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Novel methods for the treatment of low testosterone

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Author Contributions
JF study design and manuscript writing
SH study design and review

Abstract

Introduction:
Testosterone replacement therapy is a promising and growing field in modern healthcare. Several novel testosterone preparations aiming at providing an efficient drug without side effects have been developed in recent years. Several oral, nasal, gel, and self-injection preparations are now available, providing a wide variety of options customized to each individual's needs.
Areas covered:
We searched Google Scholar for keywords related to the different types of testosterone replacement therapy. This review provides information about the benefits and side effects of the newest testosterone preparations, aiming at giving a summary of the options with regard to testosterone replacement therapy to healthcare professionals.
Expert Opinion:
As testosterone replacement therapy is increasing in popularity, the development of novel ways of administration minimizing side effects associated with testosterone replacement therapy is growing. Nowadays, hypogonadal patients have several options to treat their conditions and can choose the most beneficial method for their individual condition.

Keywords:

Male infertility, Polycythemia, Sperm quality, Testosterone replacement therapy

Article Highlights:

- Side effects such as polycythemia and infertility have been causing hypogonadal patients to refrain from treating their condition with testosterone.
- Novel administration methods seem to minimize side effects, especially the increase in hemoglobin and the decrease in sperm production and quality.
- Novel short acting testosterone preparations might mimic better the endogenous testosterone production as compared to traditional long-acting preparations.
- Hypogonadal patients have many options to treat their condition. However, some of them might be too expensive.
- Health care professionals need to be informed about the various different testosterone replacement therapy options available.

1. Introduction

More and more evidence about the crucial role of testosterone in regulating several functions in the male body has been reported. Patients deficient in testosterone are at increased risk for metabolic diseases such as obesity and type 2 diabetes, cardiovascular and liver diseases, sarcopenia, and mental disorders[1] [2]. Testosterone replacement therapy (TRT) has been shown to efficiently prevent and improve several of these conditions [3]. However, traditional TRT is associated with several side effects such as hair loss, acne, gynecomastia, elevated red blood cell count, and infertility. Some of these can be prevented by the use of ancillary drugs such as aromatase inhibitors, selective estrogen receptor modulators, and 5 alpha-reductase inhibitors, increase in red blood cells and the decrease in sperm count and quality remain often the main reason for not choosing or cessation of TRT, which could lead to the onset of chronic diseases in the long run. However, several new types of testosterone preparations have been developed recently in order to minimize those side effects and ease the administration of the drug.

Testosterone was first introduced to the market as subcutaneous pellets or with an added 17α-methyl group in order to make it taken it orally. Nevertheless, the liver toxicity of the oral form lead to the development of an injectable form of esterified testosterone enanthate or cypionate, which soon replaced the oral methylated drug. The injectable enanthate and cypionate esters, having a half-life of approximately 4.5/5 days respectively, are typically injected intramuscularly every 2-3 weeks. Several different esters have also been produced since in order to customize the half-life and the injection frequency. The propionate is the fastest ester with a half-life of 0.8 days, requiring daily or every other day injections to maintain stable serum testosterone levels, whereas the phenylpropionate ester has a half-life of 1.5 days, the isocaproate ester 4 days and the decanoate ester 7.5 days. Combinations of different esters (Sustanon) have been marketed to maintain stable testosterone levels with less injections. Starting in the 2000s in Europe and followed by the United States in 2014, long-acting injectable testosterone undecanoate has been developed, improving injection frequency to 1 injection every 3 months. The transdermal gel has also been recently introduced to the market for patients reluctant to injections. The newest forms of testosterone preparations are the nasal form (Natesto), allowing easy and quick application and without the risk of transfer to other people or the pain from injections, and the oral form (Jatenzo, TLANDO), soft gel capsules delivering testosterone directly to the lymphatic system, bypassing the liver. As compared with traditional injectable TRT preparations (enanthate, cypionate), the newer short-acting methods which mimic natural T release might minimize side effects with regard to the increase of red blood cells and infertility. This review will compare the side effects of several newly developed testosterone preparations and provides new insights into the options available for patients suffering from hypogonadism.

2. Body

2.1) Traditional testosterone replacement therapy

2.1.1) Side effects of traditional testosterone replacement therapy

TRT can trigger several side effects, depending on the dosage, the frequency and, the duration of treatment. Several endocrine parameters are modified when testosterone replacement therapy is initiated, potentially leading to side effects [4]. Below are the most common side effects traditionally associated with testosterone replacement therapy:

1) Gynecomastia

High levels of testosterone can increase aromatization rates of testosterone to estradiol, triggering breast tenderness and swelling. This can be prevented by the usage of ancillary drugs such as AI (aromatase inhibitors: Aromasin, Arimidex, and Letrozole) or SERMs (selective estrogen receptor modulators: Clomiphene, Tamoxifen). The glandular tissue can also be surgically removed.

2) Acne and hair loss

Testosterone can be converted into dihydrotestosterone (DHT) via the 5 alpha reductase enzyme. Elevated DHT levels can cause acne and hair loss. However, this can be prevented by the usage of ancillary drugs such as 5 alpha-reductase inhibitors (Finasteride, Dutasteride).

3) Polycythemia

Testosterone can increase hemoglobin levels and blood viscosity, leading to potential cardiovascular risks. Besides phlebotomy, there is no treatment for TRT-induced polycythemia.

4) Infertility

Exogenous testosterone administration can lead to negative feedback on the HPGA (hypothalamic–pituitary–gonadal axis) and downregulate sperm production. Concomitant utilization of human chorionic gonadotropin (HCG) can prevent this mechanism to a certain extent but has limitations. Especially long-term TRT can have serious effects on sperm quality and quantity, requiring long-term treatment with HCG or/and human recombinant follicle stimulating hormone (rFSH) over months or even years.

5) Prostate

Past research has tried to associate testosterone with increased risks of prostate cancer. However, recent research actually showed benefits of TRT for patients with prostate cancer.

Data on this topic needs to be re-evaluated and should not negatively impact future testosterone treatment of hypogonadal men [5]

2.1.2) Effects of exogenous testosterone on natural testosterone secretion

The release of testosterone is pulsatile and not constant. The hypothalamus, anterior pituitary, and testes, forming the hypothalamic-pituitary-gonadal (HPG) axis, fine-tune the secretion of T. The pulsatile secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus triggers the pulsatile release of luteinizing hormone (LH) in the pituitary gland. The released LH then activates T production in the testes. As serum T increases, a negative feedback signal alerts the hypothalamus and pituitary to stop releasing GnRH and LH. T is released in the circadian rhythm, peaking early in the morning and declining thereafter. Therefore, testosterone preparations that lead to sustained elevated serum T levels trigger excessive negative feedback to the HPG axis, resulting in the shut-down of endogenous T production and infertility. Therefore, the closer to natural endogenous T release a T preparation can get, the fewer side effects it might cause.

2.1.3) Traditional testosterone preparations

1) Oral testosterone preparations

Oral T medications have been developed in 2 ways:

a) Alkylation of T at the C-17 position in order to resist the first-pass hepatic metabolism, leading to methyltestosterone.
Oral methyltestosterone was invented in the mid-1930s and has been the only oral T medication ever approved in the US for decades. However, serious hepatotoxic side effects have been observed, leading to wide discontinuation of this drug for the treatment of hypogonadism.

b) Fatty-acid esterification of T, leading to intestinal lymphatic system absorption without entering the portal circulation.
Even though traditional oral testosterone undecanoate has not been associated with liver toxicity and has been approved for use in many countries, (Andriol) has never been approved for the US market. The effects are highly influenced by dietary fat, resulting in highly volatile effects. Therefore, traditional oral testosterone undecanoate has never gained great acceptance for TRT, even though it is still available in several countries.

2) Injectable testosterone preparations

The goal of testosterone replacement therapy is to restore healthy testosterone levels in males with low testosterone levels. Depending on the individual, dosages usually fluctuate somewhere between 75-100 mg per week or 150-200 mg every two weeks of testosterone cypionate or enanthate. Optimally, this should lead to average levels between 400 to 700 ng/dL. On the other hand, very low doses such as 50 mg per week might worsen the condition [6]. Exogenous testosterone can downregulate the endogenous production by inhibiting the

hypothalamic-pituitary-gonadal (HPG) axis, resulting in impaired LH and FSH release and very low testosterone production. Therefore, it is important to prescribe dosages high enough to keep testosterone within the optimal range. Importantly, exogenous testosterone will not be added to endogenous testosterone, but since exogenous testosterone shuts down the HPG axis and the endogenous production, exogenous testosterone becomes the sole source of testosterone available. Too conservative testosterone replacement therapy dosages can lead to the worsening of testosterone levels and hypogonadal symptoms. On the other hand, high dosages of testosterone can lead to supraphysiological testosterone levels, especially 2-3 days after injection, increasing the risk of side effects. Supraphysiological testosterone levels increase the risk of developing serious side effects such as polycythemia and infertility. Indeed, injectable testosterone cypionate has been shown to increase hematocrit levels, reaching levels >54% in 10% of the patients who inject 100-200mg/week [7]. Another study also showed a significant increase (+6.4%) in hematocrit in patients using testosterone enanthate [8], while the longer ester undecanoate also showed an increase of 5% [9]. In comparison, one study looking at topical testosterone gel observed a 2.75% *increase* [10], and another study using oral testosterone undecanoate showed a 2% increase in hematocrit levels [11]

Since many patients choose to get the injections at a health care facility, the frequency of injections is typically every two weeks. In this case, high enough doses of testosterone need to be injected in order to maintain elevated levels for up to two weeks. Therefore, several days after injection, the levels will be too high, then within range, and at the end of the 2 weeks, the levels drop below the aimed levels. Even in the case the patient practices self-injections and could inject several times per week in order to stabilize his testosterone levels, frequent intramuscular injections would lead to scar tissue buildup, ultimately hindering injections at the same spot.

2.2) Novel testosterone replacement therapy

2.2.1) Nasal preparations

Nasal administration of T is quickly absorbed through the nasal mucosa, with serum T levels peaking ~40 min after administration. Thereafter, T is quickly metabolized and returns to initial levels within 3–6 h. 2-3 administrations of nasal T spread throughout the day might provide the necessary T, while the variations in T levels might minimize the suppressive effects of exogenous T on the HPG axis. A recent study conducted on hypogonadal men showed that 6 months of nasal testosterone treatment led to serum T levels > 300 ng/dL (90.9%), while maintaining FSH and LH within the normal range in 81.8 and 72.7% of the patients, respectively. Total motile sperm count > 5 million was maintained in 93.9% of the patients [12].

1) Oral preparations

a) Jatenzo

This testosterone undecanoate formulation is a lipophilic drug and is transported into intestinal lymphatics while bypassing the first-pass metabolism of testosterone by the liver. Upon penetration into the left subclavian vein at the thoracic duct, this drug lets esterases release

active testosterone [13]. The recommended initial dose is 237 mg 2 times per day, which should be taken with food but without the restriction of high-fat content.

One recent study administering 237-396 mg TU (150-250 mg of unesterified T equivalents), twice-daily immediately prior to a breakfast and dinner meal, approximately 12 hours apart, led to a mean serum T of 488 ng/dL after 3-4 months [14]. However, the same study showed that plasma T levels go back to baseline around 8 hours after drug administration, meaning that a more frequent administration might be beneficial in order to avoid periods with low T concentrations[14]. Interestingly, unlike the previous oral testosterone undecanoate preparation, the efficiency of this new form of oral testosterone does not seem to be affected by the fat content of meals. Indeed, the data showed similar results for meals containing from 15 up to 45 g of fats[14]. As for side effects, treatment with this drug for 3-4 months led to hypertension and HDL decrease in 3%, and hematocrit increase in 4.8% of the patients[14]. No clinically significant changes in the liver function tests reflected by AST (2.74%), ALT (-5.38%), and ALP (-14.10%) could be noted[14].

b) TLANDO

Similar to the drug above, this formula also uses a self-emulsifying drug delivery system and lymphatic absorption, allowing for a safe treatment and minimizing the risks of liver damage. One difference is that this formulation does not require dose titration, allowing an easy treatment. 225mg 2 times per day showed steady 24-hour average serum testosterone levels in 80% of patients without the need for titration[15]. Intake with food is recommended to maximize the effects but high-fat content is not necessary.

2.2.2) Testosterone Gel

There is a wide range of topical products on the market: Tostrex (Tostran, Fortesta), Androgel (Testogel), Testim and Axiron (solution), and Testavan, which is a 2% testosterone gel, currently under registration in Europe and already approved in Australia in May 2017. In Japan too, a new 2% gel is being developed [16]. Androgel 1% (5 g for 50 mg of T) was the pioneer in topical gel applications. In the EU, it was marketed as Androgel 1.62 (2.5 g for 40.5 mg of T). Then came Testim (Testosterone 1%, 5g for 50 mg of T), followed Tostrex (Tostran), sold as a 2% gel with a starting dose of 3 g (60 mg of testosterone. Fortesta (40 mg of T applied to inner thighs) and Axiron(3ml for 30 mg of T applied to each underarm) are also both 2% testosterone solutions. Testavan, also a 2% testosterone gel, is made of a hydroalcoholic and highly viscous topical formulation (1.15 g for 23 mg of T up to 3.45 g for 69 mg of T). A metered dose dispenser including a hands-free cap applicator allows minimizing exposure to the hands and potential contamination of other people.

2.2.3) Self-injection pen

Traditionally medium length testosterone esters such as enanthate or cypionate are injected intramuscularly every 1-2 weeks, leading to strong fluctuations in serum T. Even though intramuscular injections can be performed at home, frequent intramuscular injections can lead to the build-up of scar tissue and increase the risk of infections. Therefore, a novel self-injection pen has been developed to allow subcutaneous injections of testosterone enanthate. This way patients inject smaller doses of testosterone more frequently and keep more balanced serum T levels while reducing the pain and risk of intramuscular injections. A recent study showed

similar effects of self-injection subcutaneous T injections as compared to traditional intramuscular T injections, however, this was only 1 injection per week [17]. After 26 weeks of treatment, 7.5% of the patients had elevated hematocrit levels (>52%) and mean blood pressure increase by 3.4 mmHg (125.6-129.0 mmHg) and 1.8 mmHg (78.2-80.0 mmHg), respectively, from baseline. Further research is needed to see if more frequent injections with smaller dosages can lead to fewer side effects.

2.2.4) Injectable testosterone undecanoate

In the 2000's, long-acting injectable testosterone undecanoate has been introduced to the market first in Europe, followed by the USA in 2014. This drug allows the patient to inject once every three months (1000mg per injection, mainly in Europe with Nebido) or every 10 weeks (750mg per injection, mainly in the USA with Aveed). One study found that long acting testosterone undecanoate is effective and safe, especially with regard to hemoglobin and hematocrit level increases within normal ranges [18]. Interestingly, one recent study found positive effects of injectable testosterone undecanoate on renal functions Results [19]. Urea (47.0 ± 11.8 to 34.0 ± 13.9 mg/dL), uric acid (6.57 ± 1.2 to 5.49 ± 1.5 mg/dL), serum creatinine (0.90 ± 0.10 to 1.12 ± 0.9 mg/dL) decreased while GFR increased (87.0 ± 12.9 to 98.0 ± 8.0 mL/min/1.73 m^2) in the T undecanoate group. The control group showed elevated serum creatinine (1.16 ± 0.31 to 1.19 ± 0.58 mg/dL), uric acid (5.54 ± 1.2 to 5.44 ± 1.7 mg/dL), and decreased GFR (92.0 ± 20.1 to 87.0 ± 26.1 mL/min/1.73 m^2) levels. Furthermore, compared to traditional medium acting esthers, undecanoate allows more stable serum T levels and can prevent the "rollercoaster effects" often experienced with cypionate or enanthate [20]. The few injections required with this form of administration make this drug a good option for those who have difficulties adhering to their treatment protocol. (Figure 1)

3) Pharmacokinetics of testosterone preparations

With the development of short-acting T preparations, there is a wide variety of pharmacokinetics of T, ranging from sustained elevated levels for days if not weeks to several peaks during the day. Endogenous T is not constantly released but released in a pulsatile manner, with several short peaks during the day (Figure 2). Therefore, T preparations mimicking this pulsatile release with several peaks, might lead to fewer side effects as compared to constantly elevated levels. Figure 3 is a representation of the pharmacokinetics of short-acting T, including 2 oral drugs (Jatenzo, TLANDO) and 1 nasal spray (Natesto). Since Natesto is administered 3 times per day, there are 3 steep peaks that go back to initial levels about 2-3 hours later. On the other side, the oral preparations are administered 2 times per day and display 2 more gradual peaks.

Figure 4 shows the pharmacokinetics of several medium-acting gel types. Most of these preparations display a gradual increase, with a flat peak followed by a very slow decrease. Some ultimately increase slowly to peak a second time.

Figure 5 shows the pharmacokinetics of T enanthate, peaking twice after 12 and 36 hours, followed by a slow gradual decrease with sustained levels for up to 7 days.

4) Advantages of novel T preparations

4.1) Effects of different T preparations on hematocrit levels

One major side effect of TRT is the increase in hematocrit levels, sometimes leading to the discontinuation of treatment. Interestingly, one recent study showed that the death rate in patients with hematocrit >49% and <52% was lower as compared to patients with hematocrit < 49% [21]. Nevertheless, acute raises in hematocrit levels remain a major issue in TRT patients and the current threshold for changes in TRT is 54%[21].
It appears that short-acting preparations such as Natesto, Jatenzo, and TLANDO lead to the least increase in hematocrit, with Natesto even displaying decreases in hematocrit levels (Table 1).

4.2) Effects of different T preparations on gonadotropins

The more LH and FSH are suppressed due to TRT, the more side effects related to fertility can occur [22]. Figure 6 shows the % decrease of LH and FSH depending on the administration method. The nasal preparations seems to suppress LH and FSH the least, thus probably being a prime candidate for patients seeking fertility preservation.

5) Costs of novel testosterone preparations

Nowadays, hypogonadal patients have many options for treatment due to the development of several new testosterone preparations. However, many of them are priced very high and are not covered by many health insurances, making those treatment options impractical for many patients.
The nasal spray (Natesto) for example costs between costs about $300-350 for one bottle delivering 60 actuations. In one day, it is recommended to use 1 actuation for each nostril 3 times per day, meaning that one bottle will last 10 days. This would mean that the monthly costs would be around $900-1050 per month.
One oral medication (Jatenzo) ranges from about $970-1300 per bottle containing 60 capsules, with the recommended dosage of 2 capsules per day. This also makes this medication cost about $970-1300 per month. The other oral medication (Tlando) ranges about $750-950 per bottle containing 120 capsules, with 2 capsules twice per day as recommended dosage. This also puts this medication in a price range of $750-950 per month.
The self-injection pen (Xyosted) costs about $460-800 per month.
Injectable testosterone undecanaote (Aveed) costs about $1,700 per dosage, or about $800 per month.
Many patients would not be able to afford these medications at current rates without insurance coverage.

6) Conclusion

Several new testosterone preparations allow health care professionals to customize the right replacement therapy based on the needs of each individual patient. Ranging from injectable long-acting preparations allowing the patient to only administer T every 3 months, to very short-acting preparations requiring 2 or more applications per day. The benefits of choosing a short-acting preparation are minimal side effects, especially the nasal spray has shown promising data with regard to hematocrit increase and LH/FSH inhibition, probably due to the way it mimics natural T release with several small peaks during the day. The 2 oral undecanoate preparations also show promising effects with regard to side effects. Gel preparations also show excellent results in treating hypogonadism and the new auto-injection enanthate preparation might have many benefits for those opting for an injectable version without the need to get the injections at healthcare facilities. It would also be interesting to see if further improvements with regard to side effects are possible with more frequent self-injections, for example 2-3 times per week.

7) Expert Opinion

Testosterone is crucial in maintaining healthy body functions in the male. As research evolves, more and more health care professionals recognize the importance of replacing testosterone in hypogonadal patients. Research on testosterone replacement therapy in hypogonadal males is continuously evolving and shows more and more promising results in the aging male, including improvements of glucose metabolism, cardiovascular functions, liver and bone health, and mental and sexual health. However, side effects such as polycythemia and male infertility associated with exogenous testosterone administration can lead to treatment avoidance and discontinuations. Exogenous testosterone preparations have been developed for decades, without finding the optimal solution without side effects yet. Oral preparations were first marketed, followed by injectables, pellets, gel, oral preparations without liver toxicity, nasal sprays, and subcutaneous self-injection pens. Many of these preparations had their flaws, such as liver toxicity, discomfort in the way of administration, cross-contamination with other individuals, etc. Traditional testosterone administration methods are mainly injectable drugs, leading to long-term supraphysiological serum testosterone levels. These sustained high serum testosterone levels might cause a severe shut down of the hypothalamic-pituitary-gonadal axis and increase side effects. Novel ways of short acting exogenous testosterone administration include nasal and oral medications, administrated several times per day, leading to more balanced and less supraphysiological spikes in serum testosterone. Several small testosterone fluctuations might improve the occurrence of side effects as compared to sustained elevated levels. However, research on those novel testosterone preparations on side effects is still scarce to this day. More long-term research is needed to completely understand the effects of these novel drugs on several parameters including hemoglobin, and sperm quantity and quality. The development of these new medications could lead to a larger acceptance of testosterone replacement therapy including patients who could not get treatment due to side effects often seen in traditional testosterone products. Also, the ways of administration including nasal, sub-cutaneous self-injection pens, and oral preparations, are more diverse, making self-administration more easy as compared to intramuscular injections.

Current research has shown significant associations between testosterone and several body functions such as glucose/fat metabolism, bone/liver health, cardiovascular functions, and mental health. It is now evident that healthy testosterone levels are crucial in order to maintain healthy body functions in males. Accordingly, the development of novel testosterone preparations accommodating several patients' conditions is important.
A broader implementation of testosterone screening should be implemented in physical checkups for males over 30 years of age in order to rapidly discover signs of hypogonadism and prevent the associated onset of several conditions associated with low testosterone. Also, the medical coverage for novel testosterone preparations is still well developed, making the medical costs a hurdle for patients with limited financial resources.
The field of testosterone replacement therapy has never been evolving so fast, pushed by the findings of several research papers showing countless benefits for the male patient. Accordingly, administration methods of testosterone need research to provide the healthcare professionals and patients with the newest and most accurate data to make optimal choices. We hope that development in efficient and safe testosterone preparations will continue, and that pharmaceutical companies will provide those at affordable costs to patients needing them.

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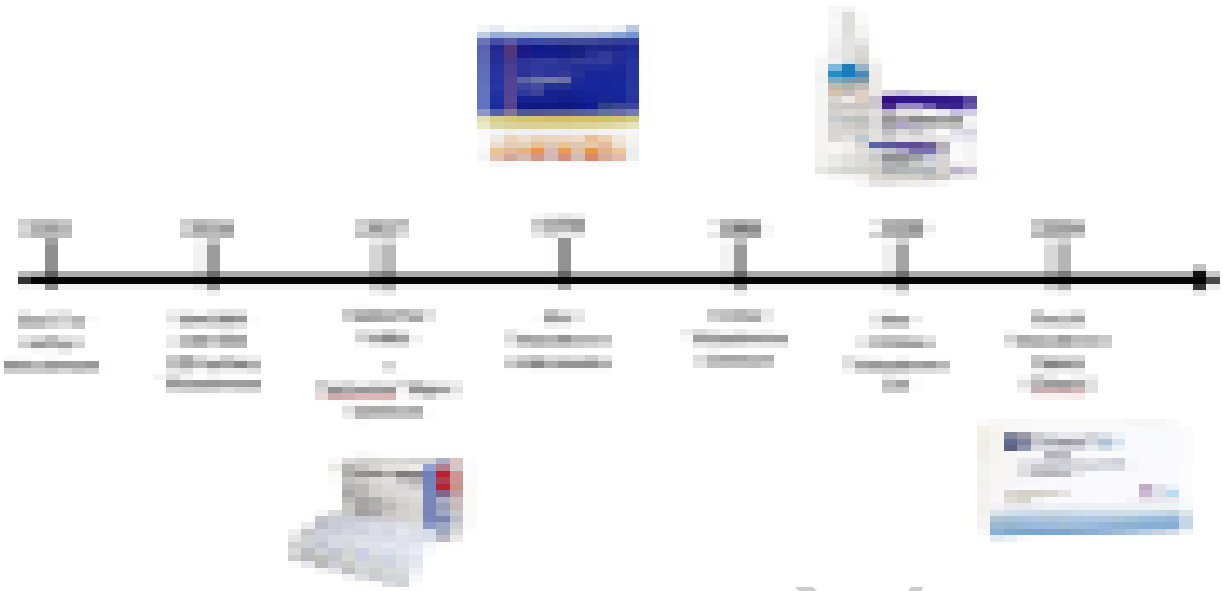
Figure & Table Legends:

Figure 1: Evolution of testosterone preparations
Figure 2: Representations of endogenous T release
Figure 3: Representations of the pharmacokinetics of novel short-acting T preparations
Figure 4: Representations of the pharmacokinetics of medium-acting T preparations
Figure 5: Representations of the pharmacokinetics of long-acting T preparations
Figure 6: Effects of different types of T preparations on FSH (dark grey) and LH (light grey). Data from [22] [14]
Table 1: Effects of different T preparations on hematocrit levels



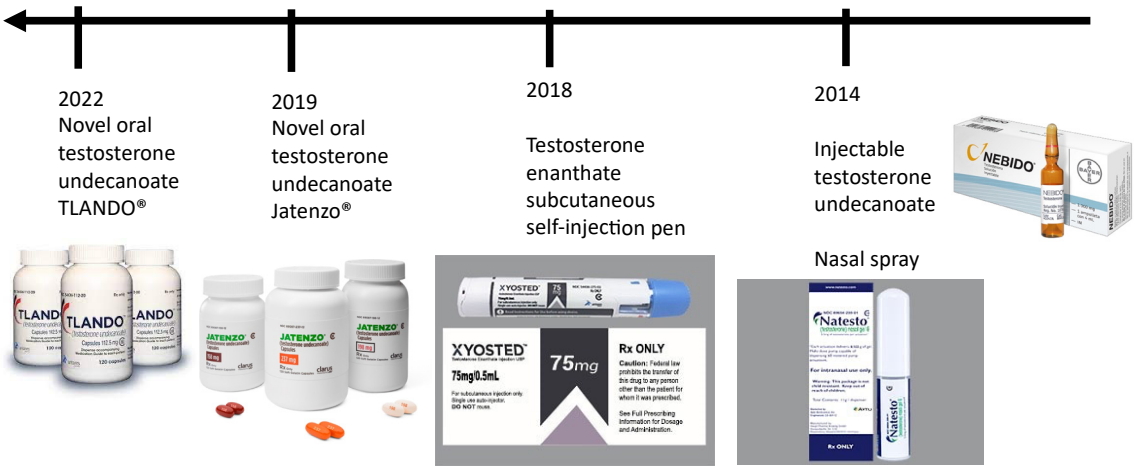


Figure 1
Evolution of testosterone preparations

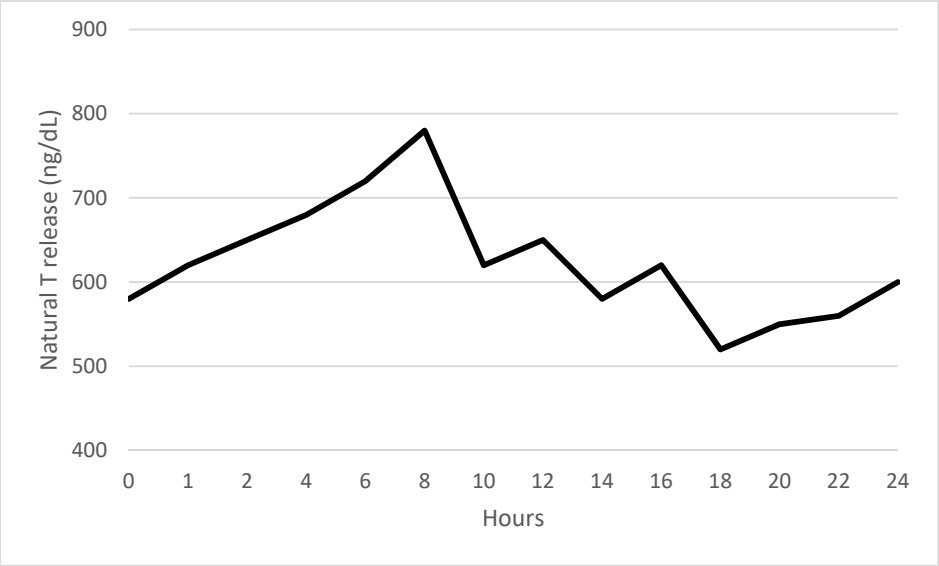


Figure 2
Representations of endogenous T release

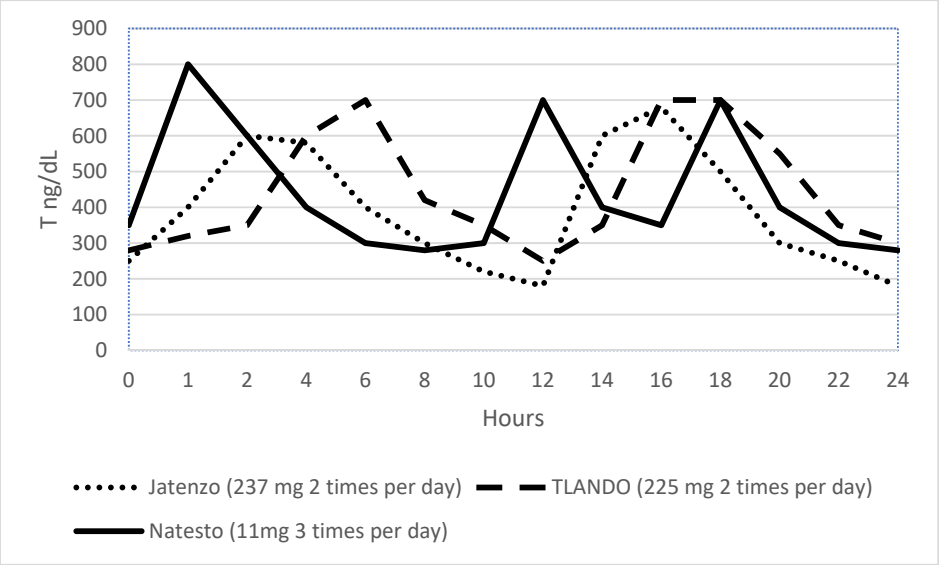


Figure 3
Representations of the pharmacokinetics of novel short-acting T preparations

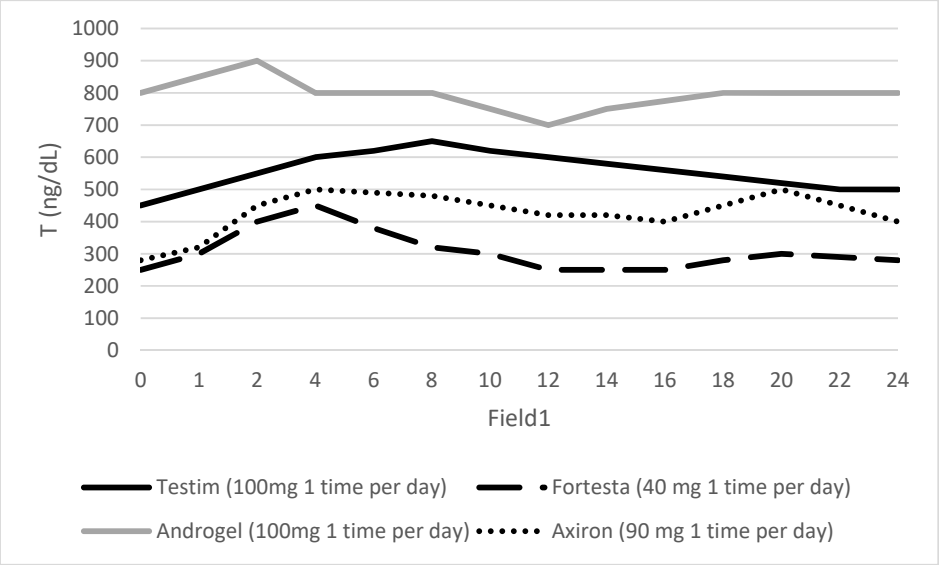


Figure 4
Representations of the pharmacokinetics of medium-acting T preparations

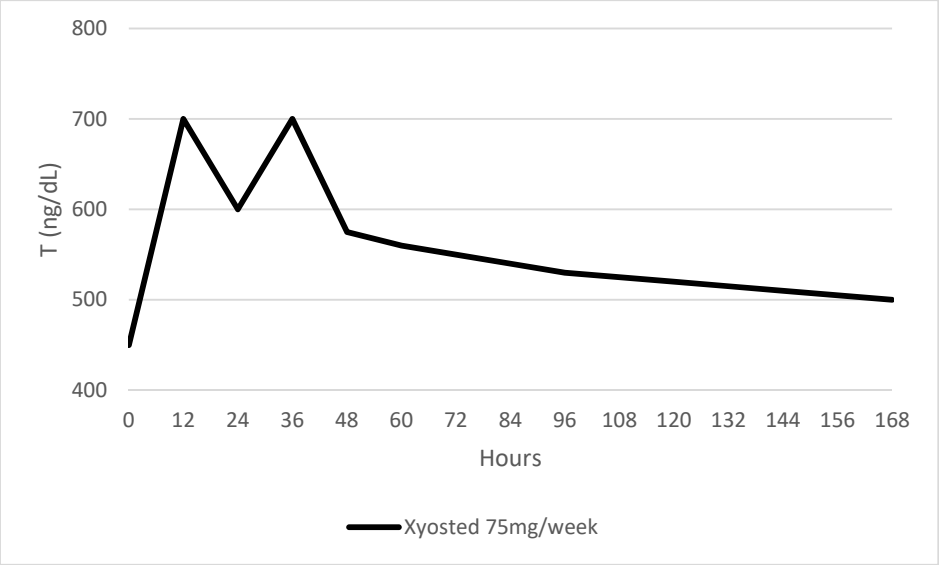


Figure 5
Representations of the pharmacokinetics of long-acting T preparations

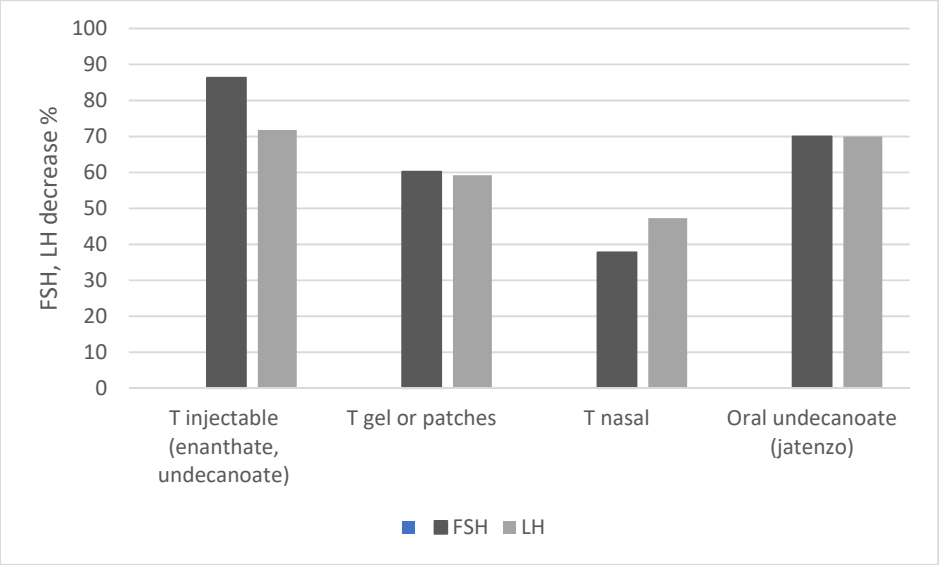


Figure 6
Effects of different types of T preparations on FSH (dark grey) and LH (light grey).
Source:[22] [14]

	Hematocrit increase (%)	Duration	Dosage	Author
Traditional methods				
Intramuscular T undecanoate	5	48 months	1000mg/12 weeks	Strange et al., 2021
T enanthate	6.4	3 months	250mg/3weeks	F Jockenhövel et al., 1997
T cypionate	5.1	2 months	200mg/2 weeks	Diaz et al., 2022
Oral T unecanaote Andriol	3.9	3 months	160mg/day	F Jockenhövel et al., 1997
Subcu T pellets	6.5	3 months	1200mg	F Jockenhövel et al., 1997
Gel	~2	3 months	50mg/day	Wang et al., 2000
Gel	~4	3 months	100mg/day	Wang et al., 2000
Novel methods				
Oral T undec Jatenzo	2.3	24 months	?	Swerdloff, et al., 2021
Oral T undec TLANDO	0.9	24 days	225mg. 2 times per day	DelConte et al., 2022
Nasal spray	-1.1	4 months	11mg/3 times per day	Diaz et al., 2022
Auto-injector	2.6-3.2	13-26 weeks	75mg/week	Gittelman et al., 2019

Table.1