Combined Levothyroxine Plus Liothyronine Compared With Levothyroxine Alone in Primary Hypothyroidism

A Randomized Controlled Trial

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Context Standard therapy for patients with primary hypothyroidism is replacement with synthetic thyroxine, which undergoes peripheral conversion to triiodothyronine, the active form of thyroid hormone. Within the lay population and in some medical communities, there is a perception that adding synthetic triiodothyronine, or liothyronine, to levothyroxine improves the symptoms of hypothyroidism despite insufficient evidence to support this practice.

Objective To evaluate the benefits of treating primary hypothyroidism with levothyroxine plus liothyronine combination therapy vs levothyroxine monotherapy.

Design, Setting, and Patients Randomized, double-blind, placebo-controlled trial conducted from May 2000 to February 2002 at a military treatment facility that serves active duty and retired military personnel and their family members. The trial included a total of 46 patients aged 24 to 65 years with at least a 6-month history of treatment with levothyroxine for primary hypothyroidism.

Intervention Patients received either their usual dose of levothyroxine (n=23) or combination therapy (n=23), in which their usual levothyroxine dose was reduced by 50 µg/d and substituted with liothyronine, 7.5 µg, taken twice daily for 4 months.

Main Outcome Measures Scores on a hypothyroid-specific health-related quality-of-life (HRQL) questionnaire, body weight, serum lipid levels, and 13 neuropsychological tests measured before and after treatment.

Results Serum thyrotropin levels remained similar and within the normal range in both treatment groups from baseline to 4 months. Body weight and serum lipid levels did not change. The HRQL questionnaire scores improved significantly in both the control group (23%; $P<.001$) and the combination therapy group (12%; $P=.02$), but these changes were statistically similar ($P=.54$). In 12 of 13 neuropsychological tests, outcomes between groups were not significantly different; the 1 remaining test (Grooved Peg Board) showed better performance in the control group.

Conclusion Compared with levothyroxine alone, treatment of primary hypothyroidism with combination levothyroxine plus liothyronine demonstrated no beneficial changes in body weight, serum lipid levels, hypothyroid symptoms as measured by a HRQL questionnaire, and standard measures of cognitive performance.

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HYPOTHYROIDISM IS ONE OF the most common endocrine disorders, occurring in up to 5% of the population of the United States and the United Kingdom.[1,2] Successful treatment of hypothyroidism requires normalizing thyroid hormone levels in peripheral tissues with the use of replacement therapy. The first available thyroid hormone preparations came from dried animal thyroid glands that contained varying amounts of both thyroxine (T_4) and triiodothyronine (T_3).[3] Levothyroxine has become the replacement medication of choice because it has a half-life of 6 days, and because it is converted to T_3 in peripheral tissues, providing stable and physiological quantities of T_3 to the body.[4] Liothyronine is also available; this form of thyroid hormone reaches peak levels 2 to 4 hours after oral administration and has a circulating half-life of 1 day.[5] Thus, steady-state levels cannot be maintained with once-daily dosing of liothyronine.

Studies in thyroidectomized rats have shown that to ensure normal tissue concentrations of both T_4 and T_3, continuous infusions of both levothyroxine and liothyronine are necessary.[6] However, when infusions of levothyroxine alone are administered to these rats at doses sufficient to normalize plasma TSH (thyrotropin [thyroid-stimulating hormone]) levels, levothyroxine therapy does normalize tissue T_3 levels.[7] In the early 1970s, before the availability of serum TSH assays, human studies on the

See also p 3002 and Patient Page.

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treatment of hypothyroidism used pharmacological doses of thyroid hormone combinations, administering 40 to 60 µg of liothyronine per day in addition to levothyroxine.[8,9] One study used a 3:1 ratio of levothyroxine to liothyronine and found anecdotally that patients preferred this combination over desiccated dried thyroid.[8] A randomized controlled trial using a 4:1 ratio of levothyroxine to liothyronine found that more patients preferred levothyroxine alone because of the high incidence of thyrotoxic symptoms with the combined therapy.[9] More recently, the results of another controlled trial, using a fixed dose of liothyronine (12.5 µg/d) with varying amounts of levothyroxine, suggested that there is a subtle benefit on mood and physical symptoms from the use of combined therapy. However, many patients in this study had serum TSH levels below the lower limit of normal.[10]

While most people with hypothyroidism are satisfied with hormone replacement of levothyroxine alone, many others continue to have significant impairment in psychological well-being.[11] We conducted a controlled trial to further investigate whether combined therapy with levothyroxine and liothyronine, while avoiding suppressed levels of serum TSH, would lead to improvements in quality of life, neurocognitive functioning, and certain physiological parameters.

METHODS

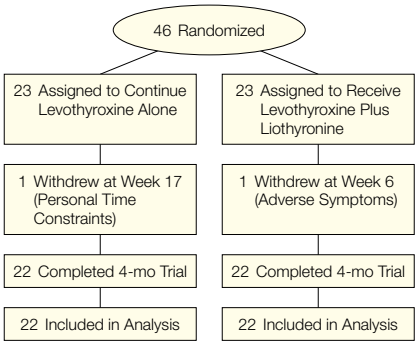
Study Design and Participants

This study was conducted at the National Naval Medical Center in Bethesda, Md, from May 2000 to February 2002. Via advertisements posted in the medical center, patients were invited to participate if they were between the ages of 18 and 65 years and if they had been receiving treatment for primary hypothyroidism for at least 6 months, including a stable dose of levothyroxine for at least 3 months. Participants were told that we were studying whether taking another thyroid hormone (liothyronine) along with levothyroxine would make them feel better and improve the way their body and mind functions. Patients were not invited if they were taking suppressive doses of thyroid hormone, were pregnant, had cardiac disease or medical problems that would significantly affect renal or liver function, or if they were taking corticosteroids, amiodarone, carafate, cholestyramine, or more than 325 mg/d of iron. The study was approved by the institutional review board and written informed consent was obtained from all participants.

Patients were randomized to receive combined levothyroxine plus liothyronine or to continue their usual dose of levothyroxine (FIGURE). Patients in the intervention group decreased their usual daily dose of levothyroxine by 50 µg and began taking 7.5 µg of liothyronine contained in a study capsule (Cytomel, liothyronine sodium tablet, King Pharmaceuticals, St Louis, Mo) twice daily, in addition to their new once-daily dose of levothyroxine. The control group also decreased their usual daily dose of levothyroxine by 50 µg and began taking 25 µg of levothyroxine contained in a study capsule (Synthroid, levothyroxine sodium tablet, USP, Abbott Laboratories, Abbott Park, Ill) twice daily, in addition to the lowered once-daily dose of levothyroxine. Synthroid was the only brand of levothyroxine used during the study. Treatment duration was 4 months.

On the first day of the study, patients took their usual dose of levothyroxine. They arrived in the morning between 7:00 AM and 7:30 AM in the fasting state for laboratory testing, and they then ate breakfast at the medical center. Neurocognitive testing, which lasted approximately 3 hours, began at approximately 8:30 AM. This was followed by an interview and physical examination and completion of a questionnaire on hypothyroid symptoms. Patients began taking the study medications the following day. On the last day of the study, patients took their known dose of levothyroxine plus a study capsule before arriving at the medical center. Serum laboratory tests were again obtained at approximately 7:30 AM, and at 8:30 AM patients repeated the evaluations described above. Therefore, blood samples were drawn approximately 1 hour after the morning dose of levothyroxine and liothyronine, and the cognitive testing was started approximately 2 hours after the morning dose of thyroid medication.

Figure. Flow Diagram of Participants in Study



The pharmacy department supervised the production, storage, and dispensing of the study capsules, which contained either 7.5 µg of liothyronine or, in an identical-appearing capsule, 25 µg of levothyroxine. Although any remaining study capsules were not counted, the patients consistently stated on the last day of the study that they had taken their medications as instructed. The pharmacy also maintained the concealed randomization list, which was stratified in blocks of 10 according to a computer-generated random number table. All study participants, physician investigators, and psychometricians administering the neurocognitive tests remained blinded throughout the study. Those involved with analyzing test results were also unaware of patient group assignments.

Biochemical Measurements

Serum TSH, free T_4, and total T_3 levels were measured by enzyme immunoassay kits (Abbott Laboratories, Abbott Park, Ill). A physician who was blinded to the drug allocation and who had no other contact with study participants evaluated TSH levels at 5 weeks. If

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Box. Symptoms Evaluated in the Hypothyroid-Specific Health-Related Quality-of-Life Questionnaire*

Weight gain
Feeling colder than others around you
Generally unwell
Needing nap during the day
Slower physically
No energy to get through day
Loss of interest in hobbies or enjoyable activities
Difficulty remembering things
Dry skin
Brittle nails
Constipation
Need for more sleep
Exhausted
Slower mentally
Lethargic
Depressed
Frustrated
Difficulty concentrating
Muscle weakness
Puffiness of hands
Tired
Less energetic
Sluggish throughout the day
More worn out
Worried
Discouraged
Deterioration of memory

*Patients were asked if they had experienced the symptoms listed during the preceding month, specifying the severity of the discomfort or problem using a 5-point scale that ranged from "not at all" (1) to "all the time" (5).

needed, the dose of levothyroxine was adjusted to keep the serum TSH level between 0.5 and 3.5 mIU/L. Thyroid function studies and levothyroxine dose adjustments were repeated every 5 weeks, if needed, until the TSH level was in the desired range. If the serum TSH level was in the desired range, then no further blood tests or medication adjustments were performed until the end of the study.

Initial fasting blood tests included a basic metabolic panel, a serum sex hormone–binding globulin (SHBG) level measured by radioimmunoassay at the Nichols Institute (San Juan Capistrano, Calif), and a serum lipid panel, measured by enzymatic colorimetric methods (Vitros 250 Chemistry System, Ortho-Clinical Diagnostics, Rochester, NY).

Physical measurements included body weight, resting heart rate, and blood pressure.

Outcome Measures

Primary outcome measures included standardized tests of neurocognitive functioning. Tests of attention and working memory (the ability to briefly hold and manipulate information in memory prior to giving a response) included the Letter-Number Sequencing and Spatial Span subtests of the Wechsler Memory Scale–Version III (WMS-III),[12] the Paced Auditory Serial Addition Test,[13] and the Auditory Consonant Trigrams Test.[14] Tests of learning and memory included the Buschke Selective Reminding Test[15,16] and additional subtests of the WMS-III: Logical Memory and Visual Reproduction.[12] The Thurstone Word Fluency Test[17] was used to measure written verbal memory, and the Grooved Peg Board Test[18] was used to measure manual dexterity and fine visual-motor coordination. Finally, patients performed the Trail-Making Test Part B,[19] which evaluates visual scanning, visual-motor coordination, attention, and cognitive flexibility. Study participants also completed the Beck Depression Inventory (BDI), which can be used to measure the degree of depressive symptoms but not to make the diagnosis of a depressive mood disorder.[20] A trained psychometrician, under the supervision of a clinical psychologist, administered all tests.

The other primary outcome measure was a health-related quality-of-life (HRQL) questionnaire, modeled after hypothyroid-specific questionnaires developed by Jaeschke et al[21] and Cooper et al.[22] Our hypothyroid HRQL questionnaire (BOX) asked about symptoms of hypothyroidism that were identified previously among people with known hypothyroidism and that improved after taking thyroid hormone.[23] Patients were asked if they had experienced the symptoms listed in the Box during the preceding month, specifying the severity of the discomfort or problem using a 5-point scale that ranged from "not at all" (1) to "all the time" (5).

Statistical Analysis

Prior to the study, we calculated that a sample size of 12 in each group would be sufficient to detect a significant difference with 90% power (with a type I error rate of $\alpha = .05$) between the combined therapy group and the control group on the Logical Memory subtest of the WMS-III. This number was based on a previous study evaluating levothyroxine treatment in patients with subclinical hypothyroidism, in which a standardized difference of 1.4 on the Logical Memory subtest of the WMS (1st ed) was observed between euthyroid patients and those with subclinical hypothyroidism.[24] In the controlled trial by Cooper et al,[22] they also used a symptom questionnaire with a 5-point scale similar to our HRQL questionnaire to measure the benefits of administering levothyroxine to patients with subclinical hypothyroidism. They found statistically significant differences with their questionnaire using 17 patients in the treatment group and 16 control patients. Parametric (*t* test) or nonparametric (Wilcoxon signed rank test or Mann-Whitney *U* test) analysis was used, depending on the results of tests (Shapiro-Wilk test) examining assumptions of the statistical model. A 2-tailed .05 significance level was used for all parameters. Analyses were performed with Analyse-it for Microsoft Excel 2002 (Redmond, Wash), General Statistics version 1.65 (Analyse-It Software Ltd, United Kingdom).

RESULTS

Forty-six participants were randomized into the 2 groups, and 44 completed the study (Figure). Baseline clinical characteristics of the 2 groups were similar (TABLE 1). The most frequent cause of hypothyroidism was autoimmune thyroiditis. There were 2 dropouts: 1 participant in the control group could not find time at the end of the

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treatment period for repeat testing; 1 participant in the combination therapy group withdrew after 5 weeks with complaints of tremulousness, fatigue, and poor performance at her place of employment (the thyroid function test results were in the normal range during the time of these symptoms: TSH, 0.73 mIU/L; free T_4, 0.64 ng/dL [8.24 pmol/L]; total T_3, 148 ng/dL [2.28 nmol/L]). Apart from these patients, there were no other adverse events in either group during the study.

TABLE 2 compares the changes from baseline to 4 months in physical and biochemical measurements. As expected, in the combined therapy group, the serum free T_4 levels fell ($P<.001$) and the serum T_3 levels rose ($P<.001$), although both levels remained within normal limits. The changes in free T_4 and T_3 were the only significant comparative differences between the study groups. Of note, serum TSH levels were similar in both groups at baseline and at 4 months. At baseline, there were no patients in either group with a TSH level less than 0.20 mIU/L; there were 2 patients in the control group with TSH levels greater than 5.0 mIU/L (actual values, 7.7 mIU/L and 7.4 mIU/L) and 3 patients in the combined therapy group with TSH levels greater than 5.0 mIU/L (actual values: 6.2 mIU/L, 6.7 mIU/L, and 7.5 mIU/L). At 5 weeks, 8 patients in the control group and 10 patients in the combined group required dose adjustment after review of the serum TSH levels. At 4 months, there was 1 patient in the control group whose TSH value was less than 0.20 mIU/L (actual value, 0.10 mIU/L) and 2 patients in the combined therapy group with TSH levels less than 0.20 mIU/L (actual values: 0.09 mIU/L and 0.12 mIU/L); there were 3 patients in the control group with TSH levels greater than 5.0 mIU/L (actual values: 5.6 mIU/L, 6.0 mIU/L, and 5.2 mIU/L) and 1 patient in the combined therapy group with a TSH level greater than 5.0 mIU/L (actual value, 7.3 mIU/L). There was no significant change in SHBG within the control group ($P=.28$) or within the combined therapy group ($P=.12$) during the treatment period.

Hypothyroid HRQL symptom scores decreased significantly in both the control group ($P<.001$) and the combined therapy group ($P=.02$) (TABLE 3).

Table 1. Baseline Patient Characteristics

Characteristic	Levothyroxine Monotherapy (n = 22)	Levothyroxine Plus Liothyronine (n = 22)
Age, mean (SD), y	45.2 (9.7)	43.1 (11.3)
Women, No. (%)	17 (77)	19 (86)
Cause of hypothyroidism, No.		
Autoimmune thyroiditis	18	13
RAI for toxic diffuse goiter	2	7
RAI for MNG	0	1
Thyroid carcinoma treatment	0	1
External radiotherapy to neck region	1	0
Thyroidectomy for treatment of MNG	1	0
Dose of levothyroxine, mean (SD)		
µg/d	131 (41)	126 (26)
µg/kg/d	1.6 (0.4)	1.8 (0.5)
Duration of therapy, mean (SD), mo	78 (79)	102 (99)

Abbreviations: MNG, multinodular goiter; RAI, radioactive iodine therapy.

Table 2. Comparison of Changes in Weight, Heart Rate, Blood Pressure, and Biochemical Measurements*

	Levothyroxine Monotherapy (n = 22)			Levothyroxine Plus Liothyronine (n = 22)			
Measurement	Baseline	4 Months	Change	Baseline	4 Months	Change	*P* Value†
Weight, kg	85.5 (18.3)	83.9 (18.9)	−1.4 (7.5)	74.9 (16.2)	74.6 (16.1)	−0.7 (4.8)	.72
Heart rate, beats/min	72 (11)	72 (10)	−0.05 (9)	73 (12)	72 (10)	−1.3 (11)	.69
Blood pressure, mm Hg							
Systolic	134 (17)	132 (20)	−1.6 (11)	126 (13)	126 (13)	−0.1 (9)	.64
Diastolic	83 (10)	79 (10)	−3.2 (7)	79 (10)	75 (8)	−4.5 (10)	.63
TSH, mIU/mL	2.2 (2.1)	2.1 (1.7)	−0.05 (2.2)	2.6 (2.0)	2.0 (1.8)	−0.6 (2.4)	.46
Free thyroxine, ng/dL	1.2 (0.2)	1.2 (0.3)	0.02 (0.28)	1.3 (0.2)	0.8 (0.2)	−0.4 (0.3)	<.001
Total triiodothyronine, ng/dL	96 (18)	87 (12)	−10 (15)	89 (16)	135 (41)	46 (39)	<.001
Sex hormone–binding globulin, µg/dL	56 (58)	62 (61)	5.7 (23)	60 (32)	75 (60)	15 (45)	.38
Cholesterol, mg/dL							
Total	206 (37)	210 (39)	4.0 (22)	206 (51)	198 (36)	−8.6 (29)	.11
LDL	121 (32)	128 (33)	6.6 (21)	121 (47)	117 (34)	−4.0 (23)	.12
HDL	47 (16)	46 (13)	−1.3 (8.7)	61 (18)	58 (14)	−2.7 (10)	.64
Triglycerides, mg/dL	188 (108)	178 (96)	−9.9 (26)	120 (55)	110 (49)	−9.9 (31)	>.99

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; TSH, thyroid-stimulating hormone.
SI conversion factors: To convert free thyroxine to pmol/L, multiply by 12.87; to convert total triiodothyronine to nmol/L, multiply by 0.0154; to convert sex hormone–binding globulin to nmol/L, multiply by 34.7; to convert total cholesterol, LDL-C, and HDL-C to mmol/L, multiply by 0.02586; to convert triglycerides to mmol/L, multiply by 0.01129.
*Data are presented as mean (SD).
†*P* values compare the mean of individual changes from baseline. Statistically significant differences were seen only from decreased thyroxine and increased triiodothyronine in the combined therapy group.

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The decrease in scores was greater in the control group than in the intervention group, but this difference was not statistically different ($P=.54$).

Results of the neuropsychological tests are shown in TABLE 4. In 12 of 13 tests, there were no significant differences between the 2 groups. The one test with a significantly different outcome was the Grooved Peg Board test, in which performance declined in the combined therapy group.

There was a significant decrease of the mean score of the BDI in the control group ($P=.005$) but not in the combined therapy group ($P=.18$, data not shown). However, only 17 patients from each study group were given the opportunity to complete the BDI, and no difference was found ($P=.21$) when comparing the group means of the individual changes in BDI scores. On the BDI, a score of 10 or less is considered normal. Prior to the study, 4 patients in the control group and 4 patients in the combined therapy group had scores greater than 10; after 4 months, 2 patients in each group had scores greater than 10.

To assess the success of blinding, study patients were asked at the end of the study to guess whether or not they believed they had been taking liothyronine. They were not informed of any symptomatic clues that might suggest the use of liothyronine. In the combined therapy group, 8 (36%) of 22 patients correctly guessed that they were taking liothyronine. In the control group, 11 (50%) of 22 patients incorrectly guessed that they were taking liothyronine. One patient in each group admitted they had no idea whether or not they had been taking liothyronine and refused to guess. The remaining patients (13 in the combined therapy group and 10 in the control group) believed that they were not taking liothyronine.

COMMENT

Compared with the use of levothyroxine alone, 4 months of partial substitution of 50 µg of levothyroxine with 7.5 µg of liothyronine, taken twice daily, improved neither the scores of a hypothyroid-specific HRQL questionnaire nor the results of any neuropsychological tests. There were no changes in body weight, blood pressure, heart rate, and serum lipid levels. The only biochemical change was the expected rise in serum T_3 levels and fall in serum free T_4 in the combined therapy group. Because the blood samples were drawn only 1 hour after the morning dose of liothyronine, serum T_3 levels may have not yet reached their peak levels at the time of the blood draw. Peak T_3 levels should have been achieved 2 to 3 hours later while patients were performing the cognitive testing. This study was well blinded, as demonstrated by the fact

Table 3. Hypothyroid Health-Related Quality-of-Life Questionnaire Scores*

	Levothyroxine Monotherapy (n = 20)†	Levothyroxine Plus Liothyronine (n = 21)†	*P* Value
Baseline	77 (26)	66 (28)	.91
4 Months	58 (23)	50 (12)	.61
Change‡	19 (18)	15 (26)	.54
% Change	–23 (21)	–12 (35)	.27

*Data are presented as mean (SD). Higher scores suggest more symptoms. Score range, 29-145. Mean (SD) score in 20 healthy individuals without clinical thyroid disease was 49 (18).
†Two participants in the control group and 1 in the intervention group were unintentionally not offered an opportunity to complete the hypothyroid health-related quality of life questionnaire either at baseline or at the end of the treatment period.
‡The difference from baseline to 4 months was significant for both the monotherapy group ($P<.001$) and the combined therapy group ($P = .02$)

Table 4. Comparison of Changes in Raw Scores of Neurocognitive Tests*

Test	Levothyroxine Monotherapy (n = 22)			Levothyroxine Plus Liothyronine (n = 22)			*P* Value†
	Baseline	4 Months	Change	Baseline	4 Months	Change	
WMS-III							
Logical Memory I	45 (7)	51 (7)	6 (6)	44 (8)	48 (10)	4 (9)	.41
Logical Memory II	29 (7)	34 (8)	5 (7)	28 (7)	33 (8)	5 (6)	.75
Visual Reproduction I	89 (11)	89 (10)	1 (7)	88 (7)	92 (8)	4 (9)	.13
Visual Reproduction II	70 (22)	80 (20)	10 (8)	72 (13)	83 (11)	10 (12)	.86
Letter Number Sequencing	12.4 (2.7)	12.5 (2.4)	0.1 (1.6)	11.3 (2.0)	10.9 (2.0)	–0.4 (1.7)	.19
Spatial Span	16.2 (3.1)	16.2 (3.1)	0.0 (2.8)	17.4 (2.6)	16.0 (3.1)	–1.4 (2.8)	.10
PASAT	48 (24)	40 (24)	–8 (15)	51 (21)	39 (18)	–11 (15)	.50
Grooved Peg Board‡	64 (10)	62 (11)	–2 (6)	63 (8)	65 (10)	2 (6)	.03§
Trails B‡	52 (16)	52 (15)	1 (11)	53 (19)	47 (16)	–6 (15)	.09
Thurston Word Fluency	18.2 (7.5)	20.9 (7.2)	2.7 (4.7)	15.7 (5.4)	18.1 (8.0)	2.4 (5.0)	.87
Auditory Consonant Trigram	51 (7)	52 (7)	1 (5)	50 (5)	51 (5)	1 (4)	.92
BSRT Long-term Storage	111 (18)	113 (20)	2 (18)	112 (16)	119 (18)	7 (12)	.27
BSRT Consistent Long-term Retrieval	79 (30)	88 (34)	10 (18)	86 (32)	93 (38)	7 (24)	.70

Abbreviations: BSRT, Bushke Selective Reminding Test; PASAT, Paced Auditory Serial Addition Test; WMS-III, Wechsler Memory Scale III.
*Data are presented as mean (SD). Higher scores indicate superior performance unless noted otherwise.
†*P* values compare the mean of individual changes from baseline.
‡A lower score indicates superior performance.
§Statistically significant for superior performance in the levothyroxine monotherapy group.

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that study patients were generally unable to detect the group to which they had been assigned.

The majority of the measurements of neurocognitive performance showed no significant differences between the 2 study groups. Only 1 of 13 cognitive tests had a significantly different outcome. This test was the Grooved Peg Board, in which subjects are asked to insert small grooved pegs into a pegboard containing a 5×5 set of slotted holes. The score is based on the time required to complete the task.[18] The combined therapy group demonstrated declining performance on this test of manual dexterity.

We chose to randomize our patients into 2 groups, rather than use a crossover design, to be able to better detect any practice effect or placebo effect. Indeed, mean scores improved in the control group as well as the combined therapy group on several of the neuropsychological tests ($P<.05$, with analysis of repeat measures, for improvement on 6 of 13 tests in the control group and 7 of 13 tests in the combined therapy group; the combined therapy group also demonstrated declining performance [$P=.03$] on Spatial Span, a test of visual working memory) and on the HRQL questionnaire (Table 3). This outcome demonstrates the significant practice effect and placebo effect that can be seen with even a 4-month period between testing. The study by Bunevicius and Prange[25] used a crossover design with patient evaluation at the end of each treatment period. Because most of the improvement found in the earlier study was limited to patients with thyroid cancer,[25] it may be significant that 13 of the 17 participants with thyroid cancer were randomized to receive the control therapy before they were crossed over to receive the combined therapy.[10] In this manner, the majority of repeat testing, with its associated practice effect, occurred after this subgroup of patients was treated with combined levothyroxine and liothyronine. The dose of liothyronine in the prior study was 12.5 µg/d for 5 weeks. We chose to use a longer treatment period in our study to allow more time for any beneficial effect of liothyronine to occur, and the twice-daily dosing of 7.5 µg of liothyronine allowed for more sustained serum levels of T_3.

Bunevicius and Prange[25] found statistically significant differences in some measurements of mood and physical symptoms, particularly in patients with a history of thyroid cancer, which comprised more than 50% of study patients. The majority of these patients took sufficient thyroid hormone to suppress the serum TSH concentration to below the lower limit of normal, which itself has been associated with an improved self-assessment of well-being or mood.[26,27] Administering more liothyronine to a patient with an already suppressed TSH level cannot lower serum TSH concentrations further, but it may change serum T_3 and SHBG concentrations. Suppression of TSH levels may explain the different changes of SHBG concentrations seen between our study and the earlier study by Bunevicius and Prange,[25] in which SHBG concentrations did increase significantly in those taking combined levothyroxine and liothyronine.

No human studies, including our own, have administered truly physiological ratios of levothyroxine to liothyronine when treating hypothyroidism. Replicating normal tissue levels of thyroid hormone in animal models required continuous infusions of both levothyroxine and liothyronine.[6] A sustained-release form of oral liothyronine might come closer to achieving physiological serum and tissue levels of T_3. Currently, most physicians titrate the dose of levothyroxine to achieve a serum TSH level within the normal laboratory range. This range includes TSH levels of up to 4.6 mIU/L.[28] However, new guidelines for patients receiving therapy for primary hypothyroidism recommend a target TSH level between 0.3 and 3.0 mIU/L[29] or between 0.5 and 2.0 mIU/L.[30] It has not been investigated whether patients benefit clinically from these treatment recommendations, and the guidelines were published after our study was completed. Nonetheless, treating to achieve a serum TSH level in the lower end of the normal laboratory range may help some patients, and this approach is probably safer and less costly than treating with a combination of levothyroxine and liothyronine, which was demonstrated in this study to be of no benefit. The guidelines referred to above also recommend using only levothyroxine when treating hypothyroidism. This study supports these guidelines by providing sound evidence that levothyroxine alone continues to be the most appropriate therapy for patients with primary hypothyroidism.

Author Contributions: Dr Clyde had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Clyde, Harari, Getka, Shakir.
Acquisition of data: Clyde, Harari, Shakir.
Analysis and interpretation of data: Clyde, Harari, Getka, Shakir.
Drafting of the manuscript: Clyde, Shakir.
Critical revision of the manuscript for important intellectual content: Harari, Getka, Shakir.
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Experience nevers errs; what alone may err is our judgment, which predicts effects that cannot be produced by our experiments.
—Leonardo da Vinci (1452-1519)

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