Does augmenting antidepressant medication in euthyroid patients with thyroid hormone supplement improve depression treatment?

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EVIDENCE-BASED ANSWER

Supplementation of specific serotonin reuptake inhibitors with triiodothyronine (T3) does not improve depression treatment in euthyroid patients (SOR: **A**, meta-analysis, systematic review, and single randomized controlled trial [RCT]). Augmenting tricyclic antidepressants with T3 in euthyroid patients may accelerate the depression response rate during the early initiation period but is equivalent to placebo at four weeks (SOR: **B**, single RCT).

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A 2008 systematic review of five randomized controlled trials (RCTs) and three small open-label studies investigated whether T3 supplementation improved depression symptoms in euthyroid adult patients with major depressive disorder (MDD) treated with specific serotonin reuptake inhibitors (SSRIs).[1] The mean age of patients was approximately 40 years old, with a slight majority of patients being female. Methodological differences between studies prevented meta-analysis. Three enhancement studies initiated T3 and the SSRI concurrently, whereas two augmentation studies started T3 in patients who did not initially respond to SSRIs or lithium. The studies used different validated self-reporting depression rating scales that graded depression severity, with higher scores indicating worse depression. Rating scales included the Hamilton Depression Rating Scale (HAMD17 and HAMD21, range 0–52), Quick Inventory of Depressive Symptoms–Self-Report (range 0–42), and Montgomery–Asberg Depression Rating Scale (MADRS, range 0–60). The primary outcome in all studies was >50% reduction in the depression rating score. Two RCT augmentation studies (n=142 and 36) showed no difference in depression severity scores comparing SSRI plus T3 with SSRI plus placebo. The three enhancement RCTs demonstrated inconsistent results. Two studies (n=113 and 57) demonstrated no difference between placebo and T3 groups; the third study (n=124) found an improved response rate (T3: 69% vs placebo: 50%, number needed to treat [NNT]=11, P=.02) and a decreased remission rate with T3 supplementation (T3: 59% vs placebo: 38%, NNT=5, P=.02). The open-label studies were small (n=25, 19, and 11, respectively) and demonstrated no differences between treatment and control groups. Significant limitations of this systematic review included study variability in number of patients, type of SSRI, and length of treatment.

A 2009 meta-analysis (n=444) evaluated the effect of T3 in addition to antidepressants on depressive symptoms in euthyroid patients with acute nonpsychotic MDD of any severity.[2] All trials compared the use of an antidepressant at any dose and 25 to 50 μg T3 daily against antidepressants at equivalent doses with placebo. Inclusion criteria for these studies were nonpsychotic major depression in acute phase of treatment. In three trials, only SSRIs were used as antidepressants. In the fourth, 52% of patients were given SSRIs, and others given venlafaxine, bupropion, nefazodone, or mirtazapine. Two of the RCTs used in this meta-analysis were part of the 2008 systematic review, but this meta-analysis specifically reviewed patients without resistant MDD. All trials used the HAMD17 or the MADRS. Response was defined as 50% or greater reduction in either

HAMD17 or MADRS scores. Remission was defined as response criteria lasting at least six weeks. No difference was observed in response or remission rates at the endpoint. Limitations of this study included variability in dosing of SSRIs and inability to draw conclusions about other antidepressant classes.

A 2012, eight-week, double-blind RCT (n=153) studied the effects of augmentation of sertraline with T3 on depressive symptoms in euthyroid adults (18–60 years old) with nonpsychotic MDD.[3] Patients' mean age was 42 years old, 62% were female, and 79% were White. Those with any other Diagnostic and Statistical Manual of Mental Disorders, Edition IV psychiatric disorder in the past year, who were pregnant or breast-feeding, or with an unstable medical condition were excluded. Both treatment and placebo groups received initial dosing of sertraline 50 mg daily, increased by 50 mg as tolerated for therapeutic effect (maximum 200 mg), along with placebo or 25 μg per day of T3 for one week, increased to 50 μg per day for the treatment group in week 2. The primary outcome (termed response by the authors) was defined as 50% reduction in baseline HAMD21 and a total <15. The secondary outcome was remission (HAMD21 <8). Neither depression response nor remission rates decreased in patients augmented with T3 compared with placebo. Similar rates of adverse events were observed between placebo and T3 groups. Limitations of this study included a single-site protocol and a patient population that was not treatment-resistant or chronically ill.

A 2001 meta-analysis including six double-blind, randomized, placebo-controlled trials investigated 125 adult patients with nonrefractory MDD treated with tricyclic antidepressants (TCAs; imipramine or amitriptyline 100–200 mg) augmented with T3 (20–62.5 mg) or placebo for 21 to 28 days.[4] Patients were majority female and euthyroid. The primary outcome was improvement of HAMD17 by >50% or to less than eight. In five of six double-blind RCTs, patients met the primary outcome more quickly when T3 was administered with TCA in patients with MDD (pooled weighted effect size 0.58, 95% CI, 0.21–0.94; $P<.002$). An accelerated response occurred as early as two days post-treatment. After 28 days, no difference was observed in MDD primary outcome measures between treatment groups. Recent trials have not investigated TCA alone; therefore, further evidence to support this claim is unavailable. Study limitations included small patient population, varying doses and type of TCA, and varying doses of T3. EBP

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