Augmenting antidepressants with triiodothyronine: An underutilized strategy

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Partial responsiveness to antidepressant monotherapy is a struggle for many depressed patients. The literature supports the effectiveness of augmenting tricyclic antidepressants (TCAs) with triiodothyronine (T3) in unipolar depression. One meta-analysis suggests that T3 may accelerate antidepressant response in patients with treatment-resistant depression.[1] Likewise, T3 augmentation can improve depressive symptoms in patients without subclinical hypothyroidism whose depression did not fully respond to selective serotonin reuptake inhibitors (SSRIs).[2] In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, patients received lithium or T3 augmentation after they failed 2 antidepressant trials.[3] Patients receiving lithium or T3 augmentation showed similar remission rates, but the latter was associated with lower discontinuation rates because of its more favorable side effect profile.

Despite its reported effectiveness, T3 may be underutilized or misunderstood by prescribers.[4] Familiarity and use of liothyronine (the exogenous levorotatory form of T3) augmentation may improve response rates for depressed patients taking antidepressants.

Thyroid workup

Untreated thyroid conditions may reduce a depressed patient's response to antidepressants.[1] Check thyroid-stimulating hormone (TSH) levels as part of a medical workup for depressed mood before initiating T3. If TSH is elevated, a free thyroxine (T4) level should be ordered to detect clinical hypothyroidism. T4 as a sole initial screening test will not reveal subclinical hypothyroidism. Likewise, unbound T3 levels may be normal in patients with hypothyroidism, which could demonstrate endogenous adaptations in deiodination. Consult with an endocrinologist if you suspect Hashimoto's thyroiditis or if a patient has other abnormal laboratory values.

Patient selection

Preliminary data suggest that women respond better to T3 augmentation than men,[1] possibly because of women's greater susceptibility to clinical and subclinical hypothyroidism. Patients also should demonstrate partial response to a TCA or SSRI at an adequate dose and duration. Reconsider augmentation if you are concerned that a patient might divert or abuse T3, such as patients with eating disorders.

Safety considerations

In general, most patients tolerate T3. However, risks of T3 supplementation include hyperthyroidism. Severely depressed

T3 augmentation can improve depressive symptoms in patients without subclinical hypothyroidism

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Disclosures

Dr. Casher is a speaker for AstraZeneca, Pfizer Inc, and Sunovion Pharmaceuticals.

Drs. Gih and Bostwick report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

TSH levels (<0.1 mIU/mL) may predispose patients to atrial arrhythmias or osteoporosis, which compromise the benefits of thyroid augmentation. Low serum TSH increases the risk of atrial fibrillation, and higher free T4 levels are associated with a graded risk of atrial fibrillation.[5] Thyroid hormone may cause bone resorption. Although 1 study did not demonstrate accelerated bone loss with exogenous levothyroxine,[6] caution is warranted in vulnerable populations, such as postmenopausal women.

T3 is a FDA pregnancy category A medication, making it a viable augmentation agent for pregnant women when lithium use may not be possible. However, we do not recommend T3 use in pregnant women without obstetric consultation.

Drug interactions

Cholestyramine decreases T3's clinical effect, as can antacids and iron and calcium supplements.[7] Similarly, carbamazepine will decrease T3 effectiveness by inducing hepatic metabolism. T3 may enhance warfarin's anticoagulant effect and increase insulin requirements among diabetic individuals.

Augmentation dosing

Liothyronine should be started at 25 mcg/d taken on an empty stomach in the morning at least 30 minutes before eating. Signs of hyperthyroidism, such as sweating, anxiety, loose stools, heat intolerance, irritability, and tachycardia, suggest that the patient may not tolerate further increases. In geriatric patients or those with elevated cardiovascular risk, consider starting T3 at 12.5 mcg/d.

After 1 to 2 weeks, increase to 37.5 or 50 mcg/d. Evidence is limited for doses >50 mcg/d, the maximum dose used in the STAR*D study. Be aware that depressed patients may be tempted to increase their T3 dose, especially if they experience increased energy or weight loss. Doses >75 mcg/d are associated with an increased mortality rate.[8]

Monitor TSH levels after the first month of augmentation or when adding medications that change absorption or metabolism of thyroid hormones. If the T3 dose is stable, annual TSH measurements are adequate. Using standard hypothyroidism guidelines, maintain serum TSH between 0.4 and 2.0 mU/L.[9] T3 levels do not need monitoring.

Response monitoring

As highlighted by STAR*D, the goal of depression treatment is remission, and symptom severity should be tracked. The self-reported 9-item Patient Health Questionnaire can complement clinical impressions as a quick and easy outcome measure when administered every 2 weeks. In STAR*D, the mean response time and time to remission for patients receiving T3 augmentation was 6 weeks and 6.6 weeks, respectively. However, 28% of patients did not achieve remission until week 14,[3] which highlights the need for an adequate trial of T3.

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