ORIGINAL ARTICLE

Combined Treatment With Sertraline and Liothyronine in Major Depression

A Randomized, Double-blind, Placebo-Controlled Trial

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Background: Antidepressant treatments that achieve a higher remission rate than those currently available are urgently needed. The thyroid hormone triiodothyronine may potentiate antidepressant effects.

Objective: To determine the antidepressant efficacy and safety of liothyronine sodium (triiodothyronine) when administered concurrently with the selective serotonin reuptake inhibitor sertraline hydrochloride to patients with major depressive disorder.

Design: Double-blind, randomized, 8-week, placebo-controlled trial.

Setting: Outpatient referral centers.

Patients: A total of 124 adult outpatients meeting unmodified *DSM-IV* criteria for major depressive disorder without psychotic features.

Interventions: Patients were randomized to receive sertraline hydrochloride (50 mg/d for 1 week; 100 mg/d thereafter) plus liothyronine sodium (20-25 µg/d for 1 week; 40-50 µg/d thereafter) or sertraline plus placebo for 8 weeks.

Main Outcome Measures: The primary outcome measure was categorical response to treatment (≥50% decrease in scores on the 21-item Hamilton Rating Scale for Depression from baseline to study end point). Remission rate (final Hamilton Rating Scale for Depression score, ≤6) was a secondary outcome measure.

Results: Intent-to-treat Hamilton Rating Scale for Depression response rates were 70% and 50% in the sertraline-liothyronine and sertraline-placebo groups, respectively ($P=.02$; odds ratio, 2.93; 95% confidence interval, 1.23-7.35); remission rates were 58% with sertraline-liothyronine and 38% with sertraline-placebo ($P=.02$; odds ratio, 2.69; 95% confidence interval, 1.16-6.49). Baseline T_3 values were lower in patients treated with sertraline-liothyronine who had remissions than in those without remissions ($t_{48}=3.36$; $P<.002$). Among patients treated with sertraline-liothyronine, remission was associated with a significant decrease in serum thyrotropin values ($F_{1,73}=4.00$; $P<.05$). There were no significant effects of liothyronine supplementation on frequency of adverse effects.

Conclusions: These results demonstrate enhancement of the antidepressant effect of sertraline by concurrent treatment with liothyronine without a significant increase in adverse effects. The antidepressant effect of liothyronine may be directly linked to thyroid function.

Trial Registration: clinicaltrials.gov Identifier: NCT00158990

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ANTIDEPRESSANT MEDICATIONS are widely used for the treatment of major depressive disorder (MDD), a severe, highly prevalent illness that has a substantial impact on public health worldwide.[1] Successful treatment with selective serotonin reuptake inhibitors (SSRIs), the most frequently used first-line agents, may require up to 8 weeks.[2,3] Full remission is achieved in fewer than 50% of patients.[4] Antidepressant treatments that achieve a better rate of success are urgently needed.

Different lines of evidence link thyroid function and depressive symptoms. Hypothyroidism may be associated with subsyndromal and clinical depression in a subset of patients, and it may respond to thyroid hormone replacement.[5] Partial substitution of the daily thyroxine (T_4) allowance with triiodothyronine (T_3) has been associated with improved mood and cognitive performance in patients with primary hypothyroidism,[6] but this finding has since been replicated only partially[7] or not at all.[8,9] Although the majority are euthyroid, patients with MDD have a higher than antici-

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pated rate of subclinical thyroid abnormalities.[10] These have been linked to a less favorable response to antidepressant treatment,[11,12] but this finding has not been consistently supported.[13,14] In addition, reduced levels of the thyroid transport protein transthyretin have been observed in the cerebrospinal fluid of patients with depression.[15-17]

The thyroid hormones T_4 and T_3 have been used to treat major depression. Research with T_3 has been more extensive and includes administration as a monotherapy[18,19] but more usually as a supplement to standard antidepressants. The T_3 supplementation studies have examined *augmentation* of clinical response in nonresponders to antidepressants, in which case the hormone is added to the antidepressant after several weeks of treatment. In *acceleration* paradigms, T_3 is administered to nonresistant patients from the outset or very early in the treatment course in conjunction with the antidepressant, and acceleration of clinical effect is examined. In *enhancement* studies, treatment outcome is examined after supplementation of an antidepressant with T_3 from the inception of treatment. Depending on the frequency of clinical evaluations, enhancement studies may also yield information on acceleration.

There is support from meta-analyses for augmentation by T_3 of the therapeutic effect of tricyclic antidepressants in patients with resistant depression[20] and for acceleration of clinical response on concurrent administration with tricyclic antidepressants.[21] Aronson et al[20] aggregated 8 studies (4 of which were randomized and double-blind) that encompassed a total of 292 patients with treatment-resistant depression, in which T_3 was added to ongoing treatment with tricyclic antidepressants. The T_3-augmentation group had a relative response of 2.09 (P=.002) compared with controls, corresponding to a 23.2% absolute improvement in response rate. The quality of the studies was uneven, the number of participants was relatively small, and the findings were not statistically significant when the analysis was restricted to the double-blind studies. Nonetheless, the overall pattern suggested that T_3 might be an effective method of augmenting the antidepressant effects of tricyclic antidepressants in patients with treatment-resistant depression. Altshuler et al[21] reported that, in 5 of 6 double-blind randomized controlled studies, T_3 was significantly more effective than placebo in accelerating clinical response (pooled, weighted effect size index was 0.58) when administered concurrently with tricyclic antidepressants to patients with major depression.

There are relatively few studies of T_3 as an augmenting agent in depressed patients treated with SSRIs. Like SSRIs, T_3 may increase serotoninergic neurotransmission in rats by desensitizing serotonin$_{1A}$ autoreceptors in the raphe nucleus and serotonin$_{1B}$ autoreceptors in the frontal cortex and hypothalamus, leading to increased synaptic concentrations of serotonin.[22-25] In an algorithm-based study, Agid and Lerer[26] found T_3 (25-50 µg for 3 weeks) to be effective in 10 of 25 patients nonresponsive to SSRIs. Similar response rates were observed in 2 other open-label studies.[27,28] In a recently published Sequenced Treatment Alternatives to Relieve Depression (STAR*D) third-step study, 142 adult outpatients with nonpsychotic MDD, following 2 failed medication trials, were randomly assigned to receive lithium carbonate (up to 900 mg/d) or T_3 (up to 50 µg/d) augmentation for up to 14 weeks.[29] Remission rates (assessed by blind raters) were 24.7% for T_3 and 15.9% for lithium, but the difference was not statistically significant. Lithium was associated with more frequent adverse effects (P=.045) and a dropout rate more than double that of T_3. In a double-blind randomized controlled trial examining the efficacy of T_3 administered with an SSRI, there was no advantage for combination treatment with paroxetine and T_3 (25-50 µg/d) compared with paroxetine and placebo.[30] This was an enhancement study in which T_3 was administered concurrently with paroxetine or placebo for 8 weeks to 106 patients with nonpsychotic MDD.[30] Patients treated with T_3 experienced more adverse events.

The current status of combination or augmentation treatment with T_3 in major depression is controversial. Some include this strategy as routine in algorithms for management of treatment-resistant depression. However, the bulk of positive evidence pertains to augmentation of tricyclic antidepressants, which now are rarely used as first-line treatment. There is limited information on the relationships of thyroid function values to clinical outcome with T_3 supplementation. It is possible that a subgroup of patients may benefit particularly. Whether T_3 potentiates the antidepressant effect of SSRIs is a core question that can be most effectively answered by comparing response and remission rates of patients who are not known to be resistant to medication and are studied from the outset of treatment. We report a double-blind placebo-controlled trial of liothyronine sodium (T_3) in combination with the SSRI sertraline hydrochloride in patients with nonresistant, nonpsychotic MDD. Thyroid function values were obtained at baseline and after treatment to investigate predictive power with respect to clinical outcome.

METHODS

PATIENTS

Male or female outpatients aged 18 to 70 years with a *DSM-IV* diagnosis of MDD without psychotic features[31] and a total 21-item Hamilton Rating Scale for Depression[32] (HRSD) score of at least 16 with item 1 (depressed mood) scored 2 or greater were eligible. Exclusion criteria were significant suicidal risk (HRSD item 3, suicide scored ≥2); any past or current thyroid disease (including subclinical hypothyroidism, defined as a thyrotropin level above the upper limit of the normal range in the presence of normal T_3 and T_4 levels and in the absence of clinical signs of hypothyroidism); a medical condition that could limit prescription of the study medication or make liothyronine treatment unsafe; lifetime history of alcohol or other drug dependence or abuse in the preceding 12 months; and previous treatment with sertraline. Female patients were not pregnant or lactating and were using adequate contraception.

Recruitment was at the Hadassah-Hebrew University Medical Center (the central site), the Be'er Ya'akov Mental Health Center, and Global Medical Institutes. Patients were recruited from local outpatient clinics and through advertisements in the media. Potential subjects underwent a structured telephone interview by a trained research assistant (R.C.), reviewed by a psychiatrist (R.C.-K.). Subjects who passed this screening were

assessed for eligibility by a psychiatrist at their first clinic visit. The study was approved by the institutional review board at each site, and all patients gave written informed consent.

STUDY DESIGN

Eligible patients were randomly assigned to receive sertraline plus liothyronine (sertraline-liothyronine group) or sertraline plus placebo (sertraline-placebo group), stratified by sex. The randomization code was generated with use of Proc Random (version 6.12; SAS Institute Inc, Cary, NC) and was stratified by sex. Blocks of numbers were preassigned to each center. Numbered treatment packages were supplied by the central pharmacy at Hadassah University Hospital for the Israeli sites and by a commercial pharmacist for the Princeton site and were allocated according to sequential entry of patients into the protocol. Patients and the clinicians who performed the ratings were blind to treatment allocation. Sertraline hydrochloride dose was 50 mg/d for the first week and, if tolerated, 100 mg/d thereafter. Liothyronine sodium (20-µg tablets at the Israeli sites and 25-µg tablets at the Princeton site) or placebo tablets (equivalent in size, weight, and color) were placed in a single opaque capsule by the pharmacy. The dose was 20 or 25 µg/d for the first week and 40 or 50 µg/d thereafter, if tolerated. Benzodiazepines, zolpidem, or zopiclone were permitted for sedation when needed. The study lasted 8 weeks and patients made 6 clinic visits.

Baseline assessments included a comprehensive medical evaluation and determination of thyrotropin, total T_3, and free T_4 levels. The hormone levels were measured by immunoassay. The assays of the Israeli patients treated at the Hadassah center were performed in the Department of Biochemistry, Hadassah-Hebrew University Medical Center (Immulite 2000 platform; Diagnostic Products Corp, Los Angeles, Calif); those of the non-Hadassah Israeli patients at American Medical Laboratories, Tel Aviv (Abbott Axsym Microparticle Enzyme Immunoassay technology; Abbott Laboratories, Abbott Park, Ill); and those of the US patients at Bio-Reference Laboratories, Elmwood Park, NJ (Roche Modular Analytics assays; Roche Diagnostics, Indianapolis, Ind). Psychiatric evaluation at baseline included the Hebrew version of the semistructured Mini–International Neuropsychiatric Interview,[33] the HRSD, and a 100-mm visual analog scale (VAS) for self-rating of mood. Information was obtained on history of depressive episodes and on the course of the current episode, including antidepressant and other treatments received. Antidepressant trials during the current episode were regarded as adequate if the dose of antidepressant was optimum and the length of treatment was 8 weeks. Treatment resistance was defined as failure to respond to at least 2 adequate antidepressant trials. At follow-up visits, baseline evaluations other than the Mini–International Neuropsychiatric Interview were repeated, and an adverse effects inventory consisting of 14 items and an unstructured inquiry was administered. Thyroid measures were reevaluated at the last visit. At the non-Hadassah sites, ratings were performed by a single clinician (J.T.A. at the Princeton site and D.G. at the Be'er Ya'akov site). Four clinicians (including L.K., S.M.-M., and T.D.) performed ratings at the Hadassah site. Each patient was rated by the same psychiatrist throughout the study. Interrater reliability was established a priori for the HRSD.

The primary outcome measure was response to treatment, defined as a 50% or greater decrease in HRSD scores from baseline to study end point in an intent-to-treat sample. Secondary outcome measures were HRSD remission (response plus a final HRSD of ≤6) and VAS response (≥50% improvement from baseline to end point) or remission (75% improvement). We anticipated a 60% response rate to sertraline and a 25% better response in nonresistant patients receiving both drugs. Power analysis (using Power and Precision 2.0; http://www.power-analysis.com) indicated that a sample size of 100 would be needed to have 80% power to detect a difference in response rate between sertraline-liothyronine and sertraline-placebo that would be significant at $\alpha < .05$, in the context of an intent-to-treat analysis including all patients who completed at least 1 clinic visit after randomization.

STATISTICAL ANALYSES

Since most of the patients were studied at the Hadassah site (n = 75), to enhance power to detect site differences, a single virtual site (non-Hadassah) was formed for the remaining patients (n = 28). Because the findings for the intent-to-treat sample (N = 103) and the completer sample (n = 74) were fully consistent, only the results of the intent-to-treat sample are reported. Continuous variables were compared by *t* tests and categorical variables by χ^2 tests. Logarithmic (base 10) transformation was applied to the baseline hormone values to achieve a normal distribution. Nominal logistic regression analyses were performed predicting HRSD or VAS response and remission rates on the basis of treatment condition, center, age, sex, and baseline score. The treatment groups were also compared for change in serial HRSD ratings of the severity of depressive symptoms by longitudinal random regression analysis, with treatment group as a fixed effect and time point as a random effect. Center, age, and sex were included as additional fixed factors. Because the longitudinal random regression model assumption that data were missing at random might not be tenable, this analysis was supplemented by repeated-measures analysis of covariance using the last observation carried forward to account for missing observations, with center, age, and sex as covariates. A parametric survival analysis was conducted to determine whether the treatment groups differed in speed of response. Independent variables in the model were treatment condition, center, age, and sex. Number of weeks to sustained response, defined by percentage change in the HRSD, provided the event time data, with nonresponders treated as censored observations. Further analyses examined whether baseline thyroid function values or the changes in these values over the treatment course were associated with clinical outcome. With respect to baseline prediction, the logistic regression analysis used to contrast the treatment conditions for efficacy was repeated, now including terms for the main effect of each of the 3 thyroid function measures, as well as the interaction of each measure with treatment condition. To corroborate and identify their source, significant interaction effects were followed by 2-way analyses of variance (treatment condition × outcome classification) on the thyroid function values. A parallel analytic approach was used to determine whether changes in the thyroid function measures over the treatment trial were associated with therapeutic outcome.

RESULTS

PATIENT SAMPLE

The sertraline-liothyronine and sertraline-placebo groups did not differ significantly in demographic or clinical features (**Table 1**), nor did the patients treated at the Hadassah compared with non-Hadassah centers. There were no patients with resistant depression in the sample, and only 4 (8%) of the 53 patients in the sertraline-liothyronine group and 7 (13%) of the 50 patients in the sertraline-placebo group had received an adequate antidepressant trial during the current episode. Of the 60 pa-

Table 1. Demographic and Background Features of the Patient Groups*

	Treatment Group	
	SERT-T_3 (n = 53)	SERT-PLB (n = 50)
Age, y	45.15 ± 58.00	40.98 ± 55.77
Sex, No. (%) F	29 (55)	29 (58)
Education, y	14.45 ± 2.77	14.28 ± 2.79
Age at first depressive episode, y	33.89 ± 13.84	29.90 ± 12.66
Duration of current episode, wk	47.29 ± 69.27	53.74 ± 99.80
No. of depressive episodes	3.00 ± 2.20	3.41 ± 3.35
No. of depressive episodes per year at risk	0.36 ± 0.31	0.47 ± 0.41
Antidepressant trial during current episode, No. (%)	13 (25)	12 (24)
Adequate antidepressant trial during current episode, No. (%)	7 (13)	4 (8)
Baseline HRSD score	20.69 ± 4.91	21.96 ± 5.27

Abbreviations: HRSD, Hamilton Rating Scale for Depression; SERT-PLB, sertraline hydrochloride plus placebo; SERT-T_3, sertraline plus liothyronine sodium.

*Values are mean ± SD unless otherwise specified. No differences between SERT-T_3 and SERT-PLB groups were significant at $P<.1$.

tients randomized to receive sertraline-placebo, 50 (83%) completed at least 1 visit and were included in the data analysis; 37 (74%) of the 50 completed the 8-week trial (**Figure 1**). Of the 64 patients randomized to receive sertraline-liothyronine, 53 (83%) completed at least 1 visit; 40 (75%) of the 53 completed the 8-week trial ($\chi^2_1=0.71$; $P=.40$). In the sertraline-placebo group, the principal reasons for noncompletion were withdrawal of consent (n=5), adverse effects (n=4), lack of efficacy (n=2), loss to follow-up (n=1), and increase in suicidal ideation (n=1). In the sertraline-liothyronine group, the principal reasons for premature discontinuation were withdrawal of consent (n=4), adverse effects (n=6), loss to follow-up (n=2), and severe protocol violation (n=1). Duration of study participation did not differ among the noncompleters in the sertraline-liothyronine (mean±SD visits, 2.96±2.11) and sertraline-placebo (mean±SD visits, 3.19±2.01) groups ($t_{27}=0.29$; $P=.77$). Thus, there did not appear to be differential participation in the intent-to-treat or completer samples as a function of treatment condition.

The mean±SD prescribed dosage of liothyronine sodium was 34.60±7.50 µg/d in the sertraline-liothyronine group and 35.21±6.95 of matched placebo in the sertraline-placebo group. The average daily dose of sertraline hydrochloride did not differ in the sertraline-liothyronine group (mean±SD, 87.59±13.28 mg/d) and the sertraline-placebo group (mean±SD, 85.50±15.65 mg/d; $P=.66$). Twenty-one patients received additional medication for sedation during the study: 9 in the sertraline-liothyronine group and 12 in the sertraline-placebo group. Clonazepam was the most frequently used sedative (n=11); the others were alprazolam (n=3), zopiclone (n=2), zolpidem tartrate (n=2), lorazepam (n=2), flunitrazepam (n=2), and diazepam (n=1).

The treatment groups did not differ in any of the thyroid function measures taken at baseline (**Table 2**). Each

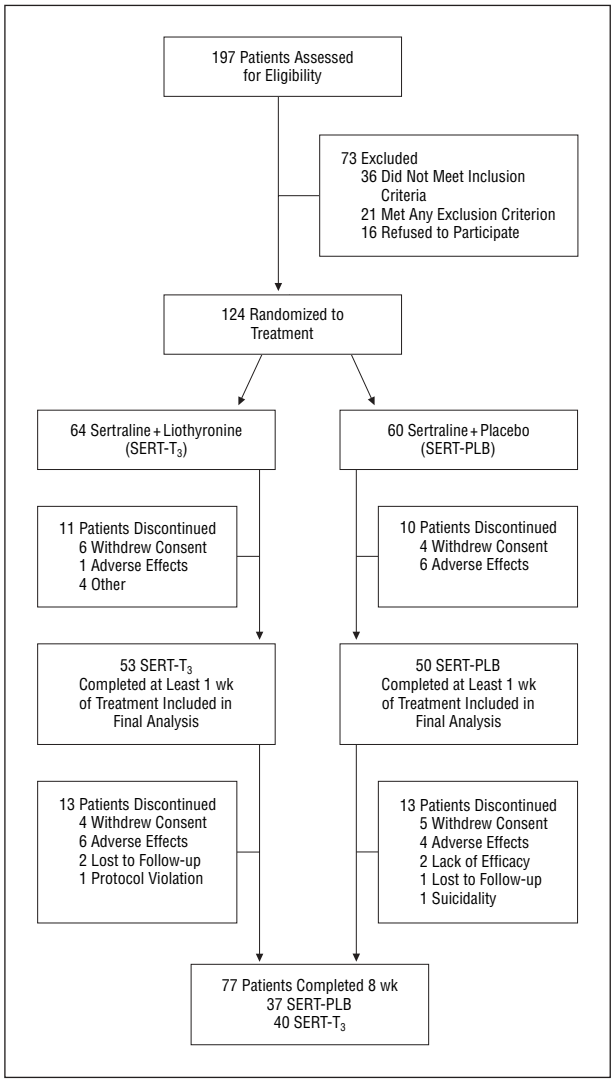

Figure 1. Flowchart of participation in the study.

Table 2. Thyroid Function Laboratory Values in Patients Before and After 8 Weeks of Treatment

	Treatment Group, Mean ± SD	
	SERT-T_3	SERT-PLB
Baseline		
TSH, mIU/L	1.7 ± 1.04	1.61 ± 0.73
Total T_3, ng/dL	117.14 ± 37.67	112.94 ± 26.12
Free T_4, ng/dL	1.06 ± 0.28	1.12 ± 0.16
Posttreatment		
TSH, mIU/L	0.41 ± 0.56	1.59 ± 0.92
Total T_3, ng/dL	148.30 ± 72.02	99.90 ± 21.52
Free T_4, ng/dL	0.58 ± 0.21	1.02 ± 0.18

Abbreviations: SERT-PLB, sertraline hydrochloride plus placebo; SERT-T_3, sertraline plus liothyronine sodium; T_3, triiodothyronine; T_4, thyroxine; TSH, thyrotropin.

SI conversion factors: To convert total T_3 to nanomoles per liter, multiply by 0.0154; to convert free T4 to picomoles per liter, multiply by 15.3846.

of the 3 repeated-measures analyses of covariance conducted on the measures collected before and after the 8-week trial yielded a main effect of treatment condi-

Table 3. Response and Remission Rates by Treatment Group

	HRSD		VAS	
	Response	Remission	Response	Remission
SERT-T_3, No. (%) (n = 53)	37 (70)	31 (58)	27 (51)	16 (30)
SERT- PLB, No. (%) (n = 50)	25 (50)	19 (38)	17 (34)	6 (12)
χ^2	5.64	5.14	3.63	4.98
P value	.02	.02	.06	.03
OR (95% CI)	2.93 (1.23-7.35)	2.69 (1.16-6.49)	2.28 (0.99-5.44)	3.58 (1.23-11.86)

Abbreviations: CI, confidence interval; HRSD, Hamilton Rating Scale for Depression; OR, odds ratio; SERT-PLB, sertraline hydrochloride plus placebo; SERT-T_3, sertraline plus liothyronine sodium; VAS, visual analog scale.

Table 4. Response and Remission Rates at Each Study Center

	No. (%)			
	HRSD		VAS	
	Response Rate	Remission Rate	Response Rate	Remission Rate
Hadassah				
SERT-PLB (n = 36)	17 (47)	13 (36)	12 (33)	4 (11)
SERT-T_3 (n = 39)	24 (62)	22 (56)	17 (44)	10 (26)
Non-Hadassah virtual center				
Total				
SERT-PLB (n = 14)	8 (57)	8 (57)	5 (36)	2 (14)
SERT-T_3 (n = 14)	13 (93)	12 (86)	10 (71)	6 (43)
Israel				
SERT-PLB (n = 4)	1 (25)	1 (25)	0	0
SERT-T_3 (n = 4)	4 (100)	4 (100)	1 (25)	1 (25)
United States				
SERT-PLB (n = 10)	7 (70)	7 (70)	5 (50)	2 (20)
SERT-T_3 (n = 10)	9 (90)	8 (80)	9 (90)	5 (50)

Abbreviations: HRSD, Hamilton Rating Scale for Depression; SERT-PLB, sertraline hydrochloride plus placebo; SERT-T_3, sertraline plus liothyronine sodium; VAS, visual analog scale.

tion (all $P \leq .004$) and a significant interaction between treatment condition and time (all $P < .001$). Paired *t* tests indicated that, over the treatment course, there was a significant decrease in thyrotropin levels in the sertraline-liothyronine group ($P < .001$). In the sertraline-placebo group, there was a slight but significant decrease in T_3 values ($P = .01$), while there was a marked increase in the sertraline-liothyronine group ($P = .001$). Levels of T_4 decreased markedly in the sertraline-liothyronine group ($P < .001$).

ANTIDEPRESSANT RESPONSE

The sertraline-liothyronine group showed significant advantage over the sertraline-placebo group in both response and remission rate, as defined by the HRSD, and in remission rate based on VAS scores (**Table 3**). The effect for VAS response rate approached significance. Of the other items in the logistic regression models, study center (Hadassah vs non-Hadassah centers) was significantly associated with the HRSD response and remission outcomes. Outcomes were superior at the non-Hadassah virtual center (all $P < .05$). Advancing age was associated with a lower rate of HRSD response ($P = .03$). Baseline HRSD scores did not have a significant relationship with any of the 4 outcome measures. The logistic regression analyses were repeated including terms for the interaction between treatment condition and center, age, and sex to determine whether any of these factors contributed to the efficacy advantage of sertraline-liothyronine relative to sertraline-placebo. None of the interaction effects approached significance. **Table 4** presents the response and remission rates for the Hadassah center and the non-Hadassah virtual center, as well as individually for the 2 facilities that composed the virtual center. For each site and for each outcome measure, there was an advantage for liothyronine relative to the placebo condition.

The findings documenting an advantage of the sertraline-liothyronine group in categorical therapeutic outcomes were supported by analyses of symptom severity. Longitudinal random regression analysis on serial HRSD scores yielded a main effect of treatment condition ($F_{1,510} = 12.06$; $P < .001$). Similarly, the repeated-measures analysis of covariance on last-observation-carried-forward serial HRSD scores, with center, age, and sex as covariates, yielded a main effect of treatment condition ($F_{1,98} = 5.68$; $P = .02$) (**Figure 2**). Including terms

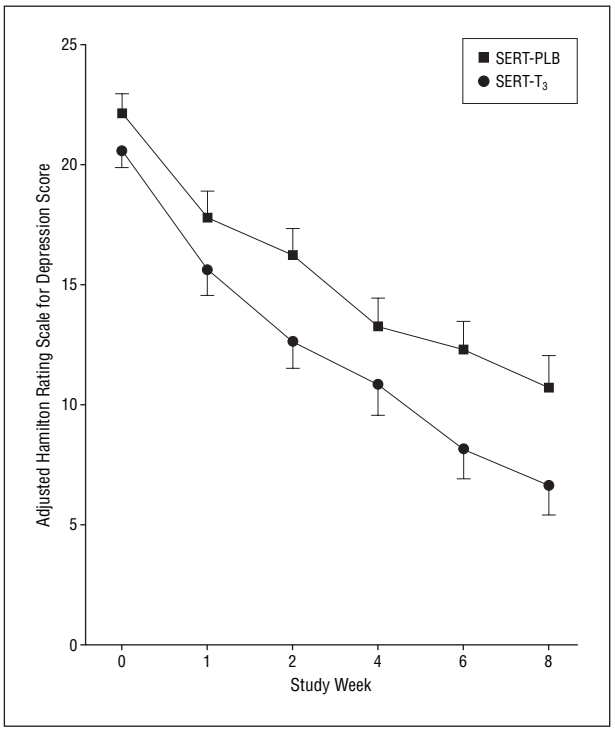

Figure 2. Adjusted (from analysis of covariance) mean Hamilton Rating Scale for Depression scores (last observation carried forward) of patients treated with sertraline hydrochloride plus liothyronine sodium (SERT-T_3) or sertraline plus placebo (SERT-PLB) for 8 weeks.

for the average daily dose of liothyronine and sertraline in the analyses of categorical and continuous clinical outcome measures did not produce any additional significant effects involving treatment condition.

Survival analysis did not show an effect of treatment condition on time to achieve response. For both the sertraline-liothyronine and sertraline-placebo groups, the median time to sustained response was 6 weeks. Thus, the combination with liothyronine influenced likelihood, but not speed, of benefit.

THYROID FUNCTION, CLINICAL CHARACTERISTICS, AND ANTIDEPRESSANT OUTCOME

Baseline values of the thyroid function measures and their bivariate interactions with treatment condition were added as terms in the logistic regression on HRSD remission status. The main effect of treatment condition remained significant (χ^2_1=5.63; P=.02) and an interaction emerged between treatment condition and baseline T_3 values (χ^2_1=5.95; P=.01) (**Figure 3**A). Post hoc analyses indicated that baseline T_3 values in the sertraline-liothyronine group were lower in patients who would later be classified as remitters than in those classified as nonremitters (107.60±23.84 vs 137.40±52.36 ng/dL [mean±SD]; t_{48}=3.36; P=.002). In contrast, remitters and nonremitters in the sertraline-placebo group did not differ in T_3 baseline values (P=.38). A cutoff T_3 level that could be applied clinically to identify patients more likely to have a remission on treatment with T_3 was not identified. The same pattern of differences emerged when HRSD response was used for outcome classification. These findings suggested that lower basal levels of T_3 were associated with better clinical outcome when sertraline was combined with liothyronine as opposed to placebo.

To examine the relationships between changes in thyroid function values over the treatment course and clinical outcome, a logistic regression analysis was conducted on HRSD remitter status. Change from pretreatment to posttreatment in the 3 thyroid function measures and the interaction of each change score with treatment condition were added as predictors in a model also containing treatment group, center, age, sex, and baseline HRSD score as predictors. The only significant effect in this analysis was the interaction between treatment condition and the change in TSH levels over the treatment course (χ^2_1=5.08; P=.02) (Figure 3B). Pretreatment and posttreatment thyrotropin levels were 1.70±0.87 and 0.28±0.45 mIU/L, respectively, in the patients who had remissions with sertraline-liothyronine treatment as compared with 1.88±1.32 and 0.76±0.70 mIU/L, respectively, in the patients who did not have remissions. The findings were unaltered when HRSD response status was used as the outcome classification. Thus, among patients treated with sertraline-liothyronine, greater reductions in thyrotropin values over the treatment course were associated with superior clinical outcome.

Duration of current depressive episode was the only clinical characteristic significantly associated with the antidepressant effect of liothyronine. Patients who responded to sertraline-liothyronine had a significantly shorter duration than did nonresponders (37.0±47.0 vs 102.6±104.5 weeks; t=–2.16; P=.03), and there was a trend in this direction for remitters compared with nonremitters (35.4±42.6 vs 141.5±105.5 weeks; t=–2.01; P=.05). Duration of the current depressive episode was not significantly associated with response or remission in the patients treated with sertraline-placebo.

ADVERSE EFFECTS

There were no significant differences in the frequency of adverse effects reported by the sertraline-liothyronine or sertraline-placebo groups, including those that might be expected to be more frequent in the patients treated with liothyronine, such as palpitations, sweating, and nervousness. Items of the adverse effects inventory that were reported by the patients at any level of severity, as well as events reported under the general inquiry section of the scale, are shown in **Table 5**. There were 2 serious events that led to withdrawal from the trial: a patient receiving sertraline-placebo developed severe suicidal ideation and a patient receiving sertraline-liothyronine required emergency thoracic surgery for a reason unrelated to the study.

COMMENT

The results of this study provide statistically significant support for enhancement of the antidepressant effect of the SSRI sertraline by concurrent treatment with liothyronine. The enhancement manifested as an approxi-

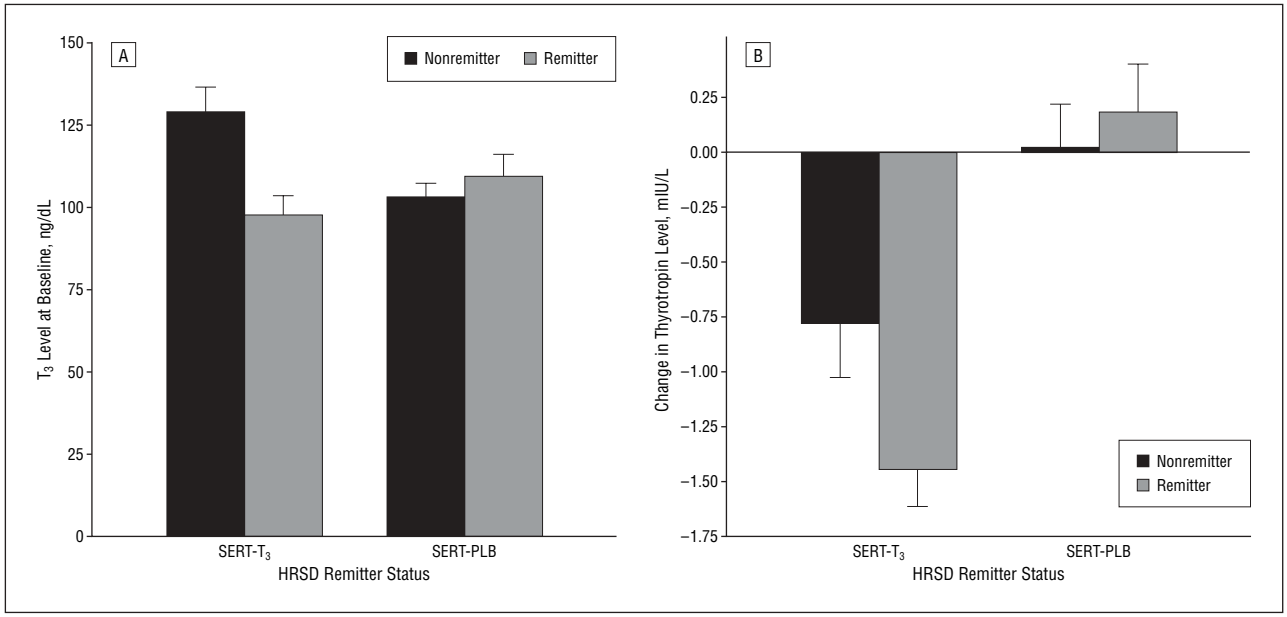

Figure 3. Thyroid hormone levels and response to treatment. A, Triiodothyronine (T_3) baseline levels in remitters and nonremitters to treatment with sertraline hydrochloride plus liothyronine sodium (SERT-T_3) or sertraline plus placebo (SERT-PLB). To convert T_3 to nanometer per liter, multiply by 0.0154. B, Change in thyrotropin levels during the course of treatment with SERT-T_3 or SERT-PLB (pretreatment-posttreatment). HRSD indicates Hamilton Rating Scale for Depression.

Table 5. Adverse Effects by Treatment Group

	No. (%)			
Adverse Effect	SERT-T_3 (n = 53)	SERT-PLB (n = 50)	χ^2_1	*P* Value
Appetite problems	34 (64)	34 (68)	0.17	.68
Dry mouth	36 (68)	34 (68)	0.00	.99
Drowsiness	31 (58)	34 (68)	1.00	.32
Nervousness	35 (66)	32 (64)	0.05	.83
Sleep difficulty	36 (68)	31 (62)	0.40	.53
Sweating	24 (45)	31 (62)	2.89	.09
Headache	32 (60)	28 (56)	0.20	.65
Diarrhea	24 (45)	27 (54)	0.78	.38
Abdominal pain	26 (49)	25 (50)	0.01	.92
Dizziness	30 (57)	25 (50)	0.45	.50
Weight problems	20 (38)	22 (44)	0.42	.52
Palpitations	25 (47)	20 (40)	0.54	.46
Sexual arousal problems	14 (26)	20 (40)	2.15	.14
Orgasm problems	15 (28)	18 (36)	0.70	.40
Constipation	19 (36)	17 (34)	0.04	.84
Sexual desire problems	7 (13)	8 (16)	0.16	.69
Flatulence	3 (6)	2 (4)	0.15	.70
Flushes	1 (2)	3 (6)	1.17	.28
Chest constriction	1 (2)	2 (4)	0.41	.52
Blurred vision	1 (2)	2 (4)	0.41	.52

Abbreviations: SERT-PLB, sertraline hydrochloride plus placebo; SERT-T_3, sertraline plus liothyronine sodium.

mately 20% greater rate of response and remission. Patients receiving sertraline-liothyronine were 2.9 times more likely to respond and 2.7 times more likely to achieve remission than were patients treated with sertraline alone. Furthermore, the antidepressant effect of liothyronine could be directly linked to thyroid function. Lower basal levels of T_3 were associated with better clinical outcome when sertraline was combined with liothyronine. For reasons that are not clear, there was a small but significant decline in T_3 levels in the patients treated with sertraline-placebo. Among patients treated with liothyronine and sertraline, greater reductions in thyrotropin values over the treatment course were associated with superior clinical outcome. There was no association of female sex with antidepressant effect of liothyronine, contrary to the previous observation of our group in an open-label augmentation study of treatment-resistant patients.[26] We observed neither a significant acceleration of response to

liothyronine nor a sex effect in this regard, unlike the meta-analysis by Altshuler et al[21] of acceleration studies. Liothyronine was well tolerated by the patients in our study. The proportion of patients who experienced adverse effects considered typical of liothyronine, such as nervousness, palpitations, and sweating, was not greater with the active hormone than with placebo.

The explanation for the observation that baseline T_3 levels predict response to liothyronine administration better than baseline thyrotropin levels is not clear and deserves further investigation. One possibility is that the therapeutic effect seen with exogenous liothyronine administration may be related to decreased ability to convert circulating T_4 to T_3 in critical regions of the brain and in the periphery but not in the pituitary. Thus, a relatively low peripheral T_3 level is undetected by the pituitary and is not compensated for through increased thyrotropin. In this context, possible causes of low T_3 levels should be considered. Theoretically, if patients have low T_3 levels, this may be a contributing factor to the depression they are experiencing and exogenous liothyronine would enhance antidepressant response. Low T_3 levels are commonly found in patients with nonthyroidal illness, but none of our patients had acute systemic illness at the time of the study. Markedly increased iodine intake could also cause a relative increase in the thyroidal T_4/T_3 ratio. This cannot be excluded because iodine intake was not determined in these patients. Antidepressants are not known to reduce T_3 levels, although in this study a significant decline in T_3 levels was observed in the sertraline-placebo group. However, patients who had received previous treatment with sertraline were excluded from the study. An alternative explanation, that relatively low T_3 levels may be caused by genetic variants in any of the 3 deiodinase genes, is intriguing. One recent study did not find an association between a polymorphism in type II deiodinase and response to paroxetine hydrochloride,[34] but further studies are needed to explore this issue.

The findings of our study differ from those of Appelhof et al,[30] who examined depressed patients treated with the SSRI paroxetine plus T_3 or placebo for 8 weeks and found no effect. An important difference between the 2 studies is the proportion of patients with chronic depression. Appelhof et al[30] reported that 44% of their sample had been depressed for more than 2 years. In our sample, the mean±SD duration of the current depressive episode was 47.29±69.27 weeks in the sertraline-liothyronine group and 53.74±99.80 weeks in the sertraline-placebo group. Only 6 patients (11%) in the sertraline-liothyronine group and 6 (12%) in the sertraline-placebo group had episodes that had lasted longer than 2 years. Chronicity of depression may limit the degree to which addition of liothyronine can increase response rate because response to antidepressant treatment is poorer in patients with longer episode duration, creating a ceiling effect in terms of potential for therapeutic effect.[35] In fact, response to sertraline-liothyronine was significantly related to duration of the current depressive episode in our study, duration being significantly shorter in patients who responded. There was also a striking difference in adverse effects between our study and that of Appelhof et al.[30] In particular, sweating was significantly more frequent in the T_3 groups in the Appelhof et al[30] study, whereas in our study there was a trend for less sweating in the liothyronine group. Given the putative noradrenergic reuptake effects of paroxetine[36,37] as well as the enhancing effects of thyroid hormone on adrenergic signaling,[38,39] it is possible that the higher adverse effect burden might be specific to the combination of T_3 with paroxetine.

There are limitations that should be taken into account in considering the results of our study. There was no washout period for previous antidepressant treatment before starting the study medication. However, only 28% of patients in the sertraline-liothyronine group and 28% in the sertraline-liothyronine group had received antidepressant treatment during the current episode. Because these few patients were equally distributed between the sertraline-liothyronine and sertraline-placebo groups, the absence of a washout period for previous antidepressant medication is unlikely to have influenced the results of the study or would have influenced the outcome equally. The maximum dosage of sertraline hydrochloride was 100 mg/d. Although this is a therapeutic dose,[40,41] we cannot exclude the possibility that a higher sertraline dosage might have achieved a response rate higher than 50% in the sertraline-placebo group. With a 60% response rate to sertraline-placebo, our sample would not have had sufficient power to demonstrate a significant effect of liothyronine supplementation. Also, the liothyronine sodium dose range was different in the Israeli (20-40 µg) and US (25-50 µg) centers. To address this issue, liothyronine dose was taken into account in all analyses. The sites differed in response and remission rates across the placebo and liothyronine conditions. However, there were no interactions between site and treatment condition in clinical outcome measures and a relative advantage for liothyronine obtained at each of the sites (Table 4), supporting the generalizability of the findings. Differences among the sites in therapeutic effects across the active and placebo conditions are commonly observed. The causes of these differences are difficult to identify; they are usually attributed to differences in sample characteristics and nonspecific aspects of the study procedures, such as provision of social support services.[42] Finally, the hormone assays were performed in different laboratories. However, all samples from any particular patient were assayed with the same kit in the same laboratory. Thus, the analyses that relate to changes in hormone levels during treatment should not be affected. As for the finding that low baseline T_3 level predicts response to treatment, because sertraline-liothyronine and sertraline-placebo groups were randomly distributed in the 3 centers, the effect of minor differences in the assays is expected to be minimal. In any case, these analyses were post hoc, and studies designed to answer these specific questions are needed.

To what extent are the findings generalizable and clinically relevant? This was an outpatient study and the inclusion and exclusion criteria were not unduly restrictive. However, patients with a lifetime history of alcohol or other drug dependence or of abuse in the preceding 12 months were excluded, as were patients with a greater than minimal level of suicidal ideation. A second consideration is whether the findings are applicable to SSRIs other than sertraline. Although open-label studies have sug-

gested that the clinical efficacy of several SSRIs is enhanced by T_3,[26-28] the only randomized, double-blind, placebo-controlled trial besides the present one did not show a clinical advantage for T_3 augmentation of the SSRI paroxetine.[30] Further controlled studies are needed to address the question of generalizability to SSRIs other than sertraline.

In the context of increasing concern over the relatively low success rate of SSRIs in clinical practice,[2] the results of this study are highly relevant and demonstrate that the effectiveness of these antidepressant agents can be substantially enhanced. We have shown that concurrent administration of liothyronine increases response and remission on treatment with sertraline by approximately 20%, a clinically significant improvement of efficacy. This level of effect may not be sufficient to warrant addition of liothyronine to treatment with SSRIs on a routine basis, but it is of sufficient magnitude to warrant addition of liothyronine in patients who can be identified as being more likely to benefit from the combination strategy. In this regard, further exploration of the relationship between response to liothyronine supplementation and pretreatment levels of T_3, as well as other indexes of thyroid function, is indicated.

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