Practice guideline for pharmacists: The management of late-onset hypogonadism

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Introduction

Late-onset hypogonadism (LOH), also known as testosterone deficiency (TD) syndrome, is a medical condition that affects middle-aged and older men due to a decline in testosterone levels as they age.[1] The European Male Aging Study reported a 0.4% annual decline in total testosterone and a 1.3% annual decline in free testosterone in its cohort of men aged 40 to 79 years.[2]

LOH is characterized by the presence of indicative signs and symptoms and a decrease in serum testosterone levels either due to testicular defects or defects of the hypothalamic-pituitary-gonadal (HPG) axis. A large, long-term study conducted in the United Kingdom and the United States showed that up to 40% of men were obtaining testosterone without documented TD.[3] Other studies have shown that there is a high prevalence of underdiagnosis of TD.[4] Because of these discrepancies, it is important that practitioners be prudent in their diagnosis and management of LOH.

Pharmacist's role in LOH management

Pharmacists are easily accessible health care professionals who are uniquely positioned to manage men with LOH by screening for it, addressing risk factors, initiating and counselling on lab testing if it is within the scope of practice and collaborating with primary care physicians (PCPs) to manage treatment. A prospective cohort study found that pharmacist management of testosterone therapy (TT) compared with PCP management led to the following[5]:

- Significantly improved monitoring of baseline parameters (54% vs 20%, $p = 0.0006$)
- More documented symptom improvement (96% vs 26%, $p < 0.001$)
- More frequent monitoring of complete blood counts (100% vs 83%, $p = 0.04$) and testosterone levels (96% vs 61%, $p = 0.003$)

This document was created to serve as a guide for Canadian pharmacists to play an important role in managing LOH.

Methods

A literature search was performed by 2 researchers (M.A., A.M.) in May 2020 and updated in August 2020 (Appendix 1, available in the online version of the article). MeSH terms were selected by the authors with the aid of a health sciences librarian at the University of Alberta. Search terms included "hypogonadism," "late onset hypogonadism," "testosterone deficiency," "pharmacist," "controversies or perspectives" and "guidelines." Clinical practice guidelines (CPGs) for LOH were obtained from DynaMed and Clinical Key. Literature searches were conducted in MEDLINE, EMBASE and Scopus to find both CPG and publications relevant to the treatment of LOH in a pharmacy context. Each database was searched independently using the same terms, and the results were limited to the English language.

M.A. and A.M. manually reviewed search results concurrently to identify CPG and reviews. Reviews were categorized as high or low priority. High priority was assigned to literature that highlighted the discrepancies between CPGs or addressed pharmacist management of LOH. Low priority was assigned to literature that focused only on the assessment or management of LOH.

The Appraisal of Guidelines for Research and Evaluation (AGREE) II tool was used to appraise the 12 CPGs identified.[6] Scoring was done independently, and scores were calculated as per the tools' recommendation. The guidelines were ranked using the scaled domain scores. The 5 guidelines addressing

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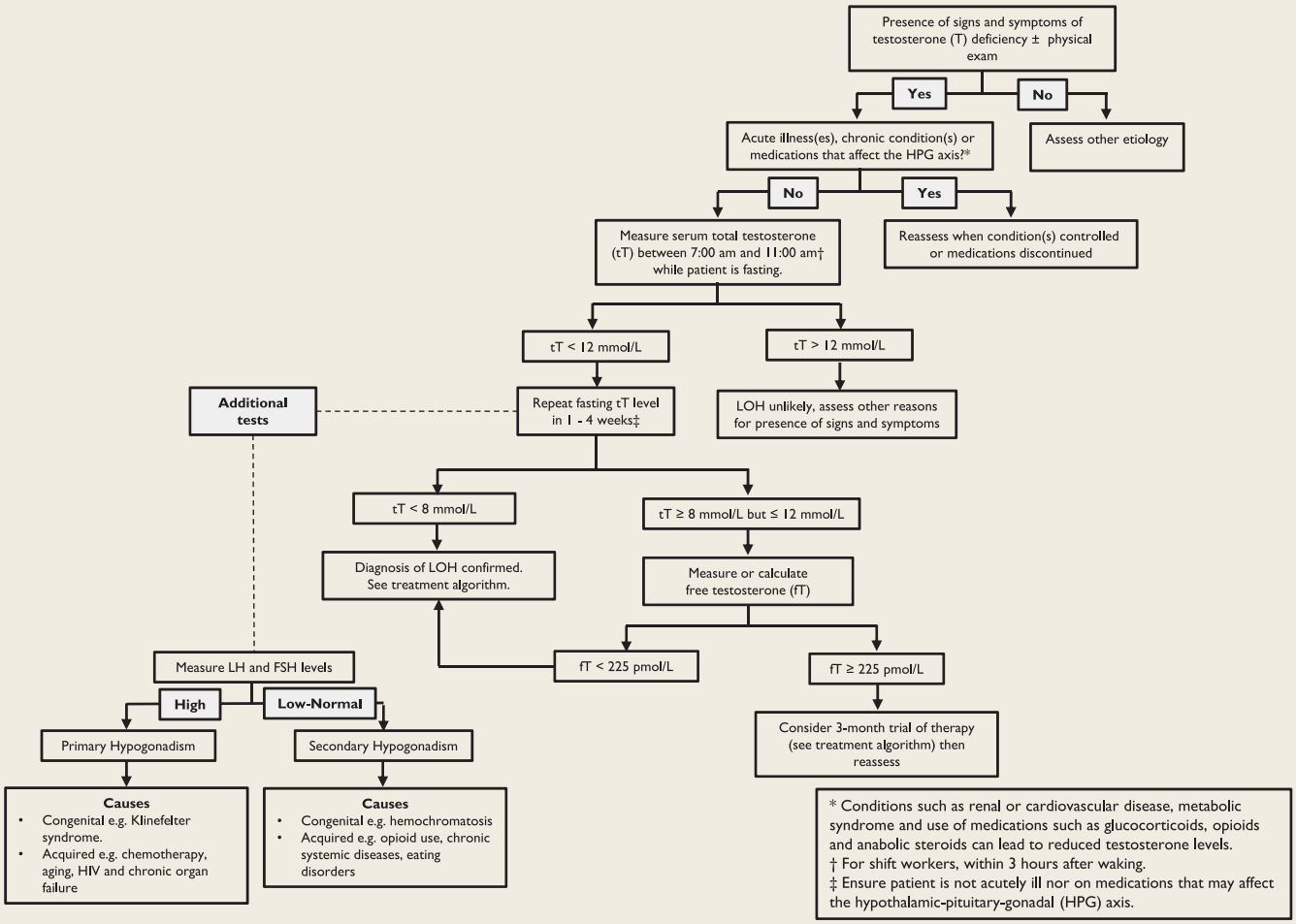
FIGURE 1 Pharmacist assessment of late-onset hypogonadism[1-3,7-13]



both diagnosis and management of LOH that had the highest scaled domain scores in multiple sections were prioritized to inform the outline, algorithm and text of this guide. Selected reviews were used to augment this guide.

Assessment and diagnosis

Diagnosis and screening

Figure 1 illustrates the approach to diagnosing LOH that requires the presence of signs, symptoms (Table 1) and positive lab tests. Signs and symptoms of LOH are subtle, nonspecific and influenced by age, concomitant medications and chronic illnesses.[2,3,7] A physical examination can help identify more specific signs that aid in the diagnosis of LOH. Note that low testosterone level alone without the presence of supporting signs and symptoms is not an indication for TT.[2,14]

Regardless of age, physical and biochemical workups should be done only in symptomatic patients or in those at risk of hypogonadism (Table 2).[1,4,7] Questionnaires are not validated, nonspecific and should not be used in the diagnosis of LOH.[2,3,8] Routine screening using questionnaires or random total testosterone levels is not recommended.[8,9]

Classification of male hypogonadism

Distinguishing between primary and secondary hypogonadism has therapeutic implications and will aid in selecting treatment (Figure 1).[2,3] In primary hypogonadism, TT is the only option, and this will impair fertility.[2,7] Patients with secondary hypogonadism may retain fertility with human chorionic gonadotropin (hCG); however, TT may also be used if maintenance of fertility is not desired.[2,3,8]

Causes of male hypogonadism

Organic hypogonadism is any proven pathology affecting the HPG axis that results in permanent hypothalamic, pituitary or testicular dysfunction. This should be treated with conventional medications (hCG or TT).[2,7]

Functional hypogonadism is the absence of alterations to the HPG axis and is caused by conditions suppressing gonadotropin and testosterone levels. This is potentially reversible

TABLE 1 Signs and symptoms of late-onset hypogonadism[1-3,8-11]

More-specific symptoms*	Less-specific symptoms	Signs
• Decreased libido • Erectile dysfunction • Decreased frequency of morning erections	• Decreased energy • Decreased motivation • Changes in mood (depression, irritability, anger) • Impaired memory • Inability to concentrate • Sleep disturbances • Hot flushes	• Decreased body/facial hair • Central obesity • Decreased testicular volume • Decreased muscle mass • Increased body fat • Gynecomastia • Osteoporosis

*The European Male Aging Study showed that the triad of symptoms under this category are typically associated with decreased serum testosterone levels.[2,15]

TABLE 2 Risk factors for low testosterone[1,2,4,7,8,14,15]

Medical conditions		Medications	
Endocrine	• Diabetes • Metabolic syndrome • Obesity	Central nervous system	• Antipsychotics • Cannabis • Alcohol
Pulmonary	• Chronic obstructive pulmonary disease	Anti-infectives	• Antiretroviral therapy • Ketoconazole
Cardiovascular	• Hypertension • Heart failure • Coronary artery disease • Atrial fibrillation	Corticosteroid	• Glucocorticoids
Renal	• End-stage renal disease	Androgen	• Anabolic androgenic steroids
Central nervous system	• Hyperprolactinemia • Pituitary disease/dysfunction	Analgesics	• Opioids
Genital	• Testicular disease/dysfunction	Oncology	• Chemotherapy + radiation
Hematologic	• Hemochromatosis	Diuretic	• Spironolactone
Inflammatory	• Rheumatoid arthritis		
Others	• Acute illness • Eating disorders • Human immunodeficiency virus • Aging		

and should be initially managed by improving associated comorbidities and by nonpharmacologic management.[2,7]

Medical history and risk factors

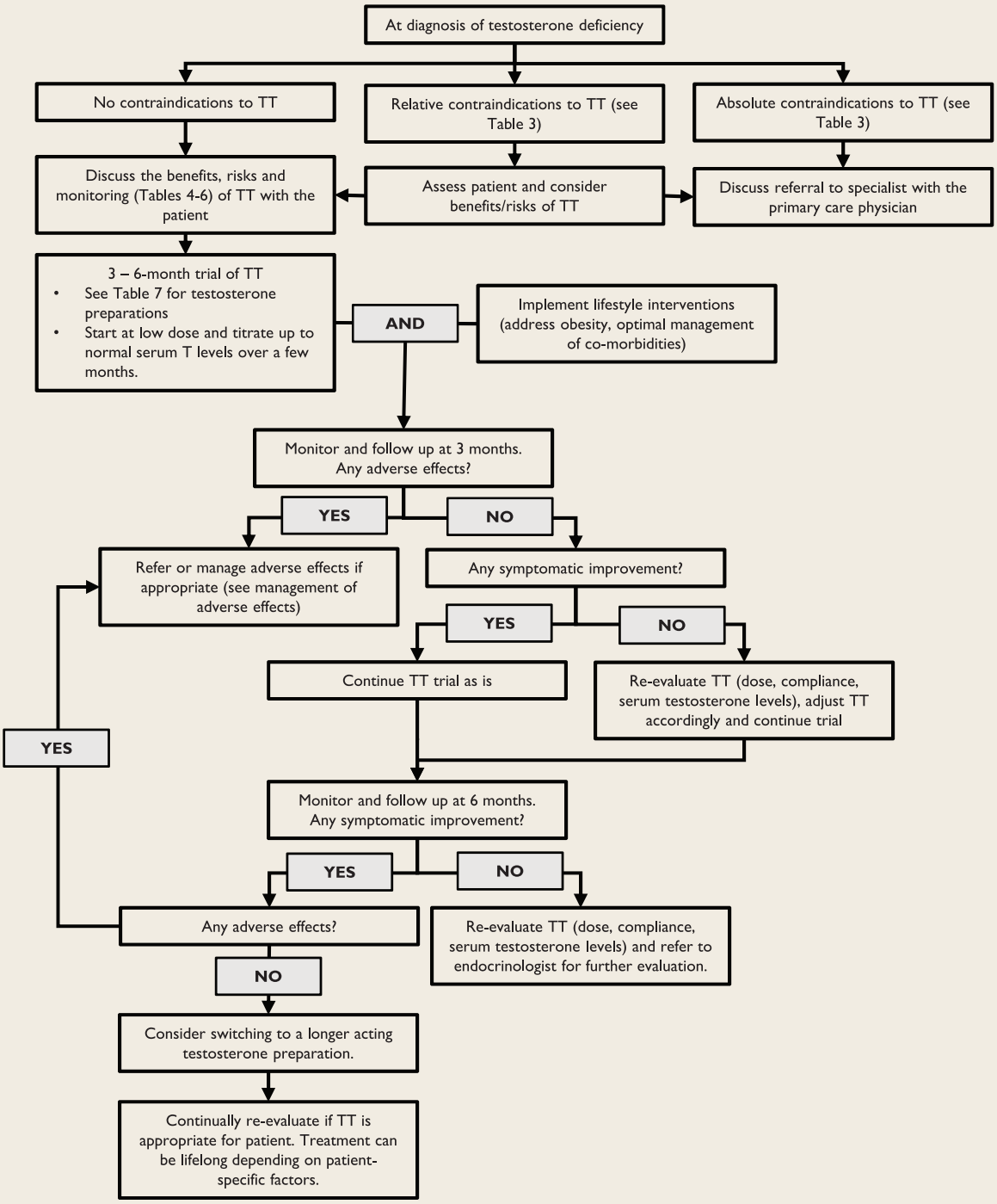
Table 2 outlines medical conditions and medications that predispose men to having low testosterone levels. The pharmacist should elicit information about smoking status, alcohol use, medical history (erectile dysfunction [ED], libido, fertility, genital trauma, pelvic surgery) and medication use (prescription, recreational, natural health products).[7,10,11,16]

Discontinuation of medications such as opioids and androgenic anabolic steroids can normalize testosterone levels within 1 month or several months to years, respectively.[7,9] The pharmacist can consider TT if medications cannot be discontinued and can discuss a specialist consult with the PCP.[7,10]

Physical examination

Physical signs may appear with the presence of low testosterone and should be investigated. Pharmacists should ask if the patient has noticed a decrease in body hair or hair growth and a difference in the distribution of body hair.[1,4,8] Height, weight, body mass index and waist circumference should be recorded.[1,2,4,8] A referral to the PCP is required to check for

FIGURE 2 Late-onset hypogonadism treatment approach[1-4,7-11,14,16-18]



the presence of acanthosis nigricans (denoting insulin resistance), gynecomastia, a decrease in testicular size and volume and a digital rectal exam (DRE) to exclude prostate abnormalities.[1,2,4,8,17]

Laboratory testing

Lab testing is essential for the diagnosis of LOH. It is recommended that testosterone levels be measured with consideration for circadian rhythm and health status (Figure 1).[1,3,7,10,11] Confirmation of low-testosterone level readings is necessary, as 30% of men have normal T concentrations on repeat measurement (Figure 1).[1,7,8,12,13]

If the total testosterone (tT) level is between 8 and 12 mmol/L inclusive, the measurement of free testosterone (fT) may be performed.[1,2,9] Unlike tT, no validated thresholds for fT are available, but some data indicate that fT less than 225

TABLE 3 Contraindications of testosterone therapy[1-4,7-11,14-17]

	Absolute	Relative
Respiratory	• Untreated severe obstructive sleep apnea	
Cardiovascular	• Severe chronic heart failure (New York Heart Association Class IV) • Major cardiovascular event, myocardial infarction or stroke within the past 6 months • Thrombophilia • Severe hypertension	• Uncontrolled or poorly controlled cardiovascular disease • Preexisting cardiovascular disease, venous thromboembolism or chronic heart failure
Genitourinary	• Severe lower urinary tract symptoms due to benign prostatic hyperplasia (American Urological Association and International Prostate Symptom score >19) • Active desire to have children	
Hepatic	• Severe hepatic dysfunction	
Renal	• Severe renal failure	
Hematologic	• Hematocrit >54% • Polycythemia	• Baseline hematocrit > 48%-54%
Oncologic	• Locally advanced or metastatic prostate cancer • High risk of recurrent prostate cancer • History of male breast cancer • Unevaluated prostate-specific antigen >4 ng/mL • Unevaluated prostate-specific antigen >3 ng/mL in men at high risk of prostate cancer (e.g., Black persons, first-degree relatives with prostate cancer) • Unevaluated prostate nodule or induration • Untreated prolactinoma	• Men with radical prostatectomy-treated low-grade prostate cancer (Gleason score <7) who are in remission with undetectable prostate-specific antigen for at least 2 years
Other		• Men subjected to occupational drug testing

pmol/L is associated with hypogonadal symptoms.[2] It is preferred that fT be measured, but fT can also be calculated if albumin and sex hormone–binding globulin are measured in conjunction with tT.[9,17]

Other tests (e.g., prolactin, estradiol) may be performed to assess patients with complicating factors, and a referral to an endocrinologist or other specialist may be discussed with the PCP.[2,8]

Treatment

TD treatment involves a combination of lifestyle interventions and TT if there are no contraindications (Figure 2; Table 3). Relative contraindications require further assessment before initiating TT (Table 3).[1,3] Treatment of LOH can be lifelong.[17] The goal for TT is to provide improvement of patient-specific symptoms[1-3,7,11-14] and to restore testosterone levels to the mid-normal range for healthy young men (14–17.5 nmol/L).[2,3,7]

Before starting TT, discuss the benefits (Table 4), risks (Table 5) and monitoring (Table 6) with the patient.[1,2,7,19] If contraindications to TT arise at any point, TT should be discontinued.[3]

Pharmacists should always be aware of any other medications the patient is taking, any possible drug interactions and how they should be managed. Notable interactions occur with insulin, anticoagulants and corticosteroids.[1]

TT can be initiated with any regimen based on patient preference, pharmacokinetic considerations, treatment burden, adverse effects and cost.[2,4] The American Urological Association (AUA) recommends commercially manufactured products over compounded products.[8,12] Patients were found to prefer a topical gel over an injection or patch because the former is more convenient, easy to use and nonstaining.[19] Generally, it is recommended that patients use short-acting preparations when trialing TT so that treatment can be adjusted or stopped if adverse effects arise.[2,4,14] Once clinical improvement is seen, TT can be switched to a longer-acting preparation.[9]

Testosterone preparations currently available in Canada are outlined in Table 7. It is important that Canadian pharmacists recognize other T preparations or alternatives outside of the Canadian market[20-23] (Appendix 2, available in the

TABLE 4 Benefits of testosterone therapy[1-4,7-11,14-17]

Dermatologic	• Increase in hair growth (beard, pubic, axillary)
CNS	• Improvement in fatigue (3-6 months) • Small improvement in depressive mood (1 month, maximum benefit may take longer to show)
Cardiovascular	• Increase in fat-free mass and lean mass (6-12 months) • Decrease in waist circumference • Decrease in total cholesterol and low-density lipoprotein (1 month) • Improvement in heart failure and exercise capacity • Improvement in electrocardiographic ST-segment depression due to exercise
Genitourinary	• Improvement in libido (1 month) • Improvement in erectile function (6-12 months)
Musculoskeletal	• Improvement in bone mineral density (6 months) • Decreased fracture risk • Increased muscle strength • Slowed progression of mobility limitations
Hematologic	• Increased hematocrit in anemic men (3-6 months)
Endocrine	• Improvement in testosterone levels • Improvement in insulin sensitivity (few days) and glycemic control (3-12 months)

TABLE 5 General adverse effects of testosterone therapy[1-4,7-11,14-17]

	Common	Uncommon
Dermatologic	• Acne and oily skin	• Male pattern baldness (can be familial)
Central Nervous System	• Aggressive behaviour	• Fluctuations in mood, libido or hot flushes; occurs in stop-start treatment or excessive fluctuations in serum testosterone levels
Respiratory		• Induction or worsening of obstructive sleep apnea
Cardiovascular	• Slight decrease in high-density lipoprotein • Increased risk of thromboembolic cardiovascular events • Fluid retention and edema	• Hypertension
Genitourinary	• Reduce sperm production and fertility (after 6-12 months of testosterone therapy) • Marginal increase in prostate volume and prostate-specific antigen levels • Breast tenderness	• Gynecomastia • Difficulty passing urine • Priapism
Musculoskeletal		• Muscle pain
Hematologic	• Hematocrit >54% • Polycythemia	
Oncologic	• Recurrence or rapid progression of prostate cancer (metastatic or high risk of recurrence) • Detection of subclinical prostate cancer	• Growth of breast cancer
Endocrine		• Weight gain

TABLE 6 General monitoring parameters[1-4,7-11,14,16,17]

	Baseline	3 months	6 months	12 months	Annually for duration of TT
Symptomatic Improvement		×	×	×	×
Adverse effects		×	×	×	×
Digital rectal exam	×		×		×
Bone mineral density*	×				×
Labs					
Testosterone†					
Prostate-specific antigen	×	×	×	×	×
Complete blood cell count	×	×	×	×	×
Lipid panel	×		×	×	×
HbA1c	×	×	×	×	×

*Bone mineral density can be monitored every 1 to 2 years.[4,9,10,14]
†Can evaluate testosterone levels sooner than 3 months to ensure physiological replacement and to allow dose titration depending on formulation used (see Table 7 and Appendix 2).[3,7,8,9] Evaluate steady-state testosterone levels if patient is using an injectable or transdermal preparation. Steady-state levels cannot be obtained with oral preparations because of their variable pharmacokinetics.[4,14]

online version of the article), as questions may arise on these formulations.

As exogenous testosterone inhibits spermatogenesis, aromatase inhibitors, hCG, selective estrogen receptor modulators or a combination thereof may be used in men interested in maintaining fertility (Appendix 2, available in the online version of the article).[8]

Monitoring and follow-up

General monitoring parameters

Monitoring parameters are outlined in Table 6. While most guidelines are in consensus regarding prostate monitoring (prostate-specific antigen [PSA], DRE), the Endocrine Society of Australia (ESA) and European Endocrine Society recommend that monitoring for prostate disease should be done for individuals with preexisting or at high risk of prostate disease. ESA provides the rationale that patients may be at higher risk of harms from prostate cancer treatment (e.g., ED, urinary incontinence, bowel dysfunction) due to increased surveillance and treatment of clinically insignificant prostate cancers.[7,10,11] It is recommended that the potential benefits and risks of monitoring for prostate cancer be discussed with the patient, that local prostate cancer guidelines should be taken into account and that shared decision making be used regarding the prostate monitoring plan.[7,8,9]

In this area, pharmacists can

- Counsel patients on what monitoring entails and when to follow up,
- Discuss with patients the risks and benefits of prostate monitoring,
- Counsel patients on the benefits and adverse effects of TT and when these will become evident and
- Know how to manage common adverse effects when they arise.

Management of adverse effects

Prostate adverse effects

An initial increase in PSA with TT is seen over the first 2 to 6 months and is greatest in men with severe hypogonadism. Therefore, the PSA levels after 6 months of TT should be used as the new baseline for monitoring.[4]

If pharmacists observe or are aware of any of the following, hold TT and discuss a specialist consultation with the PCP[16]:

- Increase in PSA levels >1.4 ng/mL within 12 months of initiating TT[1,7,9]
- Confirmed PSA >4 ng/mL at any time[1,7,10]
- In patients with a baseline PSA of >4, an increase of >0.75 ng/mL seen within any 18-month period of TT[3]
- Documented prostate abnormality[3,7,9]

Hematological adverse effects

A 5% to 10% increase in hematocrit is expected and depends on the patient's baseline values as well as the TT preparation used (e.g., intramuscular preparations are more likely to increase the hematocrit).[3] Smokers are also more likely to have elevated hematocrit.[10,11] An increase in hematocrit may be beneficial in

TABLE 7 Testosterone therapy preparations currently available in Canada[1-4,7-11,14-17,25-29]

Formulation and unit dosage	Administration	Starting or titration doses	Dosing range	Advantages	Disadvantages	PK parameters	Formulation-specific monitoring
				Oral			
Testosterone undecanoate (generics only, 40-mg capsules)	• Take with fatty food • Swallow capsule whole, do not crush or chew	40 mg bid to tid	40-240 mg bid to tid	• Oral convenience and flexible dose modification • Rarely causes a rise in T concentrations above the mid-range	• Frequent dosing • Absorption heavily reliant on food • Occasional GI and hepatotoxicity adverse effects • Variable clinical response	• Fatty food increase bioavailability to 7% • Difficult to obtain steady-state levels due to variable serum T levels	• After 2 weeks, measure serum T levels 3-5 hours after a dose is taken • Monitor LFTs
				Transdermal			
Testosterone patch (Androderm 12.5-mg patch [2.5 mg/day], 24.3-mg patch [5 mg/day])	• Nightly application to non–weight-bearing area (back, abdomen, upper arms or thighs) • Location needs to be changed daily to minimize skin irritation, and there should be an interval of 7 days between applications to same site • Can reduce incidence of skin irritation by pretreating the site with a topical corticosteroid cream or by applying cream to the site after the patch is removed	2.5-5 mg daily	2.5-10 mg daily	• Easy and convenient to use • Mimics T circadian rhythm	• Skin irritation • Occasional allergic contact dermatitis at application site • Daily administration • Visible patch • Limited dose flexibility	• Yields peak serum testosterone levels within 4 to 8 hours after application • Long-term daily administration can restore physiological levels	• Can measure serum T levels as early as 2-4 weeks after starting TT • Measure serum T levels 3-12 hours after application; adjust dose to achieve T level in the mid-normal range

(continued)

TABLE 7 (continued)

Formulation and unit dosage	Administration	Starting or titration doses	Dosing range	Advantages	Disadvantages	PK parameters	Formulation-specific monitoring
Testosterone gel 1% (Androgel 25 mg/2.5 g packet or 50 mg/5 g packet; Testim 50 mg/5 g tube)	• Apply once daily in the morning after showering • Androgel can be applied to dry intact skin of shoulders, upper arms and abdomen • Testim can be applied to dry intact skin of shoulders and upper arms • Cover application site with clothing and wash skin and hands with soap before having skin-to-skin contact with another person	50 mg daily	50-100 mg daily	• Easy and convenient to use • Flexible dosing • Readily absorbed and minimal skin irritation • Fast onset • Provides uniform and normal serum levels for 24 hours	• Possible transfer during intimate contact • Skin irritation (uncommon) • Odor, stickiness, dripping and slow to dry • Variable absorption from application to application	• 5 g of testosterone gel will deliver approximately 50 mg of testosterone to the skin's surface, and approximately 5 mg (10%) is systemically absorbed • Hydroalcoholic gel (e.g., Androderm) and pentadecalactone (e.g., Testim) products are not interchangeable • Cmax and AUC-24 were 30% higher with the pentadecalactone product • The unique scent of pentadecalactone may lead to discontinuation • Patients with higher BMI may require higher doses	• Can measure serum T levels as early as 2-4 weeks after starting TT • Measure serum T levels 2-8 hours following the gel application, after the patient has been on treatment for at least 1 week (time to steady-state levels)

(continued)

TABLE 7 (continued)

Formulation and unit dosage	Administration	Starting or titration doses	Dosing range	Advantages	Disadvantages	PK parameters	Formulation-specific monitoring
Intramuscular testosterone injection							
Testosterone enanthate (Delatestryl 200 mg/mL) Testosterone cypionate (Depo-Testosterone 100 mg/mL)	• Deep IM injection into the gluteal muscle or lateral upper thigh	100 mg every week or 200 mg every 2 weeks	50-400 mg IM every 1-4 weeks	• Low cost • Can be self-administered • Flexible dosing • Short-acting preparation allow drug withdrawal in case of adverse effects	• Pain and redness at injection site • Fluctuation in mood or libido • Increased risk of polycythemia and erythrocytosis • Rarely coughing after the injection (most likely due to a pulmonary oil microembolism) • Cautioned in patients at risk of erythrocytosis (type 2 diabetes, smokers, obese, bleeding disorders, anticoagulant usage) • Relatively contraindicated in patients with bleeding disorders or on anticoagulants due to an IM injection carrying a low risk of hematoma formation	• Wide fluctuations in circulating serum T levels • Peak levels occur about 72 hours after IM injection and are followed by a slow decline during the subsequent 1-2 weeks • Longer intervals or higher doses cause greater fluctuations in serum testosterone levels	• Can measure serum T levels as early as 3-4 cycles after starting TT • Measure serum T concentrations midway between injections

bid, twice a day; BMI, body mass index; GI, gastrointestinal; IM, intramuscularly; LFT, liver function test; tid, 3 times a day; TT, testosterone therapy.

men with anemia but more concerning in men with normal or elevated baseline hematocrit.[12]

If hematocrit is >0.54%, decrease the testosterone dose or switch to a preparation less likely to cause an increase in hematocrit (Table 7). If hematocrit remains elevated, hold TT and monitor for hypoxia and sleep apnea.[8-11] Pharmacists should offer smoking cessation or advise against smoking, as it increases the risk of hypoxia. Testosterone can be reintroduced at a lower dose once hematocrit has normalized.[1,2,4,7]

Lower urinary tract symptoms adverse effects

The US Endocrine Society notes that TT does not worsen lower urinary tract symptoms (LUTS) in men who do not have severe LUTS before TT.[24] But if substantial worsening of LUTS is observed, the TT dose can be reduced or held while discussing a specialist consultation with the PCP.[7,9,17]

Obstructive sleep apnea adverse effects

Patients should be asked about daytime fatigue and disordered sleep. Refer to the PCP for a sleep study if symptoms of sleep apnea are present.[16] If worsening of preexisting sleep apnea is observed, hold or reduce the dose of testosterone and discuss a referral to a specialist with the PCP.[16,17]

TD and comorbidities

Low testosterone is common in men with cardiovascular disease (CVD), obesity, type 2 diabetes, osteoporosis, obstructive sleep apnea (OSA), benign prostatic hyperplasia (BPH), LUTS, ED, HIV and depression.[1-4,7-11,14,19] Furthermore, TT can provide benefit for some comorbidities (e.g., osteoporosis), whereas it is relatively contraindicated in others (e.g., prostate cancer).[1-3,7] In hypogonadal men with comorbidities, pharmacists can

- Assess the appropriateness of TT,
- Collaborate with PCPs in managing TT,
- Optimally manage the patient's comorbidities and
- Educate patients about the benefits, risks and monitoring of TT in comorbid patients.

Cardiovascular disease

In 2014-2015, Health Canada and the US Food and Drug Administration (FDA) issued warnings that testosterone products were associated with serious and possibly life-threatening cardiovascular problems.[25] As time progressed, the FDA found no convincing evidence of this but still mandated that testosterone products warn about a possible increased risk of venous thromboembolism (VTE), heart failure (HF) and stroke. Moreover, the AUA and ESA noted that the evidence behind these warnings is contradictory and inconclusive.[8,10,11] European regulatory agencies have also concluded that there was no consistent evidence of increased risk of coronary artery disease associated with TT in hypogonadal men.[25]

Short-term studies have shown symptomatic improvement in men with coronary artery disease or HF, but the evidence regarding benefits and harms of TT on endpoints such as myocardial infarction, stroke or sudden cardiovascular death is lacking.[3,8] It is worth noting that it is often difficult to distinguish whether the increased cardiovascular risk is due to the underlying TD or the use of testosterone products.[8]

Because of this lack of evidence, it is recommended that when initiating TT, CVD should be assessed to ensure it is being optimally managed, and referral to a specialist should be discussed with the PCP when appropriate.[1,2] TT should be restricted to those with stable CVD and only after a discussion of potential benefits and harms.[3]

The risk of VTE is the highest in the first 6 months of starting TT. It can be mitigated by ensuring hematocrit levels do not exceed 0.54% and that testosterone levels remain within the mid-normal healthy range.[1,2] TT can lead to an exacerbation of severe chronic HF, as it causes fluid retention. HF patients may benefit from a low dose of testosterone if they are carefully monitored.[2]

Prostate cancer

There is no conclusive evidence that TT initiates prostate cancer or converts it from subclinical to clinical.[7,8,14] Therefore, TT can be cautiously considered in hypogonadal men who have been treated for local prostate cancer (surgery or radiation), are currently without evidence of active disease (e.g., increasing PSA, abnormal DRE), have low risk of recurrent prostate cancer and have had at least 1 year of follow-up.[2,3,8,12] Ultimately, TT should not solely be withheld because of the fear of prostate cancer development, but patients should be informed about the risks involving prostate growth.[12]

Obesity

The increase in testosterone levels is proportional to the amount of weight loss (i.e., 10% weight loss increases testosterone by 2-3 nmol/L).[10,11] Weight loss strategies based on diet, exercise and other lifestyle factors can increase testosterone levels as well as reduce the risk of diabetes and CVD.[2,3,10,11] In morbidly obese patients, bariatric surgery is an effective complementary option to increase circulating testosterone levels.[3,10,11]

TT can help improve body composition—decrease in fat mass, increase in lean mass—in obese men.[3] But obese men are more likely to develop adverse effects from TT compared with men of normal weight.[1]

Osteoporosis

Hypogonadal men should be treated with osteoporosis medication if diagnosed with osteoporosis and at a high risk of fractures, as TT is not indicated for reducing fracture risk.[2,7,9] However, 1 guideline suggests that hypogonadal men with osteoporosis at low risk of fractures may defer osteoporotic treatment for 1 to 2 years if they have recently started TT.[7]

OSA

There is no evidence to support that TT can result in the onset of OSA and inadequate evidence that it can result in worsening of OSA.[2] TT only transiently worsens OSA and is not an absolute contraindication unless OSA is severe and uncontrolled.[10,11]

BPH and LUTS

There is some evidence that TT provides symptomatic improvement of LUTS in hypogonadal men with BPH and no evidence that TT increases the risk of BPH or worsens LUTS in men with mild-moderate LUTS.[1,3,4,14] TT should be cautiously used in men with severe LUTS (>21 on the International Prostate Symptom Score [IPSS]).[2,3,14] Pharmacists may choose to have patients fill the IPSS at baseline and then during follow-up visits to aid in the monitoring of T therapy.

ED

TT should be used only in men presenting with both TD and ED, not isolated ED.[2,3,7,19] A combination of TT and phosphodiesterase type 5 inhibitors may be used in hypogonadal men who have not experienced an improvement in symptoms on either therapy alone.[1,3] Validated questionnaires such as the International Index of Erectile Function and shorter versions may be used at baseline and at follow-up to assess symptomatic improvement.[3,19]

HIV

Short-term (3-6 month) TT in men with HIV has shown modest gains in body weight, lean body mass and improvements in muscle strength and mood.[3,7] Most of the studies were of short duration; thus, consideration of therapy beyond 6 months should be discussed through the shared decision-making process.[3,7]

Depression

TT does not improve clinical depression in men and should not be used as the sole treatment for depression in men with or without hypogonadism.[7,9]

Conclusion

The management of LOH is complicated because of the controversies and differing recommendations made by various guidelines. Diagnosis involves the presence of signs and symptoms and positive lab tests. For men diagnosed with LOH, the combination of lifestyle interventions and TT provides symptomatic relief. Pharmacists have the skills and opportunity to manage TT in hypogonadal men, supported by the evidence-based recommendations provided in this guide. ■

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Note: *Clinical guidelines are only "guides." They are not applicable to all patients nor to all situations and are not intended to override clinician judgment.*

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