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LEARNING OBJECTIVES

Upon successful completion of this lesson, you should be able to:

1. Describe the basic physiology of the thyroid gland and thyroid hormones
2. Outline the standard diagnostic parameters and treatment strategies for thyroid disorders
3. Contrast laboratory findings, signs and symptoms of overt and subclinical thyroid disorders, and discuss controversial issues surrounding subclinical disease diagnosis and treatment
4. Compare the epidemiology, pathology and management of overt and subclinical thyroid disorders in adult, pregnant, pediatric and geriatric populations
5. Identify drugs that can affect thyroid function and recommend management of drug-induced thyroid disorders
6. Take an active role in ensuring patients receive optimal therapy for thyroid disorders.

To successfully complete the post-test for this lesson, you may need access to a recent edition (e.g., 2008, 2009) of the *Compendium of Pharmaceuticals and Specialties (CPS)* for additional information

INSTRUCTIONS

1. After carefully reading this lesson, study each question in the post-test and select the one option you believe is the best answer. Although more than one option may be considered acceptable, only one option is the *best* answer.
2. To pass this lesson, a grade of at least 70% (14 out of 20) is required. If you pass, your CEU(s) will be recorded with the relevant provincial authority(ies). (Note: some provinces require individual pharmacists to notify them.)

ANSWERING OPTIONS

- A. For immediate results, answer online at www.pharmacygateway.ca.
- B. Mail or fax the printed answer card to (416) 764-3937. Your reply card will be marked and you will be advised of your results within six to eight weeks in a letter from *Pharmacy Practice*.

Update On Nonmalignant Thyroid Disorders

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Introduction

Thyroid disease is the most common of all endocrine disorders and can affect every age group and lifestage. Since long-term therapy with prescription medications is often required for hypo- and hyperthyroidism, pharmacists are frequently involved in providing and monitoring treatment. Parameters defining thyroid disease have been evolving over the past two decades, increasing the number of patients who might benefit from treatment. The purpose of this lesson is to provide an update on current thinking with regard to non-malignant overt and subclinical thyroid disorders in adults, pregnancy, pediatrics and geriatrics. Drugs that may induce or exacerbate thyroid disorders are also reviewed.

hormones—T4 (thyroxine) and to a lesser extent T3 (triiodothyronine). Most T3 (the more active form) is produced by the breakdown of T4 in tissue outside the thyroid. Over 99% of thyroid hormones secreted from the gland are bound to plasma protein, mostly to thyroxine-binding globulin (TBG). Only free (unbound) thyroid hormones are active.

T4 is converted to T3 in peripheral tissues by deiodination. This process can be affected by nutrition, nonthyroidal hormones, drugs and illness. Progressive deiodination to inactive metabolites is the major metabolic pathway. About 20% of

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Thyroid physiology and function

Thyroid hormones are iodine-containing amino acids synthesized and secreted by the thyroid gland. They play an important role in the development of the central nervous system in infants, skeletal growth and maturation in children, and maintenance of normal metabolic homeostasis and normal function of organ systems in adults.¹⁻⁵

The first step in thyroid hormone synthesis is uptake of iodine into the thyroid gland, where it is used to form thyroid



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table 1

Signs and symptoms of thyroid dysfunction ^{1,3,4,9}		
	Hyperthyroidism	Hypothyroidism
skin, face, eyes	heat intolerance, warmth, moist skin, sweating, fine thin hair, wide stare, goiter	feeling cold, dry skin, dry hair, hair loss, brittle nails, drooping eyelids, peripheral edema, hoarse voice
cardiovascular	increased heart rate, palpitations, angina, arrhythmias	decreased heart rate
gastrointestinal system	increased appetite, more frequent bowel movements	decreased appetite with weight gain, constipation
central nervous system	hyperactivity, nervousness, tremor, emotional lability	lethargy, depression, paresthesia
musculoskeletal system	weakness, muscle fatigue	stiffness, muscle fatigue
reproductive system	menstrual irregularities, decreased fertility	heavy menstruation, infertility, impotence
metabolism	increased basal metabolic rate, hyperglycemia, decreased cholesterol and triglycerides, increased drug metabolism	decreased basal metabolic rate, increased insulin sensitivity, increased cholesterol and triglycerides, decreased drug metabolism

thyroid hormone undergoes enterohepatic circulation. This process involves conjugation in the liver, excretion to the gut in bile, hydrolysis by bacterial enzymes and reabsorption of released hormone back into the circulation.^{5,6,7}

Ultimately, secretion of thyroid hormones is regulated by thyroid-stimulating hormone (TSH) produced in the pituitary gland. TSH is regulated by two mechanisms: negative feedback from circulating thyroid hormone (i.e., as thyroid hormone levels increase, TSH secretion is inhibited and vice versa), and positive feedback from the hypothalamic hormone, thyrotropin-releasing hormone which stimulates TSH.²

Overview of diagnosis and treatment

Disorders of the thyroid may involve changes in the size or internal structure of the thyroid gland (nodules, goiter) and/or changes in the production and secretion of TSH and the thyroid hormones. The most frequent cause of primary hypothyroidism in countries where iodine intake is adequate is Hashimoto thyroiditis (an autoimmune disease that destroys the thyroid gland).

For primary hyperthyroidism, the most common cause in adults ages 20–40 is Graves' disease (an autoimmune disease that targets the thyroid gland causing diffuse enlargement and excess production and secretion of thyroid hormone).

Benign thyroid nodules are the second most frequent cause of hyperthyroidism. Toxic multinodular goiter (Plummer disease) is a more gradual and milder form of hyperthyroidism and more prevalent in middle-aged and elderly patients. Benign toxic adenomas involve a single overactive nodule and are responsible for 3–5% of hyperthyroidism cases.⁸

The initial test to assess thyroid function is usually TSH.⁹ If abnormal, levels of free T4 (F-T4) and, in some situations, free T3 (F-T3) are also measured.⁹ An elevated TSH, in combination with low F-T4 levels, indicates hypothyroidism, while low TSH with F-T4 levels above the upper limit of normal indicates hyperthyroidism.⁹ Overt (clinical) disease produces the characteristic symptoms outlined in Table 1.

In general, most patients with a thyroid disorder can either be medically cured (with surgery or radiation treatment) or managed satisfactorily on medications. Treatment of the hypothyroid patient consists of thyroid hormone replacement.³ The drug of choice is the synthetic thyroid hormone, levothyroxine, because of its uniform potency and lack of antigenicity.⁵ Options for hyperthyroidism are antithyroid drugs (propylthiouracil or methimazole), radioactive iodine or surgery.³ Adjunctive treatment for hyperthyroidism may include beta-adrenergic blockers, iodines, lithium and glucocorticoids. Doses of medication, and the frequency of monitoring, are based

on individual factors such as age, pregnancy, co-morbidities, concurrent medication and severity of the thyroid disorder.

On average, it takes 8–12 weeks for TSH levels in hypothyroidism to stabilize after thyroid hormone initiation or dosage change.⁵ TSH should be checked every two months until levels are in the normal range and annually thereafter.⁹ The symptoms of hypothyroidism may take several months to resolve.⁵ Patients treated with antithyroid drugs for hyperthyroidism should have TSH levels evaluated monthly until euthyroid (normal).⁵ Symptoms should improve in 4–8 weeks.⁵

Subclinical Thyroid Disease

Although still somewhat controversial, subclinical thyroid disorders are now recognized as legitimate medical conditions. In contrast to overt disease described above, subclinical disease presents as increased or decreased TSH values with F-T4 in the normal range. (Table 2) Symptoms are often mild or absent, so diagnosis is based primarily on laboratory evaluations.¹⁰ Subclinical thyroid disease has a higher prevalence than overt disease. In adults, subclinical hypothyroidism is estimated to be present in 4–10% of the general population,¹¹ while overt hypothyroidism is reported in less than two percent.⁹ Similarly, the prevalence of overt hyperthyroidism is reported to be about 1% but estimates of subclinical disease vary from 0.7 to 12.4%.¹² This wide range is due to variations in the definition of the disease.¹² Subclinical and overt thyroid disorders are both more common in women.^{9,11,12}

The etiology of subclinical thyroid disorders can be endogenous (causes being the same as overt disease) or exogenous (caused by treatment of overt disease).¹³ For the latter, an estimated 20% of patients receive either too little or too much of their thyroid medications.⁹ Certain drugs can also induce subclinical disease. (Table 3)

There is ongoing debate about the normal TSH range.¹⁴ Over the past 30 years the upper reference level has been lowered from 10 to 4–5 mIU/L (milli-international units per litre) for subclinical disease.¹⁴ It is now being suggested that this number should be lowered even further to 3 mIU/L.¹⁴ This is based on reports of a higher rate of antithyroid antibodies in subjects with TSH between 3 and 4.5 mIU/L and a higher rate of progression to overt thyroid disease in this subgroup.¹⁴ A recently published observational study of elderly patients found an increased risk of atrial fibrillation in patients with TSH

in the lowest quarter of the normal range versus those in the highest quarter.¹⁵ More research is needed to determine if there are benefits of treating patients with TSH values in the upper and lower regions of the normal range.

The discovery that people may have individual set-points of the hypothalamic-pituitary-thyroid axis offers a potential explanation for subclinical disease.¹⁶ Measuring TSH monthly in a small group of healthy males, researchers found that the range in TSH values in individuals was approximately one-half the average range for the whole group.¹⁶ This suggests a TSH value that falls within the population normal reference range used by laboratories may not necessarily be “normal” for an individual and reinforces that treatment decisions should be based not only on lab parameters but also on patient characteristics such as age, pregnancy, comorbidities, medication use and symptoms.¹⁴

SUBCLINICAL HYPOTHYROIDISM

The question whether to treat subclinical disease under its current definitions is still being debated. There is conflicting data on suspected associations between subclinical hypothyroidism and atherosclerosis, coronary heart disease, depression, bipolar disease, Alzheimer’s, weight gain, increased intraocular pressure, decreased bone mineral density and neuromuscular complaints.¹⁴ Similarly, studies on the benefits of treating subclinical hypothyroidism and improvement in symptoms and reduction of risk for the above conditions have produced contradictory results.¹⁴ A recent meta-analysis of cohort studies found that the risk of all-cause mortality in patients with subclinical hypothyroidism was increased only in patients less than age 65 with co-morbid conditions

such as ischemic heart disease, diabetes, and hip replacements.¹⁷

Most experts now recommend treatment for patients with subclinical hypothyroidism when TSH > 10 mIU/L.^{9,14,18} Treatment can also be considered for patients with TSH levels 5–10 mIU/L who have symptoms of hypothyroidism, cardiovascular risk factors (e.g., abnormal lipid profiles, hypertension, diabetes mellitus), are positive for antithyroid antibodies and/or are pregnant or planning a pregnancy.^{9,14,18} Levothyroxine doses in the range of 25–75 mcg daily are usually adequate to normalize TSH.¹⁴ Careful monitoring is necessary to prevent overdosing and inducing hyperthyroidism.¹⁴

SUBCLINICAL HYPERTHYROIDISM

Evidence of a link between subclinical hyperthyroidism and osteoporosis and cardiac abnormalities (particularly atrial fibrillation) is accumulating.¹⁴ Other effects for which there is less evidence include symptoms of hyperthyroidism, decrease in muscle strength and dementia.¹⁴ In the previously cited meta-analysis there was an overall relative increase in mortality of 40% in patients over 60 years with subclinical hyperthyroidism.¹⁷

Routine treatment of subclinical hyperthyroidism in young asymptomatic patients is not indicated.^{10,14} It should, however, be considered for younger patients (up to 60 years) with symptoms, and for elderly patients with or without symptoms who have a TSH < 0.1 mIU/L. In these cases, treatment can improve the quality of life and, for older individuals, decrease the risk of atrial fibrillation, cardiovascular mortality and osteoporosis.^{10,14} Treatment is also indicated when TSH values are between 0.1 and 0.4 mIU/L in patients who are frail or already have atrial fibrillation, underlying

heart disease, reduced bone mineral density or symptoms of hyperthyroidism.¹⁸

Antithyroid drugs in low doses can be used to normalize TSH in patients with subclinical hyperthyroidism.¹⁴ Radioactive iodine and surgery may be preferred for patients with underlying heart disease or atrial fibrillation.¹⁴ Patients with reduced bone mineral density should also be offered antiresorptive therapy.¹⁴

Thyroid Disease in Pregnancy

Thyroid disorders are relatively common during pregnancy and can result in serious adverse effects for both the mother and fetus. Several changes occur in the thyroid system during pregnancy. Human chorionic gonadotropin (HCG) levels rise in early pregnancy. HCG has thyroid stimulatory activity that produces a compensatory fall in TSH levels. Although usually within normal levels, in some women TSH falls below the normal range. Thyroid-binding globulin increases during pregnancy with corresponding increases in total T3 and T4 levels. These changes complicate thyroid function monitoring. Pregnancy also increases the requirements for thyroid hormone because the fetus does not start producing thyroid hormone until about the eighteenth week of gestation.¹⁹

HYPOTHYROIDISM IN PREGNANCY

Elevated TSH levels are found in 2.2–2.5% of women between the fifteenth and eighteenth week of gestation.²⁰ A recent study in the United States found 0.2% of pregnant women had overt hypothyroidism and 2.3% had subclinical hypothyroidism.²¹ The most common cause of hypothyroidism in pregnant women appears to be autoimmune thyroiditis.¹⁴ Risks associated with maternal hypothyroidism include miscarriage, gestational hypertension, placental abruptions, Caesarean sections, low birth weight and stillbirths.^{19,20} Additionally, delays in mental and motor development and cognitive impairment have been observed in children of mothers not treated for hypothyroidism during pregnancy.²⁰ In one study, lack of treatment during pregnancy was associated with lower IQ scores (an average of seven points lower than controls).²² As in other population subgroups, there are conflicting reports about whether subclinical hypothyroidism is associated with similar adverse effects.^{21,23}

Treatment with levothyroxine is indicated in overt hypothyroidism to reduce the risk of the adverse outcomes described above.²⁰ Many experts also recommend treatment of subclinical hypothyroidism although evidence of benefit at this time is limited.^{9,14,19,20} The goal of treatment is

table 2

Classification of thyroid disorders ^{4,9,10,14}				
TSH (mIU/L)		F-T4, F-T3	Diagnosis	Treatment
> 4–5	and	low	overt hypothyroidism	YES
> 10	and	normal	subclinical hypothyroidism	YES
< 4–10	and	normal	subclinical hypothyroidism	decision based on symptoms and risk factors
0.3–0.5 to 4–5	and	normal	euthyroid	NO
< 0.5	and	normal	subclinical hyperthyroidism	decision based on symptoms and risk factors
< 0.2	and	elevated	overt hyperthyroidism	YES

TSH = thyroid stimulating hormone; F-T4 = free T4; F-T3 = free T3
mIU/L = milli-international units per litre;
Normal reference ranges: F-T4 = 10–36 pmol/L (picomoles per litre); F-T3 = 3.7–6.5 pmol/L

table 3

Drug-induced thyroid disorders ^{4,6,7}	
Drug Effect	Examples of Drugs
HYPOTHYROIDISM	
inhibition of TSH secretion	dopamine, glucocorticoids, amiodarone, somatostatin, endogenous thyroid hormone
inhibition of thyroid hormone synthesis/release	lithium, thioamides, thalidomide, aminoglutethamide, amiodarone, iodides (including x-ray contrast agents), certain expectorants (iodinated glycerol), some topical antiseptics (povidone iodide)
induction of T4 & T3 metabolism	phenytoin, carbamazepine, phenobarbital, rifampin (no effect on normal thyroid function but higher levothyroxine doses may be required when administered concurrently)
decreased absorption of T4	aluminum hydroxide, calcium carbonate, iron supplements, cholestyramine, colestipol, proton pump inhibitors
decreased peripheral conversion of T4 to T3	beta-blockers, glucocorticoids, amiodarone, iodinated x-ray contrast agents
induction of autoimmune disease	interferon-alfa, interferon-beta, interleukin-2, lithium, amiodarone
HYPERTHYROIDISM	
increased TSH secretion	antipsychotics, metoclopramide, theophylline
increased thyroid hormone synthesis/release	amiodarone, iodine, lithium

to keep TSH in the normal range.⁹ Because requirements for levothyroxine increase during pregnancy, patients on levothyroxine prior to pregnancy may need dose increases of up to 50% to maintain normal serum levels of TSH and F-T4.²⁰ In a study involving nineteen pregnant patients, the average dose of levothyroxine at 20 weeks gestation was 48% higher than their pre-pregnancy dose.²⁴

Some experts recommend increasing the levothyroxine dose as soon as pregnancy is confirmed in anticipation of increased need.⁹ Requirements may change as the pregnancy progresses so patients should have their TSH levels checked when pregnancy is confirmed and every two months thereafter.⁹ The

increased requirement for thyroid hormone usually decreases after delivery and, with careful monitoring of TSH, the dose of levothyroxine can often be gradually reduced to pre-pregnancy levels.²⁵

Levothyroxine in doses used to produce normal thyroid function values in the mother does not adversely affect the infant during pregnancy or lactation.²³ Thyroid hormone is also necessary for lactation in that supplementation in a hypothyroid mother will help ensure adequate milk supply.²⁶

HYPERTHYROIDISM IN PREGNANCY

Hyperthyroidism is less common than hypothyroidism and affects approximately 0.2% of pregnancies.²⁵ Graves' disease is the most common cause of hyperthyroidism in pregnancy.²⁵ Adverse outcomes associated with severe hyperthyroidism are stillbirth, preterm delivery, intrauterine growth restriction, preeclampsia, and/or maternal heart failure.²⁵ Typically, the course of Graves' disease during pregnancy involves an exacerbation in the first trimester, improvement or even remission in the third trimester, and exacerbation again about two months after delivery.¹⁹ Symptoms are similar to those in nonpregnant patients and include palpitations, anxiety and weight loss or failure to gain weight despite normal appetite.¹⁹ In general, only symptomatic patients are treated.²⁵ Subclinical hyperthyroidism has not been reported to cause adverse pregnancy outcomes and treatment is not currently recommended.²⁷

The treatment of choice in pregnancy for overt hyperthyroidism is propylthiouracil.^{19,25} Methimazole may cross the placenta to a greater extent than propylthiouracil and has been associated with rare birth defects such as cutis aplasia (absence of skin on the scalp).²⁵ Small amounts of propylthiouracil cross the placenta and may cause hypothyroidism in the fetus.²⁸ Lower doses of propylthiouracil (50–100 mg daily versus 300–1200 mg daily) are therefore recommended in pregnancy.²⁸ The goal of therapy is a high-normal T4 level, rather than normalization of TSH levels in order to minimize fetal exposure to the drug.¹⁹ Propylthiouracil (up to 750 mg daily) and methimazole (up to 20 mg daily) have been safely used postpartum by breastfeeding mothers.²⁸

POSTPARTUM THYROIDITIS

Postpartum thyroiditis occurs after approximately eight percent of pregnancies. Type 1 diabetes mellitus, history of Hashimoto thyroiditis or postpartum thyroiditis with a previous pregnancy increase the risk of this disorder. It involves a

period of hyperthyroidism caused by inflammation of the thyroid gland which starts about two months after delivery and lasts for up to four weeks. This is often followed by a period of hypothyroidism starting about six months after delivery.

Women exhibit typical symptoms of high and low thyroid hormone levels during the different phases of this disorder. Thyroid function in most women returns to normal within a year, but 25% will develop permanent hypothyroidism in the 10 years following delivery.^{19,25}

Symptoms of postpartum thyroiditis may be attributed to the stress and anxiety involved in caring for a new infant, or to postpartum depression. Patients with these complaints should therefore be checked for thyroid function. The hyperthyroid phase generally does not require treatment. The decision whether to treat the hypothyroid phase with levothyroxine depends on the severity of symptoms. If used, it can be usually be discontinued one year after delivery. The TSH should be checked four to six weeks after discontinuation, or earlier if symptoms re-emerge.^{19,25}

Pediatric Thyroid Disorders

PEDIATRIC HYPOTHYROIDISM

Hypothyroidism may be either congenital or acquired.²⁹ The incidence of congenital hypothyroidism is 1:3000–1:4000 in infants.²⁹ Most infants are asymptomatic at birth because, as noted, maternal thyroid hormone crosses the placenta.³⁰ Signs and symptoms do not appear for 6–12 weeks or longer. Diagnosis is based on routine screening of infant's thyroid function soon after birth and it is important to start treatment early to prevent permanent effects on mental and physical development.²⁹ Initial symptoms of hypothyroidism in infants are poor feeding and growth failure.³⁰

Acquired hypothyroidism in children and adolescents is usually due to chronic autoimmune thyroiditis.²⁹ Symptoms are similar to those of adults but also include growth failure and/or delayed puberty.²⁹ Spontaneous remission of autoimmune hypothyroidism during puberty has been reported.¹⁴

The treatment for pediatric hypothyroidism is levothyroxine.^{29,31} Replacement doses in children are relatively higher than those used in adults because children clear F-T4 more rapidly.³¹ Treatment of subclinical hypothyroidism in children is controversial but may be considered in order to prevent potential effects on growth and development.³¹ It is important to avoid overtreatment as this may have adverse effects on behaviour, school per-

formance and bone density.³¹ Once growth is complete and puberty is past, the need to continue therapy can be evaluated by discontinuing levothyroxine for one month then monitoring the effect of doing so.³¹

PEDIATRIC HYPERTHYROIDISM

Hyperthyroidism in children and adolescents occurs in 0.02% and is almost always due to Graves' disease.³² It is more common in females and frequently emerges during puberty.²⁹ Although rare, it can develop in utero when mothers with prior or current Graves' disease have elevated levels of anti-thyroid antibodies.²⁹ After birth, antibodies are cleared by the infants and hyperthyroidism usually resolves within six months.²⁹ Hyperthyroidism lasting longer than six months can cause premature closure of the cranial sutures in infants, intellectual impairment, short stature, hyperactivity and infant mortality.³⁰ In adolescents, symptoms of hyperthyroidism are similar to those that occur in adults but may include accelerated growth and development.^{29,30}

Treatment choices include antithyroid drugs, radioactive iodine or thyroidectomy.²⁹ Although antithyroid drugs have typically been recommended for initial treatment, there is increasing acceptance of radioactive iodine treatment for children (10 years of age and older) and adolescents.³³ There is ongoing debate regarding the relative benefits of thyroidectomy versus radioactive iodine treatment.³² Both treatments are a permanent cure but most patients become hypothyroid and will require lifelong thyroid hormone replacement therapy.³²

Antithyroid drugs normalize thyroid hormone levels in 87–100% of children and adolescents but permanent remission is reported in less than 50%.³² Years of treatment are often required to induce remission and side effects are a concern.³³ Common minor side effects occurring in 5–10% of children include skin rashes, arthralgia, nausea and taste abnormalities.³² These can often be managed by discontinuing the drug until the symptoms resolve and then either restarting therapy with the same drug or switching to another drug.³¹ Serious side effects such as vasculitis, agranulocytosis and hepatitis occur in 2–5%,³² which have been fatal in rare cases.³³ Medication should be discontinued if any of these conditions occur.²⁹

Based on a relatively high incidence of severe liver disease associated with propylthiouracil, the American-based Endocrine Society recently endorsed the recommendation that this drug not be used as first line treatment for hyperthyroidism

in children.³⁴ Methimazole has not been associated with liver failure, and has the advantage of once daily dosing.³² Beta-adrenergic blockers (cardioselective agents such as atenolol) can be used as adjuncts as necessary to reduce nervousness, tremors, palpitations, tachycardia and hypertension.³² If remission eventually occurs, lifelong monitoring is required after antithyroid drugs are stopped.³²

Thyroid Disorders in the Elderly

Thyroid disorders, in particular hypothyroidism and thyroid nodules, are frequently present in older individuals.³⁵ In people aged 65 years and older, the prevalence of overt and subclinical hypothyroidism is 2–6% and 5–10%, respectively.³⁵ The prevalence increases with age, is higher in women than men and higher in long-term care facilities than in the community.^{35,36}

Overt hyperthyroidism is present in 0.2–2% of the elderly (> 65 years)³⁵ and up to an additional two percent have subclinical disease.³⁶ Symptoms usually associated with thyroid disease may be more subtle in older persons and may be misinterpreted as age-related changes or attributed to coexisting medical conditions.^{35,36}

HYPOTHYROIDISM IN THE ELDERLY

The most common causes of hypothyroidism in the elderly are chronic autoimmune thyroiditis, previous treatment for hyperthyroidism with radioactive iodine or thyroid surgery and use of medications that affect thyroid function (Table 3).³⁷

Elderly patients may have fewer typical symptoms (Table 1), no symptoms, or atypical symptoms such as hypertension or tachycardias.³⁸

For overt hypothyroidism, treatment with levothyroxine is indicated. In the elderly, particularly in those with coronary artery disease, a starting dose of 12.5 mcg daily is recommended.³⁷ This can be titrated upwards in small increments of 12.5–25 mcg every four weeks as tolerated until thyroid function values are normal and symptoms resolve.¹⁸ The average dose required in the elderly is 75 mcg.³⁷ The patient and caregiver should be advised to report the emergence or worsening of symptoms such as angina, dyspnea, confusion, or insomnia.³⁷ Lifelong therapy is usually required.³⁷ However, it is important to avoid overtreatment as this can lead to osteoporosis, anxiety, muscle-wasting, and atrial fibrillation.³⁶ Once stabilized, TSH levels should be measured every 6–12 months and small adjustments made as necessary.³⁶

Treatment of subclinical hypothyroidism in the elderly is a more complex decision. Research has produced conflicting results on the benefits of treatment particularly in the very elderly (> 85 years of age).¹⁴ In fact, some studies have found an association between both overt and subclinical hypothyroidism and lower mortality, possibly explained by the protective effect of reduced metabolic rate and lower adrenergic tone in this age group.¹⁴ Treatment for very elderly patients with TSH less

table 4

Resources for thyroid disorders

Thyroid Foundation of Canada

www.thyroid.ca

A non-profit organization whose mission is to support thyroid patients across Canada through awareness, education, and research. Website contains a variety of patient information on thyroid disease, information about local chapter events and links to other sources of information.

American Thyroid Association

www.thyroid.org

American site that provides patient information on thyroid disorders and current research in this area. Also contains links for healthcare professionals to American guidelines on treatment of thyroid disease.

TOP Toward Optimized Practice

www.topalbertadoctors.org/cpgs/thyroid_dysfunction.html

Investigation and Management of Primary Thyroid Dysfunction. Clinical practice guideline developed by Alberta doctors and their teams; updated in 2008.

eMedicine, Endocrinology, Thyroid

www.emedicine.com

Continually updated clinical reference for healthcare professionals and patients. Twenty monographs on different aspects of thyroid disease.

than 10 mIU/L, especially in those with underlying cardiac disease is not usually recommended.¹⁴ For younger patients, the decision to treat should be based on the presence of symptoms and individual risk factors.³⁷

It is important to periodically check the actual need for thyroid hormone supplementation in elderly patients who have been on these medications long-term.³⁶ A study in nursing home patients reported that one-half of residents evaluated were able to successfully discontinue their medication.³⁹

HYPERTHYROIDISM IN THE ELDERLY

In contrast to younger populations, toxic nodular goiter accounts for more cases of hyperthyroidism than Graves' disease in geriatric patients.³⁷ Elderly patients have fewer symptoms and these are often atypical.^{36,37} The most common manifestations of hyperthyroidism in the elderly are cardiac symptoms (atrial fibrillation, angina and heart failure) and weight loss.³⁶ Of the three treatments used for hyperthyroidism, radioactive iodine is usually preferred in the elderly.³⁷ Antithyroid medications are effective but there is a higher rate of disease recurrence and potential for side effects.³⁷ Antithyroid medications may be used for 1–2 months prior to radioactive iodine treatment to deplete thyroid stores and reduce the risk of a thyroid storm due to “dumping” of hormone into the circulation after treatment.³⁸ The antithyroid drug should be stopped for 3–5 days before and after treatment.³⁸ The dose can then be tapered over the next few months as the effect of the radioactive iodine treatment emerges.³⁸

Agranulocytosis due to antithyroid drugs may occur more frequently in older patients particularly those on propylthiouracil.³⁸ Low doses of methimazole may be safer for the elderly; as well, its once-daily dosing can help promote compliance.³⁸ Beta-adrenergic blockers may be used as adjuncts to manage symptoms such as tachycardia and tremors.³⁷ After radioactive iodine treatment, most patients eventually require supplementation with levothyroxine for treatment-induced hypothyroidism.³⁸

Subclinical hyperthyroidism is potentially more serious in the elderly population.¹⁴ The most common cause is overtreatment with thyroid hormone.¹⁴ This emphasizes the importance of monitoring thyroid function (every 6–12 months) in treated patients. Decreasing the levothyroxine dose or in some cases discontinuing the medication may be necessary to normalize TSH values.³⁸ Treatment of endogenous subclinical hyperthyroidism in the elderly is still controversial³⁸ but should be considered in light of recent evidence

that it may increase the risk of atrial fibrillation and osteoporosis.¹⁴ Treatment options are the same as those just described for overt disease in the elderly.

Drug-Induced Thyroid Disorders

Several drugs have been implicated in precipitating or exacerbating overt and subclinical thyroid disorders. These can affect thyroid function, thyroid hormone levels and thyroid laboratory values by various mechanisms.⁶ (Table 3)

AMIODARONE

Due to its high iodide content, amiodarone can induce hyper- or hypothyroidism. It partially inhibits conversion of T4 to T3 which can result in increased F-T4 and decreased F-T3 levels in the presence of normal TSH values. F-T3 must therefore be monitored as well as TSH and F-T4. These parameters should be checked three months after initiation of amiodarone treatment and every 6–12 months thereafter. Patients with a history of thyroid disorders and the elderly are at higher risk of amiodarone-induced thyroid dysfunction.

Hypothyroidism occurs in 2–4% of patients on amiodarone, with symptoms typical of reduced thyroid hormone activity. Management of hypothyroidism involves reduction in the amiodarone dose and/or supplementation with levothyroxine. In some cases, discontinuing amiodarone may be necessary. Levothyroxine must be used cautiously in patients with cardiovascular disease and the dose reduced or the drug discontinued if chest pain or other indicators of worsening cardiac condition occur. Thyroid function improves slowly over two to three months after withdrawal of amiodarone.^{6,7}

Hyperthyroidism may develop at any time during amiodarone therapy. Patients should be counselled to report symptoms such as weight loss, anxiety, tremor, heat loss as well as any worsening of angina or arrhythmias. Hyperthyroidism in patients on amiodarone is potentially serious and must be treated because it could exacerbate underlying arrhythmias and cardiovascular disease. For treatment, propylthiouracil or methimazole alone are not usually effective. Therapies that have shown some success include methimazole in combination with potassium perchlorate, beta-blockers and/or corticosteroids, and thyroidectomy. Radioactive iodine treatment is relatively contraindicated because high iodine concentrations in the thyroid and systemic circulation caused by amiodarone therapy inhibit uptake of radioactive iodine into the thyroid gland.^{6,7}

LITHIUM

Lithium inhibits thyroid hormone synthesis and blocks the release of thyroid hormone. It causes goiter in up to 5% of patients, with or without thyroid dysfunction, and hypothyroidism in up to 20% of patients. Symptoms of hypothyroidism may occur within weeks or up to years after beginning lithium therapy. Those at higher risk include women, the elderly and patients with prior history of thyroid disorders. TSH should be measured prior to lithium therapy, three months after initiation, and every 6–12 months thereafter. Hypothyroidism can usually be managed with levothyroxine supplementation while continuing lithium therapy. Hyperthyroidism occurs rarely, and usually requires lithium withdrawal.^{6,7}

Role of the pharmacist

Pharmacists can play a vital role in both the identification and treatment of thyroid disorders. For the former, pharmacists are often the first health professionals consulted for advice on mild or nonspecific symptoms that may be due to a thyroid disorder (e.g., fatigue, hair loss, brittle nails, appetite and weight changes, swellings on the throat). If noted, pharmacists can direct patients with suspicious symptoms to their physicians.

Monitoring patients' symptoms extends to those who are taking drugs known to adversely affect thyroid function. For example, with amiodarone or lithium, an effective way to do this is to first ask: “How are you managing with this medication?” followed by specific markers of thyroid dysfunction such as: “Have you noticed any changes in your skin—for example, whether it seems unusually dry?” and “What about things like your hair?... your energy or mood?... unexplained changes in your appetite or weight?”

For a confirmed thyroid disorder (and as with all medications) patient education is paramount. Seemingly simple advice about when to take thyroid medication in relation to meals or other medications can go a long way to affecting efficacy. One example is levothyroxine, which should ideally be taken on an empty stomach, but if that interferes with compliance, may be taken with food as long as the patient is consistent. Likewise, iron and/or calcium should be spaced at least six hours apart from levothyroxine. Readers are encouraged to review Table 4 for links to many other patient education points.

Patients should know when to expect benefits of therapy. Newly diagnosed patients may be surprised by the potential length of time it takes to find the “right” dose for their symptoms, and should be aware of the relatively delicate balance

and fine-tuning it can take to normalize thyroid function. Closely related, patients should know the symptoms associated with both hypo- and hyperthyroidism so they can self-monitor, contacting their doctor if signs of either occur. Likewise they should understand that most thyroid conditions are chronic, and that feeling better with medication does not mean they can stop taking it without their doctor's approval. Since medication adherence tends to be tied to knowledge of benefits, patients also need to be aware of health risks if their condition is not treated.

Pharmacists also need to be involved in the monitoring of under- or overdosing, side effects of thyroid medication, and drug-drug and drug-disease interactions. With respect to the latter, monitoring

extends into over-the-counter products and alternative remedies. A classic example of the former is sympathomimetics in cough and cold remedies for those with uncontrolled hyperthyroidism. Little benefit, if any, has been shown with alternative remedies that are "recommended for thyroid." Many of these products contain iodine and thyroid extract and may affect the physiology of thyroid hormone production. Pharmacists should always ask patients if they are taking any alternative remedies (including those marketed for fatigue), as their consumption may result in misleading thyroid function tests if the physician is unaware of their intake.

Overall, seeing patients through different stages of life—gestation, infancy, childhood, adulthood, pregnancy and advancing

age—puts pharmacists in a unique position to prevent problems and identify changing needs for thyroid disorders.

Summary

Pharmacists in both community and institutional practice require a fundamental knowledge of thyroid disorders and their management.

The definition of thyroid disease and criteria for treatment are changing and pharmacists need to be aware of these changes to adequately counsel and evaluate their patients. The importance of treating subclinical diseases in certain patients and the changing needs in some groups—especially our rapidly expanding elderly population—offers pharmacists another opportunity to be a valuable link in the healthcare chain.

Questions

To answer online, go to www.pharmacygateway.ca, CE section, CE Online, Pharmacy Practice

1 Which of the following statements about subclinical thyroid disease is not correct?

- a) The diagnosis of subclinical disease is primarily based on laboratory tests.
- b) Subclinical disease should always be treated.
- c) Treatment options for subclinical disease tend to be the same as for overt disease.
- d) Subclinical disease will often progress to overt disease.

2 Elevation of TSH values with normal F-T4 indicates:

- a) overt hyperthyroidism
- b) subclinical hyperthyroidism
- c) overt hypothyroidism
- d) subclinical hypothyroidism

Case ONE: questions 3–6

A 36-year-old woman is planning a pregnancy. She has been taking levothyroxine 100 mcg daily for several years for Hashimoto's thyroiditis. She asks you about the safety of using levothyroxine during pregnancy.

3 You can assure her that levothyroxine in physiological doses does not increase the risk of adverse pregnancy outcomes.

- a) true
- b) false

4 You may also explain that untreated hypothyroidism during pregnancy may cause all of the following adverse effects except:

- a) gestational hypertension
- b) increased risk of infant mortality
- c) high birth weight
- d) delays in motor and mental development

5 Which of the following statements about the use of levothyroxine during pregnancy is/are correct?

- a) The dose should be decreased as soon as pregnancy is confirmed.
- b) The dose may need to be increased by up to 50% during pregnancy.
- c) The dose should be adjusted based on the results of approximately bimonthly TSH values.

- d) The dose should automatically be reduced after delivery.
- e) both b) and c)

6 This patient is at risk of developing postpartum thyroiditis.

- a) true
- b) false

Case TWO: questions 7–10

When picking up her prescription for alendronate 70 mg, a 75-year-old woman tells you she is being referred to an endocrinologist because her "TSH value is very low." Her thyroid hormones are in the normal range and she feels fine. She is concerned about having to take more medication and asks you for more information.

7 Is this patient a likely candidate for treatment?

- a) No, because she is asymptomatic.
- b) No, because treatment in the elderly increases mortality risk.
- c) Yes, because she has osteoporosis.
- d) Yes, because her TSH value is abnormal.

8 If the decision is made to treat her condition, which of the following treatments is generally preferred in her age group?

- a) antithyroid drugs
- b) thyroidectomy
- c) radioactive iodine
- d) any of the above
- e) none of the above

9 Adverse effects of antithyroid drugs include all of the following except:

- a) blood dyscrasias
- b) vasculitis
- c) hepatotoxicity
- d) permanent hyperthyroidism

10 If antithyroid drug treatment were indicated for this patient, methimazole may be preferred over propylthiouracil because it:

- a) is more likely to decrease the risk of atrial fibrillation

- b) is less likely to cause agranulocytosis
- c) has once-daily dosing
- d) both b) and c)
- e) all of the above

11 Subclinical hypothyroidism in the very elderly has been linked to an increased risk of mortality.

- a) true
- b) false

12 Causes of hypothyroidism in the elderly include all of the following except:

- a) toxic nodular goiter
- b) chronic thyroiditis
- c) previous radioactive iodine treatment
- d) use of medications that inhibit thyroid function

13 Which of the following statements about lithium-induced thyroid disorders is not correct?

- a) Hypothyroidism is a frequent adverse effect of lithium therapy.
- b) Hyperthyroidism occurs less frequently than hypothyroidism.
- c) Recommended treatment of lithium-induced hyperthyroidism is lithium withdrawal.
- d) Recommended treatment of lithium-induced hypothyroidism is lithium withdrawal.

14 A woman picking up an amiodarone refill for her 78-year-old father tells you he has become quite nervous and shaky over the past month. He has been on amiodarone for several months and wonders if these symptoms might be from this drug. What information could you give this woman?

- a) Patients are at risk of developing hyperthyroidism at any time during therapy with amiodarone.
- b) Symptoms such as tremor and anxiety may be indicators of increased thyroid hormone levels.
- c) These symptoms should be evaluated by her father's doctor, especially since he has cardiovascular disease.
- d) both b) and c)
- e) all of the above

Questions

To answer online, go to www.pharmacygateway.ca, CE section, CE Online, Pharmacy Practice

15 Antithyroid drugs are effective treatment for amiodarone-induced hyperthyroidism.

- a) true
- b) false

CASE THREE: Questions 16–18

A 50-year-old patient tells you she hasn't been feeling well for the past few months—fatigue, aching muscles, frequent sweating spells, anxious and just not enjoying life. She is also concerned about weight she has been gaining. Although a recent blood test was normal for thyroid levels, she has found advertisements on the Internet for thyroid supplements that claim to treat all of these symptoms. She asks your advice.

16. Which of her symptoms is not typical of hypothyroidism?

- a) depression
- b) weight gain
- c) sweating
- d) fatigue

17 What is the major concern if she decides to purchase one of these products over the Internet?

- a) cost of the medication
- b) cost of laboratory tests
- c) inducing subclinical or overt hypothyroidism
- d) inducing subclinical or overt hyperthyroidism

18 What advice should you provide?

- a) You may have subclinical hypothyroidism. Try the supplement to see if it helps your symptoms.
- b) You may have subclinical hypothyroidism. Ask your doctor about trying a low dose of levothyroxine.
- c) You may have subclinical hyperthyroidism. Ask your doctor about trying a low dose of an antithyroid drug.
- d) These symptoms could be due to conditions other than thyroid disease. Ask your doctor for further investigation.

19 Which of the following statements about

treatment of hyperthyroidism in children is incorrect?

- a) Antithyroid drugs induce permanent remission in most children.
- b) Radioactive iodine is an acceptable treatment option in children 10 years of age and older.
- c) Thyroid surgery permanently cures hyperthyroidism in children.
- d) A cardioselective beta-blocker may be used to treat symptoms of hyperthyroidism.

20 In which of the following situations should the need for continuing levothyroxine therapy be re-evaluated?

- a) when children with hypothyroidism are past puberty
- b) one year after delivery when used for postpartum thyroiditis
- c) when elderly patients enter a long-term care home
- d) all of the above

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ce faculty

THIS MONTH

Update on Nonmalignant Thyroid Disorders

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Karen is currently a Manager at Saskatchewan Drug Information Service. She has 20 years of experience in community pharmacy, eight years as a drug information consultant and has worked extensively in medical literature research and analysis. She frequently researched and responded to questions from pharmacists and consumers about the treatment of thyroid disorders.

All lessons are reviewed by expert pharmacists for accuracy, currency and relevance to current pharmacy practice.

This lesson is valid until May 22, 2012. Information about nonmalignant thyroid disorders may change over the course of this time. Readers are responsible for determining the most current aspects of this topic.

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