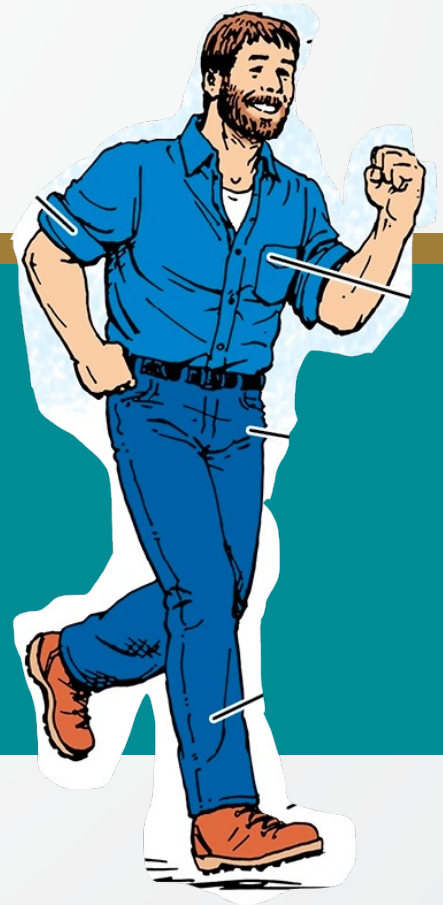
Testosterone deficiency syndrome, Androgen replacement indications and principles



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Disclosures

Drs. Sadri and Howards have *no financial disclosures or conflicts of interest* to report relevant to this presentation.

Most of the Testosterone brands available in the US will be reviewed without any specific recommendation (prefer Generics when it is available).

Learning objectives

After this presentation, the learner should be able to:

- Understanding the definition and classification of male hypogonadism
- Identify the etiologies and different categories of male hypogonadism
- Apply the latest recommendations of AUA on evaluation and management of male hypogonadism and Testosterone Therapy

TESTOSTERONE DEFICIENCY— TERMINOLOGY

- Male hypogonadism is related to relatively rare disorders of the hypothalamic–pituitary–gonadal axis. Thus the classical diagnosis of hypogonadism involves disorders like Kallman's syndrome, pituitary tumors (secondary hypogonadism) and Klinefelter syndrome, and XX-males syndrome (primary hypogonadism)
- The classical underlying diseases causing hypogonadism are thus not responsible for the majority of testosterone deficiency in men
- Men with severe hypogonadism are easily diagnosed in a straightforward way, whereas men with less severe deficiency without a definite or clearly identifiable cause are more of a challenge.
- In these cases, a combination of **primary** (testicular) and **secondary** (hypothalamic/pituitary) failure is often at hand, indicating that concomitant morbidity may affect both hypothalamic and pituitary function as well as testicular capacity to respond to gonadotropin stimulation and decreased capacity to produce testosterone

PRIMARY, SECONDARY, OR MIXED HYPOGONADIS

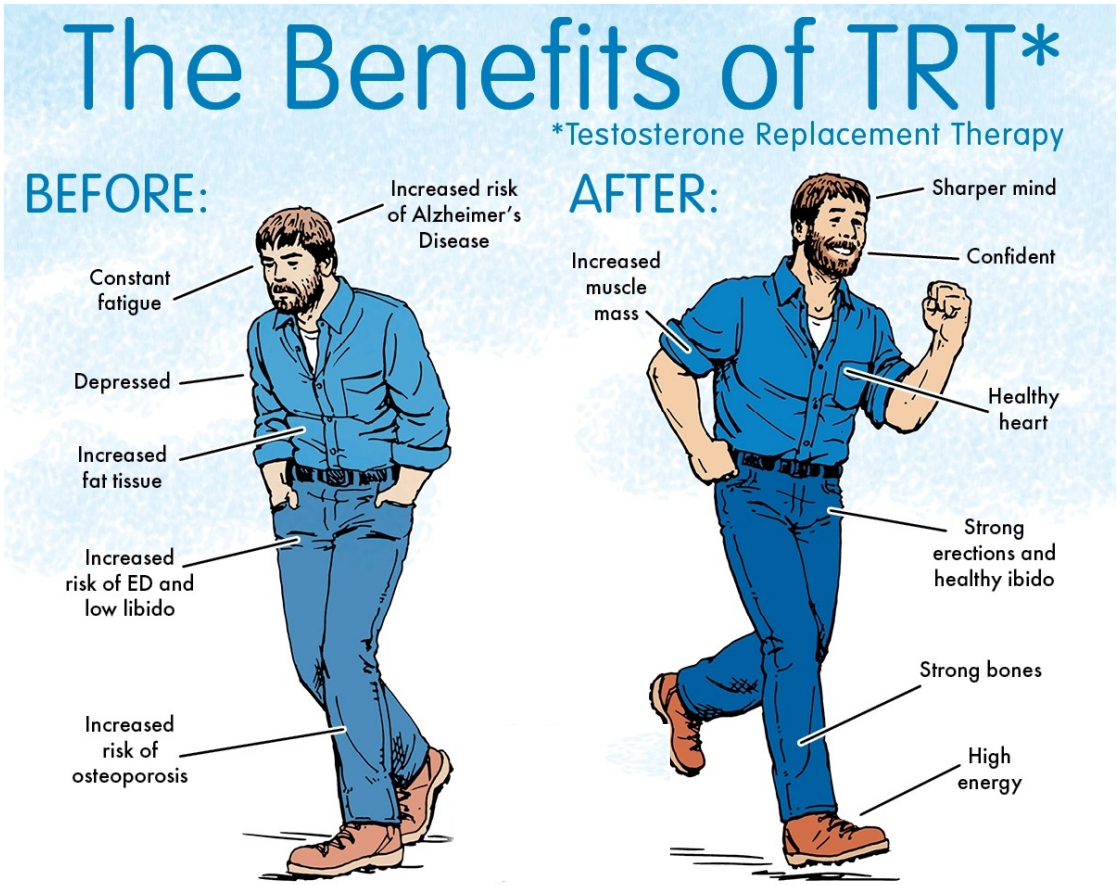
- If testosterone is low and LH is high, the condition is classified as primary hypogonadism:
  A substantial number of middle age and elderly men presents with the sign of classical primary hypogonadism

- If LH levels are low, it is classified as secondary hypogonadism

- A common clinical situation in elderly men is the presence of mid-normal LH levels and low testosterone levels, indicating an inability of the pituitary to respond to the low testosterone level

It is well-documented that testosterone replacement therapy in hypogonadal men improves:

- Muscle mass and strength,
- Bone mineral density,
- Mood,
- Sexual function (libido and erectile function),
- General appreciation of increased energy



Identifying eligible men for testosterone therapy is based on a combination of measurement serum testosterone assessment and clinical evaluation of hypogonadal symptoms.

Endocrine Society's Clinical Guidelines Classification of Symptoms and Signs of Androgen Deficiency

A. Symptoms and signs suggestive of androgen deficiency in men:

- Incomplete sexual development, eunuchoidism, aspermia
- Reduced sexual desire (libido) and activity
- Decreased spontaneous erections
- Breast discomfort, gynecomastia
- Loss of body (axillar and pubic) hair, reduced shaving
- Very small or shrinking testis (especially <5 mL)
- Inability to father children, low or zero sperm count
- Height loss, low trauma fracture, low bone mineral density
- Reduced muscle mass and strength
- Hot flushes, sweats

Endocrine Society's Clinical Guidelines Classification of Symptoms and Signs of Androgen Deficiency

B. Symptoms and signs associated with androgen deficiency that are less specific than those in group A

- Decreased energy, motivation, initiative, aggressiveness, self-confidence
- Feeling sad or blue, depressed mood, dysthymia
- Poor concentration and memory
- Sleep disturbance, increased sleepiness
- Mild anemia (normochromic, normocytic, in the female range)
- Increased body fat, body mass index
- Diminished physical or work performance

The prepubertal onset of hypogonadism results in:

- Lack of virilization
- Sustained height increase without closure of the epiphysis
- Lack of pubertal growth spurt
- Incomplete sexual development
- Aspermia

The Adult onset of hypogonadism results in:

- Reduced libido
- Reduced sexual activity
- Loss of spontaneous erections
- Erectile dysfunction
- Loss of body hair
- Reduced need to shave
- Reduced muscle mass and strength
- Flushes and sweating

Questionnaires and Interview Instruments for

HYPOGONADISM DIAGNOSIS

Table 2 Sensitivity and Specificity of Interview and Screening Questionnaires

	Sensitivity (%)	Specificity (%)
ADAM (8)	97	30
MMAS (9)	60	59
AMS (7)	83	39
Androtest (6)	68	65

ADAM questionnaire

1. Do you have a decrease in libido (sex drive)?
2. Do you have a lack of energy?
3. Do you have a decrease in strength and/or endurance?
4. Have you lost height?
5. Have you noticed a decrease in enjoyment of life?
6. Are you sad and/or grumpy?
7. Are your erections less strong?
8. Have you noticed a recent deterioration in your ability to perform sports?
9. Are you falling asleep after dinner?
10. Has there been a recent deterioration in your work performance?

If you answered YES to questions 1 or 7 or any 3 other questions, you may have a low testosterone level

AMS Questionnaire

Which of the following symptoms apply to you at this time? Please, mark the appropriate box for each symptom. For symptoms that do not apply, please mark "none".

	Symptoms:	none	mild	moderate	severe	extremely severe
	Score =	1	2	3	4	5
1.	**Decline in your feeling of general well-being** (general state of health, subjective feeling)	☐	☐	☐	☐	☐
2.	**Joint pain and muscular ache** (lower back pain, joint pain, pain in a limb, general back ache)	☐	☐	☐	☐	☐
3.	**Excessive sweating** (unexpected/sudden episodes of sweating, hot flushes independent of strain)	☐	☐	☐	☐	☐
4.	**Sleep problems** (difficulty in falling asleep, difficulty in sleeping through, waking up early and feeling tired, poor sleep, sleeplessness)	☐	☐	☐	☐	☐
5.	**Increased need for sleep, often feeling tired**	☐	☐	☐	☐	☐
6.	**Irritability** (feeling aggressive, easily upset about little things, moody)	☐	☐	☐	☐	☐
7.	**Nervousness** (inner tension, restlessness, feeling fidgety)	☐	☐	☐	☐	☐
8.	**Anxiety** (feeling panicky)	☐	☐	☐	☐	☐
9.	**Physical exhaustion / lacking vitality** (general decrease in performance, reduced activity, lacking interest in leisure activities, feeling of getting less done, of achieving less, of having to force oneself to undertake activities)	☐	☐	☐	☐	☐
10.	**Decrease in muscular strength** (feeling of weakness)	☐	☐	☐	☐	☐
11.	**Depressive mood** (feeling down, sad, on the verge of tears, lack of drive, mood swings, feeling nothing is of any use)	☐	☐	☐	☐	☐
12.	**Feeling that you have passed your peak**	☐	☐	☐	☐	☐
13.	**Feeling burnt out, having hit rock-bottom**	☐	☐	☐	☐	☐
14.	**Decrease in beard growth**	☐	☐	☐	☐	☐
15.	**Decrease in ability/frequency to perform sexually**	☐	☐	☐	☐	☐
16.	**Decrease in the number of morning erections**	☐	☐	☐	☐	☐
17.	**Decrease in sexual desire/libido** (lacking pleasure in sex, lacking desire for sexual intercourse)	☐	☐	☐	☐	☐

Have you got any other major symptoms? **Yes** ☐ **No** ☐

If Yes, please describe: _____

_____

MEASUREMENT OF SERUM TESTOSTERONE

- Most of the testosterone in the blood is bound to **SHBG** (sex hormone–binding globulin) and **albumin,** with only some 0.5% to 3% being unbound or **free**.

- Total testosterone levels are affected by circadian variation, in some areas circannual variation, and also by concomitant medical conditions and some medical treatments (opiates and glucocorticoids):
  Due to the circadian variation, serum samples should be drawn between 7 and 10 in the morning after a normal night sleep and without prior exposure to vigorous physical activity

- Fasting samples are preferred as the glucose load suppresses testosterone levels

- Low serum level should be confirmed especially in men with borderline levels.

- In clinical practice, assessment of total testosterone is most often sufficient.

- **General screening** of testosterone levels is not indicated and should so far be limited to men who seek medical attention with symptoms suggestive of testosterone deficiency and in some groups of men with specific underlying disorders known to have a high prevalence of hypogonadism.

The onset of symptoms seems to be related to prevailing testosterone levels

There is evidence that the symptoms of hypogonadism are precipitated at different testosterone levels. This implies that there may be different thresholds for specific androgen-dependent pathways.

- **Loss of libido and vigor** becomes significant below a serum testosterone level of 432 ng/dl
- **Erectile dysfunction and flushes** are significantly related to a testosterone level below 230 ng/dl
- **Type 2 diabetes and depressive symptom** became significantly more common when testosterone levels were below 288 ng/dl

INTERPRETATION OF TESTOSTERONE ASSESSMENT

There is no clear level of testosterone that unambiguously separates normal men from hypogonadal men, and there is no The uniform threshold where symptoms start to occur

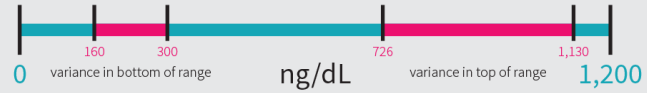
There is no level beyond which androgen therapy results in the improvement of health in all men

It's different for everyone

345 ng/dL
Feels lethargic and depressed, can't lose weight

345 ng/dL
Runs half marathons, feels content

Different labs list WIDELY different ranges



300 *If you test under 300 ng/dL and have symptoms, take your levels seriously: try options then get rechecked.*

Don't compare yourself to others

If you had high levels and they plummeted, you situation is different from that of someone who's always had moderately low levels. There is no one best level.

INDICATIONS FOR ANDROGEN ADMINISTRATION

A distinction should be made between androgen administration to compensate for androgen deficiency in primary or secondary hypogonadism and androgen administration for other reasons.
Compensation for a deficit is known as a replacement.

Table 1 Widely Accepted Indications for Androgen Replacement

- Primary or secondary hypogonadism in men (1–4)
- Induction of puberty in boys (5,6)
- Excessive constitutional growth in boys (7)
- Transsexuality (female to male) (8)
- Late-onset hypogonadism (9,10)

Apart from correction of current symptoms of androgen deficiency (e.g., inadequate virilization, loss of libido and potency, muscle atrophy, androgen deficiency anemia), the aim of testosterone administration is to prevent long-term sequelae of hypogonadism (such as osteoporosis).

Effects of Androgen Replacement in Hypogonadal Men

- Patients frequently demonstrate an increase or restoration of libido or potency as the first sign. Most men demonstrate normal libido and erections after only three to five months of testosterone replacement therapy

- Testosterone stimulates **seminal vesicular secretions and prostatic secretions**. Thus, the volume of the ejaculate increases.

- Testosterone administration has a beneficial effect on emotional state, self-confidence, and activity

- Testosterone replacement has been demonstrated to have a beneficial effect on musculature. Within 6 to 12 months from the beginning of the therapy, there is a significant increase in overall muscle mass attributable to an increase in the size of individual muscle cells. However, the number of cells remains the same. The overall result is a functional increase in **muscle strength and capacity**

Effects of Androgen Replacement in Hypogonadal Men

Bone mass is enhanced by testosterone replacement. When testosterone is given, the lower the initial bone density, the greater is the increase in bone mass. Since the aromatization of testosterone largely causes the bone anabolic effect to estradiol, dramatizable androgens should be given to obtain this effect.
For this reason, nonaromatizable androgens are unsuitable for treating hypogonadism and osteoporosis.

There is a decrease in fat tissue and an increase in lean body tissue. Men with hypogonadism demonstrate a relative increase in fat mass. This is normalized by testosterone administration. Serum testosterone levels inversely correlate with the mass of visceral adipose.

The skin is an important target for androgens. Sebum production ceases when there is an androgen deficiency. Thus, skin becomes dry and sensitive, and the growth of secondary male hair occurs slowly. Testosterone administration rapidly causes an increase in sebaceous gland activity.

During testosterone replacement, the prostate increases in size. Increased prostatic growth is not anticipated at normal replacement doses. Benign hyperplasia or, more rarely, carcinoma of the prostate may occur in older men on testosterone replacement. Although it has not been shown that testosterone replacement per se can cause these pathologies, recommendations for prostate screening apply to men on androgen replacement

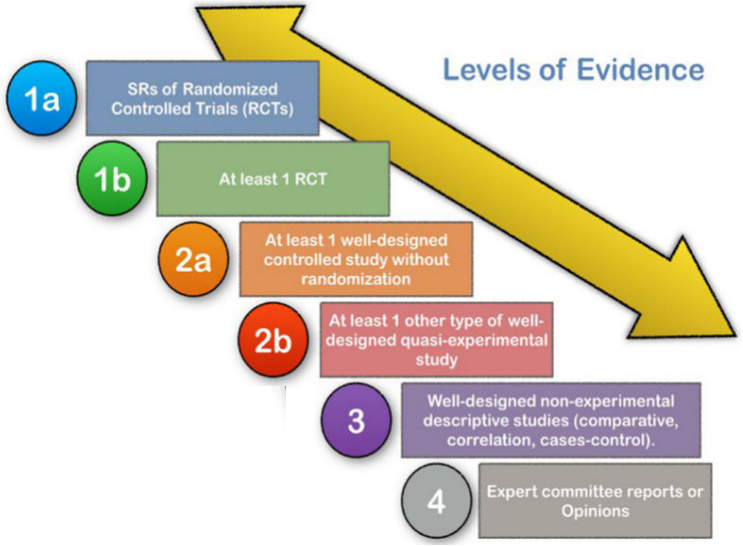
Effects of Androgen Replacement in Hypogonadal Men

The **penis** of an adult male rarely increases in size when testosterone is administered.
In addition, the testes may shrink as a result of the negative feedback, which testosterone and its metabolite estradiol exert on the gonadotropins.
Some studies suggest that there may be an increase in the size of the penis in children.
Another study has suggested that the lack of androgens in adult male hamsters has resulted in shortening of penile spines. Administration of androgens partially restored the size of penile spines in this animal model

Androgen deficiency anemia usually responds well to testosterone replacement, and the **red cell count increases within a few months**. If red cell count, hematocrit, and hemoglobin do not increase after testosterone administration, different causes of anemia must be considered

Testosterone administration usually causes a change in lipid metabolism. During the preexisting phase of hypogonadism, serum HDL cholesterol levels are often high. Testosterone causes a slight decrease in HDL cholesterol and occasionally increases LDL cholesterol. However, this testosterone effect cannot be unequivocally accepted. Androgens such as mesterolone, which do not aromatize, have the **same effect** as testosterone and its esters on serum cholesterol

Effects of Androgen Replacement in Hypogonadal Men



The level of evidence suggesting a therapeutic effect of testosterone replacemen on men with deficiency in the satisfaction with **erectile function** is **1a**

The level of evidence supporting that testosterone replacement in **aging** males causes an **increase in bone mass**, an enhancement in **erythropoiesis**, and an **increase in the lean body** is **1a**

The level of evidence indicating a therapeutic role of testosterone replacement on men with **refractory depression** is 1b

The level of evidence supporting a beneficial effect of testosterone administration in men with **secondary hypogonadism due to AIDS** wasting syndrome is 1b

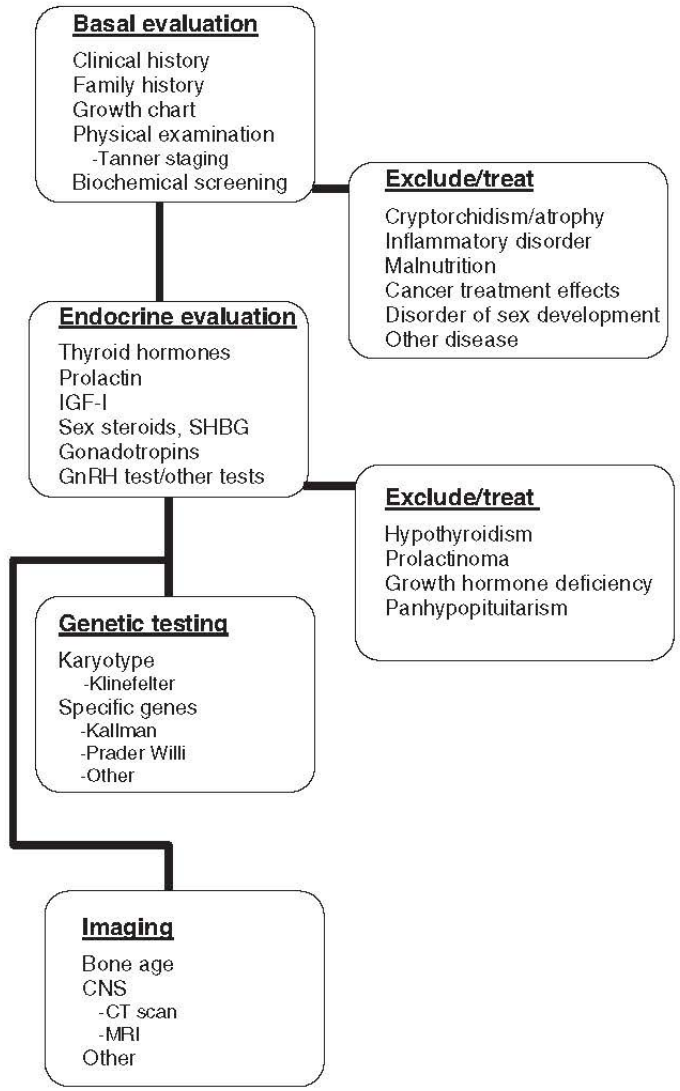
Induction of Puberty in Boys

Table 2 Causes of Delayed Puberty in Boys

Hypogonadotropic hypogonadism (central failure)	**Hypergonadotropic hypogonadism (gonadal failure)**
Idiopatic	Chromosomal, genetic
Familial (constitutional delay of growth and puberty; 85%)	Klinefelter
Isolated gonadotropin deficiency	Other
Panhypopituitarism	Undescended testes
Genetic, syndromes	Bilateral, untreated
Kallman (KAL-1, FGFR1)	Testicular atrophy
KiSS/GPR54	Testicular agenesis
GnRH-R	Torsion
Prader-Willi	Unknown cause
Leptin, Leptin-R	Iatrogenic
Disorder of sex development (DSD)	Gonadal irradiation
Tumor	Other
Craniopharyngeoma	Defects in androgen biosynthesis
Hypothalamic tumor	
Prolactinoma	
Negative calorie balance	
Chronic illness, inflammation	
Short bowel	
Anorexia nervosa	
Psychogenic	
Excessive physical activity	
Iatrogenic	
Survivors of childhood cancer	
CNS irradiation	
Brain surgery	
Total body irradiation	
Chemotherapy	

PEDIATRIC ENDOCRINOLOGY

Algorithm for work-up of delayed puberty in boys



Transsexuality (Female to Male)

Late-Onset Hypogonadism

Testosterone replacement in men with late-onset hypogonadism is expected to have a beneficial effect on bone metabolism, musculature, erythropoiesis, libido, sexual satisfaction, and general mood

Types of Testosterone Replacement Therapy

Testosterone replacement therapy is categorized according to its various routes of administration.

Oral	Sublingual	Transdermal	Intramuscular	Subcutaneous
• Pills	• Drops	• Creams • Patches • Gels • Sprays	• Injections	• Pellets

Advantages

Disadvantages

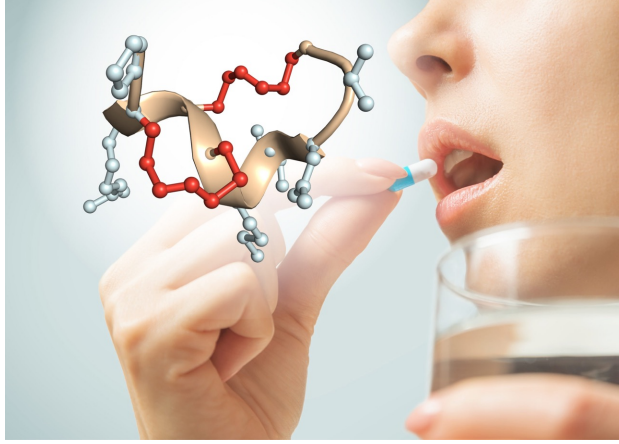
Oral testosterone

JATENZO® (testosterone undecanoate) Capsules [C-III]

1

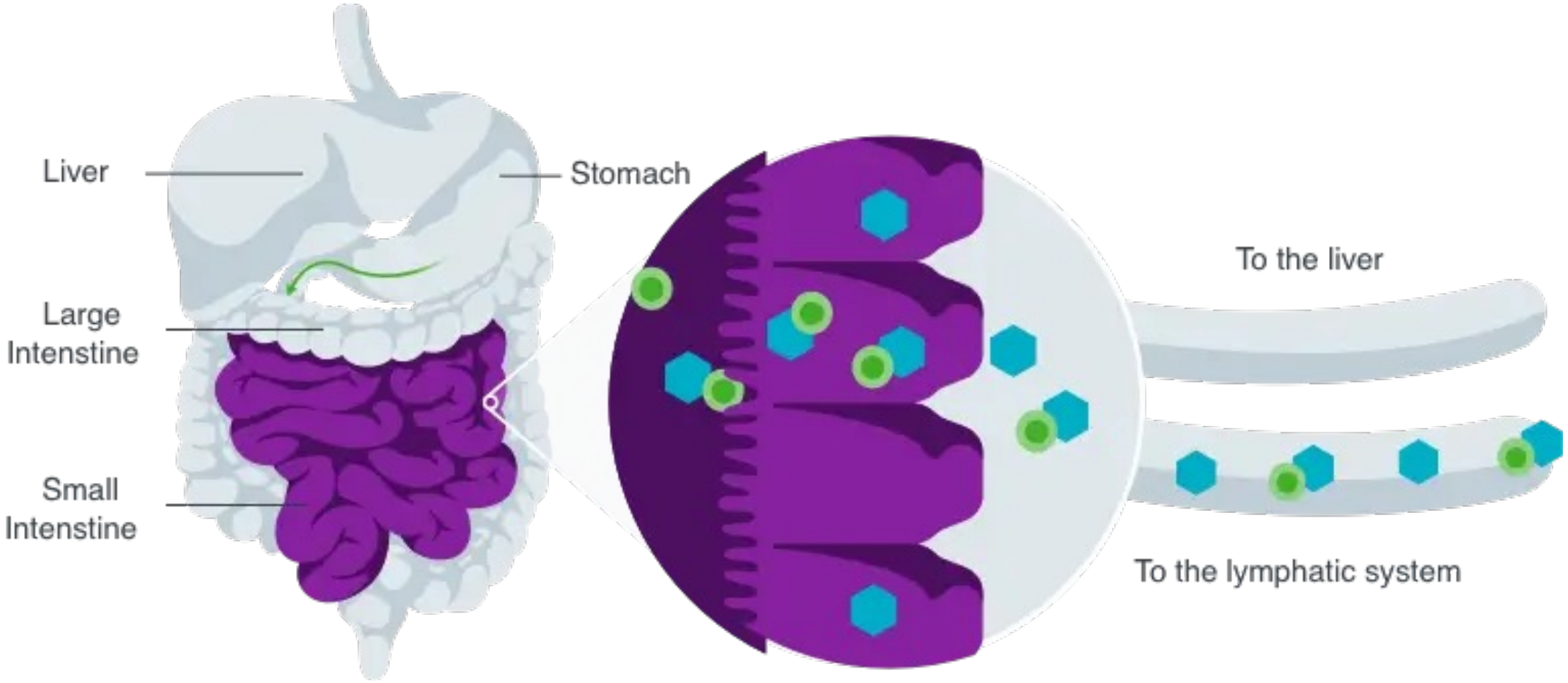
TLANDO® (testosterone undecanoate) [C-III]

KYZATREX™ TESTOSTERONE UNDECANOATE CAPSULES [C-III]



For patients who do not tolerate patches and when intramuscular injections are refused

Poor bioavailability, very expensive


Liver
Stomach
Large Intenstine
Small Intenstine
To the liver
To the lymphatic system

JATENZO®
(testosterone undecanoate) Capsules C-III

1

5 dose options (taken twice daily)

158 mg

198 mg

316 mg

396 mg

GoodRx

Jatenzo
60 capsules 237mg
SAVE

Food Lion Pharmacy		Coupon ~~$1,150~~ $933.06
Publix	7.5 miles	Coupon $940.77
Harris Teeter	4.6 miles	Coupon ~~$1,150~~ $987.88
CVS Pharmacy	3.5 miles	Coupon ~~$1,136~~ $994.91
Target (CVS)	5.4 miles	Coupon ~~$1,150~~ $994.91
Walgreens	3.2 miles	Discount $1,001.18
Walmart	5.9 miles	Discount $1,005.72
Walmart Neighborhood Market	5.6 miles	Discount $1,005.72
Costco	7.8 miles	Coupon ~~$1,150~~ $1,023.54

Atrium Health Wake Forest Baptist

Wake Forest® School of Medicine

JATENZO®
(testosterone undecanoate)
Capsules ℞

Table 1: JATENZO Dose Adjustment Scheme

Testosterone Concentration in Serum From Plain Tube Drawn 6 hours After Morning Dose	Current JATENZO Dose (mg, twice daily)	New JATENZO Dose (mg, twice daily)
Less than 425 ng/dL	158	198
	198	237
	237	316 (two 158 mg capsules)
	316 (two 158 mg capsules)	396 (two 198 mg capsules)
425 ng/dL – 970 ng/dL	No Dose Change	
More than 970 ng/dL	396 (two 198 mg capsules)	316 (two 158 mg capsules)
	316 (two 158 mg capsules)	237
	237	198
	198	158
	158	Discontinue Treatment

JATENZO®
(testosterone undecanoate)
Capsules ℞

1

Table 2: Number (%) of Patients with Adverse Reactions ≥ 2% in a 4-Month Study with JATENZO

Preferred Term	Overall (N = 166) n (%)
Headache	8 (4.8)
Hematocrit increased	8 (4.8)
Hypertension	6 (3.6)
High-density lipoprotein decreased	5 (3.0)
Nausea	4 (2.4)

TLANDO® (testosterone undecanoate) CIII

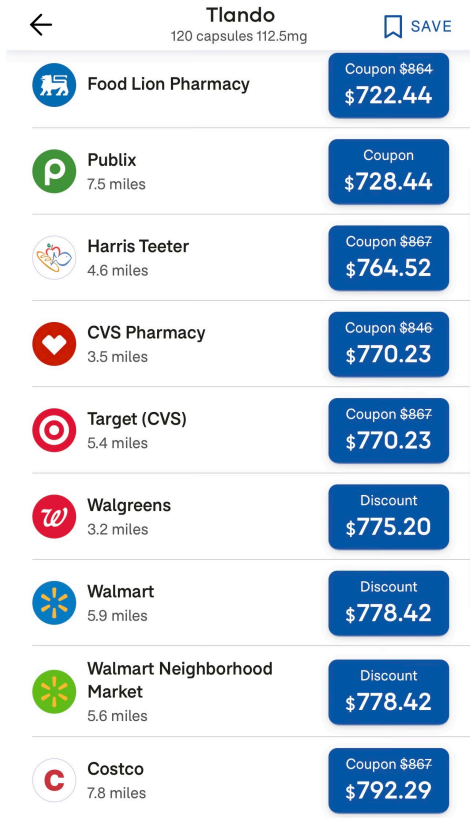
The recommended dosage of Tlando is 225 mg (taken as two 112.5 mg capsules), orally twice daily, once in the morning and once in the evening.

Monitor serum testosterone (8 to 9 hours after the morning dose) 3 to 4 weeks after initiating Tlando, and periodically thereafter.

Based on serum testosterone measurements, determine if Tlando should be continued or discontinued:

- Serum testosterone 300 - 1080 ng/dL: continue Tlando
- Serum testosterone < 300 ng/dL: discontinue Tlando
- Serum testosterone > 1080 ng/dL: discontinue Tlando

GoodRx



TLANDO® (testosterone undecanoate) CIII

Table 1 summarizes adverse reactions (>2%) reported in patients receiving Tlando in Study 18-001.

Table 1. Adverse Reactions ≥ 2% in Patients Receiving Tlando in Study 18-001	
Adverse Reaction	**Overall (N=138)** **n (%)**
Hypertension	7 (5.1)
Hematocrit increased	6 (4.3)
Upper respiratory tract infection	5 (3.6)

Table 2 summarized adverse reactions (>2%) reported during Study 16-002 in patients receiving Tlando.

Table 2. Adverse Reactions ≥2% in Patients Receiving Tlando in Study 16-002	
Adverse Reaction	**Overall (N=95)** **n (%)**
Blood prolactin increased	6 (6.3)
Weight increased	2 (2.1)
Headache	2 (2.1)
Musculoskeletal pain	2 (2.1)

LANDO XR CLINICAL TRIALS

TLANDO XR is a next-generation, novel ester prodrug of testosterone which uses the Lip'ral technology to enhance solubility and improve systemic absorption. We completed a Phase 2b dose finding study in hypogonadal men in the third quarter of 2016. The primary objectives of the Phase 2b clinical study were to determine the starting Phase 3 dose of TLANDO XR along with the safety and tolerability of TLANDO XR and its metabolites following oral administration of single and multiple does in hypogonadal men. The Phase 2b clinical trial was a randomized, open label, two-period, multi-dose PK study that enrolled hypogonadal males into five treatment groups. Each of the 12 subjects in a group received treatment for 14 days. Results of the Phase 2b study suggest that the primary objectives were met, including identifying the dose expected to be tested in a Phase 3 study. Good dose-response relationship was observed over the tested dose range in the Phase 2b study. Additionally, the target Phase 3 dose met primary and secondary end points. Overall, TLANDO XR was well tolerated with no drug-related severe or serious adverse events reported in the Phase 2b study.

Additionally in October 2014, we completed a Phase 2a proof-of-concept study in hypogonadal men. The Phase 2a open-label, dose-escalating single and multiple dose study enrolled 12 males. Results from the Phase 2a clinical study demonstrated the feasibility of a once daily dosing with TLANDO XR in hypogonadal men and a good dose response. Additionally, the study confirmed that steady state is achieved by day 14 with consistent inter-day performance observed on day 14, 21 and 28. No subjects exceeded Cmax of 1500 ng/dL at any time during the 28-day dosing period on multi-dose exposure. Overall, TLANDO XR was well tolerated with no serious AE's reported.

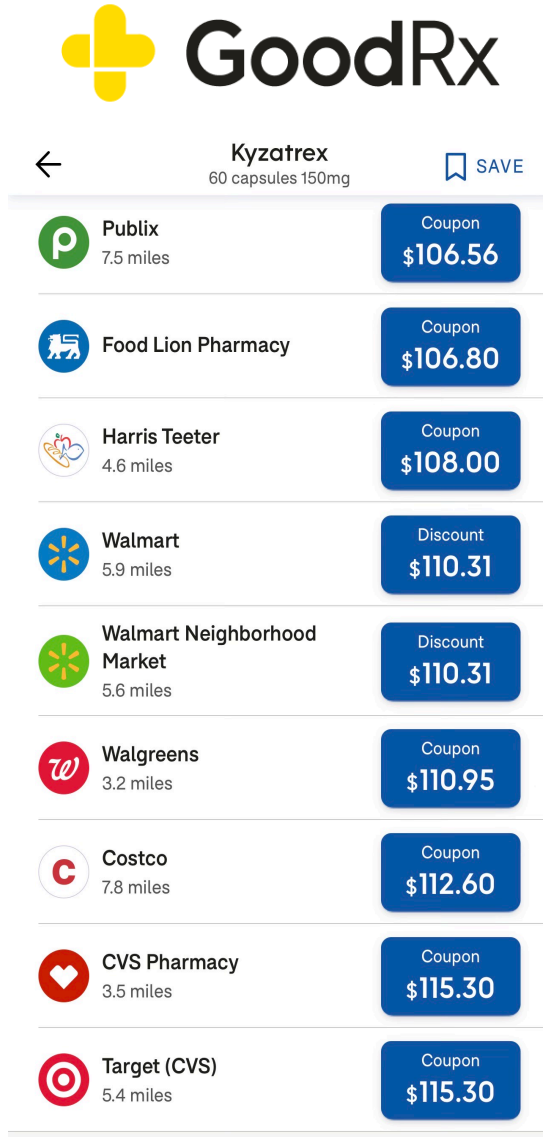
We have also completed a preclinical toxicology study with TLANDO XR.

KYZATREX™
TESTOSTERONE UNDECANOATE CAPSULES

Designed for oral delivery, Kyzatrex™ should be taken twice a day – morning and evening

Available in 100 mg, **150 mg,** and 200 mg strengths.

Measure testosterone 3 to 5 hours after morning dose beginning 7 days after initiating therapy or after dosage adjustments and then periodically thereafter.



Nasal Gel Testosterone

Natesto®
Testosterone Nasal Gel 4.5% w/w
Gel nasal de testostérone 4.5% p/p

Preserve Spermatogenesis, very low transference to partner or kids

Nasal discomfort

Nasal Gel Testosterone

Natesto®
Testosterone Nasal Gel 4.5% w/w
Gel nasal de testostérone 4.5% p/p

One pump (5.5 mg) in each nostril 3 times daily, for a total daily dose of 33 mg

Each dose should be taken 6 to 8 hours apart: once in the morning, once in the afternoon, once in the evening





Natesto®

Testosterone Nasal Gel 4.5% w/w
Gel nasal de testostérone 4.5% p/p

Natesto appears to increase testosterone while maintaining semen parameters in a majority of men.

Clinical Trial > J Urol. 2020 Sep;204(3):557-563. doi: 10.1097/JU.0000000000001078.
Epub 2020 Apr 15.

Effect of Natesto on Reproductive Hormones, Semen Parameters and Hypogonadal Symptoms: A Single Center, Open Label, Single Arm Trial

Ranjith Ramasamy [1], Thomas A Masterson [1], Jordan C Best [1], Joshua Bitran [1], Emad Ibrahim [1], Manuel Molina [1], Ursula B Kaiser [2], Feng Miao [3], Isildinha M Reis [3 4]

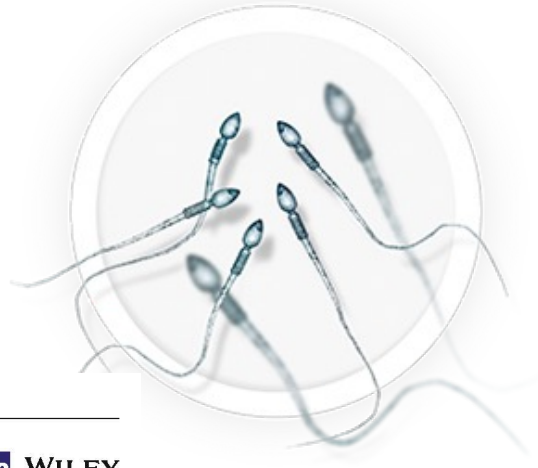
Affiliations + expand

PMID: 32294396 DOI: 10.1097/JU.0000000000001078

Received: 16 March 2022 | Revised: 7 April 2022 | Accepted: 18 April 2022
DOI: 10.1111/and.14453

ORIGINAL ARTICLE

ANDROLOGIA WILEY



Direct conversion from long-acting testosterone replacement therapy to Natesto allows for spermatogenesis resumption: Proof of concept

Parviz K. Kavoussi | Graham L. Machen | Shu-Hung Chen | Melissa S. Gilkey | Justin Chen | Yazan Hamzeh | Kenneth I. Aston | Shahryar K. Kavoussi

GoodRx

Natesto
3 nasal gel pumps 11g of 5.5mg per actuation SAVE

Walmart Restrictions apply	Discount $582.40
Walmart Neighborhood Market Restrictions apply	Discount $582.40
Walgreens Restrictions apply	Discount $582.90
CVS Pharmacy Restrictions apply	Discount ~~$1,019~~ $583.90
Target (CVS) Restrictions apply	Discount ~~$1,027~~ $583.90
Costco Restrictions apply	Discount ~~$1,056~~ $583.90
Food Lion Pharmacy Restrictions apply	Discount ~~$1,027~~ $583.90
Publix 7.5 miles	Coupon $847.56
Harris Teeter 4.6 miles	Coupon ~~$1,027~~ $847.76

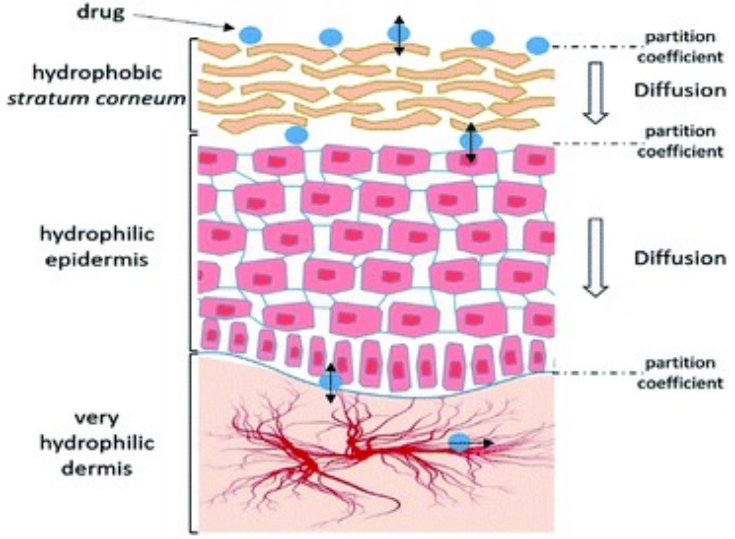
Cash patients and insured, not covered patients may fill each valid Natesto prescription or refill at the cash price of $140.

Atrium Health Wake Forest Baptist

Wake Forest® School of Medicine

Transdermal Gel

AndroGel® (testosterone gel) 1.62% CIII



very good pharmacokinetics, no fluctuation in testosterone levels, good efficacy, suitable approach if there are contraindications to injections, few side effects, individual dosing, discrete application

inadequate long-term experience, the risk for interpersonal contamination if not properly dried

AndroGel® (testosterone gel) 1.62% CIII

DOSE: 40.5 mg (Recommended Starting Dose)

	**PUMP:** Two pump presses. One applied to each upper arm/shoulder daily in the morning
	**PACKET:** One 40.5 mg packet. Half of packet applied to each upper arm/shoulder daily in the morning

AndroGel: 25 mg/2.5 g (1%) (2.5 g) [contains alcohol, usp]
AndroGel: 20.25 mg/1.25 g (1.62%) (1.25 g [DSC]); 40.5 mg/2.5 g (1.62%) (2.5 g [DSC])
AndroGel: 50 mg/5 g (1%) (5 g [DSC]) [contains alcohol, usp]
AndroGel Pump: 20.25 mg/actuation (1.62%) (75 g)

AndroGel® (testosterone gel) 1.62% CIII

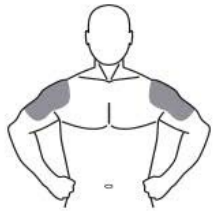
Table 1: Dose Adjustment Criteria

Pre-Dose Morning Total Serum Testosterone Concentration	Dose Titration
Greater than 750 ng/dL	Decrease daily dose by 20.25 mg (1 pump actuation or the equivalent of one 20.25 mg packet)
Equal to or greater than 350 and equal to or less than 750 ng/dL	No change: continue on current dose
Less than 350 ng/dL	Increase daily dose by 20.25 mg (1 pump actuation or the equivalent of one 20.25 mg packet)

Table 2: Application Sites for AndroGel 1.62%, Pump

Total Dose of Testosterone	Total Pump Actuations	Pump Actuations Per Upper Arm and Shoulder	
		Upper Arm and Shoulder #1	Upper Arm and Shoulder #2
20.25 mg	1	1	0
40.5 mg	2	1	1
60.75 mg	3	2	1
81 mg	4	2	2

Total Dose of Testosterone	Total packets	Gel Applications Per Upper Arm and Shoulder	
		Upper Arm and Shoulder #1	Upper Arm and Shoulder #2
20.25 mg	One 20.25 mg packet	One 20.25 mg packet	0
40.5 mg	One 40.5 mg packet	Half of contents of One 40.5 mg packet	Half of contents of One 40.5 mg packet
60.75 mg	One 20.25 mg packet AND One 40.5 mg packet	One 40.5 mg packet	One 20.25 mg packet
81 mg	Two 40.5 mg packets	One 40.5 mg packet	One 40.5 mg packet



AndroGel (testosterone gel) 1.62% C III

Table 4: Adverse Reactions Reported in >2% of Patients in the 182-Day, Double-Blind Period of AndroGel 1.62% Clinical Trial

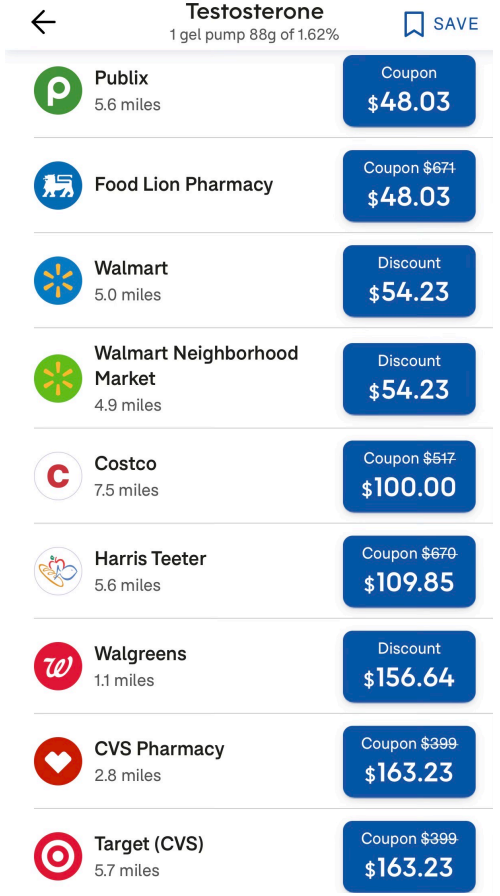
	Number (%) of Patients	
Adverse Reaction	**AndroGel 1.62% N=234**	**Placebo N=40**
PSA increased*	26 (11.1%)	0%
Emotional lability**	6 (2.6%)	0%
Hypertension	5 (2.1%)	0%
Hematocrit or hemoglobin increased	5 (2.1%)	0%
Contact dermatitis***	5 (2.1%)	0%
**PSA increased* includes: PSA values that met pre-specified criteria for abnormal PSA values (an average change from baseline > 0.75 ng/mL and/or an average PSA value >4.0 ng/mL based on two measurements) as well as those reported as adverse events.		
***Emotional lability* includes: mood swings, affective disorder, impatience, anger, and aggression.		

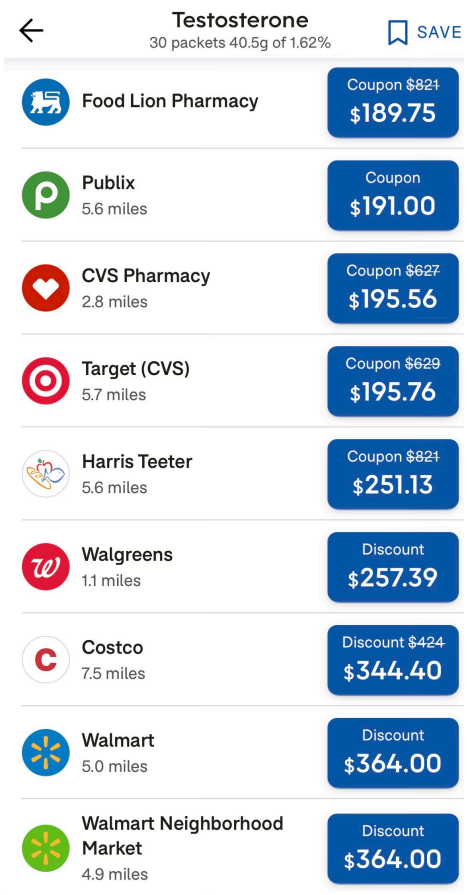
AndroGel® (testosterone gel) 1.62% CIII

Perrigo

Package Size
88 g pump (each pump dispenses 60 metered pump actuations with each pump actuation containing 20.25 mg of testosterone in 1.25 g of gel)
Each unit dose packet contains 20.25 mg of testosterone provided in 1.25 g of gel
30 packets (each unit dose packet contains 20.25 mg of testosterone provided in

GoodRx





FORTESTA® (testosterone) Gel

endo pharmaceuticals
an endo international company

The recommended starting dose of FORTESTA is 40 mg of testosterone (4 pump actuations) applied once daily to the **thighs** in the **morning**.

To ensure proper dosing, the dose should be titrated based on the serum testosterone concentration from a single blood draw 2 hours after applying FORTESTA at approximately 14 days and 35 days after starting treatment or following dose adjustment

Table 1: Dose Adjustment Criteria

Total Serum Testosterone Concentration 2 hours Post FORTESTA Application	Dose Titration
Equal to or greater than 2,500 ng/dL	Decrease daily dose by 20 mg (2 pump actuations)
Equal to or greater than 1,250 and less than 2,500 ng/dL	Decrease daily dose by 10 mg (1 pump actuation)
Equal to or greater than 500 and less than 1,250 ng/dL	No change: continue on current dose
Less than 500 ng/dL	Increase daily dose by 10 mg (1 pump actuation)

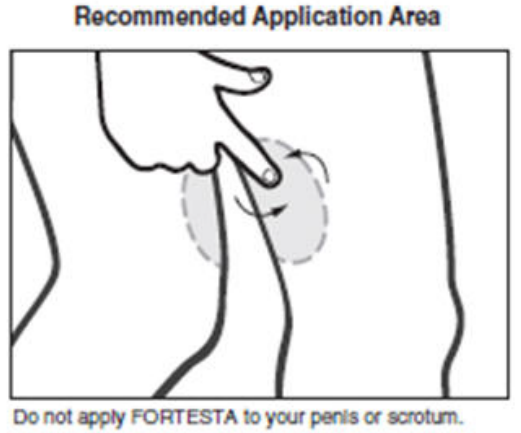


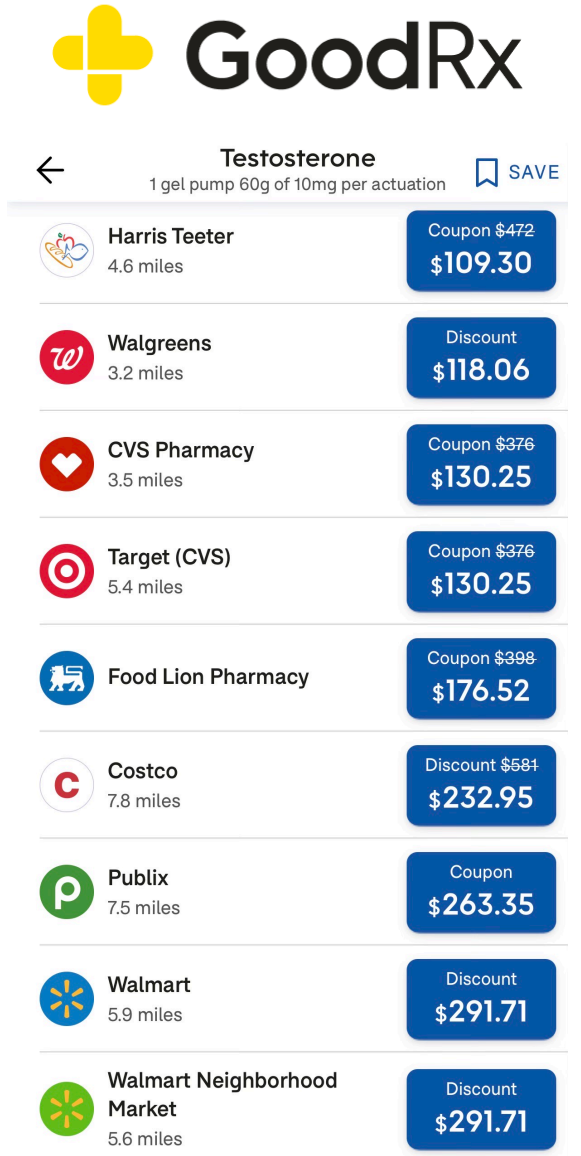
Table 3: Adverse Reactions Reported in >1% of Patients in the US Phase 3 Clinical Trial of FORTESTA

Adverse Reaction	Number (%) of Patients N = 149
Skin reaction	24 (16.1%)
Prostatic specific antigen increased	2 (1.3%)
Abnormal dreams	2 (1.3%)

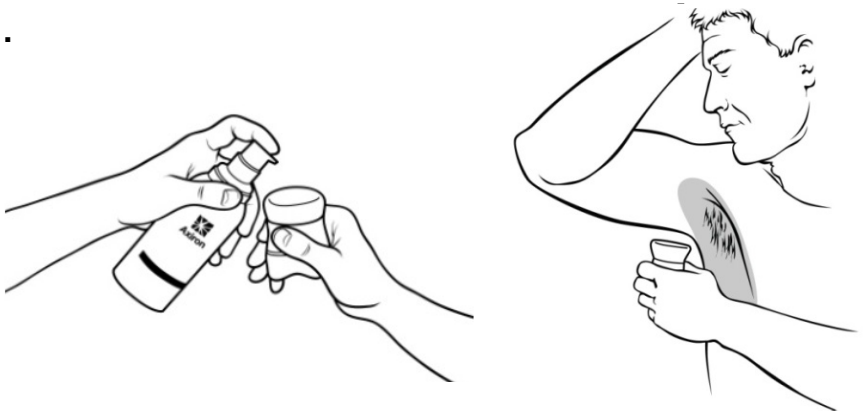
FORTESTA®
(testosterone) Gel

Table 2: Application of FORTESTA

Total Dose of Testosterone	Total Pump Actuations	Pump Actuations per Thigh	
		Thigh #1	Thigh #2
10 mg	1	1	0
20 mg	2	1	1
30 mg	3	2	1
40 mg	4	2	2
50 mg	5	3	2
60 mg	6	3	3
70 mg	7	4	3



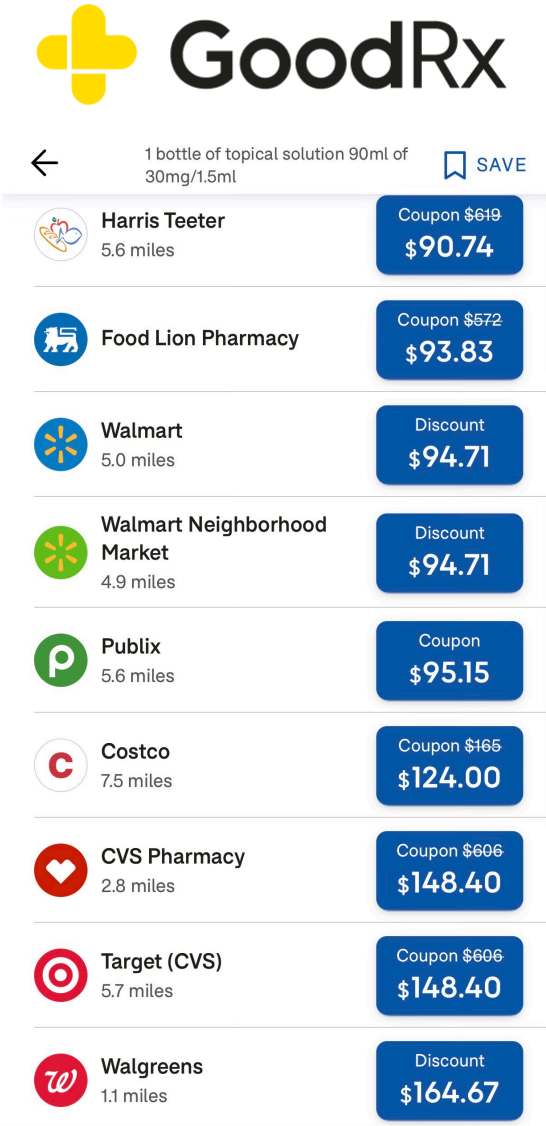
Starting AXIRON dose is 60 mg of testosterone (1 pump or 1 twist actuation of 30 mg of testosterone to each axilla), applied once daily, at the same time each morning.



Event	120 Days (155 Patients)	180 Days (71 Patients)
Application Site Irritation	11 (7%)	6 (8%)
Application Site Erythema	8 (5%)	5 (7%)
Headache	8 (5%)	4 (6%)
Hematocrit Increased	6 (4%)	5 (7%)
Diarrhea	4 (3%)	3 (4%)
Vomiting	4 (3%)	3 (4%)
PSA Increased	2 (1%)	3 (4%)

Table 1: Application Technique

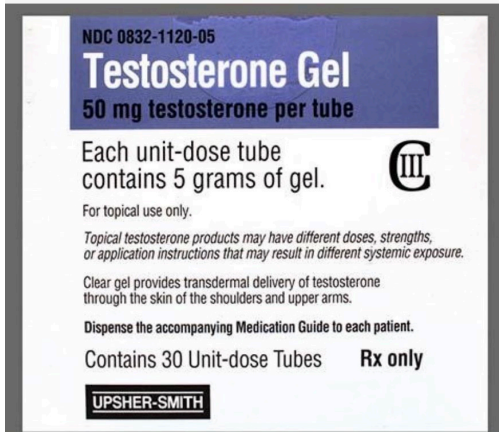
Daily Prescribed Dose of Testosterone	Number of Twist Actuations	Number of Pump Actuations	Application
30 mg (once daily)	1	1	Apply once to one axilla only (left OR right)
60 mg (once daily)	2	2	Apply once to the left axilla and then apply once to the right axilla.
90 mg (once daily)	3	3	Apply once to the left and once to the right axilla, wait for the product to dry, and then apply once again to the left OR right axilla.
120 mg (once daily)	4	4	Apply once to the left and once to the right axilla, wait for the product to dry, and then apply once again to the left AND once to the right axilla.



Testim® endo pharmaceuticals an endo international company

(testosterone gel)

Contains 50 mg testosterone in 5 g of gel per tube.



Recommended starting dose for adult males: 50 mg of testosterone (one tube) applied topically once daily.

Do NOT apply TESTIM to the genitals or abdomen

If morning pre-dose serum testosterone concentration is below normal range, increase dose to 100 mg

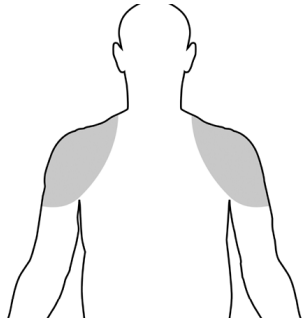
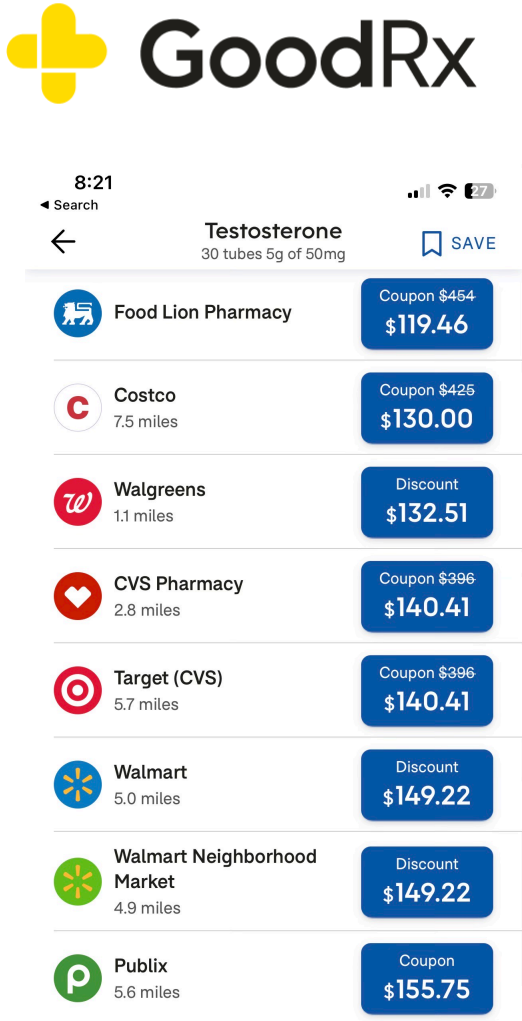


Table 1: Incidence of Adverse Reactions (Reported by ≥1% of the TESTIM Patients and Greater than Placebo) in the Controlled Clinical Trial Through 90 Days

Event	TESTIM 50 mg (n=103)	TESTIM 100 mg (n=149)	Placebo (n=99)
Application Site Reactions	2%	4%	3%
Blood Pressure Increased	1%	1%	0%
Gynecomastia	1%	0%	0%
Headache	1%	1%	0%
Hematocrit / hemoglobin Increased	1%	2%	0%
Hot Flushes	1%	0%	0%
Insomnia	1%	0%	0%
Mood Swings	1%	0%	0%
Smell Disorder	1%	0%	0%
Spontaneous Penile Erection	1%	0%	0%
Taste Disorder	1%	1%	0%

Package Size
30 tubes: 50 mg testosterone in 5 g of gel per tube



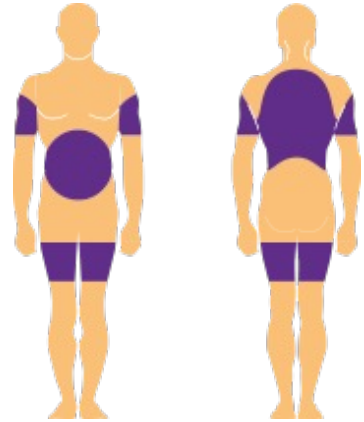
Testosterone patches

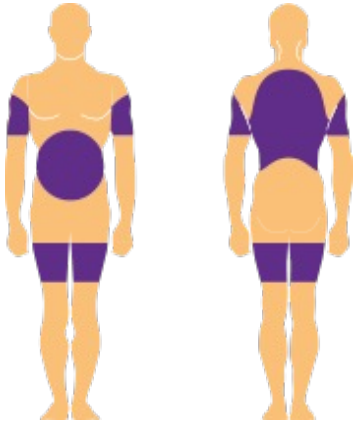
ANDRODERM®
(testosterone transdermal system)

The recommended starting dose is one ANDRODERM 4 mg/day system (not two 2 mg/day systems) applied nightly for 24 hours, delivering approximately 4 mg of testosterone per day.

Good pharmacokinetics with uniform levels, suitable when there are contraindications to injections, easy to use and maintenance of relatively uniform serum testosterone levels over time

scrotal patches—DHT increase, very expensive; nonscrotal patches—frequent, pronounced skin irritations, expensive





Testosterone patches

Androderm® is put on once daily in the evening. Some men apply it near bedtime—in the clinical trial, men put it on around 10 PM.

Wait 3 hours before showering, bathing, or swimming after applying Androderm

IF THE PATCH FALLS OFF:

Before noon: Put on a new one and wear it until you put on a new patch at your regular time that evening.

After noon: Do not put on a new one; rather, wait and apply a new patch at your regular time that evening.

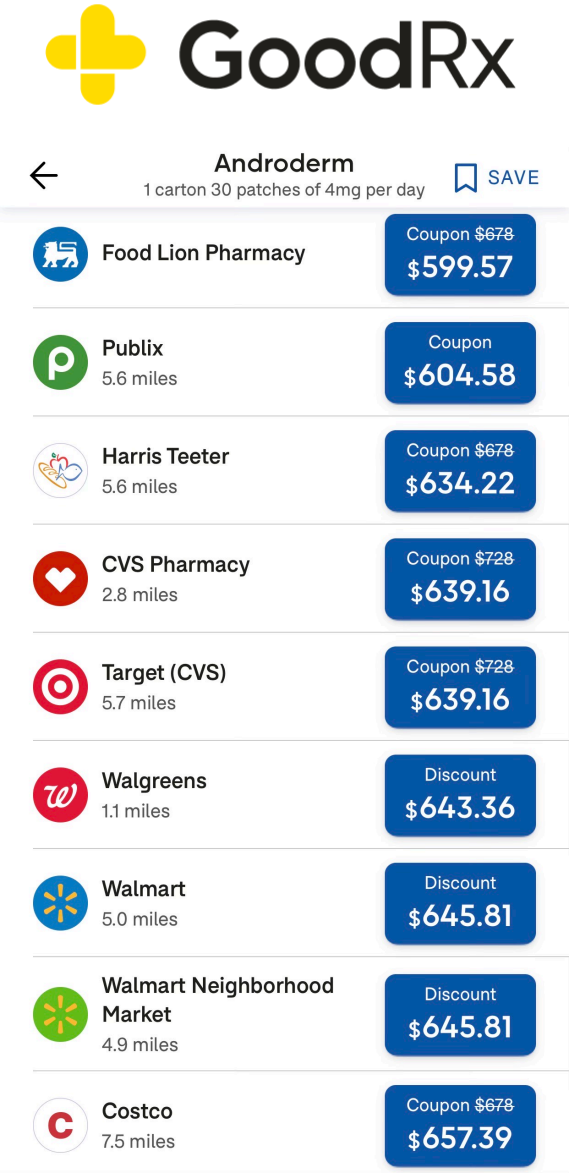
Table 1. Adverse Reactions Seen With the Use of ANDRODERM 2 mg/day, 4 mg/day, or 6 mg/day (> 3%)

Adverse Reaction	Overall N = 36 %
Application site pruritus	17
Application site vesicles	6
Back pain	6

Table 2. Adverse Reactions Seen With the Use of ANDRODERM 2.5 mg/day, 5 mg/day, or 7.5 mg/day (> 3%)

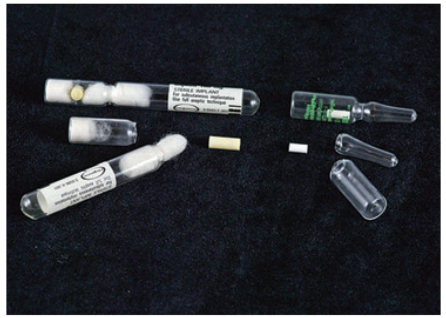
Adverse Reaction	Overall N = 122 %
Application site pruritus	37
Application site blistering	12
Application site erythema	7
Application site vesicles	6
Prostate abnormalities	5
Headache	4
Contact dermatitis to system	4
Application site burning	3
Application site induration	3
Depression	3

Serum testosterone concentrations measured in the early morning outside the range of 400 - 930 ng/dL require increasing the daily dose to:
6 mg (i.e., one 4 mg/day and one 2 mg/day system) or decreasing the daily dose to:
2 mg (i.e., one 2 mg/day system), maintaining nightly application



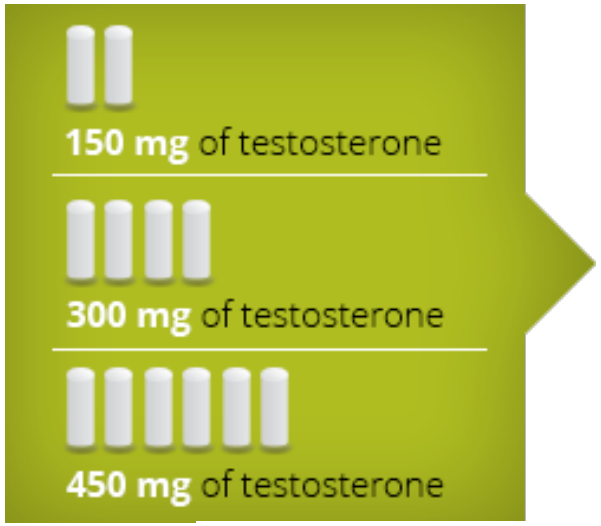
Pellet, Implant (Subcutaneous)

TESTOPEL® 75mg
(testosterone pellets) C III

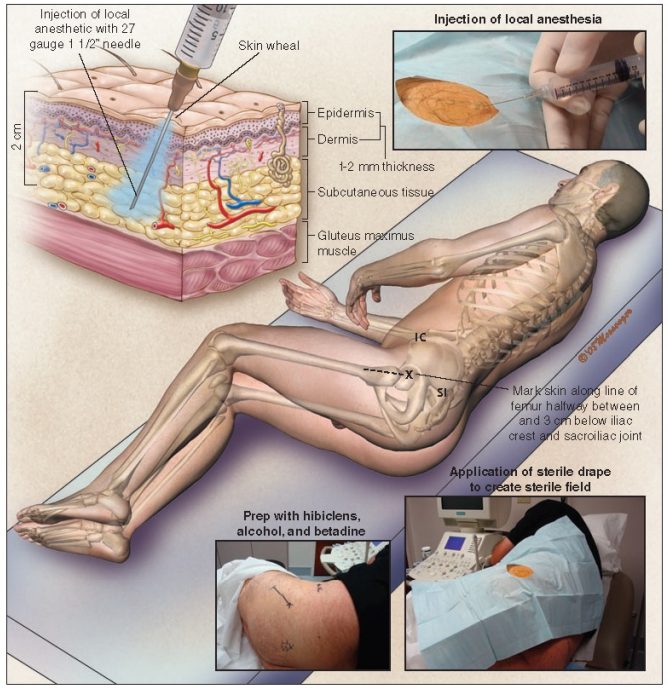


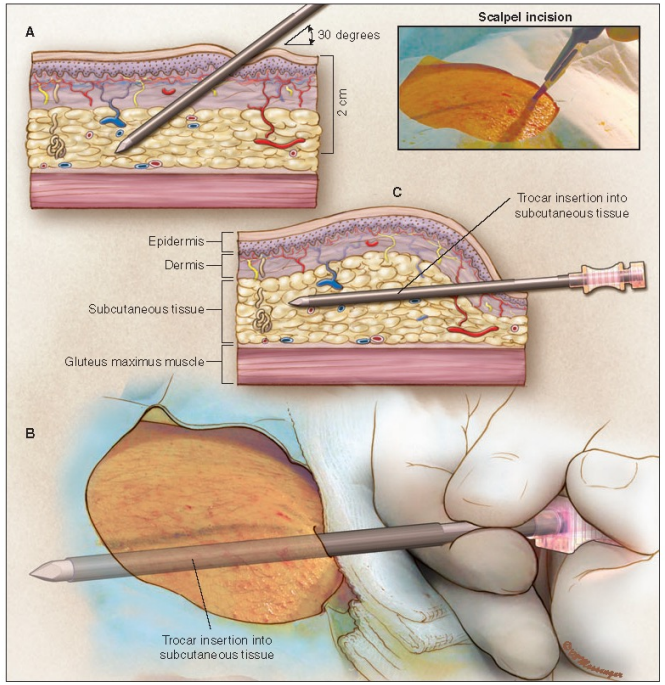
Good pharmacokinetics and pharmacodynamics with stable physiological T levels, longest duration of effect of all preparations, easily accepted by the patient

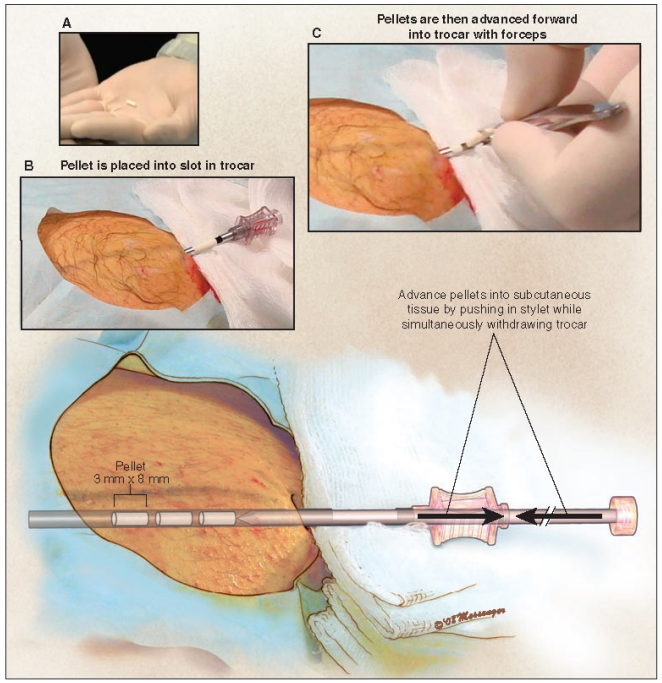
Cost for implantation process, local infections, substantial hepatotoxicity



For your appropriate patients with Low T, implant 2-6 pellets (150 mg - 450 mg) subcutaneously every 3 to 6 months







Intramuscular testosterone undecanoate (3-monthly injection)

AVEED®
(testosterone undecanoate) injection
750 mg/3 mL

Stable testosterone levels within normal range over months, easily accepted by the patient, no problems with compliance, very good efficacy, low cost

Pain at the site of injection and the need for frequent medical visits for the administration of the injections

AVEED®
(testosterone undecanoate) injection CIII
750 mg/3 mL

Three (3) mL (750 mg) is to be injected intramuscularly at initiation, at 4 weeks, and every 10 weeks thereafter

Following each injection of Aveed, observe patients in the healthcare setting for 30 minutes in order to provide appropriate medical treatment in the event of serious POME reactions or anaphylaxis

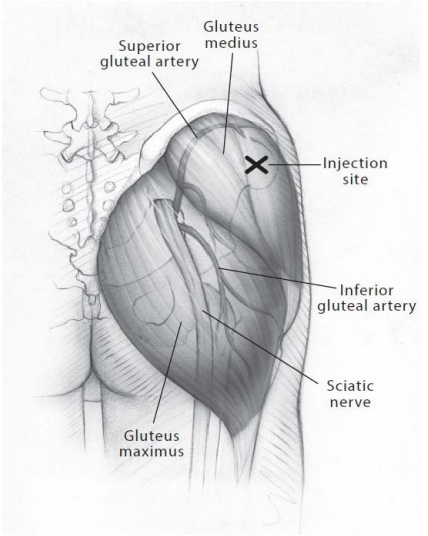


Table 1: Adverse Reactions Reported in at Least 1% of Patients in the 84-Week Clinical Study of AVEED

MedDRA Preferred Term	Number of Patients (%)
	AVEED 750 mg (N=153)
Acne	8 (5.2%)
Injection site pain	7 (4.6%)
Prostatic specific antigen increased*	7 (4.6%)
Estradiol increased	4 (2.6%)
Hypogonadism	4 (2.6%)
Fatigue	3 (2%)
Irritability	3 (2%)
Hemoglobin increased	3 (2%)
Insomnia	3 (2%)
Mood swings	3 (2%)
Aggression	2 (1.3%)
Ejaculation disorder	2 (1.3%)
Injection site erythema	2 (1.3%)
Hematocrit increased	2 (1.3%)
Hyperhidrosis	2 (1.3%)
Prostate Cancer	2 (1.3%)
Prostate induration	2 (1.3%)
Weight increased	2 (1.3%)

*Prostate-specific antigen increased defined as a serum PSA concentration >4 ng/mL.

Weekly Auto-injector (SQ)

XYOSTED®
(testosterone enanthate) injection

Available in 3 Dose Strengths

50 mg | 75 mg | 100 mg

Recommended starting dose

COLLAR ACTIVATED

*FINE **27-GAUGE** NEEDLE*

*ONLY **10 SECONDS** TO INJECT*

Collar Activated, Fine 27-Gauge Needle, Only 10 Seconds To Inject

Based upon total testosterone trough concentrations (measured 7 days after most recent dose) obtained following 6 weeks of dosing and periodically thereafter

Inside XYOSTED's collar is a fine, **27-gauge needle**. Because it's collar-activated, the needle is never visible to the patient.

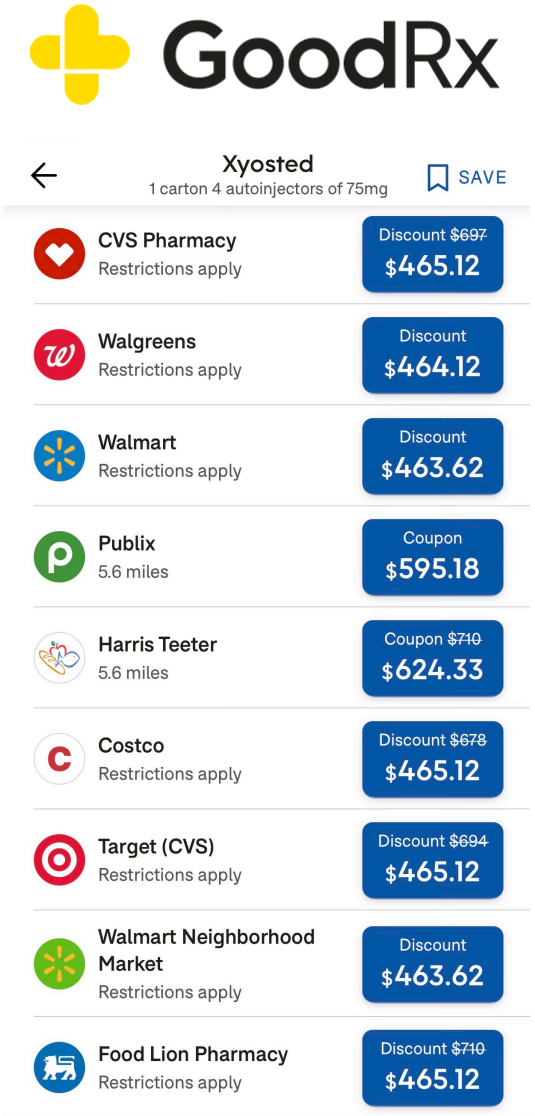
Table 1. Number (%) of Patients with Adverse Reactions ≥2% in a 1 Year study with XYOSTED

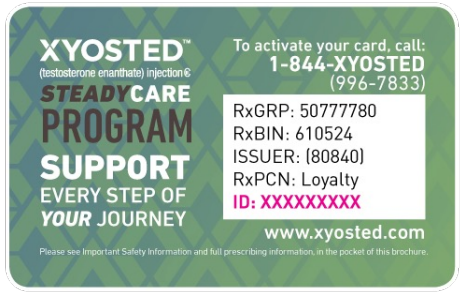
Preferred Term	Overall (N=150) n (%)
Hematocrit increased	21 (14.0)
Hypertension	19 (12.7)
Prostatic specific antigen (PSA) increased	18 (12.0)
Injection site bruising	10 (6.7)
Headache	8 (5.3)
Back pain	5 (3.3)
Blood creatine phosphokinase increased	5 (3.3)
Injection site hemorrhage	5 (3.3)
Acne	4 (2.7)
Blood testosterone increased	4 (2.7)
Cough	4 (2.7)
Edema peripheral	4 (2.7)
Injection site erythema	4 (2.7)
Prostatitis	4 (2.7)
Urinary tract infection	4 (2.7)
Abdominal pain	3 (2.0)
Arthralgia	3 (2.0)
Fatigue	3 (2.0)
Hematuria	3 (2.0)
Polycythemia	3 (2.0)
Sleep apnea syndrome	3 (2.0)
Note: Includes events that started on or after the first dosing, or existed prior to the first dose and worsened in severity or relatedness after dosing. Percentage was calculated using the number of patients in the column heading as the denominator.	

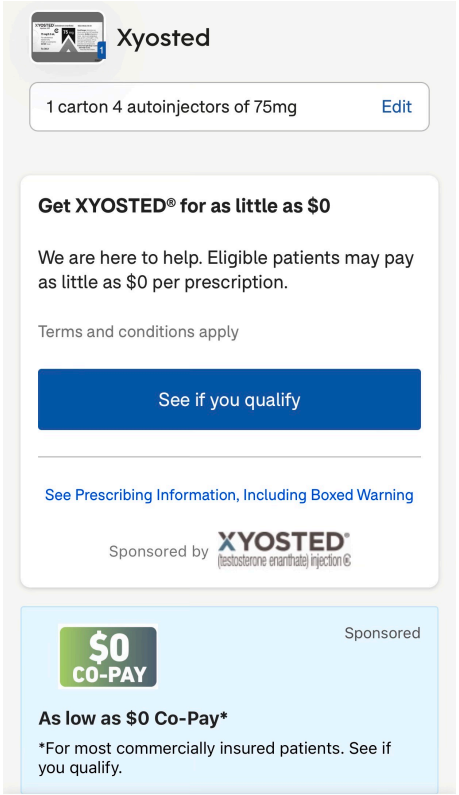
Table 2 summarizes the adverse reactions (≥2%) reported in a 6-month study with XYOSTED.

Table 2. Number (%) of Patients with Adverse Reactions ≥2% in a 6-Month Study with XYOSTED

Preferred Term	Overall (N = 133) n (%)
Hematocrit increased	11 (8.3)
Injection site hemorrhage	8 (6.0)
Blood creatine phosphokinase increased	5 (3.8)
Injection site bruising	5 (3.8)
Prostatitis	4 (3.0)



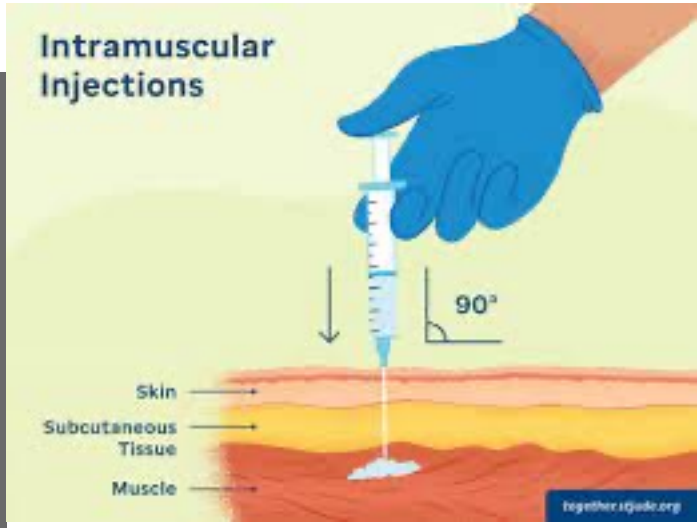




Atrium Health
Wake Forest Baptist

Wake Forest®
School of Medicine

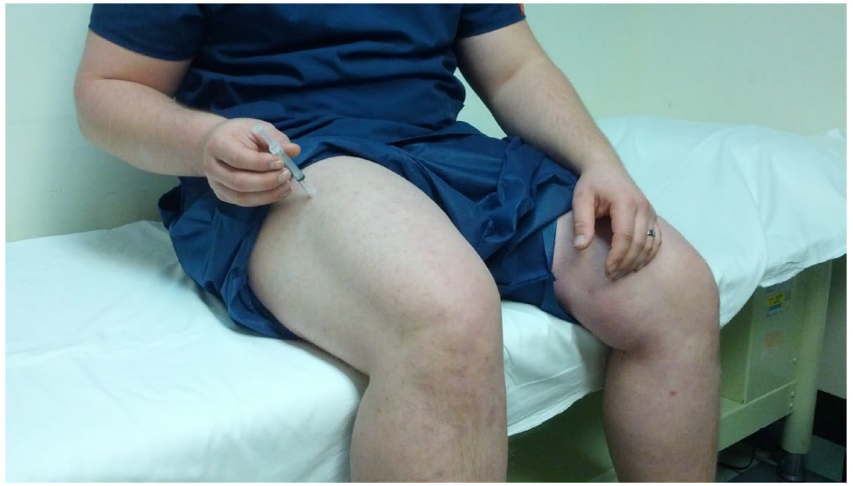
TESTOSTERONE CYPIONATE (IM)

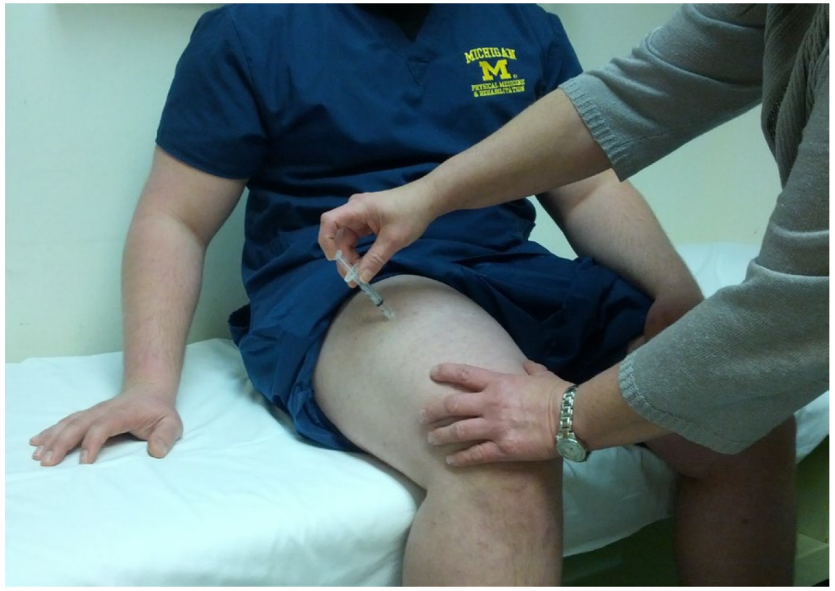


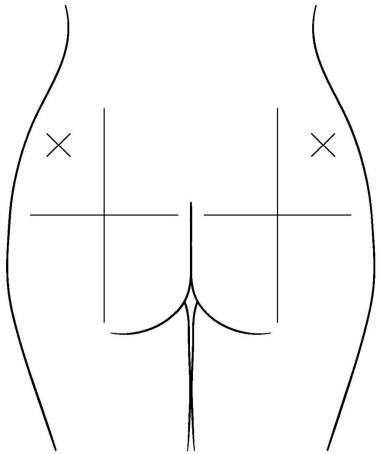
Recommended dosage is 50 mg to 400 mg administered every two to four weeks as a deep intramuscular injection in the gluteal muscle. Individualize he dose and schedule based on the patient's age, diagnosis, response to treatment, and the appearance of adverse reactions

Inexpensive, hardly any problems with compliance

Frequent painful intramuscular injections, moderate pharmacokinetics with unpleasant fluctuations for patients







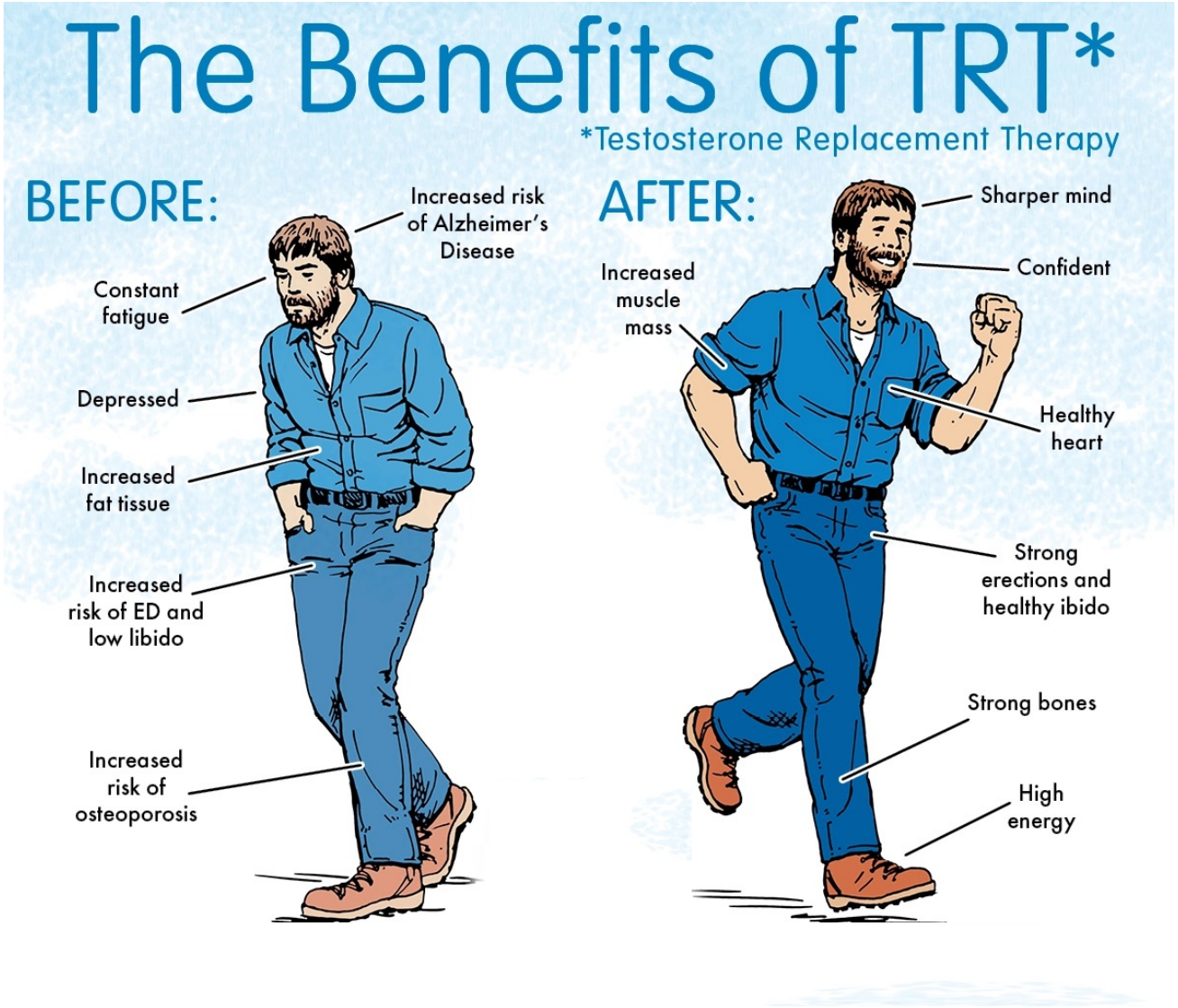
GoodRx

Testosterone cypionate
2 vials 1ml of 200mg/ml
SAVE

CVS Pharmacy	2.8 miles	Coupon ~~$60~~ $15.94
Target (CVS)	5.7 miles	Coupon ~~$60~~ $15.94
Food Lion Pharmacy		Coupon ~~$93~~ $16.18
Publix	5.6 miles	Coupon $18.36
Walgreens	1.1 miles	Discount $19.28
Walmart	5.0 miles	Discount $19.29
Walmart Neighborhood Market	4.9 miles	Discount $19.29
Costco	7.5 miles	Coupon ~~$47~~ $45.99
Harris Teeter	5.6 miles	Retail $136.64

The Benefits of TRT*

*Testosterone Replacement Therapy



American Urological Association

RECOMMENDATION

Level of Evidence A	Data derived from multiple randomized trials of meta-analyses
Level of Evidence B	Data derived from a single randomized clinical trial or non randomized studies
Level of Evidence C	Consensus of opinion of experts and/or small studies

All men with testosterone deficiency should be counseled regarding lifestyle modifications as a treatment strategy. (Conditional Recommendation; Evidence Level: Grade B)

American Urological Association

Patients should be informed that testosterone therapy may result in improvements in erectile function, low sex drive, anemia, bone mineral density, lean body mass, and/or depressive symptoms. (Moderate Recommendation; (Evidence Level: Grade B)

American Urological Association

Clinicians should discuss the risk of transference with patients using testosterone gels/creams. (Strong Recommendation; Evidence Level: Grade A)

American Urological Association

Clinicians should inform testosterone deficient patients that low testosterone is a risk factor for cardiovascular disease. (Strong Recommendation; Evidence Level: Grade B)

American Urological Association

Patients should be informed that the evidence is inconclusive whether testosterone therapy improves cognitive function, measures of diabetes, energy, fatigue, lipid profiles, and quality of life measures. (Moderate Recommendation; Evidence Level: Grade B)

Testosterone therapy should not be commenced for a period of three to six months in patients with a history of cardiovascular events. (Expert Opinion)

Prior to initiating treatment, clinicians should counsel patients that, at this time, it cannot be stated definitively whether testosterone therapy increases or decreases the risk of cardiovascular events (e.g., myocardial infarction, stroke, cardiovascular-related death, allcause mortality). (Moderate Recommendation; Evidence Level: Grade B)

The long-term impact of exogenous testosterone on spermatogenesis should be discussed with patients who are interested in future fertility. (Strong Recommendation; Evidence Level: Grade A)

Clinicians should inform patients of the absence of evidence linking testosterone therapy to the development of prostate cancer.(Strong Recommendation; Evidence Level: Grade B)

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Patients with testosterone deficiency and a history of prostate cancer should be informed that there is inadequate evidence to quantify the risk-benefit ratio of testosterone therapy. (Expert Opinion)

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Patients should be informed that there is no definitive evidence linking testosterone therapy to a higher incidence of venous thromboembolic events. (Moderate Recommendation; Evidence Level: Grade C)

In-situ prostate cancer

Locally advanced or metastatic prostate cancer

Clinicians should measure an **initial followup** total testosterone level after an appropriate interval to ensure that target testosterone levels have been achieved. (Expert Opinion)

Testosterone levels should be measured every 6-12 months while on testosterone therapy. (Expert Opinion)

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Clinicians should discuss the cessation of testosterone therapy three to six months after commencement of treatment in patients who experience normalization of total testosterone levels but fail to achieve symptom or sign improvement. (Clinical Principle)

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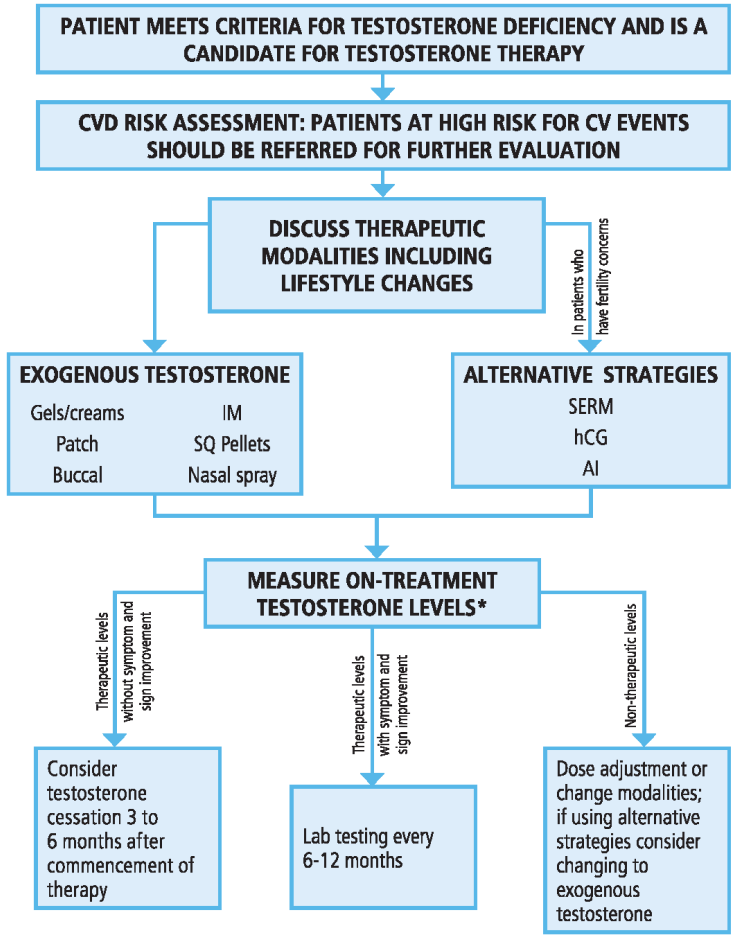
RECOMMENDATION

EVALUATION AND MANAGEMENT OF TESTOSTERONE DEFICIENCY: TREATMENT ALGORITHM



*Testosterone levels should be driven to the normal physiological range of 450-600 ng/dL (approximately equivalent to the middle tertile of the normal range).

AI = Aromatase Inhibitor
CVD = Cardiovascular Disease
hCG = Human Chorionic Gonadotropin
IM = Intramuscular Testosterone Injection
SERM = Selective Estrogen Receptor Modulator
SQ = Subcutaneous

PAST AND FUTURE SESSIONS

- Session One: Clinical investigation of the infertile male
- Session Two: Genetic causes of male infertility and their impact on future generations
- Session Three: Medical Treatments for Male Infertility
- Session Four: Surgical Treatments and Assisted Reproductive Technology (ART) for Male Infertility
- Session Five: Ejaculatory disorders, diagnosis, and management
- Session Six: Clinical investigation and laboratory analyses in male hypogonadism
- Session Seven: Testosterone deficiency syndrome, , Androgen replacement—indications and principles
- **Session Eight: Female-to-Male Transsexualism**

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