

31 - 29.31 Thyroid

Hormones

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antidepressant augmentation agents, citing such risks as osteoporosis and cardiac arrhythmias.

PHARMACOLOGICAL 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. Thyroxine (T₄) 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 percent 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 (Ludomil) 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. More than 90 percent 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 a rate of 12.5 µg a day every 3 to 7 days. REFERENCES Altshuler LL, Bauer M, Frye MA, Gitlin MJ, Mintz J. Does thyroid supplementation accelerate tricyclic antidepressant response? A review in meta-analysis of the literature. *Am J Psychiatry*. 2001;158:1617. Appelhof BC, Brouwer JP, van Dyck R, Fliers E, Hoogendijk WJ. Triiodothyronine addition to paroxetine in the treatment of major depressive disorder. *J Clin Endocrinol Metab*. 2004;89:6271. Aronson R, Offman HJ, Joffe RT, Naylor CD. Triiodothyronine augmentation and the treatment of refractory depression: A meta-analysis. *Arch Gen Psychiatry*. 1996;35:842. Bauer M, Baur H, Bergebifer A, Strohle A, Hellweg R. Effects of supraphysiological thyroxine administration in healthy controls in patients with depressive disorders. *J Affect Dis*. 2002;68:285. Baungartner A. Thyroxine and the treatment of affective disorders: An overview of the results of basic and clinical research. *Int J Neuropsychopharmacol*. 2000;3:149. Cooper-Kazaz A, Apter JT, Cohen R, Karapichev L, Mohammed-Moussa S. Combined treatment with sertraline and liothyronine in major depression: A randomized, double-blind, placebo-controlled trial. *Arch Gen Psychiatry*. 2007;64:679. Joffe RT. Thyroid hormones. In: Sadock BJ, Sadock VA, Ruiz P, eds. *Kaplan & Sadock's Comprehensive Textbook of Psychiatry*. 9th ed. Vol. 2. Philadelphia: Lippincott Williams & Wilkins; 2009:3248. Joffe RT, Sokolov ST, Levitt AJ. Lithium and triiodothyronine augmentation of antidepressants. *Can J Psychiatry*. 2006;51:791. Johansson P, Almqvist EG, Johansson J-O, Mattsson N, Hansson O, Wallin A, Blennow K, Zetterberg H, Svensson J. Reduced cerebrospinal fluid level of thyroxine in patients with Alzheimer's disease. *Psychoneuroendocrinology*. 2013;38(7):1058-1066. Koibuchi N. The role of thyroid hormone on functional organization in the cerebellum. *Cerebellum*. 2013;12(3):304-306. Lojko D, Rybakowski JK. L-Thyroxine augmentation of serotonergic antidepressants in female patients with refractory depression. *J Affect Disord*. 2007;103(1-3):252. Nierenberg AA, Fava M, Trivedi MH, Wisniewski SR,

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