Supplement to U.S. Pharmacist®
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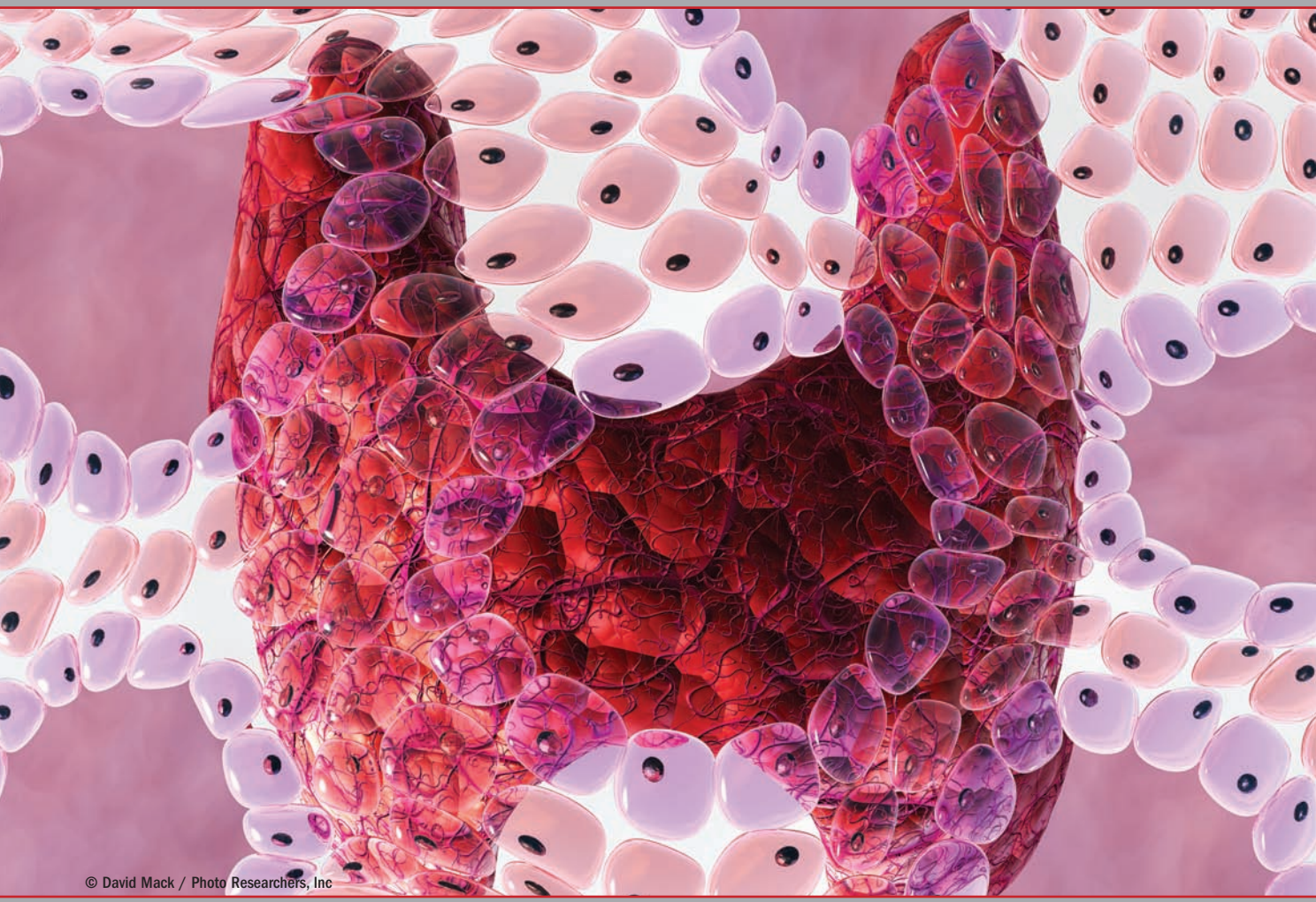
Current Challenges in the Management of Hypothyroidism



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CONTINUING EDUCATION INFORMATION

Target Audience: Pharmacists

Type of Activity: Knowledge

Program Description: The fundamental approach to pharmacologic treatment of patients with hypothyroidism—the repletion of thyroid hormones—has not changed in decades. Good management encompasses educating the patient about the disease and treatment, ensuring medication adherence, titrating dosage to assure clinical well-being, and monitoring treatment response. Despite these well-established tenets, under- and overtreatment remain common. Pharmacists can make a dramatic difference in treatment success by educating the patient and monitoring adherence. Pharmacists are well positioned to correct therapeutic inadequacies by identifying and managing common factors that affect drug availability, such as drug interactions, effects of common comorbid conditions, timing of administration, and consistency of drug formulation.

Faculty

Darrell Hulisz, RPh, PharmD
Associate Professor
Department of Family Medicine
Case Western Reserve University School of Medicine
Cleveland, Ohio
Associate Clinical Professor
Ohio Northern University, College of Pharmacy
Department of Pharmacy Practice
Ada, Ohio

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U.S. PHARMACIST CONTINUING EDUCATION

Goals: To educate pharmacists about the goals of thyroid hormone replacement in patients with hypothyroidism, describe the various thyroid hormone replacement products and their interchangeability, establish optimal strategies for safe and effective thyroid repletion, and provide strategies for ensuring patient adherence and education.

Learning Objectives: After completing this activity, participants should be better able to:
- Define goals of thyroid hormone replacement therapy in individuals with hypothyroidism
- Identify thyroid hormone replacement products, their individual potency, and safety of interchangeability among products
- Describe barriers to achieving and maintaining adequate thyrotropin concentrations in individuals with hypothyroidism
- Define strategies for optimizing the benefit:risk profile of thyroid hormone replacement therapy

PHS1201

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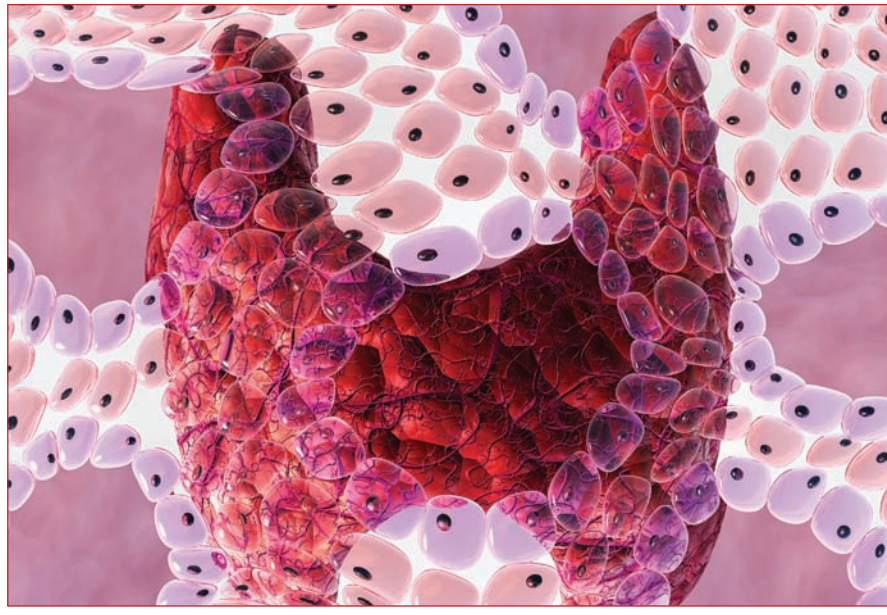


INTRODUCTION

Hypothyroidism, like many chronic conditions, is associated with long-term morbidity that can be minimized through careful management.[1,2] Primary thyroid failure is a continuous progression from a relatively symptom-free stage into overt disease in which abnormal levels of thyroid hormones are accompanied by troubling symptoms, cognitive impairment, and a heightened risk of cardiovascular morbidity.[2-4] There is ongoing debate over what constitutes "normal" levels of thyroid hormones.[5] As a result, researchers are exploring the risks posed by subclinical, asymptomatic disease, with the goal of clarifying the indications for treatment.[6]

Darrell Hulisz, RPh, PharmD
Associate Professor
Department of Family Medicine
Case Western Reserve University School of Medicine
Cleveland, Ohio
Associate Clinical Professor
Ohio Northern University, College of Pharmacy
Department of Pharmacy Practice
Ada, Ohio

POP QUIZ

Pharmacologic treatment of thyroid deficiency has undergone a transformation in recent years.

A. True
B. False

The fundamental effective pharmacologic treatment—replacement of thyroid hormones—has not changed in decades.[7] The basic approach to management encompasses educating the patient about the disease and treatment; ensuring medication adherence; titrating dosage to assure clinical well-being; and monitoring treatment response.[6] Nonetheless, under- and overtreatment are common.[1] Pharmacists are well positioned to correct this therapeutic inadequacy by identifying and correcting common reasons that affect drug availability, such as drug interactions,[3] effects of common comorbid conditions,[1,6] timing of administration,[1,8] and assuring drug formulation consistency.[9] Pharmacists can make a dramatic difference in treatment success by educating the patient and monitoring adherence.

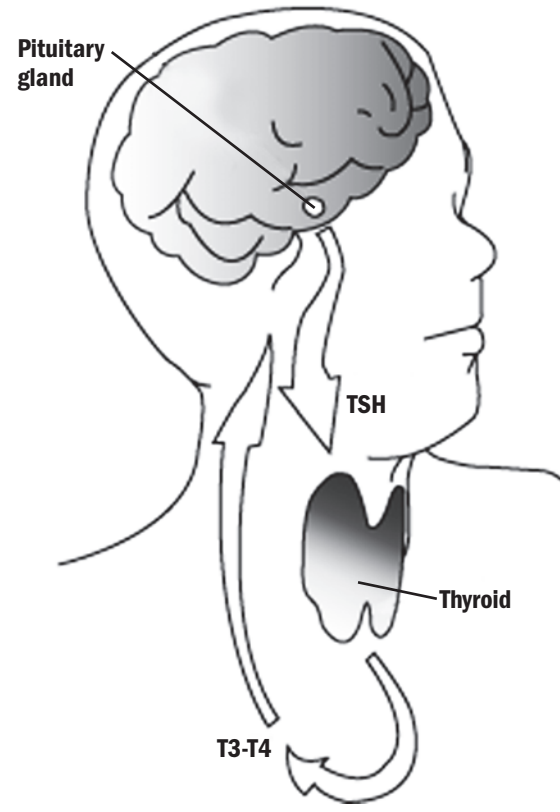
NORMAL THYROID FUNCTION

The thyroid is an endocrine gland consisting of 2 lobes connected by the isthmus.[4] It is located in the throat just beneath the larynx. Activation of the thyroid by thyroid-stimulating hormone (TSH or thyrotropin) leads to the production of thyroxine (T4), which is metabolized to a highly active form, triiodothyronine (T3).[4,10] The normal thyroid gland produces about 80% T4 and about 20% T3; however, T3 possesses about 4 times the hormone "strength" of T4.

Production of the 2 thyroid hormones is regulated via a classic endocrine feedback loop (FIGURE 1).[4,10] Low levels of T3 and T4 stimulate the release of thyrotropin-releasing hormone (TRH) in the hypothalamus. TRH, in turn, stimulates production of TSH in the pituitary gland.[4] TSH, which is released rapidly with increased TRH, determines the normal physiologic set point for thyroid hormone levels.[4]

Thyroid hormones are essential for normal metabolic functioning.[4,10] In children, these hormones are crucial determinants of normal development, especially of the central nervous system and bone.[3,4] Absence of thyroid hormone in neonates can lead to irreversible mental retardation and is associated with widespread brain abnormalities.[3] In adults, thyroid hormones maintain metabolic homeostasis by affecting the function of almost all organ systems.[4] Thyroid function helps regulate breathing, heart and nervous system functions, body temperature, muscle strength, skin dryness, menstrual cycles, weight, and cholesterol levels.[10]

Figure 1. Regulation of Normal Production of Thyroid Hormones Via a Negative Feedback Loop



TSH, which is produced in the pituitary, is the primary regulator of thyroid function. It stimulates the thyroid to produce T4 and T3. Elevated levels of thyroid hormones inhibit production of TSH.
Source: Reference 10.

HYPOTHYROIDISM

Definition and Prevalence

The National Health and Nutrition Examination Survey (NHANES) III reports that hypothyroidism affects 3.7% of the United States population.[11] The mean age at diagnosis is 60 years, and the risk increases with age.[4] The risk is 5-fold greater in persons aged ≥80 years compared with those aged 12 to 49 years.[11] The incidence is 4 times greater in women than in men.[12]

POP QUIZ

Disease severity and effectiveness of treatment is monitored by:

A. TSH levels
B. T4 levels
C. T3 levels

Hypothyroidism is characterized by abnormally elevated TSH levels resulting from activation of the thyroid feedback loop to compensate for low levels of thyroid hormones, T4 and T3.[6] TSH levels are monitored to determine the severity of disease and the effects of treatment. The definition of an abnormal TSH level is controversial, and no absolute distinction between normal and abnormal is established.[5] Nonetheless, >95% of persons without thyroid disease have TSH levels <2.5 mIU/L, and the mean normal appears to be between 1.18 and 1.40 mIU/L.[5] Levels >2.5 mIU/L warrant careful assessment of the patient's thyroid status.[5]

Worldwide, the most common cause of hypothyroidism is iodine deficiency. In the developed world, where iodine consumption usually is sufficient, hypothyroidism most often is due to chronic autoimmune thyroiditis (Hashimoto's thyroiditis), a condition characterized by high levels of circulating antibodies directed against thyroid peroxidase (TABLE 1).[3,4,6] Hypothyroidism also may result from surgical removal of the thyroid gland, thyroid gland ablation by radioactive iodine, external irradiation,

Table 1. Common Primary and Secondary Causes of Hypothyroidism[a]

Primary
• Chronic autoimmune thyroiditis (Hashimoto's disease)[b]
• Surgical removal of the thyroid gland
• Thyroid gland ablation with radioactive iodine
• External irradiation
• Biosynthetic defect in iodine organification
• Replacement of the thyroid gland by tumor (lymphoma)
• Drugs (eg, lithium, interferon, amiodarone)
Secondary
• Pituitary and hypothalamic disease

[a]Worldwide, the primary cause of hypothyroidism is iodine deficiency; the causes listed here assume iodine sufficiency.
[b]Strongly associated with other autoimmune diseases such as vitiligo, rheumatoid arthritis, Addison's disease, diabetes mellitus, and pernicious anemia.
Source: References 4, 6.

a biosynthetic defect in iodine organification, replacement of the thyroid gland by tumor, or drugs such as lithium or interferon.[6] Secondary causes include pituitary or hypothalamic failure.

POP QUIZ

Symptoms of clinical hypothyroidism:

A. Are readily identified because they are specific to the condition
B. Become apparent at TSH levels >10 mIU/L
C. Include weight loss and diarrhea

Clinical Hypothyroidism

Clinical hypothyroidism is manifested by a wide range of nonspecific signs and symptoms, as listed in TABLE 2; these usually become apparent at a TSH level >10 mIU/L.[4] Symptoms are related to duration and severity of hypothyroidism and psychological characteristics of the patient.[6] Associated morbidity includes impairment across cognitive domains such as general intelligence, complex attention and concentration, memory, perceptual and visuospatial function, ability to use language, and executive functions.[2] Severe untreated hypothyroidism can lead to myxedema coma, an uncommon life-threatening condition.[1] In neonates, hypothyroidism causes feeding problems, failure to thrive, constipation, sleepiness, and, if untreated, mental retardation.[3] Affected children may experience impairment of linear growth and bone maturation.[3]

Changes in the cardiovascular system are a prominent feature of hypothyroidism.[3] The condition is characterized by bradycardia, decreased cardiac index, pericardial effusion, increased peripheral vascular resistance, decreased pulse pressure, elevation of mean arterial pressure, and, in its most extreme form, heart failure.[3,13] Dyslipidemia is common, as evidenced by increased levels of total and low-density lipoprotein cholesterol.[14] In fact, the mean cholesterol level may be 50% above normal.[14] According to a recent Chinese survey, the dyslipidemia associated with elevated TSH may reflect a heightened risk of other components of metabolic syndrome, such as overweight/obesity, hyperglycemia, and hypertension.[15]

Subclinical Hypothyroidism

In its subclinical form, hypothyroidism symptoms are minimal or absent but serum TSH levels are elevated in the presence of normal levels of free T4 and free T3.[6] Subclinical hypothyroidism is more prevalent than overt disease, affecting 4.3% to 9% of the general population.[16,17] It is diagnosed in ≤20% of persons aged >60 years and is more common in women and persons with

Table 2. Signs and Symptoms of Hypothyroidism in Descending Order of Frequency

Symptoms
• Tiredness, weakness
• Feeling cold
• Hair loss
• Difficulty concentrating and poor memory
• Constipation
• Weight gain with poor appetite
• Dyspnea
• Hoarse voice
• Menorrhagia (later oligomenorrhea or amenorrhea)
• Paresthesia
• Impaired hearing
Signs
• Dry coarse skin; cool peripheral extremities
• Puffy face, hands, and feet (myxedema)
• Diffuse alopecia
• Bradycardia
• Peripheral edema
• Delayed tendon reflex relaxation
• Carpal tunnel syndrome
• Serouscavity effusions

Source: Reference 4.

greater dietary iodine intake.[6] Some patients revert to a euthyroid state, while others progress to overt disease. The risk of progression is highest in those with TSH >2.0 mIU/L, women, the elderly, and persons with thyroid peroxidase antibodies.[16]

In some persons, subclinical hypothyroidism is manifested by subtle findings (alterations in lipid metabolism; or cardiac, gastrointestinal, neuropsychiatric, and reproductive abnormalities) or goiter.[6] The connection between subclinical hypothyroidism and heightened cardiovascular risk is contentious, although there is a preliminary indication of an association with hyperlipidemia, arterial hypertension, and cardiovascular disease (CVD), as well as serum C-reactive protein and retinol binding protein 4 levels.[18,19] Evidence to date suggests a continuum in the cardiac changes associated with subclinical disease through hypothyroidism.[16]

POP QUIZ

Benefits associated with thyroid replacement therapy include all of the following *except:*

A. Improvements in cognitive function
B. Improved sense of well-being
C. Reversing dyslipidemia
D. Lessening the severity of hypertension

TREATMENT INDICATIONS AND BENEFITS

Hormone replacement therapy is indicated for all patients with clinical hypothyroidism.[6] The goals of therapy are to normalize TSH concentrations (or T4 levels in secondary hypothyroidism) and improve clinical well-being.[1,3] Optimizing thyroid hormone replacement is associated with reversing the dyslipidemia associated with hypothyroidism.[1,19] Treatment also has been associated with improvements in some aspects of cognitive functioning after 3 months.[2]

Just as the definition of normal TSH levels has been debated,[5] so has the goal of levothyroxine therapy. Because >95% of persons without thyroid disease have TSH levels <2.5 mIU/L, that would appear to be a reasonable upper limit. However, some experts recommend limiting it to <2 mIU/L.[21] An arbitrary lower level of 0.4 mIU/L has been recommended; much lower levels are not advised because they are associated with risk of atrial fibrillation and bone loss.[7] Patients who have had thyroid cancer usually are taking higher doses of thyroxine and their target TSH level is lower than normal.[22]

The decision to treat subclinical hypothyroidism is controversial, since most patients are asymptomatic and many revert to normal thyroid status.[1] The American Association of Clinical Endocrinologists (AACE) recommends treatment when TSH levels exceed 10 mIU/L and when TSH levels are between 5 and 10 mIU/L in a patient with goiter or positive antithyroxidase antibodies.[6] Others suggest that it may be reasonable to treat those with cardiovascular risk factors, pregnant women, and women with ovulatory dysfunction and infertility because there is some evidence of benefit.[16] Studies of the effects of hormone replacement therapy on cardiovascular morbidity and mortality have yielded contradictory results in patients with subclinical hypothyroidism.[16] Middle-aged patients appear to derive greater benefit than elderly patients.[16]

POP QUIZ

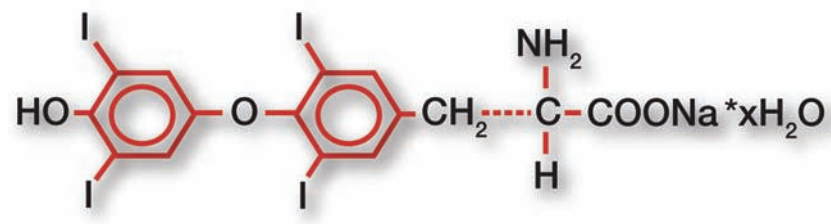
The standard of thyroid replacement therapy is:

A. Combination therapies
B. Levothyroxine
C. T3
D. T4

HORMONE REPLACEMENT OPTIONS

Hormone replacement has been the standard of treatment for hypothyroidism for more than a century.[7] The agent of choice is levothyroxine, which is identical to the T4 produced in the human thyroid gland (FIGURE 2).[6,23] Levothyroxine has several advantages: it can be given once daily, occasional missed doses are not harmful, and the extrathyroidal conversion of T4 into T3 remains operative, which may have some protective value during illness.[7]

Figure 2. Chemical Structure of Levothyroxine Sodium



The empirical formula is $C_{15}H_{10}I_4NNaO_4$.
Source: Reference 23.

Table 3. Varying Physiologic Levothyroxine Requirements According to Patient Age and Pregnancy Status

Patient Status	T4 Requirement (µg/kg body weight)
Neonate	10-15
Children 8-12 months	8-10
Children 2-10 years	4-5
Adolescents	2-3
Adults	1.5
Elderly persons	1.0-1.2
Pregnant women	1.8-2.0

Source: Reference 21.

Other treatment options include T3 alone and 4:1 combinations of T4 and T3,[3] but in general, these are not recommended.[6] T3 has a short plasma half-life, necessitating ≥2 doses a day,[3] and it may be associated with palpitations.[7] The combination therapies are not physiologic, because the normal T4:T3 secretion ratio is approximately 11:1.[3] Moreover, clinical studies have not shown combination therapy to produce a better therapeutic response.[3,24,25]

Desiccated (dried and powdered) animal thyroid (Armour® Thyroid), now mainly obtained from pigs, was the most common form of thyroid therapy before the individual active thyroid hormones were discovered. Desiccated thyroid contains T4 and T3; but the balance of T4 and T3 in nonhuman animals is not the same as that in humans. In addition, the amounts of T4 and T3 can vary in every batch of desiccated thyroid, making it more difficult to moderate blood levels. Finally, because desiccated thyroid pills have binders, they are not completely "natural."[26] There is no evidence that desiccated thyroid has any advantage over synthetic T4—and may have notable disadvantages.[6,26]

LEVOTHYROXINE

Levothyroxine is metabolized to the more biologically active T3 in target tissues.[1] It has good oral bioavailability; between 70% and 80% of an administered dose is absorbed mostly in the stomach and small intestine.[1,3] The peak serum concentration is reached in 2 to 4 hours and the half-life is 190 hours.[21] It is available as tablets, gel capsules, and a lyophilized powder for injection.[3]

Levothyroxine can be administered once daily, preferably in a fasting state,[23] because absorption is reduced by concurrent ingestion of food.[3] In general, manufacturers recommend taking levothyroxine first thing in the morning with water 30 minutes before eating breakfast.[1] Alternatively, patients may take the medication at bedtime, when, according to 1 study, absorption may be better.[7] A fatty meal reduces absorption by 40%[19]; other foods to be avoided close to ingestion include coffee,[27] fruit juices, milk, and soy products.[28]

Because levothyroxine has a narrow therapeutic window, accurate dosing is critical.[8] Dosing should be based on the patient's lean body weight[3] and tailored to the individual patient.[6] The mean replacement dose is 1.6 µg/kg of body weight per day,[3] which translates into 100 to 125 µg/d for a person who weighs 60 to 75 kg.[1] Treatment generally may be initiated at the full replacement dose in young, healthy patients.[3] In the elderly (aged >60 years) or in cardiac patients, in whom there is a theoretical risk of treatment-induced cardiac ischemia, initiating therapy in a lower daily dose (12.5-50.0 µg) is appropriate.[1,3]

Dosage reassessment and titration are often required, and the maintenance dose may vary between 75 and 250 µg.[6,7] Factors such as age, weight, pregnancy status, medications, and comorbid conditions affect dosing requirements (TABLES 3 AND 4).[21] Larger doses

Table 4. Factors That May Affect Levothyroxine Bioavailability

Reduced absorption
Dietary fiber, soy, and whole grain products
Drugs: antacids: aluminum hydroxide, bile acid sequestrants, calcium carbonate, chromium picolinate, ferrous sulphate, phosphate binders, proton pump inhibitors, raloxifene, sucralfate
Malabsorption: atrophic gastritis, celiac disease, diabetic gastroparesis, *Helicobacter pylori* gastritis, small-bowel surgery
Increased clearance
Drugs: bexarotene, carbamazepine, estrogen compounds, phenobarbitone (phenobarbital), phenytoin, rifampin, sertraline
Nephrotic syndrome
Impaired T4 to T3 conversion
Amiodarone, lithium, propranolol
Other mechanisms
Drugs: ethionamide, lovastatin, simvastatin, tyrosine kinase inhibitors
Pregnancy
Reduced levothyroxine dosage requirements
Advancing age (>65 years)
Drugs that may decrease TSH without changing free T4
Metformin, dopamine, glucocorticoids, octreotide

Source: References 1, 3, 37.

may be needed for infants and children, premenopausal women, and those with primary autoimmune hypothyroidism.[29] Conversely, thyroxine requirements decline with advancing age due to reduced thyroid hormone metabolism.[29]

The test of choice for monitoring treatment efficacy in primary hypothyroidism is TSH level; in secondary or tertiary hypothyroidism, it is free T4 levels.[3] Follow-up monitoring to determine the new steady-state concentration should occur no sooner than 6 weeks after thyroid replacement is initiated or adjusted because of the drug's prolonged half-life.[3,23] Once a stable maintenance dose is established based on clinical response and TSH levels, annual evaluation generally is adequate.[7]

Treatment During Pregnancy

The requirement for thyroid hormone increases 20% to 40% during pregnancy.[30] In women with normal glandular function, the increased need is met by increased production of thyroid hormones. In women who are hypothyroid at the onset of pregnancy or who become so during pregnancy, thyroid hormone levels should be maintained within normal limits, especially during the first half of pregnancy, to maintain maternal health and fetal development.[6,30]

Levothyroxine is considered safe during pregnancy (category A drug) because thyroid hormones do not readily cross the placental barrier.[6,23] Ideally, hypothyroid women should be given increased dosages of levothyroxine before they become pregnant. For those who are already taking hormone replacement therapy, increasing the dosage by 2 tablets a week at confirmation of pregnancy may reduce the risk of maternal hypothyroidism.[30] By 4 to 6 weeks' gestation, the dosage can be adjusted incrementally up to 30% to 50% of baseline.[31] When hypothyroidism is diagnosed during pregnancy, therapy should be instituted rapidly. The goal is to maintain TSH levels <2.5 mIU/L during the first trimester or <3 mIU/L during the second and third trimesters.[31] Less is known about whether treatment is warranted for pregnant women with subclinical hypothyroidism. Given that potential benefits outweigh potential risks, the Endocrine Society supports hormone replacement in this population.[31]

Among patients treated with thyroid replacement, those who are under- or overmedicated may be at risk for adverse health consequences associated with endogenous hypothyroidism or hyperthyroidism.

POP QUIZ

About 10% of patients treated with thyroid replacement are under- or overtreated.

A. True

B. False

Perils of Under- or Overtreament

Of patients treated with levothyroxine, 30% to 60% do not reach biochemical euthyroidism, that is, they are either undertreated or overtreated. In the Colorado Thyroid Disease Prevalence study, only 60% of people taking thyroid medication had normal serum TSH values.[32] Biochemical data from NHANES revealed that 15% of those with confirmed thyroid disease or taking thyroid medications are hypothyroid, and 18.3% are hyperthyroid.[17] In a large North American study, only 43% of patients aged >65 years were biochemically euthyroid while receiving levothyroxine.[33] Even in the United Kingdom, which rewards primary care physicians for taking the time to monitor treatment, TSH remains out of range in approximately 37% of patients.[1]

Patients who are under- or overmedicated may be at risk for adverse health consequences associated with endogenous hypothyroidism or hyperthyroidism.[1] Undertreatment may be associated with a heightened risk of CVD, particularly when serum TSH is >4.0 mIU/L.[34] The risk appears to be higher in men. The risks of overtreatment with TSH levels ≤0.1 mIU/L include atrial fibrillation, lower bone mineral density and bone quality, and fracture.[1,7,35] Older adults (aged ≥70 years) taking levothyroxine may be at significantly increased risk of fracture, with a strong dose-response relationship.[35] Overtreatment to TSH levels ≤0.03 mIU/L also may increase risk of CVD, although not to the same degree as undertreatment.[34]

Adherence

Little objective information is available about patient adherence, although most clinicians believe nonadherence is common. Estimates of nonadherence range from

22% to 82% of patients.[1] Reasons for not taking medications are forgetfulness, intolerance or side effects, and inability to pay.[36] Since omitting a dose does not immediately lead to symptom recurrence, patients do not experience the consequences of their behavior the next day.[36] One of the risks of nonadherence is that the physician will increase the dosage of levothyroxine unnecessarily when TSH results indicate inadequate control.[1,36] For patients who are persistently nonadherent, levothyroxine may be dosed once a week, although this solution is not ideal, especially for patients with a history of CVD.[3]

Comorbid Conditions

Several comorbid conditions can interfere with the absorption or increase the clearance of levothyroxine (TABLE 4).[1,3,6,37] Because gastric acidity is important for absorption of levothyroxine, conditions characterized by impaired gastric acid secretion may necessitate greater doses.[36] Celiac disease and autoimmune gastritis frequently coexist with hypothyroidism, but often are clinically silent. The requirement for high doses of levothyroxine should prompt suspicion that they may be a factor.[1] In addition, *Helicobacter pylori* gastritis and atrophic gastritis, separately or together, may affect dose requirements.

Thyroiditis affects approximately 10% of patients with type 1 diabetes[6] and can present a complex clinical picture.[1] Patients with diabetes may be subject to polypharmacy, gastroparesis, obesity, and hypoglycemic emergencies, all of which can influence levothyroxine requirements.[1] These patients may be at particularly high risk of over- or undertreatment.[33]

Drug Interactions

A wide range of drugs may interfere with levothyroxine absorption, metabolism, and action (TABLE 4).[3] A few are of particular prominence and interest.

Hypothyroid patients with gastritis should be warned that calcium- and aluminum-containing antacids may decrease absorption of levothyroxine.[23] The manufacturers recommend that levothyroxine and antacids be taken at least 4 hours apart[23] to minimize the risk. It is not clear whether proton-pump inhibitors (PPIs) affect levothyroxine absorption. Some studies have concluded that PPI therapy may necessitate an increased dosage of levothyroxine.[38-40] For patients taking both levothyroxine and a PPI, some experts suggest checking thyroid function tests after 6 months of combined therapy, especially if symptoms of hypothyroidism become apparent.[41] If necessary, the dosage of levothyroxine can be adjusted.

Amiodarone, an antiarrhythmic agent, contains 37% iodine by weight and may impair conversion of T4 to the highly active compound T3.[3] Serum T4 levels rise by 20% to 40% during the first month of therapy, then gradually decrease to the upper range of normal.[42] At the same time, serum T3 levels decrease by up to 30% within the first few weeks of therapy and remain slightly decreased or low-normal. TSH levels usually increase after initiation of amiodarone but return to normal in 2-3 months. Thyroid abnormalities have been noted in 14% to 18% of patients receiving long-term amiodarone therapy, although with lower doses (150-330 mg), the incidence of thyroid dysfunction is 3.7%. The abnormalities range from abnormal thyroid function test findings to overt thyroid dysfunction, which manifest as thyrotoxicosis or hypothyroidism. Both conditions can develop in apparently normal thyroid glands or in glands with preexisting abnormalities.[42]

Persistent Symptoms Despite Normal TSH

Some patients report a lack of well-being, despite reaching euthyroid reference range of TSH.[1,5] These patients often exhibit significant psychological impairment compared with age- and sex-matched controls.[1] Their symp-

Table 5. Therapeutic Equivalents for Approved Levothyroxine Products

Product	Manufacturer	Therapeutic Equivalents
Levo-T®	Alara Pharm	Levoxyl®, Synthroid®, Unithroid®, Levothyroxine sodium (Merck KGAA, Mylan)
Levoxyl®	Jones Pharma/King	Levo-T®, Synthroid®, Unithroid®, Levothyroxine sodium (Merck KGAA, Mylan)
Synthroid®	Abbott	Levo-T®, Levoxyl®, Unithroid®, Levothyroxine sodium (Merck KGAA, Mylan)
Unithroid®	Jerome Stevens	Levo-T®, Levoxyl®, Synthroid®, Levothyroxine sodium (Merck KGAA, Mylan)
Levothroid®	Lloyd	Levothyroxine Sodium (Mylan)
Tirosint® (soft gel capsule)	Institute Biochimique	None

Source: Adapted from References 43, 44.

toms might be better controlled with TSH levels at the lower end of the reference range.[5] But because the common symptoms of hypothyroidism are relatively nonspecific, another comorbid condition may account for the continued symptoms.[1] Persistent fatigue, for example, could reflect anemia, obesity, depression, a postviral syndrome, or obstructive sleep apnea.[1] Other autoimmune conditions that should be considered include Addison's disease, diabetes mellitus, and celiac disease.[1]

LEVOTHYROXINE PREPARATIONS

Several levothyroxine preparations are available. Agents designated by the U.S. Food and Drug Administration (FDA) as therapeutically equivalent are listed in TABLE 5.[43,44] The FDA originally proposed a potency standard of 90% to 110%[3]; but in 1997, after widespread concern about the bioequivalence of different products, the FDA imposed revised standards of 95% to 105% to regulate generic levothyroxine products and avoid adverse events attributable to interproduct variability.[43] Four brand name levothyroxine preparations are available—3 are designated as unique and not interchangeable with one another.[8] In addition, 4 generic preparations are designated equivalent to ≥1 of 4 name brands.[8]

Have the revised standards ensured bioequivalence of the available preparations? A recent survey of physicians who treat patients with hypothyroidism revealed abundant clinical evidence of product differences.[8] There were 198 reports of adverse events, including emergency or urgent visits to health care providers and missed work. Of these, 177 (89.4%) were associated with a change in the source of levothyroxine, usually to an approved generic product. These exchanges were done by the patient's pharmacy without the clinician's knowledge. Physician lack of awareness of the switch meant follow-up testing may not have been implemented. Most cases involved generic substitution for brand name levothyroxine products. Additional data on this issue can be expected with publication of the results of an ongoing clinical study evaluating whether differences between levothyroxine formulations affect thyroid functioning.[45] Given the unsettled issues about bioequivalence, the AACE recommends that patients receive the same brand of levothyroxine throughout treatment.[6]

ROLE OF THE PHARMACIST

Pharmacists are in an excellent position to educate the patient with thyroid dysfunction about the basics of thyroid physiology and pathophysiology. In particular, that means reinforcing the need to normalize thyroid hormone levels to maintain basic metabolic functioning. It may be necessary to emphasize that hypothyroidism necessitates a lifetime commitment to hormone replacement therapy to minimize the risk of adverse cardiovascular and cognitive events. Pharmacists also need to urge patients using over-the-counter products, dietary supplements, and herbal therapies to consult with their clinician to assure they are receiving optimal therapy. Pharmacists can identify patients with continued symptoms and assess the underlying causes, such as poor adherence, comorbidities, drug interactions, and a change in levothyroxine preparation. To manage patients with hypothyroidism, pharmacists should review the principles governing narrow-therapeutic-index drugs and bioequivalence of levothyroxine sodium as established by the FDA guidelines. When in doubt, pharmacists should consult the FDA *Orange Book* to verify levothyroxine therapeutic equivalence. The AACE and the American Thyroid Association are expected to publish revised guidelines on the management of hypothyroidism in the near future. In light of many long-standing questions, such as the indications for treating subclinical hypothyroidism and the appropriate TSH target range, these guidelines should prove to be useful.

How to Receive Credit

Participants wishing to earn CPE credit must:

- Read the supplement.
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REFERENCES

1. Okosieme OE. Thyroid hormone replacement: current status and challenges. *Expert Opin Pharmacother.* 2011;12:2315-2328.

2. Dugbarty AT. Neurocognitive aspects of hypothyroidism. *Arch Intern Med.* 1998;158:1413-1418.

3. Brent GA, Koenig RJ. Thyroid and anti-thyroid drugs. In: Brunton LL, Chabner B, Knollman B, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics.* 12th ed. New York, NY: McGraw-Hill; 2011:1129-1162.

4. Jameson JL, Weetman AP. Disorders of the thyroid gland. In: Fauci AS, Braunwald E, Kasper DL, et al, eds. *Harrison's Principles of Internal Medicine.* 17th ed. New York, NY: McGraw-Hill; 2009:2224-2247.

5. Wartofsky L, Dickey RA. The evidence for a narrower thyrotropin reference range is compelling. *J Clin Endocrinol Metab.* 2005;90:5483-5488.

6. AACE Thyroid Task Force. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidism and hypothyroidism. *Endocrin Pract*. 2002;8:457-469.

7. Wiersinga WM. Thyroid hormone replacement therapy. *Horm Res*. 2001;56(suppl 1):74-81.

8. Bolk N, Vissner TJ, Nihman J, Jongste IJ, Tijssen JG, Berghour A. Effects of evening vs morning levothyroxine intake: a randomized double-blind crossover trial. *Arch Intern Med.* 2010;170:1996-2003.

9. Hennessey JV, Malaban AO, Haugen BR, Levy EG. Adverse event reporting in patients treated with levothyroxine: results of the Pharmacovigilance Task Force Survey of the American Thyroid Association, American Association of Clinical Endocrinologists and the Endocrine Society. *Endocr Pract*. 2010;11:1-41.

10. NIH. Hypothyroidism. http://www.endocrine.niddk.nih.gov/pubs/Hypothyroidism/#hypothyroidism. Accessed November 21, 2011.

11. Aoki Y, Belin RM, Clickner R, Jeffries R, Phillips L, Mahaffey KR. Serum TSH and total T4 in the United States population and their association with participant characteristics: National Health and Nutrition Examination Survey (NHANES 1999-2002). *Thyroid.* 2007;17:1211-1223.

12. McGrogan A, Seamen HE, Wright JW, Vries CS. The incidence of autoimmune thyroid disease: a systematic review of the literature. *Clin Endocrinol.* 2008;69:687-696.

13. Muller AF, Berghout A, WiersingaWM, et al. Thyroid function disorders—guidelines of the Netherlands Association of Internal Medicine. *Netherlands J Med*. 2008;66:134-142.

14. Duntas LH. Thyroid disease and lipids. *Thyroid*. 2002;12:287-293.

15. Lai Y, Wang J, Jiang F, et al. The relationship between serum thyrotropin and components of metabolic syndrome. *Endocrine J*. 2011;58:23-30.

16. Biondi B, Cooper DS. The clinical significance of subclinical thyroid dysfunction. *Endocrinol Rev.* 2008;29:76-131.

17. Hollowell JG, Staehling NW, Flanders WD, et al. Serum TSH, T4, and thyroid antibodies in the United States population (1988 to 1994) National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab.* 2002;87:489-499.

18. Duntas LH, Biondi B. New insights into subclinical hypothyroidism and cardiovascular risk. *Semin Thromb Hemost*. 2011;37:27-34.

19. Lu L, Wan B, Shan Z, et al. The correlation between thyrotropin and dyslipidemia in a population-based study. *J Korean Med Sci.* 2011;26:242-249.

20. Tagami T, Tamanaha T, Shimazu S, et al. Lipid profiles in the untreated patients with Hashimoto thyroiditis and the effects of thyroxine treatment of subclinical hypothyroidism with Hashimoto thyroiditis. *Endocrin J*. 2010;57:253-258.

21. Schäffler A. Hormone replacement after thyroid and parathyroid surgery. *Dtsch Arztebl Int.* 2010;107:827-834.

22. American Thyroid Association. Thyroid. Q&A. http://www.thyroid.org/patients/qanda/060227tsh.html. Accessed November 21, 2011.

23. Synthroid® (levothyroxine sodium) [package insert]. North Chicago, IL: Abbott Laboratories; 2011. http://www.rxabbott.com/pdf/Synthroid.pdf. Accessed November 21, 2011.

24. Jonklaas J, Davidson B, Bhagat S, et al. Triiodothyronine levels in athyreatoic individuals during levothyroxine therapy. *JAMA.* 2008;299:769-777.

25. Wartofsky L. Levothyroxine therapy alone restores normal serum FT3 levels after total thyroidectomy (editorial). *Clin Thyroidol*. 2008;20:6-7.

26. American Thyroid Association. Thyroid hormone treatment brochure. 2005. http://www.thyroid.org/patients/patient_brochures/hormonetreatment.html. Accessed November 21, 2011.

27. Benvenga S, Bartolone L, Pappalardo MA, et al. Altered intestinal absorption of L-thyroxine caused by coffee. *Thyroid.* 2008;18:293-301.

28. Morris JC. How do you approach the problem of TSH elevation in a patient on high-dose thyroid hormone replacement? *Clin Endocrinol (Oxf).* 2009;70:671-673.

29. Mandel SJ Brent GA, Larsen PR. Levothyroxine therapy in patients with thyroid disease. *Ann Intern Med*. 1993;119:492-502.

30. Yassa L, Marqusee E, Fawcett R, Alexander EK. Thyroid hormone early adjustment in pregnancy (The THERAPY) Trial. *J Clin Endocrinol Metab.* 2010;95:3234-3241.

31. Endocrine Society. Management of thyroid dysfunction during pregnancy and postpartum: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2007;92(8 suppl):S1-S47.

32. Canaris CJ, Manowitz MR, Mayor G, Ridgway E. The Colorado Thyroid Disease Prevalence Study. *Arch Intern Med.* 2000;160:526-534.

33. Somwaru LL, Arnold AM, Joshi N, Fried LP, Cappola AR. High frequency of and factors associated with thyroid hormone over-replacement and under-replacement in men and women aged 65 and over. *J Clin Endocrinol Metab*. 2009;94:1342-1345.

34. Flynn RW, Bonellie SR, Jung RT, MacDonald TM, Morris AD, Leese GP. Serum thyroid-stimulating hormone concentration and morbidity from cardiovascular disease and fractures in patients on long-term thyroxine therapy. *J Clin Endocrin Metab.* 2010;95:186-193.

35. Turner MR, Camacho X, Fischer H, et al. Levothyroxine dose and risk of fractures in older adults: nested case-control study. *BMJ.* 2011;342:d2238. Accessed November 21, 2011.

36. Ward LS. The difficult patient: drug interaction and the influence of concomitant diseases on the treatment of hypothyroidism. *Arq Bras Endocrinol Metab*. 2010;54:435-442.

37. Surks MI, Sievert R. Drugs and thyroid function. *N Engl J Med.* 1995;333:1688-1694.

38. Ananthrakrishnan S, Braverman LE, Levin RM, Magnani B, Pearce EN. The effect of famotidine, esomeprazole, and ezetimibe on levothyroxine absorption. *Thyroid.* 2009;18:493-498.

39. Sachemchi I, Reich DM, Aninyei M, Wibowo F, Gupta G, Kim PJ. Effect of proton pump inhibitors on serum thyroid-stimulating hormone level in euthyroid patients treated with levothyroxine for hypothyroidism. *Endocr Pract.* 2007;13:345-349.

40. Dietrich JW, Gieselbrecht K, Holl RW, Boehm BO. Absorption kinetics of levothyroxine is not altered by proton-pump inhibitor therapy. *Horm Metab Res*. 2006;38:57-59.

41. Hulisz DT. Do PPIs interact with levothyroxine? http://www.medscape.com/viewarticle/742089. Accessed November 21, 2011.

42. Gopalan M. Thyroid dysfunction induced by amiodarone therapy. http://emedicine.medscape.com/article/129033-overview#a0199. Accessed November 21, 2011.

43. Food and Drug Administration. Orange Book: Approved drug products with therapeutic equivalence evaluations. 31st ed. http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed November 21, 2011.

44. Food and Drug Administration. Questions and answers on levothyroxine sodium products. http://www.fda.gov/Drugs/DrugSafety PostmarketDrug SafetyInformationforPatientsandProviders/ucm161266.htm. Accessed November 21, 2011.

45. ClinicalTrials.gov. http://clinicaltrials.gov/ct2/show/NCT00403390?term=levothyroxine&rank=7. Accessed November 21, 2011.

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