REVIEW

An Individualized Approach to Managing Testosterone Therapy in the Primary Care Setting

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Abstract: The incidence of testosterone deficiency and the use of testosterone therapy have increased in recent years, and currently the majority of testosterone prescriptions in the United States and Canada are written by primary care physicians. Meanwhile, the range of available testosterone therapy formulations has widened to include buccal tablets, intramuscular injections, transdermal gels, intranasal gel, subcutaneous injections, oral capsules, and subdermal pellets, each with unique pharmacokinetic and clinical characteristics. Despite the growing use of testosterone therapy and its overall efficacy and safety as demonstrated in clinical trials, concerns exist about the potential impact of testosterone therapy on spermatogenesis and fertility, development of prostate cancer, and risk of polycythemia and cardiovascular events. In addition, ongoing research aims to better characterize the effects of testosterone therapy in specific populations, such as patients aged 65 years and older, patients with obesity and type 2 diabetes, and transgender patients. The range of treatment options and the diversity of patients' goals, preferences, comorbidities, and risk factors necessitate an individualized approach to testosterone therapy that considers each patient's clinical needs alongside the distinct features of different testosterone formulations.

Keywords: testosterone deficiency, hypogonadism, comorbidity, male, clinical practice

Introduction

Testosterone deficiency, also known as hypogonadism, is a common condition characterized by low serum levels of circulating testosterone and associated with symptoms including low libido, fatigue, erectile dysfunction, decreased energy, reduced muscle mass, and depression.[1] Primary testosterone deficiency results from failure of the testes to produce sufficient testosterone, while secondary testosterone deficiency is caused by decreased production of gonadotropin hormones from the hypothalamus or pituitary glands.[2–4] In the literature, estimates of the prevalence of low testosterone with symptoms of hypogonadism in men have been shown to range from 2% to 39% because of variable definitions of testosterone deficiency,[5] with the prevalence of testosterone deficiency generally increasing with age and the presence of comorbidities.[6,7]

In the United States (US), the use of testosterone therapy has tripled in recent years, with lower trends noted in Europe.[8,9] In Canada, until 2014 there was an increase in the use of testosterone comparable to that in the US.[10,11] In Nova Scotia, Canada, where the male population remained relatively stable from 2007 to 2019, testosterone prescriptions increased yearly from 2007 to 2014, after which they plateaued or decreased with the exception of men aged 18–34.[10] Broadly, in China and Asia, the use of testosterone is more limited, as the role of testosterone therapy for the treatment of hypogonadism is controversial (possibly due to pricing or for cultural reasons).[12] The vast majority of prescribers of testosterone in Nova Scotia, Canada (average 92%), are primary care physicians (PCPs), while in the US, PCPs write more than half (approximately 60%) of testosterone therapy prescriptions.[10] Outside the US, testosterone therapy is still generally managed by endocrinologists, andrologists, and urologists, although this may change in the future.[4,13,14] PCPs also may refer patients to these specialists when additional expertise is needed to help diagnose and treat hypogonadism. Importantly, there are diagnostic criteria outlined by clinical practice guidelines that must be followed to mitigate potential under- and overtreatment of hypogonadism. The dramatic increase in prescriptions for testosterone therapy in some regions has been accompanied by an increase in the range of treatment options available, although

not all of these are available everywhere. Testosterone therapy is currently available in buccal, intramuscular (IM), transdermal, intranasal, subcutaneous (SC), oral, and subdermal formulations, each of which aims to replace testosterone to approximately physiologic levels.[1,3]

As the likelihood increases that PCPs will become more involved in the management of testosterone therapy, it is important for them to understand how to evaluate and treat patients according to clinical guidelines and in the context of each patient's individual goals, needs, preferences, histories, comorbidities, and risk factors.[4,13,15] Furthermore, individual patients presenting to primary care may have unique concerns that necessitate a tailored approach to initiating, titrating, and monitoring testosterone therapy, and the provision of follow-up care.[15] Clinical practice guidelines have been published by various societies and associations in different global regions, such as the Endocrine Society, European Academy of Urology, and European Association of Urology (EAU) in Europe; International Society of Sexual Medicine (ISSM); and American Urological Association (AUA), American College of Physicians (ACP), and Canadian Urological Association (CUA) guidelines in North America. In Asia, recommendations for the diagnosis and management of testosterone deficiency are more limited; Chinese guidelines were published in 2017, and the Japanese Urological Association published guidelines for late-onset hypogonadism in 2008 that have not yet been updated. The goal of this review is to consider strategies for individualizing testosterone therapy in the primary care setting based on the patient's needs and the relative advantages and disadvantages of available treatment options.

Identifying and Diagnosing Testosterone Deficiency

Diagnosis of testosterone deficiency can be challenging because of the wide range of symptoms observed in men with insufficient testosterone, as well as the fact that most signs and symptoms of testosterone deficiency are also associated with other conditions.[6] For example, serum testosterone concentrations can be affected by acute illness, malnourishment, certain medications (eg, glucocorticoids), obesity, diabetes, sleep disorders, and general health status.[13] The clinical presentation of testosterone deficiency is also influenced by age of onset, severity of the deficiency, and variations in androgen sensitivity.[13] In severely testosterone-deficient men, specific symptoms may include incomplete or delayed sexual development, loss of secondary sex characteristics (eg, body hair), and very small testes.[13] Common symptoms suggestive of testosterone deficiency include reduced libido, delayed ejaculation, decreased spontaneous erections, erectile dysfunction, decreased physical strength, depressed mood, fatigue, difficulty concentrating, and sleep disturbances (Table 1).[1,13]

Table 1 Symptoms and Signs Suggestive of Testosterone Deficiency

Specific symptoms and signs
• Incomplete or delayed sexual development
• Loss of body (axillary and pubic) hair
• Very small testes (<6 mL)
Suggestive symptoms and signs
• Reduced sexual desire (libido) and activity
• Decreased spontaneous erections, erectile dysfunction
• Breast discomfort, gynecomastia
• Eunuchoidal body proportions
• Inability to father children, low sperm count
• Height loss, low-trauma fracture, low bone mineral density
• Hot flushes, sweats
Nonspecific symptoms and signs associated with testosterone deficiency
• Decreased energy, motivation, initiative, and self-confidence
• Feeling sad or blue, depressed mood, persistent low-grade depressive disorder. Poor concentration and memory
• Sleep disturbance, increased sleepiness
• Mild unexplained anemia (normochromic, normocytic)
• Reduced muscle bulk and strength
• Increased body fat, body mass index

Note: 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;103(5):1715–1744, doi:10.1210/jc.2018-00229. Reprinted by permission of Oxford University Press on behalf of the Endocrine Society.[13]

The clinical evaluation of men with signs or symptoms suggestive of testosterone deficiency should begin with a physical examination, including a testicular exam, followed by 2 measurements of morning total and/or free testosterone. An accurate and reliable method should be used to determine total testosterone, preferably an assay that has been certified by an accuracy-based standardization or quality control program.[13] Free testosterone should either be directly measured from equilibrium dialysis assays if available or calculated with formulas taking into account total testosterone, sex hormone−binding globulin (SHBG), and albumin levels (eg, the Vermeulen formula).[13,16] A diagnosis of testosterone deficiency should only be made in men who have both clinical signs and symptoms of low testosterone levels and biochemical confirmation of low serum testosterone.[1] Because testosterone concentrations exhibit significant diurnal and day-to-day variations, clinical practice guidelines generally recommend 2 separate morning measurements of serum total testosterone while fasting and in the absence of acute illness to diagnose testosterone deficiency.[1,13,14,17,18] According to the AUA, a morning testosterone level of 300 ng/dL is a reasonable threshold for diagnosis, while the EAU and ISSM guidelines opt for a 350 ng/dL cutoff, though the ISSM also recommends a trial of testosterone treatment in men with >350 ng/dL who are also symptomatic.[6,14,18] The Endocrine Society provides 264 ng/dL as the lower limit of normal total testosterone for healthy, nonobese men and recommends diagnosing when unequivocally and consistently low serum total testosterone and/or free testosterone concentrations are present.[13] The cutoff for diagnosis generally is not absolute; for example, a man with a low normal testosterone level who experiences significant symptoms of testosterone deficiency may benefit from intervention.[15] Following a diagnosis of hypogonadism, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) should be measured to determine whether the hypogonadism is primary or secondary (Figure 1).[13]

The differential diagnosis may consider other endocrine disorders (eg, hypothyroidism and adrenal insufficiency), metabolic disorders (eg, obstructive sleep apnea [OSA] and obesity), psychiatric disorders (eg, depression and bipolar disorder), and other medical conditions (eg, heart failure and chronic kidney disease).[15] Clinicians should consider measuring testosterone levels in patients with a history of unexplained anemia, bone density loss, diabetes, exposure to chemotherapy or testicular radiation, HIV/AIDS, chronic narcotic use, male infertility, pituitary dysfunction, and chronic corticosteroid use even in the absence of signs and symptoms of testosterone deficiency.[1]

Initiating Testosterone Therapy

The primary goal of testosterone therapy is to improve symptoms of testosterone deficiency while minimizing potential adverse events (AEs). For example, as sexual symptoms are a main concern for men with testosterone deficiency, testosterone replacement has the potential to have a beneficial effect on aspects of sexual life.[14] The decision to initiate therapy should be made only after appropriate counseling with patients regarding the potential benefits and risks of therapy; the clinical threshold for initiating treatment may vary with each patient and requires consideration of the patient's preferences, needs, and limitations. The presence of comorbidities and the age of the patient must also be considered, as older patients (>40 years) with small, subclinical prostate tumors should not be prescribed testosterone therapy because of the potential risk that testosterone will promote tumor growth.[1,13] This is discussed further in the section on individualizing therapy in specific populations. Guidelines recommend lifestyle modifications, such as weight loss and exercise, as an integral component of testosterone deficiency management.[6] For patients who choose to initiate testosterone therapy, the target testosterone level should be in the mid-normal range, typically 450 to 600 ng/dL.[1]

All patients who are considering testosterone replacement therapy should be screened for benign prostatic hyperplasia, a personal or family history of prostate cancer, elevated hematocrit, sleep apnea, hypertension, and a personal history of cardiovascular (CV) disease and venous thromboembolism to assess their baseline health and facilitate future monitoring if testosterone therapy is initiated. Additionally, they should be counseled about the potential for exogenous testosterone to suppress hypothalamic-pituitary-gonadal (HPG) axis function and thereby impair intratesticular testosterone production, spermatogenesis, and fertility (Table 2).[1,4,19–21]

Before initiation of testosterone therapy, referral to a specialist may be required for patients at increased risk for AEs associated with testosterone therapy, including those with elevated prostate-specific antigen (PSA) or nodules or induration on digital rectal examination (Figure 2).[4]
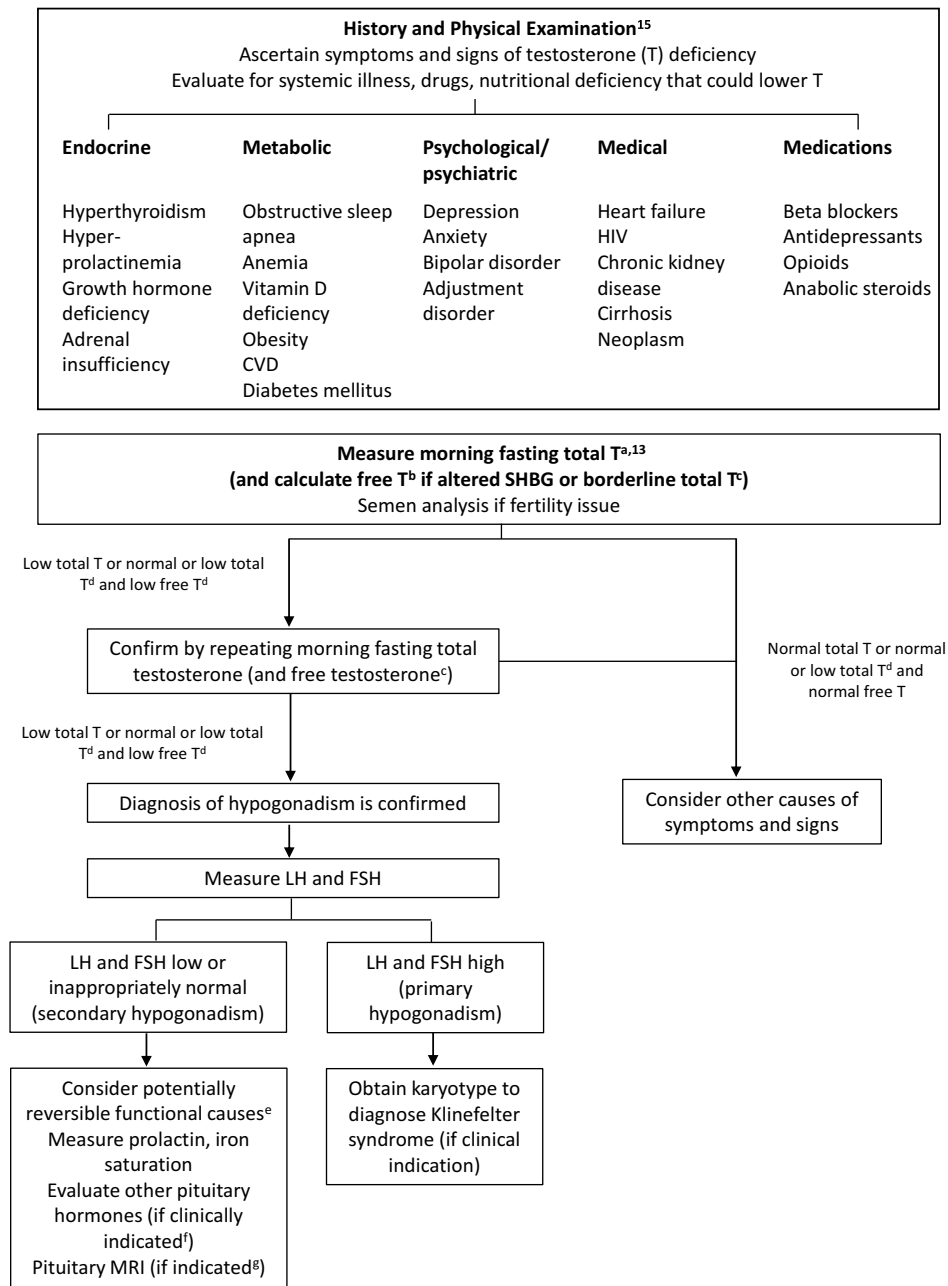
Figure 1 Evaluation and diagnosis of testosterone deficiency.

Notes: [a]The lower limit of the normal TT harmonized to the CDC standard in healthy, nonobese young men is 264 ng/dL (9.2 nmol/L); this limit could be used for TT assays that are CDC certified. For laboratories that are not CDC certified and do not participate in an accuracy-based quality control program, the reference range may vary considerably depending on the assay and reference population used. Using the lower limit of the range established in local laboratories may not accurately identify men with hypogonadism. [b]FT should be measured by an equilibrium dialysis method or estimated from total testosterone, SHBG, and albumin using a formula that accurately reflects FT by equilibrium dialysis. A harmonized reference range for FT has not been established, so reference ranges may vary considerably depending on the specific equilibrium dialysis method or the algorithm used to calculate FT. Therefore, until a harmonized reference range is established, the lower limits established by the laboratory may be used. [c]Conditions in which measurement of FT concentration is recommended are listed in Table 1. Conditions that alter SHBG levels include obesity, diabetes mellitus, use of glucocorticoids, some progestins and androgenic steroids, nephrotic syndrome, acromegaly, aging, HIV, cirrhosis and hepatitis, hypo- or hyperthyroidism, use of some anticonvulsants, estrogen use, and polymorphisms in the SHBG gene. [d]TT may also be high in some conditions in which SHBG levels are high, such as HIV or use of some anticonvulsants. [e]Potentially reversible functional causes of secondary hypogonadism include hyperthyroidism, hyperprolactinemia, growth hormone deficiency, adrenal insufficiency, obstructive sleep apnea, anemia, vitamin D deficiency, obesity, CVD, diabetes mellitus, depression, anxiety, bipolar disorder, adjustment disorder, heart failure, HIV, chronic kidney disease, cirrhosis, neoplasm, and use of beta blockers, antidepressants, opioids, and anabolic steroids. [f]If there is clinical indication of hypopituitarism or sella abnormality on imaging, evaluation of other pituitary hormones (eg, free thyroxine, morning cortisol, and adrenocorticotropic hormone stimulation test if clinical hypocortisolism is suspected) should be performed. [g]Perform pituitary imaging (MRI) to exclude pituitary and/or hypothalamic tumor or infiltrative disease when severe secondary hypogonadism (eg, serum T <150 ng/dL [5.2 nmol/L]), panhypopituitarism, persistent hyperprolactinemia, or symptoms or signs of tumor mass effect (such as new-onset headache, visual impairment, or visual field defect) are present. CT scan may be sufficient if macroadenoma is suspected or to assess parasellar bone involvement. 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;103(5):1715–1744, doi:10.1210/jc.2018-00229. Adapted by permission of Oxford University Press on behalf of the Endocrine Society.[13]

Abbreviations: CDC, Centers for Disease Control and Prevention; CT, computed tomography; CVD, cardiovascular disease, FSH, follicle-stimulating hormone; FT, free testosterone; LH, luteinizing hormone; MRI, magnetic resonance imaging; SHBG, sex hormone−binding globulin; TT, total testosterone.

Table 2 Managing Testosterone Therapy in Specific Patient Populations: Recommendations Based on the Authors' Experience

Patients	Potential Formulations	Starting Dose(s)	Key Safety and Outcomes Measures to Monitor	Key Considerations for Follow-Up Care
Patient wishing to maintain fertility	• Therapy should maintain endogenous testosterone production • Consider SERM (eg, clomiphene citrate) if low or normal gonadotropins • Gonadotropin therapy (eg, hCG, FSH) • Low suppressive testosterone therapy (intranasal testosterone) • Aromatase inhibitors if elevated estradiol	• Clomiphene citrate 25 mg every other day • Anastrozole 0.5 mg weekly • hCG 500 IU SC every other day • Intranasal testosterone gel (1 pump [5.5 mg] per nostril 3 times daily)	• Evaluate for changes in symptoms: fatigue, weight gain, hot flashes (seen in estradiol changes) • Changes from baseline semen parameters	• If inability to achieve pregnancy with unprotected intercourse is observed for >12 months, or after 6 months when the female partner is aged >35 years, refer to reproductive urologist
Patient with a steady lifestyle/ predictable schedule	• Patient preference drives therapy • Daily topical 1% testosterone gel • Intranasal gel • Weekly or biweekly IM or SC injection • Consider SC pellets	• IM dose: testosterone cypionate 200 mg/mL per week • 1% testosterone topical gel: 50 mg daily • Pellets: six 75 mg pellets • Intranasal gel: 1 pump (5.5 mg) per nostril 3 times daily	• Resolution of symptoms • Polycythemia • Changes in skin and hair patterns • Changes in lipid patterns • Changes in PSA or DRE	• Desire for fertility • Anticipated close contact with other individuals: switch from topical
Patient with high hematocrit	• Avoid depot formulations • Daily application is encouraged	• 1% testosterone topical gel: 50 mg daily • Intranasal gel: 1 pump (5.5 mg) per nostril 3 times daily	• Resolution of symptoms • Polycythemia • Changes in skin and hair patterns • Changes in lipid patterns • Changes in PSA or DRE	• Low threshold to halt therapy • Consider therapeutic phlebotomy • Obtain appropriate imaging if suspected DVT or VTE

Abbreviations: DRE, digital rectal examination; DVT, deep vein thrombosis; FSH, follicle-stimulating hormone; hCG, human chorionic gonadotropin; IM, intramuscular; IU, international unit; PSA, prostate-specific antigen; SC, subcutaneous; SERM, selective estrogen receptor modulator, VTE, venous thromboembolism.

Testosterone Formulations

To individualize testosterone therapy, PCPs should understand the differences among currently available testosterone therapies, including the dosing, route of administration, cost, and pharmacokinetic profiles of each, and consider these factors in the context of their patients' health care needs and therapeutic goals. Treatment options currently available in the US include buccal tablets, IM injections, transdermal gels, intranasal gel, SC injections, oral capsules, and subdermal pellets (Table 3).[3,4,13,15,22] Overall, most formulations of testosterone have been found to increase serum testosterone into the normal range in 75% to 97% of patients and are generally well tolerated.[23–30] Each treatment option, however, has its relative advantages and disadvantages. For instance, short-acting formulations, such as transdermal and intranasal options, may be more easily dose adjusted or discontinued in the event of treatment-related AEs, while some patients may prefer long-acting IM formulations because of their lower cost.[6,31] Importantly, serum testosterone concentrations are subject to significant diurnal, circadian, and circannual rhythms, as well as variations depending on the assay used.[13,32] As a result, formulations of testosterone that are administered daily may be considered best suited to maintain normal serum testosterone concentrations.[14] It should be noted that not all formulations are available in all regions, with transdermal gels and long-acting IM preparations with testosterone undecanoate being the most commonly available and used preparations.

Selecting a testosterone therapy that aligns with a patient's needs, preferences, and lifestyle is important because adherence to testosterone therapy is generally low, with fewer than one-fifth of first-time testosterone therapy users
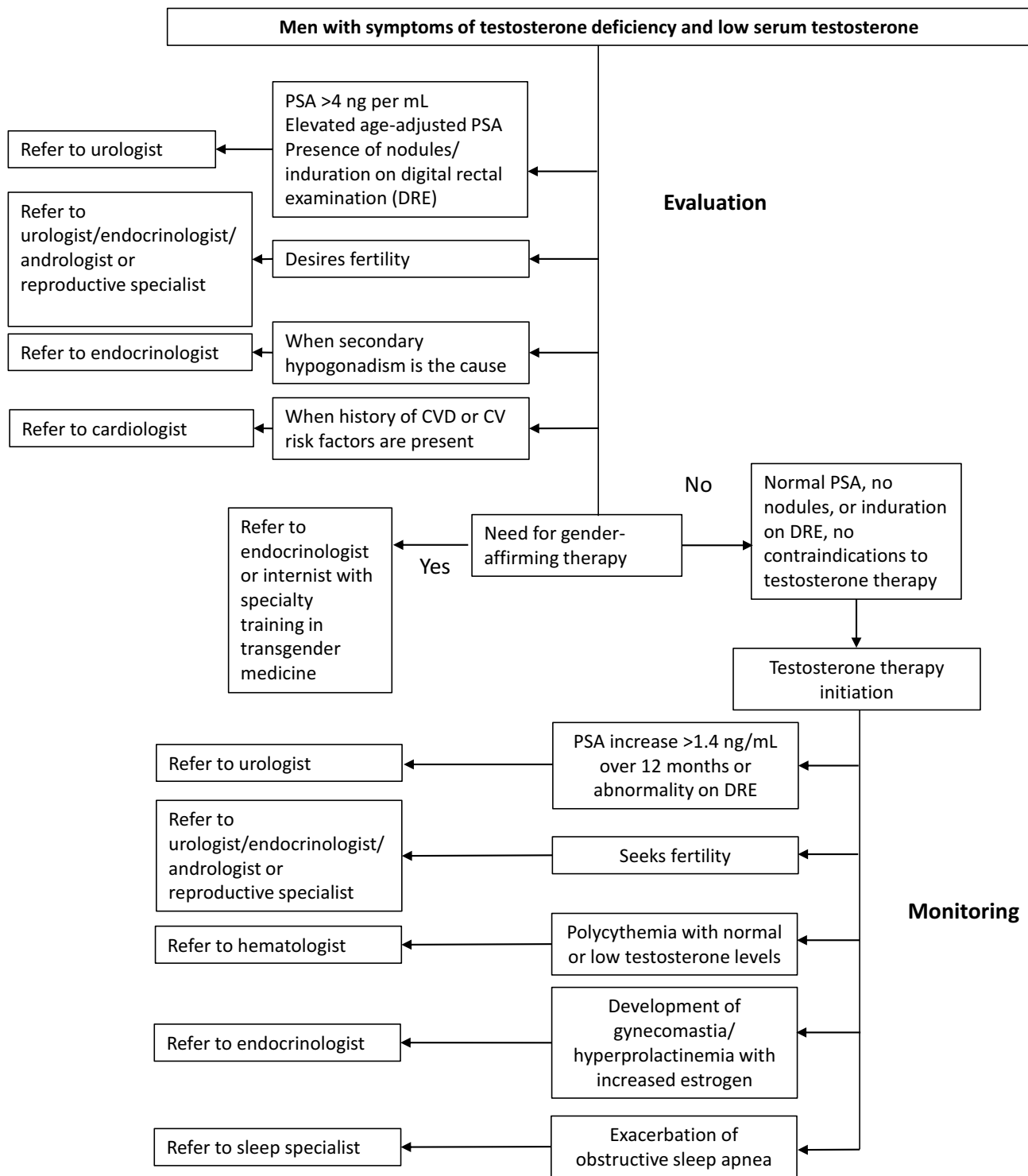
Figure 2 Indications for referral of potential candidates for testosterone therapy.
Abbreviations: CV, cardiovascular; CVD, cardiovascular disease; DRE, digital rectal examination; PSA, prostate-specific antigen.

refilling their prescriptions within 3 months.[33] Improvement in symptoms may be a notable contributor to therapy adherence and patient satisfaction; therefore, the choice of testosterone therapy should be based on more than initial patient preference for a certain route of administration or dosing frequency.[33,34]

Evaluation of available treatment options should be conducted on the basis of the AE profiles of each, including consideration of their associated risk of polycythemia, as administration of depot levels of exogenous testosterone can lead

Table 3 Summary of Testosterone Therapies

Route of Administration	Pharmacokinetics	Key Clinical Findings	
		Efficacy	**Safety**
Buccal tablets[3,25,76,77]	• Short-acting • After application, testosterone is absorbed directly into systemic circulation via the mucosa, bypassing first-pass metabolism[76] • Testosterone reaches maximal levels within the normal physiologic range in 10 to 12 hours, with return to baseline in 2 to 4 hours[76]	Normal serum testosterone range in 87% to 97% of patients	• Generally well tolerated • Most common AEs unique to buccal tablets are gum and mouth irritation and taste perversion; 4.3% of patients discontinued due to these side effects[25]
IM injections[30,35]	• Long-acting (enanthate, cypionate, or undecanoate)	Average concentrations of testosterone and its metabolites (DHT and E_2) in the eugonadal range	• Generally well tolerated • May be associated with higher risk of polycythemia
Transdermal gels[23,24,78–80]	• Steady-state • Patients with high BMI may require higher doses of transdermal testosterone formulations[13]	Normal serum testosterone in 75% to 86% of patients	• Generally well tolerated • Carries risk of transference • Has low risk of supraphysiological testosterone levels
Intranasal gel[28]	• Short-acting	Normal serum testosterone in approximately 90% of patients	• Generally well tolerated • In the Phase 3 trial, the highest number of drug-related treatment-emergent AEs (22.2%) belonged to the respiratory, thoracic, and mediastinal categories
SC injections[3,26,81]	• Long-acting (enanthate) • Administered weekly by SC injection or prefilled autoinjector[26] • No patients had a maximum testosterone level >1800 ng/dL in the phase 3 trial[26]	Normal serum testosterone range in 92% of patients	• Generally well tolerated • Small increases in systolic blood pressure (3.4 mm Hg) observed • Labeling includes a boxed warning for an increase in blood pressure that raises the risk of CV events[41]
Oral capsules[3,29,40,82–84]	• Short-acting • Dosed twice daily with food[29,40] • Some studies suggest absorption varies with lipid content of meals[40] • Peak levels roughly 4 hours after initial administration[3]	Normal serum testosterone range in 87% of patients	• Generally well tolerated • Small increases in ambulatory blood pressure occurred following 120 days of therapy • Labeling includes a boxed warning for an increase in blood pressure that raises the risk of CV events[40]
Subdermal pellets[3,37,85–87]	• Long-acting • Recommended starting dosage is 150 to 450 mg, but clinical experience has demonstrated that more pellets are needed to achieve satisfactory results[3,87]	Normal testosterone and LH levels and improvement of symptoms	• Generally well tolerated • Most common AEs unique to testosterone pellets are extrusion (8.5%), bleeding (2.3%), and infection (0.6%)[86]

Abbreviations: AE, adverse event; BMI, body mass index; CV, cardiovascular; E_2, estradiol; IM, intramuscular; LH, luteinizing hormone; SC subcutaneous.

to elevations in hemoglobin and hematocrit.[1,35] For example, IM injections of testosterone that produce supraphysiological testosterone levels may be more likely to lead to serious AEs, including polycythemia, or such AEs as injection-site pain.[1,36] Additionally, longer-acting testosterone formulations may be more likely to suppress HPG axis function and fertility.[37]

The appropriateness and selection of treatment modalities also may be driven by existing individual patient characteristics, such as age, or comorbidities that place certain patients at higher risk for conditions identified in

boxed warnings for some testosterone formulations.[38–41] Notably, boxed warnings regarding the risk for pulmonary oil microembolism and anaphylaxis appear on the label of IM testosterone formulations, including long-acting testosterone undecanoate; SC injections and oral capsule formulations also carry boxed warnings for the risk of increases in blood pressure.[39–41] In addition, the risk of transference with topical gels must be considered, particularly in men with children.[38] IM or SC injections should be avoided in patients unable or unwilling to self-inject, while buccal tablets, oral capsules, or intranasal gel may be less than ideal for patients who prefer weekly, bimonthly, or monthly dosing.[3]

Monitoring Testosterone Therapy

Given the potential risks associated with testosterone therapy and the possibility that patients' clinical needs and therapeutic goals may change over time, treatment requires ongoing and individualized monitoring, including hematologic assessments; prostate cancer screening; screening for potential dermatologic AEs, including hair loss and acne; and monitoring for testicular atrophy and gynecomastia.[13,21]

All clinical practice guidelines advise clinicians to measure total testosterone levels at appropriate intervals after initiating therapy to ensure that patients have responded to treatment.[1,6] There is consensus among the AUA, EAU, Endocrine Society, and ISSM guidelines that the recommended timing of the interval depends on the formulation.[6] At initial dosing, testosterone concentrations should be evaluated 2 to 8 hours following transdermal gel application and after 1 week to ensure that serum concentrations are in the mid-to-normal range. For buccal formulations, concentrations should be assessed immediately before or after application. For pellets, concentrations should be assessed at the end of the dosing interval and adjusted to achieve serum testosterone concentrations in the mid-to-normal range. Testosterone concentrations following administration of oral testosterone undecanoate should be monitored 3 to 5 hours after ingestion with a fat-containing meal, while serum concentrations of testosterone should be monitored at the end of the dosing interval just prior to the next injection for IM testosterone undecanoate.[13] For monitoring once appropriate levels have been established, testosterone levels in patients who initiate gel, patch, or intranasal formulations should be assessed 2 to 4 weeks after initiation; for short-acting IM or SC formulations, assessment should be made after at least 3 to 4 cycles; and for long-acting IM formulations, between the first two 10-week injections.[1,6] Testosterone levels in patients administered long-acting SC pellets should be evaluated at 2 intervals: first, at 2 to 4 weeks after initiation, followed by a second evaluation at 10 to 12 weeks.[1,6] All guidelines recommend close monitoring of hemoglobin and hematocrit during treatment.[1,13] PSA also should be monitored in men who undergo prostate cancer screening.[1] Signs and symptoms of testosterone deficiency should be assessed at every follow-up visit, and if there is no symptomatic improvement, testosterone therapy should be discontinued.[1,6]

Individualizing Therapy in Specific Populations

The potential benefits and risks of testosterone therapy vary based on the medical history of each patient, and when considering the diversity of patients seen in the primary care setting, PCPs should understand key considerations for the management of testosterone deficiency in specific patient populations. Among the specific populations are younger patients and others who wish to maintain fertility, patients with a history of CV disease, those with concerns about polycythemia, those aged 65 years and older, those with obesity or type 2 diabetes, those with a high risk of prostate cancer, those with OSA, and transgender and gender-diverse patients.

Patients Seeking to Maintain Fertility

It is essential to weigh the potential benefits of testosterone therapy against the tendency of exogenous testosterone to suppress HPG axis function, spermatogenesis, and fertility.[37,42–44] While most healthy men will recover sperm production after discontinuing exogenous testosterone if they have normal testosterone levels, we found no definitive studies that documented the recovery of spermatogenesis in either testosterone-deficient or infertile men who have used testosterone therapy.[1,45,46] Consequently, the unknown long-term impact of testosterone therapy on spermatogenesis should be discussed with patients who seek to maintain fertility. These patients may also benefit from referral to a urologist or endocrinologist/andrologist (Figure 2).[1,42]

For patients with testosterone deficiency who are interested in maintaining fertility, all guidelines advise that testosterone should not be initiated because of its effect on impairment of spermatogenesis.[6] AUA guidelines recommend the use of either selective estrogen receptor modulators or aromatase inhibitors, and acknowledge that testosterone deficiency is an off-label indication for the use of these agents.[1,6] While EAU guidelines also mention aromatase inhibitors as a possible treatment in the context of male infertility or secondary hypogonadism, they note that more evidence is needed.[14] The Endocrine Society does not provide specific treatment recommendations for patients wishing to maintain fertility.[13,14,39] Individualized use of other nonsuppressive treatment plans can also be considered for cases of secondary hypogonadism, and may include simultaneous use of clomiphene citrate or human chorionic gonadotropin (hCG) or treatment with a shorter-acting testosterone formulation that is less likely to blunt the HPG axis.[42,43] Also, in cases of secondary hypogonadism, FSH should be added to hCG as a standard therapy.[6] Although clomiphene citrate is generally well tolerated, it has been associated with such AEs as gynecomastia, weight gain, fatigue, and reduced libido.[47] Clinical trials have demonstrated that shorter-acting testosterone formulations (ie, those dosed more than once per day, such as intranasal gel) may be more likely to preserve HPG axis function, maintain LH and FSH levels in the normal range, and thus preserve spermatogenesis.[37,44]

Patients with a History of Cardiovascular Disease

Evidence consistently shows that testosterone deficiency is associated with an increased incidence of major CV events, including myocardial infarction, stroke, and CV mortality, and an increased prevalence of CV risk factors.[1] The relationship between testosterone therapy and CV disease, however, remains a significant source of controversy.[6] The topic has undergone extensive review,[6,48–51] and the totality of evidence suggests that the use of testosterone therapy at appropriate doses and with appropriate monitoring is likely to be safe for men with CV disease and may even reduce CV events in men with testosterone deficiency.[48] For example, data from a recent prospective controlled registry study suggested that long-term use of testosterone therapy in hypogonadal men was associated with a reduced risk of CV events and mortality.[52]

Patients should be informed that it cannot yet be stated definitively whether testosterone therapy increases or decreases the risk of CV events (ie, myocardial infarction, stroke, CV-related death, and all-cause mortality) and that there is no definitive evidence linking testosterone therapy to a higher incidence of acute CV disease in patients with a history of CV events.[1] AUA guidelines, however, recommend against starting testosterone therapy in men who have had a major adverse CV event (MACE), including myocardial infarction or stroke, within the past 3 to 6 months. This recommendation was adopted in part because the studies cited in the guidelines excluded men with CV events during this time frame.[1] The Endocrine Society has similarly advised against initiating testosterone therapy in men with a history of stroke or myocardial infarction in the previous 6 months. The EAU does not specify a time frame, but notes that acute CV events are a relative contraindication.[6,14]

Results from the first adequately powered randomized controlled trial evaluating the risk of MACE in hypogonadal men (TRAVERSE) are expected in late 2022, and it is hoped that they will inform clinical practice.[53]

Patients with Concerns About Polycythemia

Prior to offering testosterone therapy, clinicians should measure hemoglobin and hematocrit and inform patients about the increased risk of polycythemia, typically defined as hematocrit higher than 52%.[1] Before beginning testosterone therapy, all patients should undergo a baseline assessment of hemoglobin and hematocrit. If baseline hematocrit is greater than 50%, testosterone therapy should be withheld until the cause of the elevation is identified. A hematocrit of 54% or greater during testosterone therapy warrants intervention with a dose reduction and assessment of SHBG and free testosterone levels.[1] This cutoff is generally consistent across treatment guidelines.[39] Men with low or normal total and free testosterone and an elevated hematocrit should be referred to a hematologist (Figure 2) and possibly offered a therapeutic phlebotomy.

While it cannot be definitively determined that the incidence of polycythemia may occur with one particular modality of testosterone therapy compared with another, clinical trials have indicated that injectable testosterone and pellets are associated with greater increases in hemoglobin and hematocrit than shorter-acting formulations.[1,35] With regard to

injections, these increases in hemoglobin and hematocrit are thought to result from the elevated supraphysiological levels of testosterone that may occur in the early days after injection.[1,35]

According to the AUA, it is unclear whether the risk of polycythemia is greater among men with comorbidities that may lead to a predisposition for hypoxia, such as OSA or chronic obstructive pulmonary disease.[1] However, the development of polycythemia while receiving testosterone therapy is associated with an increased risk of MACE and venous thromboembolism.[54] In addition, a higher incidence of thromboembolic events has been observed in patients with Klinefelter syndrome who are receiving testosterone therapy compared with untreated groups.[55]

Patients Aged 65 Years and Older

Men in their fourth decade of life begin to undergo declines in total serum testosterone levels, and this continues at a rate of approximately 1.6% per year and may result in a condition known as age-related low testosterone.[31] This condition can be associated with clinical symptoms of androgen deficiency, such as sexual dysfunction. For older patients without well-established medical conditions known to cause hypogonadism, testosterone therapy may provide improvements in sexual function and quality of life but appears to offer limited benefit for other common symptoms of aging.[8]

The American College of Physicians (ACP) has provided several recommendations for managing age-related low testosterone.[31] Older men with age-related low testosterone and symptoms of sexual dysfunction seeking treatment should be counseled about the potential benefits and risks of testosterone therapy. For patients who choose to initiate therapy, symptoms should be reevaluated within 6 months and periodically thereafter. The ACP also suggests that clinicians consider prescribing IM testosterone rather than transdermal formulations because of their similar efficacy at a lower cost.[31] However, EAU guidelines suggest that short-acting formulations may be better for adjusting the dosage should AEs occur.[14,56] Clinicians should not initiate testosterone in men with age-related low testosterone to improve energy, vitality, physical function, or cognition.

Patients with Obesity or Type 2 Diabetes

Obesity (body mass index [BMI] ≥ 30 kg/m^2), increased waist circumference (>40 inches), and type 2 diabetes are often associated with low testosterone levels.[1,57] Men with any of these risk factors should be evaluated for testosterone deficiency and have their testosterone levels checked. Low testosterone levels are almost 5 times more common in obese men than in nonobese men and are nearly twice as common in men with diabetes than in those without diabetes.[1,58] Patients with obesity and/or type 2 diabetes and testosterone deficiency should be counseled regarding lifestyle modification because weight reduction, lifestyle changes, and the treatment of comorbidities can increase testosterone levels and may reduce the risk for CV disease.[1,21]

In some but not all studies, testosterone therapy has been associated with a reduction in BMI and waist size, improved glycemic control, and an improved lipid profile in hypogonadal men.[21] Preliminary evidence also suggests that long-term testosterone therapy may slow prediabetes progression to diabetes in men with hypogonadism and improve glycemic and lipid control.[59,60] It may also enhance the beneficial effects of supervised changes in diet and exercise on glycemic control and insulin sensitivity in hypogonadal men with type 2 diabetes.[61] These findings require confirmation in additional controlled trials.

In at-risk populations, including patients with obesity and type 2 diabetes, PCPs should exercise caution when prescribing IM formulations of testosterone because of the increased risk of erythrocytosis.[21] Additionally, preliminary evidence from post hoc analyses from 2 clinical trials[28,62] that analyzed the effects of nasal testosterone gel in patients with hypogonadism and BMI >35 kg/m^2 has suggested that total testosterone, free testosterone, dihydrotestosterone, and estradiol level increases were similar to those in nonobese men.[63] Patients with a high BMI may require higher doses of transdermal testosterone formulations because obesity appears to affect the pharmacokinetics of these preparations.[21] Because adipose tissue in obese individuals contains aromatase, which converts testosterone into estrogen, aromatase inhibitors have been used on an off-label basis to increase testosterone levels in obese patients.[64] Aromatase inhibitors may also be beneficial for spermatogenesis in patients with serum testosterone-to-estrogen ratios of less than 10.[64,65] However, the use of aromatase inhibitors in men can be associated with negative effects, including decreased bone density and reductions in libido.[64,66]

Patients with a History of or at Risk for Prostate Cancer

The relationship between testosterone and prostate cancer is complex. While most studies suggest no relationship between testosterone supplementation and the incidence and progression of prostate cancer, heterogeneous findings have been reported in the literature.[67] The AUA recommends that clinicians inform patients of the absence of evidence linking the use of testosterone therapy to the development of prostate cancer.[1]

Currently, clinical guidelines advise against initiating testosterone therapy in patients with untreated prostate cancer. This may include an unevaluated palpable prostate nodule, induration, or an elevated age-adjusted PSA level.[13] Although a history of prostate cancer is listed as a contraindication in the product labeling of all testosterone formulations, AUA guidelines indicate that the choice to initiate testosterone therapy in patients with such a history should be a negotiated decision that depends on perceptions of the potential benefit of treatment.[1] Essentially, the AUA states that there is inadequate evidence to quantify the risk−benefit ratio of testosterone therapy in this population.

In men aged 40 years and older without a history of prostate cancer, PSA levels should be evaluated prior to initiating testosterone therapy to exclude a diagnosis of prostate cancer.[1] After the initial screening for PSA level, American Cancer Society guidelines should be used to monitor patients. The Endocrine Society guideline on testosterone therapy in men with hypogonadism further recommends engaging the patient in shared decision-making regarding monitoring for prostate cancer.[13]

In a recent study, long-term testosterone therapy in men with functional hypogonadism was found to improve urinary function with no associated increase in prostate cancer risk.[68] In addition, when prostate cancer was observed, it was always reported within 18 months of testosterone therapy initiation, suggesting that testosterone therapy may unveil prostate cancer that was present but previously undetectable.[68] Overall, additional research is needed to further clarify the complex relationship between testosterone and prostate health.

Patients with Obstructive Sleep Apnea

OSA has been associated with decreased testosterone production along with obesity and aging.[69] As approximately half of the men with testosterone deficiency screen positive for OSA, and men receiving testosterone therapy who experience polycythemia have high rates of OSA, patients should be treated for this disorder if needed prior to commencement of testosterone therapy.[70,71] Because high-dose testosterone therapy can exacerbate OSA in some patients, it is important to ask patients about potential OSA symptoms before initiation of therapy and at follow-up visits.[69] Patients with severe untreated OSA should be stabilized prior to receiving testosterone therapy.

Transgender and Gender-Diverse Patients

Gender-affirming hormone therapy for transgender men typically includes exogenous testosterone administration, with the goal of inducing the development of male secondary sex characteristics and the suppression or regression of female secondary sex characteristics.[72] According to guidelines from the Endocrine Society, testosterone doses should be titrated to serum levels within the typical range of adult cisgender men, generally 320 to 1000 ng/dL.[73] At this time, few data exist to guide the management of testosterone therapy in transgender men, with the majority of protocols derived from experience with androgen therapy in hypogonadal cisgender men, despite the differences in the goals of treatment in the 2 populations.[72,74]

Ideally, there should be a multidisciplinary approach to patient care for transgender patients that may involve endocrinologists or referral-based surgical services, or both.[73,75] Because such multidisciplinary care is not universally available, PCPs may evaluate gender dysphoria and manage applicable hormone therapy or monitor well-being and provide primary care and referrals, depending on their comfort level and the availability of support from local specialists.[75] It would be optimal for this to be conducted in concert with specialized clinics, because many of the expected physiological changes will be permanent.

Conclusion

Testosterone therapy is the standard of care for the management of patients with symptomatic hypogonadism and is often prescribed by PCPs. Given the diversity of patients with testosterone deficiency who may present to primary care,

clinicians should undertake an individualized approach to care that is consistent with clinical guidelines and also considers each patient's needs, preferences, goals, comorbidities, history, and risk factors. Patients' specific clinical needs should inform the choice of testosterone therapy formulation, as the treatment landscape includes a range of options with different routes of administration, dosing frequencies, and pharmacokinetic and safety profiles. Individualized care is critical to the appropriate diagnosis, evaluation, treatment, monitoring, and follow-up of patients with testosterone deficiency.

Abbreviations

ACP, American College of Physicians; AE, adverse event; AUA, American Urological Association; BMI, body mass index; CDC, Centers for Disease Control and Prevention; CT, computed tomography; CV, cardiovascular; DRE, digital rectal examination; DVT, deep vein thrombosis; E_2, estradiol; FDA, US Food and Drug Administration; FSH, follicle-stimulating hormone; FT, free testosterone; hCG, human chorionic gonadotropin; HPG, hypothalamic-pituitary-gonadal; IM, intramuscular; IU, international unit; LH, luteinizing hormone; MACE, major adverse CV event; MRI, magnetic resonance imaging; OSA, obstructive sleep apnea; PCP, primary care physician; PSA, prostate-specific antigen; SC, subcutaneous; SERM, selective estrogen receptor modulator; SHBG, sex hormone–binding globulin; TT, total testosterone; VTE, venous thromboembolism.

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Disclosure

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