Physician Choice of Hypothyroidism Therapy: Influence of Patient Characteristics

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Background: Most endocrinologists encounter patients who are dissatisfied with their current hypothyroidism therapy and request combination therapy with either liothyronine (LT3) or thyroid extract.

Methods: A survey of American Thyroid Association members was conducted in 2017. Respondents were presented with 13 scenarios describing patients with hypothyroidism and were asked to choose among six therapeutic options. The index patient was satisfied taking levothyroxine (LT4) therapy. Twelve variations introduced parameters that potentially provide reasons for considering combination therapy (presence of symptoms, low serum triiodothyronine concentration, documentation of deiodinase polymorphisms). Therapeutic options included (i) continuing LT4, (ii) increasing LT4, (iii) adding LT3 to a reduced LT4 dose, (iv) adding LT3 to the current LT4 dose, (v) replacing LT4 with thyroid extract, and (vi) replacing LT4 with LT3. Repeated-measures logistic regression analysis was performed to examine both the prescribing of LT4 (options i and ii) versus all other therapies and the choice of continuing LT4 (option i) versus either increasing LT4 (option ii), adding LT3 (options iii and iv), or replacing LT4 with thyroid extract or LT3 (options v and vi).

Results: Of the 389 survey respondents, 363 physicians prescribed therapy for hypothyroidism. For the index patient, 98% of physicians continued current LT4 therapy. However, as the patient scenario incorporated other patient characteristics, physicians opted to increase LT4 dose or prescribe other therapies. The tendency to prescribe alternative therapies was powerfully increased by patient symptoms (odds ratio=25.6 [confidence interval 9–73], $p<0.0001$). Older age and the presence of a comorbidity reduced the likelihood that an alternative therapy was prescribed ($p=0.0002$ and <0.0001 , respectively). All other characteristics, except athyretic status, patient sex, and body mass index, significantly increased the likelihood that alternative therapies would be prescribed in multivariate analyses ($p<0.0001$).

Conclusions: Even with the acknowledged limitations of survey methodology, this analysis appears to show a marked increase in the willingness of physicians to prescribe combination therapy in specific circumstances. If current prescribing patterns do incorporate the use of therapies other than LT4, there is a critical need for more research into the benefits and risks of these therapies.

Keywords: hypothyroidism, combination therapy, liothyronine, thyroid extract, physician prescribing

Introduction

THE AMERICAN THYROID ASSOCIATION (ATA) guidelines for the treatment of hypothyroidism were published in 2014 (1). One of the issues that the guidelines task force was asked to examine critically was the issue of combination therapy with both levothyroxine (LT4) and liothyronine (LT3). At the time of the task force's original literature review, there were at least 13 studies that examined the issue of combination therapy (2–14). In addition, there were three meta-analyses and one systematic review (15–18). During 2012, as the task force updated the literature review, two

relevant guidelines (19,20) and one narrative review (21) were added to the literature. The European guidelines (19) and the narrative review (21) suggested that combination therapy could be considered under certain specific circumstances, whereas the 2012 American Association of Clinical Endocrinologists (AACE)/ATA guidelines (20) did not recommend combination therapy. The ATA guidelines concluded that there was insufficient evidence to recommend combination therapy (1). Since the publication of the 2014 guidelines, one additional original research study, which did not identify an advantage of combination therapy, has been published (22). In addition, the British Thyroid Association

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guidelines (23) have suggested that combination therapy could be prescribed and carefully monitored under certain circumstances, and a review of various guidelines (24) concluded that combination therapy was generally not favored. Most recently, the Italian Endocrine Society and the Italian Association of Clinical Endocrinologists have also suggested that combination therapy could be considered (25,26).

Since the 2014 hypothyroidism guidelines were published, there has been considerable reaction to the various guidelines, voiced by both physicians and patients. There are also some additional studies, since the 2009 study by Panicker *et al.* (27), regarding the consequences of deiodinase polymorphisms or impairment of deiodinase function, albeit mostly in animal studies (28), retrospective or cross-sectional rather than prospective studies (29–31), or small studies (30). The ATA conducted a Satellite Symposium at the Endocrine Society meeting in 2017 entitled “Hypothyroidism, where are we now?” The program committee for this symposium recently published the results of a survey querying patients about their level of satisfaction with their therapy, their co-existent medical conditions, and their general perceptions about hypothyroidism therapy and their treating physicians (32). The patient survey was posted on the ATA Web site, e-mailed to patients in the ATA database, distributed to members of the Alliance for Thyroid Patient Education, and further distributed on the Web sites and social media of multiple patient advocacy groups that are members of the ATA Alliance for Thyroid Patient Education. The results of the survey were used to generate discussion among a patient panel that was featured during the symposium. The survey found a low level of satisfaction among respondents with their therapy and also showed a greater level of satisfaction among patients taking thyroid extract. This survey was, by the nature of its distribution, subject to selection bias, in that patients with strong feelings about their therapy for hypothyroidism were presumably most likely to respond. In contrast, this report current describes the results of a survey of physicians about their choice of therapy for patients with hypothyroidism conducted in 2017.

Methods

Survey content and distribution

Prior surveys of ATA members have been conducted on topics covering subclinical thyroid disease (33), treatment of Graves’ disease (34), treatment of hypothyroidism (35), and management of thyroid nodules (36). These have generated 185, 157, 208, and 365 responses, respectively, from ATA members. In the wake of the previously cited diverse publications on the topic of hypothyroidism treatment, the current survey of physicians was designed to evaluate how the thyroid community in general has distilled and reacted to these multiple guidelines, reviews, and new literature on the topic of combination therapy. This survey of ATA members was designed to assess their opinions regarding the issue of hypothyroidism therapy, including combination therapy with either synthetic LT3 or desiccated thyroid extract (DTE). The survey questions are included as Supplementary Data (Supplementary Data are available online at www.liebertpub.com/thy). If survey respondents indicated that they did not prescribe therapy for hypothyroidism, they were thanked for their response, and branching logic was used to close the

survey. A link for the survey was distributed to ATA members via e-mail on several occasions in 2017. This analysis describes the responses obtained from the first deployment of the survey in February and March 2017.

The basic question was whether ATA member clinicians would consider combination therapy in a hypothyroid patient. The index patient was a 29-year-old female with Hashimoto’s hypothyroidism with normal vital signs and a body mass index (BMI) of 25 kg/m². She presented with overt hypothyroidism of at least five years duration, being compliant with therapy, and not considering pregnancy. Biochemical parameters included a thyrotropin (TSH) of 2.2 mIU/L (reference range 0.4–4.0 mIU/L), a free thyroxine (fT4) of 1.3 ng/dL (reference range 0.8–1.8 ng/dL), and a triiodothyronine (T3) value of 120 ng/dL (reference range 80–180 ng/dL). This index patient was doing well on replacement therapy. Twelve variations of this question then introduced further parameters that have been discussed in the literature as potentially providing reasons for considering combination therapy (presence of symptoms, low serum T3 concentration, documentation of deiodinase polymorphisms, etc.; see Table 1) (27,37,38). Physicians were asked to select from the following therapeutic response options for each of the 13 patient scenarios presented: (i) continue current LT4, (ii) increase LT4 dose, (iii) add 2.5 µg LT3 (Cytomel) twice daily and reduce LT4, (iv) add 2.5 µg LT3 (Cytomel) twice daily to current LT4, (v) replace LT4 with thyroid extract (e.g., Armour thyroid), or (vi) replace LT4 with LT3 (Cytomel) as single therapy.

Hypothesis to be tested by survey

The primary goal of the survey was to determine what patient-related factors affect the willingness of physicians to prescribe combination therapy. The full extent of factors considered were: (i) patient symptoms, (ii) patient serum TSH concentration, (iii) patient serum T3 concentration, (iv) patient request, (v) athyreotic state, (vi) patient preference, (vii) male sex, (viii) polymorphism status, (ix) patient age, (x) patient BMI, and (xi) patient comorbidities. The secondary goal was to determine which type of combination therapy or T3 therapy would be prescribed, if such therapy was considered. Additional predefined goals tested elsewhere were to determine what physician characteristics affected prescription of therapy and whether prescribing therapies changed over time.

Statistical analysis

Two different treatments of the data were applied. The first was a binary analysis examining whether a physician would prescribe LT4 versus any therapy other than LT4. Repeated-measures logistic regression analysis was used to examine the relationship between outcome “treatment type” and patient characteristics. The reference treatment type was LT4 (choices i and ii from the prescription options) versus anything other than LT4 (choices iii, iv, v, and vi from the prescription options). There were 13 responses for each physician, and the method of generalized estimating equations (GEE) was used to account for correlations among observations from the same participant. Multivariate repeated-measures logistic regression analysis was also conducted, controlling for all patient characteristics.

TABLE 1. PATIENT CHARACTERISTICS IN QUESTION STEM

	Question number												
	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Q17
Symptoms	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Serum TSH	2.2	2.2	3.9	2.2	3.9	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2
Serum T3	120	120	120	75	75	75	75	75	75	75	75	75	75
Requests LT3	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Athyreotic	No	No	No	No	No	No	Yes	No	No	No	No	No	No
LT3 preference	No	No	No	No	No	No	No	Yes	No	No	No	No	No
Male	No	No	No	No	No	No	No	No	Yes	No	No	No	No
Polymorphism	No	No	No	No	No	No	No	No	No	Yes	No	No	No
Age	29	29	29	29	29	29	29	29	29	29	59	29	59
BMI	25	25	25	25	25	25	25	25	25	25	25	32	25
Comorbidity	No	No	No	No	No	No	No	No	No	No	No	No	Yes

TSH, thyrotropin; T3, triiodothyronine; LT3, liothyronine; BMI, body mass index.

The second analysis examined the therapeutic response options grouped into four categories. The option to continue LT4 (option i) was used as the reference. The other therapeutic options were to increase LT4 (option ii), add 2.5 µg LT3 either with or without LT4 reduction (options iii and iv), and replace LT4 with thyroid extract or LT3 (options v and vi). The grouping of the response options was utilized due to the small numbers of these options chosen for some patient scenarios. Repeated-measures multinomial logistic regression analysis was used to examine the relationship between outcome “therapeutic option” and patient characteristics. There were 13 responses for each physician, and the method was used to account for correlations among responses from the same physician. Multivariate repeated-measures multinomial logistic regression analysis was also conducted, controlling for all patient characteristics. For both analyses, odds ratios with corresponding confidence intervals and *p*-values were calculated. Statistical significance was defined as *p* < 0.05.

Results

Physician respondents

A total of 389 individuals responded to the survey. Twenty-six individuals did not prescribe therapy for hypothyroidism and were excluded from any further analysis. Thus, the survey produced 363 first-time responses from physicians who routinely prescribe therapy for hypothyroidism. The responding physicians were 86% endocrinolo-

gists, with the other specialties represented being surgeons, nuclear medicine physicians, and “others.” Sixty-four percent of respondents were from North America, and 18% were from Europe. Twenty-three percent had been in practice for 10–20 years, and 53% had been in practice for >10 years.

Descriptive findings for a patient with symptoms

The percentage of respondents choosing each individual treatment option broken down by question number/patient scenario is shown in Table 2. Most respondents (approximately 98%) elected to continue LT4 in a biochemically euthyroid patient (TSH of 2.2 mIU/L, fT4 of 1.3 ng/dL, and T3 of 120 ng/dL) who was feeling well (question 5), with <2% of respondents choosing other options. Faced with a patient with symptoms but a normal biochemical evaluation (question 6), approximately 19% of respondents proposed an increase in the patient’s LT4 dose, 12% were willing to add LT3 with a reduction in LT4 dose, and 6% were willing to add LT3 to the current LT4 dose. When a symptomatic patient with a TSH of 3.9 mIU/L was presented (question 7), the preferred approach, chosen by 70% of physicians, was to increase the LT4 dose. Altering the biochemical profile to a TSH of 2.2 mIU/L and a slightly low T3 concentration of 75 ng/dL (question 8) resulted in increased use of LT3, with 18% of respondents adding LT3 combined with a LT4 dose reduction, and 15% simply adding LT3 to the current therapy with LT4. For a patient with a TSH of 3.9 mIU/L and a T3 of 75 ng/dL (question 9), the most frequently selected

TABLE 2. PHYSICIAN RESPONSE TO QUESTIONS REGARDING THERAPY

Therapeutic options	Percentage of respondents choosing each treatment option according to question number												
	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Q17
Continue LT4	97.8	61.6	22.6	44.5	14.6	32.0	28.1	22.6	31.4	16.5	39.2	29.7	47.0
Increase LT4	1.4	18.8	69.7	18.7	63.6	9.9	13.0	8.5	12.1	6.9	11.1	12.1	10.2
Add LT3, lower LT4	0.3	11.6	0.81	18.4	3.0	33.9	32.0	41.3	33.3	41.6	33.4	31.6	29.4
Add LT3 to LT4	0.3	6.4	6.1	15.1	17.4	17.9	21.5	23.1	18.5	28.7	11.3	21.2	8.8
Switch to DTE	0.3	1.4	0.8	3.3	1.1	6.3	5.5	4.4	4.7	3.3	5.0	5.2	4.4
LT3 only	0.0	0.3	0.0	0.0	0.3	0.0	0.0	0.0	0.0	3.0	0.0	0.3	0.3

LT4, levothyroxine.

options were to increase LT4 (64%) and to add LT3 to current LT4 (17%).

Descriptive findings with a patient request for T3

The remaining scenarios all incorporated a TSH of 2.2 mIU/L, a T3 of 75 ng/dL, and a patient request for T3 therapy, in addition to patient symptoms. The request for T3 therapy *per se* (question 10) was accompanied by 32% continuing LT4, 34% adding LT3 and lowering LT4, and 18% adding LT3. The combination of request for T3 therapy and postsurgical hypothyroidism (question 11) produced similar results, with 28% continuing LT4, 32% adding LT3 and lowering LT4, and 22% adding LT3. When a patient presented with a history of having preferred previously prescribed LT3 therapy (question 12), the most frequent therapy was addition of LT3 to a lowered LT4 dose (41%). Continuing LT4 alone and adding LT3 to LT4 were the chosen options in 23% of physicians in both cases. A male patient requesting LT3 (question 13) produced an almost identical prescribing pattern as for the otherwise similar female patient (question 10). For a patient with a documented polymorphism (presumed type 2 deiodinase variant; question 14), similar to the case of the patient with a stated preference for LT3, 42% of physicians chose adding LT3 with LT4 dose reduction. The choice of adding LT3 to the current LT4 dose was selected by 29%, the most frequent selection of this option among all the questions. An older patient, who was 59 years of age (question 15), was equally often prescribed LT3 with LT4 dose reduction as was a younger patient of 29 years of age (question 10; 33% vs. 34%), but was less often prescribed LT3 added to the same LT4 dose (11% vs. 18%). For a patient with an increased BMI of 32 kg/m² (question 16), the prescribing pattern did not substantially change compared to a similar patient with a BMI of 25 kg/m² (question 10). In the case of a 59-year-old female with osteoporosis, 47% of respondents would continue current LT4, 10% would increase LT4, 30% would add LT3 to a reduced LT4 dose, and 9% would add LT3 to the current LT4 therapy.

Switching to DTE alone was chosen as an option by <6.5% respondents across all cases, but was the option chosen by 3.3–6.3% of respondents in the cases of patients requesting LT3. LT3 as monotherapy was the most infrequent choice (mostly ≤0.3%), but 3% of physicians chose this therapy for patient with a deiodinase polymorphism.

Prescribing trends according to patient scenario and therapeutic options

The different therapeutic options chosen for each of the individual questions/patient scenarios are shown in Supplementary Figure S1. The trend to use LT4 monotherapy (blue bars) less frequently as the various patient characteristics that have been discussed as potential reasons for considering combination therapy are introduced can be seen, as the responses to questions 6–16 are examined (moving left to right across the graph). Use of LT4 monotherapy, however, increases slightly when a patient with osteoporosis is presented (question 17). The increased use of LT3, whether in conjunction with reduction or maintenance of LT4 (red and black bars), can also be seen moving from left to right across the graph. Continued use of LT3 in an older patient (question 15) and a male patient (question 13) can be seen, although ad-

dition of LT3 to current LT4 is less often chosen when older age (question 15) and the comorbidity of osteoporosis (question 17) is added to the patient characteristics. The response to each question grouped according to the six therapeutic options is shown in Supplementary Figure S2. The decreasing use of LT4 and increasing use of LT3 with progression through the sequence of questions/patient scenarios can be seen. The prescription of DTE with the patient scenarios presented in questions 10–17, which all incorporate a T3 concentration of 75 ng/dL and a request for LT3, can be seen (second grouping of columns from the right). Also illustrated on the extreme right of Supplementary Figure S2 is the selection of LT3 monotherapy by a small number of respondents in the case of a patient with a deiodinase polymorphism (question 14).

Analysis with binary therapeutic options

Univariate repeated-measures logistic regression analysis (GEE method) suggested that each of the patient characteristics except patient comorbidity influenced whether a physician prescribed LT4 versus a T3-containing therapy (see Table 3). The most influential factors in the univariate analyses were patient symptoms, T3 levels, request for T3, and presence of a polymorphism, and each of these made it more likely that the physician would prescribe T3-containing therapy. When multivariate repeated-measures logistic regression analysis was conducted to control for all patient characteristics, nonsignificant patient characteristics were athyreotic state, male sex, and BMI. The most influential characteristics were patient symptoms, T3 levels, TSH levels, presence of a polymorphism and request for T3 therapy (see Table 4), with each of these making it more likely that a physician would prescribe a therapy other than LT4 monotherapy. A stated preference also had a significant and positive effect with respect to prescribing T3. Being athyreotic, being a male, or having a BMI of 32 kg/m² (rather than 25 kg/m²) did not affect the therapy prescribed. Older age and the presence of a comorbidity made it significantly more likely the physician would prescribe LT4.

Multiple therapeutic options

When logistic regression analysis was performed to determine whether patient characteristics affected whether

TABLE 3. PATIENT CHARACTERISTICS AFFECTING PHYSICIAN PRESCRIBING OF LT4 VERSUS ANY T3-CONTAINING THERAPY—UNIVARIATE ANALYSES

<i>Patient characteristic</i>	<i>Unadjusted odds ratio [CI]</i>	<i>p-Value</i>
Symptom (Y vs. N)	101.4 [33.2–309.2]	<0.0001
T3 (75 vs. 120 ng/dL)	10.7 [8.6–13.2]	<0.0001
Requests LT3 (Y vs. N)	6.7 [5.7–7.9]	<0.0001
TSH (2.2 vs. 3.9 mIU/L)	5.4 [4.3–6.7]	<0.0001
Polymorphism (Y vs. N)	4.9 [4.1–5.9]	<0.0001
LT3 preference (Y vs. N)	3.2 [2.8–3.8]	<0.0001
Athyreotic (Y vs. N)	2.0 [1.8–2.3]	<0.0001
BMI (32 vs. 25 kg/m ²)	2.0 [1.7–2.2]	<0.0001
Male (M vs. F)	1.8 [1.6–2.0]	<0.0001
Age (59 vs. 29 years)	1.2 [1.0–1.3]	0.0169
Comorbidity (Y vs. N)	1.002 [0.86–1.17]	0.9828

CI, confidence interval.

TABLE 4. PATIENT CHARACTERISTICS AFFECTING PHYSICIAN PRESCRIBING OF LT4 VERSUS ANY T3-CONTAINING THERAPY—MULTIVARIATE ANALYSES

Patient characteristic	Adjusted odds ratio [CI]	p-Value
Symptom (Y vs. N)	25.6 [9.0–73.0]	<0.0001
T3 (75 vs. 120 ng/dL)	2.6 [2.1–3.3]	<0.0001
TSH (2.2 vs. 3.9 mIU/L)	2.4 [1.9–2.9]	<0.0001
Polymorphism (Y vs. N)	2.4 [1.9–2.9]	<0.0001
Requests LT3 (Y vs. N)	2.3 [1.9–2.8]	<0.0001
LT3 preference (Y vs. N)	1.6 [1.4–1.9]	<0.0001
Athyreotic (Y vs. N)	1.03 [0.9–1.2]	0.5634
BMI (32 vs. 25 kg/m ²)	1.0 [0.9–1.1]	0.8745
Male (M vs. F)	0.9 [0.8–1.1]	0.2827
Comorbidity (Y vs. N)	0.8 [0.7–0.9]	0.0002
Age (59 vs. 29 years)	0.7 [0.6–0.8]	<0.0001

physicians would prescribe continued LT4 (option 1) versus increasing LT4 (option 2) versus adding LT3 to the same or reduced LT4 (option 3) versus replacing LT4 with T3-containing therapy comprised of either DTE or LT3 (option 4), all patient characteristics appeared to be significant in the model ($p < 0.0001$; see Table 5). The unadjusted odd ratios and their confidence intervals are in the third and fourth columns of the table. When multivariate logistic regression analyses were performed, taking into account all patient characteristics, the athyreotic state, male sex, and BMI were no longer significant patient characteristics that affected physician prescribing patterns, with p -values of 0.1527, 0.7077, and 0.3589, respectively (shown in bold text in Table 6). All other characteristics remained significant (see right-hand column of Table 6).

Discussion

The results of this survey of physician members of the ATA conducted in early 2017 suggest that physicians taking care of patients with hypothyroidism are affected by patient characteristics, which strongly affect the particular therapies that they are willing to prescribe. This is despite the fact that the ATA guidelines for the treatment of hypothyroidism conclude that there is insufficient evidence to support prescribing T3-containing therapies (1,20), but in keeping with more recent recommendations from British and Italian Societies (23,25,26). Interestingly, a survey of ATA, Endocrine Society, and AACE members conducted in 2013 found that 0.8% of physicians would routinely use combination therapy containing LT3 for treating hypothyroidism, whereas 3.6% would use such therapy in a patient with symptoms. This contrasts with the present findings that as many as 18–41% of physicians would add LT3 therapy while reducing the LT4 dose, depending on the specific scenario, and that between 9% and 29% would add LT3 therapy while maintaining the LT4 dose, again depending upon the circumstances. The patient scenario most similar to the symptomatic patient described by Burch *et al.* in their survey (variation 1: persistent hypothyroid symptoms) is probably patient scenario #6, in whom 18% of respondents were willing to prescribe LT3 compared to the 3.6% in the prior survey.

When therapy was grouped as LT4 versus any other therapy, paramount among the factors that caused physicians to prescribe T3-containing therapies was patient symptoms,

TABLE 5. PATIENT CHARACTERISTICS AFFECTING PHYSICIAN PRESCRIBING CONTINUED LT4 VERSUS INCREASING LT4 VERSUS ADDING LT3 TO LT4 VERSUS REPLACING LT4 WITH T3-CONTAINING THERAPY—UNIVARIATE ANALYSES

Patient scenario	Therapeutic options	Univariate analyses		
		Unadjusted odds ratio	CI	
Symptoms (Y vs. N)	1 vs. 2	77.8	31.6	191.7
	1 vs. 3	582.0	80.9	>999.9
	1 vs. 4	331.3	77.2	>999.9
Serum TSH (2.2 vs. 3.9 mIU/L)	1 vs. 2	0.03	0.02	0.03
	1 vs. 3	10.5	5.8	18.8
	1 vs. 4	0.65	0.46	0.92
Serum T3 (75 vs. 120 ng/dL)	1 vs. 2	1.15	0.95	1.4
	1 vs. 3	34.0	24.0	48.1
	1 vs. 4	24.6	17.4	34.9
Requests LT3 (Y vs. N)	1 vs. 2	0.37	0.30	0.45
	1 vs. 3	26.1	19.9	34.2
	1 vs. 4	8.7	6.8	11.1
Athyreotic (Y vs. N)	1 vs. 2	0.88	0.60	1.3
	1 vs. 3	2.5	1.8	3.4
	1 vs. 4	3.0	2.1	4.3
LT3 preference (Y vs. N)	1 vs. 2	0.35	0.20	0.59
	1 vs. 3	5.0	3.6	7.0
	1 vs. 4	3.8	2.6	5.5
Male (M vs. F)	1 vs. 2	0.70	0.47	1.0
	1 vs. 3	2.3	1.7	3.2
	1 vs. 4	1.9	1.3	2.7
Polymorphism (Y vs. N)	1 vs. 2	0.78	0.47	1.3
	1 vs. 3	9.5	6.5	13.9
	1 vs. 4	12.3	8.2	18.4
Age (59 vs. 29 years)	1 vs. 2	0.36	0.27	0.48
	1 vs. 3	1.4	1.1	1.7
	1 vs. 4	0.52	0.39	0.70
BMI (32 vs. 25 kg/m ²)	1 vs. 2	0.76	0.51	1.1
	1 vs. 3	2.3	1.6	3.2
	1 vs. 4	2.7	1.9	3.9
Comorbidity (Y vs. N)	1 vs. 2	0.33	0.22	0.49
	1 vs. 3	1.0	0.78	1.4
	1 vs. 4	0.42	0.29	0.63

Option 1 = continuing LT4 (reference); option 2 = increasing LT4; option 3 = adding LT3 to same or reduced LT4; option 4 = replacing LT4 with DTE or LT3.

with an adjusted odds ratio of 25.6. Other factors favoring the prescription of therapy other than LT4 with odd ratios of 1.6–2.6 were serum T3 of 75 ng/dL rather than 120 ng/dL, TSH of 2.2 mIU/L rather than 3.9 mIU/L, presence of a deiodinase 2 polymorphism, request for T3, and stated preference for T3. Similar results were obtained when therapeutic options were continued LT4 versus increased LT4 (option 1 vs. option 2) compared with LT4 versus LT3 added to LT4 (option 1 vs. option 3), compared to LT4 versus T3 therapy with DTE or LT3 alone (option 1 vs. option 4), with adjusted odds ratio for the presence of symptoms being 48.8, 99.6, and 46.2, respectively. When symptoms were present, having a normal serum TSH, a low serum T3, a request for LT3, a preference for LT3, and a deiodinase polymorphism each independently affected the likelihood that a physician would add LT3 to LT4 with odds ratios of 3.5, 3.9, 6.6, 2.8, and 6.2, respectively. Older age and comorbidity decreased the likelihood of LT3 being added to LT4, with odds ratios of 0.57 and 0.55, respectively.

TABLE 6. PATIENT CHARACTERISTICS AFFECTING PHYSICIAN PRESCRIBING CONTINUED LT4 VERSUS INCREASING LT4 VERSUS ADDING LT3 TO LT4 VERSUS REPLACING LT4 WITH T3-CONTAINING THERAPY—MULTIVARIATE ANALYSES

Patient scenario	Therapeutic options	Multivariate analyses			
		Adjusted odds ratio	CI		p-Value for model
Symptoms (Y vs. N)	1 vs. 2	48.8	18.4	129.3	<0.0001
	1 vs. 3	99.6	13.3	748.5	
	1 vs. 4	46.2	9.2	232.3	
Serum TSH (2.2 vs. 3.9 mIU/L)	1 vs. 2	0.03	0.02	0.05	<0.0001
	1 vs. 3	3.5	1.8	6.8	
	1 vs. 4	0.22	0.13	0.35	
Serum T3 (75 vs. 120 ng/dL)	1 vs. 2	1.6	1.2	2.2	<0.0001
	1 vs. 3	3.9	2.4	6.5	
	1 vs. 4	8.0	5.0	12.8	
Requests LT3 (Y vs. N)	1 vs. 2	0.64	0.36	1.1	<0.0001
	1 vs. 3	6.6	3.9	11.1	
	1 vs. 4	3.8	2.2	6.7	
Athyreotic (Y vs. N)	1 vs. 2	1.9	1.0	3.7	0.1527
	1 vs. 3	1.1	0.65	1.9	
	1 vs. 4	1.6	0.9	3.0	
LT3 preference (Y vs. N)	1 vs. 2	0.51	0.24	1.1	<0.0001
	1 vs. 3	2.8	1.7	4.9	
	1 vs. 4	2.5	1.4	4.5	
Male (M vs. F)	1 vs. 2	1.4	0.71	2.7	0.7077
	1 vs. 3	0.97	0.57	1.7	
	1 vs. 4	0.90	0.50	1.7	
Polymorphism (Y vs. N)	1 vs. 2	1.4	0.66	3.1	<0.0001
	1 vs. 3	6.2	3.5	10.8	
	1 vs. 4	9.2	5.0	16.8	
Age (59 vs. 29 years)	1 vs. 2	0.77	0.40	1.5	0.0002
	1 vs. 3	0.57	0.34	0.96	
	1 vs. 4	0.26	0.14	0.48	
BMI (32 vs. 25 kg/m ²)	1 vs. 2	1.6	0.80	3.1	0.3589
	1 vs. 3	0.99	0.58	1.7	
	1 vs. 4	1.4	0.79	2.6	
Comorbidity (Y vs. N)	1 vs. 2	0.67	0.36	1.26	0.0423
	1 vs. 3	0.55	0.34	0.90	
	1 vs. 4	0.50	0.27	0.91	

Bold indicates nonsignificant *p*-values.

Option 1=continuing LT4 (reference); option 2=increasing LT4; option 3=adding LT3 to same or reduced LT4; option 4=replacing LT4 with DTE or LT3.

Thus, it would appear that there has been a shift in prescribing patterns since 2013, with a greater willingness to prescribe LT3-containing therapies. There is certainly an acknowledged patient desire for such therapies, and that shift could be due to patient requests. It would appear that the shift, however, is not due to additional evidence from clinical trials, as only one additional clinical trial has been conducted since 2009, and this was a negative trial (22). Prior trials have, with four exceptions, not shown any benefit with respect to improving health-related outcomes such as quality of life (4,8,13) or cognitive functioning (4,6). Five trials contributing 258 patients have shown patient preference for LT3 (2–4,6,8). However, two trials contributing 674 patients have not shown such preference (10,14). There are limited new data concerning polymorphisms (28–31), with no new trials of DTE since the study by Hoang *et al.* (39), but some new data addressing patient preferences (32). The authors speculate that the trend to prescribe combination therapy more frequently may be due to a desire to accommodate patient preferences and consider patient-centered outcomes.

Thus, while it is encouraging that physicians are listening to patients and partnering with them with respect to management of their therapy for hypothyroidism, it does appear that this trend is moving beyond current data. Some caution needs to be employed, as the risks of synthetic combination therapy have not been fully investigated (40). Trials of combination therapy have mostly been of short duration and thus were not designed to examine long-term side effects such as cardiac dysfunction or skeletal deterioration. Some reassurance of LT3 safety is provided by a study comparing outcomes in those prescribed LT4 only versus those prescribed LT4 and LT3. However, although the risk of fracture and atrial fibrillation were not increased, there was an increase in the prescription of antipsychotic medications and a trend for increasing prescription of antidepressants (41).

Similar to the situation with synthetic combination therapy with LT4 and LT3, combination therapy with thyroid extract has not been shown to improve mood or cognitive functioning (39). However, 49% of patients did prefer therapy with thyroid extract. A recent patient survey, with

acknowledged ascertainment bias, also suggested that patients preferred thyroid extract over other therapies (32). In the current study, DTE was prescribed by about 3–6% of physicians for patients with symptoms and low serum T3 levels, combined with the other various characteristics. In multivariate analyses, however, older age and the presence of a comorbidity reduced the likelihood of such prescription. There was little tendency to prescribe LT3 as monotherapy in any scenario, with one exception. Three percent of physicians chose to prescribe LT3 monotherapy for an individual with a deiodinase 2 polymorphism. This is interesting, as LT3 monotherapy has not been studied for this indication. The single study of LT3 monotherapy (42,43) was conducted in athyreotic participants, and the results were not analyzed according to polymorphism status.

This survey has important limitations, which may be representative of the limitations of surveys in general. First, the authors cannot claim that the propensity of ATA members to prescribe the different thyroid hormone options is similar to the prescribing pattern of non-ATA members who also treat patients with hypothyroidism. Second, it is possible that ATA members who are interested in prescribing combination therapy may have been more willing to respond to the survey than other members, thus artificially inflating the frequency of treatment using combination therapy. Third, it cannot be presumed that theoretical willingness to prescribe a therapy when surveyed would translate into similar practices when actually encountering a patient.

In conclusion, this recent survey shows that physicians are willing to prescribe combination therapy with synthetic LT3 under certain circumstances. Moreover, physicians are also willing to prescribe DTE, albeit at a low frequency. These practice patterns strongly highlight the urgent need for additional studies of these therapies. While there is a need not to withhold beneficial therapies, there is also a corresponding obligation to be cognizant of the potential risks of these therapies. Future studies should be pragmatic and study the population that is currently being treated (including older individuals, those with comorbidities, and men) and not just middle-aged women who have been the focus of most of the studies conducted thus far. In addition, these studies need to determine optimal dosing, optimal monitoring strategies, and the risks of long-term therapy. A long-term assessment of benefit-to-risk ratio is crucial, as hypothyroidism is a lifelong condition, and not a condition that remits after the several weeks to several months duration of most trials. Furthermore, given that benefits have not yet been shown in the population already studied, future studies should determine if specific subgroups, such as those with deiodinase polymorphisms or those who have undergone thyroidectomy, may in fact benefit. In addition, as some patients do in fact prefer LT3 combination therapy or therapy with DTE, but the benefits of these therapies cannot be detected in clinical trials, this highlights the need for more sophisticated studies, or studies based on patient-reported outcomes, so that the physiological underpinning of these preferences can be understood.

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