Thyroid hormones—levothyroxine (Synthroid, Levothroid, Levoxine) and liothyronine (Cytomel)—are used in psychiatry either alone or as augmentation to treat persons with depression or rapid-cycling bipolar I disorder. They can convert an antidepressant-nonresponsive person into an antidepressant-responsive person. Thyroid hormones are also used as replacement therapy for persons treated with lithium (Eskalith) who have developed a hypothyroid state. Successful use of thyroid hormone as an intervention for treatment-resistant patients was first reported in the early 1970s. Study results since then have been mixed; however, most show that patients taking triiodothyronine (T₃) are twice as likely to respond to antidepressant treatment versus placebo. These studies have found that augmentation with T₃ is effective with tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs). Nevertheless, many endocrinologists object to the use of thyroid hormones as antidepressant augmentation agents, citing such risks as osteoporosis and cardiac arrhythmias.

PHARMACOLOGIC ACTIONS

Thyroid hormones are administered orally, and their absorption from the gastrointestinal tract is variable. Absorption is increased if the drug is administered on an empty stomach. In the brain, T₄ (thyroxine) crosses the blood–brain barrier and diffuses into neurons, where it is converted into T₃, which is the physiologically active form. The half-life of T₄ is 6 to 7 days, and that of T₃ is 1 to 2 days. The mechanism of action for thyroid hormone effects on antidepressant efficacy is unknown. Thyroid hormone binds to intracellular receptors that regulate the transcription of a wide range of genes, including several receptors for neurotransmitters.

THERAPEUTIC INDICATIONS

The major indication for thyroid hormones in psychiatry is as an adjuvant to antidepressants. There is no clear correlation between the laboratory measures of thyroid function and the response to thyroid hormone supplementation of antidepressants. If a patient has not responded to a 6-week course of antidepressants at appropriate dosages, adjuvant therapy with either lithium or a thyroid hormone is an alternative. Most clinicians use adjuvant lithium before trying a thyroid hormone. Several controlled trials have indicated that liothyronine use converts about 50% of antidepressant nonresponders to responders.
The dosage of liothyronine is 25 or 50 μg a day added to the patient’s antidepressant regimen. Liothyronine has been used primarily as an adjuvant for tricyclic drugs; however, evidence suggests that liothyronine augments the effects of all of the antidepressant drugs.

Thyroid hormones have not been shown to cause particular problems in pediatric or geriatric patients; however, the hormones should be used with caution in elderly persons, who may have occult heart disease.

PRECAUTIONS AND ADVERSE REACTIONS

At the dosages usually used for augmentation—25 to 50 μg a day—adverse effects occur infrequently. The most common adverse effects associated with thyroid hormones are transient headache, weight loss, palpitations, nervousness, diarrhea, abdominal cramps, sweating, tachycardia, increased blood pressure, tremors, and insomnia. Osteoporosis may also occur with long-term treatment, but this has not been found in studies involving liothyronine augmentation. Overdoses of thyroid hormones can lead to cardiac failure and death.

Thyroid hormones should not be taken by persons with cardiac disease, angina, or hypertension. The hormones are contraindicated in thyrotoxicosis and uncorrected adrenal insufficiency and in persons with acute myocardial infarctions. Thyroid hormones can be administered safely to pregnant women, provided that laboratory thyroid indexes are monitored. Thyroid hormones are minimally excreted in breast milk and have not been shown to cause problems in nursing babies.

DRUG INTERACTIONS

Thyroid hormones can potentiate the effects of warfarin (Coumadin) and other anticoagulants by increasing the catabolism of clotting factors. They may increase the insulin requirement for diabetic persons and the digitalis requirement for persons with cardiac disease. Thyroid hormones should not be coadministered with sympathomimetics, ketamine (Ketalar), or maprotiline (Ludiomil) because of the risk of cardiac decompensation. Administration of SSRIs, tricyclic and tetracyclic drugs, lithium, or carbamazepine (Tegretol) can mildly lower serum T₄ and raise serum thyrotropin concentrations in euthyroid persons or persons taking thyroid replacements. This interaction warrants close serum monitoring and may require an increase in the dosage or initiation of thyroid hormone supplementation.

LABORATORY INTERFERENCES

Levothyroxine has not been reported to interfere with any laboratory test other than thyroid function indexes. Liothyronine, however, suppresses the release of endogenous T₄, thereby lowering the result of any thyroid function test that depends on the measure of T₄.
THYROID FUNCTION TESTS

Several thyroid function tests are available, including tests for T₄ by competitive protein binding (T₄ [D]) and by radioimmunoassay (T₄ RIA) involving a specific antigen–antibody reaction. Over 90% of T₄ is bound to serum protein and is responsible for thyroid-stimulating hormone (TSH) secretion and cellular metabolism. Other thyroid measures include the free T₄ index (FT₄I), T₃ uptake, and total serum T₃ measured by radioimmunoassay (T₃ RIA). Those tests are used to rule out hypothyroidism, which can be associated with symptoms of depression. In some studies, up to 10% of patients complaining of depression and associated fatigue had incipient hypothyroid disease. Lithium can cause hypothyroidism and, more rarely, hyperthyroidism. Neonatal hypothyroidism results in intellectual disability and is preventable if the diagnosis is made at birth.

Thyrotropin-releasing Hormone Stimulation Test

The thyrotropin-releasing hormone (TRH) stimulation test is indicated for patients who have marginally abnormal thyroid test results with suspected subclinical hypothyroidism, which may account for clinical depression. It is also used in patients with possible lithium-induced hypothyroidism. The procedure entails an intravenous injection of 500 mg of protirelin (TRH), which produces a sharp increase in serum TSH levels are measured at 15, 30, 60, and 90 minutes. An increase in serum TSH of 5 to 25 mIU/mL above the baseline is normal. An increase of less than 7 mIU/mL is considered a blunted response, which may correlate with a diagnosis of depression. Eight percent of all patients with depression have some thyroid illness.

DOSAGE AND CLINICAL GUIDELINES

Liothyronine is available in 5-, 25-, and 50-μg tablets. Levothyroxine is available in 12.5-, 25-, 50-, 75-, 88-, 100-, 112-, 125-, 150-, 175-, 200-, and 300-μg tablets; it is also available in a 200- and 500-μg parenteral form. The dosage of liothyronine is 25 or 50 μg a day added to the person’s antidepressant regimen. Liothyronine has been used as an adjuvant for all of the available antidepressant drugs. An adequate trial of liothyronine supplementation should last 2 to 3 weeks. If liothyronine supplementation is successful, it should be continued for 2 months and then tapered off at the rate of 12.5 μg a day every 3 to 7 days.