Combination therapy for hypothyroidism with levothyroxine plus liothyronine

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Patient Case

- A 47 -year-old woman
- A 3-year history of primary hypothyroidism
- Receiving a stable dose of LT4 for 3 years
- Her TSH is 3.0 mIU/L, her FT4 is 1.1 ng/dL
- Continued fatigue, depressed mood, and some cognitive difficulties as “brain fog”
- Her exam is unremarkable,
- BMI of 28 kg/m2
- What is the next step?

Representing the approximately 10-15% who do not feel well on LT4 monotherapy

Word cloud based on online survey of patients satisfaction on LT4 monotherapy conducted by the ATA

Areas of dissatisfaction: weight (69%), fatigue/energy levels(77%), mood(48%), and memory (58%); (showed a median score of 5 on a scale of 1 to 10)

Peterson SJ,et al An Online Survey of Hypothyroid Patients Demonstrates Prominent Dissatisfaction. Thyroid. 2018

Jonklaas J. Role of Levothyroxine/Liothyronine Combinations in Treating Hypothyroidism. Endocrinol Metab Clin North Am. 2022

Reasons for dissatisfaction

- Out of range or inappropriate TSH values
  - 40% of individuals receiving LT4 may be either undertreated or over-treated.
  - Patient-specific TSH set points
- Autoimmunity, rather than thyroid status, negatively affects QOL
  - Symptoms from another autoimmune
  - Disease, direct effect of thyroid peroxidase antibodies
- Normal thyroid physiology not achieved (T3 levels too low, free T4 levels too high, low t3/t4 ratio)
- Tissue hypothyroidism (low T3 at tissue or cellular level)
- Genetic predisposition to impaired conversion of T4 to T3/or impaired thyroid hormone entry into cells
- Accompanying comorbidities, Burden related to awareness of chronic disease, unrealistic expectations

Alternative therapies

- After excluding nonthyroid-related causes of these symptoms
- Combination therapy LT4 & LT3 is considered
- Endogenous thyroid functioning in humans: ratio of T4:T3 ~14:1 to 15:1
- If one of the goals of combination therapy is to strive for a similar ratio, this would be best achieved using small doses of synthetic LT3 with subsequent adjustments as necessary.
- Even though patients may express preference for DTE, its high T3 content makes it difficult to provide physiologic ratios.
- Monotherapy with LT3 has not been well studied.

Does combination therapy with LT4/LT3 provide better therapy for hypothyroidism?

The consequence of monotherapy versus combination therapy in rodent models

Escobar-Morreale et al first showed in hypothyroid rats (2 studies;1996)

- LT4 therapy did not achieve normal serum T3 levels, nor normal T3 levels in all tissues .
- Restoration of normal tissue levels of THs with LT4/LT3 combination therapy.

Later studies on LT4-treated rats after continuous-release pellets of LT4 and LT3 for 7 weeks (2015)

- Normalized serum T4 and T3 concentrations
- Redressed T3 deficit in peripheral tissues whereas intermittent daily doses of LT4&LT3 did not
- Markers of euthyroidism was more similar to that of control rats:
  - Serum cholesterol, mitochondrial content, liver enzymatic activity &skeletal muscle
  - The pattern of T3-responsive genes in the brain

- In rodent models, T4-induced inactivation of D2 through ubiquitination in thyrotrophic cell lines is less effective; convert T4 to T3 more efficiently than other tissues
- TSH secretion is normalized before T3 levels are fully restored in plasma and other tissues, resulting in low circulating T3 and tissue hypothyroidism

1. Escobar-Morreale HF,et al. Replacement therapy for hypothyroidism with thyroxine alone does not ensure euthyroidism in all tissues, as studied in thyroidectomized rats. The Journal of clinical investigation. 1995;
2. Escobar-Morreale HF, et al. Only the combined treatment with thyroxine and triiodothyronine ensures euthyroidism in all tissues of the thyroidectomized rat. Endocrinology. 1996
3. Werneck de Castro JP, et al. Differences in hypothalamic type 2 deiodinase ubiquitination explain localized sensitivity to thyroxine. The Journal of clinical investigation. 2015

Polymorphism of type 2 deiodinase gene (Thr92Ala-DIO2); the effects of LT4 monotherapy versus combination therapy (2019)

- Mice homozygous for the Thr92Ala-DIO2 polymorphism engage in less physical activity, sleep more, and have short-term memory problems compared with wild type mice. (hypothyroid-like pattern of T3-responsive genes in certain areas of the CNS)

- Physical activity, sleep patterns, and short-term memory in hypothyroid Thr92Ala-DIO2 homozygous mice improve more with LT4/LT3 than with LT4 therapy alone.

- The impact of the Thr92Ala-DIO2 polymorphism on the clinical treatment benefit of combination therapy in human is unknown.

Jo, Sungro, et al. "Type 2 deiodinase polymorphism causes ER stress and hypothyroidism in the brain." *The Journal of clinical investigation* 129.1 (2019):

Randomized controlled clinical trials on the effects of LT4 monotherapy versus LT4/LT3 combination therapy in human

15 trials of combination therapy with LT4/LT3

Author, year	Design	N randomized (completed)	Etiology primary hypothyroidism	Combination Therapy			
				T4:T3 ratio	Dose	Frequency (day)	Duration
Appelhof, 2005	Parallel, blinded	141 (130)	Autoimmune	10:1 or 5:1	T4: usual dose	Twice	15 weeks
Buneviciu s, 1999	Cross-over, blinded	35 (33)	Mixed Autoimmune, thyroid cancer	10:1	usual T4 dose minus 50 µg/d with T3 12.5 µg/d	Once	5 weeks
Buneviciu s, 2002	Cross-over, blinded	13 (10)	All Graves disease, Hx of subtotal thyroidectomy	6.5:1	usual T4 dose minus 50 µg/day with T3 10 µg/d	Once	5 weeks
Clyde, 2003	Parallel, blinded	46 (44)	Mixed Autoimmune, post-RAI, thyroid surgery, post-EBRT, 1 thyroid cancer	6.5:1	usual T4 dose minus 50 µg/day with T3 7.5 µg/d	Twice	4 months
Escobar-Morreale, 2005	Cross-over, blinded	28 (26)	Mixed Autoimmune, post-RAI	15:1 /12:1	T4: 100 µg/d 75 µg/d LT4 plus 5 µg/d T3	Once	8 weeks
Fadeyev, 2010	Parallel, unblinded	36 (36)	Untreated overt hypothyroidism, etiology not reported	6:1	usual T4 dose minus 25 µg/day with T3 12.5 µg/d	Once	6 months
Kaminski, 2016	Cross-over, blinded	32 (32)	Mixed Autoimmune, post-RAI, thyroid surgery	5:1	T4: 125 or 150 µg/d T3/T4: 75 µg/d LT4 &15 µg/d T3	Once	8 weeks
Nygaard, 2009	Cross-over, blinded	68 (59)	Autoimmune	4:1	usual T4 dose minus 50 with T3 20 or 50 µg/d	Once	12 weeks

Author, year	Design	N randomized (completed)	Etiology primary hypothyroidism	Combination Therapy			
				T4:T3 ratio	Dose	Frequency (day)	Duration
Rodriguez, 2005	Cross-over, blinded	30 (27)	Mixed – Autoimmune, post-RAI, thyroid surgery	7:1	T4 dose minus 50 µg/d with T3 10 µg/d	Once	6 Weeks
Saravanan, 2005	Parallel, blinded	69 (57)	Primary hypothyroidism, no thyroid cancer	8:1	usual T4 dose minus 50 µg/d with T3 10 µg/d	Once	12 Months
Sawka, 2003	Parallel, blinded	40 (33)	Primary hypothyroidism, no thyroid cancer, no thyroidectomy, no history of hyperthyroidism	3.5:1	usual T4 dose minus 50 µg/d with T3 total 25 µg/d	Twice	15 Weeks
Siegmund, 2004	Cross-over, blinded	26 (23)	Mixed – Autoimmune, post-RAI, thyroid surgery, no thyroid cancer	19:1	usual T4 dose minus 5% with T3 5% (aim 14:1 ratio LT4 to T3)	Once	12 Weeks
Valizadeh, 2009	Parallel, blinded	71 (60)	Mixed – Autoimmune, post-RAI, thyroid surgery, but no one on TSH suppressive therapy	4:1	usual T4 dose minus 50 µg/day with T3 total 12.5 µg/day	Twice	4 Months
Walsh, 2003	Cross-over, blinded	110 (101)	Mixed – Autoimmune, post-RAI, thyroid surgery, but no thyroid cancer on TSH suppressive therapy	8:1	usual T4 dose minus 50 µg/day with T3 10 µg/day	Once	10 Weeks
Shakir, 2021	Cross-over, blinded	90 (75)	Autoimmune, Postradioactive iodine, post-thyroidectomy, and idiopathic	10:1	usual T4 dose minus T3 dose based on 1:10 ratio	Once	22 Weeks

Results' Heterogeneity

Heterogeneity in serum thyroid hormones

- End of study TSH differences between groups
- T3 and FT3 differences between groups

Heterogeneity in results of objective TH-dependent metabolic effects

- Health related quality of life or mood
- Neurocognitive functioning
- Treatment preference

Thyroid hormones after combined LT4+LT3 therapy versus monotherapy

Author, year	TSH	FT4	T3 or FT3
Appelhof, 2005	lower	lower	higher (T3)
Bunevicius, 1999	same	lower	higher (T3)
Bunevicius, 2002	same	lower	same (T3)
Clyde, 2003	same	lower	higher (T3)
Escobar-Morreale, 2005 (5 mcg gp)	same	lower	same (FT3)
Escobar-Morreale, 2005 (7.5 mcg gp)	lower	lower	higher (FT3)
Fadeyev, 2010	same	lower (?)	same (FT3)?
Kaminski, 2016	same	lower	same (T3)
Nygaard, 2009	same	lower	higher (FT3)
Rodriguez, 2005	higher	lower (total T4)	higher (T3)
Saravanan, 2005	higher	lower	same (FT3)
Sawka, 2003	same	lower	higher (FT3)
Siegmund, 2004	lower	same	same (FT3)
Valizadeh, 2009	same	lower (total T4)	higher (T3)
Walsh, 2003	higher	lower	same (FT3)
Azizi, 2023	higher	lower	Same(T3&FT3)

***T4/T3 ratios achieved in combination therapy do not replicate the euthyroid state**

Health related quality of life or mood in 14 trials

- Superiority of combination therapy on multiple measures in 2 trials contributing **92** participants (Bunevicius, Nygaard)
- Superiority of combination therapy on a minority of measures in 2 trials contributing **633** participants (Saravanan ;*at 3 months, not at 12 months;* Valizadeh)
- No superiority of combination therapy in 10 trials
- The most recent trial, a subgroup analysis on symptomatic patients on LT4/LT3, showed significant Improvement(Shakir;2021)

Studies result heterogeneity

Shakir, Mohamed KM, et al. "Comparative effectiveness of levothyroxine, desiccated thyroid extract, and levothyroxine+ liothyronine in hypothyroidism." *The Journal of Clinical Endocrinology & Metabolism* 106.11 (2021)

THYROID
Volume 31, Number 11, 2021
© Mary Ann Liebert, Inc.
DOI: 10.1089/thy.2021.0270

Benefits and Harms of Levothyroxine/L-Triiodothyronine Versus Levothyroxine Monotherapy for Adult Patients with Hypothyroidism: Systematic Review and Meta-Analysis

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Background: Combined therapy with levothyroxine (LT4)/L-triiodothyronine (LT3) has garnered attention among clinicians and patients as a potential treatment alternative to LT4 monotherapy. The objective of this study was to compare the benefits and harms of LT4/LT3 combined therapy and LT4 monotherapy for patients with hypothyroidism.
Methods: A systematic search in MEDLINE, Scopus, EMBASE, Web of Science, and Cochrane Central Register of Controlled Trials was performed by a librarian from inception date until September 2020. Randomized clinical trials and quasiexperimental studies comparing combined therapy (LT4/LT3) versus monotherapy (LT4) for adult patients with hypothyroidism were considered for inclusion. Independent data extraction was performed by paired reviewers. A meta-analysis comparing standardized mean differences of the effect of each therapy was performed on clinical outcomes and patient preferences. Proportions of adverse events and reactions were assessed narratively.
Results: A total of 1398 references were retrieved, from which 18 fulfilled the inclusion criteria. Results supported by evidence at low-to-moderate certainty evidence did not display a difference in treatment effect between therapies on clinical status, quality of life, psychological distress, depressive symptoms, and fatigue; all measured with

Up to Sept 2020

- Eighteen trials of 1563 participants
- Ten studies: crossover design and eight were parallel
- Duration of treatment ranged : 5 weeks -12 months
- Comparing standardized mean differences of the effect of each therapy was performed on clinical outcomes and patient preferences

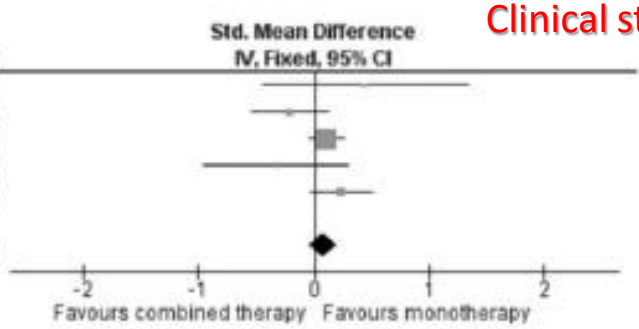
Millan-Alanis JM, et al, Benefits and Harms of Levothyroxine/L-Triiodothyronine Versus Levothyroxine Monotherapy for Adult Patients with Hypothyroidism: Systematic Review and Meta-Analysis. Thyroid. 2021

Forest plot comparing the efficacy of LT3/LT4 combined therapy versus LT4 monotherapy

A — Clinical status

Study or Subgroup	Combined therapy Mean	SD	Total	Monotherapy Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Bunevicius, 2002	-3	6.42	10	-6	6.33	10	1.7%	0.45 [-0.44, 1.34]
Hoang, 2013	-2.15	6.9	70	-0.75	6.88	70	12.5%	-0.20 [-0.53, 0.13]
Saravanan, 2005	-2.93	2.29	344	-3.19	2.29	353	62.6%	0.11 [-0.04, 0.26]
Sawka, 2007	-14.48	24.56	20	-6.02	25.63	20	3.5%	-0.33 [-0.95, 0.29]
Walsh, 2003	-0.5	1.64	110	-0.9	1.64	110	19.6%	0.24 [-0.02, 0.51]
Total (95% CI)			**554**			**563**	**100.0%**	**0.09 [-0.03, 0.20]**

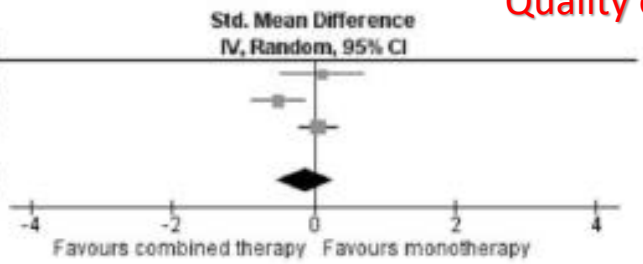
Heterogeneity: Chi² = 6.68, df = 4 (P = 0.15); I² = 40%
Test for overall effect: Z = 1.45 (P = 0.15)



B — Quality of life

Study or Subgroup	Combined therapy Mean	SD	Total	Monotherapy Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Clyde, 2003	-16	24.33	22	-19	24.63	22	24.1%	0.12 [-0.47, 0.71]
Nygaard, 2009	-10.75	10.27	59	-5.5	10.54	59	35.2%	-0.50 [-0.87, -0.13]
Walsh, 2003	-1.85	9.6	110	-2.45	9.7	110	40.8%	0.06 [-0.20, 0.33]
Total (95% CI)			**191**			**191**	**100.0%**	**-0.12 [-0.53, 0.28]**

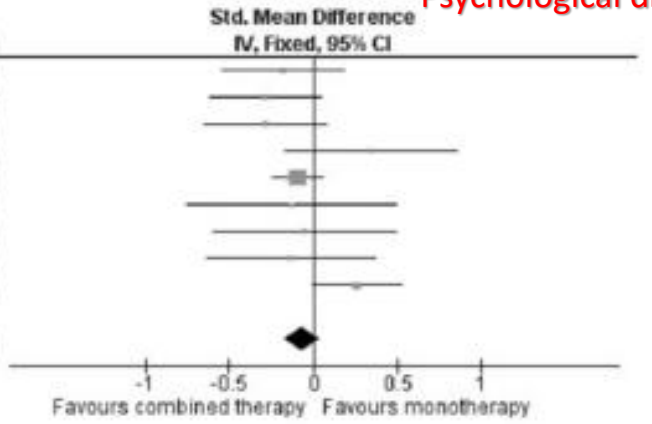
Heterogeneity: Tau² = 0.09; Chi² = 6.57, df = 2 (P = 0.04); I² = 70%
Test for overall effect: Z = 0.59 (P = 0.56)



C — Psychological distress

Study or Subgroup	Combined therapy Mean	SD	Total	Monotherapy Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Appelhoff, 2005	-7.62	7.5	90	-6.3	6.82	45	9.0%	-0.18 [-0.54, 0.18]
Hoang, 2013	-0.83	4.01	70	0.36	4.38	70	9.2%	-0.28 [-0.61, 0.05]
Nygaard, 2009	-0.36	0.49	59	-0.23	0.42	59	7.8%	-0.28 [-0.65, 0.08]
Rodriguez, 2005	-0.9	12.13	30	-4.9	10.81	30	3.9%	0.34 [-0.17, 0.85]
Saravanan, 2005	-2.74	4.9	344	-2.31	4.4	353	46.4%	-0.09 [-0.24, 0.06]
Sawka, 2007	-17.4	16.92	20	-15.3	15.78	20	2.7%	-0.13 [-0.75, 0.49]
Siegmund, 2004	-8.7	17.1	26	-7.8	17.57	26	3.5%	-0.05 [-0.59, 0.49]
Valizadeh, 2009	-0.9	8.22	30	0.4	10.71	30	4.0%	-0.13 [-0.64, 0.37]
Walsh, 2003	-2.2	11.25	110	-5.1	11.25	110	14.5%	0.26 [-0.01, 0.52]
Total (95% CI)			**779**			**743**	**100.0%**	**-0.06 [-0.17, 0.04]**

Heterogeneity: Chi² = 11.77, df = 8 (P = 0.16); I² = 32%
Test for overall effect: Z = 1.26 (P = 0.21)



Standardized mean difference (SMD) of the therapy effect between 2 arms

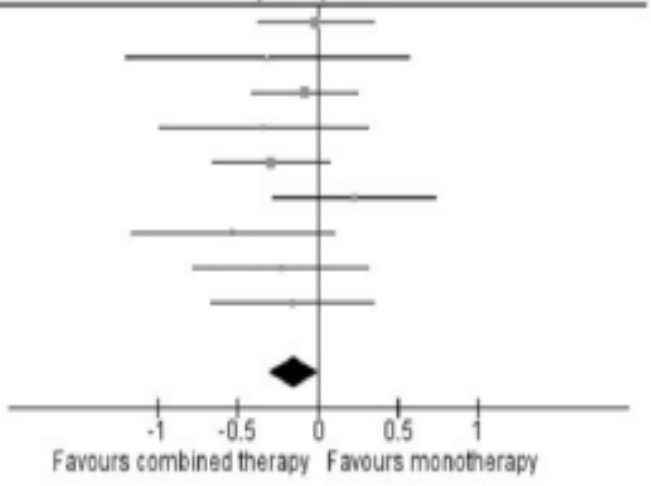
Forest plot comparing the efficacy of LT3/LT4 combined therapy versus LT4 monotherapy

D

Depressive symptoms

Study or Subgroup	Combined therapy Mean	SD	Total	Monotherapy Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Appelhof, 2005	-1.5	6.37	90	-1.4	7.9	45	18.7%	-0.01 [-0.37, 0.34]
Bunevicius, 2002	-4.9	5.63	10	-3	5.92	10	3.1%	-0.32 [-1.20, 0.57]
Hoang, 2013	-0.82	4.91	70	-0.42	4.91	70	21.8%	-0.08 [-0.41, 0.25]
Krysiak, 2018	-1.4	3.36	17	-0.2	3.55	20	5.6%	-0.34 [-0.99, 0.31]
Nygaard, 2009	-4.5	6.28	59	-2.6	6.55	59	18.2%	-0.29 [-0.66, 0.07]
Rodriguez, 2005	-3.8	8.63	30	-5.8	8.66	30	9.3%	0.23 [-0.28, 0.74]
Sawka, 2007	-10.4	10.61	20	-4.7	10.49	20	6.0%	-0.53 [-1.16, 0.10]
Siegmund, 2004	-2.3	5.8	26	-0.9	6.33	26	8.0%	-0.23 [-0.77, 0.32]
Valizadeh, 2009	-0.5	2.88	30	0	3.36	30	9.3%	-0.16 [-0.66, 0.35]
Total (95% CI)			**352**			**310**	**100.0%**	**-0.15 [-0.30, 0.01]**

Heterogeneity: Chi² = 5.38, df = 8 (P = 0.72); I² = 0%
Test for overall effect: Z = 1.85 (P = 0.06)

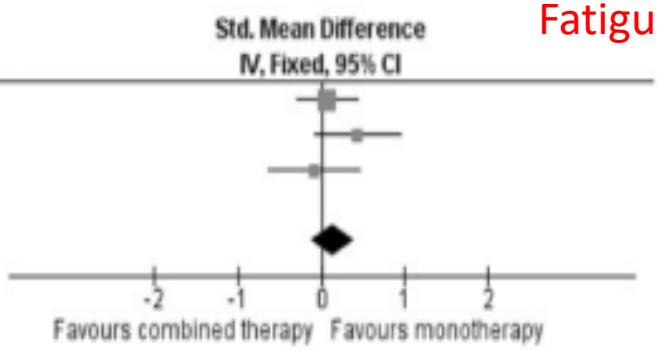


E

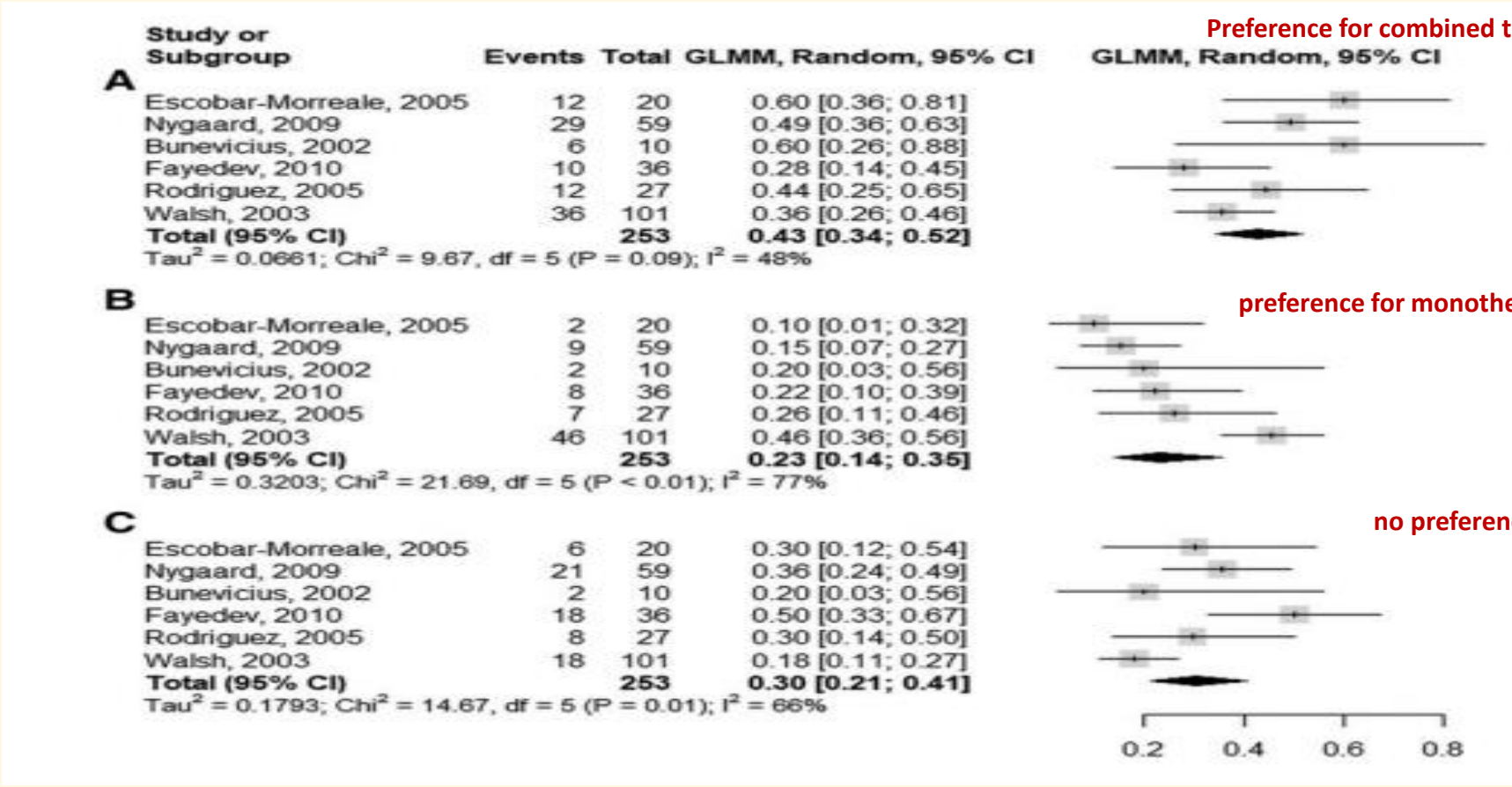
Fatigue

Study or Subgroup	Combined therapy Mean	SD	Total	Monotherapy Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Appelhof, 2005	-2.5	6.85	90	-3	6.6	45	52.0%	0.07 [-0.28, 0.43]
Rodriguez, 2005	-0.3	2.12	30	-1.2	2	30	25.4%	0.43 [-0.08, 0.94]
Siegmund, 2004	0	2.65	26	0.2	2.4	26	22.5%	-0.08 [-0.62, 0.47]
Total (95% CI)			**146**			**101**	**100.0%**	**0.13 [-0.13, 0.39]**

Heterogeneity: Chi² = 1.98, df = 2 (P = 0.37); I² = 0%
Test for overall effect: Z = 0.99 (P = 0.32)



Forest plot of patient preferences across crossover trials



Study or Subgroup	Events	Total	GLMM, Random, 95% CI
A			
Escobar-Morreale, 2005	12	20	0.60 [0.36; 0.81]
Nygaard, 2009	29	59	0.49 [0.36; 0.63]
Bunevicius, 2002	6	10	0.60 [0.26; 0.88]
Fayedev, 2010	10	36	0.28 [0.14; 0.45]
Rodriguez, 2005	12	27	0.44 [0.25; 0.65]
Walsh, 2003	36	101	0.36 [0.26; 0.46]
Total (95% CI)		**253**	**0.43 [0.34; 0.52]**
$Tau^2 = 0.0661$; $Chi^2 = 9.67$, df = 5 (P = 0.09); $I^2 = 48\%$			
B			
Escobar-Morreale, 2005	2	20	0.10 [0.01; 0.32]
Nygaard, 2009	9	59	0.15 [0.07; 0.27]
Bunevicius, 2002	2	10	0.20 [0.03; 0.56]
Fayedev, 2010	8	36	0.22 [0.10; 0.39]
Rodriguez, 2005	7	27	0.26 [0.11; 0.46]
Walsh, 2003	46	101	0.46 [0.36; 0.56]
Total (95% CI)		**253**	**0.23 [0.14; 0.35]**
$Tau^2 = 0.3203$; $Chi^2 = 21.69$, df = 5 (P < 0.01); $I^2 = 77\%$			
C			
Escobar-Morreale, 2005	6	20	0.30 [0.12; 0.54]
Nygaard, 2009	21	59	0.36 [0.24; 0.49]
Bunevicius, 2002	2	10	0.20 [0.03; 0.56]
Fayedev, 2010	18	36	0.50 [0.33; 0.67]
Rodriguez, 2005	8	27	0.30 [0.14; 0.50]
Walsh, 2003	18	101	0.18 [0.11; 0.27]
Total (95% CI)		**253**	**0.30 [0.21; 0.41]**
$Tau^2 = 0.1793$; $Chi^2 = 14.67$, df = 5 (P = 0.01); $I^2 = 66\%$			

- No statistical comparisons between the two groups
- The finding is consistent with the previous meta-analyses and suggests that patients may prefer combined therapy even though there is no difference in clinical outcomes

Meta-analysis on the RCTs regarding LT4 plus LT3 combination therapy up to Sept 2020

- Did not display a difference in treatment effect between LT4/LT3 combined therapy and LT4 monotherapy on clinical outcomes

  quality of life, psychological distress, depressive symptoms, and fatigue, all measured with standardized questionnaire.

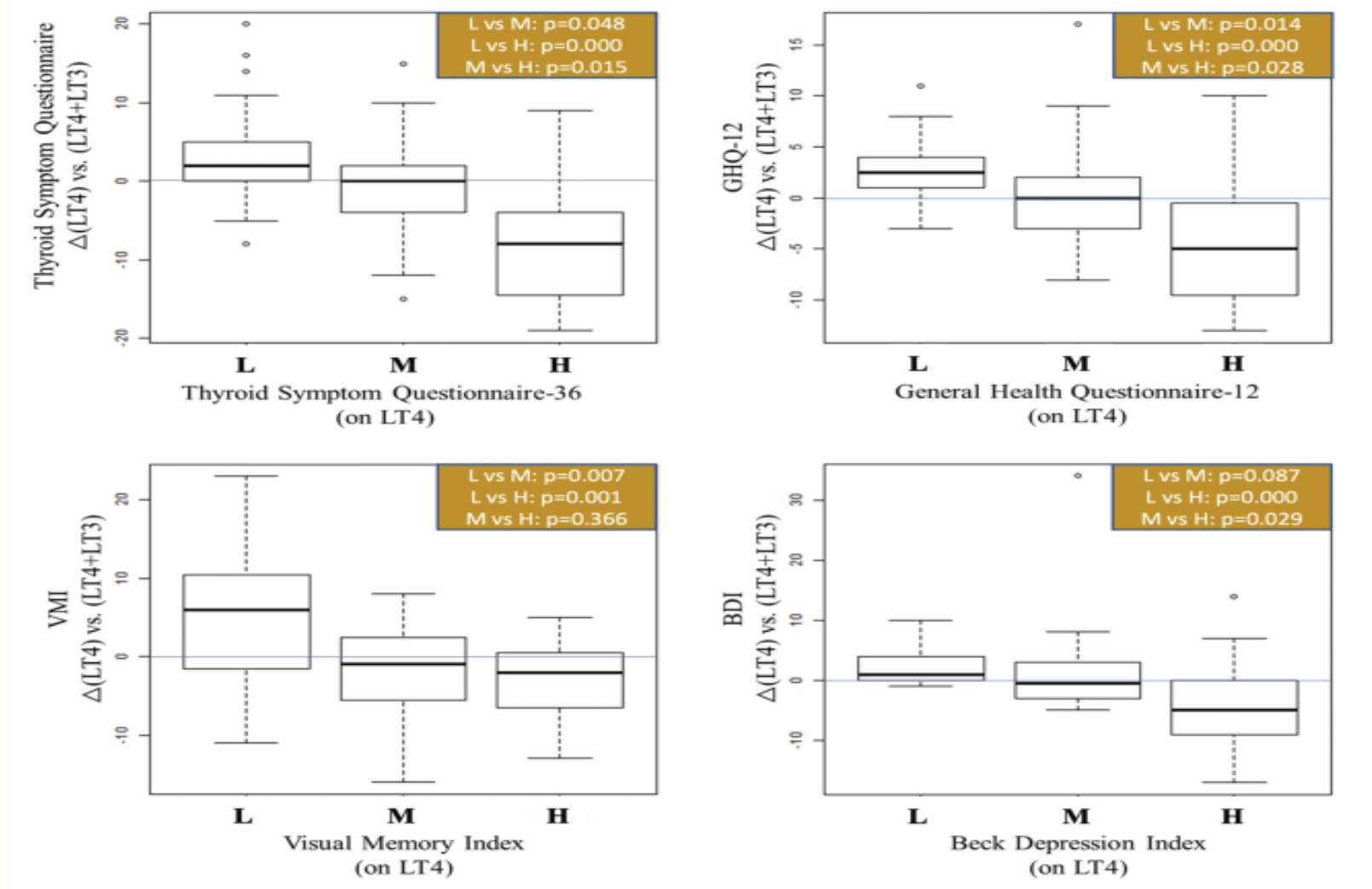
- A higher proportion of patients preferred combined therapy.
- Adverse events and reactions were similar.
- The results should be interpreted with caution as evidence supporting these findings is of low-to-moderate certainty.

Millan-Alanis JM, et al, Benefits and Harms of Levothyroxine/L-Triiodothyronine Versus Levothyroxine Monotherapy for Adult Patients with Hypothyroidism: Systematic Review and Meta-Analysis. Thyroid. 2021

LT4 therapy with LT4 + LT3 or desiccated thyroid extract (DTE); Shakir,2021

- Prospective, randomized, double-blind, crossover study
- 75 hypothyroid patients
- Duration: 22 weeks
- Results confirmed previous trials and did not detect consistent superiority of either treatment
- Subgroup analyses of the 1/3 most symptomatic patients on LT4 revealed strong preference for treatment containing T3, with improved performance on
    - **TSQ-36,**
    - **GHQ-12**
    - **BDI**
    - **Visual memory index (VMS-IV component)**

Shakir, Mohamed KM, et al. "Comparative effectiveness of levothyroxine, desiccated thyroid extract, and levothyroxine+ liothyronine in hypothyroidism." *The Journal of Clinical Endocrinology & Metabolism* 106.11 (2021)



Boxplots showing change scores from LT4 to the LT4/LT3 combination treatment, segmented by either low, medium, or high scores for those measures while on LT4.

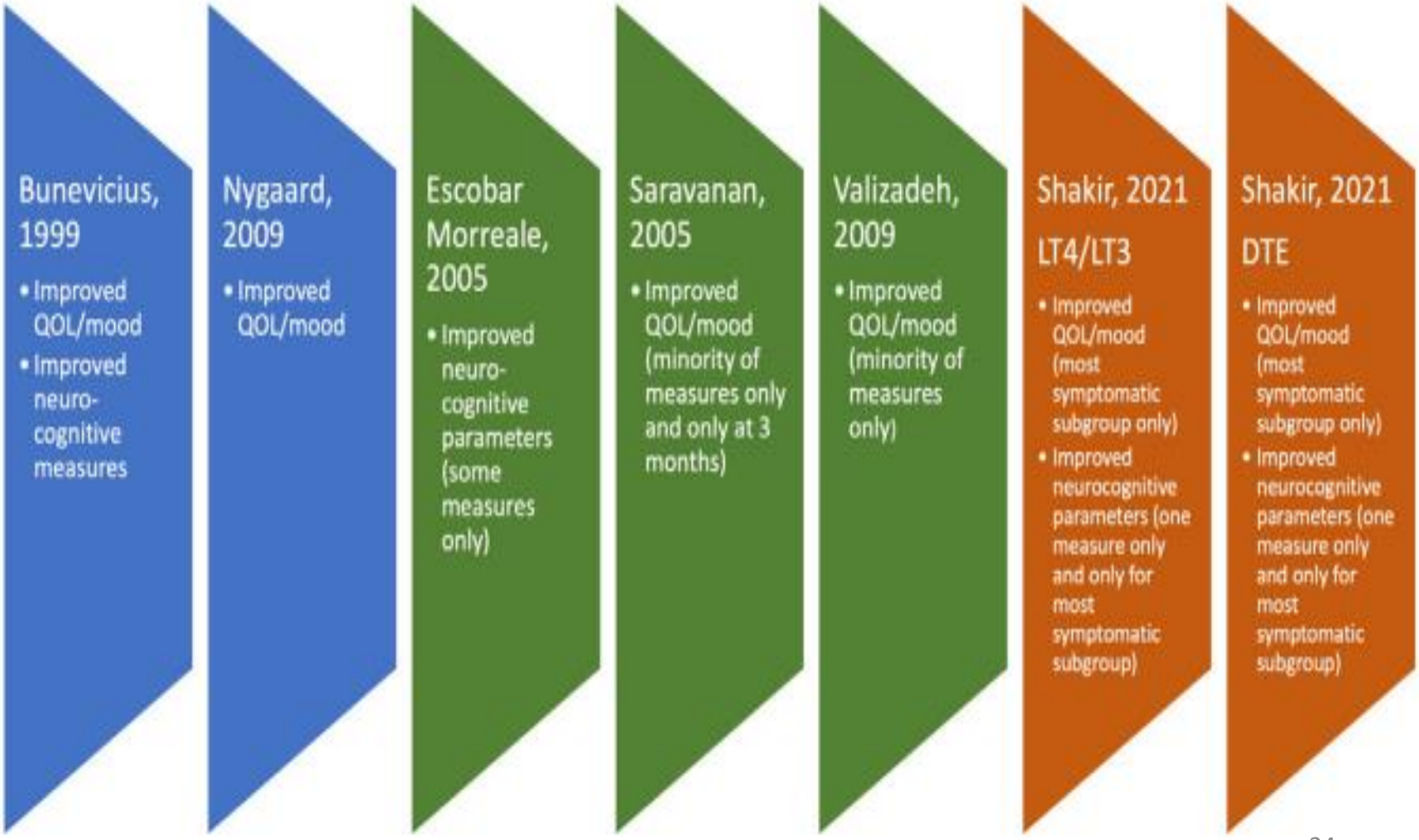
Shakir, Mohamed KM, et al. "Comparative effectiveness of levothyroxine, desiccated thyroid extract, and levothyroxine+ liothyronine in hypothyroidism." *The Journal of Clinical Endocrinology & Metabolism* 106.11 (2021)

Neurocognitive function in 11 trials

- One trial of **33** patients showed benefit on multiple measures (Bunevicius,1999)
- One trial of **26** participants showed benefit on a minority of measures (Scobar, 2005)
- Nine trials showed no benefit.
- The most recent trial (Shakir,2021); **75** patients
  - Significant improvement in 1 domain of the Wechsler memory scale-Version IV (visual memory index [VMI]) with combination therapy
  - Only for the subgroup of participants who scored worst on this test while taking LT4

Shakir, Mohamed KM, et al. "Comparative effectiveness of levothyroxine, desiccated thyroid extract, and levothyroxine+ liothyronine in hypothyroidism." *The Journal of Clinical Endocrinology & Metabolism* 106.11 (2021)

Studies showing improvement in QOL/mood or neurocognitive measures with LT4/LT3 compared with LT4



Jonklaas J. Role of Levothyroxine/Liothyronine Combinations in Treating Hypothyroidism. Endocrinol Metab Clin North Am. 2022

Selected characteristics of clinical trials of showing benefits of combination therapy (italics 5 desiccated thyroid extract) compared with LT4 monotherapy

Authors	LT3 Dosing Frequency	Approximate microgram Ratio of T4:T3	Serum T3 or FT3 Higher in T4/T3 Arm?	Trial Duration	Neuro-Cognitive Measures	QOL, Mood, Measures	Genotyping Done/Effect of Thr92Ala?
Bunevicius et al,[39] 1999	Once daily	10:1	Yes	5 wk	↑ Combo	↑ Combo	No
Escobar-Morreale et al,[43] 2005	Once daily	15:1 or 12:1	No	8 wk	↑ Combo (some parameters only)	No diff	No
Nygaard et al,[35] 2009	Once daily	4:1	Yes (FT3 index)	12 wk	n/a	↑ Combo	Retrospective, Yes
Saravanan et al,[46] 2005	Once daily	8:1	No	12 mo	n/a	↑ Combo (3 mo only) (minority of measures)	Retrospective, Yes
Shakir et al,[51] 2021	Once daily	9.5:1	Yes	22 wk	No diff (except in 1 domain in subgroup analysis of those with worst scores on LT4)	No diff (except in subgroup analysis of those with worst scores on LT4)	Prospective, No
Shakir et al,[51] 2021	*Once daily*	*4:1*	*Yes*	*22 wk*	*No diff* (except in 1 domain in subgroup analysis of those with worst scores on LT4)	*No diff* (except in subgroup analysis of those with worst scores on LT4)	*Prospective, No*
Valizadeh et al,[47] 2009	Twice daily	4:1	Yes	4mo	n/a	↑ Combo (minority of measures)	No

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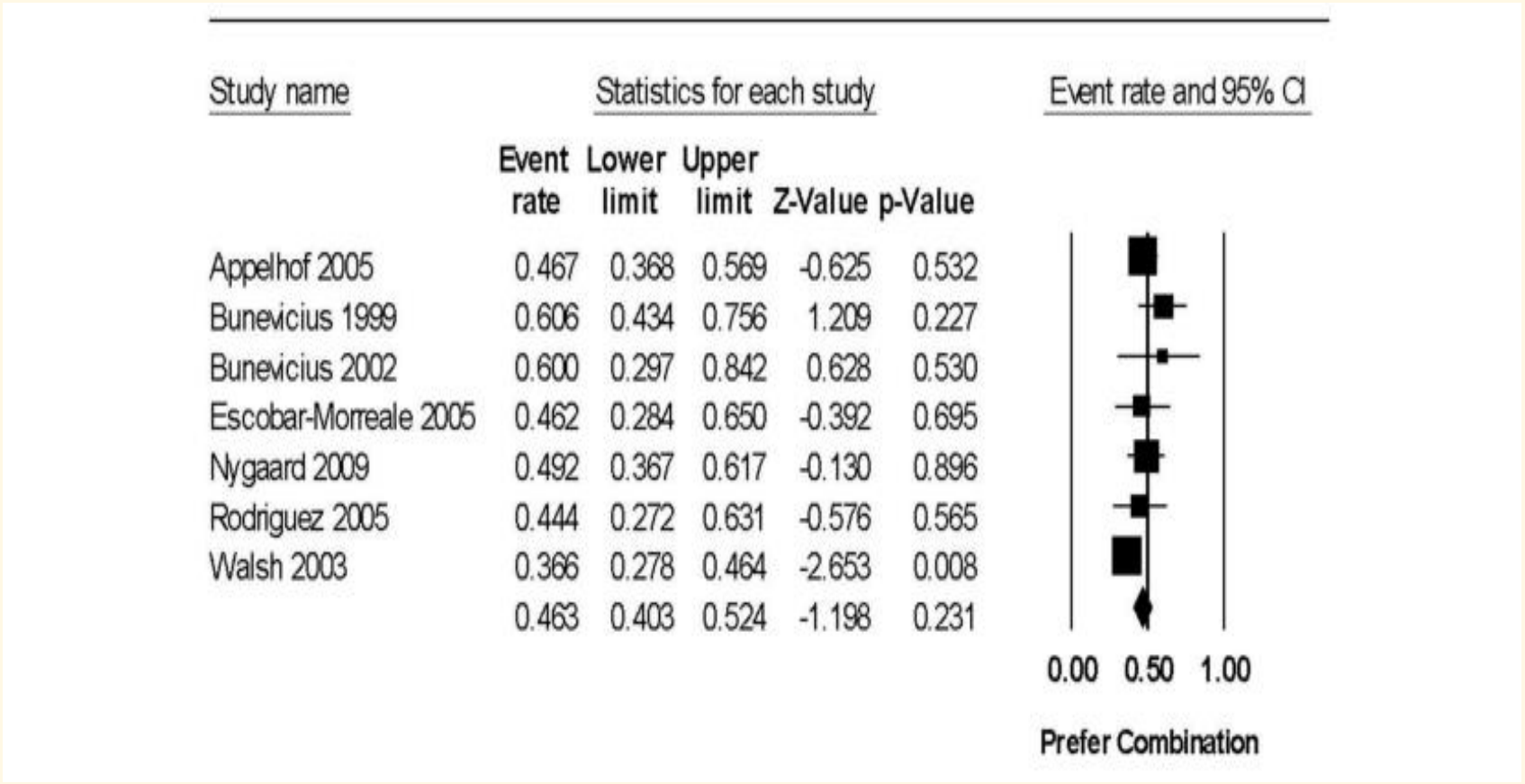
Patient preference

- **5 blinded 2-arm cross-over design trials**
  - The combination therapy was preferred in 4 trials(**128 patients**)
  - Another trial of **101** patients did not demonstrate a preference

- **2 blinded, parallel design trials**
  - A preference for combination therapy in 1 trial of **130** patients
  - No preference in another trial of **573** patients.

- **In a recent meta-analysis showed patient preference for combination therapy in some studies, overall preference did not differ; although the preference was associated with the magnitude of the LT3 dose (Akirov,2019)**

Forest plot from a random effects meta-analysis examining prevalence of preference of combination L-T3/L-T4 therapy over L-T4 alone. (Akirov,2019)



Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value
Appelhof 2005	0.467	0.368	0.569	-0.625	0.532
Bunevicius 1999	0.606	0.434	0.756	1.209	0.227
Bunevicius 2002	0.600	0.297	0.842	0.628	0.530
Escobar-Morreale 2005	0.462	0.284	0.650	-0.392	0.695
Nygaard 2009	0.492	0.367	0.617	-0.130	0.896
Rodriguez 2005	0.444	0.272	0.631	-0.576	0.565
Walsh 2003	0.366	0.278	0.464	-2.653	0.008
	0.463	0.403	0.524	-1.198	0.231

- It is not known if the individuals with no preference were indifferent or indecisive
- Preference examined as a binomial distribution of choices (preference for combination therapy vs no preference)

Akirov A, et al. A Systematic Review and Meta-Analysis of Patient Preferences for Combination Thyroid Hormone Treatment for Hypothyroidism. Front Endocrinol (Lausanne). 2019

No reproducible clinical evidence supports the efficacy of LT4/LT3 over LT4 alone

Lack of success was due to:

- Using higher amounts of T3
- High variations in serum T3 concentration due to low half-life and rapid absorption of T3
- Lack of attention to T3 surge after TSH surge during midnight.
- Small sample size, short duration, once-daily dosing regimens
- Trial heterogeneity with respect to the dosing regimens, TH levels & outcome measures
- Ignore to include sufficient N of patients who most likely to benefit from combination therapy to provide adequate power for detecting a response.

  - ✓ Those with persistent hypothyroid symptoms or dissatisfaction
  - ✓ Treated at baseline with at least 1.2 µg/kg per day of LT4
  - ✓ Who are surgically athyreotic
  - ✓ Those individuals with thyroid cancer who have received RAI therapy after thyroidectomy,

Patient Case

- A 47 -year-old woman
- A 3-year history of primary hypothyroidism
- Receiving a stable dose of LT4 for 2 years
- Her TSH is 3.0 mIU/L, her FT4 is 1.1 ng/dL
- Continued fatigue, depressed mood, and some cognitive difficulties as “brain fog”
- Her exam is unremarkable,
- BMI of 28 kg/m2
- What is the next step?

Consensus Statements to guide development of future clinical trials of LT4/LT3 combination therapy by ATA, BTA & ETA

- In 2019, the consortium headed by J. Jonklaas, released a Consensus Statements to guide the development of future clinical trials of LT4/LT3 combination therapy
- Incorporating features that might increase the likelihood of showing efficacy
- There were 28 consensus statements with at least 75% agreement
- 13 statements with 100% agreement
  - ✓ The effect of genetic polymorphisms on study outcomes
  - ✓ The inclusion of patients dissatisfied with their therapy and requiring at least 1.2 µg/kg of LT4
  - ✓ Use of twice daily LT3 or, if available, a slow-release preparation
  - ✓ Patient-reported outcomes as a primary outcome (measured by a valid & reliable tool).
  - ✓ Patient preference as a secondary outcome
  - ✓ Randomized placebo-controlled adequately powered double-blinded parallel design.

Jonklaas J,et al. Evidence-Based Use of Levothyroxine/Liothyronine Combinations in Treating Hypothyroidism: A Consensus Document. Thyroid. 2021

Guidelines and combination therapy

Society	Year	Recommendation regarding combination therapy
ETA	**2012**	It is recommended that L-T4 monotherapy remains the standard treatment of hypothyroidism *(1/+++)* There is insufficient evidence that L-T4 + L-T3 combination therapy serves the hypothyroid patient better than T4 monotherapy *(1/++0)* ***It is suggested that L-T4 + L-T3 combination therapy might be considered as an experimental approach*** in compliant L-T4-treated hypothyroid patients who have persistent complaints despite serum TSH values within the reference range… *(2/+00)*
ATA	**2014**	Levothyroxine is recommended as the preparation of choice for the treatment of hypothyroidism due to… Recommendation: For patients with primary hypothyroidism who feel unwell on levothyroxine therapy alone…, there is currently **insufficient evidence** to support the **routine use of a trial of a combination** of levothyroxine and liothyronine therapy **outside a formal clinical trial or N-of-1 trial** due to uncertainty in long-term risk benefit ratio of the treatment and uncertainty as to the optimal definition of a successful trial to guide clinical decision-making (Insufficient)

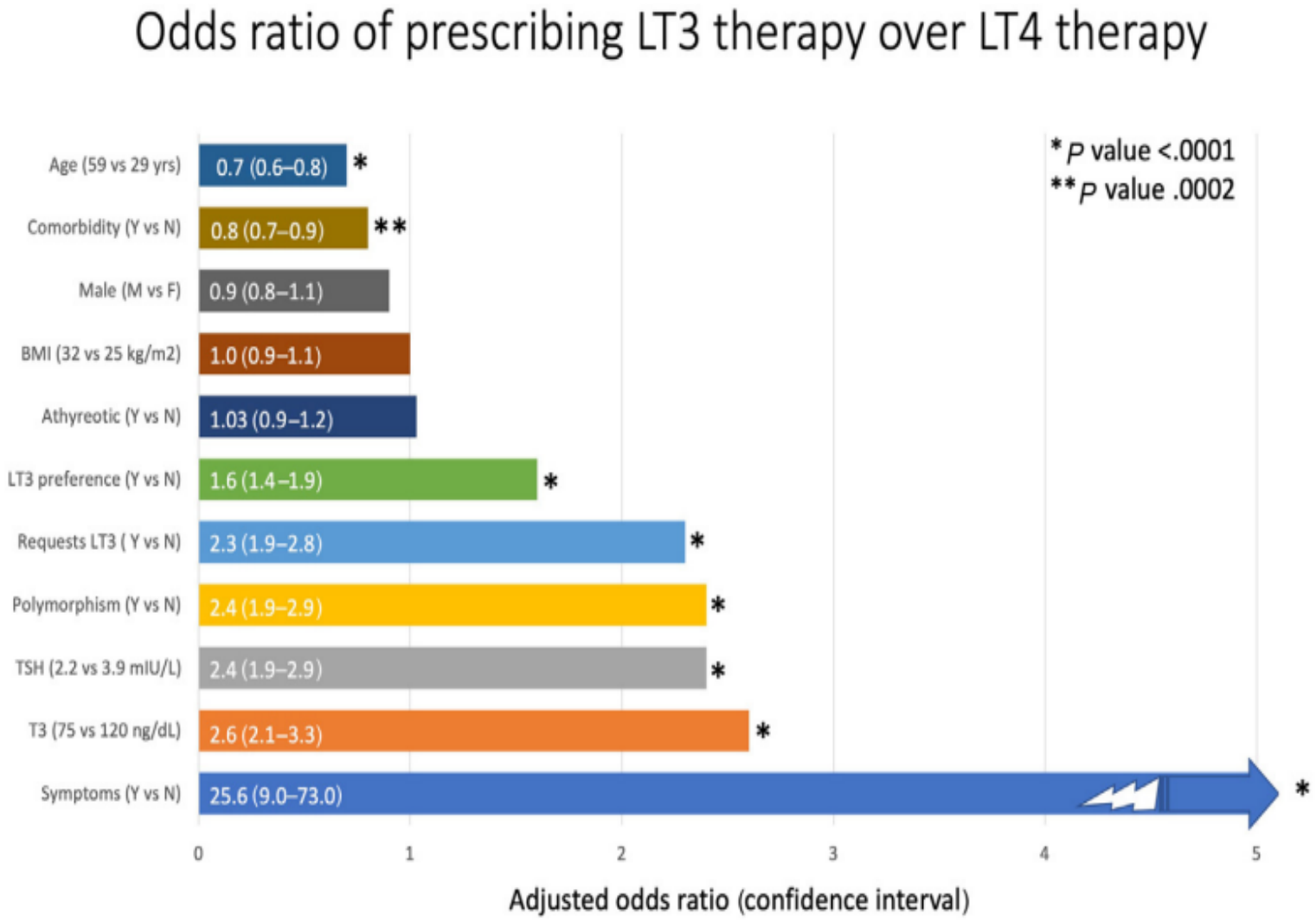
1. Wiersinga WM, Duntas L, Fadeyev V, Nygaard B, Vanderpump MP. 2012 ETA Guidelines: The Use of L-T4 + L-T3 in the Treatment of Hypothyroidism. Eur Thyroid J. 2012
2. Jonklaas J,et al. American Thyroid Association Task Force on Thyroid Hormone Replacement. Guidelines for the treatment of hypothyroidism: prepared by the American Thyroid Association task force on thyroid hormone replacement. Thyroid. 2014

Physician Practice Patterns for Prescribing of LT3 containing Products

- A 2017 survey of ATA members showed that one-third would consider alternative treatment options such as CT depending on the circumstances.
- In Iran, 32% used combination therapy in LT4-treated euthyroid cases with persistent symptoms.
- Compatible with 35% in Romania and 32% in Poland
- More than 50% of experts prescribe LT4+LT3: 73% in Sweden, 71% in Denmark, 67% in Germany, 51% in the UK, and 54% in the Czech Republic .
- In Iran, the availability of liothyronine is much more limited than levothyroxine, which may explain the lower tendency toward combination therapy.

1. Jonklaas J, Tefera E, Shara N. Physician choice of hypothyroidism therapy: influence of patient characteristics. Thyroid 2018;28(11):1416–24.
2. Jonklaas J, Tefera E, Shara N. Prescribing therapy for hypothyroidism: influence of physician characteristics. Thyroid 2019;29(1):44–52.
3. Ahmadi N, et al.A Questionnaire Survey of Iranian Endocrine Practitioners on the Use of Thyroid Hormones in Hypothyroid and Euthyroidism Patients. 2023,;Unpublished

Likelihood of prescribing LT3-containing therapy rather than LT4 therapy for several patient scenarios. (physicians then opted to increase LT4 dose or prescribe LT4/LT3 therapy



Jonklaas J, Tefera E, Shara N. Physician choice of hypothyroidism therapy: influence of patient characteristics. Thyroid 2018;28(11):1416–24.

Studies on combination therapy with levothyroxine plus sustained-release liothyronine

Rational background

- Pre-clinical and clinical evidence indicating that deiodinases fall short of restoring T3 production have opened the possibility of liothyronine role in the treatment of some hypothyroid patients.

- LT3 tablets result in a substantial peak of circulating T3 that is dissipated during the next several hours, markedly distinct from the relative stability of T3 levels in normal individuals.

- An alternative approach to improve LT3 PK properties when given orally is to delay its absorption via SR-T3 preparation.

- The goal of a SR-T3 preparation is
  - ✓ To avoid fluctuating serum T3 levels
  - ✓ Provide acceptable T3/T4 ratio
  - ✓ Increased shelf stability to ensure the maintenance of dosage
  - ✓ Minimize side effects of T3

New delivery strategies for LT3, to attain sustained-release profile (from the gastrointestinal tract or other depots)

- Slow release tablets
- Use of T3- derivatives and hybrid molecules such as T3-S, poly-zinc-T3 and glucagon-T3, nanoparticles containing T3
- Liquid formulations
- Subcutaneous implant of T3-containing matrices
- Stem cells for de novo development of the thyroid gland
- Deliver LT3 via chewable ion exchange resin that form a drug resin complex (Spectrix, Southlake TX): under testing

Slow-release tablets

- Containing a hydrophilic swellable matrix system made with hydroxy-propylmethylcellulose (HPMC), sodium carboxy methylcellulose, calcium phosphate and magnesium stearate (US Patent #5,324,522).

- Other combinations of salt and matrices including mannitol, magnesium stearate, calcium phosphate, and microporous polypropylene (US Patent #5,324,522).

- When tested in vitro the rate of LT3 release from such capsules can be modulated according to their content and grade of Methocel, and/or SimpleCap/Lactose.

Idrees T, Price JD, Piccariello T, Bianco AC. Sustained Release T3 Therapy: Animal Models and Translational Applications. Front Endocrinol (Lausanne). 2019

Evidence regarding sustained-release T3 preparations

Evidence on T3 derivatives (Animal &human studies)

- T3 sulfate a metabolite of T4 &T3 that does not have biological activity.
- Phenolic hydroxyl within the T3 molecule can be sulfated (T3-S), a reaction that inactivates T3 but enhances its water solubility and loss to the environment.
- Sulfatase in the liver can reactivate T3-S via desulfation and prevent its loss.
- Studies in thyroidectomized rats revealed that parentally administered T3-S were converted back to T3, triggering thyromimetic effects.

Santini F, Hurd RE, Lee B, Chopra IJ. Thyromimetic effects of 3,5,3'-triiodothyronine sulfate in hypothyroid rats. Endocrinology. 1993

Human studies on T3-sulfate

- 28 thyroidectomized individuals given a single dose of T3-S orally; Santini, 2014
  - A sustained-release profile with steady serum T3 levels for 48h
  - Serum T3 levels increased, with an early peak between 3-4 h
  - Followed by a variable plateau depended on the dose of T3-S
  - Plateau lasted up to 48 h
- Phase 2 study on 36 thyroidectomized hypothyroid patients (replaced 25 µg LT4 with 40 µg T3-S); Santini,2019
  - T3-S lowered serum TSH and FT4 concentrations
  - Allowed maintenance of normal levels of serum T3
  - Restoration of a physiological FT4/FT3 ratio
  - No appearance of adverse effects.

1. Santini F, et al. Steady-state serum T3 concentrations for 48 hours following the oral administration of a single dose of 3,5,3'-triiodothyronine sulfate (T3S). Endocr Pract 2014
2. Santini F, et al. Treatment of hypothyroid patients with L-thyroxine (L-T4) plus triiodothyronine sulfate (T3S). A phase II, open-label, single center, parallel groups study on therapeutic efficacy and tolerability. Front Endocrinol (Lausanne) 2019;

Poly-Zinc Liothyronine (PZL); An Animal study

- Oral gavage of PZL capsules in hypothyroid rats made a significant modification in PK properties in LT3-treated vs lt4-treated rats.
  - A 30% lower peak (T3-Cmax)
  - A longer time period remained at a plateau (about 6h)
  - No difference in T3 clearance rate
- Daily administration of either LT3 or PZL for 8 days (chronic) showed similar long-term biological effects
  - Lowered serum cholesterol, TSH
  - Stimulated hepatic expression of the Dio1 mRNA and
  - Other T3-dependent markers in the central nervous system.
  - Induced T3-dependent genes in the heart, liver and brain

PZL Restored T3-dependent biological effects while exhibiting a reduced and delayed serum T3 peak
It could be further improved by packaging PZL in SR capsules made with hydrophilic swellable matrix

1. Da Conceicao RR, et al . Metal coordinated poly-zinc-liothyronine provides stable circulating triiodothyronine levels in hypothyroid rats. Thyroid Offic J Am Thyroid Assoc. (2018)

Phase 1 single-dose, double-blind placebo-controlled trial of PZL/LT3 arms on 12 healthy volunteers

- A LT3-derived serum T3 levels exhibited the expected profile, with a T-max at 2 h and return to basal levels by 24-36 hours.

- The PZL arm provided a much improved T3 PK
  - Reached a 30% lower T3-C max than LT3
  - Plateaus lasted 6-hour.
  - Followed by a lower but much longer 12 h plateau;
  - By 24 hours serum T3 levels still exceeded ½ of Cmax
  - The AUC was greater for the PZL arm at the 12 to 24 h and 24 to 48 h

Whether this profile will translate into improved stability of serum T3 levels and more satisfactory therapy for patients will be determined in future clinical trials.

Dumitrescu AM,et al. Extended Absorption of Liothyronine from Poly-Zinc-Liothyronine: Results from a Phase 1, Double-Blind, Randomized, and Controlled Study in Humans. Thyroid. 2022

In vivo studies on SR-T3 Tablets in 3 clinical studies

- **Hennemman et al (2004)**
  - 17 hypothyroid individuals given LT4 plus SR-LT3 tablets
  - A 9% decrease in the peak T3 in the serum (Cmax)
  - Prolonged the time to Cmax from ~3.2 to 5 h
- **Jonklaas et al(2015)**
  - LT3 tablets prepared with microcrystalline cellulose and magnesium stearate (BCT303)
  - Sustained serum T3 levels were not observed.
- **Azizi et al (2023)**
  - Contained hydrophilic swellable matrix system made with HPMC
  - 19 Radioiodine-treated hypothyroid adult patients
  - Combined treatment with a single daily dose of SR-T3/LT4 (1:5 & 1:7.5 ratios) was associated with increased serum T3/T4 ratio
  - Minimal excursions in serum T3 concentration during 24 hours

1. Hennemann G, et al. Thyroxine plus low-dose, slow-release triiodothyronine replacement in hypothyroidism: proof of principle. Thyroid Offic J Am Thyroid Assoc. 2004
2. Jonklaas J, et al. Single-dose T3 administration: kinetics and effects on biochemical and physiological parameters. Ther Drug Monit. (2015)
3. Mehran L, et al . Pharmacodynamic and pharmacokinetic properties of the combined preparation of levothyroxine plus sustained- release liothyronine; a randomized controlled clinical trial. BMC Endocr Disord. 2023

Risks of Combination Therapy

- The risks of combination therapy have not been fully explored mostly due to relatively short duration.
- Potential risks include iatrogenic hyperthyroidism (T3 thyrotoxicosis), cardiac arrhythmias, and decrement in bone mineral density.
- Most studies have consisted of healthy middle-aged women, no one assessed the risk s in men, those with comorbidities, older or frail populations
- Overtreatment would be predicted as often as LT4 monotherapy
- Combination therapy should not be undertaken in pregnant women for fear of insufficient thyroid hormone reaching fetal tissues.

Risks of Combination Therapy

- Comparison of 400 LT3 with LT4 users (n=33,995) found no increase in atrial fibrillation or fractures with LT3 over a 17-year period. (Leese,2016)
  - However, increased use of antipsychotic medications associated with LT3 use, an adjusted hazard ratio of 2.26
  - A trend for increased use of antidepressants
  - A trend toward an increased hazard ratio for breast cancer

- In a registry study from Sweden conducted over an 8.1-year period, comparison of LT3 users (n =11,147) with LT4 users (n =575,461), did not replicate the trend for breast cancer or other cancers risk or mortality from breast cancer.(Planck,2021)

Leese GP, et al., Donnelly LA. Liothyronine use in a 17 year observational population-based study - the tears study. Clin Endocrinol (Oxf); 2016
Planck T, et al. Calissendorff J, et al. Liothyronine use in hypothyroidism and its effects on cancer and mortality. Thyroid 2021;31(5):732–9

Outline

- There is still currently insufficient evidence to support the routine use of combination of levothyroxine and liothyronine therapy
- Claims of slow release LT3 formulations based on changing the composition of the tablets have not been confirmed in clinical trials or have only minimally affected Cmax and Tmax.
- A number of new strategies and compounds are being explored but details aren't always available due to commercial interests and protection of intellectual property.
- So far, T3-S and PZL have shown promising results in animal models but formal phase-1 clinical trials have not been conducted.

Clinical Care Points

- For hypothyroid patients not restored to baseline health with levothyroxine, causes arising from coexistent medical conditions, stressors, lifestyle, and psychosocial factors should be addressed.
- If addressing such factors does not improve quality of life, there may be benefit to use of combination therapy with LT4 and LT3.
- Monitoring for adverse effects, particularly in older or frail individuals, is necessary, and combination therapy should not be used during pregnancy.
- Once they have completed clinical trials, SR-T3 preparations may become available as improved therapies for patients with hypothyroidism.

Methods for calculating L-T4 and L-T3 dosages for T4+T3 combination therapy

T4 monotherapy	100 µg L-T4 = dose x	150 µg L-T4 = dose x	200 µg L-T4 = dose x
T4+T3 combination, method A, µg			
L-T3 dose y (y = x : 17)	5.88	8.82	11.76
L-T4 dose z (z = x – 3y)	82.36	123.54	164.71
L-T3 dose (round off)	6.25	9.37	12.5
L-T4 dose (round off)	87.5	125	162.5
L-T4:L-T3 dose ratio	14:1	13:1	13:1
T4+T3 combination, method B1, µg			
L-T3 dose y (y = 0.8x : 17)	4.70	7.05	9.41
L-T4 dose z (z = 16y × 1.25)	94.12	141.18	188.24
L-T3 dose (round off)	6.25	6.25	9.37
L-T4 dose (round off)	87.5	125	187.5
L-T4:L-T3 dose ratio	14:1	20:1	20:1
T4+T3 combination, method B2, µg			
L-T3 dose y (y = 0.7x : 17)	4.12	6.18	8.24
L-T4 dose z (z = 16y × 1.43)	94.21	141.31	188.42
L-T3 dose (round off)	6.25	6.25	9.37
L-T4 dose (round off)	87.5	125	187.5
L-T4:L-T3 dose ratio	14:1	20:1	20:1
T4+T3 combination, method C, µg			
L-T3 dose y (y = x : 20)	5	7.5	10
L-T4 dose z (z = x – 3y)	85	127.5	170
L-T4 dose (round off)	87.5	125	175
L-T4:L-T3 dose ratio	17:1	17:1	17:1

Dose x = Daily L-T4 dose in µg that has normalized serum TSH during T4 monotherapy.

Therapeutic substitution of L-T3 for L-T4 was achieved at approximately 1:3 ratio.

Daily L-T3 dose in g is called dose y.
Daily L-T4 dose in g is called dose z, calculated as x – 3y (to adjust for the pharmacodynamic equivalence ratio of 1:3 for L-T3 and L-T4)
Assuming 80% absorption of L-T4 and 100% absorption of L-T3 the dose of L-T4 and L-T3 in L-T4 + L-T3 combination therapy is calculated as follows (method B1):
Method C is the simplest protocol, although it does depend on the availability of L-T3 strength.

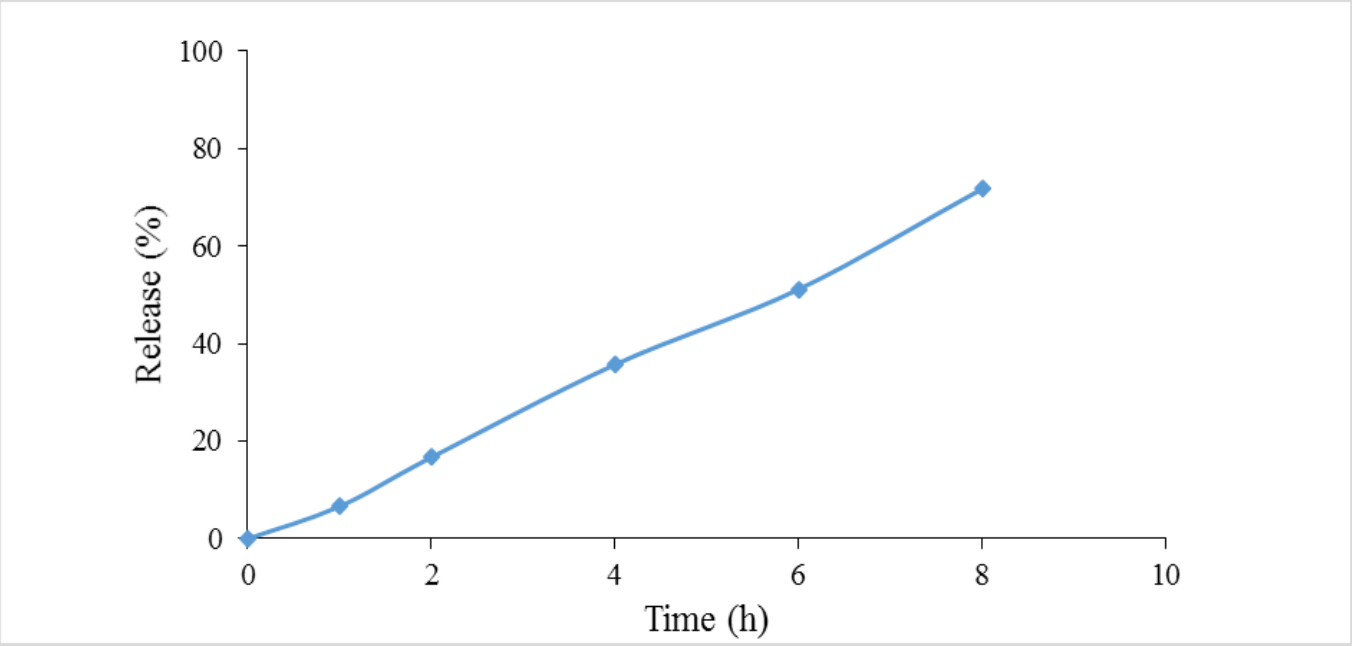
The most recent study by Azizi et al

- A parallel randomized clinical trial
- 19 Radioiodine-treated hypothyroid adult patients, who attained euthyroidism with LT4 monotherapy
- Investigated the PK and PD of the 2 combined preparations of LT4+SR-T3.
- Three arms with LT3/LT4 ratios of 9/68.5(1:7.5) and 12/60 (1:5), and a control group with LT4 monotherapy.
- For PD study, thyroid hormone profile was evaluated at 8 and 12 wk.
- To assess PK properties repeated measurements after 1, 2, 4, 6, 8, and 24 hours at the last visit.
- T3 Tmax achieved during 3-4 hours

Combined treatment with ratios of 1:5 yields more improved T3/T4 serum ratio and T3-derived pharmacokinetics, while keeping serum T3 concentrations relatively stable within 24 hours with minimal excursions.

Mehran L, et al . Pharmacodynamic and pharmacokinetic properties of the combined preparation of levothyroxine plus sustained- release liothyronine; a randomized controlled clinical trial. BMC Endocr Disord. 2023

In vitro drug release of T3 from sustained-release T3 tablet, in pH 6.8 phosphate buffer USP



The tablet is designed to release T-3 at a constant rate about 10 h after oral administration
Wet granulation method of tablet formulation contained hydrophilic swellable matrix system made with hydroxy propylmethylcellulose (HPMC)