Triiodothyronine Augmentation for Treatment-Resistant Depression

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Treatment-resistant depression (TRD) is a significant burden on the individual, family, community, and health care system.[1] The definition of TRD is varied as are treatment guidelines.[1,2] Up to one-third of patients with depression fail to respond to adequate trials of at least 2 antidepressant medications with compliance.[2] Up to 100 million individuals globally might have TRD according to epidemiologic studies.[3] Up to one-third of patients with depression, especially females, present with atypical features, which is considered a treatment-resistant risk factor.[4] Up to one-third of patients with depression might have subclinical thyroid dysfunction as well.[5] Thyroid hormone supplementation has been used as augmentation for depression for decades in many guidelines.[5] Thyroid hormone disturbance can lead to a wide range of reversible mental illnesses, including TRD.[5]

Furthermore, thyroid function disturbance can lead to atypical features of depression.[5] Brain hypothyroid state is an entity observed in atypical depression with normal peripheral thyroid function tests that can significantly respond to thyroid hormone augmentation.[5] Brain hypothyroidism could occur due to malfunction in thyroid receptors or poor uptake of thyroid hormone by the brain cell.[5] Elevated corticosteroid levels also play a role in depression through reverse conversion of T4 to rT3, which is commonly observed to be elevated in the cerebrospinal fluid of TRD patients.[5] T3 augmentation contributes to increased gene expression through stimulating thyrotropin-releasing hormone and corticotropin-releasing factor and increases the synthesis of brain-derived neurotrophic factor.[6,7] T3 can potentially increase the sensitivity of serotonin receptors and serotonin, norepinephrine, and γ-aminobutyric acid levels in the frontal lobe.[7] Studies have shown that T3 supplementation is more effective than T4, since it is the active intracellular version of T4 that bypasses the enzymatic conversion process.[8] Thyroid hormones play a vital role in depression-related cognitive dysfunction through their role in neurogenesis, synaptic plasticity, and long-term potentiation,[6] key role processes in TRD management.[6] We describe a case of a middle-aged woman with TRD and atypical features who failed several therapeutic trials but safely responded to T3 augmentation.

Case Report

A 48-year-old white perimenopausal woman with obesity (body mass index: 34 kg/m^2) and hypertension presented to the outpatient psychiatric clinic seeking treatment for chronic clinical TRD. She had been in several failed medication trials over the last 2 years including selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors, bupropion, lithium, olanzapine, aripiprazole, and Adderall. She was currently on daily bupropion XL 450 mg, fluoxetine 40 mg, and aripiprazole 15 mg for over a year but still reported low mood with mild reactivity and lack of motivation, high appetite, hypersomnia, and lack of concentration. Her Patient Health Questionnaire–9 (PHQ-9)[9] score consistently ranged between 16 and 20. No suicidal, homicidal, manic/hypomanic, or psychosis symptoms were reported. She refused to consider electroconvulsive therapy, transcranial magnetic stimulation, or ketamine given concerns about cognitive, memory, and other side effects. The patient denied any active medical condition, use of illegal recreational substances or alcohol, and any family history of a psychiatric condition. All laboratory values were within normal range including thyroid function test. The patient was given a trial of a small dose of T3 liothyronine 10 µg, and after 2 weeks, the dose was increased to 25 µg/d. Within 4 weeks, the patient reported significant change in her mood, motivation, energy, concentration, and cognitive function with no side effects (PHQ-9 score <7). Thyroid function tests, including T3, T4, rT3, and TSH, followed up after a 1-month and 6-month period were all within normal range, and no physical or mental adverse effects were reported after 6 months of T3 treatment.

Discussion

The advantage of augmenting with T3 is consistent with previous research, and this report also shows that T3 augmentation can be beneficial for TRD with atypical features. T3 treatment was safe and effective with no physical or mental adverse effects. This report is consistent with others showing that women taking SSRIs are more likely to respond to T3 treatment. T3, being the active component, can bypass the depression-induced enzymatic inhibition of D2 (type 2 iodothyronine deiodinase).[5] T3 supplementation can improve depression-related cognitive impairment and pseudodementia[6,7] as seen in our case. T3 treatments were more effective and better tolerated than T4 augmentation of

antidepressants.[5] A study[10] comparing T4 treatment to a combination of T3/T4 found almost 50% of the patients prefer the combination treatment, and about two-thirds (7 of 11) reported better quality of life, depression, anxiety, and cognitive scale. In a prospective study, Appelhof et al[11] compared the addition of T3 (25 µg vs 50 µg) vs placebo in depressed patients taking paroxetine. T3 in a 25-µg dose was similar to placebo regarding side effect profile, while T3 at the 50-µg level was associated with sweating, tremor, nervousness, and palpitations in one-third of the sample (N = 28).[11] Joffe et al[12] and the Sequenced Treatment Alternatives to Relieve Depression study[13] reported that T3 augmentation is as effective as lithium addition with a better safety profile.[5–8] Moderie et al[14] reported that premenopausal women with TRD are more likely to respond to T3 augmentation compared to postmenopausal or male TRD patients. Furthermore, the addition of T3 to antidepressant-respondent patients adds no further benefit nor stabilizes the remission.[8,9,14] Although T3 can be safely combined with lithium for bipolar depression including the rapid-cycling form, the benefit was limited and inconsistent.[15]

In conclusion, T3 augmentation was a fast and effective option, even in atypical TRD, and safer than other augmenters like antipsychotics or lithium.[9,14] Kelly and Lieberman[16] in their study (N = 14) reported no bone density changes observed after 2 years of T3 high-dose treatment (150 µg) compared to the inconsistent report of bone density adverse effects of T4 treatment after a 1-year duration. Endocrine specialists have no clear preference for the use of T4 vs T3/T4 in treating hypothyroid illness.[8] Annual thyroid function test that includes free T3, free T4, and rT3 is recommended follow-up with annual bone density evaluation in postmenopausal women.[7]

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