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REVIEW ARTICLE

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Current evidence for the treatment of hypothyroidism with levothyroxine/levotrijodothyronine combination therapy versus levothyroxine monotherapy

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Summary

Objective: Hypothyroidism is relatively common, occurring in approximately 5% of the general US population aged ≥12 years. Levothyroxine (LT4) monotherapy is the standard of care. Approximately, 5%-10% of patients who normalise thyroid-stimulating hormone levels with LT4 monotherapy may have persistent symptoms that patients and clinicians may attribute to hypothyroidism. A long-standing debate in the literature is whether addition of levotriiodothyronine (LT3) to LT4 will ameliorate lingering symptoms. Here, we explore the evidence for and against LT4/LT3 combination therapy as the optimal approach to treat euthyroid patients with persistent complaints.

Methods: Recent literature indexed on PubMed was searched in March 2017 using the terms "hypothyroid" or "hypothyroidism" and "triiodothyronine combination" or "T3 combination." Relevant non-review articles published in English during the past 10 years were included and supplemented with articles already known to the authors.

Findings: Current clinical evidence is not sufficiently strong to support LT4/LT3 combination therapy in patients with hypothyroidism. Polymorphisms in deiodinase genes that encode the enzymes that convert T4 to T3 in the periphery may provide potential mechanisms underlying unsatisfactory treatment results with LT4 monotherapy. However, results of studies on the effect of LT4/LT3 therapy on clinical symptoms and thyroid-responsive genes have thus far not been conclusive.

Conclusions: Persistent symptoms in patients who are biochemically euthyroid with LT4 monotherapy may be caused by several other conditions unrelated to thyroid function, and their cause should be aggressively investigated by the clinician.

| INTRODUCTION 1

A 53-year-old woman presents with a 3-year history of primary hypothyroidism. She has been receiving a stable dose of levothyroxine (LT4) replacement monotherapy and has had thyroid-stimulating hormone (TSH) levels of 0.5-2.5 mIU/L, well within the guideline-recommended range (0.45-4.12 mIU/L),¹ for more than 12 months. At her most recent visit, she reports

continued fatigue, hair loss and some cognitive difficulties that she describes as "brain fog." She asks about adding levotriiodothyronine (LT3) to her treatment as "bioidentical" therapy, based on an article that she brought along.

Hypothyroidism is a relatively common condition. In the US National Health and Nutrition Examination Survey (NHANES) III, a prevalence of 4.6% was noted in participants \geq 12 years of age.² A meta-analysis of data from hypothyroidism studies conducted in

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Europe estimated a prevalence of 3.05%.³ The frequency of elevated TSH increases with age, and in those aged 40 to 69 years, the prevalence of elevated TSH is significantly higher in women than in men.² As TSH levels physiologically rise with aging, T3 levels decline to the same extent in those without thyroid disease, whereas T4 levels remain largely unchanged in the healthy elderly.⁴

In patients with primary hypothyroidism, the thyroid gland is unable to maintain adequate secretion of hormones, triggering the pituitary gland to release greater amounts of TSH to compensate.⁵ However, owing to dysfunction of the thyroid gland, endogenous production of thyroid hormones remains insufficient. Clinical manifestations of this insufficiency can vary greatly because thyroid hormone receptors are present in most organs and tissues of the body.⁵ The cardiovascular, pulmonary, gastrointestinal, musculoskeletal and neurological systems can all be affected as well as the kidneys, skin and connective tissues. The severity of the signs and symptoms of hypothyroidism can range from subclinical to debilitating. In the United States, where iodine deficiency is rare, the most common cause of hypothyroidism is autoimmune thyroiditis.¹

Our hypothetical patient above fits the typical demographic profile of a patient with hypothyroidism. However, her continued symptoms, despite seemingly successful normalisation of thyroid function as reflected by serum TSH, and her request to consider LT3 supplementation present a clinical quandary. A number of questions arise. Although thyroxine (T4) is considered a prohormone to the active form (ie, T3), T4 has a longer half-life⁶ and is converted to T3 intracellularly, whereas T3 interacts with thyroid hormone receptor to affect thyroidhormone-responsive genes. Is there good clinical evidence to support the superiority of LT4/LT3 combination therapy for the treatment of patients with troublesome symptoms despite normal TSH levels? Is there benefit in adding LT3 to an LT4 monotherapy regimen? Here, we review the evidence and rationale that underpin current approaches to treatment and explore potential solutions to the problem of persistent symptoms in a patient who has achieved a normal TSH level with LT4 replacement therapy.

1.1 | Literature search methods

Because older research has been well summarised,⁷ recent literature indexed on PubMed was searched in March 2017 using the terms "hypothyroid" or "hypothyroidism" and "triiodothyronine combination" or "T3 combination." After limiting the results to the past 10 years and to non-review articles published in English, 72 articles were found; of these, 17 were relevant based on their analysis and discussion of thyroid replacement therapies, specifically LT4/LT3 combination therapy, in patients with hypothyroidism and are included here.

1.2 | Historical development of treatment for hypothyroidism

Initially, thyroid replacement therapies were desiccated thyroid extract preparations of animal origin, which contained variable amounts

Review criteria

 There is long-standing debate about whether addition of levotriiodothyronine (LT3) to levothyroxine (LT4) will ameliorate persistent symptoms of hypothyroidism. To explore the evidence for and against LT4/LT3 combination therapy, recent literature was searched using the terms "hypothyroid" or "hypothyroidism" and "triiodothyronine combination" or "T3 combination." In all, 72 relevant non-review articles published in English were found; 17 were included and supplemented with articles already known to the authors.

Message for the clinic

Current clinical evidence is insufficient to support LT4/LT3 combination therapy in patients with hypothyroidism. Findings on the effect of LT4/LT3 therapy on clinical symptoms and thyroid-responsive genes have been inconclusive. In patients who are biochemically euthyroid with LT4 monotherapy but have persistent symptoms, clinicians should thoroughly investigate alternative causes, such as endocrine and autoimmune disorders, haematological conditions, end-organ damage, nutritional deficiencies, metabolic syndromes, concomitant drugs, and lifestyle.

of T4 and T3.^{8,9} Development of synthetic formulations of both hormones enabled the administration of preparations with exact quantities of hormones; their testing as replacement therapy began in the 1950s.⁷ Early clinical studies demonstrated that an LT4:LT3 ratio of 4:1 produced a similar clinical response compared with desiccated thyroid extract⁸ and returned patients to euthyroid status as determined by clinical markers, including normalised cholesterol and protein-bound iodine levels.¹⁰

In 1970, it was demonstrated that the serum T3 found in the blood of patients receiving LT4 monotherapy was derived from peripheral conversion of the administered LT4.¹¹ This finding provided a mechanism to explain the observation that circulating T3 levels were physiologic in patients treated with LT4 monotherapy,¹² implying that exogenous LT3 was not required for the treatment of hypothyroidism. A prospective, well-controlled study by Jonklaas and colleagues compared circulating T3 and T4 levels in 50 patients before and after they underwent near-total or total thyroidectomy.¹³ LT4 monotherapy resulted in normalised T3 levels in patients, further suggesting that T3 treatment is not required to achieve the usual endogenous levels of T3¹³ although not all studies confirmed these findings (see below). Research in rats has indicated that, in certain tissue types, increased T4 levels inhibit endogenous conversion of T4 to T3; however, it is acknowledged that this effect is likely to be relatively modest in humans because of interspecies differences in peripheral conversion.¹⁴ Despite this,

there remains a persistent concept that addition of LT3 has a role in the treatment of hypothyroidism, that is, to improve persistent symptoms.¹⁵ Others point to findings that approximately one-fifth of thyroidectomised patients treated with LT4 in a large retrospective study did not have free T3 or free T4 in the reference range although TSH levels were normal.¹⁶ They argue that conversion of LT4 to T3 is not adequate in some patients, who may benefit from addition of LT3 to ameliorate lingering symptoms. However, the study itself did not evaluate such symptoms, so it is not known whether values of free T3 and free T4 outside the reference range were associated with or responsible for continuing complaints in euthyroid patients receiving LT4.16 Across clinical studies, patients with hypothyroidism who attained normal TSH levels with LT4 treatment had free LT3 levels that were, in general, statistically lower than controls (although often still in the expected laboratory range) and free T4 levels that were generally within normal limits although mean values were higher than in control subjects. However, there were many variations in the dosing, TSH results and timing of the blood draw in relation to ingestion of LT4 among these studies, which likely affected the observed levels of T3, T4 and T4/T3 that were reported.¹⁶⁻²⁵

1.3 | Hypotheses supporting LT3 replacement: Genetic evidence

What is the proposed biological rationale for considering LT3 in combination with LT4?

In the periphery, T4 is converted to T3 by deiodinases.²⁶ Several single-nucleotide polymorphisms have been identified in deiodinase genes, and relationships between thyroid hormone levels and 2 polymorphisms in the deiodinase type 2 (D2) gene, D2-Thr92Ala²⁷ and D2-ORFa-Gly3Asp,²⁸ have been investigated. Theoretically, polymorphisms could result in lower enzyme activity and therefore less conversion of T4 to T3 in the periphery, with even small changes in hormone levels having important long-term consequences.²⁷ Individuals with such polymorphisms potentially would require LT3 replacement to attain euthyroidism. There is no clear evidence, however, to support relationships between D2 gene polymorphisms, thyroid parameters and negative clinical consequences.

In initial studies, the D2-ORFa-Gly3Asp polymorphism, but not the D2-Thr92Ala polymorphism, was correlated with lower levels of some circulating thyroid hormones, including plasma T4 and free T4 but not T3 or free T3.^{27,28} In an early clinical trial (N = 141), however, no relationship was seen between either D2 polymorphism and neurocognitive outcomes, well-being, or treatment preference in patients randomised to double-blind treatment with LT4 alone or LT4/LT3 combination therapy.²⁹ A larger post hoc analysis ³⁰ examined patients (N = 552) receiving stable LT4 monotherapy who either remained on monotherapy or were switched to LT4/LT3 combination therapy for 12 months.³¹ Despite a large placebo effect in both treatment groups, a small but statistically significant between-treatment difference of 2.3 points on the General Health Questionnaire (GHQ)–12 was seen at 3 months that favoured LT4/LT3 therapy versus LT4 monotherapy

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in patients with the D2-Thr92Ala polymorphism; however, the difference of 1.4 points at 12 months was not significant. No differences were observed in thyroid hormone levels with LT4/LT3 treatment, however, and, most importantly, the study was underpowered to detect gene-treatment interactions because of the low frequency of this polymorphism in the population (16%).³⁰

Most recently, the effects of the D2-Thr92Ala polymorphism were investigated in a cross-sectional study of 12 625 participants from the LifeLines cohort, including 364 (88% female) patients who received LT4 treatment.³² In both populations, no correlations were noted between the polymorphism and thyroid parameters, health-related quality of life (QoL), cognitive functioning, the presence of metabolic syndrome, or the use of blood pressure or cholesterol-lowering drugs.³² However, the women receiving LT4 (only 52% of whom had a TSH level in the expected range) had impaired QoL, compared with age- and body mass index (BMI)-matched healthy controls, and authors speculated that this impairment may have been related to comorbid conditions.³² Given that these recent results contradict earlier research, further studies are needed to fully understand the implications of D2 polymorphisms in the treatment of overt hypothyroidism.

1.4 | Associations between thyroid hormone levels and patient-reported symptoms

The patient in our case presentation has reported symptoms of continued fatigue, hair loss and "brain fog" that she associates with her diagnosis of primary hypothyroidism. What is the evidence that such symptoms are associated with thyroid dysfunction when TSH levels have been consistently within the normal range for more than 1 year?

Several studies that have evaluated associations between patientreported symptoms and the presence of overt hypothyroidism suggest that symptoms, even in newly diagnosed patients, may not reliably signal the existence of the hypothyroid condition. One study found that, on average, patients newly diagnosed with hypothyroidism (n = 76) reported experiencing 30.2% of symptoms from a panel of 17 traditional hypothyroid symptoms, whereas matched euthyroid controls (n = 147) reported experiencing 16.5% of those symptoms, a difference that was significant. However, only two symptoms that were present, hoarse voice and muscle cramps, remained significantly associated with hypothyroidism in multivariate analysis.³³ Patients who reported changes in ≥7 symptoms from a panel of typical traditional hypothyroid symptoms in the past year were significantly more likely to be hypothyroid.³³ However, it should be noted that many patients newly diagnosed with overt hypothyroidism complain of no or few current or changed symptoms.³³ The same investigators demonstrated that the percentage of euthyroid and hypothyroid patients presenting with a series of individual symptoms was quite similar, further illuminating the difficulty that clinicians may have in detecting overt hypothyroidism by symptoms alone when confronted with an array of nonspecific complaints.³⁴ Additionally, more than 15% of euthyroid individuals complain of more than four typical hypothyroid symptoms,³⁴ making confirmation of an actual hypothyroid state (which would be likely to favourably respond to thyroid replacement) all the more difficult in the

Author, Year	Patients	Study design	Treatments	Key findings
Smith et al, 1970 ⁵⁴	Patients treated for hypothyroidism with 200 or 300 µg T4 ≥ 6 mo; judged to be euthyroid (n = 87 completers)	Double-blind crossover with two 2-mo periods	Same dose of LT4 alone (200 or 300 μg/d) or in combination with LT3 in an LT4 (80 μg):LT3 (20 μg) ratio of 4:1 per tablet	 Significantly higher rate of AEs during LT4/LT3 treatment vs LT4 monotherapy 18% preferred LT4/LT3; 33% preferred LT4; 48% had no preference
Studies concluding tha	t LT4/LT3 combination therapy is objective	ely superior to LT4 monotherapy		
Taylor et al, 1970 ⁵⁵	Patients who had thyroidectomy for nodular goitre or thyroid cancer (n = 13)	Observational	LT4 and LT3 with an LT4:LT3 ratio of 9:1, subsequently changed to 4:1, and then further modified to 3.33:1; 1-3 tablets depending on whether patient felt "completely well"	 The combination maintained the euthyroid state Author opinion: particularly good for patients not entirely well with LT4 alone
Bunevicius et al, 1999 ⁴⁴	Patients with chronic autoimmune thyroiditis or thyroid cancer (n = 33 completers) treated by near-total thyroidectomy who were receiving LT4 (100-300 μ g/d) at a stable dose for ≥3 mo	Randomised, blinded crossover with two 5-wk periods	LT4 at usual dose or minus 50 μg and adding LT3 (12.5 μg) with LT4:LT3 ratios ranging from 3:1 to 15:1 (12.5 μg) with compare the state of the stat	 Mean TSH levels were within normal levels and similar after both treatments (<i>P</i> = .56) Several cognitive tests (Digit Symbol and Digit Span tests) and mood subscales (global score, fatigue-inertia, depression-dejection and anger-hostility) significantly favoured combination treatment Significantly more patients favoured combination therapy (<i>P</i> = .001)
Bunevicius and Prange, 2000 ⁴⁵	Further analysis of Bunevicius et al, 1999, by diagnostic group (n = 11, autoimmune thyroiditis; n = 15, thyroid cancer)	Randomised, blinded crossover with two 5-wk periods	LT4 at usual dose or with LT3, with LT4:LT3 ratios ranging from 3:1 to 15:1	 Cognitive and mood benefits of combined treatment were significant only in patients in the thyroid cancer diagnostic group
Bunevicius et al, 2002 ⁴³	Female patients with subtotal thyroidectomy for Grave disease, receiving LT4 $\gtrsim 100~\mu g/d~(n=10~completers)$	Randomised, double- blind, crossover study with two 5-wk periods	Usual dose (100 or 150 μg/d) or usual dose minus 50 μg LT4 with addition of 10 μg LT3 (ratios of 5:1 or 10:1)	 No statistically significant differences observed with combination LT4/LT3 vs LT4 monotherapy 6 patients preferred combination therapy, 2 patients preferred monotherapy and 2 had no preference
Nygaard et al, 2009 ⁵⁰	Patients with spontaneous hypothy- roidism at diagnosis; stable LT4 treatment for ≥ 6 mo and TSH 0.1-5.0 mIU/L at screening (n = 59 completers)	Randomised, double- blind, crossover with two 12-wk periods	LT4 alone or minus 50 μg LT4 with addition of 20 μg LT3 at a mean LT4:LT3 ratio of 4:1 (range, 2.5:1 to 8:1); doses of LT4 adjusted at 4 wk (open-label) to maintain BL TSH levels	 A significant placebo effect was seen (10/11 measures); beneficial effects were seen with combination LT4/LT3 vs LT4 monotherapy only on QoL and depression (7/11 measures) 49% preferred LT4/LT3; 15% preferred LT4; 35% had no preference
				(Continues)

 TABLE 1
 Studies of LT4 monotherapy versus LT4/LT3 combination therapy

Author, Year Studies without objec	Patients tive differences but concluding LT4/LT3 con	Study design mbination therapy is subjectivel	Treatments y preferred over LT4 monotherapy by patients	Key findings
Appelhof et al, 2005 ⁴²	Patients receiving adequate LT4 replacement for primary autoim- mune hypothyroidism ≥ 6 mo (n = 130 completers)	Randomised, controlled, 15-wk trial	LT4 alone (n = 48), LT4:LT3 ratio of 10:1 (n = 46), or LT4:LT3 ratio of 5:1 (n = 47), provided in blister packs; study medication was adjusted at 5 wk as needed based on TSH level	 Primary outcome, patient preference for treatment, was in favour of LT4/LT3. Trend for increasing proportion of patients expressing preference for study treatment with increasing proportion of LT3 (LT4 alone, 29%; LT4:LT3 10:1, 41%; LT4:LT3 5:1, 52%); but preference for study medication correlated with weight loss, not decrease in TSH TSH levels decreased from BL with all 3 treatments; to a greater extent (to below normal levels) in patients receiving LT4/LT3 Significant weight loss occurred in patients who received LT4:LT3 5:1; no significant differences between treatments for improvements on QoL questionnaires; no clear pattern by treatment of changes on cognitive tests
Escobar-Morreale 2005 ²²	Women diagnosed with overt primary hypothyroidism with maintained normal TSH with stable LT4 100 μ g for \ge 1 y (n = 26 completers)	Randomised, double- blind, crossover design with three 8-wk periods	14 patients received LT4 100 μg alone for 8 wk, followed by LT4 75 μg + LT3 5 μg (LT4:LT3 ratio of 15:1) for 8 wk (n = 13), followed by LT4 87.5 μg + LT3 7.5 μg (LT4:LT3 ratio of 12:1; add-on combination) for 8 wk (n = 12) 14 patients received LT4 75 μg + LT3 5 μg for 8 wk, followed by LT4 100 μg alone for 8 wk, followed by LT4 87.5 μg + LT3 7.5 μg for 8 wk	 After the first treatment period, no differences were seen between LT4 vs combination therapy except in backward and total Digit Span tests (primary assessments) Add-on combination (second 8-wk period) represented over-replacement, with levels of TSH below the normal range in 10 patients (primary assessment); no other differences were noted between LT4 and the add-on combination except for the copies score of the Digit Symbol Substitution test and completion time on the Visual Scanning test (primary assessments). At study end, 12 patients preferred combination treatment, 2 preferred LT4, 6 preferred the add-on combination, and 6 had no preference (primary assessment); note that add-on combination threapy was always last and thus effectively unblinded

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Author, Year	Patients	Study design	Treatments	Key findings
Studies concluding the	at LT4 monotherapy should remain standar	d therapy		
Levitt and Silverberg, 2002 ⁴⁹	Euthyroid patients with hypothyroid- ism treated with stable LT4 doses, with ≥ 1 persistent symptom of hypothyroidism (n = 59 completers)	Double-blind, 3-6 mo study (outcome was evaluated once TSH levels were normal for 2 mo)	Twice-daily dosing with LT4 at the current dose or LT4/LT3 at a ratio of 15:1	 There was no group or group-by-time interaction on the Sunnybrook Hypothyroid Symptom Severity scale or Clinical Global Impression of Improvement Although no overall advantage was seen with LT4/LT3 vs LT3, the patients with greatest reduction in LT4 equivalent dose had the greatest improvement on outcome measures Improvement in symptoms was correlated with changes in lipids
Clyde et al, 2003 ⁴⁶	Patients with primary hypothyroidism receiving stable doses of LT4 for ≥ 3 mo (n = 44 completers)	Randomised, double- blind, placebo- controlled, 4-mo study	22 patients continued LT4 monotherapy (mean dose at BL, 131 μ g/d); 22 received LT4 + LT3 with 50 μ g of the usual dose (mean dose at BL, 126 μ g/d) substituted with 7.5 μ g LT3 twice daily; doses adjusted every 5 wk as needed to maintain TSH in the normal range	 Serum TSH levels in both groups were similar at BL and 4 mo No between-treatment differences were seen on assessment of QoL: 1 of 13 neurocognitive assessments was significantly different in favour of monotherapy
Sawka et al, 2003 ⁵²	Patients with diagnosed primary hypothyroidism receiving a stable dose of LT4 for 6 mo, normal BL T5H, and symptoms of depression (n = 40)	Randomised, double- blind, controlled, 15-wk study	20 patients allocated to continued LT4 (mean dose, 120 μ g) and 20 to LT4/LT3 (prestudy dose of LT4 [mean dose, 132 μ g] was dropped by 50% and LT3 started at 12.5 μ g twice daily)	 Mean TSH concentrations remained in the normal range during the study; there was no significant treatment effect on TSH level No between-group differences were seen on measures of mood or well-being
Walsh et al, 2003 ⁵⁷	Patients with primary hypothyroidism diagnosis of ≥ 6 mo, stable LT4 dose of ≥ 100 µg in previous 2 mo, and serum TSH between 0.1 and 4.0 mIU/L; included patients satisfied/not satisfied with treatment (n = 110; 101 completers)	Double-blind, randomised, controlled, 2-group, crossover design for two 10-wk treatment periods, separated by 4 wk of T4 alone	56 patients allocated to LT4, followed by LT4/LT3; 54 patients were randomised to LT4/LT3, followed by LT4. LT4 was received at patients' usual dose; for combined treatment, daily LT4 dose was reduced by 50 μ g and replaced with 10 μ g LT3 (liothyronine)	 No between-treatment differences were noted in treatment satisfaction scores No significant differences were found on most QoL or cognitive assessments; any significant differences favoured LT4 treatment alone Among patients who were satisfied (n = 46) or unsatisfied (n = 55) with treatment at BL, no differences in QoL or cognition were seen
Siegmund et al, 2004 ⁵³	Patients with hypothyroidism receiving stable long-term LT4 replacement therapy (100-175 μg; n = 23 completers)	Randomised, double- blind, crossover study with two 12-wk periods	LT4 was received at the same dosage or 95% of LT4 dose with 5% substituted with LT3 (LT4:LT3 ratio equivalent to an absorbed molar mixture of 14:1), administered in matching blinded capsules. After 6 wk in each period, treatment was adjusted to control hormonal/metabolic parameters	 TSH was more strongly suppressed by LT4/LT3 vs LT4 alone; mean TSH values were within the normal range There were no significant differences overall in mood or cognitive function with LT4/LT3 vs LT4 alone Patients with TSH <0.02 mlU/L with LT4/LT3 had significantly more depressive symptoms

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Author, Year	Patients	Study design	Treatments	Key findings
Rodriguez et al, 2005 ⁵¹	Patients receiving LT4 and normal TSH for ≥ 3 mo (n = 27 completers)	Randomised, double- blind, crossover design with two 6-wk periods	Patients received their usual dose of LT4 or the usual dose of LT4 minus 50 μg with the addition of 10 μg LT3 (ratio of substituted LT4/LT3 was 5:1)	 No significant between-group differences were seen in measures of fatigue, depression, working memory No significant between-group differences were seen regarding hypothyroid symptoms Among the 27 who completed the study, 7 preferred LT4, 8 had no preference and 12 preferred LT4/LT3
Saravanan et al, 2005 ³¹	Patients who were receiving LT4 \ge 100 µg, TSH within normal limits for the past 15 mo and no LT4 dose adjustment in the past 3 mo (n = 697; n = 573 analysed)	Randomised, parallel- group, controlled, 12-mo trial	Patients received their original dose of LT4 (n = 353) or the original LT4 dose minus 50 μ g with the addition of 10 μ g LT3 (n = 344)	 No significant differences between treatments were noted on measures of well-being at 3 or 12 mo, except GHQ-12 and HADS at 3 mo (not sustained at 12 mo) Authors noted that the placebo effect in this study was large and sustained
Valizadeh et al, 2009 ⁵⁶	Patients receiving LT4 for ≥ 6 mo and at a stable dose for ≥ 3 mo, sufficient to normalise TSH (n = 71)	Randomised, double- blind, parallel-group, 4-mo study	Patients received their usual dose of LT4 (n = 35) or the original LT4 dose minus 50 µg with the addition of 6.25 µg LT3 twice daily (n = 34) The average dose of LT4 was 100 µg/d; therefore, the typical ratio of LT4/LT3 was 4:1 LT4 dosages were adjusted after 1 mo as needed to normalise TSH levels	 No changes from BL in TSH levels in either group No significant changes from BL in weight, heart rate, blood pressure or lipids in either group No between-group differences found for psychosocial outcomes, except for GHQ-28 anxiety/insomnia subscore favouring LT4/LT3 combination therapy
Fadeyev et al, 2010 ⁴⁷	Premenopausal women with untreated overt primary hypothy- roidism (n = 36)	Randomised, controlled, non-blinded, 6-mo study	20 patients received LT4 1.6 μg/kg; 16 patients received LT4 1.6 μg/kg with the dose reduced by 25 μg and replaced by 12.5 μg of LT3	 No between-treatment differences in TSH were noted at BL or 6 mo Total and LDL cholesterol levels were significantly lower with LT4/LT3 vs LT4 No between-group differences in heart rates were observed A slightly greater increase was seen in a marker of bone resorption with combination treatment At the last visit, 10 patients expressed preference for combination treatment 18 expressed no preference
Kaminski et al, 2016 ⁴⁸	Patients aged 15-65 y, diagnosed with primary hypothyroidism, receiving stable doses of LT4 in the previous 6 mo (125 or 150 μ g/d; n = 32)	Randomised, double- blind, crossover study with two 8-wk periods	Usual dose of LT4 or 75 μg of LT4 + 15 μg of LT3 (LT4/ LT3 ratio 5:1)	 Free T4 levels were significantly lower and resting heart rate was slightly higher with LT4/LT3 vs LT4 monotherapy Other outcomes (QoL, lipids, BMI) were similar
AE, adverse event; BL LT3, levotriiodothyror	, baseline; BMI, body mass index; GHQ, Ge ine; TSH, thyroid-stimulating hormone.	eneral Health Questionnaire; I	HADS, Hospital Anxiety and Depression Scale; LDL, low-den:	sity lipoprotein; QoL, quality of life; LT4, levothyroxine;

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absence of sensitive thyroid function testing of TSH, with or without testing of free T4.³⁵ These investigations support the need to objectively document the presence of a hypothyroid state with appropriate thyroid function tests before initiating any form of thyroid hormone replacement^{1,36} because relying on symptoms of hypothyroidism to generate changes in replacement may be fraught with imprecision.

A large questionnaire-based study found that levels of psychological well-being were slightly but significantly lower in 597 patients receiving LT4 to correct hypothyroidism compared with 551 age- and sex-matched controls without thyroid disease (mean GHQ-12 score, 12.09 vs 11.39, respectively; mean Thyroid Symptom Questionnaire [TSQ] score, 12.55 vs 11.52).³⁷ However, the results may have been confounded by inclusion bias; patients receiving LT4 may have associated lower levels of well-being with their diagnosis of thyroid dysfunction and would have been more likely to have responded to a questionnaire investigating symptoms of hypothyroidism.³⁸ Furthermore, symptoms in some patients may have been due to subclinical hypothyroidism resulting from LT4 under-treatment; this condition would not have been detected based on the way that the normal range of TSH was calculated in the study.³⁸

Quality of life and hypothyroid symptoms have been investigated in patients who, like the woman in our case, were receiving LT4 therapy to normalise TSH levels. In one study, the association between thyroid hormone levels and QoL measures was assessed in 697 patients with hypothyroidism (84% female [586/697]; mean age, 57.3 years) who had been receiving LT4 at a stable dose for \geq 3 months.³⁹ At the time of QoL assessment, 32% of patients had TSH levels outside the range of 0.3-4 mIU/L.³⁹ Analyses of the relationships between the GHQ-12 and TSQ scores with thyroid hormone measurements suggested that free T4 and TSH levels correlated with psychological well-being in the entire population, as well as in the subset with TSH levels within the normal range. No relationship, however, was observed between free T3 levels and well-being.³⁹

A second recent study investigated the relationship between thyroid hormone levels and QoL or fatigue in 143 patients (69.2% female; mean age, 50.2 years) who had recovered from total thyroidectomy and postoperative radioactive iodine (¹³¹I) remnant ablation for the appropriate treatment of thyroid carcinoma. These individuals had been receiving LT4 suppression at a stable dose for at least the previous 10 weeks and had median TSH levels of 0.042 mIU/L (below the expected range) and median T3 levels of 1.93 nmol/L (well within the expected range).⁴⁰ Overall, QoL was lower in these patients than in a reference population. No associations were noted between thyroid function test results (including TSH, free T4, total T4 and total T3) and measures of QoL or fatigue.⁴⁰ A determinant of QoL measures in these patients was the total number of medications with which they were being treated, but not whether they had been told they were cured of their cancer, had a higher BMI, or had developed hypoparathyroidism as a result of the surgery. QoL was also related to the time since their initial diagnosis of thyroid cancer, with increase in positive QoL associated with increasing time since the initial diagnosis. These findings suggested that the nonspecific complaints of fatigue or impaired well-being in patients with hypothyroidism are not predictably due to a deficiency of circulating T3 and would not be expected to improve by increasing either the LT4 dose or adding LT3 therapy.

A recently published study of NHANES data investigated whether 469 individuals who were receiving LT4 at doses sufficient to produce normal levels of TSH are similar to matched healthy control subjects in terms of thyroid function, thyroid-hormone-related markers and other clinical factors.⁴¹ Some differences in hormone levels and clinical parameters were identified in patients compared with healthy controls, including lower serum free and total T3, relatively higher serum free and total T4, and thus higher T4:T3 ratios. The values of free T3 and free T4 were no different in patients with higher normal TSH (\geq 1.75 mIU/L) compared with those with lower normal TSH (< 1.75 mIU/L). Overall, patients treated with LT4 were significantly more likely to be concomitantly treated with beta-blockers, statins and antidepressants than their matched controls, yet they had similar QoL and neuropsychiatric measures. In multivariate regression, the T4:T3 ratio was significantly associated with age and calorie consumption in patients treated with LT4 and with age and sex in matched controls.⁴¹ The authors concluded that LT4 treatment in patients with hypothyroidism, even when TSH is normalised, does not produce a euthyroid state because (for unknown reasons) BMI is higher although calorie intake and physical activity are lower than in healthy subjects.41

1.5 | Clinical studies of LT4/LT3 combination therapy versus LT4 monotherapy

The patient in the case presentation has asked about treatment with a combination of LT4 and LT3 instead of her current LT4 monotherapy. What is the clinical evidence that this therapeutic adjustment would improve her persistent symptoms?

1.5.1 | Individual studies

Studies comparing QoL, mood and cognitive outcomes and patients' preference for treatment with LT4/LT3 combination therapy versus LT4 monotherapy are described in Table 1.^{22,31,42-57} Among these 17 studies, 1 older study using very high LT4 and LT4/LT3 doses found that LT4 monotherapy had a more favourable adverse event profile and was preferred by patients versus LT4/LT3 combination therapy.⁵⁴ This study should likely be viewed from a historical perspective only because the conditions of treatment are dissimilar to the more modern studies listed below.⁵⁴ Of the remaining 16 studies, 4 (comprising five publications) found that LT4/LT3 combination therapy versus LT4 monotherapy produced improvements in QoL, mood and/or cognition.43-45,50,55 In two studies without obvious objective differentiation, the authors nonetheless noted a subjective preference for LT4/ LT3 combination therapy over LT4 monotherapy.^{22,42} The results of 10 studies, however, were neutral, finding no consistent advantage for monotherapy or combination treatment.^{31,46-49,51-53,56,57} Thus. the comparisons of LT4/LT3 combination therapy versus LT4 monotherapy produced mixed and equivocal results. It should be noted that there were large placebo effects in two of these studies: one that found an advantage with LT4/LT3 combination treatment and one in which results did not favour either treatment.^{31,50} This suggests that patients who undergo adjustment of thyroid hormones can experience changes in mood that may not be attributable to active treatment.

1.5.2 | Integrated analyses

Given the ambiguous and conflicting results of individual studies, several research groups have conducted integrated analyses to better discern the role of LT4/LT3 versus LT4 therapy in patients with hypothyroidism. It should be noted that the limited number of available published research articles resulted in a large overlap in source material among these integrated analyses; all of them included a common set of eight articles,^{22,31,42,44,46,52,53,57} in addition to several other articles that differed from analysis to analysis. In a systematic review of 9 controlled trials that included 1056 patients, no reproducible benefit in mood, QoL or psychometric performance was found with LT4/LT3 combination therapy compared with LT4 monotherapy.⁵⁸ A meta-analysis of 11 randomised trials (N = 1216) found no differences in bodily pain, depression, anxiety, fatigue, cognitive function or QoL outcomes in patients treated with LT4/ LT3 combination therapy versus LT4 monotherapy.⁵⁹ In 2007, a meta-analysis of nine controlled studies (N = 1141) also found that there was no significant difference between LT4/LT3 and LT4 therapy in measures of mood although the authors noted that combined treatment was the preferred treatment in the studies that measured patient preference (no preference, 23%; preference for LT4, 32%;

TABLE 2Potential causes of persistentsymptoms in euthyroid patients receivingLT4

preference for LT4/LT3, 46%).⁶⁰ The fourth integrated analysis, a meta-analysis of 10 randomised double-blind trials (N = 1153), found nothing but sporadic improvements associated with LT4/LT3 versus LT4 therapy in mood, cognitive function, QoL outcomes or adverse effects.⁶¹ By this analysis, no difference was noted in patient preference between treatment regimens.⁶¹

The four integrated analyses, by virtue of their large pooled sample size relative to individual studies, generally indicated few or no differences between the two therapeutic approaches (rather than identifying significant effects of LT4/LT3 combination therapy vs LT4 monotherapy noted in individual studies). This reinforces the overall conclusion that there is no reproducible clinical evidence to support the efficacy of LT4/LT3 over LT4 alone. A caveat for all LT4/LT3 combination studies should be noted, however: once-daily dosing of LT3 replacement therapy does not maintain a steady-state physiologic concentration of this molecule. Indeed, once-daily administration of LT3 is associated with peaks and troughs in T3 concentration,^{62,63} and serum T3 levels are more stable when patients are treated with LT4 alone compared with T3 alone.⁶⁴ The use of an alternative LT3 formulation⁶⁵ or LT3 dosing 3 times a day may be required to fully evaluate the effectiveness of combination treatment.^{36,62,66}

1.6 | Other considerations for LT4/LT3 combination therapy

As already described, individual results from most controlled studies and results from integrated analyses indicated that there were no significant differences in outcomes with LT4/LT3 or LT4 treatment.

Endocrine/autoimmune	Nutritional	Lifestyle
Diabetes mellitus	Vitamin B12 deficiency	Stressful life events
Adrenal insufficiency	Folate deficiency	Poor sleep patterns
Hypopituitarism	Vitamin D deficiency	Work-related exhaustion
Celiac disease	Iron deficiency	Alcohol excess
Pernicious anaemia	Metabolic	Others
Haematological	Obesity	Obstructive sleep apnoea
Anaemia	Hypercalcaemia	Viral and postviral syndromes
Multiple myeloma	Electrolyte imbalance	Chronic fatigue syndrome
End-organ damage	Drugs	Carbon monoxide poisoning
Chronic kidney disease	Beta-blockers	Depression and anxiety
Chronic liver disease	Statins	Polymyalgia rheumatica
Congestive cardiac failure	Opiates	Fibromyalgia

Adapted with permission from Okosieme O, Gilbert J, Abraham P, et al. Management of primary hypothyroidism: statement by the British Thyroid Association Executive Committee. *Clin Endocrinol (Oxf)* 2016; 84:799-808. LT4, levothyroxine.

TABLE 3 Clinical practiv	ce guideline recommendatior	ns regarding LT4 monotherapy	and LT4/LT3 combination treatment		
Association, Year	Treatment goals	LT4 monotherapy	LT4/LT3 combination	Thyroid extract	Role of genotyping
American Association of Clinical Endocrinologists/ American Thyroid Association clinical practice guidelines, 2012 ¹	Primary hypothyroidism (TSH levels > 10 mIU/L) should be treated to the target TSH range (in non-pregnant women) of 0.45-4.12 mIU/L	Patients should be treated with LT4 monotherapy	The evidence does not support using LT4/LT3 combination therapy	No evidence supports that desiccated thyroid hormone is better than LT4 monotherapy, and it should not be used	No role described
European Thyroid Association guidelines, 2012 ⁷³	Goal of LT4/LT3 therapy is to resolve persistent complaints despite a normal TSH in patients receiving LT4 monotherapy	Standard treatment should be with LT4 monotherapy	 LT4/LT3 therapy might be considered as an experimental approach when Patients compliant with LT4 have normal TSH but have persistent complaints Patients have already received support to deal with the chronic nature of hypothyroidism Associated autoimmune diseases have been ruled out 	Thyroid extracts should not be used; they may have high T3 levels that could be harmful	Data that suggest that well-being and preference for LT4/ LT3 therapy are influenced by polymorphisms are limited
American Thyroid Association guidelines, 2014 ³⁶	 Goals of LT4 replacement Provide resolution of the symptoms/signs, including biological and physiologic markers Achieve normal TSH, with improvement in thyroid hormone concentrations Avoid overtreatment, especially in elderly patients 	LT4 is recommended treatment per its • Efficacy in resolving symptoms • Long history of use • Favourable side-effect profile • Ease of administration • Good intestinal absorption • Long serum half-life • Low cost	No consistent strong evidence supports the superiority of LT4/ LT3 over LT4; the routine use of LT4/LT3 is not recommended	Not recommended owing to lack of data suggesting it is superior to LT4; safety concerns	Genetic testing is not recommended as a guide to selecting therapy
Position statement of the Italian Society of Endocrinology and the Italian Thyroid Association, 2016^{71}	Goal of LT4 therapy to restore clinical and biochemical euthyroidism	 Standard treatment based on known efficacy, long history of treatment, favourable biochemical profile and low cost Under- and over-treatment should be avoided owing to known adverse effects 	Although some LT4/LT3 combinations are available in Italy, they do not provide a correct physiologic combination These should be avoided Separate preparations of LT4 and LT3 should be used when combined treatment is indicated Routine use not recommended in adult hypothyroid patients with persistent symptoms, owing to insufficient evidence 	The routine use of thyroid extracts is not recommended because it may result in high serum T3 levels, causing symptoms of thyrotoxicosis	Evidence currently insufficient for guiding treatment
Italian Association of Clinical Endocrinologists guide for clinical practice, 2016 ⁷²	 Replacement therapy goals Resolution of symptoms/ signs of hypothyroidism Normal serum TSH and fasting FT4 levels QoL improvement 	LT4 should be the first choice for all hypothyroid patients	 LT4/LT3 is generally not recommended owing to a lack of evidence A trial may be considered when TSH values are symptoms remain and coexistent non-thyroid problems are ruled out 	Insufficient safety information exists to support the use of extracts to treat hypothyroidism	No recommendations
British Thyroid Association statement, 2016 ⁶⁸	Goals are to restore physical and psychological well-being and to normalise serum TSH	LT4 is the treatment of choice	 Evidence to support the superiority of LT4/LT3 over LT4 is lacking; T4 should be used routinely A trial could be considered in patients compliant with LT4 who have continued symptoms despite TSH values in the reference range if they have received adequate chronic disease support and other autoimmune diseases have been ruled out 	Routine use not recommended	Genetic characterisa- tion of polymorphisms is not recommended as a guide to the use of combination therapy

QoL, quality of life; FT4, free thyroxine; LT3, levotriiodothyronine; LT4, levothyroxine; TSH, thyroid-stimulating hormone.

However, the reports had aspects that limit the extent to which their findings can be extrapolated. The results were derived from relatively short-term trials, with the longest study extending 1 year.³¹ A large, long-term observational study with a maximum 17-year followup evaluated morbidity and mortality in patients treated with LT3 (n = 400; 327 patients received the LT3 with LT4, and 73 patients received LT3 alone) or LT4 alone (n = 33 955).⁶⁷ No statistically significant between-treatment differences were observed in the incidences of death, cardiovascular disease, atrial fibrillation, diabetes or fracture outcomes.⁶⁷ The only difference that reached statistical significance was an increase in the new use of antipsychotic drugs, an effect that was associated with the use of LT3 (adjusted hazard ratio, 2.26 [95% CI, 1.64-3.11]; P < .01).⁶⁷ These data suggest that long-term treatment with LT3 is generally safe although the preponderance of longterm experience in the treatment of hypothyroidism involves LT4 monotherapy.

A common theme of analyses of patients with hypothyroidism is that they have poorer overall health relative to matched controls. Although statistical methods may be used to adjust for these confounding factors in a large population, this is impossible for the individual patient. Therefore, for patients receiving LT4 monotherapy and experiencing persistent symptoms despite normal TSH, alternative causes should be considered. It may be appropriate to investigate cardiac, renal, hepatic or metabolic conditions; concomitant drugs (including those taken over the counter); and other factors, such as lifestyle, nutritional deficiencies and sleep disorders (Table 2).⁶⁸ Among commercially available over-the-counter herbal and dietary supplements, some may contain variable but clinically relevant amounts of T3 and/or T4 that can cause thyrotoxic effects.^{69,70} Because the relationship between thyroid function and symptoms is loose, particularly in older patients, addressing these potential sources of symptoms often attributed to recalcitrant hypothyroidism may well be an avenue to clinical improvement.

At the very least, consideration of these alternative explanations for the nonspecific symptoms occurring in patients who otherwise appear hypothyroid seems inherently appropriate. Continued attribution of these symptoms to a hypothyroid state in the face of normal TSH may result not only in the misdiagnosis of some potentially serious conditions (Table 2), but also serious exacerbation of symptoms or threat to life if, for example, adrenal insufficiency goes unrecognised. Adjustment of the approach to thyroid hormone replacement by adding LT3 for nonspecific symptoms seems to lack a substantial predictive prospect of success. As the physician seeks the correct underlying cause of the symptom, the patient may require assurance that hypothyroidism is unlikely to be the problem.

1.7 | Guideline recommendations

Guidelines for the treatment of patients with hypothyroidism consistently recommend LT4 monotherapy as the treatment of choice, recommend against the routine use of LT4/LT3 combination treatment, and recommend against the use of desiccated thyroid extract. Recommendations from recent clinical practice guidelines on treatment goals, LT4 monotherapy, LT4/LT3 combination therapy, use of desiccated thyroid extract and the role of genotyping in the treatment of hypothyroidism are presented in Table 3.^{1,36,68,71-73} Additionally, these guidelines suggest that the clinical evidence is insufficient at present to use genetic polymorphisms to guide treatment.

A large survey was conducted among endocrinologists who were active members of The Endocrine Society, the American Thyroid Association (ATA), and the American Association of Clinical Endocrinologists (AACE) to assess current clinical practice⁷⁴ in the context of 2012 guidelines published by a joint task force of the AACE and ATA.¹ Regarding the use of LT4 versus LT4/LT3 for the treatment of hypothyroidism, more than 99% of 743 respondents indicated that they would choose LT4 for initial therapy, consistent with guideline recommendations.⁷⁴ For patients with persistent symptoms despite achieving normal TSH values with LT4, the survey showed that 84% of 843 respondents would test for other underlying causes for the symptoms, 11% would send the patient back to the primary care physician for further tests, 4% would add LT3 to LT4 and fewer than 1% would refer the patient to mental health services or increase the LT4 dose.⁷⁴ The authors speculated that the main reason for the low percentage of respondents who would add LT3 is the lack of clinical evidence for its benefit.⁷⁴

2 | SUMMARY

Our hypothetical patient, who continues to complain of symptoms despite achieving TSH levels consistently within the normal range with LT4 monotherapy, is based on a recognised subset of patients encountered in clinical practice. Available evidence suggests that her persistent symptoms will not be resolved by the addition of LT3 and that they may be due to factors other than thyroid dysfunction.

It is estimated that 5%-10% of patients with hypothyroidism treated with LT4 with normal TSH levels continue to experience nonspecific symptoms which may be attributed to hypothyroidism.⁷³ Current clinical evidence, however, is not sufficiently strong to support the use of LT4/LT3 combination therapy in patients with hypothyroidism. Several genetic polymorphisms have been investigated in an effort to explore potential mechanisms underlying unsatisfactory treatment results and to provide a predictive marker for success with LT4/LT3 combination treatment in patients who have persistent symptoms; however, results thus far have not been conclusive. Instead, persistent symptoms in patients who are biochemically euthyroid may be caused by several other conditions unrelated to thyroid function. A thorough investigation to determine other potential causes, including endocrine and autoimmune disorders, haematological conditions, end-organ damage, nutritional deficiencies, metabolic syndromes, concomitant drugs and lifestyle, is warranted.68

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AUTHOR CONTRIBUTIONS

This manuscript reflects the opinions of the authors and was initiated at the suggestion of J. V. Hennessey, who identified the need for a review on this topic, provided the primary organisation of the literature review, the scope of the endeavour, the focus of review, the methods for identifying the most recent literature and the addition of relevant citations of great clinical importance. Both authors were involved from the initiation of this project, reviewed the manuscript and provided extensive comment on the main clinical points to be emphasised, the limitations of the literature cited, and relevance of these limitations in applying the information to clinical care at all stages of development. The authors determined the final content, maintained complete control over the content, and read and approved the final manuscript. No payment was made to the authors for the writing of the manuscript.

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