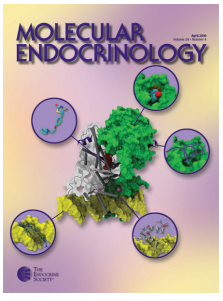
JCEM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

Thyroxine-Triiodothyronine Combination Therapy Versus Thyroxine Monotherapy for Clinical Hypothyroidism: Meta-Analysis of Randomized Controlled Trials

Simona Grozinsky-Glasberg, Abigail Fraser, Ethan Nahshoni, Abraham Weizman and Leonard Leibovici

J. Clin. Endocrinol. Metab. 2006 91:2592-2599 originally published online May 2, 2006; , doi: 10.1210/jc.2006-0448



0021-972X/06/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 91(7):2592–2599

doi: 10.1210/jc.2006-0448

Thyroxine-Triiodothyronine Combination Therapy *Versus* Thyroxine Monotherapy for Clinical Hypothyroidism: Meta-Analysis of Randomized Controlled Trials

Simona Grozinsky-Glasberg, Abigail Fraser, Ethan Nahshoni, Abraham Weizman, and Leonard Leibovici

Endocrine Institute (S.G.-G.) and Department of Medicine E (A.F., L.L.), Rabin Medical Center, and Geha Mental Health Center (E.N., A.W.), Petah-Tiqva 49100, Israel; and Sackler Faculty of Medicine (E.N., A.W., L.L.), Tel-Aviv University, Ramat-Aviv, Tel-Aviv 69978, Israel

Context: In some patients symptoms of hypothyroidism persist despite therapy with T_4.

Objective: The objective of the study was to compare the effectiveness of T_4-T_3 combination *vs.* T_4 monotherapy for the treatment of clinical hypothyroidism in adults.

Data Sources: PubMed, EMBASE, LILACS, and the Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched in September 2005. References of all included trials were scanned for additional studies. We put no restrictions on language, year of publication, or publication status.

Study Selection: All randomized trials that compared the effectiveness of T_4-T_3 combination *vs.* T_4 monotherapy for the treatment of clinical hypothyroidism in adults were included.

Data Extraction: The data were extracted by two independent reviewers.

Data Synthesis: We included 11 studies, in which 1216 patients were randomized. No difference was found in the effectiveness of combination *vs.* monotherapy in any of the following symptoms: bodily pain [standardized mean difference (SMD) 0.00, 95% confidence interval (CI) −0.34, 0.35], depression (SMD 0.07, 95% CI −0.20, 0.34), anxiety (SMD 0.00, 95% CI −0.12, 0.11), fatigue (SMD −0.12, 95% CI −0.33, 0.09), quality of life (SMD 0.03, 95% CI −0.09, 0.15), body weight, total serum cholesterol, triglyceride levels, low-density lipoprotein, and high-density lipoprotein. Adverse events did not differ between regimens.

Conclusions: T_4 monotherapy should remain the treatment of choice for clinical hypothyroidism. **(*J Clin Endocrinol Metab* 91: 2592–2599, 2006)**

HYPOTHYROIDISM IS A common disorder, affecting about 5% of people over the age of 60 yr (1, 2). In the United Kingdom, more than 1% of the population receives T_4 replacement therapy for hypothyroidism (3). T_4 is the replacement medication of choice because it has a half-life of 6 d, providing stable and physiological quantities of T_3 to the body. T_3 therapy is also available. It reaches peak levels 2–4 h after oral administration and has a circulating half-life of 1 d. Thus, steady-state levels cannot be maintained with once-daily dosing of T_3 (4).

Studies of hypothyroid rats (after thyroidectomy or after radioiodine therapy) failed to show normalization in tissue concentration of T_4 and T_3 with T_4 monotherapy. However, normalization was achieved with a combination of T_4 and T_3 (5). In humans, this issue remains controversial. In some patients symptoms of hypothyroidism persist despite T_4 therapy. A survey conducted in the United Kingdom found that 32% of patients treated with T_4 were above the threshold for significant psychiatric morbidity according to the abbreviated General Health Questionnaire (GHQ-12), compared with 26% of controls (3). It is not clear whether this is due to comorbidity or because standard T_4 replacement therapy is in some way inadequate for these patients (6, 7).

Successful treatment of hypothyroidism with the use of replacement therapy should result in improved signs and symptoms as well as normal thyroid hormone levels in peripheral tissues. We performed a systematic review and meta-analysis comparing the effectiveness of T_4-T_3 combination therapy *vs.* T_4 monotherapy for the treatment of clinical hypothyroidism in adults.

Materials and Methods

Search

We searched PubMed, EMBASE, LILACS, and The Cochrane Central Register of Controlled Trials in September 2005. The terms hypothyroidism and similar terms, thyroxine and similar terms, triiodothyronine and similar terms, or combination therapy and similar terms were crossed (8). References of all included trials were scanned for additional studies. We put no restrictions on language, year of publication, or publication status.

Selection

We included all randomized or quasirandomized trials (in which the allocation to study groups is not equivalent to the throw of a coin, *e.g.* birth date) that compared the effectiveness of T_4-T_3 combination therapy *vs.* T_4 monotherapy for the treatment of clinical hypothyroidism in adults. Two reviewers independently inspected each reference identified by the search and applied the inclusion criteria. For possibly rele-

First Published Online May 2, 2006

Abbreviations: CI, Confidence interval; FT4, free T_4; SMD, standardized mean difference; TT3, total T_3; WMD, weighted mean difference.

vant articles or in cases of disagreement between the two reviewers, we obtained and independently inspected the full article and applied inclusion criteria.

Data abstraction

Two reviewers independently extracted the data and assessed the methodological quality of included trials. In case of any disagreement between the two reviewers, a third reviewer was consulted. We discussed data extraction, documented decisions, and contacted the authors of trials for missing data or clarifications when necessary.

We assessed the quality of the following trial characteristics: allocation concealment, generation of the allocation sequence, and blinding. We graded allocation concealment and generation as adequate, unclear, or inadequate. Adequate allocation concealment was defined as the use of central randomization, numbered or coded bottles or containers, drugs prepared by the pharmacy, serially numbered sealed opaque envelopes, or other convincing measures. Adequate allocation generation was defined as the use of random-number table, random-number generator, computer generated, coin-tossing, or shuffling. We also recorded data on method of analysis (intention to treat or per protocol), number of dropouts, trial design (parallel or crossover design and washout period), length of follow-up until outcome assessment, and the questionnaires used to assess outcomes.

Our predefined primary outcomes were symptoms (bodily pain, fatigue, anxiety, depression, and insomnia) and quality of life. Secondary outcomes included cognitive performance, thyroid function test levels, serum lipids levels, adverse effects, and weight changes. To decide which questionnaires were most appropriate for assessment of the predefined outcomes, we consulted two senior psychiatrists who were blinded to trial results.

Quantitative data synthesis

When an outcome was assessed using different scales and the direction of the scales was different, *i.e.* higher scores indicated improved outcomes in some scales and worse outcomes in others, we standardized the direction by using the inversion of measurements of one of the two types of scales. We pooled data recorded at the end of follow-up in each trial unless otherwise specified. Weighted mean differences (WMD) and 95% confidence intervals (CIs) were calculated for continuous data measured. All biochemical determinations (including TSH) were expressed in the same units for all trials, and thus, the WMD was used for data synthesis.

If continuous outcomes were conceptually the same but measured using different questionnaires, the standardized mean difference (SMD) was used. Relative risks and 95% CIs were calculated for dichotomous data and pooled using the Mantel-Haenszel method. A fixed-effect model was used unless significant heterogeneity was observed, and then a random effects model was used. Heterogeneity in the results of the trials was assessed using a χ^2 test and the I-square measure of inconsistency. We predefined significant heterogeneity as a χ^2 test $P < 0.1$ or an I-square measure greater than 50% (9). For our primary analysis, we divided trials into trials with a crossover and noncrossover design to assess whether the results of these two groups of trials differed. Metaregression was performed to assess the effect of T_3 dosage, percentage of athyreotic patients, and length of follow-up on trial results.

Results

Eleven randomized trials, performed between the years 1999 and 2005 (Fig. 1), in which 1216 patients were randomized, were included in the review. Six were crossover trials. Trial characteristics and methodology are presented in Tables 1 and 2, respectively. Details of the questionnaires used to assess outcomes in included trials can be found in the supplemental data published on The Endocrine Society's web site at http://jcem.endojournals.org (22–37). Appelhof *et al.* (11) included two arms treated with combination therapy, one with a 10:1 ratio between T_4 and T_3 and the second with a 5:1 ratio, in addition to the arm receiving monotherapy. We included the 10:1 ratio study arm in the meta-analyses because this dose was similar to the doses used in the other studies and to avoid including the monotherapy group twice. Replacing the data from the arm treated with a 10:1 ratio of T_4 and T_3 with results from the 5:1 ratio arm had no substantial effect on the results for any of the outcomes. Saravanan *et al.* (19) assessed the outcomes at 3 and 12 months, respectively. We included in our review the 3-month results because this was the closest period to that used in the other studies.

Symptom improvement and quality of life

No difference was found in the effectiveness of combination therapy or monotherapy in any of the following symptoms: bodily pain (SMD 0.00, 95% CI −0.34, 0.35; four studies,

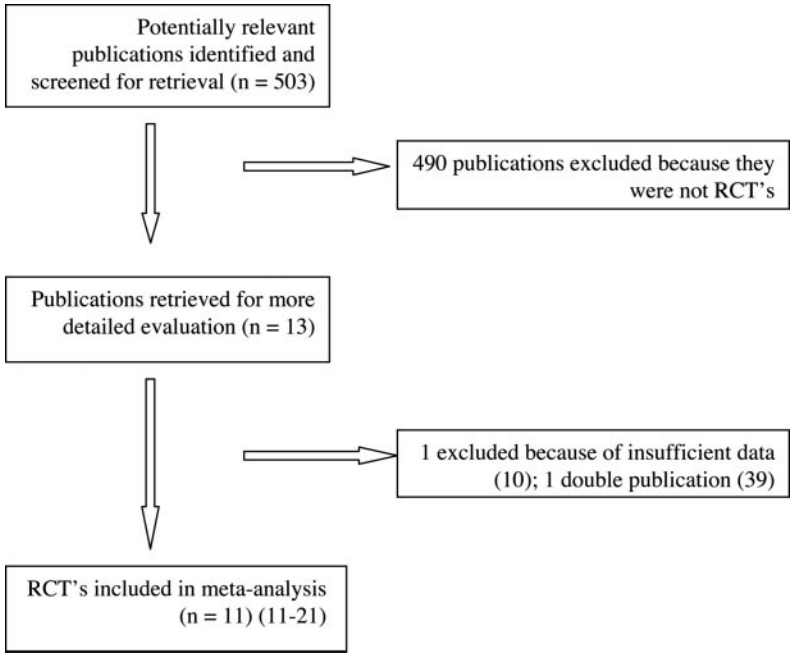


FIG. 1. Publications identified for study and exclusions. RTC, Randomized controlled study.

TABLE 1. Characteristics of included trials

Study	Dose of T_4, μg/d	Dose of T_4+T_3, μg/d	No. of patients	Females, %	Etiology of hypothyroidism	Prestudy period with stable T_4	Assigned treatment period	Outcomes
Appelhof 2005 (11)	Usual dose	T_4: usual dose minus 25 μg/d; T_3: dose required to achieve either a 10:1 T_4 to T_3 ratio or a 5:1 T_4 to T_3 ratio (two separate study arms)	141	85.10	Thyroiditis, 100%	≥6 months	15 wk	Patient satisfaction, symptoms, mood, cognition, QOL
Bunevicius 1999 (12)	Usual dose	T_4: usual dose minus 50 μg/d; T_3: 12.5 μg/d	35	88.5	Thyroiditis, 45.7%; cancer, 48.5%	≥3 months	5 wk	Cognition, depression
Bunevicius 2002 (13)	Usual dose	T_4: usual dose minus 50 μg/d; T_3: 10 μg/d	13	100	Thyroiditis and subsequent surgery, 100%	Not mentioned	5 wk	Cognition, mood
Clyde 2003 (14)	Usual dose	T_4: usual dose minus 50 μg/d; T_3: 15 μg/d	46	78.2	Thyroiditis, 67.4%; surgery, −2.1%; cancer, 2.1%; radioiodine therapy, −21.7%	3 months	4 months	Symptoms of hypothyroidism, QOL, cognition
Escobar-Morreale 2005 (15)	100 μg/d	T_4: 75 μg/d; T_3: 5 μg/d	28	100	Thyroiditis, −82.1%; radioiodine therapy, 17.8%	≥12 months	8 wk	Cognition, mood, QOL, TFT
Levitt 2005 (20)	Usual dose	T_4: usual dose minus 50 μg/d; T_3: dose required to achieve a 15:1 T_4 to T_3 ratio (a biopotency of T_4 to T_3 ratio of 4:1 or 2.5:1, two study arms)	50	45	Thyroiditis, 100%	6 months	9 months	Symptoms of hypothyroidism, QOL, cognition, mood
Rodriguez 2005 (21)	Usual dose	T_4: usual dose minus 50 μg/d; T_3: 10 μg/d	30	83	Thyroiditis, 77%; surgery, −10%; radioiodine therapy, −13%	≥3 months	16 wk	Symptoms, cognition (memory)
Saravanan 2005 (19)	Usual dose	T_4: usual dose minus 50 μg/d; T_3: 10 μg/d	697	83.8	Primary hypothyroidism, 71.56%	≥3 months	3 months	Symptoms, QOL, cognition, mood
Sawka 2003 (16)	Usual dose	T_4: usual dose minus 50 μg/d; T_3: 25 μg/d	40	90	Thyroiditis, 100%	6 months	15 wk	Symptoms of hypothyroidism
Siegmund 2004 (17)	Usual dose	T_4: usual dose minus 5%; T_3: dose required to achieve a 14:1 T_4 to T_3 ratio	26	81	Thyroiditis, 92%; surgery, 8%	Unspecified long term	12 wk	Cognition, mood, QOL
Walsh 2003 (18)	≥100 μg/d	T_4: ≥50 μg/d; T_3: 10 μg/d	110	92	Thyroiditis, 85%; surgery, 11%; radioiodine therapy, 4%	2 months	10 wk	Symptoms of hypothyroidism, QOL, cognition

QOL, Quality of life; TFT, thyroid function tests.

TABLE 2. Methodological aspects of included studies

Study	Crossover	Allocation generation	Allocation concealment	ITT analysis	Blinding	Questionnaires used to measure included outcomes
Appelhof 2005 (11)	Yes	A, computer-generated sequence of randomization	A, concealed randomization sequence	No	Double blind	SCL-90; POMS; Digit Symbol Test; Digit Span Test (forward and backward)
Bunevicius 1999 (12)	Yes	B, not specified	A, prearranged randomization schedule handled by pharmacy	No	Triple blind	BDI; POMS; STAI; Digit Symbol Test; Digit Span Test (forward and backward)
Bunevicius 2002 (13)	Yes	B, not specified	A, prearranged randomization schedule handled by pharmacy	No	Double blind	BDI; Digit Symbol Test; Digit Span Test (forward and backward)
Clyde 2003 (14)	No	A, computer-generated random numbers table	A, concealed randomization list maintained by pharmacy	No	Triple blind	BDI; Digit Span Test (forward and backward); HRQL
Escobar-Morreale 2005 (15)	Yes	A, computer-generated sequence of randomization	A, central allocation by independent investigator	No	Double blind	VAS; POMS; Digit Symbol Test; Digit Span Test (forward and backward); SF 36 (general health)
Levitt 2005 (20)	No	A, randomization tables	B, capsules prepared by pharmacy	No	Double blind	IDS; Digit Symbol Test; SHSS
Rodriguez 2005 (21)	Yes	A, randomly assignment	A, allocation performed by pharmacy staff using a computer program	Yes	Double blind	Digit Span Test (forward and backward); BDI; PFS
Saravanan 2005 (19)	No	A, sequential allocation of study numbers	B, unclear	Yes	Double blind	HADS; TSQ
Sawka 2003 (16)	No	B, not specified	A, central allocation by pharmacy	No	Triple blind	SCL 90; MOS
Siegmund 2004 (17)	Yes	B, not specified	B, unclear	No	Double blind	BDI; EWL 60; STAI; Digit Symbol Test; Digit Span Test (forward and backward); FAW (contentment)
Walsh 2003 (18)	Yes	A, shuffling	A, sealed opaque envelopes	No	Double blind	VAS; Digit Symbol Test; Digit Span Test (forward and backward); SF 36 (general health)

A, Adequate; B, unclear; VAS, Visual Analogs Scales; POMS, Profile of Mood States Scale; SF 36, Short Form Questionnaire; IDS, Inventory of Depressive Symptomatology Scale; SHSS, Severity of Hypothyroid Symptoms Scale; HADS, Hospital Anxiety and Depression Scale; TSQ, Thyroid Symptoms Questionnaire; SCL-90, Symptom Check-List-90; MOS, Medical Outcomes Study; BDI, Beck Depression Inventory; EWL 60, German Version of POMS; STAI, Spielberger State-Trait-Anxiety Inventory; FAW, a physical well-being scale; PFS, Piper Fatigue Scale; ITT, intention to treat; HRQL, health-related quality of life.

Fig. 2); quality of life (SMD 0.03, 95% CI −0.09, 0.15; Fig. 3); depression (SMD 0.07; 95% CI −0.20, 0.34; all studies, Fig. 4); fatigue (SMD −0.12, 95% CI −0.33, 0.09; six studies, Fig. 5); and anxiety (SMD 0.00, 95% CI −0.12, 0.11; seven studies, Fig. A1 in supplemental data). Due to scarcity of data, we could not assess the effect of combination therapy on sleeping patterns.

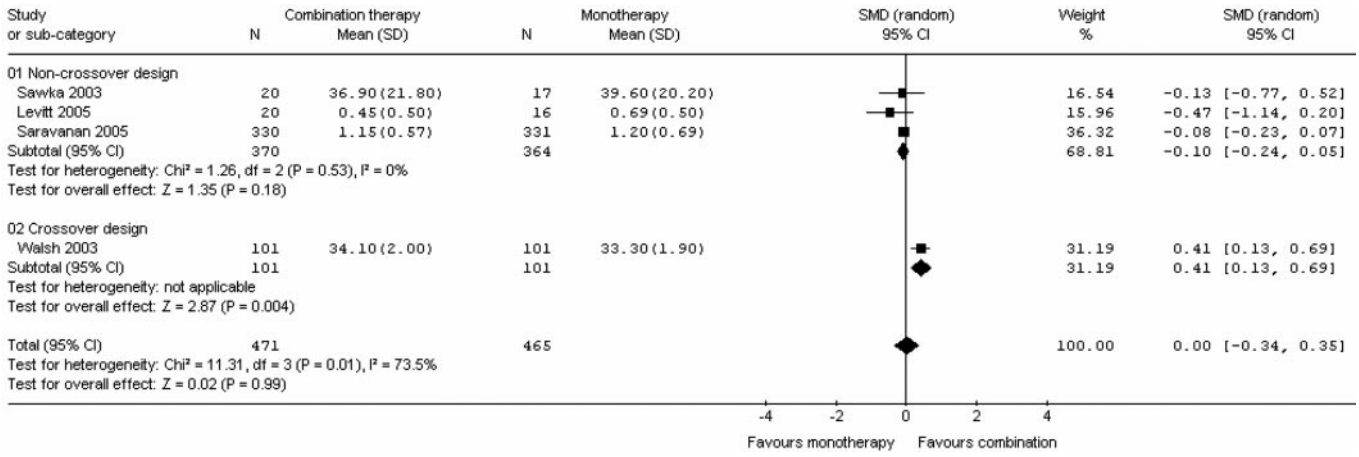


FIG. 2. The effect of monotherapy and combination therapy on bodily pain.

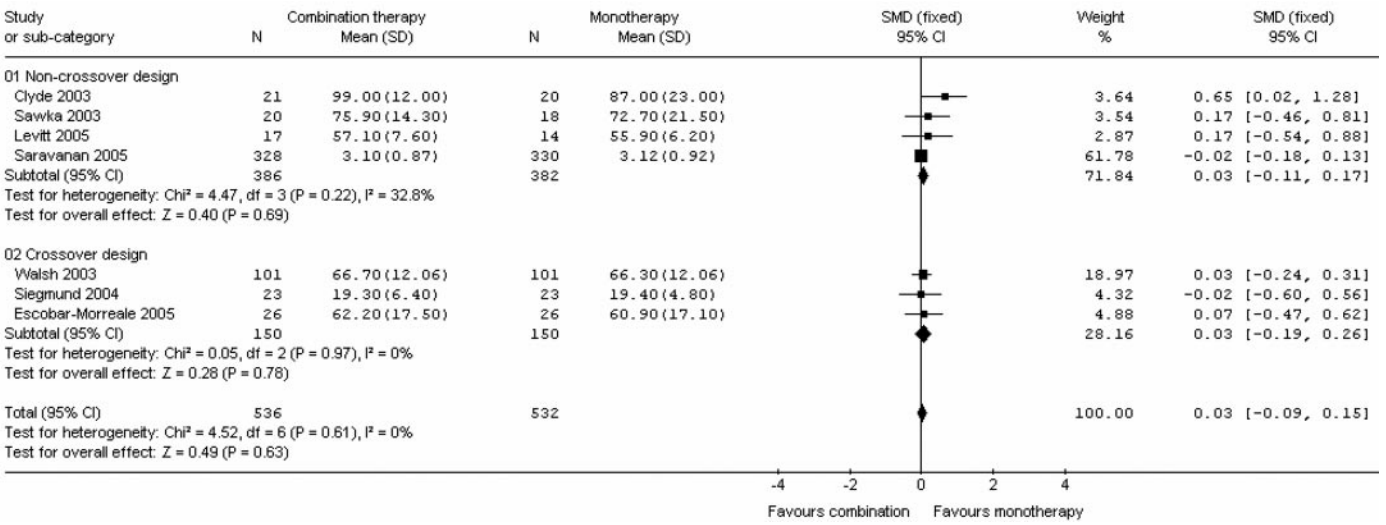


FIG. 3. The effect of the combination therapy *vs.* monotherapy on quality of life.

Cognitive function

Cognitive function was tested in the included trials using two standard, well-validated tests: the Symbol Digit Modalities (31), which assesses cognitive efficiency and ability to undertake a novel task, and the Digit Span Sub-Test (both forward and backward) of the Wechsler Adult Intelligence Scale III (32), which assesses immediate auditory memory, attention, and concentration. Seven studies (11–13, 15, 17, 18, 20) reported results of the Symbol Digit Modalities Test. No significant difference was detected (WMD 0.15, 95% CI −0.79, 1.08), (Fig. A2 in supplemental data).

Eight studies reported results of the Digit Span Sub-Test (both forward and backward) of the Wechsler Adult Intelligence Scale III (11–15, 17, 18, 21). No significant difference was found between the two treatment groups: forward subtest, WMD −0.02 (95% CI −0.25, 0.22; Fig. A3 in supplemental data); backward subtest, WMD −0.07 (95% CI −0.30, 0.15; Fig. A4 in supplemental data).

Weight changes

Weight changes were measured in seven studies (11, 13, 14, 18–21). In three of four studies, weight remained stable or decreased during the study period (11, 14, 18). Bunevicius *et al.* (13) did not specify weight at baseline. In the study by Clyde *et al.* (14), baseline mean weight in the two treatment groups was significantly different, and we therefore used the change in weight in each group in the analysis. The weight in the combination group was lower at the end of the study, and this difference reached statistical significance, but the magnitude of the difference is negligible: WMD −0.10 kg; 95% CI −0.13, −0.07 kg; Fig. A5 in supplemental data).

Biochemistry results

The results of the thyroid function tests [TSH, free T_4 (FT4), and total T_3 (TT3), supplemental Figs. A6, A7, and A8] and the serum lipid levels (total cholesterol, low-density lipopro-

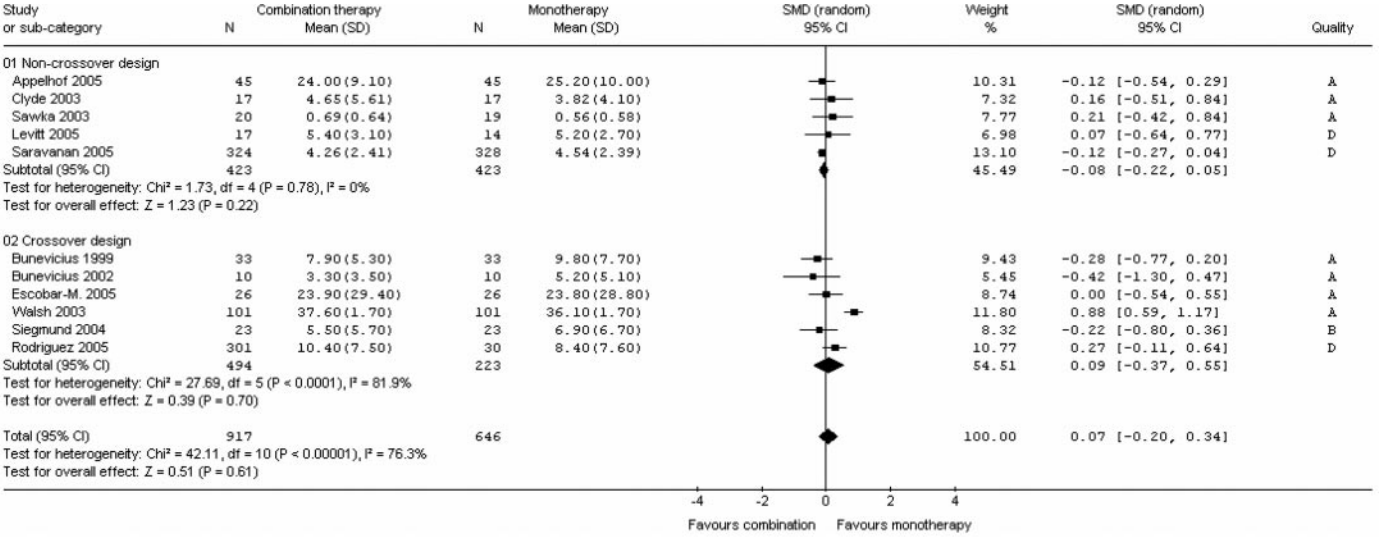


FIG. 4. The effect of monotherapy and combination therapy on depression.

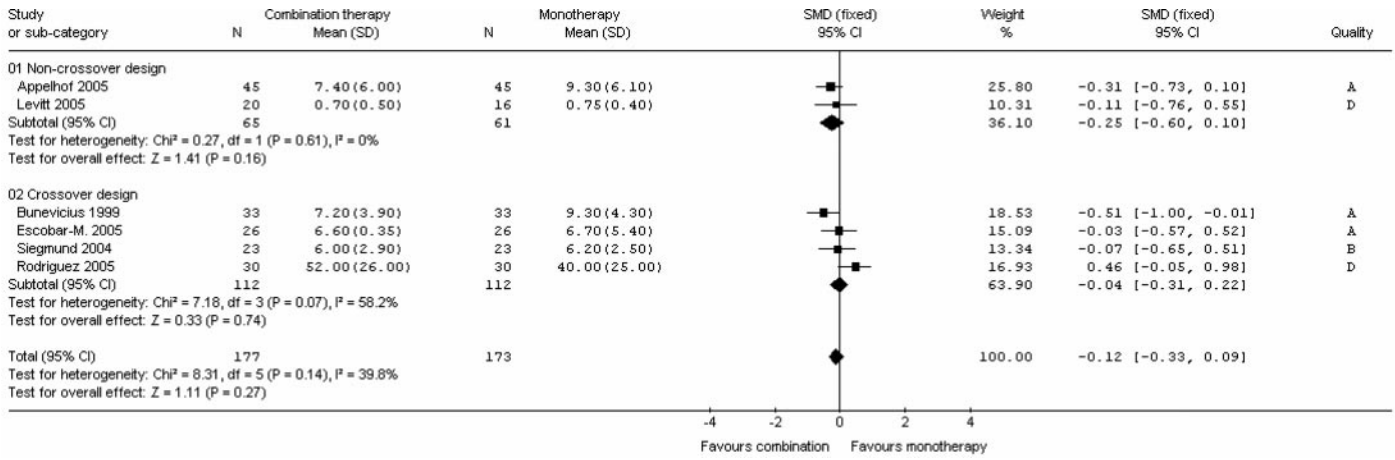


FIG. 5. The effect of monotherapy and combination therapy on fatigue.

tein, high-density lipoprotein, and triglycerides, supplemental Figs. A9, A10, A11, and A12) are documented in Table 3, and but for levels of T_4 (as expected), no differences were apparent between study groups.

Adverse effects

All studies reported adverse effects, which were similar between study groups (relative risk 1.19, 95% CI 0.63, 2.24) (Fig. 6).

Sensitivity analysis

Because eight of the 11 studies were graded A (adequate) for allocation concealment, sensitivity analysis was not performed. Meta-regression demonstrated no association among length of follow-up, percentage of athyreotic patients or dose of T_3, and trial results for the primary outcomes.

Discussion

T_4-T_3 combination therapy used as replacement therapy for patients treated for hypothyroidism provided no advantage when compared with standard T_4 monotherapy in the randomized, controlled trials included in the present review. There was no benefit in terms of symptoms (fatigue, bodily pain, anxiety, depression) and no improvement in quality of life. Moreover, the analysis of the impact of combination therapy on cognition shows no improvement in cognitive efficiency and the ability to undertake a novel task, immediate auditory memory, attention, and concentration. Lipid profile was not improved in patients prescribed combination therapy, and there was no significant difference in terms of weight change.

TABLE 3. Comparisons of biochemistry results at end of study

Outcome	No. of studies	No. of patients	Weighted mean difference (95% CI)
TSH, μ U/ml	11	1283	0.16 (−0.37, 0.68)
FT4, pmol/liter	10	1249	−3.78 (−4.95, −2.62)
TT3, nmol/liter	6	447	0.24 (−0.06, 0.55)
Total cholesterol, mg/dl	8	1222	0.64 (−2.66, 3.94)
LDL, mg/dl	4	173	−0.08 (−11.16, 11.00)
Triglycerides, mg/dl	5	272	−9.37 (−25.45, 6.72)
HDL, mg/dl	3	121	2.78 (−8.12, 13.69)

LDL, Low-density lipoprotein; HDL, high-density lipoprotein.

Trials also varied in the T_4 to T_3 ratio, the absolute doses prescribed, and duration of treatment. However, the differences in primary outcomes did not depend on T_3 dose and duration of treatment.

Whether combination therapy offers an advantage is of particular interest for patients who are dissatisfied with monotherapy or continue to be symptomatic despite monotherapy and normalized serum free T_4 and TSH levels. Four trials addressed this group of patients. Walsh *et al.* (18) found no benefit associated with combination therapy in a subgroup of patients dissatisfied with the results of monotherapy. Appelhof *et al.* (11) found that results for patients in the highest tertile of SCL-90 (psychiatric Symptoms Checklist) total scores did not differ from the overall results. Bunevicius *et al.* (12) reported no difference in results for depressed patients, compared with patients without depression, and Rodriguez *et al.* (21) reported no difference in patients with high and low fatigue levels.

Only one trial (12) found significant benefit of combination therapy over the monotherapy. It was later suggested that this benefit was associated with the cause of hypothyroidism and that only athyreotic thyroid cancer patients benefited from combination therapy, whereas patients with autoimmune thyroiditis did not (13, 38). However in the present review, we were unable to show a relation between the percentages of athyreotic patients included in the study and the effect of combination therapy on symptoms.

Limitations

It should be noted that we used mean (± SD) TSH values in the meta-analysis, although TSH values are not normally distributed. In addition, five of the included studies were crossover studies. Therefore, observations are not independent because the same patients receive both therapies (combination and monotherapy).

Implications for practice and research

Given the conclusive evidence, monotherapy with T_4 should remain the standard treatment for hypothyroidism. It is doubtful whether further trials evaluating combination therapy are needed because the chances that the accumulated evidence will change are low.

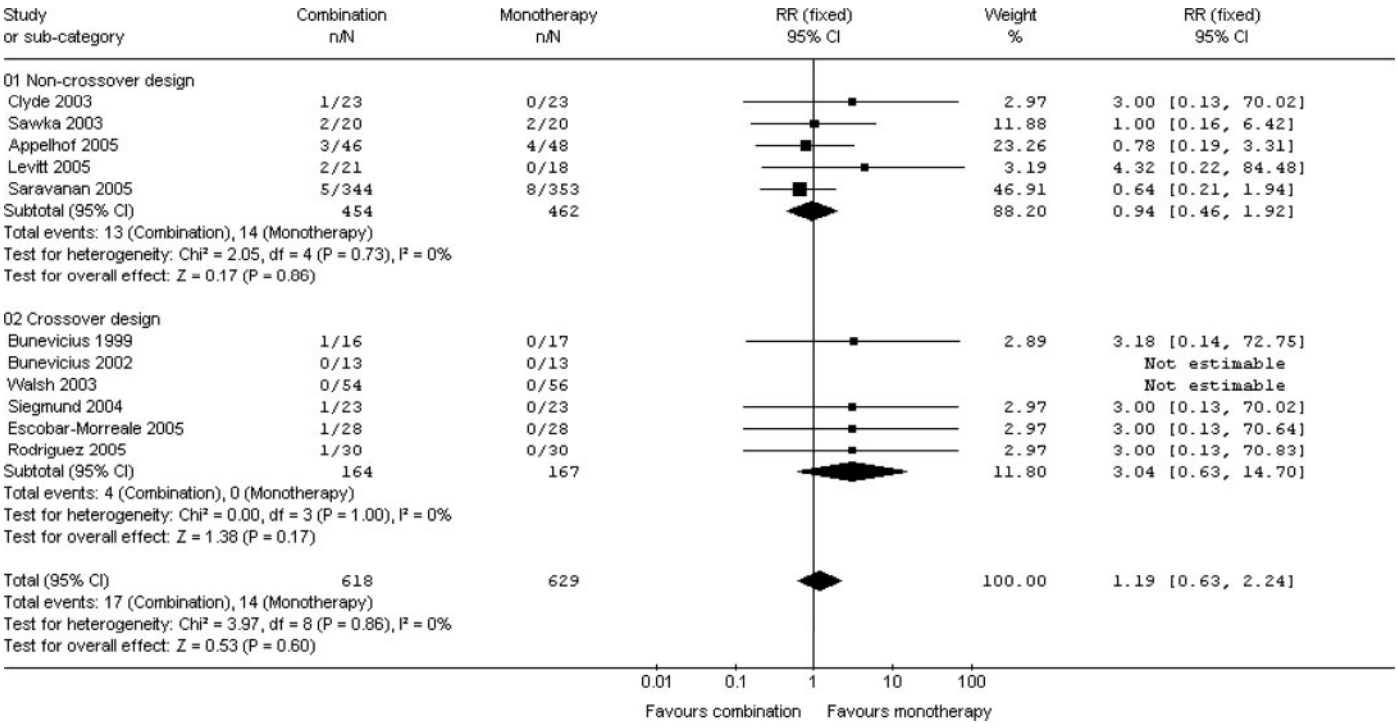


FIG. 6. Adverse events in the two study arms.

Acknowledgments

We are grateful to Drs. P. W. Clyde, B. C. Appelhof, J. P. Walsh, J. A. Levitt, and P. Saravanan for kindly supplying additional data. We thank the Cochrane Endocrine Disorders Group for their guidance and support.

Received February 27, 2006. Accepted April 24, 2006.

Address all correspondence and requests for reprints to: Leonard Leibovici, M.D., Department of Medicine E, Beilinson Campus, Petah-Tiqva 49100, Israel. E-mail: leibovic@post.tau.ac.il.

The authors have no conflict of interest to declare.

References

1. **Vanderpump MP, Tunbridge WM, French JM, Appleton D, Bates D, Clark F, Evans JG, Hasan DM, Rodgers H, Tunbridge F, Young ET** 1995 The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. Clin Endocrinol (Oxf) 43:55–68
2. **Shapiro LE, Surks MI** 2001 Hypothyroidism. In: Becker KL, Bilezikian JP, Bremner WJ, Hung W, Kahn CR, Loriaux DL, Nylen ES, Rebar RW, Robertson GL, Snider RH, Wartofsky L, eds. Principles and practice of endocrinology and metabolism. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 445–454
3. **Saravanan P, Chau WF, Roberts N, Vedhara K, Greenwood R, Dayan CM** 2002 Psychological well-being in patients on 'adequate' doses of l-thyroxine: results of a large, controlled community-based questionnaire study. Clin Endocrinol (Oxf) 57:577–585
4. **Larsen PR, Davies TF, Schlumberger MJ, Hay ID** 2003 Thyroid physiology and diagnostic evaluation of patients with thyroid disorders. In: Larsen II, Kronenberg HM, Melmed S, Polonsky KS, eds. Williams textbook of endocrinology. 10th ed. Philadelphia: W. B. Saunders; 331–373
5. **Escobar-Morreale HF, del Ray FE, Obregon MJ, de Escobar GM** 1996 Only combined treatment with thyroxine and triiodothyronine ensures euthyroidism in all tissues of the thyroidectomized rat. Endocrinology 137:2490–2502
6. **Ladenson PW** 2002 Psychological well-being in patients. Clin Endocrinol (Oxf) 57:575–576
7. **Walsh JP, Stuckey BG** 2001 What is the optimal treatment for hypothyroidism? Med J Aust 174:141–143
8. **Grozinsky S, Fraser A, Vidal L, Leibovici L** 2005 Thyroxine monotherapy versus thyroxine-triiodothyronine combination therapy for hypothyroidism. (Protocol) The Cochrane Database of Systematic Reviews, Issue 3. Article no. 10.1002/14651858.CD005448
9. **Higgins JPT, Thompson SG, Deeks JJ, Altman DG** 2003 Measuring inconsistency in meta-analyses. BMJ 327:557–560
10. **Smith RN, Taylor SA, Massey JC** 1970 Controlled clinical trial of combined triiodothyronine and thyroxine in the treatment of hypothyroidism. BMJ 4:145–148
11. **Appelhof BC, Fliers E, Wekking EM, Schene AH, Huyser J, Tijssen JG, Endert E, van Weert HCPM, Wiersinga WM** 2005 Combined therapy with levothyroxine and liothyronine in two ratios, compared with levothyroxine monotherapy in primary hypothyroidism: a double-blind, randomized, controlled clinical trial. J Clin Endocrinol Metab 90:2666–2674
12. **Bunevicius R, Kazanavicius G, Zalinkevicius R, Prange Jr AJ** 1999 Effects of thyroxine as compared with thyroxine plus triiodothyronine in patients with hypothyroidism. N Engl J Med 340:424–429
13. **Bunevicius R, Jakubonien N, Jurkevicius R, Cernicat J, Lasas L, Prange Jr AJ** 2002 Thyroxine vs thyroxine plus triiodothyronine in treatment of hypothyroidism after thyroidectomy for Graves' disease. Endocrine 18:129–133
14. **Clyde PW, Harari AE, Getka EJ, Shakir KM** 2003 Combined levothyroxine plus liothyronine compared with levothyroxine alone in primary hypothyroidism: a randomized controlled trial. JAMA 290:2952–2958
15. **Escobar-Morreale HF, Botella-Carretero JI, Gomez-Bueno M, Galan JM, Barrios V, Sancho J** 2005 Thyroid hormone replacement therapy in primary hypothyroidism: a randomized trial comparing L-thyroxine plus liothyronine with l-thyroxine alone. Ann Intern Med 142:412–424
16. **Sawka AM, Gerstein HC, Marriott MJ, MacQueen GM, Joffe RT** 2003 Does a combination regimen of thyroxine (T_4) and 3, 5, 3′-triiodothyronine improve depressive symptoms better than T_4 alone in patients with hypothyroidism? Results of a double-blind, randomized, controlled trial. J Clin Endocrinol Metab 88:4551–4555
17. **Siegmund W, Spieker K, Weike AI, Giessmann T, Modess C, Dabers T, Kirsch G, Sänger E, Engel G, Hamm AO, Nauck M, Meng W** 2004 Replacement therapy with levothyroxine plus triiodothyronine (bioavailable molar ratio 14:1) is not superior to thyroxine alone to improve well-being and cognitive performance in hypothyroidism. Clin Endocrinol (Oxf) 60:750–757
18. **Walsh JP, Shiels L, Lim EM, Bhagat CI, Ward LC, Stuckey BG, Dhaliwal SS, Chew GT, Bhagat MC, Cussons AJ** 2003 Combined thyroxine/liothyronine treatment does not improve well-being, quality of life, or cognitive function compared to thyroxine alone: a randomized controlled trial in patients with primary hypothyroidism. J Clin Endocrinol Metab 88:4543–4550
19. **Saravanan P, Simmons DJ, Greenwood R, Peters TJ, Dayan CM** 2005 Partial substitution of thyroxine (T_4) with tri-iodothyronine in patients on T_4 replacement therapy: results of a large community-based randomized controlled trial. J Clin Endocrinol Metab 90:805–812
20. **Levitt JA, Silverberg J,** T_4 plus T_3 for hypothyroidism: a double-blind comparison with usual T_4. Proc of the 74th Annual Meeting of the American Thyroid Association, Los Angeles, CA, 2002
21. **Rodriguez T, Lavis VR, Meininger JC, Kapadia AS, Stafford LF** 2005 Substitution of liothyronine at a 1:5 ratio for a portion of levothyroxine: effect on

fatigue, symptoms of depression, and working memory versus treatment with levothyroxine alone. Endocr Pract 11:223–233
22. **Wewers ME, Lowe NK** 1990 A critical review of visual analogue scales in the measurement of clinical phenomena. Res Nurs Health 13:227–236
23. **Derogatis LR, Lipman RS, Covi L** 1973 SCL-90: an outpatient psychiatric rating scale—preliminary report. Psychopharmacol Bull 9:13–28
24. **Laux L, Glanzmann P, Schaffner P, Spielberger CD** 1981 State-Trait-Angstinventar (STAI). Teoretische Grundlagen und Handanweisung: Beltz Testgesellschaft
25. **McNair DM, Lorr M, Droppleman LF** 1992 Manual: profile of mood states. San Diego, CA: Educational and Industrial Testing Service
26. **Janke W, Debus G** 1978 Die eigenschaftsworterliste (EWL-K)—ein verfahren zur erfassung der befindlichkeit. 1st ed. Gottingen, Germany: Hogrefe
27. **McHorney CA, Ware Jr JE, Rogers W, Raczek AE, Lu JF** 1992 The validity and relative precision of the MOS short-and long-form health status scales and Darmouth COOP charts. Med Care 30:MS253–MS265
28. **Ware Jr JE, Sherbourne CD** 1992 The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 30:473–483
29. **Jaeschke R, Guyatt G, Gerstein H, Patterson C, Molloy W, Cook D, Harper S, Griffith L, Carbotte R** 1996 Does treatment with L-thyroxine influence health status in middle-aged and older adults with subclinical hypothyroidism? J Gen Intern Med 11:744–749
30. **Frank R** 1991 Korperliches wohlbefinden. [Physical well-being.] In: Abele A, Becker P, eds. Weinheim-Munchen, Germany: Wohlbefinden Juventa; 71–95
31. **Edincott J, Nee J, Harrison W, Blumenthal R** 1993 Quality of Life Enjoyment and Satisfaction Questionnaire: a new measure. Psychopharmacol Bull 29: 321–326
32. **Centofani CC, Smith A** 1979 The Single and Double Simultaneous (Face-Hand) Stimulation Test (SDSS). Los Angeles: Western Psychological Services
33. **Wechsler D** 1997 Wechsler Adult Intelligence Scale III: technical manual. San Antonio, TX: The Psychological Corp.
34. **Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J** 1961 An inventory for measuring depression. Arch Gen Psychiatry 4:561–571
35. **Rush AJ, Trivedi MH, Ibrahim HM, Carmody TJ, Arnow B, Klein DN, Markowitz JC, Ninan PT, Kornstein S, Manber R, Thase ME, Kocsis JH, Keller MB** 2003 The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. Biol Psychiatry 54:573–583
36. **Bjelland I, Dahl AA, Haug TT, Neckelmann D** 2002 The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res 52:69–77
37. **Piper BF, Dibble SL, Dodd MJ, Weiss MC, Slaughter RE, Paul SM** 1998 The revised Piper Fatigue Scale: psychometric evaluation in women with breast cancer. Oncol Nurs Forum 25:677–684
38. **Escobar-Morreale HF, Botella-Carretero JI, Escobar del Rey F, Morreale de Escobar G** 2005 Review: treatment of hypothyroidism with combinations of levothyroxine plus liothyronine. J Clin Endocrinol Metab 90:4946–4954
39. **Joffe RT, Sawka AM, Marriott MJ, MacQueen GM, Gernstein HC** 2004 Does substitution of T_4 with T_3 plus T_4 for T_4 replacement improve depressive symptoms in patients with hypothyroidism? Ann NY Acad Sci 1032:287–288

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.