Pharmacological therapies for male sexual dysfunction

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Epidemiology

- **52%** of men aged 40-70 years of age
- 10 million American men
- In Iran (2019): **35.6%** of men complained about sexual problems
- The most prevalent problems in men
  - Erection dysfunction: **40.4%**
  - Ejaculation dysfunction: **32.5%**
  - Prevalence of sexual drive dysfunction in Iranian men: **10.6%**

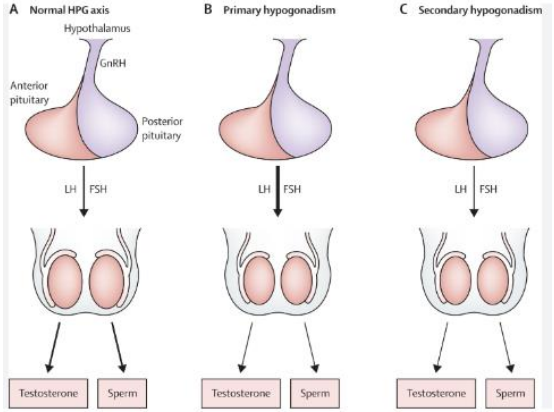
The main sexual dysfunctions in men

- In order to manage male sexual dysfunction, 3 main disorders are noted:

Late onset hypogonadism (LOH)

Erectile dysfunction (ED)

Premature ejaculation (PE)



Late onset hypogonadism (LOH)

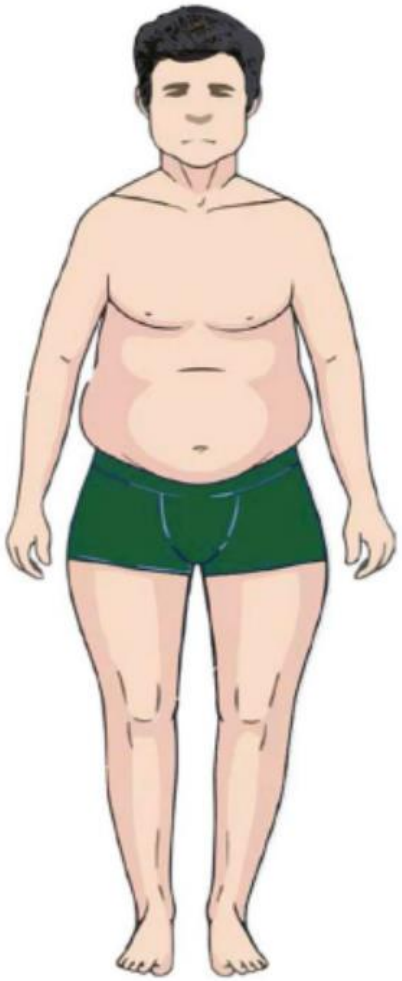
- **LOH** is a disorder associated with decreased functional activity of the testes, with decreased production and/or action of androgens and/or impaired sperm production

- This disorder is created as a result of poor testicular function or inadequate stimulation of the testes by the hypothalamic-pituitary-gonadal (HPG) axis as well as several congenital or acquired disorders causing impaired action of androgens
- The diagnosis of LOH is essential before hormone therapy

Common symptoms and signs associated with LOH

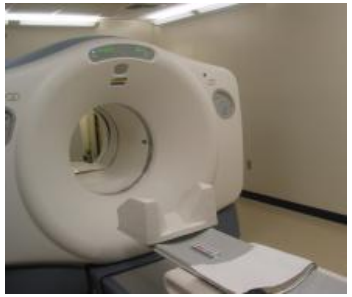
Symptoms

- Sexual dysfunction
- Low motivation / Vitality
- Poor concentration / Memory
- Hot flushes / sweating
- Infertility



Signs

- Reduced body hair
- Gynecomastia
- Reduced Testicular Volume
- Obesity
  Reduced Muscle Mass
- Anemia
- Reduced Bone Density



Screening and diagnostic evaluation of late onset hypogonadism (LOH)

- Check for concomitant diseases, drugs, and substances interfering testosterone production/action.
- Total testosterone (TT) must be measured in the morning (7-11 am) and in the fasting state, with a reliable method and repeat on at least two separate occasions before starting testosterone therapy.
- A TT of **12 nmol/L (3.5 ng/ml)** represents a reliable threshold to diagnose LOH.
- **Free testosterone <225 pmol/l** has been suggested as a possible cut-off to diagnose LOH.
- Measure FSH, LH (to differentiate between primary and secondary), and prolactin (if sexual desire is low or other suggestive signs/symptoms and low or low-to-normal testosterone are present).
- Perform pituitary **MRI** if prolactin is elevated or symptoms of a pituitary mass and/or presence of other anterior pituitary hormone deficiencies or severe hypogonadism (TT< 6 nmol/l).

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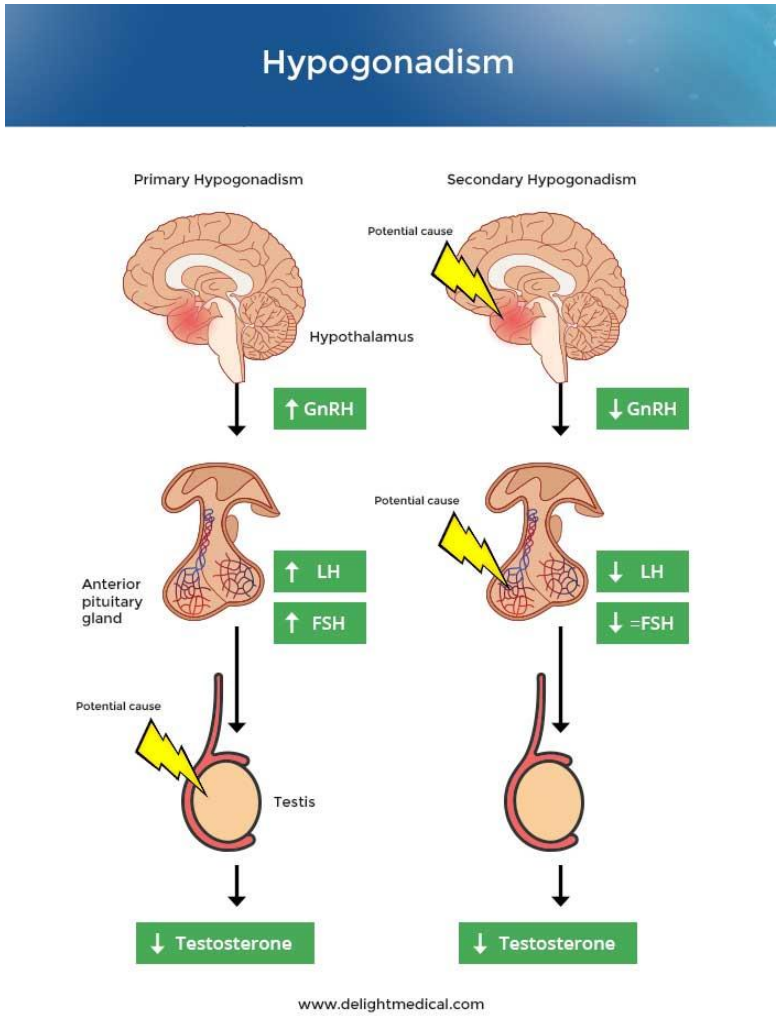
Primary or secondary hypogonadism

- Measuring **TT and LH** in all men with clinical manifestations consistent with hypogonadism.
- A value of **LH ≥ 9.4 IU/L**, in the presence of low total or calculated free testosterone, suggests **primary hypogonadism**.
- For **LH concentrations < 9.4 IU/L**, measuring FSH is helpful in the differential diagnosis between primary and secondary hypogonadism.



Who are candidates for testosterone therapy?

- Patients with symptomatic hypogonadism without specific contraindications, in particular those with less complicated situation and aging subjects are suitable candidates for receiving testosterone therapy

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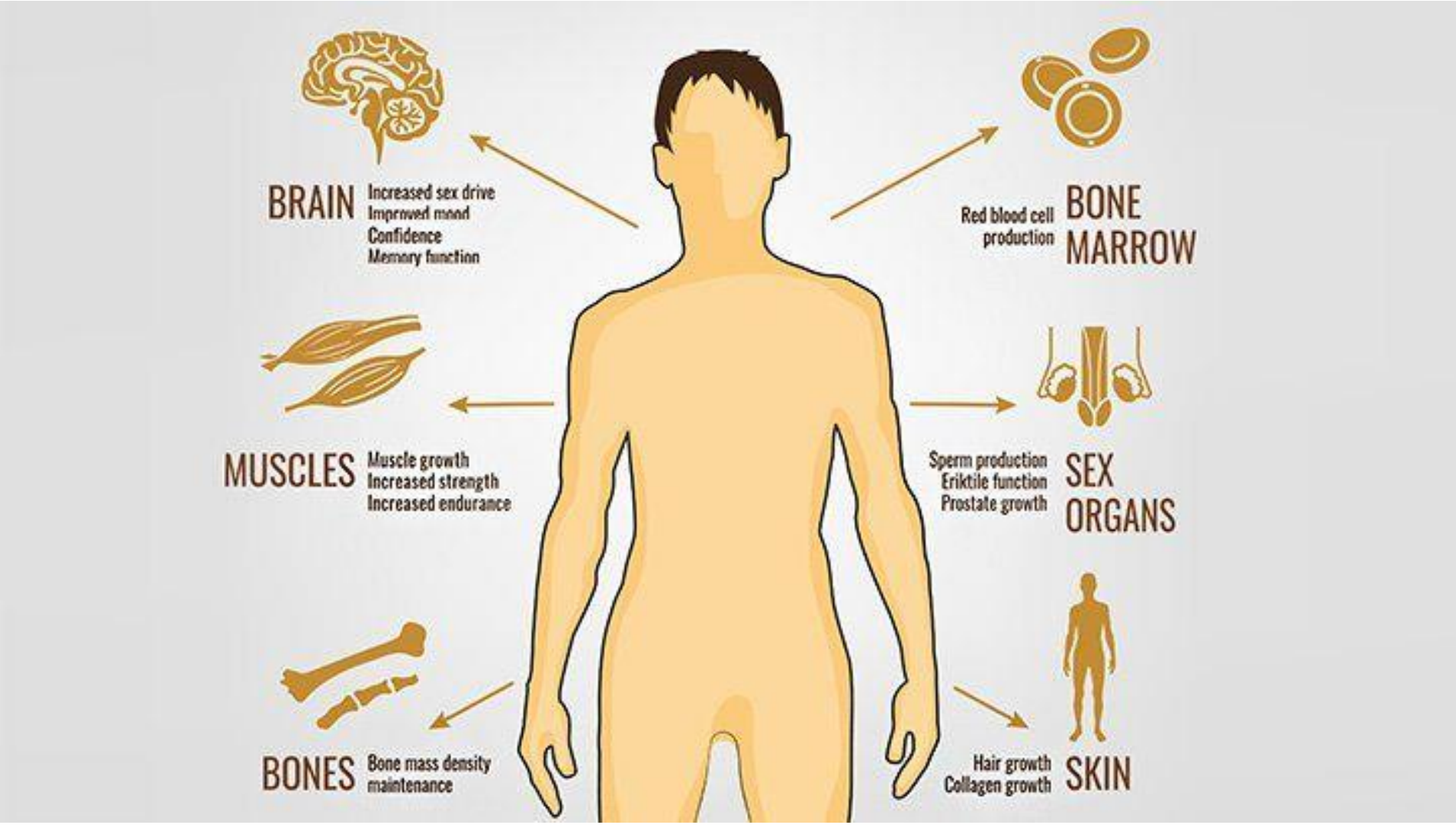
Italian Society of Andrology and Sexual Medicine (SIAMS) and the Italian Society of Endocrinology (SIE)- 2022

Therapeutic effects of testosterone therapy



JAMA Psychiatry
American Medical Association

Association of Testosterone Treatment With Alleviation of Depressive Symptoms in Men

A Systematic Review and Meta-analysis

Andreas Walther, PhD, Jonas Breidenstein, BSc, and Robert Miller, PhD

- 1890 hypogonadal men from 27 RCTs
- The positive effect of testosterone therapy on depressive symptoms

Open Access Research

BMJ Open

Testosterone therapy in hypogonadal men: a systematic review and network meta-analysis

Jesse Elliott,[1] Shannon E Kelly,[1] Adam C Millar,[2] Joan Peterson,[3] Li Chen,[1] Amy Johnston,[1] Ahmed Kotb,[4] Becky Skidmore,[5] Zemin Bai,[1] Muhammad Mamdani,[6] George A Wells[1]

- 87 RCTs and 51 NRS
- Compared to placebo, TRT improved quality of life, libido, depression, and erectile function.
- Most were at high or unclear risk of bias, with short treatment duration and follow-up.

Accepted Manuscript

Testosterone therapy and venous thromboembolism: A systematic review and meta-analysis

Damon E. Houghton, Mouaz Alsawas, Patricia Barrioneuvo, Mouaffaa Tello, Wigdan Farah, Brad Beuschel, Larry J. Prokop, J. Bradley Layton, M. Hassan Murad, Stephan Moll

- **Six RCTs** (n=2,236) and **5 observational studies** (n=1,249,640)
- **No significant association** between testosterone and VTE
- Limited data from RCTs and heterogeneity in observational studies: Inconclusive results

Review J Sex Med. 2022 Aug;19(8):1243-1254. doi: 10.1016/j.jsxm.2022.05.145.
Epub 2022 Jun 23.

Cardiovascular Morbidity and Mortality in Men – Findings From a Meta-analysis on the Time-related Measure of Risk of Exogenous Testosterone

Giuseppe Fallara [1], Edoardo Pozzi [1], Federico Belladelli [1], Christian Corsini [1], Luca Boeri [2], Paolo Capogrosso [3], Francesco Montorsi [1], Andrea Salonia [4]

- **10** studies were included involving **179,631** hypogonadal men
- Men treated with TT were at **lower mortality risk** from all causes relative to the control
- However, TT was associated with **unfavorable effect on cardiovascular events**

Main contraindications of testosterone therapy

Absolute contraindications

- Locally advanced or metastatic prostate cancer
- Male breast cancer
- Men with an active desire to have children
- Hematocrit > 54%
- Uncontrolled or poorly controlled congestive heart failure

Relative contraindications

- Severe lower urinary tract symptoms
- Baseline haematocrit 48–50%
- Familial history for venous thromboembolism

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The effect of different administrations of testosterone therapy on adverse prostate events: A Bayesian network meta-analysis

- TT **does not** lead to abnormal prostate-specific antigen (PSA) changes and increased risk of Pca in patients with hypogonadism or low testosterone level.
- Compared with other preparations of TT, intramuscular injection proved better in minimizing Pca cases and was more likely to result in fewer prostate biopsy cases.

Recommendations for testosterone therapy outcome

Recommendations	Strength rating
The use of **testosterone therapy in eugonadal men** is **not indicated**.	Strong
Use **testosterone as first-line treatment** in patients with symptomatic hypogonadism and mild ED.	Strong
Use combination of **PDE5Is and testosterone therapy** in **more severe forms of ED** as it may result in better outcomes.	Weak
Use conventional medical therapies for severe depressive symptoms and osteoporosis.	Strong
Do not use testosterone therapy to improve body composition, reduce weight, and benefit cardiometabolic profile.	Weak
Do not use testosterone therapy to improve cognition vitality and physical strength in ageing men.	Strong

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Recommendations for choice of treatment for late-onset hypogonadism

Recommendations	Strength rating
Treat, when indicated, **organic causes of hypogonadism** (e.g., pituitary masses, hyperprolactinemia, etc.).	Strong
Improve lifestyle and reduce weight (eg, obesity); withdraw, when possible, concomitant drugs that impair testosterone production; treat comorbidity before starting testosterone therapy.	Weak
Fully **inform patients** about **expected benefits and adverse effects of any treatment** option. Select the testosterone preparation in a joint decision process, only with fully informed patients.	Strong
The aim of testosterone therapy is to restore serum testosterone concentration to the average normal range for young men	Weak
Use **testosterone gels** rather than long-acting depot administration when starting initial treatment, so that therapy can be adjusted or stopped in case of treatment-related adverse effects.	Weak

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Testosterone therapy formulations and their characteristics

Formulation and dose	Administration and monitoring	Advantages	Disadvantages
Transdermal topical Testosterone (T) gels and axillary solution 50–100 mg of 1% Testogel®, 40–70 mg of 2% Tostran®, 23-46 mg of Testavan® or 20.25–81 mg of 16.2 mg/g (Testogel® pump) transdermal gel once daily 60 mg of T solution applied in the axillae once daily (not available in the UK)	Clear alcohol gel available in sachets, tubes and pumps containing, applied dry, clean skin on shoulders, abdomen, upper arms or thighs (avoid the genital area). Monitor total T 2–6 h post-gel application, 2–3 weeks posttreatment initiation or dose adjustment, aiming for mid-normal reference range total T.	Convenient, flexible and easy application; good skin tolerability. Effective, provides T levels within normal range for 24 h. Steady physiological levels of serum T with no 'peak and troughs' between applications. Dose easily adjustable to individual needs. No pain of injections.	May cause skin dryness and irritation for some patients. Takes time to apply. Potential of transfer to a female partner or child by direct skin-to-skin contact. Fear of transfer may inhibit intimacy; patient education minimises potential of transfer. Increased DHT levels due to presence of 5α-reductase in the skin. Considerable inter- and intra-individual T levels require close dose titration.

Society for Endocrinology guidelines for testosterone replacement therapy in male hypogonadism- 2021

Testosterone therapy formulations and their characteristics

Long-acting T undecanoate IM injections 1000 mg in 4 ml (Nebido®) ampoule of oily preparation every 10–14 weeks 	Injected slowly deep into the gluteal muscle. The second injection (loading dose) is given at 6 weeks, and the third dose 12 weeks after the second. Injection interval is adjusted based on trough total T level just before the third injection, aiming for the lower end of normal reference range level. Monitor trough total T and FBC every 3–5 injections or annually.	Effective, maintains physiological serum T levels for 3 months or longer. Smoother serum T profile compared to short-acting T injections, with less noticeable 'peak and trough' symptoms. Convenient, 3-monthly administration without the side effects seen with T implants.	Pain, discomfort and adverse reaction at injection site. Requires large muscle bulk for injection. Lifestyle restrictions as it cannot be self-administered. Not recommended as first-line treatment option due to inability of withdrawal in case of adverse events (AE). Rare AE of pulmonary micro-embolism presenting with severe coughing episode during injection.

Society for Endocrinology guidelines for testosterone replacement therapy in male hypogonadism- 2021

Testosterone therapy formulations and their characteristics

Short-acting T injections 1. Combination of testosterone esters 250 mg/ml (Sustanon®) IM every 3–4 weeks (propionate 30 mg, phenylpropionate 60 mg, isocaproate 60 mg, decanoate 100 mg); 2. Testosterone enanthate or cypionate 150–200 mg IM every 2 weeks or 50–100 mg IM or SC once a week	Oily preparation (1 ml) injected slowly into the gluteal muscle or upper thigh. Adjust injection interval based on trough total T level at the end of the injection aiming for the lower end of the normal reference range. Monitor trough total T and FBC every 6–12 months.		Potentially unpleasant "peak & trough" symptoms due to supraphysiological T levels postinjection which decline to hypogonadal range by the next injection. Risk of polycythaemia due to supraphysiological T levels. Pain, discomfort at injection site. Lifestyle restrictions for patients not self-injecting.
Bio-adhesive Buccal T tablet 30 mg controlled-release tablets applied to the upper gum twice daily (not available in the UK)	T is absorbed gradually from the buccal mucosa over 12 h. Applied on healthy, clean gum; the solid tablet softens and moulds to the shape of the gum. Monitor T 2–6 h post-tablet application, 2–3 weeks posttreatment initiation, aiming for mid-normal reference range total T.		

Society for Endocrinology guidelines for testosterone replacement therapy in male hypogonadism- 2021

Testosterone therapy formulations and their characteristics

Formulation and dose	Administration and monitoring	Advantages	Disadvantages
Subcutaneous T implants Testosterone pellets 100 or 200 mg to a total of 600–1200 mg T per dose (rarely administered)	3–6 pellets every 4–6 months. Pellets implanted in the subcutaneous adipose tissue with a surgical incision under local anaesthetic.	Serum T peaks at 1 month and is sustained in normal range for up to 6 months. Convenience—twice or thrice a year application.	Painful procedure with high risk of infection at the insertion point and scar tissue. Risk of spontaneous extrusion after implantation.
Oral T undecanoate capsules 40 mg 1–3 capsules (40–120 mg) twice or thrice daily with meals	Taken orally; absorption is improved when taken with a fatty meal. Swallow without chewing.	Easy and convenient administration. Suitable for patients who cannot tolerate other forms of treatment and those who require low levels of T, not a preferred treatment option.	Low bioavailability and very high inter- and intra-individual variability in absorption resulting in insufficient serum T levels. Normal serum T level attained for only up to 3–5 h.

Society for Endocrinology guidelines for testosterone replacement therapy in male hypogonadism- 2021

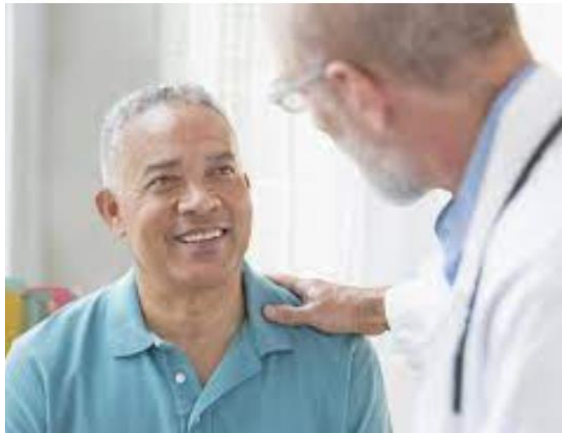
اشکال تستوسترون موجود در ایران

- متیل تستوسترون قرص خوراکی (25mg)
- تستوسترون انانتات تزریقی پرنترال ۱۰۰ و ۲۵۰ mg/1mL
- تستوژل ژل، سرنوژل و آندروژل موضعی ۱ درصد 5g
- آندراستانولون و آندراکتیم ژل موضعی ۲.۵ ٪ ۸۰ گرم(ژل دی هیدرو تستوسترون)
- سوستانون تزریقی پرنترال، آندرون تزریقی و آندوزیکس-آی اچ پرنترال ۲۵۰ میلی گرم (تزریقی تستوسترون انانتات)
- آندرون و آندوزیکس-آی اچ تزریقی پرنترال ۱۰۰ میلی گرم (تزریقی تستوسترون انانتات)
- آندریول تستوکپس کپسول خوراکی ۴۰ mg (کپسول تستوسترون اندکانوات)

How to follow-up patients who are receiving testosterone?

- Evaluation should perform for the following items:
  - Clinical symptoms of LOH
  - BMI and WC
  - Digital rectal examination
  - Blood pressure

- Measuring the haematocrit (Hct) **3-6 months** after initiation of TRT and then annually
  - If Hct is **> 54%,** TRT should be discontinued, until Hct decreases to a safe level
- Evaluate the patient for hypoxia and sleep apnoea



European Association of Urology Guidelines on Sexual and Reproductive Health—2021 Update

Erectile dysfunction (ED)

Definition

ED is defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance

Epidemiology

Erectile dysfunction (ED) affects between 12.9% and 28.1% of men worldwide

Etiology

- Organic
- Psychogenic
- Mixed

Risk factors

- Age
- Medical conditions such as diabetes mellitus, dyslipidaemia, hypertension, MetS, and CVD
- BMI/obesity/waist circumference
- Hyperhomocysteinemia
- Lack of exercise
- Smoking
- pharmacotherapeutic agents for CVD

Association with CVD risk

- Myocardial infarction
- Cerebrovascular events
- All-cause mortality, with a trend towards an increased risk of CV mortality

ED, therefore, can be an early manifestation of coronary artery and peripheral vascular disease, and should not be regarded only as a QoL issue, but also as a potential warning sign of CVD

Recommendations on diagnostic evaluation of erectile dysfunction

- Take a **comprehensive medical and sexual history**
- Consider factors like **life stressors**, **cultural aspects**, and **cognitive/thinking style** of the patient regarding their sexual performance
- Use a **validated questionnaire** related to ED to assess all sexual function domains (eg, the International Index of Erectile Function) and the effect of a specific treatment
- Include a focused **physical examination** in the initial assessment of men with ED to identify underlying medical conditions and comorbid genital disorders that may be associated with ED
- Assess **routine laboratory tests**, including **glucose** and **lipid profile** and **total testosterone**, to identify and treat any reversible risk factors and lifestyle factors that can be modified
- Include **specific diagnostic tests** in the initial evaluation of ED in the presence of specific conditions

Is ED curable?

ED can be treated successfully with a number of therapeutic options, but it cannot be cured.

The only exceptions are psychogenic ED, post-traumatic arteriogenic ED in young patients, and hormonal causes (eg, hypogonadism) which can potentially be cured with specific treatments.

Pharmacological agents for ED

Oral pharmacotherapy

Topical/ Intraurethral alprostadil

Intra-cavernous injection therapy

Hormone replacement therapy

Use CBT as a psychological approach (include the partner) combined with medical treatment to maximize treatment outcomes.

Oral pharmacotherapy for ED

- Phosphodiesterase type 5 inhibitors (PDE5 inhibitor) are **vasodilating drug**
- Use of phosphodiesterase type 5 inhibitors (PDE5Is) as a first-line therapeutic option for ED (**effective in more than 80% men with ED**)
- These drugs:
  - **dilate** the corpora cavernosa of the penis
  - **facilitating erection** with sexual stimulation

PDE5 inhibitors Regimens

- **On demand:**
  - All three (Sildenafil, Tadalafil, and Vardenafil)
- **Scheduled:**
  - Tadalafil 5mgs daily
- **Combination:**
  - Limited data:
  - Data on: Tadalafil 5mgs daily + Sildenafil 50 on demand

Adverse effects

- All PDE5 inhibitors are generally well tolerated
- Side effects: depends on **the dose** and **type of agent**.
- The most common adverse effects with using these drugs include:
  - Headache (very common)
  - Dizziness,
  - Flushing,
  - Dyspepsia,
  - Nasal congestion or rhinitis
  - Back pain and muscle aches
  - Anterior optic neuropathy and hearing loss although the absolute risk increase is small.

World Journal of Urology
https://doi.org/10.1007/s00345-020-03233-9

ORIGINAL ARTICLE

Efficacy and safety of oral phosphodiesterase 5 inhibitors for erectile dysfunction: a network meta-analysis and multicriteria decision analysis

Camilla R. Madeira[1] · Fernanda S. Tonin[1] · Mariana M. Fachi[1] · Helena H. Borba[2] · Vinicius L. Ferreira[3] · Leticia P. Leonart[1] · Aline F. Bonetti[1] · Rogerio P. Moritz[3] · Angela C. L. B. Trindade[2] · Alan G. Gonçalves[2] · Fernando Fernandez-Llimos[4] · Roberto Pontarolo[2]

- Overall, 184 articles representing 179 randomized controlled trials
- All PDE5i were significantly more efficient than placebo.
- **Sildenafil 25 mg** was statistically **superior** to all interventions in improving erectile dysfunction measured by IIEF, **followed by sildenafil 50 mg** .
- Taladafil 10 mg and 20 mg also presented good profiles (73% and 76%, respectively).
- Avanafil was less effective interventions.

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- **Mirodenafil** 150 mg was the treatment that caused more adverse events, especially flushing and headaches.
- **Sildenafil** 100 mg was more related to visual disorders, while **vardenafil** was more prone to cause nasal congestion.

World Journal of Urology
https://doi.org/10.1007/s00345-018-2583-1

REVIEW

Comparative efficacy and safety of phosphodiesterase type 5 inhibitors for erectile dysfunction in diabetic men: a Bayesian network meta-analysis of randomized controlled trials

Xinyang Liao[1] · Shi Qiu[1] · Yige Bao[1] · Wanyu Wang[2] · Lu Yang[1] · Qiang Wei[1]

Received: 9 September 2018 / Accepted: 26 November 2018

- 1056 records, of which 15 randomized trials with 5274 patients
- PDE5I administrations: efficient and well-tolerated in diabetic men.
- Among these administrations, **vardenafil** PRN and **mirodenafil** PRN seem to have a possible advantage of efficacy and avoiding adverse effects compared to others.
- There is no significant difference between regular and on-demand regimens of PDE5Is.

The most common PDE5Is for ED

- Four potent selective PDE5Is have currently been approved by the European Medicines Agency (EMA) for the treatment of ED, including
  - Sildenafil (Viagra)
  - Tadalafil (Cialis)
  - Vardenafi
  - Avanafil

European Association of Urology Guidelines on Sexual and Reproductive Health—2021 Update

اشکال داروهای مهارکننده های تیپ ۵ فسفودی استراز (PDE5I) موجود در ایران

- سیلدنافیل ژل موضعی ۱ ٪ ۱۵ و ۲۰ گرم (ژل سیلدنافیل سیترات)
- ویاگرا یا سیلدنافیل قرص خوراکی ۵۰ و ۱۰۰ میلی گرم (بصورت سیترات)
- سیلدنافیل قرص بازشونده در دهان خوراکی (۲۵ و ۵۰ میلی گرم) (بصورت سیترات)
- یوفوژل (ویژه آقایان) ژل موضعی ۱ ٪ (۲۰ گرم ژل سیلدنافیل سیترات)
- ارکژل ژل موضعی ۱ ٪ (۱۵ گرم ژل سیلدنافیل سیترات)
- دیرکتا ژل موضعی ۱ ٪ (۳۰ گرم ژل سیلدنافیل سیترات)
- ویگاژل ژل موضعی ۱ ٪ (۳۰ گرم ژل سیلدنافیل سیترات)
- تادالافیل قرص خوراکی (۲/۵، ۵، ۱۰ و ۲۰) mgقرص تادالافیل)

- واردنافیل، آوانافیل و میرودنافیل: در ایران موجود نمی باشد.

Contraindications for prescribing PDE5Is

- Patients with **recent CVD**
- **Coadministration of PDE5Is with antihypertensive agents**: result in small additive decreases in blood pressure
- Absolut contraindication:
  - Patients who are **using any form of organic nitrate** (eg, nitroglycerine, isosorbide mononitrate, and isosorbide dinitrate)
  - Patients receiving **other nitrate preparations used to treat angina**, such as nicorandil, an antianginal vasodilator drug that acts by increasing nitric oxide bioavailability

Patient Education – Keys to PDE-5i Success

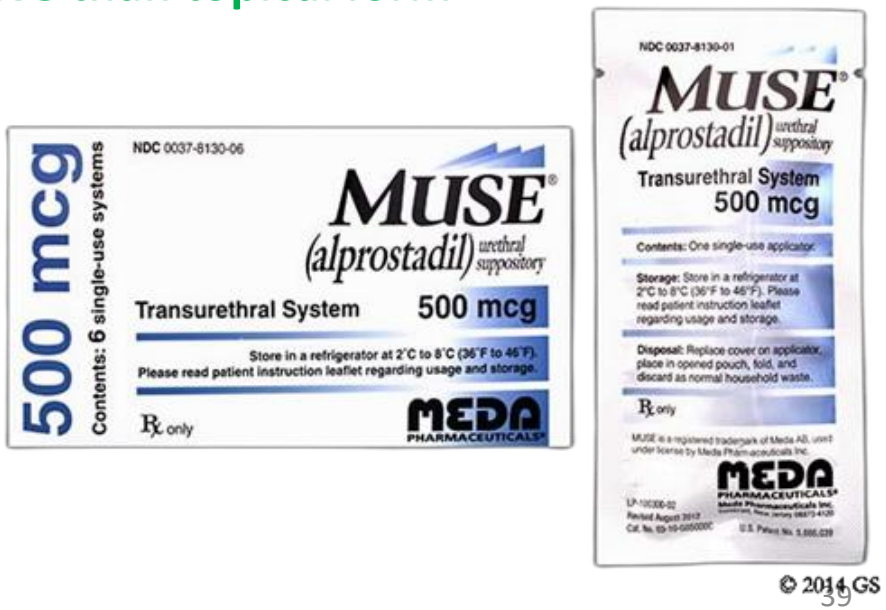
- Patient Education critical to success
  - Take **30 min** in advance of sex (**1 hr** for Tadalafil)
  - Mental and physical stimulation required
    - Not a “magic” erection pill, best of partner aware
    - Anxiety can counteract effects of medication
  - Try medication several times
  - Efficacy of the drugs varies from patient to patient
    - Try at least 2 drugs before declaring failure
  - Warn patient about side-effects, and reassure them that they won’t die by taking PDE-5i

Failure of PDE5 inhibitors

- Wrong dose
- Wrong timing
- Drug-Drug Interaction
- Psycho-emotional effect such as anxiety

Topical/intraurethral alprostadil

- This is a vasoactive agent
- It can be administered per urethra with **two different formulation**:
  - **Topical route using a cream** that includes a permeation enhancer in order to facilitate absorption of alprostadil (200 and 300 mg) via the urethral meatus
  - **Intraurethral insertion of a specific formulation of alprostadil** (125–1000 mg) in a medicated pellet (MUSE) - **This method is direct and more effective than topical form**



Adverse effects

- Penile erythema
- Penile burning
- Pain

usually resolve within 2 h of application

- Dizziness
- Hypotension

are rare.

Intracavernous injection therapy

- Overall, the success rate is high (85%)
- Intracavernous alprostadil is most efficacious as a monotherapy at a dose of 5–40 mg
- The use of an automatic pen that avoids a view of the needle may be useful to resolve fear of penile puncture.

Adverse effects

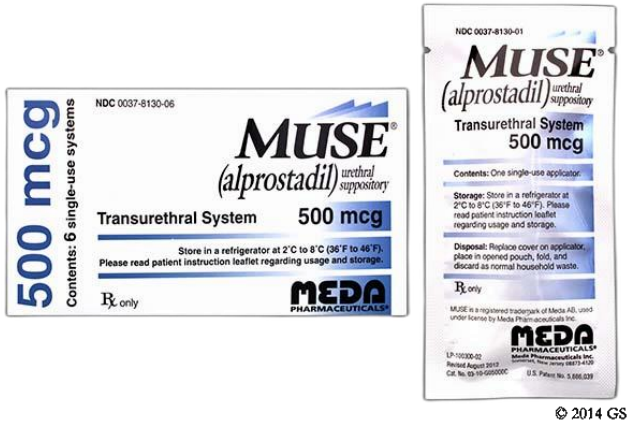
- Penile pain (1–11%)
- Excessively prolonged undesired erections and priapism (0.25–1%)
- Persisting (tunical) fibrosis (5–7%)
- Systemic side effects (i.e.., mild hypotension) are uncommon.

Contraindications

- Men with a history of hypersensitivity to alprostadil
- Men at risk of priapism (prolonged erection of the penis)
- Men with bleeding disorders

اشکال داروی آلپروستادیل موجود در ایران

- آلپروستادیل پودر برای تهیه محلول تزریقی پرنترال ۲۰ میکروگرم پودر برای تهیه محلول تزریقی پروستاگلاندین ای یک (آلپروستادیل))
- موس استیک پیشابراهی ۵۰۰ تا ۱۰۰۰ میکرو گرم)استیک پروستاگلاندین ای یک (آلپروستادیل))



Hormonal treatment

- When clinically indicated, testosterone therapy (intramuscular or transdermal) can be considered for men
  - Low or low-normal testosterone levels + concomitant problems with their sexual desire, erectile function, + dissatisfaction derived from intercourse and overall sexual life.
- Refer to an endocrinologist for:
  - managing patients with certain hormonal abnormalities or endocrinopathies.

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European Association of Urology

Platinum Priority – Andrology
Editorial by XXX on pp. x–y of this issue

Meta-analysis of Results of Testosterone Therapy on Sexual Function Based on International Index of Erectile Function Scores

- TTh significantly improves erectile function and other sexual parameters
- **Sexual dysfunction should be considered a hallmark manifestation of T deficiency, since those symptoms can be significantly improved with normalization of serum T.**
- Therefore,
  - **TTh alone** may be considered a reasonable treatment for hypogonadal men with milder degrees of erectile dysfunction
  - But **the addition of other treatments**, such as phosphodiesterase type 5 inhibitors, may be more appropriate for men with more severe erectile dysfunction

Premature ejaculation (PE)

- According to EAU guidelines, PE (lifelong and acquired) is a male sexual dysfunction characterized by the following:
    1. **Lifelong PE:** This is a persistent or consistent condition that has been present since the first sexual experience. It is characterized by ejaculation within about one minute of vaginal penetration, inability to delay ejaculation, and negative personal consequences. It is likely caused by a combination of biological and psychological factors. It may respond to pharmacological in addition to behavioral therapy.

    2. **Acquired PE:** This is a condition that develops later in life after a period of normal ejaculatory function. It is characterized by a significant and bothersome reduction in ejaculatory latency, usually to about three minutes or less. It is often related to identifiable causes, such as medical conditions, medications, or stress. It may improve by treating the underlying cause or by using pharmacological or behavioral therapy or both

Premature ejaculation (PE)

3. **Natural variable PE:** This is a normal variation of ejaculatory latency that occurs occasionally in some men, depending on the situation and partner. It is not considered a disorder and does not require treatment.

4. **Premature-like ejaculatory dysfunction:** This is a subjective perception of ejaculating too soon, despite having a normal or even prolonged ejaculatory latency. It is associated with psychological factors, such as anxiety. It may benefit from psychosexual counseling or education.

Some principals to manage PE

- **Pharmacotherapy** must be considered as the first-line treatment for patients with lifelong PE.

- **Treating the underlying cause** (eg, ED, prostatitis, lower urinary tract symptoms, anxiety, hyperthyroidism, etc.) must be the initial goal for patients with acquired PE.

- **In lifelong PE,** behavioral techniques are not recommended alone, and pharmacotherapy must be considered as the basis of treatment.

- **In acquired PE,** combination of behavioral therapy with medical interventions may be most effective therapeutic approach compared to medical treatment alone.

European Association of Urology Guidelines on Sexual and Reproductive Health—2021 Update

Other pharmacological treatment

- **Daily or on-demand** use of **selective serotonin reuptake inhibitors (SSRIs)** and **clomipramine**, and **on demand topical anaesthetic agents** have consistently shown efficacy in PE
- **Dapoxetine** (30 and 60 mg) is the first on-demand oral pharmacological agent approved for lifelong and acquired PE in many countries, except for the USA.
- **Paroxetine** was found to be superior to **fluoxetine**, **clomipramine**, and **sertraline**
- **Tramadol**, a mild opioid receptor agonist that also promotes reuptake inhibition of serotonin and noradrenaline, has been demonstrated to be effective as an off-label on-demand oral therapy in men with a history of lifelong PE
- Side effects include nausea, diarrhea, headache, and dizziness, constipation, sedation, dry mouth, and addiction.
- As a whole, long-term outcomes of pharmacological treatments are unknown

Other options for managing PE

- Moreover, the eutectic metered-dose aerosol spray of **lidocaine** (150 mg/ml) and prilocaine (50 mg/ml) combination is the first topical formula to be officially approved for the on demand treatment

- Based on available data, the recommended dose of **lidocaine/prilocaine s**pray is one dose (namely, three sprays) to be applied on the glans penis **at least 5 min** before sexual intercourse

- All other medications used in PE are off-label indications

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Pharmacotherapies for the treatment of Premature Ejaculation

Drug	Daily Dose	On-demand dosing
First Line:		
Paroxetine	10–40 mg	20 mg (+/-10 mg daily)
Clompramine	12.5–50 mg	25–50 mg
Sertraline	50–200 mg	50–100 mg
Fluoxetine	20–40 mg	
Citalopram	20–40 mg	
Second Line:		
Tramadol		25–100 mg
Terazosin	5 mg	
Alfuzosion	6–10 mg	
Sildosin	4 mg	
Tamsulosin	0.4 mg	
Doxazosin	4 mg	

Disorders of Ejaculation: An AUA/SMSNA Guideline- 2021

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Check for updates

ORIGINAL ARTICLE

First International Journal of Andrology ANDROLOGIA WILEY

Comparative efficacy and safety of drug treatment for premature ejaculation: A systemic review and Bayesian network meta-analysis

- The **combination of SSRI and PDE5i** therapy was the most effective treatment for PE.
- **Local anesthetics** were **very effective**, but local side effects could not be evaluated in that meta-analysis.
- **Tramadol** had significant effects, and the side effects are weak, but it was **very addictive**.

Conclusions

- Before beginning the treatment, **accurate evaluation** and **diagnosis** using standard tests are essential
- Symptomatic patients with values of **TT < 12 nmol/L (3.5 ng/ml)** should be considered for testosterone therapy
- **Contraindications** of each of pharmacological agents should be addressed to choose the best candidates
- **PDE5 inhibitors** are the first line treatment for managing ED
- **Combination of PDE5Is and testosterone therapy** can be more effective that each of them alone in severe forms of ED
- Patients treated with pharmacological agents should be **monitored in the regular interval** to assess efficacy and side affects.

Thanks for your attention!