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REVIEW



Developments and challenges for new and emergent preparations for male hypogonadism treatment

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ABSTRACT

Introduction: The specific role of testosterone (T) replacement therapy in patients with late onset hypogonadism is still conflicting. Several available preparations have been developed to restore either fertility and normal testosterone (T) levels (secondary hypogonadism) or just T levels (primary hypogonadism).

Areas covered: Advantages and limitations related to available new treatments will be discussed in detail. In addition, possible news related to preparations in the pipeline will be discussed.

Expert opinion: The selection of a specific T preparation should be adequately discussed with each subject. Transdermal T preparations are those that can preserve, after a unique morning administration, the circadian rhythmicity of T secretion. Conversely, short-acting preparations (such as oral or intranasal) need two- or three-times daily administration, potentially reducing patient compliance. Long acting T preparations, such as injectable T undecanoate have the advantage of bimestrial or trimestral administration, reducing the required number of administrations. The use of non-steroidal selective androgen receptor modulators (SARM), a heterogeneous class of compounds selectively acting on androgen receptor targets, remains investigational due to the lack of the full spectrum of T's action and the possible risk of side effects, despite their potential use in the treatment of muscle wasting and osteoporosis.

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1. Introduction

Androgen action is mediated through the androgen receptor (AR), a ligand-dependent nuclear transcription factor, a member of the steroid hormone nuclear receptor family, and most closely related to the progesterone receptor. The most potent ligand for AR is dihydrotestosterone (DHT), an androgen formed by testosterone (T) reduction through specific 5- α -reductase isoenzymes present in target tissues. However, T, the main androgen produced by the testis, can also bind to the AR in nanomolar concentrations, while other androgens, such as androstenedione and dehydroepiandrosterone, show one to two log units lower affinity than T or DHT. Upon ligand binding, AR is translocated to the nucleus, where, in a dimeric form, activates transcriptional activity, by interacting with androgen responsive elements (ARE) and regulating gene transcription. However, within the cytoplasm, androgens can also activate an AR-mediated, rapid, non-genomic pathway involving mitogen-activated protein kinase (MAPK) signalling cascades and extracellular signal-regulated kinase (ERK) activation. T and androstenedione, besides AR activation, can also stimulate estrogen receptors (ER α and ER β) upon their conversion to estradiol and estrone, through P450 aromatase. In contrast, DHT cannot be aromatized into estrogens. In summary, T exerts its biological activity through an effect on

AR, either directly or indirectly, upon its conversion to DHT, and through ER α and ER β , upon its conversion to estradiol [1].

Male hypogonadism, a syndromic condition characterized by any T deficiency, is frequent, particularly in middle-aged and older men (so-called late-onset hypogonadism, LOH). An observational study performed on 3219 men aged 40 years or older from the general population of eight European countries (EMAS study) indicated that a total T concentration below 10.5 nmol/L (300 ng/dL) is present in almost 14% of the general population [2]. Of those, the large majority are characterized by inappropriately low luteinizing hormone (LH) levels (below 9.4 mU/L), therefore suggesting a central defect (secondary hypogonadism). Only one out of seven of these hypogonadal men showed increased LH levels, such as in primary hypogonadism. In addition, 9.5% of middle-aged and older European men showed increased levels of LH with a still normal T level (compensated hypogonadism) [2]. However, according to all the scientific societies involved in the field, the aforementioned low T should be considered and treated only when associated with symptoms [3–8]. The latter point has also been accepted by one of the most recent clinical practice guidelines published so far [9]. The same guideline [9] also indicated that a T threshold of 12 nmol/L should be considered for diagnosing LOH, based on positive results derived from meta-analyses of intervention trials with T in

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Article highlights

- Although the suggested cutoffs to start testosterone treatment, in symptomatic men, differ among available guidelines, European position emphasized that 12 nM represents the best threshold.
- Preliminary results with nasal testosterone showing a minor effect on erythropoiesis, need to be confirmed.
- New oral formulations with self-emulsifying delivery system have shown good results but these preparations are not available in Europe.
- Data related to developing preparations including kisspeptin or neuropeptide Y agonists or IL1 antagonist are too preliminary.
- An accurate discussion with each individual patient on the advantages and disadvantages of each testosterone preparations, to allow a metered prescription is mandatory.

LOH [10]. This point is in line with other European guidelines [5,9,11](cit), although not with others [3,6]. More recently, the direct measurement of sex hormone binding globulin and the determination of calculated free T have also been suggested as crucial points in the diagnosis of LOH [9,12]. However, it is important to recognize that no consensus on the cutoff T levels for starting T replacement therapy (TRT) has been obtained among all available recommendations [13].

The main symptoms potentially associated with LOH are sexual dysfunction, infertility, low motivation and vitality, poor concentration and memory, hot flushing, and sweating [9]. Signs that could be associated with male hypogonadism are reduced body hair, small testes, gynecomastia, changes in body composition (reduced muscle mass and increased fat mass), reduced bone density, and anemia [9]. A previous study from the EMAS research group indicated that only three sexual symptoms (erectile dysfunction, loss of libido and reduced spontaneous erection) were indeed significantly associated in a syndromic form with a low T, while psychological or physical symptoms were not [14]. It should be recognized that, due to its observational nature, the EMAS study cannot adequately address the causality of low T [15]. In addition, other criticisms related to the EMAS study have been previously reported [15]. However, by using the EMAS definition for LOH, based on low T (<11 nmol/L) along with the aforementioned sexual symptom, the resulting prevalence of symptomatic male hypogonadism in the European general population is far less, i.e. 2% [14]. Nonetheless, even symptomatic LOH is affecting a considerable portion of the European aging male population (one out of fifty adult men) [14].

Based on the aforementioned data and the results obtained from TRT outcomes, there is general agreement that sexual symptoms are the most specific associated with LOH and that TRT is able to improve sexual function in hypogonadal subjects [13]. However, the role of TRT in improving other symptoms including physical and psychological ones is still the objective of an intense debate. Similar considerations can be drawn for TRT metabolic and cardiovascular (CV) outcomes [15]. The topic is further complicated by the fact that the treatment of hypogonadism related-symptoms has been considered as a rejuvenating attempt to obtain eternal youth, at least by some medical cultures [16]

Low T is also associated with an increased risk of cardiovascular (CV) morbidity and mortality, as reported by all the meta-analyses performed so far [17]. This relationship offers two possible interpretations: i) low T is often associated with other conditions that *per se* increase CV risk, or ii) low T is directly causing CV issues. The former possibility is more obvious. In fact, several medical conditions characterized by an increased CV risk, such as diabetes mellitus (DM), metabolic syndrome (MetS), and obesity, show a 2–3 fold increased prevalence of LOH [17–20]. LOH in the latter conditions is now also called ‘functional hypogonadism’ because it is potentially reversible by treating the underlying metabolic derangements [18–21]. On the other hand, it is less clear if pharmacological treatment of LOH with TRT is able to decrease the risk of CV events in otherwise hypogonadal subjects. In fact, meta-analyses of available placebo-controlled trials did not show any signal in this direction, even though meta-analyses of pharmaco-epidemiological studies indicate that TRT can reduce overall mortality and CV morbidity [22]. However, pharmaco-epidemiological studies should be considered with caution due to the lack of completeness of follow-up and the management of missing data. Accordingly, data from the ‘Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Efficacy Response in Hypogonadal Men (TRAVERSE)’ study, a large randomized, double-blind, placebo-controlled (RCT), including 5246 symptomatic hypogonadal (total T <10.4 nmol/L) men with preexisting or a high risk of CVD, confirmed the lack of advantages or risks related to CV disease of TRT over placebo [23]. However, it should be recognized that in the latter trial, more than 60% of men in the active or placebo arms dropped out off the study indicating dissatisfaction with the treatment.

Considering the relatively high prevalence of LOH in the general population, its associated symptoms and signs, and finally, its possible deleterious effects not only on sexual but also on general health, it is obvious that there is a need for efficacious treatment of this condition. TRT is universally accepted as the best option, in particular when the problem is due to organic damage to the hypothalamus-pituitary-testis (HPT) axis (so-called ‘organic hypogonadism’) [3,6]. More controversy exists on functional hypogonadism, because, in this case, treating the underlying metabolic condition, with lifestyle measures (e.g. physical exercise), or even bariatric surgery, is efficient in restoring normal T levels [20,21,24,25] and is recommended as the first approach by some of the available guidelines [3,6]. Although the aforementioned lifestyle measures are indeed effective in increasing T levels [18,21], the long-term outcomes of dieting and physical exercise are frequently negative, and bariatric surgery is not cost-effective. On the other hand, the cost of TRT should also be considered and discussed with the patients. Finally, the latest guideline on TRT in male hypogonadism suggests TRT even in functional hypogonadism, in particular when the reversal of the underlying condition cannot be expected in a reasonable time frame [9].

TRT can be administered by several routes, each one having its advantages and disadvantages. Limitations to TRT use in hypogonadal men are dictated by several factors, including the patient's need, possible side effects, the patient's choice, and last but not least, contraindications.

The aim of this review is to provide our expert opinion on possible concerns associated with TRT use and their relative challenges, with the main focus on new available TRT preparations or those that are in development. Considering the conflicting approach in male hypogonadism management as derived from the different available guidelines [3–9,11], our expert opinion will be based on the European position [5,9,11]. Possible differences and incongruence with other suggestions will also be analyzed.

2. Methods

A comprehensive narrative review was performed using Medline, Embase, and Cochrane search and including the following words: (('testosterone'[MeSH Terms] OR 'testosterone'[All Fields] OR 'testosteron'[All Fields] OR 'testosterones'[All Fields] OR 'testosterone s'[All Fields]) AND ('hormone replacement therapy'[MeSH Terms] OR ('hormone'[All Fields] AND 'replacement'[All Fields] AND 'therapy'[All Fields]) OR 'hormone replacement therapy'[All Fields] OR ('replacement'[All Fields] AND 'therapy'[All Fields]) OR 'replacement therapy'[All Fields])) AND ((humans[Filter]) AND (male[Filter]) AND (english[Filter])). Publications from NaN Invalid Date NaN up to NaN Invalid Date NaN were included. When available, meta-analytic data was preferred.

3. Results

3.1. Patient's need for fertility

3.1.1. Challenges

Intratesticular T, under LH control, plays a pivotal role in the initiation and maintenance of spermatogenesis, acting on the peritubular and Sertoli cells of seminiferous tubules [26,27]. However, T concentrations within the testis are two log units higher than in the peripheral circulation [27], and only at this high concentration does it act positively on Sertoli cells, supporting spermatogenesis [28]. Hence, pharmacological administration of T for replacement purposes (TRT) has no positive effect on spermatogenesis, because it does not increase the intratesticular concentration of T in a meaningful manner. In addition, through a T-induced suppression of gonadotropin (Gn) levels (negative feedback), TRT has a profound negative effect on spermatogenesis, also suppressing the endogenous testicular production of T. Accordingly, T preparations are one of the cornerstones of male hormonal contraception [28]. Hence, T preparations should not be used when fertility is desired, at least in secondary (central) hypogonadism. In that case, the use of Gn-releasing hormone (GnRH) or Gn themselves represents the treatment of choice [18,29]. However, GnRH does not offer any advantage despite a higher cost when compared to Gn [18]. A previous use of TRT did not negatively affect responsiveness to subsequent Gn therapy, as derived from meta-analysis [18].

At variance, GnRH or Gn therapy is not indicated in primary hypogonadism, since Gn levels are already elevated, whereas TRT represents the treatment of choice [18]. In azoospermic subjects with primary hypogonadism, testicular sperm extraction (TESE) could be offered because it has an overall success rate of sperm retrieval of up to 50%, even in genetic forms, such as Klinefelter syndrome [30]. In primary hypogonadism, the effect of a previous TRT on TESE outcomes is under debate [30–32], without convincing evidence of a negative effect.

3.1.2. Possible solutions with available or in development T preparations

Although TRT-induced suppression of Gn and sperm production is supposed to be a class effect, a short-acting new formulation of T has been claimed to have a less suppressive effect on pituitary function and spermatogenesis. In particular, nasal T (NT) gel administration (NT 11 mg b.i.d. or t.i.d.), through a metered-dose pump applicator has shown a lower effect on suppressing LH levels [33]. This finding was derived from a post hoc analysis of a multicenter, open-label, dose-ranging phase 3 study, testing NT for 90 days in 306 hypogonadal men ($T < 10.4$ nmol/L) [34]. However, in that study, Gn levels were tested once at study entry and again after 90 days [33]. 17-hydroxyprogesterone (17-OHP) circulating levels were taken as a surrogate marker for intratesticular T [35] in a recent two-center randomized study comparing T administration in 75 hypogonadal men ($T < 10.4$ nmol/L) through subcutaneous pellet (TP; 800 mg), T cypionate (TC; 200 mg x 2 weeks), or NT (11 mg t.i.d) for 16 weeks [36]. The three treatment arms reached comparable levels of circulating T, whereas the 4-month change in 17-OHP in the NT group (–33.3% from baseline) was less than the change seen in TC (–65.3% from baseline) or TP (–44% from baseline), suggesting a lower effect on intra-testicular T. However, it should be clarified that a consistent portion of the circulating 17-OHP in men is derived from the adrenal gland and therefore does not fully represent the testicular source. In another 60-day, single-center, uncontrolled trial, NT (11 mg t.i.d) maintained spermatogenesis in the majority of the 60 hypogonadal ($T < 12$ nmol/L) men enrolled reducing in a non-significant manner serum Gn levels [37]. The author's interpretation is that the rapid rise and fall of T levels following nasal T administration allows for the maintenance of Gn levels and spermatogenesis [37]. The short duration of the study, the high drop-out rate, and the trend toward a stepwise decline of both Gn levels and sperm parameters are the main limitations of that study, which needs further confirmation, despite being interesting.

3.2. Secondary erythrocytosis

3.2.1. Challenges

Activation of AR is often associated with a dose-dependent increase in erythrocyte mass (erythrocytosis) through mechanisms that are less well-defined. Originally, T was demonstrated to increase erythropoietin levels [38], but this finding was later confirmed in some [39] but not all studies [40]. More recently, it was demonstrated that T administration to healthy volunteers, under experimental hypogonadism, dose-dependently decreased hepcidin levels, a master iron regulatory protein.

The effect was dose-dependent and more apparent in older subjects than in younger subjects [39,41]. Erythrocytosis (also called polycythemia) is defined as an increase in erythrocyte mass above the sex-specific normal range, i.e. in the male gender, hemoglobin level >16.5 g/dL or hematocrit >49% [42]. In primary erythrocytosis (polycythemia vera, a myeloproliferative neoplastic process), it is associated with an increased risk of venous or arterial thrombosis, vasomotor symptoms, or splenomegaly [42]. However, in secondary erythrocytosis -such as those conditions related to TRT – although limited evidence has documented possible risks [43–45], there is no definitive evidence for an increased risk of thrombosis, and, therefore, phlebotomy is not routinely recommended when T is used and prescribed according to available recommendations [42]. However, it can sometimes be required due to the development of polycythemia, especially in high risk patients [45]. The

Endocrine Society [3] and the European Academy of Andrology [11] guidelines suggest considering not starting TRT or using lower dosages in subjects with a hematocrit > 50% [3], or >52% [11], at baseline, particularly in those patients at high CV risk [11]. Nevertheless, it is important to recognize that all the meta-analyses published so far indicate that TRT increases mean hematocrit by up to 5% and the risk of erythrocytosis by up to 7-fold [22,46,47] (see also Figure 1). However, the rise could be even higher [48] especially in older men [40,49] or in those with associated morbidities such as sleep apnea or chronic obstructive pulmonary diseases [42].

3.2.2. Possible solutions with available or in development T preparations

Considering that elevated hematocrit is the most frequent adverse event related to TRT and that this elevation represents

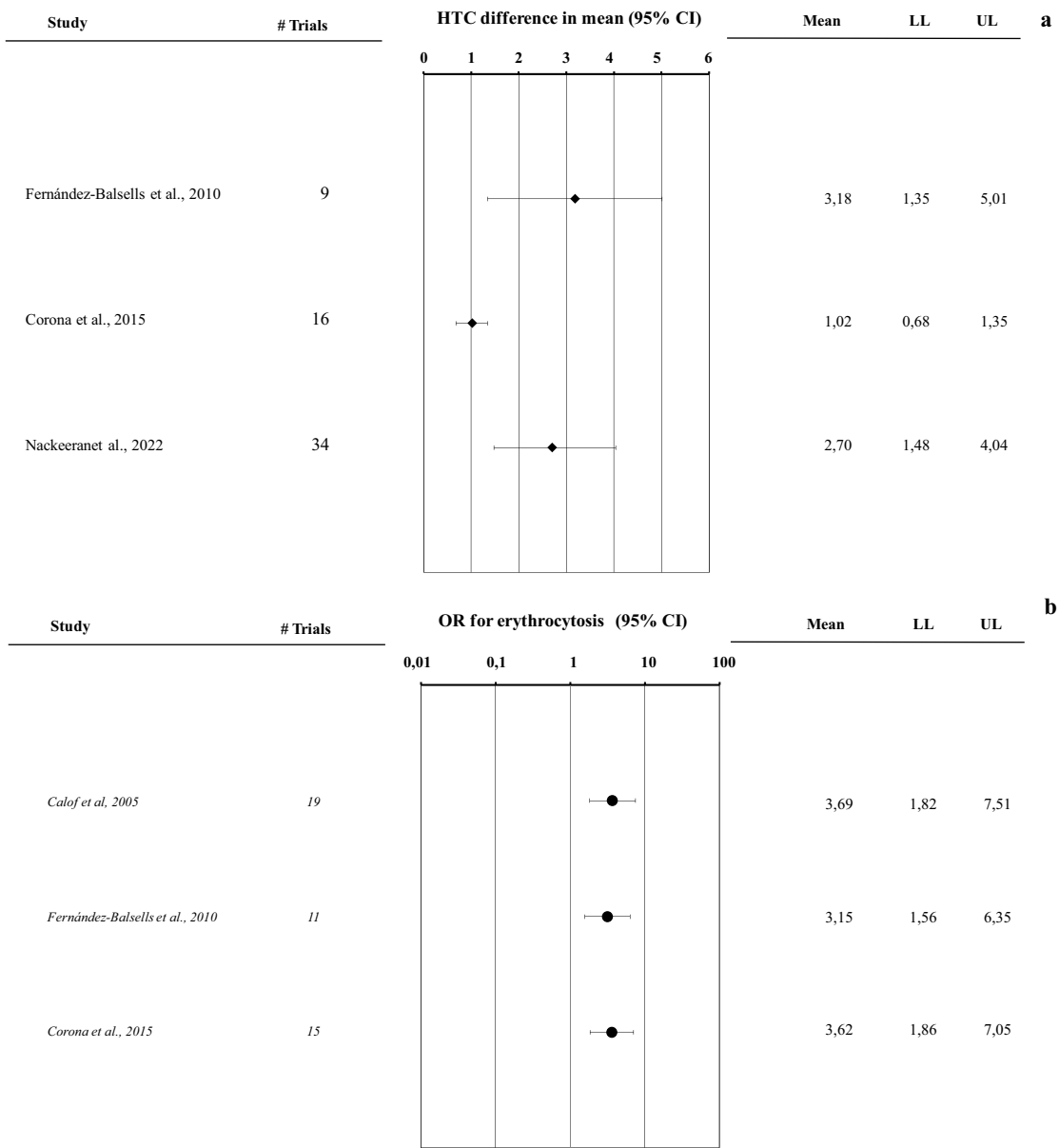


Figure 1. Mean hematocrit (HTC) increase (a) or risk for developing erythrocytosis (b) after testosterone replacement therapy versus placebo according to the data derived from available meta-analysis.

a class effect, i.e. shared by all the so far available preparations [13], much attention is devoted to identifying formulations associated with a reduced rate of erythrocytosis. Although in a previous meta-analysis, in line with what was reported by Dob et al. [50], gel formulations appeared less likely to induce erythrocytosis than other preparations [22], this was not confirmed by a more recent network meta-analysis [47]. Nonetheless, it appears that the intramuscular T enanthate or cypionate (TC) preparations are associated with a greater risk of hematocrit increase [43]. Therefore, all the published guidelines suggest frequent monitoring of hematocrit, in particular during the first year of treatment [13]. The most recently published guidelines recommend monitoring hematocrit, along with PSA and T levels, at 3 and 6 months and then annually [9]. Phlebotomy, low-dose aspirin (100 mg/day), or even discontinuation of TRT are the proposed interventions in cases of elevated hematocrit [13].

A recent report suggests that NT administration is associated with a lower risk of polycythemia and an overall hematocrit increase than TC [43]. Hence, as stated above, this preliminary result is interesting but needs to be confirmed in the ongoing enrollment of the same study and in other studies. Accordingly, long term data on NT is still lacking.

3.3. Patient's preference

3.3.1. Challenges

TRT is available through different routes of administration, including oral, parenteral, transdermal, intranasal, and implants. Table 1 summarizes the worldwide available TRT options including possible advantages and disadvantages for each preparation.

The main patient complaints include the risk of pain and discomfort for all injectable preparations, along with possible skin irritation with patches, oral irritation with buccal systems, and nasal irritation with nasal preparations (Table 1). In addition, cost represents another important issue at least for some patients.

Oral drug administration is one of the most convenient and extensively utilized routes for drug delivery because of safety considerations, convenience of administration, suitability for long-term use, and flexibility in dosage adjustment [51,52]. In addition, oral therapy is often considered the preferred method of drug delivery by patients [53]. Upon oral administration, although some gastric absorption is possible, the majority of drug entry is through passive diffusion or active absorption through the enterocytes of the small intestine, with subsequent delivery to the liver through the portal vein and, thereafter, to the systemic circulation [52]. Oral native T is well absorbed by the small intestine, but it is subject to oxidation in the intestinal mucosa and further metabolism in the liver after the first-pass [54]. Hence, the final delivery to the systemic circulation of the native hormone is poor, and therefore, oral native T has never been licensed for TRT use. To overcome pre-systemic metabolism, alkylation in position 17 α (e.g. methylation) is effective, but this chemical modification results in formulations (methyltestosterone and oxymetholone) that

should not be used due to liver toxicity [55]. An alternative solution is T esterification in position 17 β with a long chain fatty acid, such as the prodrug undecanoate acid. The long-chain prodrug strategy allows mesenteric lymph flow absorption that circumvents the portal vein (Figure 2). In particular, lipophilic long-chain T esters are absorbed through the blind-ended lymphatic capillaries (lacteals and then sub-mucosal), collected by pre-nodal mesenteric afferents connected with central mesenteric lymph nodes. From them, through the efferent lymphatic, they converge into the cisterna chyli and thoracic chyli duct and, finally, to the internal jugular vein or to the subclavian vein, therefore reaching the systemic circulation [54] (Figure 2). Based on these considerations [56], T undecanoate (TU) has been present for a long time in the European market; formulated first in a 40 mg dose with an oleic acid vehicle and thereafter with a castor oil/propylene glycol vehicle that confers more stability at room temperature [57]. This preparation has never been approved by the Food and Drug Administration (FDA), because of the great inter- and intra-individual variability in the T response and its erratic absorption. In fact, TU absorption was appreciable only after a high-fat meal and negligible in the fasting state [58,59]. In addition, upon oral TU administration (80 mg), the level of the prodrug was tenfold higher than that of native T and it was associated with supraphysiological levels of DHT, due to a high conversion also in the mesenteric bed [56,59].

3.3.2. Possible solutions with available or in development T preparations

In order to improve absorption through the mesenteric lymphatic system, lipid-based delivery systems were designed, including cyclodextrins, nanoparticles, solid dispersions, permeation enhancers, and self-emulsifying delivery systems [53]. In particular, the self-emulsifying delivery system (SEDDS) [60] for TU was chosen by two US companies (JATENZO, Tolmar Pharmaceuticals, Inc. Buffalo Grove, IL, and TLANDO, Lipocine, Salt Lake City, UT) and approved by the FDA. The SEDDS is an isotropic mixture of oils, surfactants, solvents, and co-solvents/surfactants that can self-emulsify in the intestine, enhancing undecanoic acid and so drug absorption. SEEDS strategy allows absorption of TU during a regular meal without the necessity of a high-fat one. The results of clinical trials with these two TU formulations have been recently reviewed elsewhere [61–64]. JATENZO is available in three dosing formulations (158, 198, and 237 mg) that should be taken b.i.d. and need titration. TLANDO uses a fixed dose (225 mg b.i.d) that does not need titration. Both TU preparations demonstrated eugonadal steady 24-hour average serum T levels in more than 80% of hypogonadal patients. In addition, hypogonadism-related sexual symptoms were improved with both preparations [61–64]. Besides the expected increase in hematocrit (see before), both TU preparations were associated with mild and transient gastrointestinal side effects and, more importantly, with a 3–5 mmHg increase in systolic blood pressure (BP). Hence, the FDA required a black box warning that these drugs can induce a BP rise that might increase the risk of

Table 1. Characteristics of available T preparations. Only brand names have been quoted. POME=pulmonary oil microemulsolism. * available only in the Australian market; **Available only in the US market.

Formulation (Commercial name)	Chemical structure	t 1/2	Standard dosage	Advantages	Disadvantages
TESTOSTERONE PREPARATIONS					
Oral					
Testosterone undecanoate castor oil/propylene glycol vehicle (Andriol)	17- β -hydroxylester	2–5 hours	40–160 mg 2 times daily	<ul style="list-style-type: none"> –no apparent hepatotoxicity –Oral convenience –Modifiable dosage –Quick reversal 	<ul style="list-style-type: none"> –Unpredictable absorption depending on dietary fat content –Must be taken with fatty meals –risk of disproportionately high conversion of testosterone to DHT during absorption.
Testosterone undecanoate self-emulsifying delivery system (Jatenzo)	17- β -hydroxylester	2–5 hours	158, 198, 237 mg 2 times daily	<ul style="list-style-type: none"> –no apparent hepatotoxicity –Oral convenience –Modifiable dosage –Quick reversal 	<ul style="list-style-type: none"> –Must be taken with meals –Gastrointestinal side effects –increase in blood pressure –risk of disproportionately high conversion of testosterone to DHT during absorption.
Testosterone undecanoate self-emulsifying delivery system (TLANDO)	17- β -hydroxylester	2–5 hours	225 mg 2 times daily	<ul style="list-style-type: none"> –no apparent hepatotoxicity –Oral convenience –No titration –Quick reversal 	<ul style="list-style-type: none"> –Must be taken with meals –Gastrointestinal side effects –increase in blood pressure –risk of disproportionately high conversion of testosterone to DHT during absorption.
Testosterone undecanoate self-emulsifying delivery system (Kyzatrez)	17- β -hydroxylester	2–5 hours	100, 150, 200 mg 2 times daily	<ul style="list-style-type: none"> –no apparent hepatotoxicity –Oral convenience –Modifiable dosage –Quick reversal 	<ul style="list-style-type: none"> –Must be taken with meals –Gastrointestinal side effects –increase in blood pressure –risk of disproportionately high conversion of testosterone to DHT during absorption.
Parenteral					
Testosterone enanthate (Testoviron Delatestryl Xyosted)	17- β -hydroxylester	4–5 days	250 mg every 2–3 weeks	<ul style="list-style-type: none"> –Low cost –Short-acting product among parenteral preparations allowing drug withdrawal in case of adverse effects 	<ul style="list-style-type: none"> –Variable pharmacokinetics within and between individuals in circulating testosterone levels –Multiple injections –discomfort from injections –Relative risk of polycythemia –Risk of POME –High fluctuations within and between individuals in circulating testosterone levels –Multiple injections –discomfort from injections –Relative risk of polycythemia –Risk of POME
Testosterone cypionate (Depo-Testosterone)	17- β -hydroxylester	8–10 days	200 mg every 2–3 weeks	<ul style="list-style-type: none"> –Low cost –Short-acting product among parenteral preparations allowing drug withdrawal in case of adverse effects 	<ul style="list-style-type: none"> –High fluctuations within and between individuals in circulating testosterone levels –Multiple injections –discomfort from injections –Relative risk of polycythemia –Risk of POME
Testosterone propionate (Testovis)	17- β -hydroxylester	20 hours	100 mg every 2 days	<ul style="list-style-type: none"> –Low cost –Very short-acting product among parenteral preparations allowing drug withdrawal in case of adverse effects 	<ul style="list-style-type: none"> –Variable pharmacokinetics within and between individuals in circulating testosterone levels –Multiple injections –discomfort from injections –Relative risk of polycythemia –Risk of POME
Testosterone ester mixture Propionate (30 mg) Phenylpropionate (60 mg) Isocaproate (60 mg) Decanoate (100 mg) (Sustanon)	4-androsten-3-one-17 beta-hydroxy-androst-4-en-3-one	4–5 days	250 mg every 3 weeks	<ul style="list-style-type: none"> –Low cost –Short-acting product among parenteral preparations allowing drug withdrawal in case of adverse effects 	<ul style="list-style-type: none"> –Variable pharmacokinetics within and between individuals in circulating testosterone levels –Multiple injections –discomfort from injections –Relative risk of polycythemia –Risk of POME

(Continued)

Table 1. (Continued).

Formulation (Commercial name)	Chemical structure	t 1/2	Standard dosage	Advantages	Disadvantages
Testosterone undecanoate in castor oil (Nebido)	17- β -hydroxylster	34 days	1,000 mg every 12–14 weeks	<ul style="list-style-type: none"> –Steady-state testosterone level without short term fluctuation –Long-lasting product among parenteral preparations –Less frequent administration 	<ul style="list-style-type: none"> –Pain at injection site –discomfort from injections –Long-acting preparation not allowing rapid drug withdrawal in case of adverse effects –Relative risk of polycythemia –Risk of POME
Testosterone undecanoate in castor oil (Aveed)**	17- β -hydroxylster	34 days	750 mg every 10 weeks	<ul style="list-style-type: none"> –Steady-state testosterone level without short term fluctuation –Long-lasting product among parenteral preparations –Less frequent administration 	<ul style="list-style-type: none"> –Pain at injection site –discomfort from injections –Long-acting preparation not allowing rapid drug withdrawal in case of adverse effects –Relative risk of polycythemia –Risk of POME
Surgical implants (Testopel)	Native testosterone	4–6 months	75 mg implants lasting up to 6 months	–Long duration and constant serum testosterone level	<ul style="list-style-type: none"> –Placement is invasive –Risk of extrusion and site infections –Relative risk of polycythemia
Transdermal					
Testosterone patches (andrioderm)	Native testosterone	10 hours	50–100 mg/day	–Steady-state testosterone levels without short-term fluctuation	<ul style="list-style-type: none"> –Possible skin irritation –risk of disproportionately high conversion of testosterone to DHT during absorption.
Testosterone gel 1–2% Androgel Testogel Tostrex/Forresta Testavan	Native testosterone	6 hours	50–100 mg/day	–Steady-state testosterone levels without short-term fluctuation	<ul style="list-style-type: none"> –Possible skin irritation –Possible transfer during intimate contact –risk of disproportionately high conversion of testosterone to DHT during absorption.
Testosterone 5% cream AndroForte*	Native testosterone	NA	25 mg/day	–Steady-state testosterone levels without short-term fluctuation	<ul style="list-style-type: none"> –Possible skin irritation –Possible transfer during intimate contact –risk of disproportionately high conversion of testosterone to DHT during absorption.
Underarm testosterone solution 2% (Axiron)	Native testosterone	6 hours	60–120 mg/day	–Steady-state testosterone levels without short-term fluctuation	<ul style="list-style-type: none"> –Possible skin irritation –Possible transfer during intimate contact –risk of disproportionately high conversion of testosterone to DHT during absorption.
Transmucosal					
Testosterone buccal system (Striant)	Native testosterone	12 hours	30 mg 2 times daily	–Steady-state testosterone levels without short-term fluctuation	<ul style="list-style-type: none"> –Possible oral irritation –Unpleasant taste –dislodging of tablets –risk of disproportionately high conversion of testosterone to DHT during absorption.
Testosterone nasal	Native testosterone	6 hours	metered dose pump with 5.5 mg/activation 11 mg 3 times daily	–potentially reduced risk of adverse events	<ul style="list-style-type: none"> –Nasal irritation –high fluctuations levels over 24 h –risk of disproportionately high conversion of testosterone to DHT during absorption.

NA = not applicable.

major adverse cardiovascular events (MACE). Due to this risk, the use of oral TU preparations should be limited to hypogonadal conditions associated with structural or genetic etiologies (the so-called organic hypogonadism, see before).

Very recently, the FDA approved another preparation of TU, Kyzatrez (Marius Pharmaceuticals, Raleigh, NC; U.S.A.), supplied as 100, 150, and 200 mg of TU capsules containing as carriers Vitamin E, phytosterol esters, polyoxyl 40 hydrogenated castor oil and propylene glycol monolaurate [65]. Results of an open-label multicenter study involving 155 hypogonadal men treated with titrated 100–400 mg of Kyzatrez suggest a lower effect of this preparation on systolic blood pressure, with an average increase of 1.7 mmHg, more evident in those taking antihypertensive medications at study entry [66]. Nonetheless, the same boxed warning was required for Kyzatrez.

Considering that in a meta-analysis [67] of available observational studies ($n = 11$) TRT was able to significantly decrease both systolic and diastolic BP (more than 6 mmHg) and that in another meta-analysis [68] of placebo-controlled trials ($n = 17$), a minimal (less than 1 mmHg), but insignificant, increase in BP was observed, results with oral TU preparations are surprising. One more recent meta-analysis of randomized placebo-controlled TRT trials (including individual participant data sets) suggests that the percentage of treated subjects with hypertension is similar in the two arms [69]. One possible explanation is that in the most recent trials involving oral TU, the regulatory authorities required more stringent and sensitive measurements of BP parameters, including ambulatory BP monitoring, than in the past [61,63].

A lipidic native T (LNT) formulation was developed by Diurnal Ltd. (Cardiff Medicentre, Cardiff, UK) and tested in a phase 1 study in 24 men with hypogonadism. Results suggest that a 200 mg dose of LNT gave a similar concentration of circulating T than 80 mg of TU and was food-independent, i.e. suitable even in the fasting condition [59]. In addition, supra-physiological concentrations of DHT were not observed [59].

Concerning patient satisfaction with oral TU, a recently published open-label single trial involving 40 hypogonadal men previously treated with different T preparations (pellets, injectables, and nasal) switched after a washout to JATENZO 237 mg b.i.d. titrated according to T levels. Results suggest that patient satisfaction, as measured by the Treatment Satisfaction Questionnaire for Medication (TSQM-9), was significantly increased by switching to oral TU after 14 weeks and six months [70].

3.4. Prostate-related unwanted effects

3.4.1. Challenges

AR has a primary role in orchestrating prostate differentiation during early fetal life and facilitating arborization of epithelial buds by acting on mesenchymal stromal cells and their paracrine growth factor secretion (so-called andromedins, e.g. KGF, IGF-1) [71]. Besides differentiation, AR induces a continuous, but wave-shaped burst stimulation of prostate growth during the entire male life. The first wave is during the aforementioned fetal life. The second wave is during puberty, and the last wave begins at midlife and continues during senescence [71].

In human prostate homogenates, T and DHT bind to AR with a $K_d = 1.6$ and 0.17 nmol/L, respectively, and stimulate the proliferation of stromal prostate cells with an $EC_{50} = 0.4$ nM [71]. Maximal stimulation was obtained at 10 nmol/L, and no further growth was observed at higher concentrations [71]. According to 'in vitro' data, the surrogate marker of prostate growth, circulating prostate-specific antigen (PSA), increases as a function of endogenous T levels up to 10 nmol/L, without further increases [72]. This is tantamount to saying that T is associated with prostate growth only in hypogonadal individuals, but not in eugonadal ones. Accordingly, data from T trials showed no difference in prostate-related events or prostate cancer (PC) when T-treated men were compared with those enrolled in the placebo group at the endpoint [73]. Similarly, a recent network meta-analysis further confirmed the overall prostate safety of all T preparations [74]. However, the latter study recognized a high heterogeneity in the trials included, particularly in the dosage and timing of T administration [74]. In addition, in a recent placebo-controlled RCT performed in Florence, we reported a T-related increase in prostate volume after 6 months of treatment in hypogonadal subjects [75]. Other short-term trials observed the same phenomenon [10,73].

The aforementioned T-induced prostate growth has historically raised many concerns about the safety of TRT in hypogonadal subjects, even though it is obviously more related to the normalization of T (i.e. T shifting from a hypogonadal to an eugonadal range) than to an abnormal proliferative burst. Actually, there are still warning labels on the available T preparations regarding the risk of BPH and urinary retention.

3.4.2. Possible solutions with available or in development T preparations

There was and still is interest in developing prostate-sparing regimens of TRT, based mainly on reducing DHT formation upon T administration. The most obvious solutions are two: i) to reduce T to DHT conversion through 5 α reductase inhibitors, which reduce prostatic DHT levels and prostate size; or ii) to use steroidal or non-steroidal AR agonists that do not undergo metabolism to DHT.

The use of a 5 α reductase inhibitor (5ARI) as an add-on to TRT was originally investigated in 70 hypogonadal men (total $T < 12$ nmol/L) aged 65 years or older [76,77]. They were treated with T enanthate 200 mg every two weeks with or without finasteride (5 mg) or with a placebo for 36 months. TRT with or without finasteride improved bone mineral density (BMD) at the lumbar spine and, to a lesser extent, at the hip [77] and improved physical performance [76], along with a decrease in fat mass and a parallel increase in muscle mass [76]. Interestingly, while T alone induced an increase in PSA and prostate volume, the addition of finasteride prevented the PSA increase and blunted the rise in prostate volume [76]. However, the rate of polycythemia was similar with or without finasteride [76]. In those studies, no information is available on sexual functioning. However, 5ARI, used for treating benign prostatic hyperplasia (BPH), in meta-analyses [78,79] showed potential side effects on sexual functioning, including erectile dysfunction, reduced sexual desire [78] and ejaculatory dysfunctions [79]. Hence, all these points should be adequately discussed with the patients before 5ARI prescriptions.

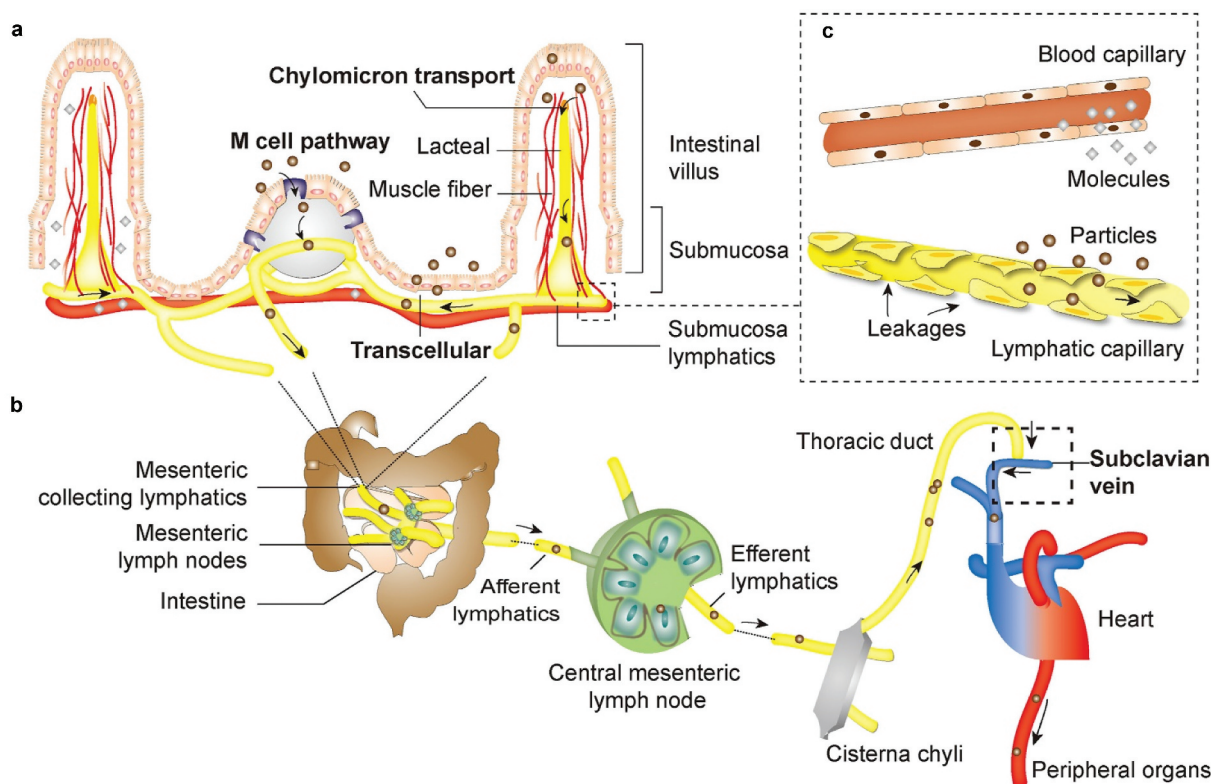


Figure 2. Schematic presentation of the structures of the lymphatic systems involved in transport of particulates and macromolecules. (a) intestinal lymphatics; (b) lymphatic circulation; (c) comparison of blood and lymphatic capillaries. Figure reproduced with permission from [45].

To overcome the sexual side effects of 5ARI, non-hypercalcemic analogs of vitamin D, such as BXL353 or elocalcitol (BXL628), were investigated in preclinical [80] and clinical studies [81]. Preclinical studies, performed using human BPH cells, indicated that BXL353 counteracted T and DHT-induced cell growth and decreased T-stimulated ventral prostate growth in castrated rats [80]. Vitamin D receptor (VDR) activation is associated, in human prostate cells, with an antagonistic activity on some androgen (KGF, IGF-1) action [80]. Although a placebo-controlled, phase 2 study demonstrated elocalcitol efficacy in reducing spontaneous prostate growth in subjects with BPH [80], the compound was not further developed for this purpose, most probably because its efficacy was lower than that of finasteride.

19-Nortestosterone (Nandrolone) decanoate is a synthetic derivative of native T, obtained by removing the 19-methyl group. Considering that it is metabolized by 5 α reductase into a weak androgen (5 α -dihydronandrolone), it is supposed to exert a lower growth effect on the prostate [82]. In fact, preclinical studies suggest weaker stimulation on the ventral prostate of castrated rats than native T [83]. However, its illicit use for anabolic purposes, despite the limited androgenic bioactivity of its metabolite, the consequent prescribing limitation, along with a claimed, although not demonstrated, negative effect on erectile function, strongly limit its use as a therapy for hypogonadism [82]. A 19-nortestosterone derivative, 7 α -methyl-19-nortestosterone (MENT), was developed in the early 1960s and proposed for the treatment of male hypogonadism with a less

growth-promoting effect on the prostate (because of a lack of conversion to DHT), but later on, it was not further developed for this purpose by Bayer [84].

Non-steroidal selective androgen receptor modulators (SARM) are a heterogeneous class of compounds that are supposed to act selectively on AR targets by modulating ARE activity through the recruitment of distinct coactivators or corepressors [85]. In addition, they share the inability to be further metabolized to estrogens and DHT and, therefore, they have potentially lower or null activity in promoting prostate growth [85]. A phase 2 trial (SAR-202) with different doses (15 and 25 mg) of the orally administered SARM OPK-88004 compared to placebo on serum PSA in men with BPH (ClinicalTrials.gov Identifier: NCT03297398) was terminated and the results were never published. The same compound has been tested in a placebo-controlled, randomized, double-blind trial, involving 114 hypogonadal men who had undergone radical prostatectomy for low-grade prostate cancer for at least 2 years [86]. They were treated for 12 weeks with 1, 5 or 15 mg OPK-88004 or with a placebo. Results showed a positive, dose-dependent effect of OPK-88004 on body composition (i.e. lean mass increased and fat mass decreased), without a negative effect on PSA, hematocrit, or liver function. Due to a marked decrease in SHBG levels, total T, but not free T, decreased, without a significant change in LH [86]. However, impaired sexual function, as measured by several instruments, was not improved [86]. The lack of efficacy on sexual functioning is in apparent contrast with preclinical studies [87],

however, studies in humans demonstrated that aromatization to estrogen is critical for explaining the full efficacy of T on sexual activity [88,89]. SARMs appear very attractive for treating several conditions associated with male hypogonadism [85,87,89,90], even though most of them are orally available, however, hepatotoxicity was observed in many clinical studies [91], limiting their further development. In fact, to date, no SARM has received approval for any therapeutic use from either the FDA or EMA.

4. Conclusions

Apart from the relative contraindications reported in the guidelines [3–5,7–9,11], one of the main limitations related to TRT administration in hypogonadal men is erythrocytosis which can develop in a dose-dependent manner with almost all the available T preparations [13,47]. Preliminary results with nasal T [43], showing a minor effect on erythropoiesis, need to be confirmed by larger studies because they involve a very small cohort of hypogonadal subjects.

Another important issue is related to fertility desire. Although the preliminary results with intranasal T administration are interesting [33,34], the data published so far are inconclusive in suggesting this formulation above the others for men interested in fathering. Hence, a rapid switch to Gn administration is still the best option, at least in all subjects with a diagnosis of a secondary hypogonadism.

SEDDS technology has greatly improved the oral availability of non-hepatotoxic T undecanoate formulations, but FDA-approved preparations are still not yet available in Europe. In addition, these formulations should still be taken with meals twice a day [92,93] and are associated with mild adverse events such as gastrointestinal side effects and with an unexpected increase in blood pressure, not reported with the other preparations [66–68].

Historical concerns about the negative effect of TRT on the prostate prompted the development of AR ligands with prostate-sparing properties by negating the formation of DHT. Considering that DHT is important for normal sexual functioning, its lower formation might justify the disappointing results with SARM when sexual dysfunction was an issue [87]. In addition, the lack of the full spectrum of T actions and the possible risk of side effects represent other limitations related to the use of SARMS, despite their potential utility in the treatment of muscle wasting and osteoporosis.

5. Expert opinion

A large body of evidence has clearly documented that TRT is useless for eugonadal patients [15]. Although the suggested cutoffs to start TRT differ among available guidelines, the European position emphasized that total T levels below 12 nM represent the best threshold [5,9,11]. The utility of calculated free T (<220 pM) has been recently proposed by the Italian Society of Sexual Medicine and Andrology [9] but is not completely supported by other European positions [5,11]. An accurate diagnosis based on the presence of specific symptoms and the biochemical determination of reduced T levels represents the cornerstone of a successful treatment. In particular, we want to emphasize that during the last two decades, a tremendous increase in T

prescriptions has been observed, particularly in the US market [94]. Accordingly, a previous survey indicated that up to 30% of men who were prescribed T in the US were not checked for T levels prior to their TRT prescription or underwent T evaluation only after the prescription [94]. Considering the possible aforementioned side effects related to TRT, particularly when TRT is not prescribed according to recommended guidelines [95] the latter finding can justify, at least partially, the different positions released by the FDA [96] and EMA [97] on CV safety related to TRT. However, it should be recognized that the long-term CV safety of TRT still represents a conflicting issue. One of the most recent meta-analyses showed that TRT does not increase short-term or medium-term CV risk in men with hypogonadism [69]. The same study emphasized the paucity of data evaluating TRT-related long-term CV safety. In addition, although the TRAVERSE study did not report any differences in MACE risk after 2 years of treatment, a mild, although significant, increased risk of arrhythmias, and atrial fibrillation, in particular, as well as of venous thromboembolism, has been reported in the active arm when compared to placebo [23]. The high (>60%) dropout observed during the study and the lack of formal adjudication of the latter events, which were secondary endpoints (venous thromboembolism) and investigator-reported (arrhythmias), represent crucial bias in the data interpretation [23].

Following the above consideration, it is our opinion that when a symptomatic man (particularly when sexual symptoms are present) has a low T level for any reason, the best solution is to replace his deficiency with any of the available T preparations (Table 1). Lifestyle modifications and weight loss should be strongly encouraged in all overweight and obese subjects since they can result in better outcomes when compared to TRT alone. Data from the Testosterone treatment to prevent or revert type 2 diabetes in men enrolled in a lifestyle program (T4DM) – a large double-blind placebo-controlled RCT, including more than 1000 subjects with a waist circumference ≥ 95 cm, total $T \leq 14.0$ nmol/L, and impaired glucose tolerance or newly diagnosed T2DM – are in line with the latter observation. The included subjects were treated with long-acting injectable TU or placebo for 2 years, along with a detailed lifestyle program. Final results showed that the active treatment arm resulted in a better improvement in body composition, glycometabolic profile, and in International Index of Erectile Function Domain scores [48]. The latter benefits seem to disappear in a recent long-term analysis performed five years after the cessation of TU treatment [98]. However, the inclusion of around 600 out of 1007 represents a possible source of bias in the data analysis [98].

T is not only a hormone but also a prohormone with the ability to be converted into two biologically active hormones: DHT and estradiol. Both of them play important physiological roles, including bone metabolism, sexual functioning, and supporting male skin and body hair characteristics. Hence, the use of compounds (steroid and non-steroid) unsuitable for aromatization and/or 5 α -reduction may not completely correct the hypogonadal state and its associated symptoms. Accordingly, the available evidence derived from the use of SARM for the treatment of male hypogonadism is essentially not satisfactory [89]. Similar considerations can be derived from the use of aromatase inhibitors or estrogen selective responsive elements (SERM),

frequently advocated for the treatment of hypogonadism, particularly in those subjects with an intact hypothalamus-pituitary-testis axis who request to preserve fertility [99].

Other options have been tested for the treatment of male hypogonadism, but still at experimental levels. Both kisspeptin agonists (such as TAK-448 or TAK-683 [100,101] and neurokinin-B agonists (such as Senktide and [MePhe7]NKB [101] have been proven to stimulate gonadotropin secretion. However, the requirement of a pulsatile administration for the former and the lack of clinical data for the latter option, represent crucial limitations. Similarly, the promising preliminary data on restoring T levels in men with MetS, obtained by the use of anakinra, a recombinant human IL-1 receptor antagonist, have never been confirmed by other authors [102].

In young individuals, circadian rhythmicity of T secretion by the testis was described in the late 1960s [103] and later confirmed by data modeling in the elderly [93]. Hence, a physiological T substitution is obtained more through T transdermal administration [93] than with other preparations, either short- or long-acting. In fact, transdermal preparations allow for higher T levels in the morning and lower levels at night [93]. In contrast, short-acting preparations (oral or intranasal) need two- or three-times daily administration, including in the evening. Long-acting preparations (parenteral) act as a depot and obviously do not allow any circadian rhythmicity.

However, very long-acting preparations, such as injectable TU, have the great advantage of bimestrial or trimestral administration. In fact, four to six yearly T injections can relieve the patient from being reminded daily that they suffer from an irreversible condition, such as Klinefelter Syndrome [9].

In conclusion considering that the use of TRT in LOH remains a controversial issue and that many T preparations are available on the market, we strongly suggest discussing with each individual patient the advantages and disadvantages of each preparation, therefore allowing a metered prescription of TRT. It should be noted that despite their intrinsic pharmacological and clinical advantages, the cost of the newer T formulations including gels, long-acting parenteral formulations and nasal or new oral preparations, is much higher when compared to older oral or T-ester products. This aspect represents another point to be adequately discussed with the patient before a T prescription, particularly in those countries where TRT is not reimbursed by the National Health Care Service. Weight loss and lifestyle modification programs should be discussed with patients in order to plan a multiple step-approach characterized by a potential progression improvement. In subjects with LOH, weight loss achievement, along with underlying symptoms improvement, may prompt TRT withdrawal and a new T level evaluation after a reasonable washout period.

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References

Papers of special note have been highlighted as either of interest (*) or of considerable interest () to readers.**

1. Naamneh Elzenaty R, du Toit T, Flück CE. Basics of androgen synthesis and action. *Best Pract Res Clin Endocrinol Metab.* 2022 Jul;36(4):101665. doi: [10.1016/j.beem.2022.101665](https://doi.org/10.1016/j.beem.2022.101665)
2. Tajar A, Forti G, O'Neill TW, et al. Characteristics of secondary, primary, and compensated hypogonadism in aging men: evidence from the European male Ageing study. *J Clin Endocrinol Metab.* 2010 Apr;95(4):1810–1818. doi: [10.1210/jc.2009-1796](https://doi.org/10.1210/jc.2009-1796)
3. Bhasin S, Brito JP, Cunningham GR, et al. Testosterone therapy in men with hypogonadism: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2018 May 1;103(5):1715–1744. doi: [10.1210/jc.2018-00229](https://doi.org/10.1210/jc.2018-00229)
4. Lunenfeld B, Mskhalaya G, Zitzmann M, et al. Recommendations on the diagnosis, treatment and monitoring of testosterone deficiency in men. *Aging Male.* 2021 Dec;24(1):119–138. doi: [10.1080/13685538.2021.1962840](https://doi.org/10.1080/13685538.2021.1962840)
5. Salonia A, Bettocchi C, Boeri L, et al. EAU Working Group on Male Sexual and Reproductive Health. European Association of Urology Guidelines on Sexual and Reproductive Health-2021 Update: male sexual dysfunction. *Eur Urol.* 2021 Sep;80(3):333–357. doi: [10.1016/j.eururo.2021.06.007](https://doi.org/10.1016/j.eururo.2021.06.007)
- of interest.
6. Yeap BB, Grossmann M, McLachlan RI, et al. Endocrine Society of Australia position statement on male hypogonadism (part 1): assessment and indications for testosterone therapy. *Med J Aust.* 2016 Aug 15;205(4):173–178. doi: [10.5694/mja16.00393](https://doi.org/10.5694/mja16.00393)
7. Morales A, Bebb RA, Manjoo P, et al. Diagnosis and management of testosterone deficiency syndrome in men: clinical practice guideline. *CMAJ.* 2015 Dec 8;187(18):1369–1377. doi: [10.1503/cmaj.150033](https://doi.org/10.1503/cmaj.150033)
8. Khera M, Adaikan G, Buvat J, et al. Diagnosis and treatment of testosterone deficiency: recommendations from the fourth international consultation for sexual medicine (ICSM 2015). *J Sex Med.* 2016 Dec;13(12):1787–1804. doi: [10.1016/j.jsxm.2016.10.009](https://doi.org/10.1016/j.jsxm.2016.10.009)
9. Isidori AM, Aversa A, Calogero A, et al. Adult- and late-onset male hypogonadism: the clinical practice guidelines of the Italian Society of Andrology and sexual medicine (SIAMS) and the Italian Society of Endocrinology (SIE). *J Endocrinol Invest.* 2022 Dec;45(12):2385–2403. doi: [10.1007/s40618-022-01859-7](https://doi.org/10.1007/s40618-022-01859-7)
- of interest.
10. Corona G, Torres LO, Maggi M. Testosterone therapy: what we have learned from trials. *J Sex Med.* 2020 Mar;17(3):447–460. doi: [10.1016/j.jsxm.2019.11.270](https://doi.org/10.1016/j.jsxm.2019.11.270)
11. Corona G, Goulis DG, Huhtaniemi I, et al. European Academy of Andrology (EAA) guidelines on investigation, treatment and monitoring of functional hypogonadism in males: endorsing organization. *Eur Society Endocrinol Andrology.* 2020 Sep;8(5):970–987. doi: [10.1111/andr.12770](https://doi.org/10.1111/andr.12770)
- of interest.
12. Corona G, Cucinotta D, Di Lorenzo G, et al. Congenital adrenal hyperplasia, disorders of sex development, and infertility in

- patients with POR gene pathogenic variants: a systematic review of the literature. *J Endocrinol Invest.* 2023 Jan 25;46(1):1–34. doi: [10.1007/s40618-022-01849-9](#)
13. Giagulli VA, Castellana M, Lisco G, et al. Critical evaluation of different available guidelines for late-onset hypogonadism. *Andrology.* 2020 Nov;8(6):1628–1641. doi: [10.1111/andr.12850](#)
 14. Wu FC, Tajar A, Beynon JM, et al. Identification of late-onset hypogonadism in middle-aged and elderly men. *N Engl J Med.* [2010 Jul 8];363(2):123–135. doi: [10.1056/NEJMoa0911101](#)
 - **of interest.**
 15. Handelsman DJ. Androgen Misuse and Abuse. *Endocr Rev.* 2021 Jul 16;42(4):457–501. doi: [10.1210/edrev/bnab001](#)
 - **of interest.**
 16. Nieschlag E. Late-onset hypogonadism: a concept comes of age. *Andrology.* 2020 Nov;8(6):1506–1511. doi: [10.1111/andr.12719](#)
 17. Corona G, Vignozzi L, Sforza A, et al. Risks and benefits of late onset hypogonadism treatment: an expert opinion. *World J Mens Health.* 2013 Aug;31(2):103–125. doi: [10.5534/wjmh.2013.31.2.103](#)
 18. Rastrelli G, Vignozzi L, Corona G, et al. Pharmacotherapy of male hypogonadism. *Curr Opin Pharmacol.* 2023 Feb;68:102323.
 19. Corona G, Vena W, Pizzocaro A, et al. Testosterone therapy in diabetes and pre-diabetes. *Andrology.* 2023 Feb;11(2):204–214. doi: [10.1111/andr.13367](#)
 20. Corona G, Rastrelli G, Vignozzi L, et al. The role of testosterone treatment in patients with metabolic disorders. *Expert Rev Clin Pharmacol.* 2021 Sep;14(9):1091–1103. doi: [10.1080/17512433.2021.1938548](#)
 21. Corona G, Rastrelli G, Morelli A, et al. Treatment of functional hypogonadism Besides pharmacological substitution. *World J Mens Health.* 2020 Jul;38(3):256–270. doi: [10.5534/wjmh.190061](#)
 22. Corona GG, Rastrelli G, Maseroli E, et al. Testosterone replacement therapy and cardiovascular risk: a review. *World J Mens Health.* 2015 Dec;33(3):130–142. doi: [10.5534/wjmh.2015.33.3.130](#)
 23. Lincoff AM, Bhasin S, Flevaris P, et al. Cardiovascular safety of testosterone-replacement therapy. *N Engl J Med.* [2023 Jul 13];389(2):107–117. doi: [10.1056/NEJMoa2215025](#)
 - **of considerable interest.**
 24. Wittert GA, Grossmann M, Yeap BB, et al. Testosterone and type 2 diabetes prevention: translational lessons from the T4DM study. *J Endocrinol.* 2023 Sep 1;258(3). doi: [10.1530/JOE-22-0223](#)
 25. Green DJ, Chasland LC, Naylor LH, et al. New horizons: testosterone or exercise for cardiometabolic health in older men. *J Clin Endocrinol Metab.* 2023 Aug 18;108(9):2141–2153. doi: [10.1210/clinem/dgad175](#)
 26. Handelsman DJ. Testosterone, spermatogenesis, and unravelling the mysteries of puberty. *Endocrinology.* 2020 Sep 1;161(9). doi: [10.1210/endocr/bqaa120](#)
 27. Walker WH. Molecular mechanisms of testosterone action in spermatogenesis. *Steroids.* 2009 Jul;74(7):602–607. doi: [10.1016/j.steroids.2008.11.017](#)
 28. Thirumalai A, Amory JK. Emerging approaches to male contraception. *Fertil Steril.* 2021 Jun;115(6):1369–1376. doi: [10.1016/j.fertnstert.2021.03.047](#)
 29. Rastrelli G, Maggi M, Corona G. What are the pharmacological considerations for male congenital hypogonadotropic hypogonadism? *Expert Opin Pharmacother.* 2022 Jun;23(9):1009–1013. doi: [10.1080/14656566.2022.2084690](#)
 30. Tharakan T, Corona G, Foran D, et al. Does hormonal therapy improve sperm retrieval rates in men with non-obstructive azoospermia: a systematic review and meta-analysis. *Hum Reprod Update.* 2022 Aug 25;28(5):609–628. doi: [10.1093/humupd/dmac016](#)
 31. Caroppo E, Colpi GM. Hormonal treatment of men with Nonobstructive Azoospermia: what does the evidence suggest? *J Clin Med.* 2021 Jan 20;10(3):387. doi: [10.3390/jcm10030387](#)
 32. Pook CJ, Cocco A, Grandone A, et al. The Evidence for Fertility Preservation in Pediatric Klinefelter Syndrome. *Front Reprod Health.* 2021;3:629179. doi: [10.3389/frph.2021.629179](#)
 33. Gronski MA, Grober ED, Gottesman IS, et al. Efficacy of Nasal Testosterone Gel (Natesto®) Stratified by Baseline Endogenous Testosterone Levels. *J Endocr Soc.* 2019 Sep 1;3(9):1652–1662. doi: [10.1210/js.2019-00183](#)
 34. Rogol AD, Tkachenko N, Bryson N. Natesto™, a novel testosterone nasal gel, normalizes androgen levels in hypogonadal men. *Andrology.* 2016 Jan;4(1):46–54. doi: [10.1111/andr.12137](#)
 35. Winters SJ, Takahashi J, Troen P. Secretion of testosterone and its Δ^4 precursor steroids into spermatic vein blood in men with varicocele-associated infertility. *J Clin Endocrinol Metab.* 1999 Mar;84(3):997–1001. doi: [10.1210/jc.84.3.997](#)
 36. Diaz P, Reddy R, Blachman-Braun R, et al. Comparison of intratesticular testosterone between men receiving nasal, intramuscular, and subcutaneous pellet testosterone therapy: evaluation of data from two single-center randomized clinical trials. *World J Mens Health.* 2023 Apr;41(2):390–395. doi: [10.5534/wjmh.210261](#)
 37. Ramasamy R, Masterson TA, Best JC, et al. Effect of Natesto on reproductive hormones, semen parameters and hypogonadal symptoms: a single center, open label, single arm trial. *J Urol.* 2020 Sep;204(3):557–563. doi: [10.1097/JU.0000000000001078](#)
 38. Mirand EA, Gordon AS, Wenig J. Mechanism of testosterone action in erythropoiesis. *Nature.* 1965 Apr 17;206(981):270–272. doi: [10.1038/206270a0](#)
 39. Bachman E, Travison TG, Basaria S, et al. Testosterone induces erythrocytosis via increased erythropoietin and suppressed hepcidin: evidence for a new erythropoietin/hemoglobin set point. *J Gerontol A Biol Sci Med Sci.* 2014 Jun;69(6):725–735. doi: [10.1093/gerona/glt154](#)
 40. Coviello AD, Kaplan B, Lakshman KM, et al. Effects of graded doses of testosterone on erythropoiesis in healthy young and older men. *J Clin Endocrinol Metab.* 2008 Mar;93(3):914–919. doi: [10.1210/jc.2007-1692](#)
 41. Bachman E, Feng R, Travison T, et al. Testosterone suppresses hepcidin in men: a potential mechanism for testosterone-induced erythrocytosis. *J Clin Endocrinol Metab.* 2010 Oct;95(10):4743–4747. doi: [10.1210/jc.2010-0864](#)
 42. Mithoowani S, Laureano M, Crowther MA, et al. Investigation and management of erythrocytosis. *CMAJ.* 2020 Aug 10;192(32):E913–e918. doi: [10.1503/cmaj.191587](#)
 43. Ory J, Diaz P, Rivero MJ, et al. Comparing rates of polycythemia in hypogonadal men using nasal testosterone gel versus intramuscular testosterone: update of a randomized clinical trial. *Eur Urol Focus.* 2023 Jan;9(1):14–16. doi: [10.1016/j.euf.2022.09.001](#)
 44. Ohlander SJ, Varghese B, Pastuszak AW. Erythrocytosis following testosterone therapy. *Sex Med Rev.* 2018 Jan;6(1):77–85. doi: [10.1016/j.sxmr.2017.04.001](#)
 45. Madsen MC, van Dijk D, Wiepjes CM, et al. Erythrocytosis in a large cohort of trans men using testosterone: a long-term follow-up study on prevalence, determinants, and exposure years. *J Clin Endocrinol Metab.* 2021 May 13;106(6):1710–1717. doi: [10.1210/clinem/dgab089](#)
 46. Fernández-Balsells MM, Murad MH, Lane M, et al. Clinical review 1: adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis. *J Clin Endocrinol Metab.* 2010 Jun;95(6):2560–2575. doi: [10.1210/jc.2009-2575](#)
 47. Nackeeran S, Kohn T, Gonzalez D, et al. The effect of route of testosterone on changes in hematocrit: a systematic review and Bayesian network meta-analysis of randomized trials. *J Urol.* 2022 Jan;207(1):44–51. doi: [10.1097/JU.0000000000002188](#)
 48. Wittert G, Bracken K, Robledo KP, et al. Testosterone treatment to prevent or revert type 2 diabetes in men enrolled in a lifestyle programme (T4DM): a randomised, double-blind, placebo-controlled, 2-year, phase 3b trial. *Lancet Diabetes Endocrinol.* 2021 Jan;9(1):32–45. doi: [10.1016/S2213-8587\(20\)30367-3](#)
 - **of considerable interest.**
 49. Jones SD Jr., Dukovac T, Sangkum P, et al. Erythrocytosis and polycythemia secondary to testosterone replacement therapy in the aging male. *Sex Med Rev.* 2015 Apr;3(2):101–112. doi: [10.1002/smrj.43](#)

50. Dobs AS, Meikle AW, Arver S, et al. Pharmacokinetics, efficacy, and safety of a permeation-enhanced testosterone transdermal system in comparison with bi-weekly injections of testosterone enanthate for the treatment of hypogonadal men. *J Clin Endocrinol Metab.* 1999 Oct;84(10):3469–3478. doi: [10.1210/jcem.84.10.6078](#)
51. Date T, Paul K, Singh N, et al. Drug-Lipid Conjugates for Enhanced Oral Drug Delivery. *AAPS Pharm Sci Tech.* 2019 Jan 4;20(2):41. doi: [10.1208/s12249-018-1272-0](#)
52. Zhang Z, Lu Y, Qi J, et al. An update on oral drug delivery via intestinal lymphatic transport. *Acta Pharm Sin B.* 2021 Aug;11(8):2449–2468. doi: [10.1016/j.apsb.2020.12.022](#)
53. Atkinson MJ, Sinha A, Hass SL, et al. Validation of a general measure of treatment satisfaction, the treatment satisfaction questionnaire for medication (TSQM), using a national panel study of chronic disease. *Health Qual Life Outcomes.* 2004 Feb 26;2(1):12. doi: [10.1186/1477-7525-2-12](#)
54. Farthing MJ, Vinson GP, Edwards CR, et al. Testosterone metabolism by the rat gastrointestinal tract, in vitro and in vivo. *Gut.* 1982 Mar;23(3):226–234. doi: [10.1136/gut.23.3.226](#)
55. Westaby D, Ogle SJ, Paradinas FJ, et al. Liver damage from long-term methyltestosterone. *Lancet.* 1977 Aug 6;2(8032):262–263. doi: [10.1016/S0140-6736\(77\)90949-7](#)
56. Nieschlag E, Mauss J, Coert A, et al. Plasma androgen levels in men after oral administration of testosterone or testosterone undecanoate. *Acta Endocrinol (Copenh).* 1975 Jun;79(2):366–374. doi: [10.1530/acta.0.0790366](#)
57. Köhn FM, Schill WB. A new oral testosterone undecanoate formulation. *World J Urol.* 2003 Nov;21(5):311–315. doi: [10.1007/s00345-003-0372-x](#)
58. Schnabel PG, Bagchus W, Lass H, et al. The effect of food composition on serum testosterone levels after oral administration of Andriol® Testocaps®. *Clin Endocrinol (Oxf).* 2007 Apr;66(4):579–585. doi: [10.1111/j.1365-2265.2007.02781.x](#)
59. Newell-Price J, Huatan H, Quirke J, et al. An oral lipidic native testosterone formulation that is absorbed independent of food. *Eur J Endocrinol.* 2021 Oct 5;185(5):607–615. doi: [10.1530/EJE-21-0606](#)
60. Gursoy RN, Benita S. Self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs. *Biomed Pharmacother.* 2004 Apr;58(3):173–182. doi: [10.1016/j.biopha.2004.02.001](#)
61. Bhat SZ, Dobs AS. Testosterone replacement therapy: a narrative review with a Focus on new oral formulations. *touchRev Endocrinol.* 2022 Nov;18(2):133–140. doi: [10.17925/EE.2022.18.2.133](#)
62. Patel M, Muthigi A, Ramasamy RJ. JATENZO®: challenges in the development of oral testosterone. *Int J Impot Res.* 2022 Nov;34(7):721–724. doi: [10.1038/s41443-021-00461-4](#)
63. Swerdloff RS, Dudley RE. A new oral testosterone undecanoate therapy comes of age for the treatment of hypogonadal men. *Ther Adv Urol.* 2020 Jan;12:1756287220937232. doi: [10.1177/1756287220937232](#)
64. Miller JA, Nguyen TT, Loeb C, et al. Oral testosterone therapy: past, present, and future. *Sex Med Rev.* 2023 Apr 3;11(2):124–138. doi: [10.1093/sxmrev/qead003](#)
65. Asghar AA, Hashmi MR, Ahmed R, et al. Kyzatrex - oral testosterone replacement therapy. *Ann Med Surg.* 2022 Oct;82:104625.
66. White WB, Bernstein JS, Rittmaster R, et al. Effects of the oral testosterone undecanoate Kyzatrex™ on ambulatory blood pressure in hypogonadal men. *J Clin Hypertens (Greenwich).* 2021 Jul;23(7):1420–1430. doi: [10.1111/jch.14297](#)
67. Corona G, Giagulli VA, Maseroli E, et al. Testosterone supplementation and body composition: results from a meta-analysis of observational studies. *J Endocrinol Invest.* 2016 Sep;39(9):967–981. doi: [10.1007/s40618-016-0480-2](#)
68. Corona G, Giagulli VA, Maseroli E, et al. THERAPY of ENDOCRINE DISEASE: testosterone supplementation and body composition: results from a meta-analysis study. *Eur J Endocrinol.* 2016 Mar;174(3):R99–116. doi: [10.1530/EJE-15-0262](#)
69. Hudson J, Cruickshank M, Quinton R, et al. Adverse cardiovascular events and mortality in men during testosterone treatment: an individual patient and aggregate data meta-analysis. *Lancet Healthy Longev.* 2022 Jun;3(6):e381–e393. doi: [10.1016/S2666-7568\(22\)00096-4](#)
70. Reddy R, Rivero MJ, Patel M, et al. Patient Satisfaction After Switching to Jatenzo (Oral Testosterone Undecanoate): Update on an Open-label, Single-arm Clinical Trial. *Eur Urol Focus.* 2023 Jan;9(1):17–19. doi: [10.1016/j.euf.2022.08.005](#)
71. Corona G, Baldi E, Maggi M. Androgen regulation of prostate cancer: where are we now? *J Endocrinol Invest.* 2011 Mar;34(3):232–243. doi: [10.1007/BF03347072](#)
72. Rastrelli G, Corona G, Vignozzi L, et al. Serum PSA as a predictor of testosterone deficiency. *J Sex Med.* 2013 Oct;10(10):2518–2528. doi: [10.1111/jsm.12266](#)
73. Snyder PJ, Bhasin S, Cunningham GR, et al. Lessons from the testosterone trials. *Endocr Rev.* [2018 Jun 1];39(3):369–386. doi: [10.1210/er.2017-00234](#)
- of considerable interest.
74. Zeng B, Qiu S, Xiong X, et al. The effect of different administrations of testosterone therapy on adverse prostate events: a bayesian network meta-analysis. *Front Endocrinol.* 2022;13:1009900. doi: [10.3389/fendo.2022.1009900](#)
75. Rastrelli G, Cipriani S, Lotti F, et al. Testosterone does not affect lower urinary tract symptoms while improving markers of prostatitis in men with benign prostatic hyperplasia: a randomized clinical trial. *J Endocrinol Invest.* 2022 Jul;45(7):1413–1425. doi: [10.1007/s40618-022-01776-9](#)
76. Page ST, Amory JK, Bowman FD, et al. Exogenous testosterone (T) alone or with finasteride increases physical performance, grip strength, and lean body mass in older men with low serum T. *J Clin Endocrinol Metab.* 2005 Mar;90(3):1502–1510. doi: [10.1210/jc.2004-1933](#)
77. Amory JK, Watts NB, Easley KA, et al. Exogenous testosterone or testosterone with finasteride increases bone mineral density in older men with low serum testosterone. *J Clin Endocrinol Metab.* 2004 Feb;89(2):503–510. doi: [10.1210/jc.2003-031110](#)
78. Corona G, Tirabassi G, Santi D, et al. Sexual dysfunction in subjects treated with inhibitors of 5α-reductase for benign prostatic hyperplasia: a comprehensive review and meta-analysis. *Andrology.* 2017 Jul;5(4):671–678. doi: [10.1111/andr.12353](#)
79. Gacci M, Ficarra V, Sebastianelli A, et al. Impact of medical treatments for male lower urinary tract symptoms due to benign prostatic hyperplasia on ejaculatory function: a systematic review and meta-analysis. *J Sex Med.* 2014 Jun;11(6):1554–1566. doi: [10.1111/jsm.12525](#)
80. Crescioli C, Ferruzzi P, Caporali A, et al. Inhibition of spontaneous and androgen-induced prostate growth by a nonhypercalcemic calcitriol analog. *Endocrinology.* 2003 Jul;144(7):3046–3057. doi: [10.1210/en.2002-0210](#)
81. Colli E, Rigatti P, Montorsi F, et al. BXL628, a novel vitamin D3 analog arrests prostate growth in patients with benign prostatic hyperplasia: a randomized clinical trial. *Eur Urol.* 2006 Jan;49(1):82–86. doi: [10.1016/j.eururo.2005.08.014](#)
82. Pan MM, Kovac JR. Beyond testosterone cypionate: evidence behind the use of nandrolone in male health and wellness. *Transl Androl Urol.* 2016 Apr;5(2):213–219. doi: [10.21037/tau.2016.03.03](#)
83. Cristina RT, Hanganu F, Dumitrescu E, et al. The impact of exogenic testosterone and nortestosterone-decanoate toxicological evaluation using a rat model. *PLoS One.* 2014;9(10):e109219. doi: [10.1371/journal.pone.0109219](#)
84. Nieschlag E, Kumar N, Sitruk-Ware R. 7α-methyl-19-nortestosterone (MENTR): the population council's contribution to research on male contraception and treatment of hypogonadism. *Contraception.* 2013 Mar;87(3):288–295. doi: [10.1016/j.contraception.2012.08.036](#)
85. Christiansen AR, Lipshultz LI, Hotelling JM, et al. Selective androgen receptor modulators: the future of androgen therapy? *Transl Androl Urol.* 2020 Mar;9(Suppl 2):S135–S148. doi: [10.21037/tau.2019.11.02](#)
86. Pencina KM, Burnett AL, Storer TW, et al. A Selective Androgen Receptor Modulator (OPK-88004) in Prostate Cancer Survivors: A Randomized Trial. *J Clin Endocrinol Metab.* 2021 Jul 13;106(8):2171–2186. doi: [10.1210/clinem/dgab361](#)

87. Solomon ZJ, Mirabal JR, Mazur DJ, et al. Selective androgen receptor modulators: Current knowledge and clinical applications. *Sex Med Rev.* 2019 Jan;7(1):84–94. doi: [10.1016/j.sxmr.2018.09.006](https://doi.org/10.1016/j.sxmr.2018.09.006)
88. Finkelstein JS, Yu EW, Burnett-Bowie SA. Gonadal steroids and body composition, strength, and sexual function in men. *N Engl J Med.* 2013 Dec 19;369(25):2457. doi: [10.1056/NEJMoa1206168](https://doi.org/10.1056/NEJMoa1206168)
- **of interest.**
89. Kang J, Chen R, Tharakan T, et al. Novel androgen therapies including selective androgen receptor modulators. *Best Pract Res Clin Endocrinol Metab.* 2022 Sep;36(5):101686. doi: [10.1016/j.beem.2022.101686](https://doi.org/10.1016/j.beem.2022.101686)
90. Yi P, Rehmel JF, Cassidy K, et al. Disposition and metabolism of LY2452473, a selective androgen receptor modulator, in humans. *Drug Metab Dispos.* 2012 Dec;40(12):2354–2364. doi: [10.1124/dmd.112.047613](https://doi.org/10.1124/dmd.112.047613)
91. Mohideen H, Hussain H, Dahiya DS, et al. Selective Androgen Receptor Modulators: An Emerging Liver Toxin. *J Clin Transl Hepatol.* 2023 Feb 28;11(1):188–196. doi: [10.14218/JCTH.2022.00207](https://doi.org/10.14218/JCTH.2022.00207)
92. Bremner WJ, Vitiello MV, Prinz PN. Loss of circadian rhythmicity in blood testosterone levels with aging in normal men. *J Clin Endocrinol Metab.* 1983 Jun;56(6):1278–1281. doi: [10.1210/jcem-56-6-1278](https://doi.org/10.1210/jcem-56-6-1278)
93. Gupta SK, Lindemulder EA, Sathyan G. Modeling of circadian testosterone in healthy men and hypogonadal men. *J Clin Pharmacol.* 2000 Jul;40(7):731–738. doi: [10.1177/00912700022009486](https://doi.org/10.1177/00912700022009486)
94. Layton JB, Kim Y, Alexander GC, et al. Association between direct-to-consumer advertising and testosterone testing and initiation in the United States, 2009–2013. *JAMA.* 2017 Mar 21;317(11):1159–1166. doi: [10.1001/jama.2016.21041](https://doi.org/10.1001/jama.2016.21041)
95. Corona G, Rastrelli G, Di Pasquale G, et al. Testosterone and cardiovascular risk: meta-analysis of interventional studies. *J Sex Med.* 2018 Jun;15(6):820–838. doi: [10.1016/j.jsxm.2018.04.641](https://doi.org/10.1016/j.jsxm.2018.04.641)
96. FDA drug safety communication FDA cautions about using T products for low T due to aging requires labeling change to inform of possible increased risk of heart attack and stroke with use 2013 [cited 2023 Oct]. Available from: <https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-cautions-about-using-testosterone-products-low-testosterone-due>.
97. PRAC review does not confirm increase in heart problems with testosterone medicines 2014 [cited 2023 Oct]. Available from: <https://www.ema.europa.eu/en/news/prac-review-does-not-confirm-increase-heart-problems-testosterone-medicines>
98. Handelsman DJ, Grossmann M, Yeap BB, et al. Long-term outcomes of testosterone treatment in men: a T4DM post-randomisation observational follow-up study. *J Clin Endocrinol Metab.* 2023 Aug 25. doi: [10.1210/clinem/dgad485](https://doi.org/10.1210/clinem/dgad485)
99. Ide V, Vanderschueren D, Antonio L. Treatment of men with central hypogonadism: alternatives for testosterone replacement therapy. *Int J Mol Sci.* 2020 Dec 22;22(1):21. doi: [10.3390/ijms22010021](https://doi.org/10.3390/ijms22010021)
100. Tsoutsouki J, Abbara A, Dhillon W. Novel therapeutic avenues for kisspeptin. *Curr Opin Pharmacol.* 2022 Dec;67:102319. doi: [10.1016/j.coph.2022.102319](https://doi.org/10.1016/j.coph.2022.102319)
101. Millar RP, Newton CL. Current and future applications of GnRH, kisspeptin and neurokinin B analogues. *Nat Rev Endocrinol.* 2013 Aug;9(8):451–466. doi: [10.1038/nrendo.2013.120](https://doi.org/10.1038/nrendo.2013.120)
102. Ebrahimi F, Urwyler SA, Straumann S, et al. IL-1 antagonism in men with metabolic syndrome and Low Testosterone: a randomized clinical trial. *J Clin Endocrinol Metab.* 2018 Sep 1;103(9):3466–3476. doi: [10.1210/jc.2018-00739](https://doi.org/10.1210/jc.2018-00739)
103. Resko JA, Eik-Nes KB. Diurnal testosterone levels in peripheral plasma of human male subjects. *J Clin Endocrinol Metab.* 1966 May;26(5):573–576. doi: [10.1210/jcem-26-5-573](https://doi.org/10.1210/jcem-26-5-573)