

# **HYPOTHYROIDISM TREATMENT FAILURE: DIFFERENTIAL DIAGNOSIS**

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## Hypothyroidism Treatment Failure: Differential Diagnosis

Several guidelines and treatment algorithms provide initial dosing and titration schedules for thyroid hormone replacement therapy in patients with hypothyroidism due to autoimmune thyroiditis or following thyroidectomy for benign thyroid disease.<sup>1-4</sup> In patients who suffer from these conditions, the target thyroid stimulating hormone (TSH, thyrotropin) range with levothyroxine (LT<sub>4</sub>) treatment is 0.5 mIU/L to 2.0 mIU/L,<sup>5</sup> whereas TSH target concentrations are significantly lower for patients undergoing TSH suppression following thyroidectomy for thyroid cancer: from <0.1 mIU/L to 1.0 mIU/L, depending on risk of cancer recurrence.

Levothyroxine must be titrated over several weeks to achieve TSH concentrations within these target ranges. Once LT<sub>4</sub> has been titrated to the maintenance dose, few compliant patients will experience major fluctuations in their TSH concentration or exhibit the signs and symptoms of either hypo- or hyperthyroidism.

Far and away the most common reason for LT<sub>4</sub> therapy failure leading to TSH concentrations above the target range is noncompliance (Figure 1). Patients are more likely to adhere to a treatment regimen when they feel informed about their disease and its treatment, and clinicians can greatly improve patient compliance with LT<sub>4</sub> therapy by discussing the importance of taking their medication on the prescribed schedule and by actively directing patients to educational resources. Several Web-based resources are available that include information for both clinicians and patients:

- The American Thyroid Association Web site: [www.thyroid.org](http://www.thyroid.org)
- The Hormone Foundation (an affiliate of The Endocrine Society): [www.hormone.org](http://www.hormone.org)
- Thyroid Awareness Month Web site (sponsored by the American Association of Clinical Endocrinologists): [www.aace.com/pub/tam2004/index.php](http://www.aace.com/pub/tam2004/index.php)
- ThyroidToday.com

When noncompliance is ruled out as the cause for treatment failure, abrupt changes in TSH concentration can be explained by other factors, including LT<sub>4</sub> product switching, pregnancy or estrogen treatment, or the initiation of treatment for a nonthyroidal illness with certain medications (Figure 1, see below). Physicians are under increasing pressure by health care decision makers to prescribe generic medications, despite the fact that studies have demonstrated that small differences in LT<sub>4</sub> product formulation or dose can cause clinically significant increases or decreases in TSH concentrations that could be detrimental to an individual patient.<sup>6-8</sup> Sometimes an LT<sub>4</sub> product switch occurs without the knowledge of either the prescribing physician or the consulting physician.

Based on US Food and Drug Administration (FDA) bioequivalence testing, only 1 generic LT<sub>4</sub> compound has been established as bioequivalent to, and thus interchangeable with, a single branded LT<sub>4</sub> product, Unithroid™.<sup>9</sup> All other branded LT<sub>4</sub> products are not interchangeable, leading several important medical organizations in the endocrinology field to suggest caution before substituting LT<sub>4</sub> products.<sup>10,11</sup> Patients who have experienced an increase or decrease in TSH concentration as a consequence of LT<sub>4</sub> product switching should either be returned to the original LT<sub>4</sub> product or have the dose of the new LT<sub>4</sub> product adjusted to achieve TSH

concentrations within the target range of 0.5 mIU/L to 2.0 mIU/L.<sup>5</sup> This latter recommendation can only be achieved by rechecking serum TSH 6 to 8 weeks after the patient has started taking the new LT<sub>4</sub> product.

Finally, certain coexisting conditions and medications can either interfere with LT<sub>4</sub> absorption or enhance LT<sub>4</sub> clearance, resulting in decreased bioavailability of LT<sub>4</sub> that can lead to insufficient TSH suppression and the possible development of hypothyroid signs and symptoms (Table 1).<sup>12</sup> Dietary fiber, bile acid sequestrants, and iron supplements can interfere with LT<sub>4</sub> absorption, thereby increasing the dose required for clinical benefit.<sup>12,13</sup> By increasing serum thyroxine binding globulin (TBG) levels, estrogen (from oral contraceptive pills, hormone replacement therapy, or during pregnancy) can also increase the LT<sub>4</sub> dose needed to maintain normal TSH concentrations.<sup>12</sup> Several other drugs may decrease the efficacy of LT<sub>4</sub> therapy by enhancing the metabolism and clearance of thyroxine (T<sub>4</sub>) or decreasing the conversion of T<sub>4</sub> to triiodothyronine (T<sub>3</sub>), including anticonvulsant medications, rifampicin, and sertraline.<sup>12,14</sup> Adjustment of LT<sub>4</sub> dose or time of administration may be necessary to avoid the adverse effects of these agents.

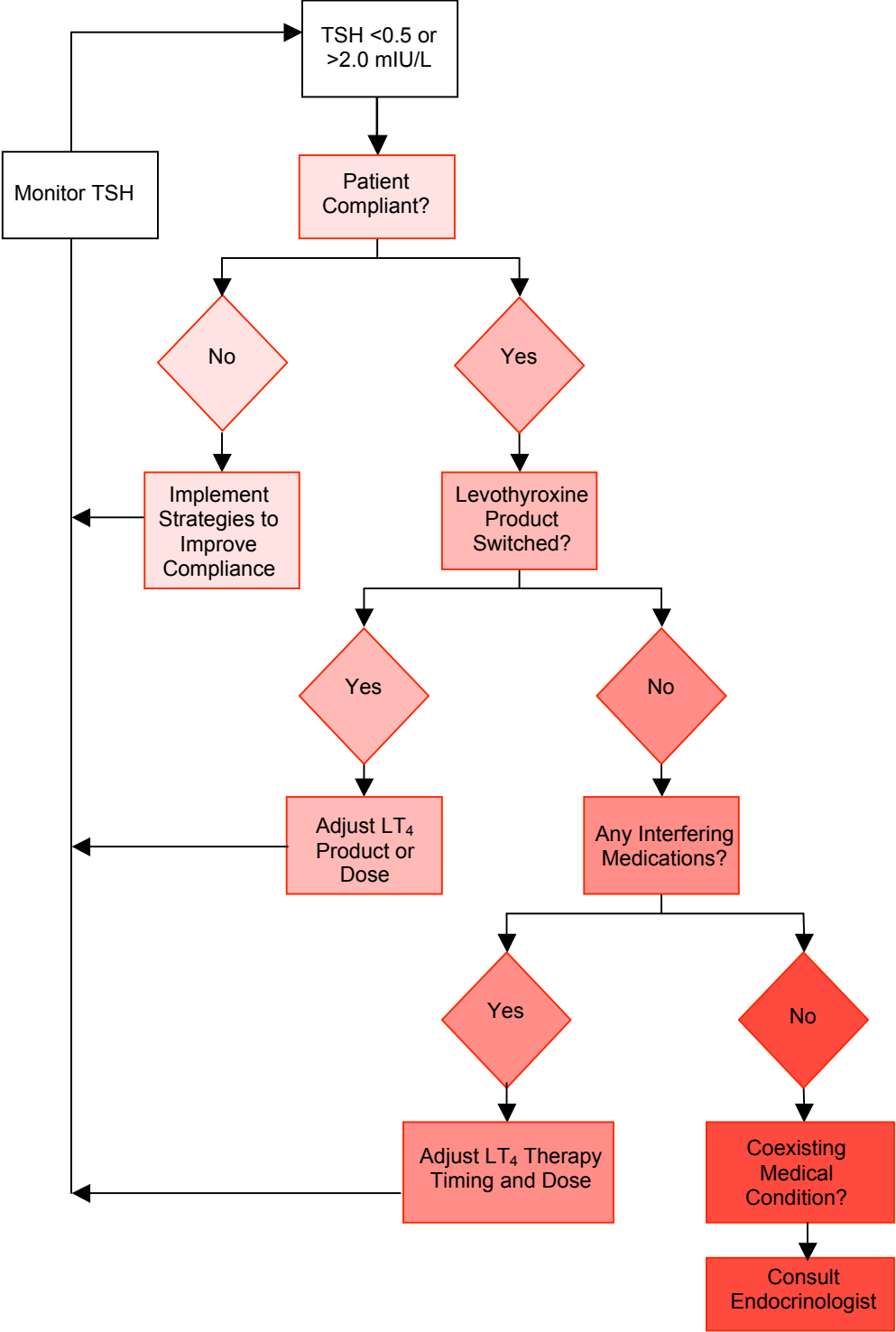
**Table 1. Conditions and Medications That Can Reduce LT<sub>4</sub> Efficacy.**<sup>12</sup>

<b>Effect</b>	<b>Condition/Drug</b>
Decreased LT <sub>4</sub> absorption	Malabsorptive disorders
	Dietary fiber
	Bile acid sequestrants (cholestyramine)
	Aluminum hydroxide
	Calcium carbonate
	Ferrous sulfate
	Sucralfate
Increased T <sub>4</sub> clearance	Anticonvulsants (phenytoin, carbamazepine, phenobarbital)
	Antibiotics (rifampicin)
Decreased conversion to T <sub>3</sub>	Antidepressants (sertraline)
Other mechanisms	Amiodarone
	Estrogen

In pregnancy, as well as with estrogen therapy, there is an increased requirement for LT<sub>4</sub> because of an increase in TBG.<sup>15</sup> An increase in lean body mass also increases the LT<sub>4</sub> dose requirement, whereas the loss of lean body mass, usually as a consequence of aging, decreases the LT<sub>4</sub> dose requirement.

Compliant patients who have not undergone product switching but who continue to have inconsistent TSH and thyroid hormone laboratory values should be referred to an endocrinologist for evaluation of underlying pathologies. Sometimes the results from biochemical blood tests and the patient's symptoms are inconsistent and difficult to evaluate. In these cases, an endocrinologist, who is experienced in handling complex thyroid disease, is usually the best consultation resource for the primary care physician. Often, 1 or 2 visits by a patient to such a specialist can save precious time and unnecessary expense involved in retesting and diagnosis of a complex thyroid problem.

**Figure 1. Hypothyroidism Treatment Failure: Differential Diagnosis**



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