
dutch®

dutchwebinars

Testosterone Delivery Options in 2026: Injections, Gels, Pellets & Beyond

Mark Holthouse, MD,FAAFM, FMCP-M

August 26th, 2026

Testosterone Modes of Delivery

Mark Holthouse MD, FAAFP, FMCP-M

Chief Medical Officer at Functional Medicine Institute

IFM Teaching Faculty 2013-2025

Loma Linda University - Teaching Faculty

Speaker A4M

Acronym Table:

Acronym	Meaning
BP	Blood Pressure
DHT	5α-dihydrotestosterone (5α-DHT)
FDA	Federal Drug Administration
FSH	Follicle Stimulating Hormone
FSIAD	Female Sexual Interest
HPA	Hypothalamic Pituitary Adrenal
HPG	Hypothalamic-Pituitary-Gonadal
HSDD	Hypoactive Sexual Desire Disorder
HTN	Hypertension (High blood pressure)
LH	Luteinizing Hormone
MASLD	Metabolic Dysfunction-Associated Steatotic Liver Disease
MCT	Medium Chain Triglycerides
Qs	As needed
Qhs	At bedtime
REMS	Risk Evaluation and Mitigation Strategy
RX	Prescription
SC	Sub cutaneous delivery
SL	Sublingual
T	Testosterone
TRT	Testosterone Replacement Therapy
T. Testo	Total Testosterone

A Word About Testosterone Replacement Vs Optimization in Men & Women

Replacement

- T. Testo levels < 300ng/dl x 2 different days in men. Not in women
- Follows endocrine society guidelines
- Insurance often covers Rx if meets guidelines
- No FDA approved testosterone product for women and all are considered “off-label.”

*E29.1 Testicular Hypofunction - Primary

*E23.0 Hypopituitarism - Secondary

*E89.5 Post procedural Low Testosterone

Optimization

- Based on symptoms of low T
- Not restricted to the < 300 ng/dl x 2
- Still follows most of the endocrine society guidelines
- All off-label use in women and men fall under this category of treatment
- Best done not billing insurance
- Code for signs/symptoms: Fatigue, Low libido, erectile dysfunction, sarcopenia, osteoporosis, prediabetes, MASLD etc.

*Do not use ICD-10 codes unless meets criteria if billing insurance

Testosterone in Women

- There is no FDA-approved testosterone indication in women
- Women treated at around 10% male dosing when it is used. Great data supporting sexual health and mood in pre, peri and postmenopausal women
- Expert panels recommend T for postmenopausal women with FSIAD or HSDD as optimization
- FDA has approved several non-testosterone medication for FSIAD (Female sexual interest and arousal disorder) aka Hypoactive sexual desire disorder.
  - Flibanserinerin (Addyi) - daily oral brain neurotransmitter to stimulate sexual desire
  - Bremelanotide (de (Vyleesi) - injectable, on demand 45 min prior to need
- Ironically, there are non-hormonal FDA-approved treatments for vasomotor symptoms as well:
  - Fezolinetant (Veozah) and Elinzanetant - Neurokinin receptor
  - Paroxetine (Brisdelle) - SSRI for hot flashes

Testosterone Delivery Continues to Evolve

- **Injectables:** Cypionate, Enathate, Proprionate, Undeconoate Esters
- **Buccal implants:** Striant
- **Creams and Gels:** Testim, Androgen, compounded
- **Patches:** Testoderm
- **Nasal Gels:** Natesto nasal
- **Topical roll-on transdermal:** Axiron - brand discontinued
- **Pellets:** Not all are created equal
- **Oral-lymphatics:** Oral Undecanoate - Gen 3-Kyzatrex
- **Nano-Liposomal sublingual forms:** Modified nanoemulsion of free underivatized Testosterone (15mg Testosterone)

Personalization Based on Many Factors

- $ Cost
- Insurance eligibility
- Optimization vs deficiency
- Convenience
- Onset of action
- * Duration of exposure
- Central suppression
- Erythrocytosis/Acne/Gynecomastia
- Fertility concerns
- Testicular atrophy
- Ease of dosing adjustment
- Mood, hair loss, acne

Making TRT Personal- Injectables

Common Preparations:

- Testosterone cypionate –generally the most affordable TRT at around $40/month
- Testosterone enanthate
- Testosterone undecanoate (long-acting depot formulation)

Mechanism of Delivery:

- Testosterone esters dissolved in oil and injected into muscle
- Esters release systemically very slowly
- Esterases cleave the ester, releasing the T

Making TRT Personal- Injectables

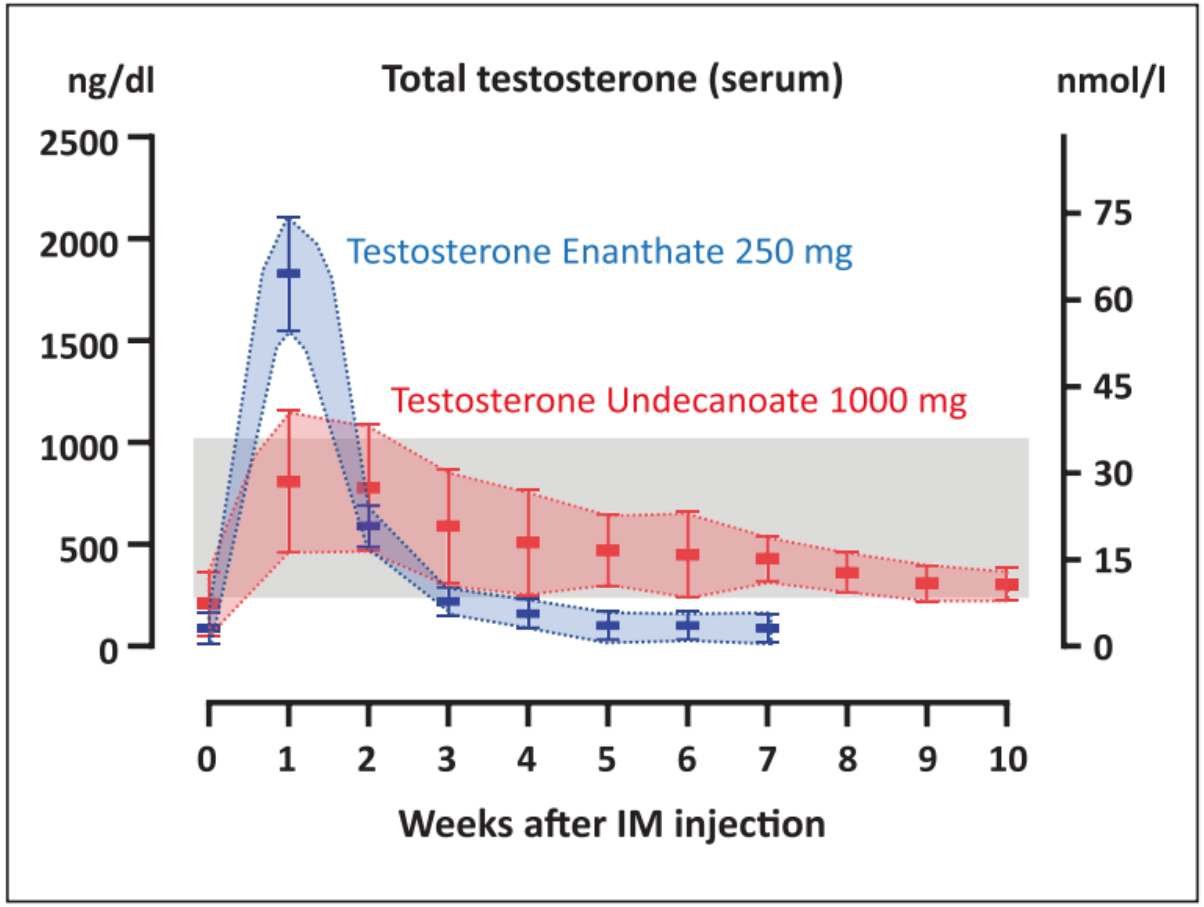
Shorter-acting esters (cypionate/enanthate)

- Peak serum levels 24–48 hours
- Supraphysiologic peaks seen
- Gradual exponential decline over 7–14 days
- Wide peak-trough variability (especially with weekly or biweekly dosing)
- Best physiologic practice is twice weekly dosing at a minimum
- 10ml vial of 200mg/ml 0.25ml (50mg) inj sc Monday and Thursday

Long-acting undecanoate (AVEED only US brand)

- Flatter curve than short-acting esters
- Long half-life (~10–14 weeks between injections)
- Reduced fluctuation but sustained exposure
- REMS training required by FDA-pulmonary oil micro-embolisms, and anaphylaxis

Making TRT Personal- Injectables



Rey RA, et al. Androgen Treatment in Adolescent Males With Hypogonadism. Am J Mens Health. 2020

Limitations with Injectables

- No diurnal variation
- No ultradian pulsatility
- Peak often exceeds physiologic morning levels
- Troughs may fall below physiologic range
- Suppresses LH/FSH rapidly and profoundly
- High incidence of Erythrocytosis and aromatization
- Hexane extraction of highly processed seed oils used as vehicle (Can use MCT from compounders)
- User must be fine with frequent injections

Yassin AA, Haffejee M. Testosterone depot injection in male hypogonadism: a critical appraisal. Clin Interv Aging. 2007;2(4):577-90. PMID: 18225458; PMCID: PMC2686335.

Subcutaneous Pellets

- Pellets have been used in men and women for over 80 years and have been used widely in Australia and Europe
- TestoPel brand FDA-approved for men since 1972
- Soy or Yam based crystalline powder compressed into pellets are inserted subcutaneously (typically hip/gluteal region)
- Many compounded versions with dosing platforms and methods available: SottoPelle, BioTe, EvexiPel. Other compounders: Belmar Pharmacy, Women's International Pharmacy
- Slowly dissolve over 3-6 months
- Minimal daily fluctuation
- Long steady-state plateau
- Gradual taper over months

Subcutaneous Pellets

Not all pellets or pellet methods are created equal

- Some products less likely to expulsion than others
- Some with sustained release cellulose
- Some with less traumatic insertion tools and methods
- Some with micro doses of steroid to reduce scar tissue formation
- Some with horizontal vs vertical compression for more consistent dosing
- Some with dosing platforms providing calculations that are more accurate
- *Get adequately trained prior to offering this form of TRT delivery*
- Male range 1400mg-3000mg q 5-6 months
- Female range 50mg-137.5mg q 3-4 months (start low and work up based on symptoms and side effects
- I try to avoid serum level > 1200ng/dl in men and 125ng/dl in women

Subcutaneous Pellets- Good and the Bad

Pros

- One of the most convenient methods of TRT
- Minor procedure
- Well tolerated
- Often less erythrocytosis and aromatization when dosed correctly compared to inj.
- No needle injection

Cons

- One of the more expensive TRT options. $$. ($1500/year)
- Steep learning curve and training required
- Important to know how to handle side effect as they cannot be removed
- Decreased efficacy towards the end of the dosing cycle

Other Less Common Modes of TRT Delivery

Nasal Gel: Natesto

- Quick onset of action within minutes
- Short ½ life of 10-100 minutes
- 5.5mg/pump
- 1 pump in each nostril 3 times a day
- Nasal irritation

Testosterone Buccal Systems: Striant mucosal adhesive tablet

- 30mg tablet - like adhesive to gum or inner cheek twice daily
- Change in sense of taste

Testosterone Creams/Gels-Traditionally Most Popular Mode

- Creams are from compounders and usually less $$ than non-compounded Rx.
- The FDA-approved drugs are usually gels and patches: AndroGel, Testim, (supplying 50-100mg a day). Very $$ if not covered by insurance.

Pharmacokinetics

- Rise within 2-4 hours after application
- Steady state within 24 hours
- Maintains mid-normal levels throughout day
- T levels decline overnight with creams/gels
- Flatter curve than endogenous physiology
- Minimal ultradian fluctuation during the day
- Some morning rise if creams/gels applied in AM
- Still lacks ultradian pulses
- Lower amplitude than endogenous AM peak
- Continuous dermal absorption
- Can spike DHT

Testosterone Patches

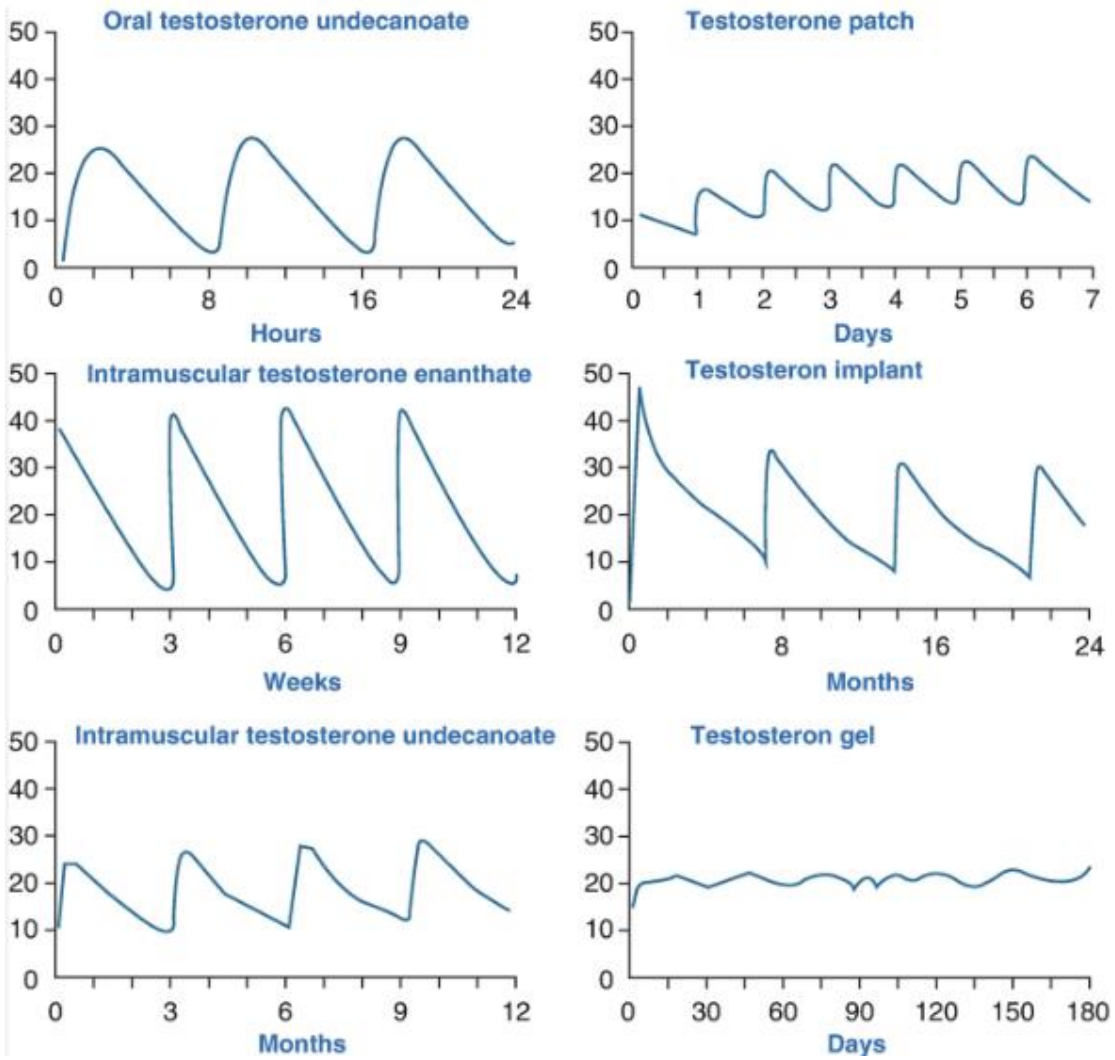
Testoderm/Androderm

- Convenience
- If applied QHS, can mimic physiologic AM T spike (closer to diurnal rhythm than creams/gels)
- Can be expensive
- Commonly causes a dermatitis from the adhesive
- Cannot get wet for 4 hours after application
- Must constantly rotate application sites
- Less likely to contaminate others than creams and gels
- Flatter curve than endogenous physiology
- Minimal ultradian fluctuation during the day
- Still lacks ultradian pulses
- Continuous dermal absorption
- Can spike DHT

Comparing Pharmacokinetics Profiles: Creams/Gels and Patches

	Axiron Roll-On	Creams/Gels	Patches
Steady State Timeline	Within 24 hr.	Within 24 hr.	Within 24 hr.
Daily Rhythm Profile	Flater/Stable curve over 24 hrs.	Flater/Stable curve over 24 hrs.	Mimics diurnal rhythm spikes early, drops later
Primary Dosing Site	Axillary	Shoulders, abdomen, thighs or scrotum	Back, abdomen, thighs, upper arms
Skin Irritation Risk	Low/Moderate	Low/Moderate	High Risk

Comparing Pharmacokinetics Profiles



Kalinchenko, S., Tyuzikov, I., Mskhalaya, G., Tishova, Y. (2017). Testosterone Therapy: Oral Androgens. In: Hohl, A. (eds) Testosterone. Springer, Cham.

Oral Testosterone Undecanoate

- Testosterone undecanoate is testosterone esterified with an 11-carbon fatty acid chain
- This modification:
  - Increases lipophilicity
  - Promotes incorporation into chylomicrons
  - Facilitates intestinal lymphatic absorption
  - Partially bypasses portal hepatic metabolism

Oral Testosterone Undecanoate

Absorption Mechanism

- Dissolves in dietary fats
- Incorporated into micelles in the intestine
- Absorbed into enterocytes
- Packaged into chylomicrons
- Transported via lymphatic system
- Enters systemic circulation through the thoracic duct avoiding immediate hepatic exposure

Pharmacokinetics

- Rapid rise (typically 2-4 hours)
- Requires fat-containing meal for optimal absorption
- Twice-daily dosing common
- Moderate peak-through variability
- No ultradian pulsatility

Oral Testosterone Undecanoate

- Fast-acting
- Less central HPG LH/FSH suppression than other TRT delivery depending on dose
- Watch for HTN
- Raises DHT profoundly
- Best mode for raising free testosterone relative to total testosterone
- Approx $160/month
- Must check blood levels within 3-5 hours of AM dosing

Historic Perspective

Current testosterone replacement therapies were developed with a primary goal:

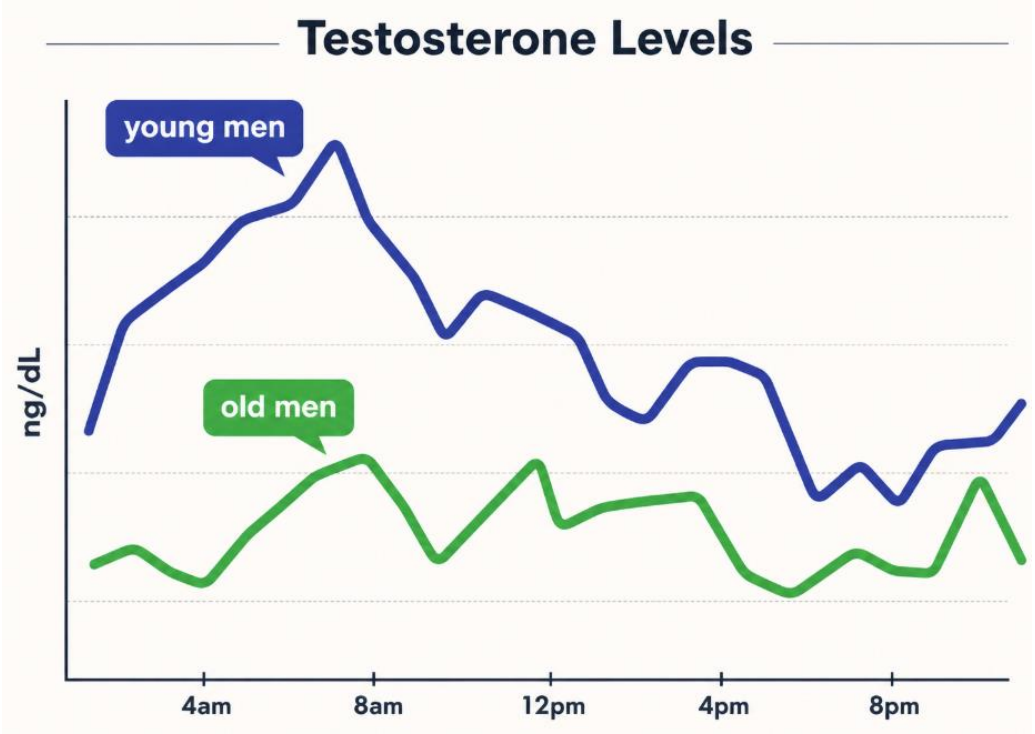
- Raise serum testosterone into reference range, not to replicate physiologic rhythm

Endocr J. Author manuscript; available in PMC: 2015 Jan 27.

Published in final edited form as: Endocr J. 2009 Jul 17;56(6):729–737. doi: 10.1507/endocrj.k09e-185

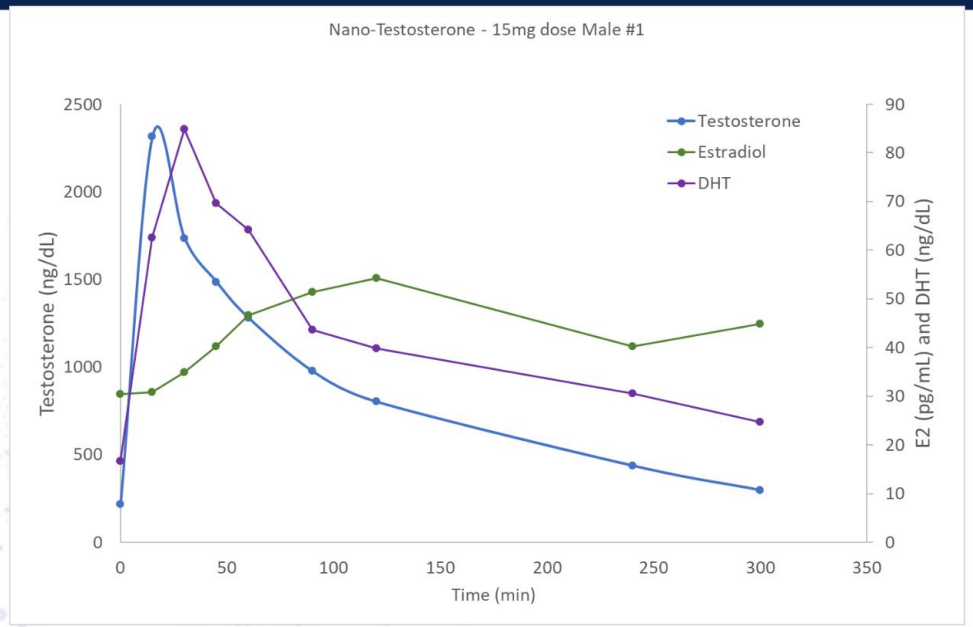
GnRH Pulsatility, the Pituitary Response and Reproductive Dysfunction

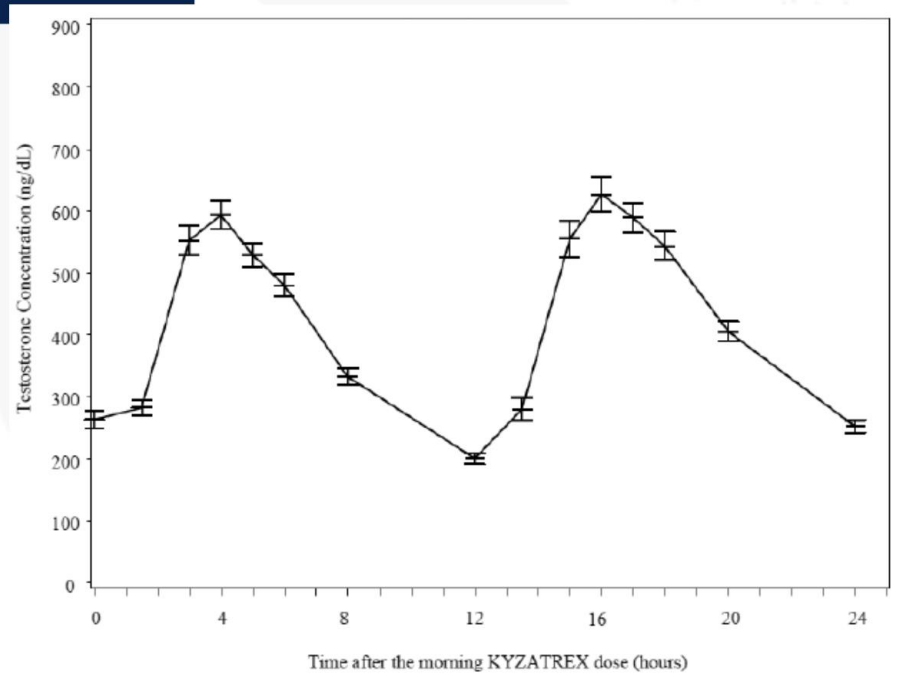
Rie Tsutsumi [1,2,3], Nicholas JG Webster [1,2,*]



Pharmacokinetic Profiles

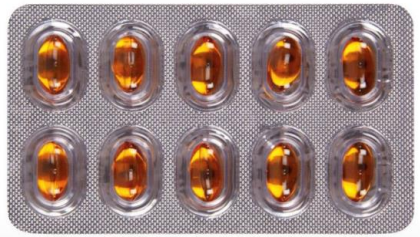
QS Oral Nano Testosterone versus versus Kazatrex Oral SEDS Testosterone Undecanoate





QS– modified nanoemulsion of free underivatized Testosterone (15mg Testosterone)

Kazatrex – self-emulsifying Testosterone Undecanoate (200mg Testosterone



Sustained Elevations of T Vs Pulsatile Short Acting Sublingual Release

- In the human HPG axis, LH and subsequent T pulses on an hourly basis during the day.
- TRT that most closely simulates an hourly, pulsatile pattern avoids many pitfalls of sustained T levels throughout a dosing cycle.
  - Lack of central suppression of LH/FSH
  - Lack of Erythrocytosis
  - Less chance for gynecomastia and testicular atrophy
  - Decreased androgen receptor desensitization
  - Much lower doses are effective; 5mg for women and 15mg for men in case studies
  - Possible maintenance of male fertility
  - SL delivery allows testosterone to be directly delivered to the systemic circulation bypassing first pass liver metabolism and hepatotoxicity

Why Consider Oral Nano-liposomal TRT?

- Androgen receptors respond differently to transient vs. sustained ligand exposure
- Pulsatile exposure allows receptor reset
- Chronic saturation may alter transcriptional responsiveness
- **Testosterone and LH Ultradian Pulses throughout the day**
- T decline begins shortly after awakening
- Progressive reduction throughout the day
- Lowest levels typically observed in the late afternoon/evening
- Superimposed ultradian pulses remain present
- In young men, the amplitude of this decline is pronounced. In older men, it becomes flatter.

Purpose of the Diurnal T Decline in Young Men

Anabolic Transition

- Moving from anabolic dominance toward evening parasympathetic predominance
- Coordination with melatonin rise in the evenings

Androgen Receptor Latency

- Reduced exposure allows receptor re-sensitization
- Prevents continuous transcriptional activation

HPG Axis Feedback Modulation

- Intermittent suppressive feedback avoids prolonged suppression signals
- Continuous testosterone therapy eliminates the trough that may be biologically meaningful.

Loss of HPG LH/T Rhythmicity in Aging Men

- Decreased peak morning testosterone
- Reduced amplitude of diurnal variation
- Lower LH pulse amplitude
- Impaired sleep-associated T rise
- Similar to the decline in heart rate variability with aging men

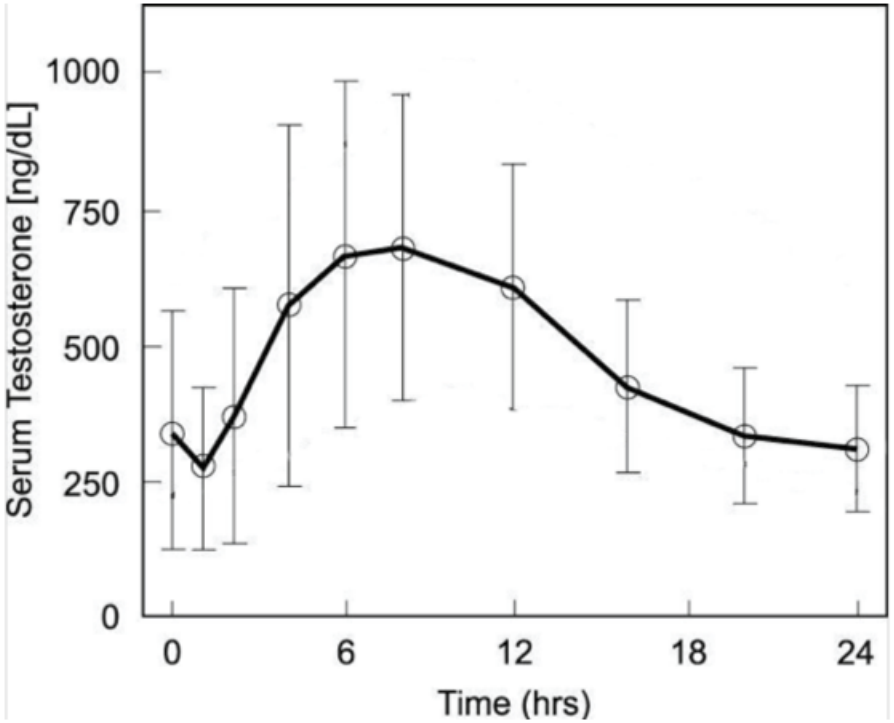
Rhythmicity Important With Many Bodily Functions

- Metabolic flexibility
- NAD+ and biologic clock circadian rhythmicity
- Muscle strength
- Insulin sensitivity - in the AM
- Cortisol peak - in the AM
- Testosterone pulse dosing in REM sleep and during the day
- BP peak in AM
- GH secretion in deep sleep
- Melatonin increased at night
- Mitochondrial function
- Cognitive and mood regulation
- Spermatogeneisis

The Magnitude of T Peak Amplitude Levels Activates Genes.

Circadian T amplitude affects:

- Mitochondrial biogenesis
- Insulin sensitivity
- Neurotransmitter regulation
- Nitric oxide signaling



Changes in serum testosterone levels over a 24 hour period.

Testosterone Timing Coordinates With Many Hormones

Morning testosterone peak enhances:

- Insulin sensitivity
- Muscle protein synthesis sis
- Readiness for the day

Reduces Chronic Receptor Saturation

- A pulsatile exposure may preserve tissue responsiveness.

Aligns with Chronobiology Medicine is increasingly recognizing:

- Circadian pharmacology
- Time-dependent drug metabolism

Hormone–clock gene interaction

The TRT Delivery Systems of the Future Should Consider

- Replicate normal circadian amplitude
- Mimic pulsatile physiologic signaling where possible
- Preserve regulator axis potency
- Minimize chronic receptor occupation
- Align TRT timing with internal physiology

References and Citations

- Bittman EL. Timing in the Testis. J Biol Rhythms. 2016 Feb;31(1):12-36. doi: 10.1177/0748730415618297. Epub 2015 Dec 8. PMID: 26656623.
- Bremner WJ, Vitiello MV, Prinz PN. Loss of circadian rhythmicity in blood testosterone levels with aging in normal men. J Clin Endocrinol Metab. 1983 Jun;56(6):1278-81. doi: 10.1210/jcem-56-6-1278. PMID: 6841562.
- Diver MJ, Imtiaz KE, Ahmad AM, Vora JP, Fraser WD. Diurnal rhythms of serum total, free and bioavailable testosterone and of SHBG in middle-aged men compared with those in young men. Clin Endocrinol (Oxf). 2003 Jun;58(6):710-7. doi: 10.1046/j.1365-2265.2003.01772.x. PMID: 12780747.
- Edelstein D, Basaria S. Testosterone undecanoate in the treatment of male hypogonadism. Expert Opin Pharmacother. 2010 Aug;11(12):2095-106. doi: 10.1517/14656566.2010.505920. PMID: 20642374.
- Liu J, Li Y, Zhang X, Bu P, Du X, Fang L, Feng Y, Guo Y, Han F, Jiang Y, Li Y, Lin J, Liu M, Liu W, Long M, Mu J, Sun N, Wu H, Xie J, Xie J, Xie L, Yu J, Yuan H, Zha Y, Zhang Y, Zhu S, Wang J; Chinese Hypertension League expert consensus committee on the management of nocturnal hypertension. Management of nocturnal hypertension: An expert consensus document from Chinese Hypertension League. J Clin Hypertens (Greenwich). 2024 Jan;26(1):71-83. doi: 10.1111/jch.14757. Epub 2023 Dec 21. PMID: 38126623; PMCID: PMC10795100.faf229. doi: 10.1093/ckj/sfaf229. PMID: 40927380; PMCID: PMC12415516.
- Mallamaci F, Torino C, Tripepi G. Hypertension burden in CKD: is nocturnal hypertension the primary culprit? Clin Kidney J. 2025 Jul 17;18(9):s
- Miner M, Wang C, Kaminetsky J, Khera M, Goldstein I, Carson C 3rd, Chidambaram N, King S, Dobs A. Safety, efficacy, and pharmacokinetics of oral testosterone undecanoate in males with hypogonadism. Andrology. 2025 May;13(4):882-893. doi: 10.1111/andr.13747. Epub 2024 Sep 10. PMID: 39252657; PMCID: PMC12006877.

References and Citations

- Pastuszak AW, Gomez LP, Scovell JM, Khera M, Lamb DJ, Lipshultz LI. Comparison of the Effects of Testosterone Gels, Injections, and Pellets on Serum Hormones, Erythrocytosis, Lipids, and Prostate-Specific Antigen. Sex Med. 2015 Sep;3(3):165-73. doi: 10.1002/sm2.76. Epub 2015 Aug 12. PMID: 26468380; PMCID: PMC4599554.
- Petrie EC, Matsumoto AM, Bremner WJ. Modulation of luteinizing hormone pulse amplitude by the frequency of luteinizing hormone-releasing hormone stimulation and by testosterone in castrated, hypothalamic-lesioned male rats. Biol Reprod. 1988 Feb;38(1):143-9. doi: 10.1095/biolreprod38.1.143. PMID: 3130108.
- Roth MY, Dudley RE, Hull L, Leung A, Christenson P, Wang C, Swerdloff R, Amory JK. Steady-state pharmacokinetics of oral testosterone undecanoate with concomitant inhibition of 5α-reductase by finasteride. Int J Androl. 2011 Dec;34(6 Pt 1):541-7. doi: 10.1111/j.1365-2605.2010.01120.x. Epub 2010 Oct 24. PMID: 20969601; PMCID: PMC4269219.
- Tsutsumi R, Webster NJ. GnRH pulsatility, the pituitary response and reproductive dysfunction. Endocr J. 2009;56(6):729-37. doi: 10.1507/endocrj.k09e-185. Epub 2009 Jul 17. PMID: 19609045; PMCID: PMC4307809.
- Veldhuis JD, King JC, Urban RJ, Rogol AD, Evans WS, Kolp LA, Johnson ML. Operating characteristics of the male hypothalamo-pituitary-gonadal axis: pulsatile release of testosterone and follicle-stimulating hormone and their temporal coupling with luteinizing hormone. J Clin Endocrinol Metab. 1987 Nov;65(5):929-41. doi: 10.1210/jcem-65-5-929. PMID: 3117834.
- Woodward SH. Autonomic regulation during sleep in PTSD. Neurobiol Stress. 2022 Sep 6;21:100483. doi: 10.1016/j.ynstr.2022.100483. PMID: 36532367; PMCID: PMC9755032.
- Yassin AA, Haffejee M. Testosterone depot injection in male hypogonadism: a critical appraisal. Clin Interv Aging. 2007;2(4):577-90. PMID: 18225458; PMCID: PMC2686335.

Become a Provider Today!

Exclusive hormone education for DUTCH providers

- Comprehensive Report
- Clinical Support & Education
- Peer Reviewed & Validated Research

New DUTCH Providers are eligible for 50% off their first five test kits.

50% off*

*Special offer of 50% off first five test kits is invalid 60 days after new provider registration."

Thank You!

Mark Holthouse, MD,FAAFM, FMCP-M

August 26th, 2026

Testosterone Modes of Delivery

dutchwebinars