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A Systematic Review of Clinical Practice Guidelines' Recommendations on Levothyroxine Therapy Alone versus Combination Therapy (LT₄ plus LT₃) for Hypothyroidism

Abstract

Purpose: Patients with hypothyroidism are increasingly enquiring about the benefit of using combination therapy of levothyroxine (LT₄) and liothyronine (LT₃) as a potential treatment for hypothyroidism. Combination therapy, however, remains controversial. The purpose of this study was to systematically review available hypothyroidism treatment recommendations from clinical practice guidelines from around the world to identify the consensus regarding combination therapy.

Source: Clinical practice guidelines were obtained from searches of PubMed, EMBASE, and MEDLINE, using several combinations of MeSH terms. The search was limited to clinical guidelines in English-language publications, published between January 1, 1990 and May 1, 2015. A quantitative approach was utilized for data synthesis.

Principal Findings: Thirteen guidelines were identified, including three regarding pregnancy, two regarding pediatric populations and eight regarding adult populations. There were six guidelines from North America, four guidelines from Europe and three guidelines from South America. Twelve of the guidelines were published after 2010. Nine guidelines addressed combination therapy of LT₄ plus LT₃, and all nine concluded that LT₄ therapy alone is the standard of care, with insufficient evidence to recommend widespread combination therapy. Only the 2012 ETA Guidelines and the 2015 BTA Guidelines concluded that combination therapy could be used, although only in certain circumstances and as an experimental treatment.

Conclusion: This systematic review illustrates that clinical practice guidelines worldwide do not recommend and do not support routine use of combination LT₄ and LT₃ therapy to treat hypothyroidism.

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Hypothyroidism is a common metabolic condition characterized by deficiency in endogenously-produced thyroid hormone. Prevalence studies have reported that hypothyroidism affects between 0.5% and 4.1% of the human population, with increased incidence in females and with advanced age [1,2,3]. Up to 3% of the population in Western countries are prescribed thyroid replacement therapy [4].

Standard treatment for hypothyroidism consists of oral administration of levothyroxine (LT4); a synthetic form of thyroxine (T4). Thyroid hormone was first isolated in the Mayo Clinic in 1915 [5] and synthesized in 1926 [6]. LT4 was first marketed in 1958 [7,8] and is now one of the most commonly prescribed medications in the United States [9].

The normal thyroid secretes both thyroxine and 3,5,3'-triiodothyronine (T3) into systemic circulation, in a T4:T3 ratio of roughly 5:1. T4 is subsequently deiodinated in peripheral tissues to form the remainder of an individual's T3, which is the active thyroid metabolite. Peripheral deiodination of T4 results in the vast majority of total daily production of T3 [10,11].

In hypothyroid patients, some continue to report inadequate control of symptoms, as well as generalized malaise, despite being on an appropriate LT4 dosage, with thyroid-stimulating hormone (TSH) levels in the normal range [12,13,14]. A large UK questionnaire in 2002 concluded that there was subjectively increased "impairment in psychological wellbeing" in hypothyroid patients, compared to sex- and age-matched controls [15]. This questionnaire analyzed the subgroup of patients on LT4 therapy with normal TSH values, and reported that this group also had comparatively higher survey responses of dissatisfaction with their current mental status. Interest has therefore increased in finding additional treatments to alleviate ongoing patient symptoms. Patients and patient groups have advocated for the use of synthetic T3 in treating hypothyroidism, believing that its addition to their regimen would create a more natural treatment plan [16,17]. Consequently, several studies have compared combination LT3-LT4 therapy with conventional LT4 monotherapy. Worldwide hypothyroidism treatment guidelines have been updated to address this issue.

The objective of this paper was to review, compare and contrast current hypothyroidism treatment guidelines from various global jurisdictions, in order to identify the consensus regarding combination therapy.

Methods

Clinical practice guidelines related to hypothyroidism treatment were obtained from a combination of scientific search

engines. The PubMed database was searched with the MeSH terms "hypothyroidism" and "treatment", while limiting article types to "practice guidelines" and "therapy". The search was limited to English-language, and published dates between January 1, 1990 and May 1, 2015. To ensure all possible guidelines were located, the PubMed database was again searched, without any restrictions, using the MeSH terms "hypothyroidism" and "guidelines".

The EMBASE database was searched, through the Ovid search engine, using the terms "hypothyroidism", with the limit "therapy", and combining it with a search for "practice guidelines". The MEDLINE database was searched, also through the Ovid search engine, using the search "hypothyroidism AND guideline".

The guidelines that were obtained were then reviewed to identify inclusion of a discussion regarding T3 treatment. For those that discussed T3 therapy, they were subsequently assessed if the guidelines favoured or did not favour T3 use. Finally, the original sources that had been used as references to form the various guidelines were reviewed.

Results

Thirteen clinical practice guidelines were located that were relevant to hypothyroidism treatment. The article search using the PubMed database (with restrictions) yielded 40 findings, of which nine were true clinical practice guidelines regarding hypothyroidism. The article search using the PubMed database (with no restrictions) yielded 440 results, of which 13 were true relevant guidelines. The article search using the EMBASE database yielded 23 findings, of which only two were true clinical practice guidelines related to hypothyroidism. The article search using the MEDLINE database yielded 103 findings, of which nine were true clinical practice guidelines related to hypothyroidism. Table 1 outlines the results of each database search.

In total, thirteen clinical practice guidelines were identified that detailed hypothyroidism treatment. Two of these guidelines were intended for pediatric populations, eight guidelines were intended for non-pregnant adults and three guidelines were intended for hypothyroidism during pregnancy. There were six guidelines from North America, four guidelines from Europe and three guidelines from South America. Twelve of the guidelines were published after 2010. Four of the thirteen acquired guidelines did not reference or comment on T3 use. The remaining nine guidelines, which made reference to combination therapy of LT4 and LT3, ultimately concluded that LT4 therapy alone should remain the standard of care. Each guideline cited insufficient supportive

TABLE 1. Results of Hypothyroidism Guidelines Found Through Database Searches

Results	PubMed (with restrictions)	PubMed (no restrictions)	EMBASE	MEDLINE
Included:	9	13	2	9
Excluded due to:				
Not a recognized primary guideline for hypothyroidism treatment	13	233	10	46
Not in English	4	22	4	15
Topic is not specifically on hypothyroidism	8	171	7	28
Duplicate publication	3	3	1	
Outdated edition	4	7	1	7
Total number of papers	40	440	23	103

TABLE 2. Hypothyroidism Guidelines

	Guideline (Jurisdiction)	Year	T3-T4 Combination Therapy
1	NAIM (Netherlands)	2008	Addressed – not recommended
2	ATA – Pregnancy (USA)	2011	Addressed – not recommended
3	ES - Pregnancy (USA)	2012	Addressed – not recommended
4	AACE/ATA (USA)	2012	Addressed – not recommended
5	ETA (Europe)	2012	Addressed – recommended with limitations
6	BSEM (Brazil)	2013	Not addressed
7	BSEM – Pediatrics (Brazil)	2013	Not addressed
8	LATS (Latin America)	2013	Addressed – not recommended
9	ATA (USA)	2014	Addressed – not recommended
10	TOP Working Group (Alberta)	2014	Not addressed
11	ESPE – Pediatrics (Europe)	2014	Addressed – not recommended
12	ACOG – Pregnancy (USA)	2015	Not addressed
13	BTA (UK)	2015	Addressed – recommended with limitations

See Appendix 1 for full listings.

evidence as their rationale for not recommending widespread standard use of combination therapy. Table 2 lists the identified guidelines, and summarizes their position on combination therapy. Table 3 summarizes the primary literature referenced in the various guidelines.

The 2012 European Thyroid Association (ETA) was the only organization to thoroughly address this issue, as combina-

tion therapy was the focus of a special 15-page report by a task force commissioned by the ETA to study this clinical question. The ETA ultimately determined that T3 treatment should only be considered as an experimental treatment, with specific caveats. The ETA did not recommend routine T3 therapy, and stated that its guidelines for T3 use were only to enhance its safety and counter its indiscriminate use. The main safety con-

TABLE 3. Primary Literature Referenced in Guidelines

	Paper (Article Type)	Year	Conclusion re: T3-T4 Combination Treatment	Referenced in Guidelines
1	Smith (RCT)	1970	-	ETA (ATA*)
2	Bunevicius (RCT)	1999	+	ATA, ETA, LATS, BTA
3	Bunevicius (RCT)	2002	+	ATA, ETA
4	Clyde (RCT)	2003	-	ATA, ETA
5	Walsh (RCT)	2003	-	ATA, ETA
6	Sawka (RCT)	2003	-	ATA, ETA
7	Cassio (RCT)	2003	-	ESPE
8	Siegmund (RCT)	2004	-	ATA, ETA
9	Appelhof (RCT)	2005	-	ATA, ETA, NAIM
10	Escobar-Morreale (RCT)	2005	-	ATA, ETA, BTA
11	Rodriguez (RCT)	2005	-	ATA, ETA
12	Saravana (RCT)	2005	-	ATA, ETA
13	Grozinsky-Glasberg (Meta-Analysis)	2006	-	ESPE, ETA, LATS, NAIM, BTA
14	Nygaard (RCT)	2009	+	ATA, ETA
15	Valizadeh (RCT)	2009	-	ATA
16	Ma Chao (Meta-Analysis)	2009	-	ETA, LATS
17	Fadeyev (RCT)	2010	-**	ATA

+ = favourable

- = unfavourable

* ATA noted this study, but it was not used in their analysis because the study dosages of LT4 were higher than are used in current clinical practice, and 1970 pre-dated using TSH measurements (therefore, patients may have been over-replaced).

** No symptom benefit, but favourable for lipid profile

cern referenced in the ETA guidelines was T3's unknown chronic effects, due to a lack of long-term data for combination therapy, especially for patients with bone disease or cardiovascular diseases other than cardiac arrhythmias. The ETA recommended a lower dose of LT3 than previously used in combination therapies, also stating that this was to enhance its safety.

The ETA recommends an experimental trial of T3-T4 combination therapy only for patients with ongoing symptoms despite good adherence to LT4 therapy, and a serum TSH within the normal reference range for over six months. The recommendations stipulated that, prior to commencing therapy, other autoimmune conditions must be ruled out, including type 1 diabetes mellitus, adrenal insufficiency and celiac disease. The ETA guidelines also recommended that the patient

should be provided with support to deal with the chronic nature of their disease. A trial of three months was recommended; if persistent symptoms did not improve after three months, T4 monotherapy was to be resumed. The ETA cautioned that there could be a placebo effect when determining symptom resolution, such that patients may initially report improved symptoms with combination therapy, but that symptoms may resume later. T3-T4 combination therapy was not recommended in patients at risk for cardiac arrhythmias, as an abrupt increase in serum T3 could provoke an arrhythmia. Also, its use was not recommended during pregnancy, due to insufficient data on fetal consequences. The ETA referenced eleven randomized, controlled trials (RCTs) investigating combination therapy. Three trials were favourable towards using T3-T4 combination therapy and eight did not support

combination therapy use. Two meta-analyses were referenced, both of which were not favourable towards combination therapy use.

The 2014 American Thyroid Association (ATA) recommended against the routine use of T4-T3 combination therapy as a form of thyroid replacement therapy. The ATA also recommended against routine use of a trial of combination therapy, outside of a formal clinical trial or N-of-1 trial, due to uncertainty of the long-term risks and benefits of the treatment and the uncertainty of what constitutes a successful trial. The ATA guidelines noted that previous trials have been limited by relatively short-term follow-up periods and that there is insufficient long-term outcome data. The ATA concluded that there was a lack of clear, consistent evidence of benefit of using combination therapy over established LT4 monotherapy, and there was no proven, reproducibly efficacious dose combination. Consequently, the ATA did not recommend individual experimental trials of combination therapy and indicated that high-quality RCTs were needed to prove if any specific subgroup of patients with primary hypothyroidism would specifically benefit from combination therapy. The ATA referenced 13 randomized, controlled trials investigating combination therapy. The ATA referenced the same three trials referenced in the ETA guidelines, which were favourable towards using T3-T4 combination therapy. The remaining ten trials, of which eight were also referenced by the ETA guidelines, concluded that there was no benefit to combination therapy.

The 2013 Latin American Thyroid Society (LATS) guidelines used the same references, including one study favouring combination therapy, and both of the meta-analyses previously discussed that did not support combination therapy. The LATS concluded that combination therapy was not recommended due to a lack of solid supportive evidence of clinical benefit. Their referenced evidence was quoted as Grade A.

The 2013 European Society for Paediatric Endocrinology (ESPE) referenced one trial that was conducted with a pediatric population and one meta-analysis, both of which were not favourable towards combination therapy. Only LT4 monotherapy was recommended, and the ESPE briefly stated there was no evidence of superiority of combination treatment. They cited the high degree of efficiency of endogenous deiodinases as an explanation for why adding LT3 would not have a clinical benefit.

The Netherlands Association of Internal Medicine (NAIM) 2008 Thyroid Function Disorders guidelines advised that T3-T4 combination therapy not be standard therapy for primary hypothyroidism. The NAIM guidelines referenced one meta-analysis and one large Dutch trial.

The Endocrine Society did not recommend using T3 in their guidelines on thyroid dysfunction in pregnancy (USPSTF recommendation Level C). In their guidelines for thyroid disease in pregnancy, the ATA strongly recommended not to use thyroid preparations other than T4 (USPSTF recommendation Level A).

In a statement published in May 2015, the British Thyroid Association provided a comparative overview of the ETA and ATA guidelines. Their statement highlighted that there is no proven evidence of benefit with T3-T4 combination therapy, and it should not be used routinely due to its potential for harm; however, they did state that if an endocrinologist chooses to embark on a trial of T3-T4 combination therapy, this should only be done for those who have unambiguously not benefited from T4, and following a complete discussion of the potential risks and benefits.

Discussion

Upon review of worldwide hypothyroidism treatment guidelines, and the primary research referenced within those guidelines, it is clear that the literature does not support widespread combination T3-T4 use in the treatment of hypothyroidism. International clinical practice guidelines reflect this lack of sufficient evidence.

It is noteworthy that relatively few of the worldwide endocrine and thyroid associations have published independent clinical practice guidelines on this topic. The guidelines reported here are the product of a thorough search for guidelines related to hypothyroidism. No treatment guidelines were located that specifically discussed hypothyroidism treatment in the following major global thyroid associations: Asia & Oceania Thyroid Association [18], Japan Endocrine Society [19], Korean Thyroid Association [20], or the Iran Thyroid Society. No relevant guidelines were published on these organizations' respective websites.

Most guidelines provide little discussion of combination T3-T4 treatment, or simply dismiss it as there being insufficient evidence to justify its use. The guidelines that did discuss combination therapy referenced essentially the same primary research in supporting their decisions. From our search, we found that fifteen RCTs have investigated combination therapy, with results that are heavily against the use of combination treatment. Three of the fifteen RCTs concluded that combination treatment was overall beneficial, and two of those were written by the same author. Two meta-analyses were found on this topic, and both concluded that LT4 treatment alone should be the standard of care.

The ETA's task force, however, recognized a potential possibility of benefit with T3, and suggested circumstances under which a trial of therapy may be warranted. In contrast, the ATA demurred, and concluded that there is not even enough evidence to recommend experimental office-based trials. Both guidelines were thorough in their analyses, and used the same primary literature; the differences appear to be differences of opinion and interpretation of the known facts on the part of the guideline authors.

The ATA specifically addressed the ETA's guidelines. Both guidelines agree that there is insufficient evidence that combination treatment is superior to monotherapy and that LT4 remains the standard of treatment. Both also strongly discourage T3 use during pregnancy. The pivotal difference between the two groups is that the ETA guidelines allowed for the consideration of combination therapy in specified situations, while the ATA guidelines concluded that the evidence does not permit even this reserved suggestion.

Additionally, the ATA noted that the outcome measure of success for combination treatment is difficult to quantify, as it relates to amelioration of subjective symptoms, and not correction of an objective abnormality, such as a T3 level. In fact, T3 levels are generally within the normal laboratory range on LT4 monotherapy and normal T3 levels have been achieved post-thyroidectomy with only traditional T4 replacement [21].

The ATA's report recognized that the "trial" approach to combination therapy, as described by the ETA, could possibly enhance the well-being of an individual patient; however, the ATA noted that this approach would provide no substantial conclusions about combination treatment. Its success and applicability for future patients, and thus its true role within hypothyroidism treatment, would remain unknown.

The ATA "stressed" that any experimental therapy must "meet professional and institutional ethical standards", and that additional high-quality RCTs are needed to prove if any specific subgroup of patients may actually benefit from combination therapy. These RCTs would need to track adverse effects, and examine long-term outcomes. Additionally, future RCTs could investigate patients on LT4, with normal TSH but low T3, and study if combination therapy raises their T3 while improving symptoms.

As noted above, there is some evidence that combination T3-T4 treatment may be beneficial in certain subsets of the hypothyroid population; for example, patients with a deficiency in type 2 deiodinase (DIO2) could result in decreased T3 in the brain, thereby potentially affecting psychological symptoms. The deiodinase enzymes catalyze the metabolism of T4 to T3 in peripheral tissues, by removing the 5'-iodine on

the outer ring of T4. Type 1 deiodinase occurs mainly in the liver, kidney and muscle, while type 2 deiodinase is found primarily in the central nervous system and adipose tissue. Type 3 deiodinase converts T4 into reverse T3 (rT3), an inactive product [22].

According to Panicker [23], hypothyroid patients on LT4 monotherapy with a specific single-nucleotide polymorphism (SNP) in the DIO2 gene scored higher in the General Health Questionnaire (indicating worse symptoms). No other SNPs, in DIO1 or DIO3, showed any significant changes on the survey. The SNP did not have any effect on baseline thyroid function. This same SNP was also shown to have an improved response to combination therapy. As this genetic polymorphism was only present in 16% of the patients in that study, the low prevalence would likely have been missed in the other RCTs, which were not sufficiently powered for this genetic subpopulation. Consequently, genetic polymorphisms in the DIO2 gene may predict who would benefit from T3-T4 combination therapy.

Nonetheless, an earlier report by Appelhof [24] specifically investigated patients with two different polymorphisms in type 2 deiodinase and concluded that these polymorphisms did not explain any differences in well-being, neurocognitive function, or appreciation for T3-T4 combination therapy. Clearly, further research in this area is warranted.

Conclusion

This systematic review illustrates the consensus of clinical practice guidelines worldwide, which do not recommend and do not support routine use of combination LT4 and LT3 therapy to treat hypothyroidism.

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