

How should thyroid replacement be initiated?

■ EVIDENCE-BASED ANSWER

Levothyroxine (LT4) should be used alone as initial replacement for patients with hypothyroidism (strength of recommendation [SOR]: **A**). The optimal initial dose is 1.6 µg/kg/d for healthy people aged 60 years or younger (SOR: **B**). Patients aged more than 60 years may require less levothyroxine to achieve therapeutic serum thyroid hormone replacement, so initial replacement should be decreased to 25 to 50 µg daily (SOR: **C**).

Since patients with known heart disease may develop dysrhythmias, angina, and myocardial infarctions when started on full replacement doses, experts recommend starting 12.5 to 25 µg daily for this population (SOR: **C**). Brand-name (Synthroid, Levoxyl, etc) and generic LT4 are bioequivalent (SOR: **B**), although the US Food and Drug Administration (FDA) does not consider these products to be interchangeable until proven therapeutically equivalent.

■ EVIDENCE SUMMARY

Initial thyroid replacement with synthetic LT4 is recommended because LT4 is safe, effective, reliably relieves symptoms, and normalizes lab tests for hypothyroid patients.^{1,2}

Two recent randomized trials comparing LT4 alone or LT4 and LT3 together for a total of 86 adult hypothyroid patients found similar outcomes. One study, which enrolled patients with hypothyroidism and mild depressive symptoms, assessed scores on the Symptom Check-List-90, the Comprehensive Epidemiological Screens for Depression, and the Medical Outcomes Study health status questionnaire at baseline and multiple times over the duration of the study. For these outcomes, no differences were found between the LT4 alone and combination LT4-LT3 treatment groups within 90% confidence intervals.³ A second study assessed changes in body weight, lipid pro-

file, hypothyroid-specific health-related quality-of-life scores, and 13 neuropsychological measures pre- and posttreatment. This study detected no difference in body weight and serum lipids at baseline and after treatment. The hypothyroid-specific health-related quality-of-life scores similarly improved for both treatment groups. Twelve of 13 neuropsychological tests demonstrated no differences between treatment groups; the Grooved Peg Board Test of manual dexterity and fine visual-motor coordination demonstrated a slight improvement for the LT4 alone treatment group.⁴

The initial dose of LT4 can be based on the age and health status of the patient. The mean replacement dose of LT4 is 1.6 µg/kg/d for healthy patients aged ≤60 years.⁵⁻⁷ Patients aged >60 years should be started on 25 to 50 µg daily. An uncontrolled cohort study of 84 patients found that for patients aged >60 years, 25- to 50-µg doses of LT4 resulted in similar serum thyrotropin (TSH) levels as the higher (1.6 µg/kg/d) doses required for younger patients.⁷ Based on expert opinion, patients of any age with heart disease should be given lower doses of 12.5 to 25 µg daily as initial treatment.^{1,2}

The choice of the LT4 preparation continues to be debated. In 1997, a bioequivalence study compared 2 generic brands to 2 name brands by having 22 women with hypothyroidism, who were euthyroid on replacement medication, take each preparation for 6 weeks.⁸ The area under the curve, peak serum concentration, and time to peak concentration for 3 indexes of thyroid function (thyroxine, triiodothyronine, and free T4 index) were not significantly different and met the FDA criterion for relative bioequivalence. However, they did not examine therapeutic equivalence and from a clinical perspective, some researchers and pharmaceutical companies felt that the authors could not comment on whether the products were interchangeable.^{8,9} The FDA now requires thyroxine bioavailability and bioequivalence studies to evaluate product substitution.¹⁰ The FDA lists Levothyroxine Sodium (Mylan) to be therapeutically equivalent and therefore interchangeable with Unithroid.¹¹

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■ RECOMMENDATIONS FROM OTHERS

The American Association of Clinical Endocrinologists Thyroid Task Force recommends the use of a high-quality brand preparation of LT₄ rather than desiccated thyroid hormone, combinations of thyroid hormones, or LT₃.¹² It recommends a mean replacement dosage of LT₄ of 1.6 µg/kg of body weight per day with initial dose ranging from 12.5 µg daily to a full replacement dosage based on the age, weight, and cardiac status of the patient.

UpToDate states that although LT₄ products are standardized, subtle differences between preparations exist, and products should be interchanged only with sufficient monitoring after the change. In addition, they recommend generally avoiding generics because the pharmacy may interchange products without physicians being aware.¹ The Physicians' Information and Education Resource from the American College of Physicians states "Name-brand LT₄ products provide more consistent potency than generic preparations. The cost of brand-name LT₄ products is only slightly more than that of generic preparations."²

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■ CLINICAL COMMENTARY

Instruct patients about the timing of levothyroxine and potential interactions

The starting dose of levothyroxine for hypothyroid patients is based on age, severity of the disease, duration of the disease, and existing comorbid conditions. For healthy adults 60 years of age or younger, the optimal starting dose is 1.6 µg/kg/d. For patients more than 60 years of age, the initial dose is 25 to 50 µg/d. To avoid cardiac complications among persons with known heart disease, the recommended initial levothyroxine dose is 12.5 µg/d. In my experience, these guidelines work well in initiating treatment for hypothyroidism.

Few of my patients have noted any difference between generic and brand-name thyroid supplements. Knowing what other medications the patient is taking is important, since medications such as estrogen can decrease the bioavailability of levothyroxine by increasing binding proteins. It is also important to instruct patients about the timing of levothyroxine intake, because some medications can affect absorption (eg, cholestyramine, calcium, or iron).

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