Andrew Wilson, DO[3]

[1] Western University of Health Sciences - College of Osteopathic Family Medicine of the Pacific and Touro University College of Osteopathic Medicine, Pomona, CA

[2] Western University of Health Sciences - College of Osteopathic Medicine of the Pacific, Pomona, CA

[3] Dept. of Medicine, San Antonio Military Medical Center, Joint Base San Antonio-Fort Sam Houston, TX

KEYWORDS:

Hypogonadism

Men's Health

Testosterone

Testosterone Treatment

Abstract: Treatment for hypogonadism is increasing, particularly in the senior population, but low testosterone levels are also on the rise in young men. Hypogonadism treatment represents a unique challenge to clinicians due to label warnings and the negative stigma of being diagnosed and treated for testosterone deficiency. Recent studies of testosterone formulations are showing promising data results of a reduction in adverse impacts. Recent studies have also shown that treating low testosterone is important to significantly reducing the associated risk of diabetes, obesity, metabolic syndrome, osteoporosis, and cardiovascular problems. Physicians need to consider these updated studies and testosterone formula options to educate patients and provide them with a safe and effective testosterone therapy.

INTRODUCTION

Male hypogonadism is defined as a clinical syndrome that results from failure of the testes to produce physiological levels of testosterone due to the disruption of one or more levels of the hypothalamic-pituitary-testicular axis.[1] Male hypogonadism affects between four and five million men in the United States.[2] It is associated with older males, but there is a growing prevalence of low testosterone levels in younger men. Testosterone levels tend to peak in adolescence and early adulthood, with levels declining by about 1 percent each year starting at age 30.[3] With testosterone concentrations declining as men age[4] and the increasing marketing campaigns raising awareness of hypogonadism symptoms, prescriptions for testosterone therapy have risen significantly increasing in recent years.[5]

In adult males, hypogonadism can impact them physically, mentally, and emotionally. Physical symptoms include erectile dysfunction, decreased bone and muscle mass, a decrease in beard and hair growth, and the development of breast tissue. Additionally, patients may become fatigued more easily, have reduced libido, and sometimes impaired focus and cognition. Patients exhibiting any one of these symptoms, combined with a total serum testosterone levels <300 ng/dL are diagnosed according to the endocrine guidelines as hypogonadal.[6]

If a repeat assay confirms low testosterone, luteinizing hormone (LH) should be measured to determine whether the cause is primary or secondary. The secondary cause is indicated by LH levels of <2 ng/mL while LH levels of >10 ng/mL indicates primary testicular failure. If the levels fall within a normal range, this suggests an age-related, decreased hypothalamic response to declining testosterone levels.[1]

This article will describe the risks and benefits of testosterone therapy along with identifying the varieties of testosterone replacement formulations currently available with the advantages and disadvantages of each identified.

RISKS AND BENEFITS OF TESTOSTERONE THERAPY

Testosterone replacement therapy provides many potential benefits to men with symptomatic hypogonadism. Studies have documented that treating low testosterone is important to significantly reduce the associated risk of diabetes, obesity, metabolic syndrome, osteoporosis, and cardiovascular problems.[7] These have been linked to the increase in fat mass and a decrease in muscle mass with declining testosterone. Testosterone replacement therapy has also been proven to impact a man's quality of life, by improving his mood and energy level.[8]

CORRESPONDENCE:
Steven H. Barag, DO, FACOFP | drbarag@gmail.com

 Print ISSN: 1877-573X

TABLE 1:

Potential improvements with testosterone replacement therapy.[9]

Libido
Erectile Dysfunction
Muscle strength and body composition
Mood
Cognition

The potential risks associated with testosterone replacement therapy also need to be considered in relation to the potential benefits. *See Table 2 for a list of these potential risks.*

TABLE 2:

Potential risks with testosterone replacement therapy.[9]

Erythrocytosis
Increases in prostate-specific antigen
Worsening of prostate disorders
Dermatologic
Worsening of existing obstructive sleep apnea
Suppression of Luteinizing Hormone
Decreased intra-testicular testosterone concentrations
Reduced spermatogenesis

In recent years, the U.S. Food and Drug Administration (FDA) has added warnings to testosterone products.

In 2009, the FDA required a box warning for transdermal gel products because of the risk of transference to women and children. In 2014, a warning on the increased events of venous thromboembolism was added to all testosterone products.[9] The following year, it was mandated that all testosterone manufacturers should include the increased risk of heart attack and stroke on the label[9] due to two concerning reports of increased CV risk with TTh. After publication, both of these studies received a significant amount of scrutiny. In the case of Vigen et al., it was originally reported that men who received TTh had an absolute rate of MI, stroke, or death of 25.7% compared with 19.9% in untreated men.[11] Soon after publication, it was discovered the authors had reversed the actual results, and the absolute rate of events was only 10.1% for men that received TTh and 21.2% in untreated men.[13] Additionally, the authors revealed they had miscategorized nearly 1,000 subjects (almost 10% of the patient population) of an all-male cohort to be women.

Considering that past studies suggested that low serum T level is associated with increased cardiovascular events, along with the growing warning label copy, it's understandable why patients may be hesitant to consider testosterone replacement treatment. However, recent studies of current testosterone formulations have shown promising data minimizing adverse impacts. One example is the retrospective cohort study of male veterans who received their medical care at the Veterans Health Administration (VHA) between December 1999 and May 2014. Their results concurred with a previous VA study. Shores et al.[14] analyzed data from seven VA medical centers. They found that TRT was associated with a significant decrease in all-cause mortality (HR: 0.61, CI 95%, P < 0.0001). While supporting the results of Shores et al., this study adds significantly to its conclusions both due to much larger sample size and also by more accurately identifying those who received and responded to the TRT.

The FDA added additional warnings to the testosterone package labeling in 2016 warning of the potential abuse of testosterone and other anabolic androgenic steroids. The potential adverse effects outlined by the FDA included stroke, depression, and aggression.

Additional evidence-based studies are needed so clinicians can better understand the potential risks of testosterone replacement therapy and resolve the significant uncertainty regarding the effect of testosterone replacement therapy on cardiovascular outcomes.

TESTOSTERONE REPLACEMENT THERAPY FORMULATIONS

Table 3 documents the variety of testosterone replacement formulations currently approved for use in the United States. Physicians need to consider multiple factors in choosing which formulation is best suited for their patient including ease of use and cost factors.

INJECTABLE FORMULATIONS

Intramuscular

Intramuscular injections have been used for years due to its efficacy and cost-effectiveness.

For intermediate acting therapies, there are two options. First, testosterone cypionate (Depo® testosterone) is dosed 100-200 mg every two weeks or 50-100 mg every week in the thigh or buttock.[13] Advantages include ease of home injections, infrequent treatment; a three-fold increase in testosterone within two days, affordability, and high efficacy. Disadvantages are fluctuating testosterone levels as testosterone levels gradually decrease until the next injection, and pain and irritation at the injection site.[12] Approximate cost is between $18.45 -$98.07. The second option is testosterone enanthate (Delatestryl®) with a 200 mg/mL dose every two weeks with an average cost of $23.46. Advantages include effective and affordable but in short supply.[13]

For long-acting treatment, the testosterone preparation available is testosterone undecanoate (Aveed®). Usual dosing is 750 mg initially, then 750 mg at four weeks, then 750 mg every ten weeks ongoing with the site of application is the buttock. The advantage is it's long-acting while disadvantages are that it needs to be administered in an office/hospital by a REMS-certified provider and there is a risk of pulmonary oil micro embolism and anaphylaxis. The cost is approximately $1,050 plus any fees associated with the cost of injection.[12]

INJECTABLE FORMULATIONS

INTRAMUSCULAR

INTERMEDIATE ACTING THERAPIES

TESTOSTERONE CYPIONATE (DEPO® TESTOSTERONE)[12,16]

- Dose: 100-200 mg every two weeks or 50-100 mg, weekly in thigh or buttock.
- Advantages: ease of home injections, infrequent treatment; three-fold increase in testosterone within two days, affordability, high efficacy.
- Disadvantages: fluctuating testosterone levels as testosterone levels gradually decrease until the next injection, pain and irritation at injection site.
- Average Cost: Between $18.45 -$98.07.

TESTOSTERONE ENANTHATE (DELATESTRYL®)[13, 17, 18]

- Dose: 200 mg/mL dose every two weeks
- Advantages: effective and affordable
- Disadvantages: short supply
- Average Cost: $23.46

FOR LONG-ACTING TREATMENT

TESTOSTERONE UNDECANOATE (AVEED®)[12]

- Dosing: 750 mg initially, then 750 mg at four weeks, then 750 mg every ten weeks ongoing, site of application the buttock.
- Advantages: long-acting
- Disadvantages: needs to be administered in an office/hospital by a REMS-certified provider, risk of pulmonary oil micro embolism and anaphylaxis.
- Average Cost: approximately $1,050 plus any fees associated with the cost of injection.

TRANSDERMAL FORMULATIONS

GELS

AndroGel® and Testim®[19]

- Dose: Available in 1% gels applied 50-100 mg daily on dry intact skin on the back, abdomen, upper thighs, and arms. AndroGel® is also available 1.62% gel in a metered dose pump.
- Advantages: steady serum testosterone concentration
- Disadvantages: risk of transfer, the need for a daily application, occasional skin irritation, inability of some to achieve normal T levels.
- Average Cost: $175 to 400 for generic and $480 to 550 for a brand name.

2% SOLUTIONS

Fortesta®[19]

- Dose: metered dosed pump, between 10-70 mg daily on dry, intact skin on the front and inner thighs.
- Advantages: Ease of application
- Disadvantages: possibility of redness/ irritation at the application site, acne
- Average Cost: from $160-400

AXIRON®[19]

- Dose: 30-120 mg per day on the dry, intact skin of the axilla.
- Advantages: ease of application, reduced risk of transfer
- Disadvantages: possibility of redness/ irritation, acne
- Average Cost: $260-1,200 per month.

PATCH

ANDRODERM® PATCH[19]

- Dose: between 2-6 mg daily, applied onto dry, intact skin of the arm or torso.
- Advantages: limited risk of transfer, no injection necessary.
- Disadvantages: About one-third of men report skin irritation; patch applied daily.
- Average cost: monthly $475-510.

ALTERNATIVE

NASAL Natesto®[20]	• Dose: is delivered with two pumps, one in each nostril, three times daily. • Advantages: minimal risk of secondary transference • Disadvantages: rhinorrhea, epistaxis, sinusitis, and nasal scabs • Average cost: $600-700 per month.
IMPLANTED SUBCUTANEOUS PELLET Tetopel®[22]	• Dose: 150-450 mg every 3 to 6 months into the subcutaneous fat of the buttock, lower abdominal wall, or thigh. • Advantages: no risk of transfer or need for daily treatment. • Disadvantages: extrusion infection, fibrosis at pellet sites. • Average cost: $150-175 plus the cost of pellet placement based on a dose of 150mg every three months.
BUCCAL Striant SR®[19, 23]	• Dose: 30 mg twice daily. Adheres to the depression in the gingiva superior to upper incisors, • Advantages: less invasive, levels normalize in 24 hours , • Disadvantages: frequent administration, gingival irratation • Average cost: The cost is $550-600 per month.
ORAL (TESTOSTERONE UNDECANOATE) Andriol®[24]	• Dose: 40-80mg, three times a day • Advantages: injections are not necessary, frequent dosing is required • Disadvantages: relatively low dose of testosterone delivered • Average cost: $200-300 per month

TRANSDERMAL FORMULATIONS

Gels

AndroGel® and Testim® are available in 1% gels applied 50-100 mg daily on dry, intact skin on the back, abdomen, upper thighs, and arms. The benefit of a steady serum testosterone concentration is balanced out by the risk of transfer, the need for a daily application, occasional reported skin irritation and the inability of some to achieve normal T levels.[21] The cost is $175 to 400 for generic and $480 to 550 for a brand name. AndroGel® is also available in a 1.62% gel in a metered dose pump.

A 2% solution, Fortesta® in a metered dosed pump, is dosed between 10-70 mg daily on dry, intact skin on the front and inner thighs.[22] Ease of application is the primary benefit countered by the possibility of redness/irritation at the application site, plus acne may occur. Costs range from $160-400.[22] Another 2% metered dosed pump application available is Axiron®, dosed 30-120 mg per day on the dry, intact skin of the axilla.[22] Primary advantages include ease of application and reduced risk of transfer with the possibility of redness/irritation and acne are potential side effects.[22] The range of cost is $260-1,200 per month.[19]

Patch

The first testosterone patch was developed for placement on the scrotal skin to maximize hormone absorptions. Due to skin irritation and adherence problems, the nonscrotal transdermal patch was invented with permeation enhancers to overcome the limited ability of nonscrotal skin to absorb testosterone.

The Androderm® patch is dosed between 2-6 mg daily and applied onto dry, intact skin of the arm or torso.[23] There is a limited risk of transfer and no injection necessary. About one-third of men do report skin irritation and the patch must be applied daily.[23] Average monthly cost is $475-510. Androderm® is currently the only transdermal testosterone patch available in the United States.[19]

ALTERNATIVES

Nasal

Natesto® is delivered with two pumps, one in each nostril, three times daily. There is a minimal risk of secondary transference with rhinorrhea, epistaxis, sinusitis, and nasal scabs as potential side effects (<4% for each respectively).[22] Cost ranges from $600-700 per month. According to a recent 90-day, randomized study in hypogonadal men, those treated with nasal gel showed statistically significant improvements in each of the five domains of erectile function and mood, both of which showed the most benefit by day 30, with smaller increases until day 90. An additional finding from this study showed that treatment with nasal gel successfully restored normal serum testosterone levels while maintaining mean luteinizing hormone (LH) and follicle stimulating hormone (FSH) concentrations within the normal reference range, which is important for retaining the natural pathways of hormones. This has the potential of preserving testicular volume and fertility, which are major issues caused by suppressed LH and FSH.[25]

Implanted Subcutaneous Pellet

Tetopel® is dosed in pellet form, 150-450 mg every 3 to 6 months. The pellets are implanted at a clinic or hospital by a trained provided under sterile conditions into the subcutaneous fat of the buttock, lower abdominal wall, or thigh.[22] There is no risk of transfer or need for daily treatment.[22] Risks include extrusion infection and fibrosis at pellet sites. The cost is $150-175 plus the cost of pellet placement based on a dose of 150mg every three months.[22] Moskovic et al. investigated a small series of young men with Klinefelter's who would be requiring lifetime T replacement and compliance with the Testopel® formulation was better than gels or injections.

Buccal

Striant SR® adheres to the depression in the gingiva superior to upper incisors, 30 mg twice daily. The advantage is that it is less invasive, levels normalize in 24 hours, but it requires frequent administration and there is gingival irritation reported. The cost is $550-600 per month.[19]

Oral (Testosterone undecanoate)

Andriol® is taken orally with a fat-containing meal, 40-80mg, three times a day and is available in many countries outside of the United States.[22] While injections are not necessary, frequent dosing is required and there is a relatively low dose of testosterone delivered.[22] The cost is $200-300 per month.[22] New self-emulsifying formulations are under development and expected to be available in the next 1-2 years.

MONITORING AND FOLLOW-UP

For all formulations of testosterone therapy outlined in this article, it is imperative for clinicians to have regular follow up visits with their patients to monitor serum T levels after ~3 months of initiating therapy. Additional labs should be ordered every six months to monitor PSA, hematocrit, gonadotropins - luteinizing hormone & follicle-stimulating hormone, and secondary testosterone metabolites; estradiol (E2) and dihydrotestosterone (DHT) are all key components to monitor the effects of the TTh and its impact on the hypogonadal-pituitary-gonadal (HPG) axis.[29] Practice guidelines for monitoring patients after initiation of TRT are available through the Endocrine Society at *https://www.endocrine.org/education-andpractice-management/clinical-practice-guidelines*.

CONCLUSION

The risks and benefits of testosterone replacement therapy need to be the focus of in-depth discussion with male hypogonadism patients when deciding on a treatment plan. Recent studies of new testosterone formulations and delivery methods have shown restoration of normal testosterone levels while maintaining normal LH, FSH, and hematocrit levels.[14,17] Most forms of testosterone are notorious for transference to spouses, children, and pets.[22] The new formulations, with the significantly reduced risk of secondary transference, afford much more consideration by clinicians and patients as an appropriate therapeutic option.

Lipshultz looked at testosterone replacement therapy patient satisfaction rates at Baylor via a survey based on patient recall and documented that the choice of therapy was heavily influenced by physician recommendation with 53, 31, and 17 % choosing injections, gels, and Testopel®, respectively.

New methods of delivery and dosing have proposed benefits by exploring bioavailability that mimics the body's physiological process of testosterone production. As physicians, it is important to educate patients on testosterone therapy options by informing them of the ease and safety of use based on evidence-based studies.

The continued growth of this two billion dollar testosterone market has led to the recent increase in direct to patient advertising and marketing. These stand-alone, for profit, low T clinics and men's health spas are exactly why proper counseling and education is critical for the patient to understand the best options, clinically.

It is important for family physicians to continue to explore, study, and consider all intramuscular, transdermal and novel treatment options to provide patients with evidence-based, safe and most effective testosterone therapy recommendation for their patients.

AUTHOR DISCLOSURES:
No relevant financial affiliations

REFERENCES:

1. Decaroli M, Rochira V. Aging and sex hormones in males. Virulence. 2016;8(5):545-57. doi:10.1080/21505594.2016.1259053.
2. Bhasin S, Cunningham GR, Hayes FJ, et al.: Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2010;95(6):2536–59. 10.1210/jc.2009-2354.
3. Finkelstein JS, Lee H, Burnett-Bowie SA, et al. Gonadal steroids and body composition, strength, and sexual function in men. N Engl J Med 2013; 369:1011.
4. Harman SM, Metter EJ, Tobin JD, et al. : Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metab.2001;86(2):724–31. 10.1210/jcem.86.2.7219.
5. Tan RS, Salazar JA: Risks of testosterone replacement therapy in aging men. Expert Opin Drug Saf.2004;3(6):599–606. 10.1517/14740338.3.6.599.
6. Bhasin S et al., Testosterone Therapy in Men with Androgen Deficiency Syndromes: An Endocrine Society Clinical Practice Guideline. Jour. Of Clinical Endo. & Metabolism. 2010.
7. Behre HM, Kliesch S, Leifke E, et al. Long-term effect of testosterone therapy on bone mineral density in hypogonadal men. J Clin Endocrinol Metab 1997; 82:2386.
8. Haider K, Haider A, Doros G, Traish A. Long-Term Testosterone Therapy Improves Urinary and Sexual Function, and Quality of Life in Men with hypogonadism: Results from a Propensity Matched Subgroup of a Controlled Registry Study. The Journal of Urology. 2017. doi:10.1016/j.juro.2017.07.039.
9. Bassil N, Alkaade S, Morley JE. The benefits and risks of testosterone replacement therapy: a review. Ther Clin Risk Manag 2009;5:427-48.
10. Decaroli M, Rochira V. Aging and sex hormones in males. Virulence. 2016;8(5):545-570. doi:10.1080/21505594.2016.1259053.
11. Vigen R, O'Donnell CI, Baron AE, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. JAMA. 2013; 310 (17):1829-1836.
12. Finkle WD, Greenland S, Ridgeway GK, et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. Plos One. 2014; 29;9(1)76.
13. Morgentaler A, Lunenfeld B. Testosterone and cardiovascular risk: world's experts take unprecedented action to correct misinformation. Aging Male. 2014;17:63-65.
14. Testosterone and Cardiovascular Risk in Men: A Systematic Review and Meta-analysis of Randomized Placebo-Controlled Trial Haddad, Rudy M. et al.Mayo Clinic Proceedings , Volume 82 , Issue 1 , 29 – 3.
15. FDA. Topic Testosterone gel products: secondary exposure of children to topical testosterone products. PostMarket Reviews – Volume 2, November 3, 2009. www.fda.gov/Drugs/DrugSafety/DrugSafetyNewsletter/ucm189806.htm. Accessed March 28, 2015.
16. The Journal of Clinical Endocrinology & Metabolism, Volume 97, Issue 6, 1 June 2012, Pages 2050–2058, https://doi.org/10.1210/jc.2011-2591.
17. European Heart Journal, Volume 36, Issue 40, 21 October 2015, Pages 2706–2715, https://doi.org/10.1093/eurheartj/ehv346.
18. Food and Drug Administration. Drugs@FDA: FDA approved drug products. 2018; Retrieved from https://www.accessdata.fda.gov/scripts/cder/drugsatfda/.
19. Snyder PJ. Testosterone treatment of male hypogonadism, In A.M. Matsumoto and KA Martins (Eds.) UpToDate. 2018: Retrieved from www.uptodate.com.
20. American Society of Health-System Pharmacists. Testosterone enanthate injection. 2014; Retrieved from http://www.ashp.org/menu/DrugShortages/CurrentShortages/Bulletin.aspx?id=1045.
21. Ullah MI, Riche DM, Koch CA. Transdermal testosterone replacement therapy in men. Drug Design, Development and Therapy. 2014;8:101-112. doi:10.2147/DDDT.S43475.
22. Thirumalai, A., Berkseth, K., Amory, John, Treatment of Hypogonadism: Current and Future Therapies. F1000 Research. Doi:10.12688/f1000research.10102.1.
23. Pastore MN, Kalia YN, Horstmann M, Roberts MS. Transdermal patches: history, development and pharmacology. Alexander S, ed. British Journal of Pharmacology. 2015;172(9):2179-2209. doi:10.1111/bph.13059.

24. Rogol A, Tkachenko N, Bryson N. Natesto™, a novel testosterone nasal gel, normalizes androgen levels in hypogonadal men. Andrology. 2015;4(1): 46-54. doi:10.1111/andr.12137.
25. Connors, MD William et al. "Mp89-06 Preservation of Normal Concentrations of Pituitary Gonadotropins Despite Achievement of Normal Serum Testosterone Levels in Hypogonadal Men Treated with a 4.5% Nasal Testosterone Gel." The Journal of Urology, vol. 197, no. 4, 2017.
26. Moskovic DJ, Freundlich RE, Yazdani P, Lipshultz LI, Khera M. Subcutaneous implantable testosterone pellets overcome noncompliance in adolescents with Klinefelter syndrome. J Androl. 2012;33(4):570–3. doi: 10.2164/jandrol.111.013979
27. Ross RJM, Jabbar A, Jones TH, et al. Pharmacokinetics and tolerability of a bioadhesive buccal testosterone tablet in hypogonadal men. Eur J Endocrinol. 2004; 150(1) 57-63.
28. Hassan J, Barkin J. Testosterone deficiency syndrome: Benefits, risks, and realities associated with testosterone replacement therapy. Can J Urol. 2016; 23(Suppl 1), 20-30.
29. Rivas AM, Mulkey Z, Lado-Abeal J, Yarbrough S. Diagnosing and managing low serum testosterone. Proceedings (Baylor University Medical Center). 2014;27(4):321-324.
30. Pastuszak AW, Mittakanti H, Liu JS, Gomez L, Lipshultz LI, Khera M. Pharmacokinetic evaluation and dosing of subcutaneous testosterone pellets. J Androl. 2012;33(5):927–37. doi: 10.2164/jandrol.111.016295.
31. Rogol A, Tkachenko N, Bryson N. Natesto™, a novel testosterone nasal gel, normalizes androgen levels in hypogonadal men. Andrology. 2015;4(1): 46-54. doi:10.1111/andr.12137.