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Prescribing Therapy for Hypothyroidism: Influence of Physician Characteristics

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Background: Physician characteristics and perceptions and their effect on choice of therapies for patients with thyroid cancer have been well studied. Some data also exist about physician characteristics and prescribing treatment for subclinical hypothyroidism. The effect of physician characteristics on prescribing thyroid preparations for treating overt hypothyroidism is less studied.
Methods: Members of the American Thyroid Association were surveyed in 2017. Physicians were presented with 13 different theoretical patients with hypothyroidism and asked to choose among six therapeutic options, including levothyroxine, synthetic combination therapy, thyroid extract, and liothyronine monotherapy. The 13 patient scenarios incorporated parameters that potentially provide reasons for considering combination therapy (presence of symptoms, low serum triiodothyronine concentration, and documentation of deiodinase polymorphisms). Repeated-measures logistic regression analysis was performed to examine the prescribing of the various therapies. Data regarding the responding physicians were also collected. These data included number of years in practice, country of practice, and specialty. Multivariate repeated-measures logistic regression analysis of prescribing patterns was also conducted controlling for all patient and physician characteristics.
Results: Of the 389 survey respondents, 93% prescribed therapy for hypothyroidism. Fifty-three percent of respondents had been in practice for >20 years, and 23% had been in practice for 11–20 years. Sixty-four percent practiced in North America, and 18% practiced in Europe. Eight-six percent were endocrinologists, and 5% were surgeons. In multivariate analysis, physicians from North America were both more likely to prescribe any triiodothyronine-containing therapies (odds ratio [OR] = 1.8 [confidence interval (CI) 1.3–2.4]) and more likely to add liothyronine to levothyroxine therapy (OR = 1.9 [CI 1.2–2.9]). In addition, they were more likely to prescribe desiccated thyroid extract or liothyronine monotherapy (OR = 1.7 [CI 1.0–2.9]).
Conclusions: A previous analysis of this survey showed that patient characteristics profoundly affect physician prescribing patterns. The current multivariate analysis shows that physician characteristics affect prescribing patterns. Whether this is due to impact upon physicians of patient-related experiences, media exposure, influence from pharmaceutical companies, educational activities, or other concerns cannot be determined. However, these results have potential importance for understanding physician–patient interactions at a time when the benefits and risks of triiodothyronine-containing therapies have not been fully documented.

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

Introduction

Multiple guidelines concerning the treatment of hypothyroidism have been published. These guidelines originate from both North America and Europe, and have been published during a time period spanning 2012–2016.

The American Thyroid Association (ATA) Guidelines for the Treatment of Hypothyroidism were published in 2014 (1). At the time of the initial preparation of the guidelines, the preliminary literature review yielded at least 13 studies that examined the issue of combination therapy (2–14), as well as three meta-analyses and one systematic review (15–18). During 2012, an updated literature review revealed two additional guidelines from Europe and North America (19,20) and one narrative review authored by American and European experts (21). The European guidelines (19) and the narrative review (21) suggested that combination therapy with both levothyroxine (LT4) and liothyronine (LT3) could

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be considered under certain specific circumstances, whereas the 2012 American Association of Clinical Endocrinologists (AACE)/ATA guidelines (20) did not recommend combination therapy. The 2014 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 guidelines (23) have suggested that combination therapy could be prescribed and carefully monitored under certain circumstances. Most recently, the Italian Endocrine Society and the Italian Association of Clinical Endocrinologists have also suggested that combination therapy could be considered (24,25). None of these guidelines have supported the use of desiccated thyroid extract (DTE).

This current report describes the results of a survey of physicians about their choice of therapy for patients with hypothyroidism conducted in 2017. The goals of the survey were to determine which patient and physician characteristics affected prescribing and whether prescribing patterns changed over time. This analysis addresses the effect of the characteristics of the prescribing physicians on their prescribing patterns.

Methods

Survey content and distribution

This survey was designed to determine which therapy for hypothyroidism ATA members would prescribe for a particular patient. The study was approved by the Georgetown University Institutional Review Board, and the survey questions are included in the Supplementary Data (Supplementary Data are available online at www.liebertpub.com/thy). A link for the survey was distributed to ATA members via email on several occasions in 2017. This analysis describes the responses obtained from the first release of the survey in February and March 2017.

The index patient was a 29-year-old female with Hashimoto's hypothyroidism who was faring well on replacement therapy. She had normal vital signs and a body mass index of 25 kg/m^2. She was described as having overt hypothyroidism of at least five years duration, being compliant with therapy, and not considering pregnancy. Laboratory findings included a thyrotropin (TSH) value of 2.2 mIU/L (reference range 0.4–4.0 mIU/L), a free thyroxine (fT4) value 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). Twelve patient scenarios then introduced parameters that have been discussed in the literature as potentially providing reasons for considering combination therapy (presence of symptoms, low serum T3 concentration, a patient request for T3, documentation of deiodinase polymorphisms, etc.) (26–28) (see Table 1A). Physicians were asked to select from the following therapeutic 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 (see Table 1B).

Hypothesis to be tested by survey

One of the goals of the survey was to determine if any physician characteristics affected their choice of therapy for patients. The characteristics considered were: (i) number

Table 1. (A) Patient Characteristics in Question Stem and (B) Physician Response to Questions Regarding Therapy

	Characteristics present in question stem according to question number												
(A) Patient characteristics	*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, mIU/L	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, ng/dL	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
	Percentage of respondents choosing each treatment option according to question number												
(B) Therapeutic Options	*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, ↓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

TSH, thyrotropin; T3, triiodothyronine; LT3, liothyronine; BMI, body mass index; LT4, levothyroxine; DTE, desiccated thyroid extract.

of years in practice (in training [reference] vs. 5–10 years vs. 11–20 years vs. >20 years), (ii) country of practice (North America vs. South America vs. Europe vs. Asia vs. Other [outside North America = reference]), and (iii) area of specialty (endocrinologist vs. surgeon vs. nuclear medicine physician vs. internist or primary-care physician [reference] vs. other).

Statistical analysis

The results of the survey are initially presented as percentage of physicians selecting each therapeutic option for each patient scenario. Two different treatments of the data were then applied. The first was a binary analysis examining whether a physician would prescribe LT4 versus any therapy other than LT4. The second examined the therapeutic response options grouped into four categories. The grouping of the response options was utilized due to the small number of respondents choosing some of the response options.

For the binary analysis, repeated-measures logistic regression analysis was used to examine the relationship between the treatment chosen (LT4 [reference] vs. anything other than LT4) and both patient characteristics (reported in Jonklaas *et al.*) (29) and physician characteristics (reported here). The chosen therapy was coded as 1 if physicians prescribed anything other than LT4 (choices c, d, e, and f from the prescription options) and 0 if physicians prescribed LT4 (choices a and b from the prescription options). Thus, continuing LT4 and increasing LT4 were compared to the T3-containing therapy options. There were 13 responses for each physician, and the method of generalized estimating equations 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 (reported in Jonklaas *et al.*) (29) and physician characteristics (reported here).

For the second analysis, the therapy options were grouped as follows: continue LT4 (option a), increase LT4 (option b), add 2.5 μg LT3 either with or without LT4 reduction (options c and d), and replace LT4 with DTE or LT3 (options e and f). This comparison therefore has four groups in which increasing LT4 (#2), using LT3 added to LT4 (#3), or replacing LT4 with thyroid extract or T3 alone (#4) are compared with continuing the same LT4 (#1). The choice to ''continue current LT4'' was used as the reference. Repeated-measures multinomial logistic regression analysis was used to examine the relationship between the therapy chosen and patient characteristics (reported in Jonklaas *et al.*) (29) and physicians characteristics (reported here). Each physician has 13 responses, and this method was used to account for correlations among observations from the same physician. Multivariate repeated-measures multinomial logistic regression analysis was also conducted controlling for all patient characteristics (reported in Jonklaas *et al.*) (29) and physician characteristics (reported here). Additional analyses also examined detailed breakdown by country of practice. For both analyses, odds ratios with corresponding confidence intervals (CI) and *p*-values were calculated. Statistical significance was defined as $p < 0.05$.

Results

Physician respondents

The survey produced 363 first-time responses from physicians who routinely prescribed therapy for hypothyroidism. These responses represent 20% of the 2017 ATA membership of 1798. The responding physicians were 86% endocrinologists, 64% were from North America, and 18% were from Europe. Twenty-three percent had been in practice for 11–20 years, and 53% had been in practice for >20 years (see Table 2).

Descriptive findings for the patient scenarios

The percentage of respondents choosing each individual treatment option broken down by the 13 different patient scenarios is shown in Table 1B.

Table 2. Characteristics of Physicians Responding to the Survey for the First Time (Number of Respondents = 363)

Question regarding physician characteristic	*Response options*	*Percentage (%)*	*% ATA composition in 2017*
Do you prescribe and adjust LT4 therapy for patients with hypothyroidism?	Yes	100	
	No[a]	0	
How many years have you been in practice?	In training	2.8	
	<5 years	8.8	
	5–10 years	12.6	
	11–20 years	22.5	
	>20 years	53.3	
Where do you practice?	North America	63.5	74
	South America	6.6	3
	Europe	17.6	9
	Asia	8.0	12
	Other	4.4	1
Which best describes your specialty?	Endocrinologist	86.0	63
	Surgeon	4.7	18
	Nuclear medicine physician	4.1	3
	Internist or primary-care physician	1.7	17
	Other	3.6	

[a]Results only reported for those who answered yes.
ATA, American Thyroid Association.

Analysis with binary therapeutic options

Patient characteristics. Multivariate repeated-measures logistic regression analysis was conducted to control for all patient characteristics (see Supplementary Table S1) (29). Several patient characteristics made it more likely that a physician would prescribe a therapy other than LT4 monotherapy. These were patient symptoms, T3 levels, TSH levels, presence of a polymorphism, request for T3 therapy, and a stated preference for T3 therapy, with a p-value of <0.0001 in each case. Being athyreotic, being male, or having a body mass index (BMI) of 32 kg/m^2 (rather than 25 kg/m^2) did not affect the therapy prescribed. Older age and presence of a comorbidity made it significantly more likely the physician would prescribe LT4 ($p < 0.0001$ and 0.0002, respectively).

Physician characteristics. Univariate analysis (see Table 3A) showed that the number of years in practice did not significantly affect whether a physician choose LT4 monotherapy versus other therapies. Country of practice (North America vs. other countries) significantly affected choice of therapy, with physicians practicing in North America being more likely to prescribe therapy other than LT4 ($p < 0.0001$). Physician specialty did not affect prescribing patterns. When multivariate analyses were performed (see Table 3B), physician country of practice remained a significant factor ($p < 0.0001$).

Multiple therapeutic options

Patient characteristics. When logistic regression analysis was performed to determine whether patient characteristics affected whether 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 ($p < 0.0001$; Supplementary Table S2) (29). 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. All other characteristics remained significant.

Physician characteristics. Univariate analysis (see Table 4) suggested that the number of years in practice and country of practice affected prescribing patterns. Physicians with ≥11 years in practice were more likely to increase LT4 doses compared to physicians in training, with an odds ratio of 3.6 [CI 1.4–9.6] for physicians in practice for 11–20 years and an odds ratio of 2.8 [CI 1.1–7.1] for physicians with >20 years in practice. Physicians practicing in North America were more likely to add LT3 to LT4 therapy than physicians practicing in other areas, with an odds ratio of 1.8 [CI 1.2–2.7]. When multivariate analyses were performed, only country of practice remained significant, with physicians practicing in North America being more likely to add LT3 to LT4 (OR = 1.9 [CI 1.2–2.9]) and more likely to prescribe DTE or LT3 monotherapy (OR = 1.7 [CI 1.0–2.9]).

Detailed country comparisons

Analyses of therapeutic response options utilizing a detailed comparison of options chosen according to country of practice of the prescribing physician are shown for both univariate analyses (Supplementary Table S3) and multivariate analyses (Table 5). As illustrated in Table 5, there were significant differences in prescribing T3-containing therapies for North America versus all other countries, North America versus South America, and North America versus Europe, with physicians in North America more likely to prescribe T3 in all cases. There were also significant differences between South America versus all other countries for

Table 3. Physician Characteristics Affecting Physician Prescribing of LT4 Versus any T3-Containing Therapy

(A) Univariate analyses			*(B) Multivariate analyses*		
Physician characteristic	*Unadjusted OR [CI]*	p-*Value*	*Physician characteristic*	*Adjusted OR [CI]*	p-*Value*
Number of years in practice			Number of years in practice		
In training (reference)	—	—	In training (reference)	—	—
<5 years	1.6 [0.7–3.8]	0.24	< 5 years	1.7 [0.7–4.1]	0.22
5–10 years	1.5 [0.7–3.4]	0.31	5–10 years	1.5[0.7–3.6]	0.31
11–20 years	1.6 [0.7–3.5]	0.23	11–20 years	1.8 [0.8–4.0]	0.18
>20 years	1.2 [0.6–2.6]	0.63	>20 years	1.3 [0.6–2.8]	0.55
Country of practice			Country of Practice		
Other (reference)	—	—	Other (reference)	—	—
North America	**1.8 [1.4–2.4]**	**<0.0001**	North America	**1.8 [1.3–2.4]**	**<0.0001**
Specialty			Specialty		
Internist or primary care (reference)	—	—	Internist or Primary Care (reference)	—	—
Endocrinologist	0.99 [0.5–2.6]	0.99	Endocrinologist	1.0 [0.4–2.8]	0.95
Surgeon	1.6 [0.5–4.9]	0.45	Surgeon	1.7 [0.5–5.5]	0.38
Nuclear medicine Physician	0.6 [0.2–1.9]	0.40	Nuclear Medicine Physician	0.9 [0.3–2.9]	0.80
Other	1.6 [0.5–4.9]	0.45	Other	1.7 [0.5–5.3]	0.37

Significant comparisons are indicated in bold.
OR, odds ratio; CI, confidence interval.

Table 4. Physician Characteristics Affecting Physician Prescribing Continued LT4 Versus Increasing LT4 Versus Adding LT3 to LT4 Versus Replacing LT4 with T3-Containing Therapy

(A) Univariate analyses

Physician characteristic	*Therapeutic options*	*Unadjusted odds ratio*	*Confidence interval*		p-*Value for model*
Years in practice (in training = reference)					
<5 years	1 vs. 2	2.2	0.77	6.3	0.041
	1 vs. 3	0.96	0.25	3.7	
	1 vs. 4	5.5	0.95	32.2	
5–10 years	1 vs. 2	2.3	0.83	6.3	
	1 vs. 3	1.4	0.39	5.0	
	1 vs. 4	3.2	0.57	18.1	
11–20 years	**1 vs. 2**	**3.6**	**1.4**	**9.6**	
	1 vs. 3	1.6	0.48	5.5	
	1 vs. 4	5.1	0.96	26.8	
>20 years	**1 vs. 2**	**2.8**	**1.1**	**7.1**	
	1 vs. 3	0.8	0.25	2.6	
	1 vs. 4	3.6	0.71	18.0	
Country of practice (outside North America = reference)					
North America	1 vs. 2	0.89	0.66	1.2	0.0088
	1 vs. 3	**1.8**	**1.2**	**2.7**	
	1 vs. 4	1.6	0.95	2.6	
Specialty (internist or primary care = reference)					
vs endocrinologist, surgeon, nuclear medicine physician, other					0.24

(b) Multivariate analyses

Physician characteristic	*Therapeutic options*	*Adjusted odds ratio*	*Confidence interval*		p-*Value for model*
Years in practice (in training = reference)					
vs. <5 years, 5–10 years, 11–20 years, >20 years					0.067
Country of practice (outside North America = reference)					
North America	1 vs. 2	0.92	0.68	1.3	0.0073
	1 vs. 3	**1.9**	**1.2**	**2.9**	
	1 vs. 4	**1.7**	**1.0**	**2.9**	
Specialty (internist or primary care = reference)					
vs. endocrinologist, surgeon, nuclear medicine physician, other					0.35

Significant comparisons are indicated in bold.
Continuing LT4 = therapeutic option 1 (reference); increasing LT4 = therapeutic option 2; adding LT3 to same or reduced LT4 = option 3; replacing LT4 with DTE or LT3 = option 4.

both the binary and grouped comparisons (physicians in South America being less likely to prescribe T3) and between Europe versus other countries for the binary comparison (physicians in Europe being less likely to prescribe T3).

Discussion

A previous comprehensive survey about the treatment of hypothyroidism 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 (30). Although the effects of physician characteristics were reported for some aspects of the management of hypothyroidism in this survey, they were not reported for the use of combination therapy, likely because its infrequent use precluded such analyses. The finding that 3.6% of physicians were willing to prescribe combination therapy in 2013 contrasts with the present findings that as many of 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 results of this 2017 survey suggest that approximately one third of physicians taking care of patients with hypothyroidism are willing to prescribe therapies other than LT4. This is in the setting of the 2012 and 2014 ATA guidelines for the treatment of hypothyroidism concluding that there is insufficient evidence to support routine prescribing of T3-containing therapies (1,20), but more in keeping with recent recommendations

Table 5. Multivariate Analyses of Detailed Country Comparisons of Therapeutic Options

(A) Comparison of binary response options
LT4 vs. any T3-containing therapy

Country of practice	*Adjusted OR*	*CI*	p-*Value*
North America vs. others	**1.8**	**1.3–2.4**	**0.0001**
South America vs. others	**0.38**	**0.2–0.68**	**0.0010**
Europe vs. others	**0.62**	**0.4–0.9**	**0.014**
Asia vs. others	0.86	0.48–1.5	0.61
North American vs. South America	**2.9**	**1.7–5.2**	**0.0002**
North America vs. Europe	**1.8**	**1.2–2.7**	**0.0027**
North America vs. Asia	1.4	0.8–2.6	0.23

(B) Comparison of grouped response options[a]

Country of practice	*Treatment options*	*OR*	*CI*	p-*Value*
North America vs. others	1 vs. 2	0.92	0.68–1.3	0.59
North America vs. others	**1 vs. 3**	**1.9**	**1.2–2.9**	**0.0056**
North America vs. others	**1 vs. 4**	**1.70**	**1.0–2.9**	**0.0444**
South America vs. others	**1 vs. 2**	**0.47**	**0.26–0.85**	**0.012**
South America vs. others	**1 vs. 3**	**0.17**	**0.07–0.43**	**0.0002**
South America vs. others	1 vs. 4	0.39	0.14–1.1	0.069
Europe vs. others	1 vs. 2	1.34	0.92–1.9	0.12
Europe vs. others	1 vs. 3	0.81	0.47–1.4	0.45
Europe vs. others	1 vs. 4	0.54	0.28–1.0	0.065
Asia vs. others	1 vs. 2	0.73	0.41–1.3	0.29
Asia vs. others	1 vs. 3	0.74	0.3–1.7	0.47
Asia vs. others	1 vs. 4	0.88	0.4–2.3	0.80
North American vs. South America	**1 vs. 2**	**1.9**	**1.1–3.5**	**0.027**
North American vs. South America	**1 vs. 3**	**6.4**	**2.5–16.0**	**<0.0001**
North American vs. South America	1 vs. 4	2.9	1.0–8.1	0.043
North America vs. Europe	1 vs. 2	0.76	0.5–1.1	0.16
North America vs. Europe	1 vs. 3	1.5	0.8–2.6	0.17
North America vs. Europe	**1 vs. 4**	**2.1**	**1.03–4.0**	**0.042**
North America vs. Asia	1 vs. 2	1.3	0.69–2.2	0.46
North America vs. Asia	1 vs. 3	1.7	0.72–3.8	0.23
North America vs. Asia	1 vs. 4	1.4	0.5–3.6	0.51

Controlling for all physician characteristics (number of years in practice, country of practice, and specialty). Significant comparisons are indicated in bold.

[a]Continuing LT4 = therapeutic option 1 (reference); increasing LT4 = therapeutic option 2; adding LT3 to same or reduced LT4 = option 3; replacing LT4 with DTE or LT3 = option 4.

from British and Italian Societies that T3-containing therapies can be considered (23–25). A clear limitation of this study is that the survey did not include questions about which hypothyroidism guidelines physicians were familiar with.

With respect to patient characteristics (described in Jonklaas *et al.*) (29) (see Supplementary Tables S1 and S2), the tendency to prescribe T3-containing therapies was greatly increased by patient symptoms, patient request for T3, and stated preference for T3. Older age and the presence of a comorbidity reduced the likelihood that a T3-containing therapy would be prescribed. Athyreotic status, patient sex, and BMI did not affect prescribing patterns. With respect to physician characteristics affecting prescribing patterns, in univariate analyses, trainees were less likely to increase LT4 doses in the setting of a normal serum TSH than more experienced physicians, perhaps suggesting a greater tendency for trainees to maintain standard-of-care practices. In both univariate and multivariate analyses, physicians practicing in North America were more likely to add LT3 to LT4 therapy than physicians practicing in other countries. Physicians practicing in Europe and South America were less likely to prescribe T3-containing therapies compared to all other countries and compared to North America. However, the authors did not question respondents regarding the availability of LT3 by prescription in their country of practice. So, the prescribing pattern in the various countries could be affected by both physician willingness to prescribe and LT3 availability. LT3 has historically been available in areas outside of North America, with availability in the United Kingdom, for example, being described in the TEARS study (31). However, availability by prescription in all countries identified in this survey cannot be assumed.

There appears to be scant literature regarding the effect of physician characteristics on their prescribing patterns with respect to therapy for hypothyroidism. The survey focused on patients with overt hypothyroidism, and respondents were members of a specialty society. In contrast, a survey of general practitioners from Europe and New Zealand conducted in approximately 2014 examined LT4 prescribing patterns for treatment of subclinical hypothyroidism (32,33). The country the prescribing physician was from and several characteristics of the patient case (age,

vitality status, and serum TSH) all affected the decision to prescribe LT4 (33). In further analyses, the study authors found that country, TSH value of case, physician characteristic (sex and years of experience), time since the physician last diagnosed hypothyroidism in their own practice, and age of the physician's patient population all influenced LT4 prescribing. However, after adjusting for all these physician and patient variables (32), there was still significant unexplained between-physician variation in prescribing LT4.

Unexplained variation in practice patterns extends to other thyroid disorders. The physician decision to perform remnant ablation with radioactive iodine in a patient with low-risk thyroid cancer varies significantly by geographic region, practice setting, and physician specialty (34). The fact that outcomes of patients with low-risk thyroid cancer do not vary according to whether radioiodine therapy is used (35) raises the possibility that these decisions are not based on patient characteristics relevant to the disease biology but on other potentially irrelevant characteristics. Other factors that affect whether physicians will prescribe radioiodine include whether they trained with surgeons with thyroid cancer expertise (36), characteristics of the hospital where the patient is being treated (37), and both physician and patient worry about patient death from thyroid cancer (38). Physician worry about patient death was documented, even with patients with low-risk disease, and was greater for physicians with less experience in treating thyroid cancer (38). Variations in thyroid cancer management also extend to use of thyroid hormone suppression therapy (39). In addition to geographic variation, many of these other factors, such as physician specialty, uncertainty about management, physician training, and experience, may also be applicable to decision making regarding the treatment of hypothyroidism.

The survey is limited by the fact that it was directed solely at ATA members. The number of members responding to the survey was fairly small and represented approximately 20% of the total ATA membership in 2017. Moreover, even if a larger percentage of ATA members had responded, another limitation of these data is that they are likely not generalizable to prescribing physicians who are not members of the ATA. In addition to not having a comparison group of physicians who did not belong to a professional society, the study also did not have a comparison group from another professional society such as the Endocrine Society or the American Association of Clinical Endocrinologists. Other limitations of this study include not querying physicians about which guidelines they had read and not collecting data about physician sex and practice setting (e.g., academic institution vs. private practice). The study also only queried respondents about their years of experience and not their age. Furthermore, the patient scenarios were presented in the same order to all physicians, rather than in a random order, making it harder to correct for an order effect. There was no option for the respondent to provide an alternative prescribing option if they did not wish to choose any of the options provided. Physicians were also not asked whether T3-containing therapies were available for prescription in their country of practice, whether they prescribed combination therapy to patients in their own practice, when they had last prescribed combination therapy in their own practice, or the age range of patients seen in their practice, and so these characteristics could not be included in the analysis.

In summary, this study shows that a proportion of physicians are willing to prescribe combination therapy to patients with hypothyroidism. Prescribing patterns are affected not only by the characteristics of the patient, but also by the characteristics of the physician. Although it seems counter-intuitive that prescribing patterns are not most affected by the recommendations of the clinical practice guideline within that geographic area, it may instead show that all guidelines are widely disseminated throughout all geographic regions, and physicians may be particularly influenced by the most recent guidelines. In addition, physicians may consider many other factors to inform their decision regarding whether to prescribe combination therapy. Such factors may include availability of T3-containing products, local prescribing patterns, patient preferences, media exposure, and interaction with pharmaceutical companies. Physicians obviously seek to do more than ''do no harm'' and actively try to provide benefits for their patients, which may lead to placing considerable weight on patient preference. This highlights the need for better studies of physiologic combination therapy regimens that more rigorously examine patients' preferences, patient-reported outcomes, and quality of life.

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Author Disclosure Statement

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References

1. Jonklaas J, Bianco AC, Bauer AJ, Burman KD, Cappola AR, Celi FS, Cooper DS, Kim BW, Peeters RP, Rosenthal MS, Sawka AM; American Thyroid Association Task Force on Thyroid Hormone Replacement 2014 Guidelines for the treatment of hypothyroidism: prepared by the American Thyroid Association Task Force on Thyroid Hormone Replacement. Thyroid **24:**1670–1751.
2. Appelhof BC, Fliers E, Wekking EM, Schene AH, Huyser J, Tijssen JG, Endert E, van Weert HC, Wiersinga WM 2005 Combined therapy with levothyroxine and liothyronine in two ratios, compared with levothyroxine monotherapy in primary hypothyroidism: a double-blind, randomized, controlled clinical trial. J Clin Endocrinol Metab **90:**2666–2674.
3. Bunevicius R, Jakubonien N, Jurkevicius R, Cernicat J, Lasas L, Prange AJ Jr 2002 Thyroxine vs thyroxine plus triiodothyronine in treatment of hypothyroidism after thyroidectomy for Graves' disease. Endocrine **18:**129–133.
4. Bunevicius R, Kazanavicius G, Zalinkevicius R, Prange AJ Jr 1999 Effects of thyroxine as compared with thyroxine

plus triiodothyronine in patients with hypothyroidism. New Engl J Med **340:**424–429.
5. Clyde PW, Harari AE, Getka EJ, Shakir KM 2003 Combined levothyroxine plus liothyronine compared with levothyroxine alone in primary hypothyroidism: a randomized controlled trial. JAMA **290:**2952–2958.
6. Escobar-Morreale HF, Botella-Carretero JI, Gomez-Bueno M, Galan JM, Barrios V, Sancho J 2005 Thyroid hormone replacement therapy in primary hypothyroidism: a randomized trial comparing L-thyroxine plus liothyronine with L-thyroxine alone. Ann Intern Med **142:**412–424.
7. Fadeyev VV, Morgunova TB, Melnichenko GA, Dedov, II 2010 Combined therapy with L-thyroxine and L-triiodothyronine compared to L-thyroxine alone in the treatment of primary hypothyroidism. Hormones (Athens) **9:**245–252.
8. Nygaard B, Jensen EW, Kvetny J, Jarlov A, Faber J 2009 Effect of combination therapy with thyroxine (T4) and 3,5,3′-triiodothyronine versus T4 monotherapy in patients with hypothyroidism, a double-blind, randomised cross-over study. Eur J Endocrinol **161:**895–902.
9. Rodriguez T, Lavis VR, Meininger JC, Kapadia AS, Stafford LF 2005 Substitution of liothyronine at a 1:5 ratio for a portion of levothyroxine: effect on fatigue, symptoms of depression, and working memory versus treatment with levothyroxine alone. Endocr Pract **11:**223–233.
10. Saravanan P, Simmons DJ, Greenwood R, Peters TJ, Dayan CM 2005 Partial substitution of thyroxine (T4) with triiodothyronine in patients on T4 replacement therapy: results of a large community-based randomized controlled trial. J Clin Endocrinol Metab **90:**805–812.
11. Sawka AM, Gerstein HC, Marriott MJ, MacQueen GM, Joffe RT 2003 Does a combination regimen of thyroxine (T4) and 3,5,3′-triiodothyronine improve depressive symptoms better than T4 alone in patients with hypothyroidism? Results of a double-blind, randomized, controlled trial. J Clin Endocrinol Metab **88:**4551–4555.
12. Siegmund W, Spieker K, Weike AI, Giessmann T, Modess C, Dabers T, Kirsch G, Sanger E, Engel G, Hamm AO, Nauck M, Meng W 2004 Replacement therapy with levothyroxine plus triiodothyronine (bioavailable molar ratio 14 : 1) is not superior to thyroxine alone to improve well-being and cognitive performance in hypothyroidism. Clin Endocrinol **60:**750–757.
13. Valizadeh M, Seyyed-Majidi MR, Hajibeigloo H, Momtazi S, Musavinasab N, Hayatbakhsh MR 2009 Efficacy of combined levothyroxine and liothyronine as compared with levothyroxine monotherapy in primary hypothyroidism: a randomized controlled trial. Endocr Res **34:**80–89.
14. Walsh JP, Shiels L, Lim EM, Bhagat CI, Ward LC, Stuckey BG, Dhaliwal SS, Chew GT, Bhagat MC, Cussons AJ 2003 Combined thyroxine/liothyronine treatment does not improve well-being, quality of life, or cognitive function compared to thyroxine alone: a randomized controlled trial in patients with primary hypothyroidism. J Clin Endocrinol Metab **88:**4543–4550.
15. Escobar-Morreale HF, Botella-Carretero JI, Escobar del Rey F, Morreale de Escobar G 2005 REVIEW: Treatment of hypothyroidism with combinations of levothyroxine plus liothyronine. J Clin Endocrinol Metab **90:**4946–4954.
16. Grozinsky-Glasberg S, Fraser A, Nahshoni E, Weizman A, Leibovici L 2006 Thyroxine-triiodothyronine combination therapy versus thyroxine monotherapy for clinical hypothyroidism: meta-analysis of randomized controlled trials. J Clin Endocrinol Metab **91:**2592–2599.
17. Joffe RT, Brimacombe M, Levitt AJ, Stagnaro-Green A 2007 Treatment of clinical hypothyroidism with thyroxine and triiodothyronine: a literature review and metaanalysis. Psychosomatics **48:**379–384.
18. Ma C, Xie J, Huang X, Wang G, Wang Y, Wang X, Zuo S 2009 Thyroxine alone or thyroxine plus triiodothyronine replacement therapy for hypothyroidism. Nucl Med Commun **30:**586–593.
19. Wiersinga WM, Duntas L, Fadeyev VV, Nygaard B, Vanderpump MPJ 2012 2012 ETA guidelines: the use of L-T4 + L-T3 in the treatment of hypothyroidism. Eur Thyroid J **1:**55–71.
20. Garber JR, Cobin RH, Gharib H, Hennessey JV, Klein IL, Mechanick JI, Pessah-Pollack R, Singer P, Woeber KA 2012 Clinical practice guidelines for hypothyroidism in adults co-sponsored by the American Association of Clinical Endocrinologists (AACE) and the American Thyroid Association, Inc. (ATA). Thyroid **22:**1200–1235.
21. Biondi B, Wartofsky L 2012 Combination treatment with t4 and t3: toward personalized replacement therapy in hypothyroidism? J Clin Endocrinol Metab **97:**2256–2271.
22. Kaminski J, Miasaki FY, Paz-Filho G, Graf H, Carvalho GA 2016 Treatment of hypothyroidism with levothyroxine plus liothyronine: a randomized, double-blind, crossover study. Arch Endocrinol Metab **60:**562–572.
23. Okosieme O, Gilbert J, Abraham P, Boelaert K, Dayan C, Gurnell M, Leese G, McCabe C, Perros P, Smith V, Williams G, Vanderpump M 2016 Management of primary hypothyroidism: statement by the British Thyroid Association Executive Committee. Clin Endocrinol **84:**799–808.
24. Biondi B, Bartalena L, Chiovato L, Lenzi A, Mariotti S, Pacini F, Pontecorvi A, Vitti P, Trimarchi F 2016 Recommendations for treatment of hypothyroidism with levothyroxine and levotriiodothyronine: a 2016 position statement of the Italian Society of Endocrinology and the Italian Thyroid Association. J Endocrinol Invest **39:**1465–1474.
25. Guglielmi R, Frasoldati A, Zini M, Grimaldi F, Gharib H, Garber JR, Papini E 2016 Italian Association of Clinical Endocrinologists Statement—replacement therapy for primary hypothyroidism: a brief guide for clinical practice. Endocr Pract **22:**1319–1326.
26. Appelhof BC, Peeters RP, Wiersinga WM, Visser TJ, Wekking EM, Huyser J, Schene AH, Tijssen JG, Hoogendijk WJ, Fliers E 2005 Polymorphisms in type 2 deiodinase are not associated with well-being, neurocognitive functioning, and preference for combined thyroxine/3,5,3′-triiodothyronine therapy. J Clin Endocrinol Metab **90:**6296–6299.
27. Panicker V, Saravanan P, Vaidya B, Evans J, Hattersley AT, Frayling TM, Dayan CM 2009 Common variation in the DIO2 gene predicts baseline psychological well-being and response to combination thyroxine plus triiodothyronine therapy in hypothyroid patients. J Clin Endocrinol Metab **94:**1623–1629.
28. Medici BB, la Cour JL, Michaelsson LF, Faber JO, Nygaard B 2017 Neither baseline nor changes in serum triiodothyronine during levothyroxine/liothyronine combination therapy predict a positive response to this treatment modality in hypothyroid patients with persistent symptoms. Eur Thyroid J **6:**89–93.

29. Jonklaas J, Tefera E, Shara N 2018 Physician choice of hypothyroidism therapy: influence of patient characteristics. Thyroid **28:**1416–1424.
30. Burch HB, Burman KD, Cooper DS, Hennessey JV 2014 A 2013 survey of clinical practice patterns in the management of primary hypothyroidism. J Clin Endocrinol Metab **99:** 2077–2085.
31. Leese GP, Soto-Pedre E, Donnelly LA 2016 Liothyronine use in a 17 year observational population-based study—the TEARS study. Clin Endocrinol **85:**918–925.
32. Boef AG, le Cessie S, Dekkers OM, Frey P, Kearney PM, Kerse N, Mallen CD, McCarthy VJ, Mooijaart SP, Muth C, Rodondi N, Rosemann T, Russell A, Schers H, Virgini V, de Waal MW, Warner A, Gussekloo J, den Elzen WP 2016 Physician's prescribing preference as an instrumental variable: exploring assumptions using survey data. Epidemiology **27:**276–283.
33. den Elzen WP, Lefebre-van de Fliert AA, Virgini V, Mooijaart SP, Frey P, Kearney PM, Kerse N, Mallen CD, McCarthy VJ, Muth C, Rosemann T, Russell A, Schers H, Stott DJ, de Waal MW, Warner A, Westendorp RG, Rodondi N, Gussekloo J 2015 International variation in GP treatment strategies for subclinical hypothyroidism in older adults: a case-based survey. Br J Gen Pract **65:**e121–132.
34. Sawka AM, Rotstein L, Brierley JD, Tsang RW, Thabane L, Gafni A, Straus S, Kamalanathan S, Zhao B, Goldstein DP, Rambaldini G, Ezzat S 2007 Regional differences in opinions on adjuvant radioactive iodine treatment of thyroid carcinoma within Canada and the United States. Thyroid **17:**1235–1242.
35. Hall SF, Irish J, Groome P, Griffiths R, Hurlbut D 2017 Do lower-risk thyroid cancer patients who live in regions with more aggressive treatments have better outcomes? Thyroid **27:**1246–1257.
36. Schuessler KM, Banerjee M, Yang D, Stewart AK, Doherty GM, Haymart MR 2013 Surgeon training and use of radioactive iodine in stage I thyroid cancer patients. Ann Surg Oncol **20:**733–738.
37. Haymart MR, Banerjee M, Stewart AK, Koenig RJ, Birkmeyer JD, Griggs JJ 2011 Use of radioactive iodine for thyroid cancer. JAMA **306:**721–728.
38. Papaleontiou M, Banerjee M, Yang D, Sisson JC, Koenig RJ, Haymart MR 2013 Factors that influence radioactive iodine use for thyroid cancer. Thyroid **23:**219–224.
39. Haymart MR, Banerjee M, Yang D, Stewart AK, Sisson JC, Koenig RJ, Doherty GM, Griggs JJ 2013 Variation in the management of thyroid cancer. J Clin Endocrinol Metab **98:**2001–2008.

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