An Open Study of Triiodothyronine Augmentation of Selective Serotonin Reuptake Inhibitors in Treatment-Resistant Major Depressive Disorder

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Objective: In an open trial, we investigated the efficacy of triiodothyronine (T_3) adjuvant to selective serotonin reuptake inhibitors (SSRIs) in subjects with major depressive disorder (MDD) resistant to SSRI treatment.

Method: Twenty subjects who met DSM-IV criteria for MDD (mean ± SD age = 44.3 ± 10.3 years; 55% [N = 11] women) and had failed to respond to a course of treatment of at least 8 weeks with an SSRI antidepressant were enrolled in a 4-week open-label augmentation treatment with T_3 50 μg/day. Atypical and melancholic subtypes of MDD were diagnosed using Structured Clinical Interview for DSM-IV Axis I Disorders criteria. We administered the 17-item Hamilton Rating Scale for Depression (HAM-D-17) 4 times during the study (which was conducted between 2001 and 2003).

Results: During T_3 augmentation, the severity of depression decreased from an initial mean ± SD HAM-D-17 score of 20.5 ± 3.6 to a final HAM-D-17 score of 14.0 ± 7.1 ($p < .001$). Seven subjects (35.0%) were treatment responders (HAM-D-17 reduction ≥ 50%), and 6 subjects (30.0%) achieved clinical remission (final HAM-D-17 ≤ 7). The 5 subjects with atypical depression experienced significantly ($p < .01$) greater clinical improvement (final HAM-D-17 scores 6.6 ± 1.8 vs. 16.4 ± 4.5), and higher rates of treatment response (100% [5/5] vs. 13.3% [2/15]) and remission (80.0% [4/5] vs. 13.3% [2/15]), compared to subjects with nonatypical MDD. The 8 subjects with melancholic MDD experienced significantly ($p < .05$) greater depression severity at the end of the study compared to nonmelancholic MDD subjects (final HAM-D-17 scores = 18.3 ± 6.6 vs. 11.1 ± 6.1).

Conclusion: Triiodothyronine augmentation of SSRIs may be a promising treatment strategy in SSRI-resistant MDD, particularly in subjects with the atypical MDD subtype.

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Thyroid hormones have been studied for several decades as augmentation of tricyclic antidepressants (TCAs) in treatment-resistant subjects with major depressive disorder (MDD). Of 5 double-blind, controlled studies[1–5] on thyroid hormone augmentation of TCAs, 3[2,4,5] reported positive results, with response rates between 50% and 65%, while the 2 negative studies[1,3] had very low numbers of subjects (between 8 and 16). A meta-analysis of 8 studies,[1–8] with a total of 292 patients, led Aronson and coworkers[9] to conclude that depressed subjects treated with triiodothyronine (T_3) augmentation of TCAs were twice as likely to respond to treatment compared with controls.

In contrast, few researchers have studied the efficacy of thyroid hormones as adjuvants to selective serotonin reuptake inhibitors (SSRIs).[10–12] In open studies, high-dose thyroxine (T_4) induced clinical remission (HAM-D < 10) in 4 of 5 treatment-resistant MDD subjects[10] and in 7 of 9 treatment-resistant MDD subjects.[11] In both studies, however, MDD subjects were treated with a variety of antidepressant combinations, including TCAs and SSRIs. In another open study,[12] 10 (40%) of 25 prospectively assessed SSRI nonresponders became responders after T_3 was added to their SSRI treatment. Of interest, none of the males in the study[12] responded to T_3 augmentation, which led the authors to hypothesize a gender-based differential efficacy of T_3 augmentation of SSRIs. Our current study adds to the existing literature, as only 1 other study to date[12] has prospectively investigated T_3 augmentation of SSRIs in SSRI-resistant MDD.

In the present study, we investigated the efficacy of T_3 augmentation to SSRIs in subjects with MDD resistant to SSRI treatment. In exploratory analyses, we also assessed treatment efficacy in subjects with melancholic and atypical MDD.

METHOD

Twenty subjects between the ages of 18 and 65 years (mean ± SD age = 44.3 ± 10.3 years; 11 women, 55.0%) were recruited for a treatment study completed at Massachusetts General Hospital (Boston) between 2001 and 2003. Institutional review board–approved written informed consent was obtained from all study participants.

At screening, all subjects were required to have met criteria for MDD, diagnosed by physician-administered Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Edition (SCID-I/P)[13]; to have a score of ≥ 16 on the 17-item Hamilton Rating Scale for Depression (HAM-D-17)[14]; and to have shown minimal or no response to a standard course of antidepressant treatment with an SSRI. A standard course was defined as the following medications taken for ≥ 8 weeks, with ≥ 4 weeks at a stable dose: fluoxetine ≥ 40 mg/day, sertraline ≥ 100 mg/day, paroxetine ≥ 40 mg/day, citalopram ≥ 40 mg/day, or escitalopram ≥ 20 mg/day. Melancholic and atypical subtypes of MDD were diagnosed using SCID criteria.

The exclusion criteria for this study were women of childbearing potential not on medically accepted means of contraception; women lactating or pregnant; and subjects with serious suicidal risk, serious or unstable medical illness, medical disorders in which T_3 treatment was contraindicated (e.g., adrenal insufficiency, myxedema, diabetes, history of coronary artery disease or cardiac arrhythmias, history of hyperthyroidism, seizure disorder), abnormal thyroid-stimulating hormone (TSH) levels, history of organic mental disorders, substance use disorders (including alcohol) active within the last year, any psychotic disorder, bipolar disorder, history of multiple adverse drug reactions, or hypersensitivity to T_3.

After a 1-week evaluation phase, all subjects started at the baseline visit a 4-week open treatment with T_3 50 μg daily. The SSRIs were continued at preenrollment doses. The HAM-D-17,[14] the Clinical Global Impressions scale (CGI),[15] and the Beck Depression Inventory (BDI)[16] were administered at screen, baseline, week 2, and week 4. Patients had initial TSH, T_3, T_4, and free T_4 levels measured prior to initiation of treatment and again at 4 weeks follow-up with a solid-phase radioimmunoassay (Massachusetts General Hospital Laboratories, Boston). Blood pressure, heart rate, and weight were measured at each study visit. Treatment response was defined as HAM-D-17 reduction ≥ 50% during the study; remission was defined as a final HAM-D-17 score ≤ 7.

At the end of the 4-week study, patients continued with open clinical follow-up for another 8 weeks, during which only CGI scales were administered and changes in antidepressant treatment were allowed. Subjects were instructed to take T_3 50 μg/day for 4 additional weeks at the end of the study and then taper the dose over 2 weeks.

We performed all analyses of clinical data using the last observation carried forward. Given the small sample size, group differences in demographic and clinical variables were computed using nonparametric tests (Wilcoxon signed rank test for paired data, Wilcoxon rank sum test for unpaired data) and χ^2 tests. Statistical significance was defined at the .05 level, 2-tailed.

RESULTS

The demographic and clinical characteristics of our subjects are presented in Table 1. For this group, the length of the current MDD episode was a mean ± SD of 35.1 ± 46.9 months (median = 16 months); 13 of 20 subjects had a history of chronic MDD with current episode ≥ 12 months. The mean ± SD age at onset of MDD was 26.2 ± 14.4 years (median = 19.5 years). Depression severity at baseline was a mean ± SD HAM-D-17 score of 20.5 ± 3.6 (range, 16–30).

Nineteen of 20 subjects completed a 4-week course of T_3 augmentation; 1 subject discontinued after 2 weeks due to side effects (muscle aches, fatigue, photophobia). After 4 weeks of treatment, the mean ± SD severity of depression dropped from HAM-D-17 = 20.5 ± 3.6 to HAM-D-17 = 14.0 ± 7.1, which was a statistically significant improvement ($z = -3.44$, $p < .001$). The mean ± SD percent improvement in HAM-D-17 scores was 32.1% ± 32.9%. Seven subjects (35.0%) were treatment responders (HAM-D-17 score reduction ≥ 50%), and 6 subjects (30.0%) achieved clinical remission (final HAM-D-17 score ≤ 7).

All participants had normal thyroid function; the mean ± SD pretreatment TSH level was 1.75 ± 0.71 mIU/L (range, 0.78–3.30 mIU/L), and pretreatment levels of T_3, T_4, and free T_4 were within normal limits. No differences in pretreatment TSH levels were noted between future treatment responders (TSH = 1.82 ± 0.72 mIU/L) and nonresponders (TSH = 1.71 ± 0.45 mIU/L) ($z = -0.05$, $p = .96$). Eighteen of 20 subjects had TSH suppression (TSH < 0.1 mIU/L) after 4 weeks of treatment with T_3. There was no significant difference between end-of-study TSH levels of treatment responders (TSH = 0.14 ± 0.11 mIU/L) and nonresponders (TSH = 0.08 ± 0.04 mIU/L) ($z = -0.15$, $p = .88$). One of the 2 subjects with TSH nonsuppression responded to treatment; the other did not. As expected, posttreatment T_3 levels were abnormally high (354 ± 145 ng/dL), while T_4 (2.96 ± 1.15 μg/dL) and free T_4 (0.65 ± 0.19 ng/dL) levels were low.

Table 1. Clinical and Demographic Characteristics of Subjects With Major Depressive Disorder (MDD)

Variable	All Subjects (N = 20)	Melancholic MDD (N = 8)	Melancholic vs Nonmelancholic MDD Statistic	Melancholic vs Nonmelancholic MDD p Value	Atypical MDD (N = 5)	Atypical vs Nonatypical MDD Statistic	Atypical vs Nonatypical MDD p Value
Age, mean ± SD, y	44.3 ± 10.3	42.0 ± 10.0	z = –0.89	.37	41.8 ± 4.4	z = –0.48	.63
Women, N (%)	11 (55.0)	5 (62.5)	$\chi^2 = 0.30$[a]	.58	1 (20.0)	$\chi^2 = 3.30$[a]	.069
SSRI dose, mean ± SD, mg[b]	54 ± 29	50 ± 15	z = –0.08	.94	40 ± 0	z = –1.31	.19
HAM-D score, mean ± SD							
Initial	20.5 ± 3.6	21.5 ± 4.8	z = –0.54	.59	20.4 ± 2.1	z = –0.39	.69
Final	14.0 ± 7.1	18.3 ± 6.6	z = –2.20	.028*	6.6 ± 1.8	z = –2.66	.0076*
% Improvement	32.1 ± 32.9	14.7 ± 27.3	z = –1.85	.064	67.8 ± 8.2	z = –2.75	.006*
Treatment response, N (%)[c]	7 (35.0)	1 (12.5)	$\chi^2 = 2.97$[a]	.085	5 (100)	$\chi^2 = 12.38$[a]	.0004*
Remission, N (%)[d]	6 (30.0)	1 (12.5)	$\chi^2 = 1.94$[a]	.16	4 (80.0)	$\chi^2 = 7.94$[a]	.005*
CGI-S score, mean ± SD							
Initial	4.3 ± 0.7	4.6 ± 0.9	z = –1.12	.26	4.2 ± 0.4	z = –0.13	.89
Final	3.4 ± 1.7	4.3 ± 1.8	z = –1.81	.069	1.6 ± 0.5	z = –2.66	.006*
CGI-I score, mean ± SD							
Initial	4.0 ± 0.5	4.0 ± 0.5	z = –0.23	.81	3.8 ± 0.4	z = –0.57	.57
Final	3.0 ± 1.1	3.3 ± 1.0	z = –0.81	.42	1.8 ± 0.5	z = –2.53	.011*
BDI score, mean ± SD							
Initial	23.4 ± 6.9	26.1 ± 9.1	z = –1.08	.28	20.8 ± 5.8	z = –0.91	.35
Final	17.1 ± 11.2	22.6 ± 12.1	z = –1.77	.076	7.0 ± 5.1	z = –2.48	.013*

[a]df = 1.
[b]Equivalent mg fluoxetine.
[c]HAM-D score reduction ≥ 50% during treatment.
[d]Final HAM-D score ≤ 7 at end of study.
*Values statistically significant at the .05 level.
Abbreviations: BDI = Beck Depression Inventory, CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D = 17-item Hamilton Rating Scale for Depression, SSRI = selective serotonin reuptake inhibitor.

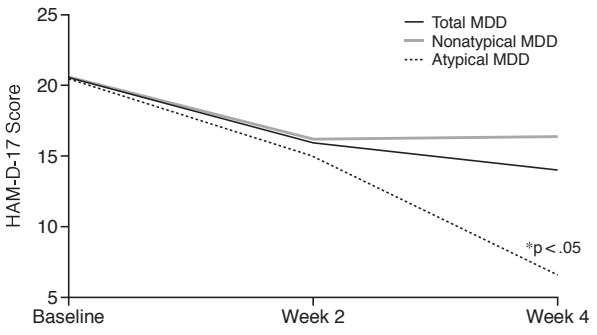
Although there were no significant differences in baseline depression severity, compared to subjects with nonatypical MDD, the 5 subjects with atypical depression experienced significantly greater clinical improvement (final mean ± SD HAM-D-17 scores = 6.6 ± 1.8 vs. 16.4 ± 4.5; Figure 1) and higher rates of treatment response (100% [5/5] vs. 13.3% [2/15]) and remission (80.0% [4/5] vs. 13.3% [2/15]) ($p < .01$ for all analyses). At the end of the study, mean ± SD CGI-S scores also showed significantly ($p < .01$) lower severity of depression (1.6 ± 0.5 vs. 3.9 ± 1.5) and greater clinical improvement (CGI-I scores 1.8 ± 0.5 vs. 3.3 ± 1.0) for subjects with atypical depression compared to nonatypical MDD. When severity of depression was measured with the patient-rated BDI, the 5 subjects with atypical depression also showed significantly lower end-of-study BDI scores than subjects with nonatypical MDD (7.0 ± 5.1 vs. 20.5 ± 10.7; $p < .02$).

The 8 subjects with melancholic MDD experienced significantly ($p < .03$) greater severity of depression at the end of the study as measured by the HAM-D-17 (final scores = 18.3 ± 6.6 vs. 11.1 ± 6.1) compared to subjects with nonmelancholic MDD, although baseline severity between melancholic and nonmelancholic subjects was comparable.

No relationship was found between gender and any of the measures of treatment outcome ($p > .05$ for all analyses).

The thyroid augmentation was relatively well tolerated. Adverse events present in 2 subjects (10% of the group) were fatigue and diaphoresis; adverse events present in 1 subject (5%) were tremor, dry mouth, headaches, muscle aches, and vivid dreams. No adverse events were present in more than 2 subjects. Only 1 subject discontinued treatment due to adverse events. Blood pressure did not change significantly during the study ($p > .05$ for all analyses); systolic blood pressure changed by a mean ± SD of 0.1 ± 12.5 mm Hg (range, –38 to +16 mm Hg), and diastolic blood pressure, by a mean ± SD of –1.8 ± 10.4 mm Hg (range, –26 to +16 mm Hg). Heart rate increased significantly ($p < .05$) by 6.3 ± 12.4 bpm

Figure 1. 17-Item Hamilton Rating Scale for Depression (HAM-D-17) Severity of Depression Ratings



*Statistically significant difference in HAM-D-17 scores between atypical and nonatypical MDD at endpoint.
Abbreviation: MDD = major depressive disorder.

(range, –18 to +34 bpm) during the study, from 76 ± 12 bpm (range, 60 to 96 bpm) at study onset to 82 ± 9 bpm (range, 66 to 96 bpm) at the end of the study. During the 4-week treatment, subjects' weight decreased by a mean ± SD of 2.5 ± 6.6 lb (range, –20 to +7 lb), which was not statistically significant ($p > .05$).

After the 4-week treatment, study subjects were followed for 8 additional weeks, during which changes in antidepressant treatment were allowed. Of note, all responders to T_3 augmentation (including the 5 subjects with atypical MDD) sustained their initial response at week 12. None of the initial nonresponders became responders during follow-up.

DISCUSSION

Based on our data, T_3 augmentation of SSRIs may be a promising treatment strategy for some individuals with SSRI-resistant MDD. The 35% response rate in our study is similar to the 40% rate reported by Agid and Lerer,[12] the only other study to date prospectively investigating T_3 augmentation of SSRIs in SSRI-resistant MDD. However, unlike the former study,[12] we noted no differential efficacy of T_3 augmentation in men compared with women.

The efficacy of T_3 augmentation of SSRIs in our study appeared significantly higher in the 5 subjects with atypical MDD, 100% of whom experienced treatment response. The rate of treatment response was much lower in subjects with melancholic MDD (12.5%). To our knowledge, this is the first study reporting a differential effect of T_3 augmentation in atypical MDD. Although important, this result is based on exploratory, post hoc analysis of our data; it will require replication in future larger-scale studies.

We also did not find a relationship between the outcome of T_3 augmentation and thyroid function tests before or after treatment. Most (18 of 20) subjects experienced markedly decreased TSH levels after treatment, as expected, with no relationship to treatment outcome. In this small sample, the treatment with a relatively large dose of T_3 was well tolerated, associated with modest but statistically significant increases in heart rate but no significant changes in blood pressure; only 1 subject discontinued the study because of side effects.

Our study has several limitations: small sample size and open design with no placebo comparator, which makes it difficult to assess the true efficacy of T_3 augmentation. Subjects in our study had experienced treatment failure with different SSRIs; it is conceivable that T_3 augmentation may have selective efficacy with different SSRIs, and a study with failure of only 1 SSRI would have been preferable. Another limitation may be the short duration of our study (4 weeks). We have followed previous studies in the literature[4,5,8] that reported efficacy of T_3 augmentation after 4 weeks or less. Moreover, our initial results appeared to be stable during the 8-week follow-up period after our study. However, it is possible that a longer study may have led to different results.

In summary, our results suggest a possible role for T_3 augmentation of SSRIs in SSRI-resistant MDD. Triiodothyronine augmentation of SSRIs may be more effective in subjects with atypical MDD and less effective in melancholic MDD.

Drug names: citalopram (Celexa), escitalopram (Lexapro), fluoxetine (Prozac and others), paroxetine (Paxil and others), sertraline (Zoloft).

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