

An Online Survey of Hypothyroid Patients Demonstrates Prominent Dissatisfaction

AU1 ▶

Sarah J. Peterson,¹ Anne R. Cappola,² M. Regina Castro,³ Colin M. Dayan,⁴ Alan P. Farwell,⁵
James V. Hennessey,⁶ Peter A. Kopp,⁷ Douglas S. Ross,⁸ Mary H. Samuels,⁹
Anna M. Sawka,¹⁰ Peter N. Taylor,⁴ Jacqueline Jonklaas,¹¹ and Antonio C. Bianco¹

Background: Approximately 15% more patients taking levothyroxine (LT4) report impaired quality of life compared to controls. This could be explained by additional diagnoses independently affecting quality of life and complicating assignment of causation. This study sought to investigate the underpinnings of reduced quality of life in hypothyroid patients and to provide data for discussion at a symposium addressing hypothyroidism.

Methods: An online survey for hypothyroid patients was posted on the American Thyroid Association Web site and forwarded to multiple groups. Respondents were asked to rank satisfaction with their treatment for hypothyroidism and their treating physician. They also ranked their perception regarding physician knowledge about hypothyroidism treatments, need for new treatments, and life impact of hypothyroidism on a scale of 1–10. Respondents reported the therapy they were taking, categorized as LT4, LT4 and liothyronine (LT4 + LT3), or desiccated thyroid extract (DTE). They also reported sex, age, cause of hypothyroidism, duration of treatment, additional diagnoses, and prevalence of symptoms.

Results: A total of 12,146 individuals completed the survey. The overall degree of satisfaction was 5 (interquartile range [IQR] = 3–8). Among respondents without self-reported depression, stressors, or medical conditions ($n = 3670$), individuals taking DTE reported a higher median treatment satisfaction of 7 (IQR = 5–9) compared to other treatments. At the same time, the LT4 treatment group exhibited the lowest satisfaction of 5 (IQR = 3–7), and for the LT4 + LT3 treatment group, satisfaction was 6 (IQR = 3–8). Respondents taking DTE were also less likely to report problems with weight management, fatigue/energy levels, mood, and memory compared to those taking LT4 or LT4 + LT3.

Conclusions: A subset of patients with hypothyroidism are not satisfied with their current therapy or their physicians. Higher satisfaction with both treatment and physicians is reported by those patients on DTE. While the study design does not provide a mechanistic explanation for this observation, future studies should investigate whether preference for DTE is related to triiodothyronine levels or other unidentified causes.

AU3 ▶

Keywords: hypothyroidism, levothyroxine, combination therapy, desiccated thyroid extract, TSH, T3

Introduction

HYPOTHYROIDISM IS A COMMON endocrine problem that requires lifelong treatment with thyroid hormone (1). Currently, the standard treatment for hypothyroidism is daily

administration of levothyroxine (LT4) at doses that normalize serum thyrotropin (TSH) (2,3). Even though thyroxine (T4) is intrinsically active in some settings (4), many tissues have deiodinases that activate T4 to triiodothyronine (T3), the biologically active thyroid hormone. The prevailing viewpoint

AU2 ▶

¹Division of Endocrinology and Metabolism, Rush University Medical Center, Chicago, Illinois.

²Division of Endocrinology, Diabetes, and Metabolism, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania.

³Division of Endocrinology, Mayo Clinic, Rochester, Minnesota.

⁴Thyroid Research Group, Systems Immunity Research Institute, Cardiff University School of Medicine, Cardiff, United Kingdom.

⁵Division of Endocrinology, Diabetes and Nutrition, Boston Medical Center/Boston University, Boston, Massachusetts.

⁶Division of Endocrinology, Beth Israel Deaconess Medical Center, Boston, Massachusetts.

⁷Feinberg School of Medicine, Northwestern University, Chicago, Illinois.

⁸Thyroid Associates, Massachusetts General Hospital, Boston, Massachusetts.

⁹Oregon Clinical and Translational Research Institute, Oregon Health and Science University, Portland, Oregon.

¹⁰University Health Network and University of Toronto, Toronto, Canada.

¹¹Division of Endocrinology, Georgetown University, Washington, DC.

is that a dose of LT4 that normalizes serum TSH resolves most/all hypothyroid symptoms (5).

However, a cross-sectional investigation of LT4-treated patients reported impaired psychological well-being compared to control individuals (6). The level of dissatisfaction of individuals on the general health questionnaire was 21% higher in LT4-treated patients compared to controls. Stronger differences (34%) were seen when a thyroid-specific questionnaire was used (6). Patients may complain of symptoms overlapping with hypothyroidism such as sluggishness, lethargy, sleepiness, memory problems, depression, cold intolerance, hoarseness, dry skin, body weight gain, and constipation (1). They may switch physicians multiple times and may use unconventional therapies, such as dietary supplements, nutraceuticals, and over-the-counter products. Symptoms consistent with hypothyroidism are nonspecific and cannot be used to identify hypothyroid patients among euthyroid controls (7,8). Hence, guidelines recommend withholding treatment with thyroid hormone when the diagnosis is not biochemically confirmed (2). Compared to healthy individuals who may report less than optimal quality of life (QoL) at rates of 25–35% (6), patients carrying diagnoses of chronic medical conditions report diminished QoL (9,10). Chronic conditions treated with daily medication further compromises patients' perception of the quality of their lives (11). Individuals treated with medications with predictable side effects further experience worse QoL (10). Thus, it is expected that patients with Hashimoto's thyroiditis too may complain of diminished QoL independent of thyroid function (12–15). Among factors influencing the frequency with which a typical symptom such as fatigue will be reported in LT4-treated subjects are sex, employment status, and physical activity rather than thyroid function (16).

The existence of a subset of LT4-treated hypothyroid patients who have nonspecific symptoms who report poor QoL indicators has led to questions as to whether monotherapy with LT4 is adequate for all patients (3,17). Among National Health and Nutrition Examination Survey (NHANES) participants, LT4-treated patients with a normal serum TSH exhibit a 15–20% decrease in the ratio of circulating T3/T4 (18), and about 15% of these patients may not maintain normal serum T3 levels (19). This could result from differences in D2 regulation between the hypothalamus and peripheral tissues, as has been shown in a hypothyroid rat model (20). In fact, replacement with LT4 might not fully restore all aspects of euthyroidism, as seen in females taking LT4 who have lower energy expenditure compared to euthyroid women with similar age and body mass index (BMI) (21). In addition, the NHANES data cited above (18) indicate that individuals taking LT4, with TSH values within the normal reference range, have a higher BMI, despite reporting lower calorie intake corrected by body weight, in the setting of a reported lower physical activity levels. Additionally, the LT4-treated subjects were significantly more often taking statins, beta-blockers, and antidepressants compared to euthyroid participants matched by age, sex, and race/ethnicity (18). Following additional statistical analysis, it was demonstrated that LT4-treated subjects reported an increased frequency of episodes of memory problems/confusion and were less likely to report being in excellent/good health (22). An attempt to enhance effectiveness of thyroid hormone replacement with higher doses of LT4 may explain at least in part why some patients may exhibit suppressed TSH (23).

Fueled by a hypothesis that subnormal T3 levels contribute to residual symptoms, a total of 14 double-blind placebo-controlled trials of combination therapy have been conducted. Based on these trials, it is not clear that combination therapy is superior to monotherapy in managing hypothyroidism. These trials provided heterogeneous results with respect to health-related QoL and mood and neurocognitive functioning, although there was a patient preference for combination therapy in some of the trials (6,24–36). A single randomized trial of desiccated thyroid extract (DTE) therapy compared to LT4 failed to identify differences in neurocognitive testing or in symptoms (primary outcome) but showed weight loss and treatment preference for DTE (37). Currently the American Thyroid Association (ATA) guidelines do not recommend the routine use of combination therapy (2).

The objective of the current analysis was to probe the perceptions, comorbidities, and treatment selections of survey respondents who expressed a low overall degree of satisfaction with their therapy.

Methods

Study participants

Hypothyroid individuals were invited to participate in an online English language survey to determine their perceptions regarding the treatment that they received for hypothyroidism. Participants were asked to report which thyroid hormone they were currently taking for treatment of hypothyroidism, demographic characteristics, etiology and duration of hypothyroidism, and concomitant medical conditions.

Survey development and distribution

The Hypothyroidism Treatment Survey was created by the program committee members of the Satellite Symposium on Hypothyroidism organized by the ATA that occurred in spring 2017 in Orlando, Florida. The program committee members deemed it important to describe the patient perspective regarding hypothyroidism treatment and to share the results with program registrants. The survey questions were created to identify demographic and treatment characteristics of individuals being treated for hypothyroidism, coupled with information about their satisfaction with their therapy.

Participants were asked to provide their sex, age (categorized as <40, 41–50, 51–60, 61–70, or >70 years old), cause of their hypothyroidism (categorized as “Hashimoto's/ autoimmune disease,” “surgery/removal of thyroid,” “radioactive iodine [RAI] for overactive thyroid,” “I do not know,” or “other”), and duration of hypothyroidism treatment (categorized as <1, 1–5, 6–10, or >10 years). To recognize confounding conditions that may contribute to symptoms overlapping with those of hypothyroidism, participants were asked if they thought that stress or other medical problems could be contributing to their symptoms and were asked to identify any relevant medical problems that they had (including heart disease, lung disease, diabetes, bone or muscle disease, gastrointestinal disease, cancer that is not thyroid cancer, thyroid cancer, and depression).

Treatment was defined as taking a thyroid hormone for hypothyroidism. Individuals were asked to select the type of thyroid hormone they were taking (categorized as levothyroxine, [including generic or branded forms of levothyroxine],

HYPOTHYROIDISM TREATMENT SATISFACTION

levothyroxine and LT3 [liothyronine, Cytomel], natural thyroid or DTE [Armour Thyroid, Nature-Throid], “I do not know,” or “other” [with the option to specify the thyroid hormone treatment]). The three treatments subjected to further analysis were LT4, LT4 + LT3, and DTE. Perception regarding treatment was examined by asking participants to rank, on a scale of 1–10, their satisfaction with treatment and with the current physician treating their hypothyroidism (where 1 = “not satisfied” and 10 = “completely satisfied”), the perceived knowledge of their physician about treatment of hypothyroidism (where 1 = “not at all knowledgeable” and 10 = “very knowledgeable”), their assessment of the need for new treatments for hypothyroidism (1 = “no need” and 10 = “strong need”), and the impact of hypothyroidism on their life (1 = “not affected” and 10 = “strongly affected”). In addition to reporting the median and 25th and 75th percentile of the responses, the distribution of the responses was also presented in graphic form. Additional questions assessed participants’ experiences with their medical care for hypothyroidism. Respondents were asked to categorize the number of times they changed physician because they were not satisfied with their hypothyroidism treatment (categorized as none, once, 2–4 times, 5–9 times, or ≥10 times), identify relevant aspects of their life affected by hypothyroidism/thyroid hormone treatment (categorized as weight management, fatigue or energy levels, mood, and memory or other problems with thinking), and prevalence of seeking alternative form of hypothyroidism treatment, not prescribed by your doctor (yes/no).

The survey was available online from January 28, 2017, to March 30, 2017. A link to the survey was posted on the ATA Web site and distributed via e-mail to patients within the ATA database and to the members of the ATA Alliance for Thyroid Patient Education. Members of the ATA were encouraged to distribute the survey further by sharing on group Web sites and social media. Additionally, the link was included in the Signal eNews, a monthly newsletter e-mailed to ATA members. No identifying or protected health information was collected from participants. IP address was recorded only for the purpose of eliminating duplicate responses. As the study was available online and not individually distributed to patients, no information is available regarding response rate. The study was exempt from Institutional Review Board approval, given the anonymous and non-interventional nature of the survey.

Initial analysis was conducted on the total sample (comprised of respondents taking LT4, LT4 + LT3, or DTE). In addition, four subgroups were created based on disease characteristics in order to analyze perceptions further regarding treatment of hypothyroidism according to the three treatments. Subgroup 1 comprised respondents without self-reported depression, stress, or medical conditions. Subgroup 2 comprised a matched subgroup of females, created due to difference in age, sex, and hypothyroid treatment between respondents taking LT4, LT4 + LT3, and DTE, where those taking LT4 and DTE (the two largest groups of respondents) were matched 2:1 by age, hypothyroidism treatment, etiology of hypothyroidism, and treatment duration to individuals taking LT4 + LT3 (the smallest group of respondents) to account for baseline differences. Subgroup 3 comprised respondents with depression but no reported life stressors or medical conditions. Subgroup 4 comprised respondents with

thyroid cancer but no self-reported depression, life stressors, or medical condition.

Statistical methods

Both frequency (percent) and median (interquartile range [IQR; 25th–75th percentile]) were used to describe the data. The Kruskal–Wallis test was used to compare difference in ranked median perception across the three medication treatment groups (LT4 vs. LT4 + LT3 vs. DTE). If a significant difference was observed, the Mann–Whitney *U*-test was used to perform between group analyses. The chi-square test of association was utilized to determine difference in categorical variables across the three medication treatment groups (LT4 vs. LT4 + LT3 vs. DTE). Logistic regression was utilized to determine the association between dissatisfaction of hypothyroid treatment (categorized as ranking treatment satisfaction as 1–10) with demographic data, characteristics of hypothyroidism, self-reported depression, stress or medical conditions, and hypothyroid treatment. A univariate logistic regression was used to determine demographic, hypothyroidism characteristic, self-reported conditions, and medication variables that were significantly associated with treatment dissatisfaction for the entire population. A multivariate logistic regression was performed for the entire population and for subgroup 1. Any variable that was significantly associated with categorical treatment satisfaction was entered into the multivariate logistic regression models. Additionally, a multivariate logistic regression was completed to determine the association between treatment dissatisfaction with demographic, hypothyroidism characteristic, self-reported conditions by hypothyroid medication (LT4 vs. LT4 + LT3 vs. DTE).

Analyses were completed with IBM SPSS Statistics for Windows v22.0 (IBM Corp.). Due to the multiple comparisons performed, a conservative *p*-value of <0.001 was utilized to identify statistically significant differences between groups. This rigorous *p*-value was chosen in order to avoid over-interpreting results in the setting of a survey-based data set.

Results

A total of 12,146 respondents completed the survey, and all subsequent analyses were performed based on the self-reported responses to questions about medical history and hypothyroidism treatment. Respondents who were not taking medication for hypothyroidism (*n* = 53) were excluded. Of the remaining 12,093 individuals (Supplementary Table S1; Supplementary Data are available online at www.liebertpub.com/thy), 485 were excluded because they were taking a medication for hypothyroidism other than LT4, LT4 + LT3, or DTE. An additional 442 were excluded due to survey completion from the same IP address and concern that the data represented duplicate surveys. As a result, the total sample of respondents that was further analyzed comprised 11,166 individuals (Fig. 1).

The female:male ratio of respondents was approximately 21:1, and age was relatively evenly distributed across the four age categories (Table 1). The most prevalent cause of hypothyroidism was Hashimoto’s/autoimmune disease (43%). However, 34% of respondents identified another cause other than Hashimoto’s/RAI/surgery, or were unsure of hypothyroidism etiology (Table 1). Only 7% of individuals were

◀ST1

◀F1

◀T1

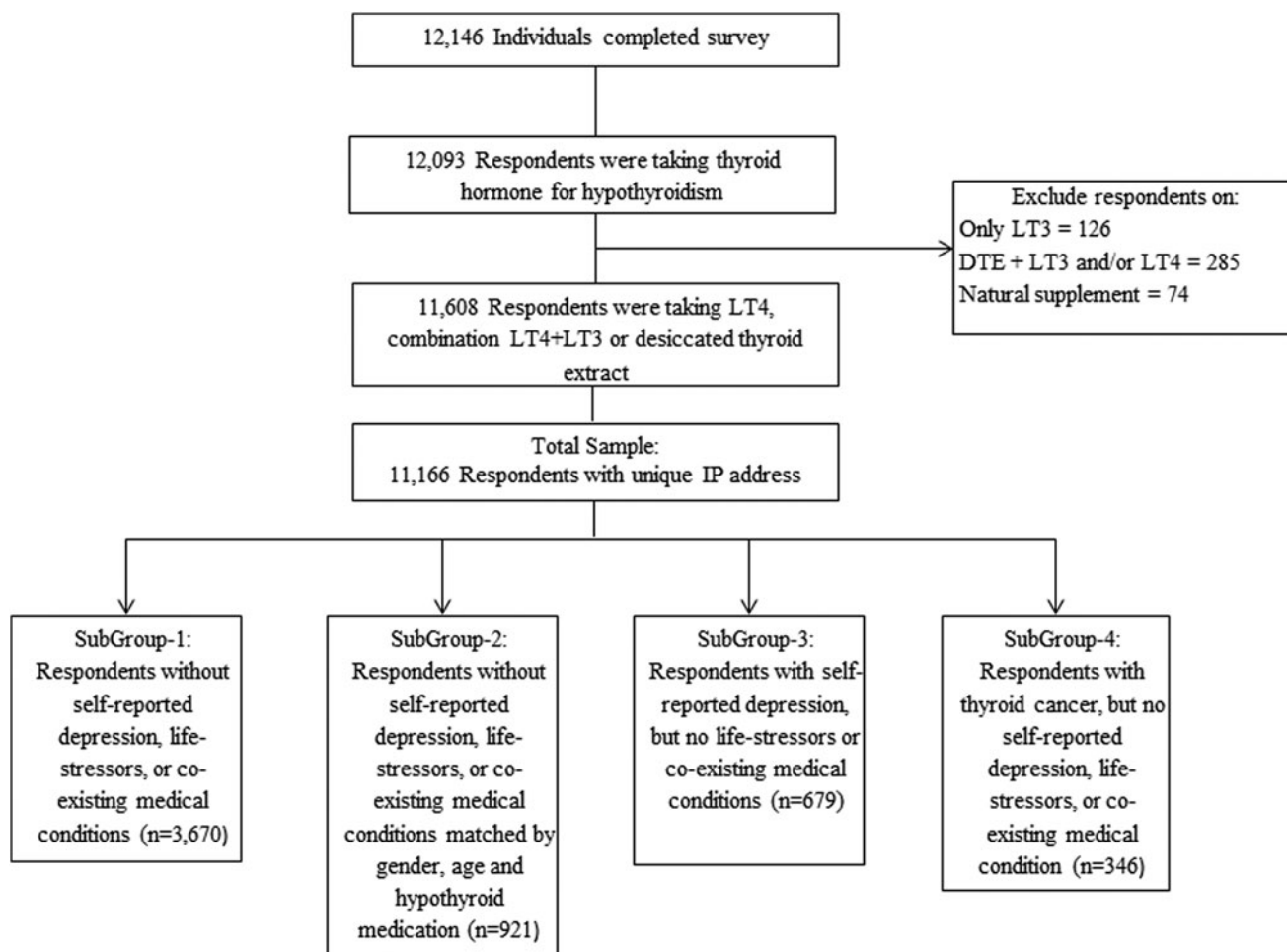


FIG. 1. Flow diagram of survey respondent eligibility.

treated for hypothyroidism for less than one year; the majority (63%) had been on treatment for more than six years. One third of patients stated that their current stress level could be contributing to hypothyroid-related symptoms; another third reported co-existing medical conditions, with the most common one being depression (27%). Only 6% of respondents self-reported depression without any other comorbidities (Table 1).

Within the total sample, 6949 individuals were taking LT4 monotherapy, 978 reported taking combination LT4 + LT3, and 3239 received DTE (Table 1). When considering perceptions regarding their treatment for hypothyroidism, on a scale from 1 to 10, with 10 being the highest, the median response indicating treatment satisfaction was 5 (IQR = 3–8; Table 1). Among those who were frustrated with their hypothyroidism treatment, the relevant areas identified as causing dissatisfaction were weight management (69%), fatigue or energy level (77%), mood (45%), and memory or other problems thinking (58%). The median response describing satisfaction with the patient’s current physician was 6 (IQR = 3–6), and assessment of the doctor/physician knowledge regarding hypothyroidism treatment was 5 (IQR = 3–8); 54% of the sample reported changing physicians more than twice because of dissatisfaction with treatment. Almost all respondents believed that there was a strong need for new treatments for hypothyroidism (median

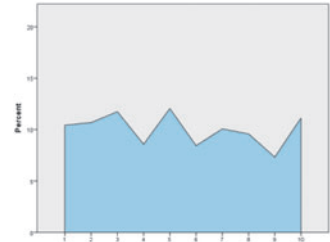
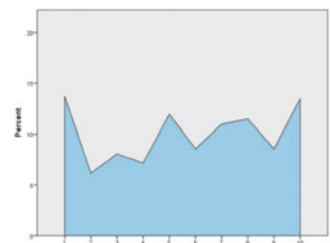
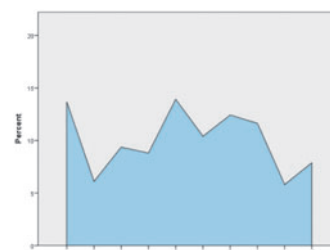
10 [IQR = 8–10]) and perceived a significant influence of hypothyroidism on life (median 10 [IQR = 8–10]; Table 1).

Next, multiple analyses were utilized to compare the responses within the total sample according to their specific treatment (Table 2). When examining the three treatment subgroups, the distribution of sex, age, etiology, and treatment duration were significantly different. Individuals treated with DTE had the highest median satisfaction with treatment (7 [IQR = 4–8]) compared to those taking LT4 (5 [IQR = 3–7]) or LT4 + LT3 (5 [IQR = 3–7]). In particular, as shown in the graphic representations, the distribution of responses was markedly different between those taking DTE versus LT4 (Table 2). Individuals on DTE predominately responded positively with an upward trend, such that responses were more frequent at the positive end of the scale. Conversely, individuals on LT4 were more likely to respond negatively, exhibiting a distribution with a downward trend, such that responses were more frequent at the negative end of the scale (Table 2). This varied distribution between groups can also be described by examining the number of patients who ranked satisfaction with treatment as not satisfied (ranked 1 or 2) or completely satisfied (ranked 9 or 10). Approximately 20% of respondents taking LT4 and LT4 + LT3 were not satisfied with treatment, while 14% of DTE users were not satisfied. In comparison, 22% of DTE users were completely satisfied compared to 10% of LT4 and

◀ T2

TABLE 1. DEMOGRAPHIC DATA, HYPOTHYROID DISEASE CHARACTERISTICS, AND PERCEPTIONS REGARDING HYPOTHYROID TREATMENT FOR THE TOTAL SAMPLE (N= 11,166)

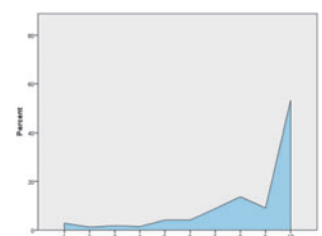
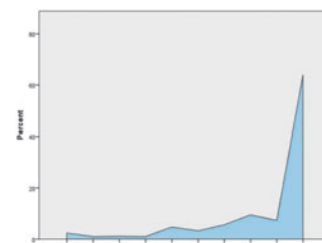
| Survey section | Survey question | Possible response | Respondents |
|---|---|---------------------------------|--------------|
| Demographics | Sex ^a | Female | 10,664 (96%) |
| | | Male | 502 (4%) |
| | Age ^a | 31–40 years | 2464 (22%) |
| | | 41–50 years | 3217 (29%) |
| | | 51–60 years | 2830 (25%) |
| ≥61 years | | 2655 (23%) | |
| Hypothyroid etiology and treatment | Etiology of hypothyroidism ^a | Hashimoto/autoimmune | 4812 (43%) |
| | | Radioactive iodine | 858 (8%) |
| | | Surgery | 1694 (15%) |
| | | Other/not known | 3802 (34%) |
| | What thyroid hormone are you currently taking? ^a | LT4 | 6949 (62%) |
| | | LT4 + LT3 | 978 (9%) |
| Hypothyroid treatment duration ^a | <1 year | 814 (7%) | |
| | 1–5 years | 3337 (30%) | |
| | 6–10 years | 2486 (22%) | |
| | >10 years | 4529 (41%) | |
| Self-reported medical history | Is a condition not related to thyroid hormone causing your symptoms? | Current stress levels | 2297 (21%) |
| | | Other medical problem | 2148 (19%) |
| | | Both stress and medical problem | 1430 (13%) |
| | | No condition identified | 5291(47%) |
| | Do you have any of these medical problems? | Heart disease | 510 (5%) |
| | | Lung disease | 316 (3%) |
| | | Diabetes | 681 (6%) |
| | | Bone/muscle disease | 868 (8%) |
| | | GI disease | 1506 (14%) |
| | | Cancer (non-thyroid) | 243 (2%) |
| Depression | 2965 (27%) | | |
| Perception regarding hypothyroid treatment | How satisfied are you with the treatment you receive? ^b | 1 = not satisfied | 5 (3–8) |
| | | 10 = very satisfied | |
| | If you are not satisfied, indicate relevant areas you feel are affected by your thyroid treatment | Weight management | 7729 (69%) |
| | | Fatigue or energy levels | 8597 (77%) |
| | | Mood | 5059 (45%) |
| | | Memory | 6433 (58%) |
| | How satisfied are you with your current physician who treats you for your thyroid condition? ^b | 1 = not satisfied | 6 (3–8) |
| 10 = very satisfied | | | |
| How knowledgeable is your doctor and/or physicians in general about hypothyroid treatment? ^b | 1 = not knowledgeable | 5 (3–8) | |
| | 10 = very knowledgeable | | |



(continued)

TABLE 1. (CONTINUED)

| Survey section | Survey question | Possible response | Respondents |
|----------------|--|--|--|
| | How many times have you changed doctors because you were not satisfied with the treatment you were receiving? ^a | Never Once 2–4 times 5–9 times >10 times | 3185 (29%) 1944 (17%) 4375 (39%) 1349 (12%) 313 (3%) |
| | How would you rate the need for new treatments for hypothyroidism? ^b | 1=no need 10=strong need | 10 (8–10) |
| | Tried alternative hypothyroid treatment not prescribed by doctor | Yes No | 3108 (28%) 8058 (71%) |
| | How has your life been affected by your hypothyroidism? ⁺ | 1=not affected 10=strongly affected | 10 (8–10) |



^aSummarized as frequency (%).

^bSummarized as median (IQR).

LT4, levothyroxine; LT3, liothyronine; DTE, desiccated thyroid extract; GI, gastrointestinal; IQR, interquartile range.

SF1 ▶ LT4 + LT3 respondents (Supplementary Fig. S1). Individuals taking DTE were less likely to report problems with weight management, fatigue/energy level, mood, or memory when compared to those taking LT4 or LT4 + LT3 (Table 2). Individuals taking DTE had a higher median satisfaction with their current physician (7 [IQR=4–9]) compared to those taking LT4 (5 [IQR=3–8]) or LT4 + LT3 (6 [IQR=3–8]). Perceived physician knowledge was slightly higher in the

SF2 ▶ DTE subgroup compared to the LT4 subgroup (Supplementary Figs. S2 and S3). Of note, 29% and 21% of individuals taking DTE and LT4 + LT3 changed doctors five or more times because they were not satisfied with their treatment compared to only 7% of respondents taking LT4. Those taking DTE or LT4 + LT3 were more likely to have tried alternative treatment forms not prescribed by their doctor and thought their lives had been more affected by hypothyroidism (10 [IQR=9–10]), although this latter parameter was very high in all three subgroups (Table 2).

The univariate analysis testing the association between demographic data and the characteristics of the disease revealed that the following parameters were associated with a higher likelihood of treatment dissatisfaction (odds ratio [OR] >1.0): (i) female; (ii) changing physician twice or more; (iii) complaints about weight management, fatigue or low energy levels, mood, and memory; (iv) tried alternative treatment for hypothyroidism; and (v) depression (Table 3). In contrast, (i) being aged >60 years, (ii) having hypothyroidism due to RAI or surgical thyroidectomy, and (iii) being on LT4 + LT3 or DTE therapy were associated with a lower

likelihood of treatment dissatisfaction (OR <1.0; Table 3). These associations remained statistically significant, even when testing was done through multivariate analysis (Table 4). Independently of type of treatment, concerns over weight management, fatigue, mood, and memory were associated with dissatisfaction (OR >1; Supplementary Table S2).

Analyses of subgroups 1–4

Subgroup 1 (Supplementary Table S3; n=3670) captures respondents without self-reported depression, life stressors, or medical conditions. Those taking LT4 had a median reported treatment satisfaction of 5 (IQR=3–7; Table 5). Their perception regarding treatment of hypothyroidism were as follows: physician satisfaction of 5 (IQR=3–8) and physician knowledge of 5 (IQR=3–8). Individuals taking combination therapy with LT4 + LT3 experienced slightly higher treatment satisfaction (6 [IQR=3–8]), with similar physician satisfaction and perceived physician knowledge. Respondents taking DTE had the highest scores in treatment satisfaction (7 [IQR=5–9]) and physician satisfaction (7 [IQR=4–9]). Regardless of treatment modality, all respondents ranked at the highest level (9 or 10) the need for new treatments and the perception of how much their lives had been affected by hypothyroidism (Table 5). Additionally, respondents taking DTE were less likely to report weight management concerns, fatigue/low energy levels, mood issues, or memory problems compared to those on LT4 or

◀T4
◀ST2
◀ST3
◀T5

T3 ▶

TABLE 2. COMPARISON OF DEMOGRAPHIC DATA, CHARACTERISTICS OF HYPOTHYROIDISM, AND PERCEPTIONS REGARDING HYPOTHYROIDISM TREATMENT BY SELF-REPORTED MEDICATION (LT4, LT4 + LT3, OR DTE) FOR THE TOTAL SAMPLE (N = 11,166)

| Survey question | Possible response | LT4 (n = 6949) | LT4 + LT3 (n = 978) | DTE (n = 3239) | p-Value |
|--|---|---|--|--|---|
| Sex ^a | Female Male | 6546 (94%) 403 (6%) | 944 (97%) 34 (3%) | 3174 (98%) 65 (2%) | <0.0001 |
| Age ^a | 31–40 years 41–50 years 51–60 years ≥61 years | 1553 (22%) 1857 (27%) 1709 (25%) 1830 (26%) | 230 (23%) 286 (29%) 258 (27%) 204 (21%) | 681 (21%) 1074 (33%) 863 (27%) 621 (20%) | <0.0001 |
| Etiology of hypothyroidism ^a | Hashimoto/autoimmune Radioactive iodine Surgery Other | 2587 (37%) 629 (9%) 1149 (17%) 2587 (38%) | 475 (49%) 67 (7%) 185 (19%) 251 (26%) | 1750 (54%) 162 (5%) 360 (12%) 967 (30%) | <0.0001 |
| Hypothyroid treatment duration ^a | <1 year 1–5 years 6–10 years >10 years | 609 (9%) 2012 (29%) 1507 (22%) 2821 (41%) | 32 (3%) 268 (27%) 245 (25%) 433 (44%) | 173 (5%) 1057 (33%) 734 (23%) 1275 (39%) | <0.0001 |
| Is a condition not related to thyroid hormone causing your symptoms? | Current stress levels Other medical problem Both stress/medical problem | 1482 (21%) 1325 (19%) 872 (13%) | 186 (19%) 217 (22%) 132 (14%) | 629 (19%) 606 (19%) 426 (13%) | 0.04 |
| Do you have any of these medical problems? | No condition identified Heart disease Lung disease Diabetes Bone/muscle disease GI disease Cancer (non-thyroid) Depression | 3270 (47%) 368 (5%) 217 (3%) 474 (7%) 571 (8%) 906 (13%) 166 (2%) 1976 (28%) | 443 (45%) 36 (4%) 21 (2%) 53 (5%) 71 (7%) 156 (16%) 15 (2%) 249 (26%) | 1578 (49%) 106 (3%) 78 (2%) 154 (5%) 226 (7%) 444 (14%) 62 (1%) 740 (23%) | <0.0001 0.05 <0.0001 0.08 0.04 0.11 <0.0001 |
| How satisfied are you with the treatment you receive? ^b | 1 = not satisfied 10 = very satisfied | 5 (3–7) | 5 (3–7) | 7 (4–8) ^{c,d} | <0.0001 |
| If you are not satisfied, indicate relevant areas you feel are affected by your thyroid treatment ^a | Weight management Fatigue or energy levels Mood Memory | 4889 (70%) 5547 (80%) 3369 (49%) 4150 (60%) | 704 (72%) 793 (81%) 458 (47%) 612 (63%) | 2136 (65%) 2257 (70%) 1232 (38%) 1671 (52%) | <0.0001 <0.0001 <0.0001 <0.0001 |

(continued)

TABLE 2. (CONTINUED)

| Survey question | Possible response | LT4 (n = 6949) | LT4 + LT3 (n = 978) | DTE (n = 3239) | p-Value |
|---|--|---|---|---|---------|
| How satisfied are you with your current physician who treats you for your thyroid condition? ^b | 1 = not satisfied 10 = very satisfied | 5 (3–8) | 6 (3–8) | 7 (4–9) ^{c,d} | <0.0001 |
| | | | | | |
| How knowledgeable is your doctor and/or physicians in general about hypothyroid treatment? ^b | 1 = not knowledgeable 10 = very knowledgeable | 5 (3–8) | 5 (3–8) | 5 (2–8) | 0.012 |
| | | | | | |
| How many times have you changed doctors because you were not satisfied with the treatment? ^a | Never Once 2–4 times 5–9 times >10 times | 2775 (39%) 1476 (21%) 2408 (33%) 456 (6%) 92 (1%) | 163 (16%) 156 (15%) 481 (48%) 176 (17%) 37 (4%) | 372 (11%) 407 (12%) 1636 (48%) 783 (23%) 190 (6%) | <0.0001 |
| | | | | | |
| How would you rate the need for new hypothyroid treatments? ^b | 1 = no need 10 = strong need | 10 (8,10) | 10 (9,10) ^c | 10 (10,10) ^c | <0.0001 |
| | | | | | |
| Tried alternative hypothyroid treatment not prescribed ^a | Yes No | 1316 (19%) 5633 (81%) | 309 (32%) 669 (68%) | 1483 (46%) 1756 (54%) | <0.0001 |
| | | | | | |
| How has your life been affected by your hypothyroidism? ^b | 1 = not affected 10 = strongly affected | 9 (7–10) | 10 (8–10) ^c | 10 (9–10) ^c | <0.0001 |
| | | | | | |

^aSummarized as frequency (%).

^bSummarized as median (IQR).

^cSignificantly different from respondents taking LT4 by Mann–Whitney U-test ($p < 0.0001$).

^dSignificantly different from respondents taking LT4 + T3 by Mann–Whitney U-test ($p < 0.0001$).

TABLE 3. UNIVARIATE ASSOCIATION BETWEEN DEMOGRAPHIC DATA AND CHARACTERISTICS OF HYPOTHYROIDISM WITH DISSATISFACTION OF HYPOTHYROIDISM TREATMENT (CATEGORIZED AS RANKING TREATMENT SATISFACTION AS 1–5) FOR THE TOTAL SAMPLE (N=11,166)

| Survey question | Possible response | OR [CI] | p-Value |
|--|--------------------------|-------------------|---------|
| Sex | Female | 1.68 [1.40–2.02] | <0.0001 |
| Age | 31–40 years | Reference | |
| | 41–50 years | 0.99 [0.89–1.10] | 0.821 |
| | 51–60 years | 0.87 [0.78–0.97] | 0.012 |
| | >61 years | 0.565 [0.51–0.63] | <0.0001 |
| Etiology | Hashimoto/autoimmune | Reference | |
| | Radioactive iodine | 0.80 [0.69–0.92] | 0.002 |
| | Surgery | 0.82 [0.73–0.91] | <0.0001 |
| | Other | 0.97 [0.89–1.06] | 0.533 |
| Treatment duration | ≥6 years | 0.93 [0.86–1.01] | 0.07 |
| Change physician | Twice or more | 1.53 [1.42–1.63] | <0.0001 |
| Relevant areas that are affected by thyroid treatment | Weight management | 3.11 [2.86–3.38] | <0.0001 |
| | Fatigue or energy levels | 5.83 [5.25–6.47] | <0.0001 |
| | Mood | 4.21 [3.89–4.56] | <0.0001 |
| | Memory | 4.20 [3.88–4.55] | <0.0001 |
| Tried alternative hypothyroid treatment not prescribed by doctor | Yes | 1.45 [1.34–1.58] | <0.0001 |
| Self-reported stress or medical condition | | 0.96 [0.89–1.04] | 0.289 |
| Self-reported depression | | 1.66 [1.53–1.81] | <0.0001 |
| Hypothyroid treatment | LT4 | Reference | |
| | LT4 + LT3 | 1.04 [0.92–1.19] | 0.512 |
| | DTE | 0.41 [0.37–0.44] | <0.0001 |

A significant OR of >1 indicates dissatisfaction with hypothyroidism treatment. OR, odds ratio; CI, confidence interval.

TABLE 4. MULTIVARIATE ASSOCIATION BETWEEN DEMOGRAPHIC DATA AND CHARACTERISTICS OF HYPOTHYROIDISM WITH DISSATISFACTION OF HYPOTHYROIDISM TREATMENT (CATEGORIZED AS RANKING TREATMENT SATISFACTION AS 1–5) FOR THE TOTAL SAMPLE (N=11,166) AND FOR SUBGROUP 1 (RESPONDENTS WITHOUT DEPRESSION, STRESSORS, OR MEDICAL CONDITIONS, N=3670)

| Survey question | Possible response | OR [CI] for the entire sample (n=11,166) | OR [CI] for subgroup 1 (respondents without depression, stressors, or medical conditions, n=3670) |
|--|--------------------------|--|---|
| Sex | Female | 1.26 [1.02–1.57]* | 1.22 [0.89–1.68] |
| Age | 31–40 years | | Reference |
| | 41–50 years | 1.13 [1.00–1.28] | 1.16 [0.96–1.40] |
| | 51–60 years | 1.20 [1.05–1.36]* | 1.19 [0.98–1.44] |
| | >61 years | 0.87 [0.76–0.99]* | 0.93 [0.76–1.13] |
| Etiology | Hashimoto/autoimmune | | Reference |
| | Radioactive iodine | 0.78 [0.66–0.92]* | 0.75 [0.59–0.96]* |
| | Surgery | 0.76 [0.66–0.86]** | 0.79 [0.65–0.96]* |
| | Other | 1.10 [0.99–1.22] | 1.12 [0.96–1.31] |
| Treatment duration | ≥6 years | 0.85 [0.78–0.93]** | 0.88 [0.77–1.01] |
| Change physician | Twice or more | 1.65 [1.49–1.82]** | 1.53 [1.32–1.78]** |
| Relevant areas that are affected by thyroid treatment | Weight management | 1.95 [1.77–2.15]** | 2.17 [1.88–2.52]** |
| | Fatigue or energy levels | 2.71 [2.40–3.05]** | 3.05 [2.58–3.61]** |
| | Mood | 2.07 [1.88–2.28]** | 2.37 [2.05–2.74]** |
| | Memory | 2.04 [1.86–2.25]** | 2.19 [1.89–2.52]** |
| Tried alternative hypothyroid treatment not prescribed by doctor | Yes | 1.63 [1.47–1.81]** | 1.67 [1.42–1.96]** |
| Self-reported stress or medical condition | | 0.75 [0.69–0.82]** | n/a |
| Self-reported depression | | 1.13 [1.02–1.25]* | n/a |
| Hypothyroid treatment | LT4 | | Reference |
| | LT4 + LT3 | 0.58 [0.50–0.68]** | 0.49 [0.39–0.63]** |
| | DTE | 0.28 [0.25–0.31]** | 0.28 [0.24–0.34]** |

Significant OR of >1 indicates dissatisfaction with hypothyroidism treatment. *p<0.05; **p<0.0001.

TABLE 5. COMPARISON MEDIAN (IQR) PERCEPTION OF SATISFACTION REGARDING HYPOTHYROID TREATMENT BY SELF-REPORTED MEDICATION

| <i>Subgroup 1: Respondents without depression, stressors, or medical conditions</i> | <i>LT4</i> (n=2206) | <i>LT4 + LT3</i> (n=316) | <i>DTE</i> (n=1148) | <i>p-Value</i> |
|---|------------------------|-----------------------------|-------------------------|----------------|
| How satisfied are you with the treatment you receive? | 5 (3–7) | 6 (3–8) | 7 (5–9) ^{a,b} | <0.0001 |
| How satisfied are you with your current physician who treats you for your thyroid condition? | 5 (3–8) | 6 (3–8) | 7 (4,9) ^a | <0.0001 |
| How knowledgeable is your doctor and/or physicians in general about hypothyroid treatment? | 5 (3–8) | 5 (3–8) | 5 (2–8) | 0.04 |
| How would you rate the need for new hypothyroid treatments? | 10 (8–10) | 10 (10–10) ^a | 10 (10–10) ^a | <0.0001 |
| How has your life been affected by your hypothyroidism? | 9 (7–10) | 10 (9–10) ^a | 10 (8–10) ^a | <0.0001 |
| <i>Subgroup 2: Respondents without depression, stressors, or medical condition matched by sex, age, and hypothyroid treatment</i> | <i>LT4</i> (n=614) | <i>LT4 + LT3</i> (n=307) | <i>DTE</i> (n=614) | <i>p-Value</i> |
| How satisfied are you with the treatment you receive? | 5 (3–7) | 6 (3–8) | 7 (5–9) ^{a,b} | <0.0001 |
| How satisfied are you with your current physician who treats you for your thyroid condition? | 5 (3–8) | 6 (3–8) ^a | 7 (3–9) ^a | <0.0001 |
| How knowledgeable is your doctor and/or physicians in general about hypothyroid treatment? | 5 (2–7) | 5 (3–8) | 5 (2–8) | 0.05 |
| How would you rate the need for new hypothyroid treatments? | 10 (8–10) | 10 (10–10) ^a | 10 (10–10) ^a | <0.0001 |
| How has your life been affected by your hypothyroidism? | 9 (7–10) | 10 (8–10) | 10 (8–10) | <0.0001 |
| <i>Subgroup 3: Respondents with depression but without stressors or medical conditions</i> | <i>LT4</i> (n=457) | <i>LT4 + LT3</i> (n=42) | <i>DTE</i> (n=180) | <i>p-Value</i> |
| How satisfied are you with the treatment you receive? | 4 (1–6) | 4 (2–6) | 5 (3–7) ^a | <0.0001 |
| How satisfied are you with your current physician who treats you for your thyroid condition? | 5 (2–7) | 5 (2–8) | 6 (3–8) ^a | 0.001 |
| How knowledgeable is your doctor and/or physicians in general about hypothyroid treatment? | 4 (2–6) | 5 (2–7) | 4 (2–8) | 0.824 |
| How would you rate the need for new hypothyroid treatments? | 10 (9–10) | 10 (10–10) | 10 (10–10) ^a | <0.0001 |
| How has your life been affected by your hypothyroidism? | 10 (8–10) | 10 (10–10) | 10 (10,10) ^a | <0.0001 |
| <i>Subgroup 4: Thyroid cancer without depression, stressors, or medical conditions</i> | <i>LT4</i> (n=224) | <i>LT4 + LT3</i> (n=48) | <i>DTE</i> (n=74) | <i>p-Value</i> |
| How satisfied are you with the treatment you receive? | 5 (3,8) | 6 (4–8) | 7 (3–8) | 0.224 |
| How satisfied are you with your current physician who treats you for your thyroid condition? | 7 (4–8) | 6 (3–9) | 6 (2–8) | 0.117 |
| How knowledgeable is your doctor and/or physicians in general about hypothyroid treatment? | 7 (4–9) | 6 (4–9) | 4 (3–7) ^a | <0.0001 |
| How would you rate the need for new hypothyroid treatments? | 10 (7–10) | 10 (10–10) | 10 (10–10) | <0.0001 |
| How has your life been affected by your hypothyroidism? | 10 (8–10) | 10 (10–10) ^a | 10 (9–10) | <0.0001 |

^aSignificantly different from respondents taking LT4 by Mann–Whitney *U*-test ($p < 0.0001$).

^bSignificantly different from respondents taking LT4 + T3 by Mann–Whitney *U*-test ($p < 0.0001$).

HYPOTHYROIDISM TREATMENT SATISFACTION

- T6** ▶ LT4 + LT3 (Table 6). The multivariate analysis of patient dissatisfaction revealed ORs of >1.0 for (i) weight management, fatigue, mood, and memory; (ii) changing physicians twice or more; and (iii) tried alternative treatment for hypothyroidism (Table X+1).
- AU4** ▶ In contrast, ORs of <1.0 were found for (i) hypothyroidism caused by RAI and surgery and (ii) therapy with LT4 + LT3 or DTE (Table 4).
- ST4** ▶ Subgroup 2 (Supplementary Table S4; *n* = 1535) is a matched subset of subgroup 1, with the respondents taking LT4 and DTE being matched 2:1 by sex (only female respondents), age, etiology of hypothyroidism, and treatment duration to individuals taking LT4 + LT3. The matching resulted in the size of the groups being reduced to 1535 respondents (Table 5). Despite the matching, the results obtained in subgroup 2 remained very similar to subgroup 1 (Tables 5 and 6).
- ST5** ▶ Subgroup 3 (Supplementary Table S5, *n* = 679) respondents who reported depression but did not report stressors or other medical conditions in general ranked lower on all parameters when compared to other subgroups. The median perception of those taking LT4 regarding treatment satisfaction was 4 (IQR = 1–6), physician satisfaction was 5 (IQR = 2–7), and physician knowledge was 4 (IQR = 2–6; Table 5). Individuals on LT4 + LT3 reported similar perceptions (Table 5). Respondents taking DTE had the highest scores for treatment satisfaction (5 [IQR = 3–7]) and physician satisfaction (6 [IQR = 3–8]), albeit lower than subgroups 1 and 2. Perception

of physician knowledge remained low (4 [IQR = 2–8]), similar to other treatment groups. Respondents using all treatment modalities ranked at the highest level (rank 10) the need for new treatments and the perception of how much their lives had been affected by hypothyroidism (Table 5). Within this group, respondents taking DTE were less likely to report fatigue/low energy levels and memory problems compared to those on LT4 or LT4 + LT3, though the difference did not reach the statistical significance criterion of *p* < 0.001 (Table 6).

Subgroup 4 (Supplementary Table S6; *n* = 346) respondents (those with thyroid cancer but no other reported comorbidities) exhibited a similar upward trend in treatment satisfaction with DTE, although not reaching statistical significance (Table 5). Perceptions about physician satisfaction also did not exhibit statistical significance between treatments. Notably, physician knowledge exhibited a downward trend, with patients on DTE ranking the lowest (4 [IQR = 3–7]). As before, the need for new treatments and impact of hypothyroidism on their lives were ranked at the highest level (Table 5). Within this group, there was a trend toward respondents taking LT4 + LT3 being more likely to report weight management as a relevant area affected by hypothyroidism compared to LT4 users. There was a trend toward those taking DTE being less likely to report fatigue/low energy levels and mood issues compared to those on LT4 or LT4 + LT3 (Table 6). Respondents taking DTE exhibited a

◀ **ST6**

TABLE 6. COMPARISON OF HYPOTHYROID SIDE-EFFECTS THAT ARE A PRIMARY CONCERN TO RESPONDENTS BY SELF-REPORTED MEDICATION

| <i>Subgroup 1: Respondents without depression, stressors, or medical conditions</i> | LT4 (<i>n</i> = 2206) | LT4 + LT3 (<i>n</i> = 316) | DTE (<i>n</i> = 1148) | p-Value |
|---|---------------------------|--------------------------------|---------------------------|---------|
| Weight management | 69% | 74% | 64% ^{a,b} | <0.0001 |
| Fatigue/energy levels | 75% | 76% | 64% ^{a,b} | <0.0001 |
| Mood | 42% | 40% | 30% ^{a,b} | <0.0001 |
| Memory or other problems with thinking | 55% | 59% | 44% ^{a,b} | <0.0001 |
| <i>Subgroup 2: Respondents without depression, stressors, or medical condition matched by sex, age, and hypothyroid treatment</i> | LT4 (<i>n</i> = 614) | LT4 + LT3 (<i>n</i> = 307) | DTE (<i>n</i> = 614) | p-Value |
| Weight management | 71% | 74% | 59% ^{a,b} | <0.0001 |
| Fatigue/energy levels | 81% | 77% | 62% ^{a,b} | <0.0001 |
| Mood | 47% | 40% | 29% ^{a,b} | <0.0001 |
| Memory or other problems with thinking | 62% | 59% | 43% ^{a,b} | <0.0001 |
| <i>Subgroup 3: Respondents with depression but without stressors or medical conditions</i> | LT4 (<i>n</i> = 457) | LT4 + LT3 (<i>n</i> = 42) | DTE (<i>n</i> = 180) | p-Value |
| Weight management | 77% | 71% | 75% | 0.690 |
| Fatigue/energy levels | 87% | 93% | 77% | 0.002 |
| Mood | 64% | 60% | 58% | 0.252 |
| Memory or other problems with thinking | 74% | 71% | 61% | 0.005 |
| <i>Subgroup 4: Thyroid cancer without depression, stressors, or medical conditions</i> | LT4 (<i>n</i> = 224) | LT4 + LT3 (<i>n</i> = 48) | DTE (<i>n</i> = 74) | p-Value |
| Weight management | 59% | 79% | 64% | 0.031 |
| Fatigue/energy levels | 77% | 85% | 65% | 0.026 |
| Mood | 44% | 50% | 28% | 0.028 |
| Memory or other problems with thinking | 55% | 65% | 45% | 0.087 |

^aSignificantly different from respondents taking LT4 by chi-square test (*p* < 0.0001).

^bSignificantly different from respondents taking LT4 + T3 by chi-square test (*p* < 0.0001).

trend toward being less likely to report memory problems compared to LT4 + LT3 users (Table 6).

Discussion

The present study reports the results of a large-scale assessment of patients' perceptions about hypothyroidism. It should be emphasized that the study is based on responses provided by a self-selected sample that is unlikely to represent the >10 million Americans being treated for hypothyroidism. For example, we know that women comprise approximately 80% of all hypothyroid cases (38), whereas here a 21:1 ratio was observed between female and male respondents (Table 1). Also, based on the authors' experience, <10% of the hypothyroid patients are on DTE, and yet here it was observed that 29% of the respondents were taking DTE (Table 1). Thus, a number of elements in the cohort are acknowledged that indicate this is not a bias-free population. However, the self-reported issues with weight management, fatigue/energy levels, mood, and memory observed in this study corroborate findings reported previously (6), as well as the observation of increased BMI and issues with memory and confusion observed in LT4-treated hypothyroid individuals (18,22).

The results of this survey suggest that dissatisfaction with hypothyroidism treatment and treating physicians are important problems for patients. Furthermore, a strong need for development of new treatments for hypothyroidism was identified. These are noteworthy findings, as among physicians, treatment of hypothyroidism is considered to be straightforward. The median reported satisfaction with treatment in the entire group of only 5 on a scale of 1–10 is remarkable and concerning, even if this only reflects the situation in a small portion of patients. In light of the high prevalence of hypothyroidism, the findings suggest a significant burden of unsuccessfully resolved symptoms across the population, particularly in women. At face value, these results indicate that although physicians believe that hypothyroidism is an eminently treatable condition, a portion of such patients believe their lives have been greatly affected by the disease and are unhappy with their treatment and physicians. Almost universally, they believe there is a need for the development of new treatment forms. It is also remarkable that there is a clear preference for DTE in the whole group, as well as when the group was broken down into multiple subgroups. Of course, the study is limited by the potential intrinsic sample bias. However, the suggestion that something "real" is being captured is bolstered by the finding that the survey did not demonstrate a clear positive patient response to synthetic combination therapy with LT4 + LT3.

The focus of prior research into combination therapy has been on synthetic LT4 + LT3 rather than DTE. The 14 trials of synthetic LT4 + LT3 that have been completed thus far show some patient preference for combination therapy, but have failed to show obvious superiority of LT4 + LT3 (6,24–30,32–36). Thyroid-related symptoms were generally not improved with combination therapy, other than when TSH suppression was achieved. Parameters such as QoL, mood, and neurocognitive performance were only improved in a minority of studies. These studies each have limitations (e.g., once daily dosing, short duration study, small study size, disparate TSH values between study groups) that have been previously reviewed extensively (2,39). Failure to demonstrate superiority of LT4 +

LT3 could be due to any combination of these shortcomings in study design or the drug formulation. However, it is also possible that synthetic combination therapy is not superior to LT4. The one double-blind, randomized, placebo-controlled trial of DTE versus LT4 also failed to show that DTE resulted in improvement in a number of neuropsychological measures or symptoms (37). Two secondary outcomes—preference for DTE and modest weight loss—were associated with DTE use. However, participants only took each therapy for 16 weeks in the study, and long-term data were not reported. A preference for LT4 + LT3 has also been shown to be associated with the weight loss achieved during therapy, although TSH suppression was a confounding factor (24). In an attempt to query patients, a Danish Internet-based questionnaire surveyed 293 individuals on combination therapy, revealing that 84% of patients who had residual symptoms while on monotherapy perceived improved symptoms after switching to combination therapy, and 81% stated a clear preference for continuing combination therapy (40). Few physicians are willing to prescribe combination therapy to manage residual symptoms (41), and minimal information is available to describe prescription patterns of DTE.

If the randomized, placebo-controlled clinical trials have not shown benefits of either LT4 + LT3 or DTE, but patients surveys (40) and online patient forum opinions suggest that combination therapy is preferred, this reflects either uncontrolled bias or lack of identification of the appropriate patient group for clinical trial enrollment. Prospective clinical trials of combination therapy have not been conducted that have specifically recruited dissatisfied patients or patients with the lowest circulating T3 levels. No trials have incorporated assessment of deiodinase or thyroid hormone transporter polymorphisms into their primary design. Retrospective data suggest that patient preference may be linked to a patient's complement of thyroid hormone metabolism-associated polymorphisms (42,43).

If DTE provides more satisfactory therapy for patients with hypothyroidism, it is possible that this is due to (i) patient preference for higher treatment doses, (ii) patients being rendered T3 thyrotoxic, (iii) the presence of some other orally active substance other than T4 and T3 within the DTE, (iv) a confounding factor such as use of other complementary or alternative medicine in users of DTE, or (v) an as yet unidentified aspect of thyroid physiology. It is important to keep in mind though that DTE, like LT4, does not restore normal thyroid hormone homeostasis. Circulating levels of T3 are increased during DTE therapy and may transiently exceed the upper limits of normal, while the average blood levels of T4 are below the lower limit of normal. High levels of T3 are known to enhance mood in studies of patients with depression, and it is possible that patient preference for DTE reflects a positive effect of supra-physiologic T3 levels on mood. At the same time, it is unknown whether transient supra-physiologic T3 levels are safe or whether they could promote arrhythmias, especially in older or susceptible patients. With respect to patients potentially preferring higher doses, it has recently been shown in a randomized blinded trial that patients preferred the LT4 dose that they believed was the highest, even if they had not correctly identified this is the highest dose (44).

A major strength of this study is the large sample size. However, limitations of the study include sampling and/or recall bias, subjectivity, a lack of an external control (e.g., patients treated for other endocrine disorders or other chronic

medical conditions), and the use of a non-validated survey instrument. With respect to the first limitation, the increased likelihood that patients with significant dissatisfaction with their therapy for hypothyroidism were more likely to have been motivated to complete the survey than those who felt unaffected by their hypothyroidism, or even those who felt happy with their treatment, is acknowledged. To highlight this, 50% of the survey respondents had changed their physician twice or more. In addition, two thirds of respondents believed that stress or physical comorbidities other than hypothyroidism might account for at least part of their symptoms. It is anticipated, although not verified, that this questionnaire attracted dissatisfied patients or was preferentially publicized among groups of dissatisfied patients. It is therefore anticipated that one end, or possibly both ends, of the spectrum of opinion about treatment have been captured. If it is assumed that approximately 15% of treated patients feel worse than individuals without thyroid disease, and if a subset of these patients has been captured, the results, despite the inherent bias, nevertheless indicate a significant unmet need among patients. The study also seems to have captured predominately females. It is known that hypothyroidism affects women and men at a ratio of 9:1, and yet the respondents exhibited a ratio of 21:1.

With respect to the third and fourth limitations, because the diagnosis of hypothyroidism is self-reported, it is not possible to say for sure whether the respondents do not include a significant number of individuals who are taking thyroid hormone because of a misdiagnosis of hypothyroidism or for a condition other than hypothyroidism, for example fibromyalgia. Additionally, hypothyroid patients may also mistakenly attribute unrelated symptoms or decreased QoL to their thyroid condition. Once a patient has been diagnosed with a chronic condition such as hypothyroidism, there is a natural tendency for a patient to associate their spectrum of symptoms with this condition. The attribution of these symptoms may be mistaken. If there is mis-attribution of symptoms, then these symptoms would not be expected to resolve with adjustment of therapy for hypothyroidism. It is well known that patients with hypothyroidism have a greater disease burden than the general population (6,45), and that hypothyroid patients treated to achieve a normal TSH may remain symptomatic (46,47). However, not only does manipulation of thyroid status in these individuals fail to resolve symptoms (35,44), but also treatment of euthyroid individuals with hypothyroid-like symptoms does not resolve symptoms (48). An attempt was made to mitigate these particular limitations by requesting that respondents report co-existent medical conditions and by examining subgroups who did not have these conditions. In general, the findings remained generally unaltered in these subgroup analyses. However, it is not known if other medical conditions have been fully captured that might be the major source of some of the symptoms reported.

In conclusion, it is clear that a subset of patients with hypothyroidism are not satisfied with their current therapy or their physicians. Future surveys should aim at sampling representative cohorts of hypothyroid individuals to describe patient experience and satisfaction with treatment globally. The overall limitation of the studies performed so far highlights the need for high-quality research to study treatments for hypothyroidism. Such treatments may include hormonal therapies, supportive care interventions, life-style modification interventions (e.g., exercise, diet), or complementary/

alternative treatments. Definitive trials need to be adequately statistically powered to detect clinically significant changes in important patient outcomes, attempt to provide steady levels of T3, and specifically target individuals who are symptomatic. Failure to conduct well-designed studies to advance understanding in this area promotes reliance on anecdotal case reports/series, self-report survey studies (such as this one), and observational registry data. The QoL issues raised by this survey need to be considered when making medical decisions to render patients permanently hypothyroid, and these issues should be discussed with patients. More research is also needed into weighing the risks and benefits of strategies to preserve thyroid function in situations where this may be a reasonable option (e.g., active surveillance of papillary microcarcinoma, or use of hemithyroidectomy instead of total thyroidectomy in low-risk differentiated thyroid cancer). In the absence of a better understanding of hypothyroidism treatment, patients will continue to experience unresolved symptoms and be exposed to the risks and expenses of treatments with unproven benefits and possible harm (49).

Acknowledgments

The authors wish to thank the ATA for hosting the survey that generated these data, and the ATA staff who launched and administered the survey, especially Bobbi Smith, Adonia Coates, and Kelly Hoff. They also gratefully acknowledge the multiple patient advocacy groups that broadcasted the survey and the participation of patients with hypothyroidism who took the time to contribute to this survey.

Author Disclosure Statement

The authors have nothing to disclose.

◀AU8

References

1. Chaker L, Bianco AC, Jonklaas J, Peeters RP 2017 Hypothyroidism. *Lancet* **390**:1550–1562.
2. 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.
3. Wiersinga WM, Duntas L, Fadéyev V, Nygaard B, Vanderpump MP 2012 2012 ETA guidelines: the use of L-T4 + L-T3 in the treatment of hypothyroidism. *Eur Thyroid J* **1**: 55–71.
4. Gil-Ibanez P, Belinchon MM, Morte B, Obregon MJ, Bernal J 2017 Is the intrinsic genomic activity of thyroxine relevant *in vivo*? Effects on gene expression in primary cerebrocortical and neuroblastoma cells. *Thyroid* **27**:1092–1098.
5. McAninch EA, Bianco AC 2016 The history and future of treatment of hypothyroidism. *Ann Intern Med* **164**:50–56.
6. Saravanan P, Chau WF, Roberts N, Vedhara K, Greenwood R, Dayan CM 2002 Psychological well-being in patients on “adequate” doses of L-thyroxine: results of a large, controlled community-based questionnaire study. *Clin Endocrinol (Oxf)* **57**:577–585.

7. Canaris GJ, Steiner JF, Ridgway EC 1997 Do traditional symptoms of hypothyroidism correlate with biochemical disease? *J Gen Intern Med* **12**:544–550.
8. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC 2000 The Colorado thyroid disease prevalence study. *Arch Intern Med* **160**:526–534.
9. Ladenson PW 2002 Psychological wellbeing in patients. *Clin Endocrinol (Oxf)* **57**:575–576.
10. Massolt ET, van der Windt M, Korevaar TI, Kam BL, Burger JW, Franssen GJ, Lehmpul I, Kohrle J, Visser WE, Peeters RP 2016 Thyroid hormone and its metabolites in relation to quality of life in patients treated for differentiated thyroid cancer. *Clin Endocrinol (Oxf)* **85**:781–788.
11. Bould H, Panicker V, Kessler D, Durant C, Lewis G, Dayan C, Evans J 2012 Investigation of thyroid dysfunction is more likely in patients with high psychological morbidity. *Fam Pract* **29**:163–167.
12. Ott J, Promberger R, Kober F, Neuhold N, Tea M, Huber JC, Hermann M 2011 Hashimoto's thyroiditis affects symptom load and quality of life unrelated to hypothyroidism: a prospective case-control study in women undergoing thyroidectomy for benign goiter. *Thyroid* **21**:161–167.
13. Quinque EM, Villringer A, Kratzsch J, Karger S 2013 Patient-reported outcomes in adequately treated hypothyroidism—insights from the German versions of ThyDQoL, ThySRQ and ThyTSQ. *Health Qual Life Outcomes* **11**:68.
14. Wekking EM, Appelhof BC, Fliers E, Schene AH, Huyser J, Tijssen JG, Wiersinga WM 2005 Cognitive functioning and well-being in euthyroid patients on thyroxine replacement therapy for primary hypothyroidism. *Eur J Endocrinol* **153**:747–753.
15. Hedman C, Djarv T, Strang P, Lundgren CI 2017 Effect of thyroid-related symptoms on long-term quality of life in patients with differentiated thyroid carcinoma: a population-based study in Sweden. *Thyroid* **27**:1034–1042.
16. Alhashemi A, Jones JM, Goldstein DP, Mina DS, Thabane L, Sabiston CM, Chang EK, Brierley JD, Sawka AM 2017 An exploratory study of fatigue and physical activity in Canadian thyroid cancer patients. *Thyroid* **27**:1156–1163.
17. McAninch EA, Bianco AC 2016 The history and future of treatment of hypothyroidism. *Ann Intern Med* **164**:50–56.
18. Peterson SJ, McAninch EA, Bianco AC 2016 Is a normal TSH synonymous with “euthyroidism” in levothyroxine monotherapy? *J Clin Endocrinol Metab* **101**:4964–4973.
19. Gullo D, Latina A, Frasca F, Le Moli R, Pellegriti G, Vigneri R 2011 Levothyroxine monotherapy cannot guarantee euthyroidism in all athyreotic patients. *PLoS One* **6**: e22552.
20. Werneck de Castro JP, Fonseca TL, Ueta CB, McAninch EA, Abdalla S, Wittmann G, Lechan RM, Gereben B, Bianco AC 2015 Differences in hypothalamic type 2 deiodinase ubiquitination explain localized sensitivity to thyroxine. *J Clin Invest* **125**:769–781.
21. Samuels MH, Kolobova I, Smeraglio A, Peters D, Purnell JQ, Schuff KG 2016 Effects of levothyroxine replacement or suppressive therapy on energy expenditure and body composition. *Thyroid* **26**:347–355.
22. Corrigenda 2017 *J Clin Endocrinol Metab* **102**:1406.
23. Taylor PN, Iqbal A, Minassian C, Sayers A, Draman MS, Greenwood R, Hamilton W, Okosieme O, Panicker V, Thomas SL, Dayan C 2014 Falling threshold for treatment of borderline elevated thyrotropin levels—balancing benefits and risks: evidence from a large community-based study. *JAMA Intern Med* **174**:32–39.
24. 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.
25. Bunevicius R, Kazanavicius G, Zalinkevicius R, Prange AJ Jr 1999 Effects of thyroxine as compared with thyroxine plus triiodothyronine in patients with hypothyroidism. *N Engl J Med* **340**:424–429.
26. Bunevicius R, Jakuboniene 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.
27. 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.
28. Escobar-Morreale HF, Botella-Carretero JJ, 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.
29. 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.
30. 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 crossover study. *Eur J Endocrinol* **161**:895–902.
31. 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.
32. 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.
33. 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 (Oxf)* **60**:750–757.
34. 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.
35. 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.

HYPOTHYROIDISM TREATMENT SATISFACTION

36. 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.

37. Hoang TD, Olsen CH, Mai VQ, Clyde PW, Shakir MK 2013 Desiccated thyroid extract compared with levothyroxine in the treatment of hypothyroidism: a randomized, double-blind, crossover study. *J Clin Endocrinol Metab* **98**:1982–1990.

38. Aoki Y, Belin RM, Clickner R, Jeffries R, Phillips L, Mahaffey KR 2007 Serum TSH and total T4 in the United States population and their association with participant characteristics: National Health and Nutrition Examination Survey (NHANES 1999–2002). *Thyroid* **17**:1211–1223.

39. Jonklaas J 2017 Persistent hypothyroid symptoms in a patient with a normal thyroid stimulating hormone level. *Curr Opin Endocrinol Diabetes Obes* **24**:356–363.

40. Michaelsson LF, Medici BB, la Cour JL, Selmer C, Roder M, Perrild H, Knudsen N, Faber J, Nygaard B 2015 Treating hypothyroidism with thyroxine/triiodothyronine combination therapy in Denmark: following guidelines or following trends? *Eur Thyroid J* **4**:174–180.

41. 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.

42. Carle A, Faber J, Steffensen R, Laurberg P, Nygaard B 2017 Hypothyroid patients encoding combined MCT10 and DIO2 gene polymorphisms may prefer L-T3 + L-T4 combination treatment—data using a blind, randomized, clinical study. *Eur Thyroid J* **6**:143–151.

43. 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.

44. Samuels M, Kolobova I, Niederhausen M, Janowsky J, Schuff K 2017 Effects of altering levothyroxine (L-T4) doses on quality of life, mood and cognition in L-T4 treated subjects: a double-blinded, randomized, controlled trial. *Thyroid* **27**:TBD (abstract).

45. Thvilum M, Brandt F, Almind D, Christensen K, Brix TH, Hegedus L 2014 Increased psychiatric morbidity before and after the diagnosis of hypothyroidism: a nationwide register study. *Thyroid* **24**:802–808.

46. Bianchi GP, Zaccheroni V, Solaroli E, Vescini F, Cerutti R, Zoli M, Marchesini G 2004 Health-related quality of life in patients with thyroid disorders. *Qual Life Res* **13**:45–54.

47. Samuels MH, Kolobova I, Smeraglio A, Peters D, Janowsky JS, Schuff KG 2014 The effects of levothyroxine replacement or suppressive therapy on health status, mood, and cognition. *J Clin Endocrinol Metab* **99**:843–851.

48. Pollock MA, Sturrock A, Marshall K, Davidson KM, Kelly CJ, McMahon AD, McLaren EH 2001 Thyroxine treatment in patients with symptoms of hypothyroidism but thyroid function tests within the reference range: randomised double blind placebo controlled crossover trial. *BMJ* **323**:891–895.

49. Jonklaas J 2016 Risks and safety of combination therapy for hypothyroidism. *Expert Rev Clin Pharmacol* **9**:1057–1067.

Address correspondence to:
 Antonio C. Bianco, MD, PhD
 Division of Endocrinology and Metabolism
 Rush University Medical Center
 1735 W Harrison St, Cohn Building Rm 212
 Chicago, IL 60612

E-mail: abianco@deiiodinase.org

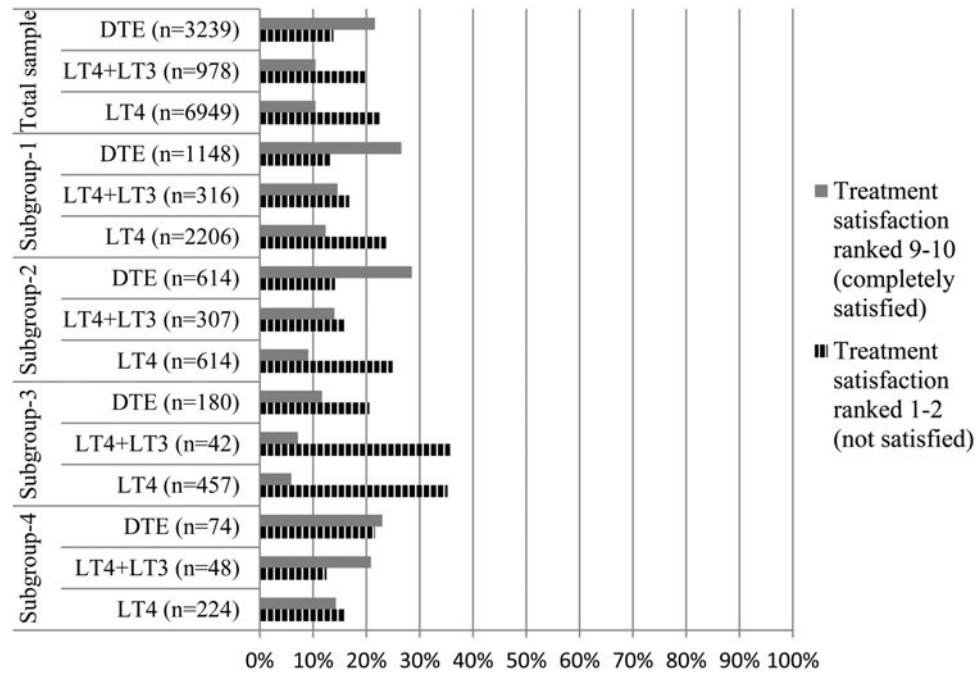
Jacqueline Jonklaas, MD
 Division of Endocrinology
 Georgetown University
 4000 Reservoir Road, NW, Bldg. D Suite 230
 Washington, DC 20007

E-mail: jonklaaj@georgetown.edu

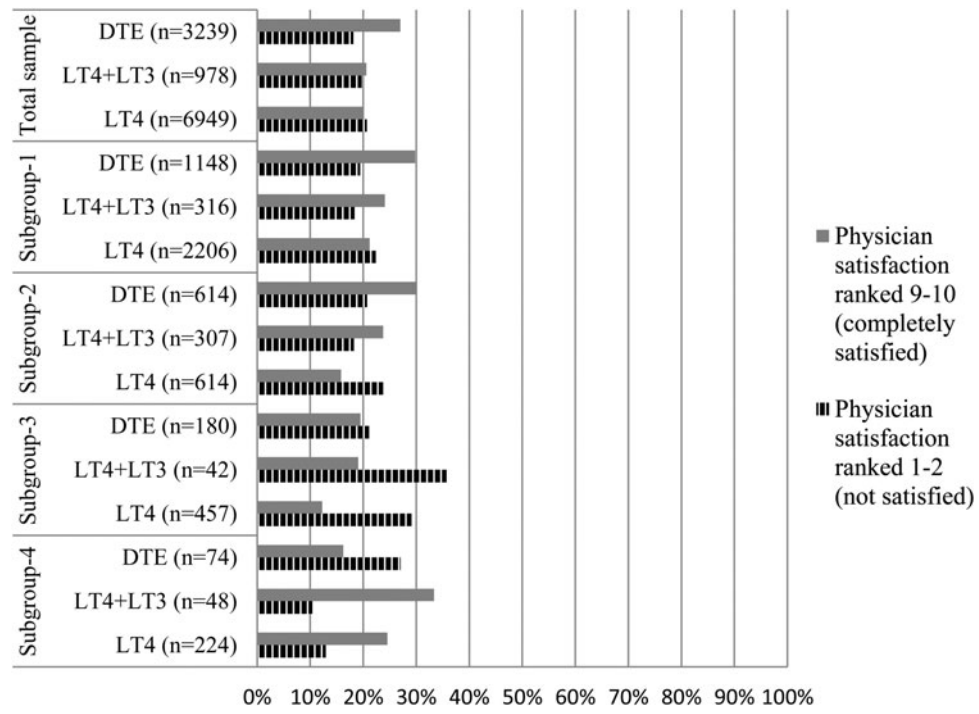


◀AUS

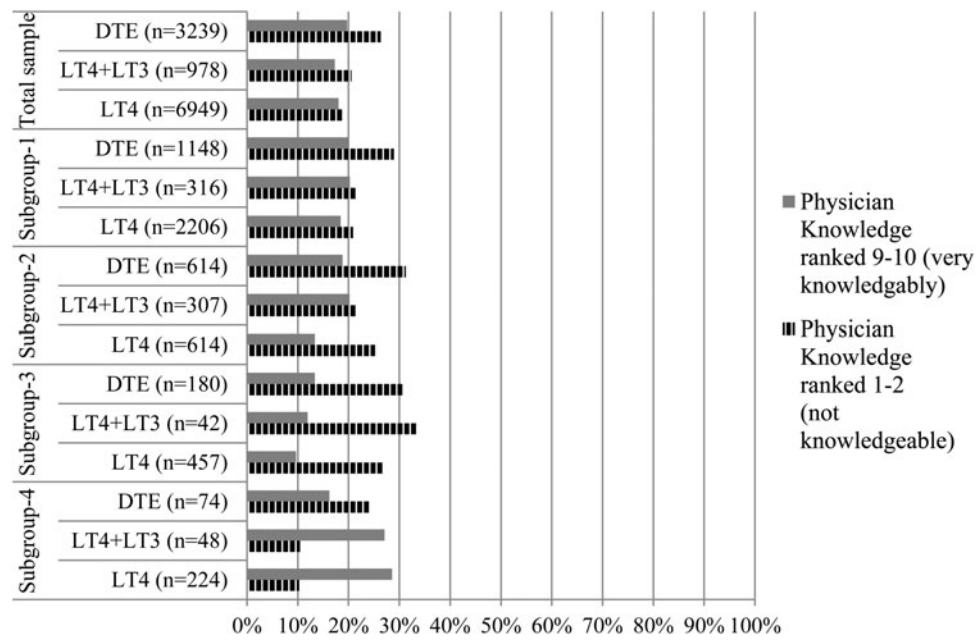
Supplementary Data



SUPPLEMENTARY FIG. S1. Comparison of respondents who ranked treatment satisfaction 1–2 (not satisfied) versus 9–10 (completely satisfied) by treatment category and analysis group.



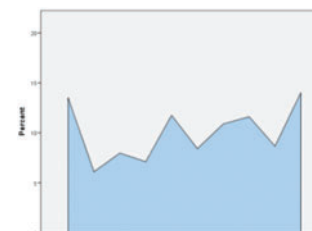
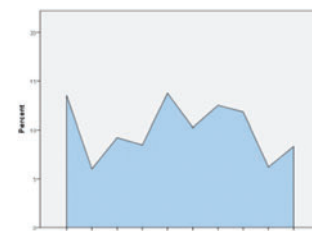
SUPPLEMENTARY FIG. S2. Comparison of respondents who ranked physician satisfaction 1–2 (not satisfied) versus 9–10 (completely satisfied) by treatment category and analysis group.



SUPPLEMENTARY FIG. S3. Comparison of respondents who ranked physician knowledge 1–2 (not knowledgeable) versus 9–10 (completely knowledgeable) by treatment category and analysis group.

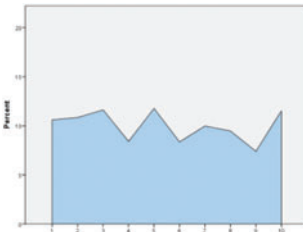
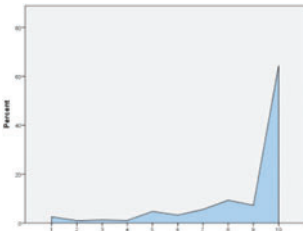
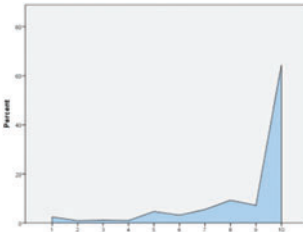
SUPPLEMENTARY TABLE S1. DEMOGRAPHIC DATA, HYPOTHYROID DISEASE CHARACTERISTICS AND PERCEPTIONS REGARDING HYPOTHYROID TREATMENT FOR THE ENTIRE COHORT (N= 12,093)

| Survey section | Survey question | Possible response | Respondents |
|---|--|--------------------------|--------------|
| Demographics | Sex ^a | Female | 11,562 (96%) |
| | | Male | 531 (4%) |
| | Age ^a | 31–40 years | 2600 (22%) |
| | | 41–50 years | 3498 (29%) |
| | | 51–60 years | 3107 (26%) |
| ≥61 years | | 2887 (24%) | |
| Hypothyroid etiology and treatment | Etiology of hypothyroidism ^a | Hashimoto/autoimmune | 5215 (43%) |
| | | Radioactive iodine | 931 (8%) |
| | | Surgery | 1836 (15%) |
| | | Other | 4111 (34%) |
| | What thyroid hormone are you currently taking? ^a | LT4 | 7207 (60%) |
| | | LT3 | 126 (1%) |
| | | LT4 + LT3 | 1013 (8%) |
| | | DTE | 3388 (28%) |
| | | DTE + LT4/LT3 | 285 (2%) |
| | | Other | 74 (1%) |
| Hypothyroid treatment duration ^a | <1 year | 852 (7%) | |
| | 1–5 years | 3626 (30%) | |
| | 6–10 years | 2676 (22%) | |
| | >10 years | 4939 (41%) | |
| Self-reported medical history | Condition not related to thyroid hormone cause symptoms? | Current stress levels | 3989 (33%) |
| | | Other medical problem | 3885 (32%) |
| | Do you have any of these medical problems? | Heart disease | 549 (5%) |
| | | Lung disease | 344 (3%) |
| | | Diabetes | 721 (6%) |
| | | Bone/muscle disease | 941 (8%) |
| | | GI disease | 1606 (13%) |
| | | Cancer (non-thyroid) | 261 (2%) |
| | | Depression | 3145 (26%) |
| | | | |
| Perception regarding hypothyroid treatment | How satisfied are you with the treatment you receive? ^b | 1 = not satisfied | 5 (3–8) |
| | | 10 = very satisfied | |
| | If you are not satisfied, indicate relevant areas you feel are affected by your thyroid treatment ^a | Weight management | 8271 (68%) |
| | | Fatigue or energy levels | 9208 (76%) |
| | | Mood | 5393 (45%) |
| Memory | | 6868 (57%) | |
| How satisfied are you with your current physician who treats you for your thyroid condition? ^b | 1 = not satisfied | 6 (3–8) | |
| | 10 = very satisfied | | |



(continued)

SUPPLEMENTARY TABLE S1. (CONTINUED)

| <i>Survey section</i> | <i>Survey question</i> | <i>Possible response</i> | <i>Respondents</i> |
|-----------------------|--|--|--|
| | How knowledgeable is your doctor and/or physicians in general about hypothyroid treatment? ^b | 1 = not knowledgeable 10 = very knowledgeable | 5 (3–8)  |
| | How many times have you changed doctors because you were not satisfied with the treatment you were receiving? ^a | Never Once 2–4 times 5–9 times >10 times | 3364 (28%) 2080 (17%) 4741 (39%) 1542 (13%) 366 (3%) |
| | How would you rate the need for new treatments for hypothyroidism? ^b | 1 = no need 10 = strong need | 10 (8–10)  |
| | Tried alternative hypothyroid treatment not prescribed by doctor | Yes No | 3440 (28%) 8653 (72%) |
| | How has your life been affected by your hypothyroidism? ⁺ | 1 = not affected 10 = strongly affected | 10 (8–10)  |

^aSummarized as frequency (%).

^bSummarized as median (IQR).

SUPPLEMENTARY TABLE S2. MULTIVARIATE ASSOCIATION BETWEEN DEMOGRAPHIC DATA AND CHARACTERISTICS OF HYPOTHYROIDISM WITH DISSATISFACTION OF HYPOTHYROIDISM TREATMENT (CATEGORIZED AS RANKING TREATMENT SATISFACTION AS 1–5) FOR THE TOTAL SAMPLE (N=11,166) AND BY HYPOTHYROID TREATMENT (LT4, N=6949; LT4 + LT3, N=978; AND DTE, N=3239)

| | <i>OR [CI] for respondents taking LT4 (n=6949)</i> | <i>OR [CI] for respondents taking LT4 + LT3 (n=978)</i> | <i>OR [CI] for respondents taking DTE (n=3239)</i> |
|---|--|---|--|
| Sex | | | |
| Female | 1.32 [1.04–1.69]* | 1.13 [0.51–2.50] | 1.02 [0.58–1.83] |
| Age | | | |
| 31–40 years | Reference | Reference | Reference |
| 41–50 years | 1.15 [0.97–1.35] | 1.03 [0.70–1.51] | 1.19 [0.95–1.49] |
| 51–60 years | 1.14 [0.97–1.35] | 1.06 [0.71–1.58] | 1.38 [1.09–1.75]* |
| >61 years | 0.80 [0.68–0.94]* | 1.09 [0.71–1.67] | 1.05 [0.80–1.36] |
| Etiology | | | |
| Hashimoto/autoimmune | Reference | Reference | Reference |
| Radioactive iodine | 0.85 [0.69–1.05] | 0.73 [0.42–1.29] | 0.65 [0.44–0.97]* |
| Surgery | 0.74 [0.63–0.87]** | 0.82 [0.56–1.21] | 0.85 [0.65–1.11] |
| Other | 1.21 [1.05–1.38]* | 0.85 [0.60–1.20] | 1.06 [0.88–1.27] |
| Treatment duration | | | |
| ≥6 years | 0.75 [0.66–0.84]** | 1.28 [0.94–1.75] | 0.99 [0.84–1.18] |
| Change physician | | | |
| Twice or more | 1.98 [1.76–2.24]** | 1.47 [1.08–1.99]* | 0.98 [0.80–1.20] |
| Relevant areas that are affected by thyroid treatment | | | |
| Weight management | 2.13 [1.88–2.40]** | 1.51 [1.09–2.08]* | 1.71 [1.41–2.06]** |
| Fatigue or energy levels | 2.50 [2.15–2.90]** | 3.46 [2.27–5.27]** | 3.04 [2.41–3.83]** |
| Mood | 2.13 [1.89–2.41]** | 1.97 [1.46–2.67]** | 1.96 [1.63–2.35]** |
| Memory | 2.02 [1.79–2.28]** | 1.53 [1.12–2.10]* | 2.26 [1.88–2.73]** |
| Tried alternative hypothyroid treatment | 2.03 [1.73–2.38]** | 1.22 [0.90–1.65] | 1.38 [1.17–1.63]** |
| Self-reported stress or medical condition | 0.73 [0.65–0.82]** | 0.94 [0.71–1.25] | 0.72 [0.61–0.85]** |
| Self-reported depression | 1.16 [1.01–1.32]* | 1.16 [0.83–1.61] | 1.07 [0.88–1.30] |

Significant OR of >1 indicates dissatisfaction with hypothyroidism treatment.

* $p < 0.05$; ** $p < 0.0001$.

SUPPLEMENTARY TABLE S3. DEMOGRAPHIC DATA, HYPOTHYROID DISEASE CHARACTERISTICS, AND PERCEPTIONS REGARDING HYPOTHYROID TREATMENT FOR RESPONDENTS WHO HAD NO DEPRESSION, REPORTED LIFE STRESSORS, OR MEDICAL CONDITIONS (SUBGROUP 1, N=3670)

| Survey question | Possible response | LT4 (n = 2206) | LT4 + LT3 (n = 316) | DTE (n = 1148) | p-Value |
|--|--------------------------|----------------|----------------------|------------------------|---------|
| Sex ^a | Female | 2073 (94%) | 307 (97%) | 1125 (98%) | <0.0001 |
| | Male | 133 (6%) | 9 (3%) | 23 (2%) | |
| Age ^a | 31–40 years | 543 (25%) | 71 (22%) | 251 (21%) | <0.0001 |
| | 41–50 years | 602 (27%) | 97 (32%) | 388 (33%) | |
| | 51–60 years | 512 (23%) | 81 (26%) | 295 (26%) | |
| | ≥61 years | 549 (25%) | 67 (21%) | 214 (19%) | |
| Etiology of hypothyroidism ^a | Hashimoto/autoimmune | 767 (35%) | 130 (41%) | 596 (52%) | <0.0001 |
| | Radioactive iodine | 234 (11%) | 27 (9%) | 66 (6%) | |
| | Surgery | 400 (18%) | 70 (22%) | 155 (14%) | |
| | Other | 805 (36%) | 89 (28%) | 331 (29%) | |
| | | 185 (8%) | 11 (4%) | 55 (5%) | <0.0001 |
| Hypothyroid treatment duration ^a | <1 year | 687 (31%) | 95 (30%) | 390 (34%) | <0.0001 |
| | 1–5 years | 498 (22%) | 87 (28%) | 261 (23%) | |
| | 6–10 years | 836 (38%) | 123 (40%) | 442 (39%) | |
| How satisfied are you with the treatment you receive? ^b | 1 = not satisfied | 5 (3–7) | 6 (3–8) ^c | 7 (5–9) ^{c,d} | <0.0001 |
| | 10 = very satisfied | | | | |
| If you are not satisfied, indicate relevant areas you feel are affected by your thyroid treatment ^a | Weight management | 1520 (69%) | 233 (74%) | 730 (64%) | <0.0001 |
| | Fatigue or energy levels | 1654 (75%) | 241 (76%) | 733 (64%) | <0.0001 |
| | Mood | 932 (42%) | 126 (40%) | 348 (30%) | <0.0001 |
| | Memory | 1219 (55%) | 187 (59%) | 509 (44%) | <0.0001 |
| How satisfied are you with your current physician who treats you for your thyroid condition? ^b | 1 = not satisfied | 5 (3–8) | 6 (3–8) | 7 (4–9) ^c | <0.0001 |
| | 10 = very satisfied | | | | |

(continued)

SUPPLEMENTARY TABLE S3. (CONTINUED)

| Survey question | Possible response | LT4 (n=2206) | LT4 + LT3 (n=316) | DTE (n=1148) | p-Value |
|--|--|---|--|--|---------|
| How knowledgeable is your doctor and/or physicians in general about hypothyroid treatment? ^b | 1 = not knowledgeable 10 = very knowledgeable | 5 (3,8) | 5 (3,8) | 5 (2,8) ^c | 0.04 |
| How many times have you changed doctors because you were not satisfied with the treatment you were receiving? ^a | Never Once 2-4 times 5-9 times >10 times | 872 (40%) 440 (20%) 726 (33%) 141 (6%) 27 (1%) 10 (8-10) | 51 (16%) 56 (18%) 146 (46%) 58 (18%) 5 (2%) 10 (10-10) ^c | 115 (10%) 125 (11%) 559 (49%) 280 (24%) 69 (6%) 10 (10-10) ^c | <0.0001 |
| How would you rate the need for new hypothyroid treatments? ^b | 1 = no need 10 = strong need | 425 (19%) 1781 (81%) | 91 (29%) 225 (71%) | 534 (47%) 614 (54%) | <0.0001 |
| Tried alternative hypothyroid treatment not prescribed by doctor ^a | Yes No | 9 (7-10) | 10 (8-10) ^c | 10 (8-10) ^c | <0.0001 |
| How has your life been affected by your hypothyroidism? ^b | 1 = not affected 10 = strongly affected | | | | |

^aSummarized as frequency (%); differences between groups determined by chi-square analysis.

^bSummarized as median (IQR); differences between groups determined by Kruskal-Wallis test.

^cSignificantly different from respondents taking LT4 by Mann-Whitney U-test.

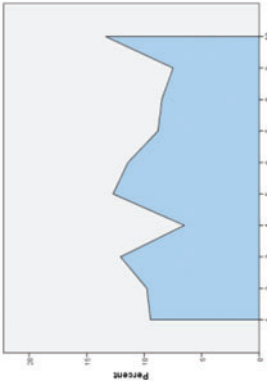
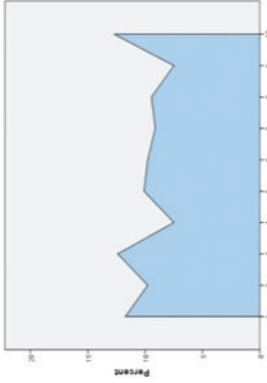
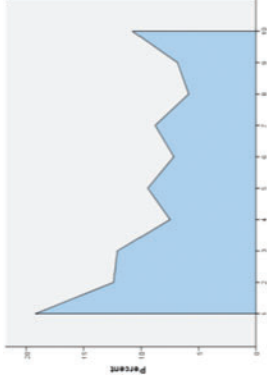
^dSignificantly different from respondents taking LT4 + T3 by Mann-Whitney U-test.

SUPPLEMENTARY TABLE S4. DEMOGRAPHIC DATA, HYPOTHYROID DISEASE CHARACTERISTICS, AND PERCEPTIONS REGARDING HYPOTHYROID TREATMENT FOR RESPONDENTS WHO HAD NO DEPRESSION, REPORTED LIFE STRESSORS, OR MEDICAL CONDITIONS WHO ARE MATCHED BY MEDICATION, SEX, AND AGE (SUBGROUP 2, N= 1535)

| Survey question | Possible response | LT4 (n = 614) | LT4 + LT3 (n = 307) | DTE (n = 614) | p-Value |
|--|--------------------------|---------------|----------------------|----------------------|---------|
| Sex ^a | Female | 614 (100%) | 307 (100%) | 614 (100%) | n/a |
| Age ^a | 31-40 years | 140 (23%) | 70 (23%) | 140 (23%) | 1.000 |
| | 41-50 years | 190 (31%) | 95 (31%) | 190 (31%) | |
| | 51-60 years | 160 (26%) | 80 (26%) | 160 (26%) | |
| | ≥61 years | 124 (20%) | 62 (20%) | 124 (20%) | |
| Etiology of hypothyroidism ^a | Hashimoto/autoimmune | 256 (42%) | 128 (42%) | 283 (46%) | 0.441 |
| | Radioactive iodine | 52 (9%) | 26 (9%) | 46 (8%) | |
| | Surgery | 134 (22%) | 67 (22%) | 102 (17%) | |
| | Other | 172 (28%) | 86 (28%) | 183 (30%) | |
| Hypothyroid treatment duration ^a | <1 year | 22 (4%) | 11 (4%) | 24 (4%) | 1.000 |
| | 1-5 years | 184 (30%) | 92 (30%) | 182 (30%) | |
| | 6-10 years | 174 (28%) | 87 (28%) | 174 (28%) | |
| | >10 years | 234 (38%) | 117 (38%) | 234 (38%) | |
| How satisfied are you with the treatment you receive? ^b | 1 = not satisfied | 5 (3-7) | 6 (3-8) ^c | 7 (5-9) | <0.0001 |
| | 10 = very satisfied | | | | |
| If you are not satisfied, indicate relevant areas you feel are affected by your thyroid treatment ^a | Weight management | 434 (71%) | 228 (74%) | 363 (59%) | <0.0001 |
| | Fatigue or energy levels | 497 (81%) | 235 (77%) | 381 (62%) | <0.0001 |
| | Mood | 291 (47%) | 122 (40%) | 177 (29%) | <0.0001 |
| | Memory | 381 (62%) | 180 (59%) | 266 (43%) | <0.0001 |
| How satisfied are you with your current physician who treats you for your thyroid condition? ^b | 1 = not satisfied | 5 (3-8) | 6 (3-8) ^c | 7 (3-9) ^c | <0.0001 |
| | 10 = very satisfied | | | | |

(continued)

SUPPLEMENTARY TABLE S4. (CONTINUED)

| Survey question | Possible response | LT4 (n=614) | LT4 + LT3 (n=307) | DTE (n=614) | p-Value |
|--|--|--|---|--|---------|
| How knowledgeable is your doctor and/or physicians in general about hypothyroid treatment? ^b | 1 = not knowledgeable 10 = very knowledgeable |  5 (2-7) |  5 (3-8) |  5 (2-8) | 0.05 |
| How many times have you changed doctors because you were not satisfied with the treatment you were receiving? ^a | Never Once 2-4 times 5-9 times >10 times | 232 (38%) 127 (21%) 208 (34%) 39 (6%) 8 (1%) | 49 (16%) 55 (18%) 143 (47%) 55 (18%) 5 (2%) | 58 (9%) 67 (11%) 298 (49%) 150 (24%) 41 (7%) | <0.0001 |
| How would you rate the need for new hypothyroid treatments? ^b | 1 = no need 10 = strong need | 10 (8-10) ^c | 10 (10-10) ^c | 10 (10-10) ^c | <0.0001 |
| Tried alternative hypothyroid treatment not prescribed by doctor ^a | Yes No | 116 (19%) 498 (81%) | 88 (29%) 219 (71%) | 292 (48%) 322 (52%) | <0.0001 |
| How has your life been affected by your hypothyroidism? ^b | 1 = not affected 10 = strongly affected | 9 (7-10) | 10 (8-10) | 10 (10-10) | <0.001 |

^aSummarized as frequency (%); differences between groups determined by chi-square analysis.

^bSummarized as median (IQR); differences between groups determined by Kruskal-Wallis test.

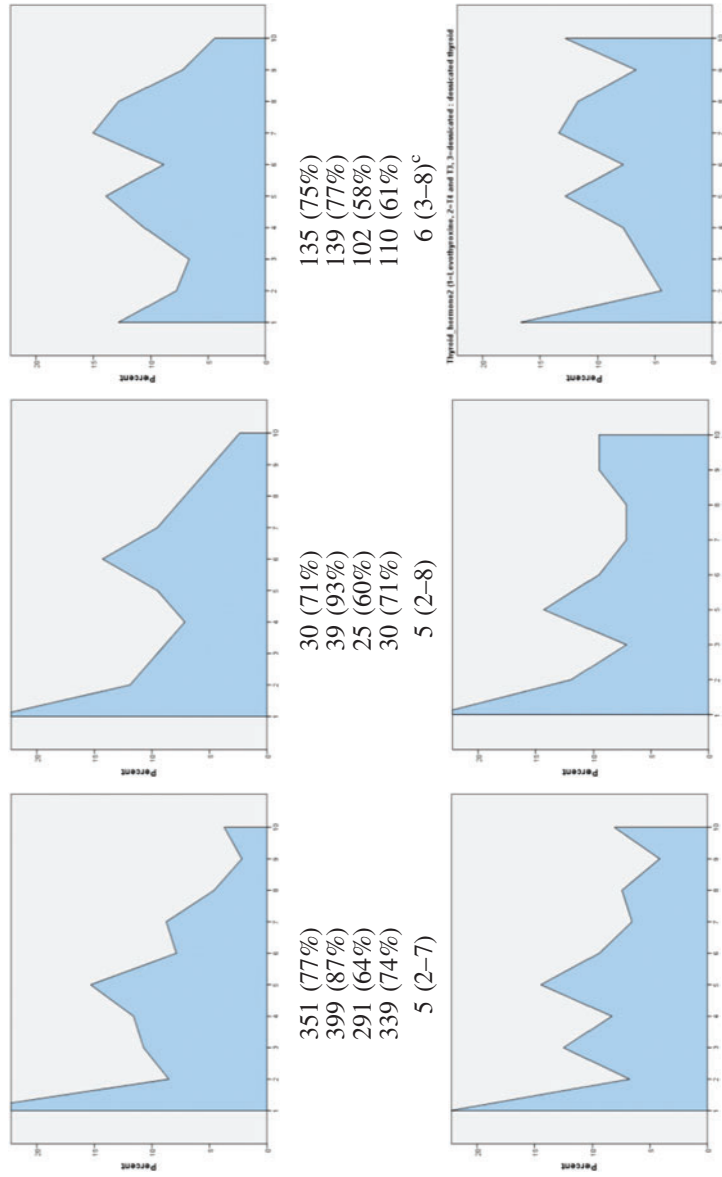
^cSignificantly different from respondents taking LT4 by Mann-Whitney U-test.





SUPPLEMENTARY TABLE S5. DEMOGRAPHIC DATA, HYPOTHYROID DISEASE CHARACTERISTICS, AND PERCEPTIONS REGARDING HYPOTHYROID TREATMENT FOR RESPONDENTS WITH DEPRESSION BUT NO REPORTED LIFE STRESSORS OR MEDICAL CONDITIONS (SUBGROUP 3, N=679)

| Survey question | Possible response | LT4 (n=457) | LT4 + LT3 (n=42) | DTE (n=180) | p-Value |
|--|--------------------------|-------------|------------------|----------------------|---------|
| Sex ^a | Female | 446 (98%) | 41 (98%) | 178 (99%) | 0.578 |
| | Male | 11 (2%) | 1 (2%) | 2 (1%) | |
| Age ^a | 31-40 years | 116 (25%) | 9 (21%) | 46 (26%) | 0.843 |
| | 41-50 years | 143 (31%) | 13 (31%) | 60 (33%) | |
| | 51-60 years | 92 (20%) | 12 (29%) | 42 (23%) | |
| | ≥61 years | 106 (23%) | 8 (19%) | 32 (11=8%) | |
| Etiology of hypothyroidism ^a | Hashimoto/autoimmune | 182 (40%) | 18 (43%) | 96 (53%) | 0.013 |
| | Radioactive iodine | 31 (7%) | 6 (14%) | 13 (7%) | |
| | Surgery | 63 (14%) | 6 (14%) | 18 (10%) | |
| | Other | 181 (40%) | 12 (29%) | 53 (30%) | |
| | | | | | |
| Hypothyroid treatment duration ^a | <1 year | 41 (9%) | 1 (2%) | 5 (3%) | 0.088 |
| | 1-5 years | 119 (26%) | 11 (26%) | 49 (27%) | |
| | 6-10 years | 95 (21%) | 13 (31%) | 44 (24%) | |
| | >10 years | 202 (44%) | 17 (41%) | 82 (46%) | |
| How satisfied are you with the treatment you receive? ^b | 1 = not satisfied | 4 (1-6) | 4 (2-6) | 5 (3-7) ^c | <0.0001 |
| | 10 = very satisfied | | | | |
| If you are not satisfied, indicate relevant areas you feel are affected by your thyroid treatment ^a | Weight management | 351 (77%) | 30 (71%) | 135 (75%) | 0.690 |
| | Fatigue or energy levels | 399 (87%) | 39 (93%) | 139 (77%) | |
| | Mood | 291 (64%) | 25 (60%) | 102 (58%) | |
| | Memory | 339 (74%) | 30 (71%) | 110 (61%) | |
| How satisfied are you with your current physician who treats you for your thyroid condition? ^b | 1 = not satisfied | 5 (2-7) | 5 (2-8) | 6 (3-8) ^c | 0.001 |
| | 10 = very satisfied | | | | |



(continued)



SUPPLEMENTARY TABLE S5. (CONTINUED)

| Survey question | Possible response | LT4 (n = 457) | LT4 + LT3 (n = 42) | DTE (n = 180) | p-Value |
|--|-------------------------|---------------|-------------------------|-------------------------|---------|
| How knowledgeable is your doctor and/or physicians in general about hypothyroid treatment? ^b | 1 = not knowledgeable | 4 (2-6) | 5 (2-7) | 4 (2-8) | 0.824 |
| | 10 = very knowledgeable | 161 (35%) | 9 (21%) | 14 (8%) | |
| How many times have you changed doctors because you were not satisfied with the treatment you were receiving? ^a | Never | 70 (15%) | 7 (17%) | 25 (14%) | <0.0001 |
| | Once | 188 (41%) | 17 (41%) | 91 (51%) | |
| | 2-4 times | 34 (7%) | 8 (19%) | 34 (19%) | |
| | 5-9 times | 4 (1%) | 1 (2%) | 16 (9%) | |
| | >10 times | 10 (9-10) | 10 (10-10) ^c | 10 (10-10) ^c | |
| How would you rate the need for new hypothyroid treatments? ^b | 1 = no need | 87 (19%) | 14 (33%) | 78 (43%) | <0.0001 |
| | 10 = strong need | 370 (81%) | 28 (67%) | 102 (57%) | |
| Tried alternative hypothyroid treatment not prescribed by doctor ^a | Yes | 10 (8-10) | 10 (10-10) ^c | 10 (10-10) ^c | <0.0001 |
| | No | 10 (8-10) | 10 (10-10) ^c | 10 (10-10) ^c | |
| How has your life been affected by your hypothyroidism? ^b | 1 = not affected | 10 (8-10) | 10 (10-10) ^c | 10 (10-10) ^c | <0.0001 |
| | 10 = strongly affected | 10 (8-10) | 10 (10-10) ^c | 10 (10-10) ^c | |

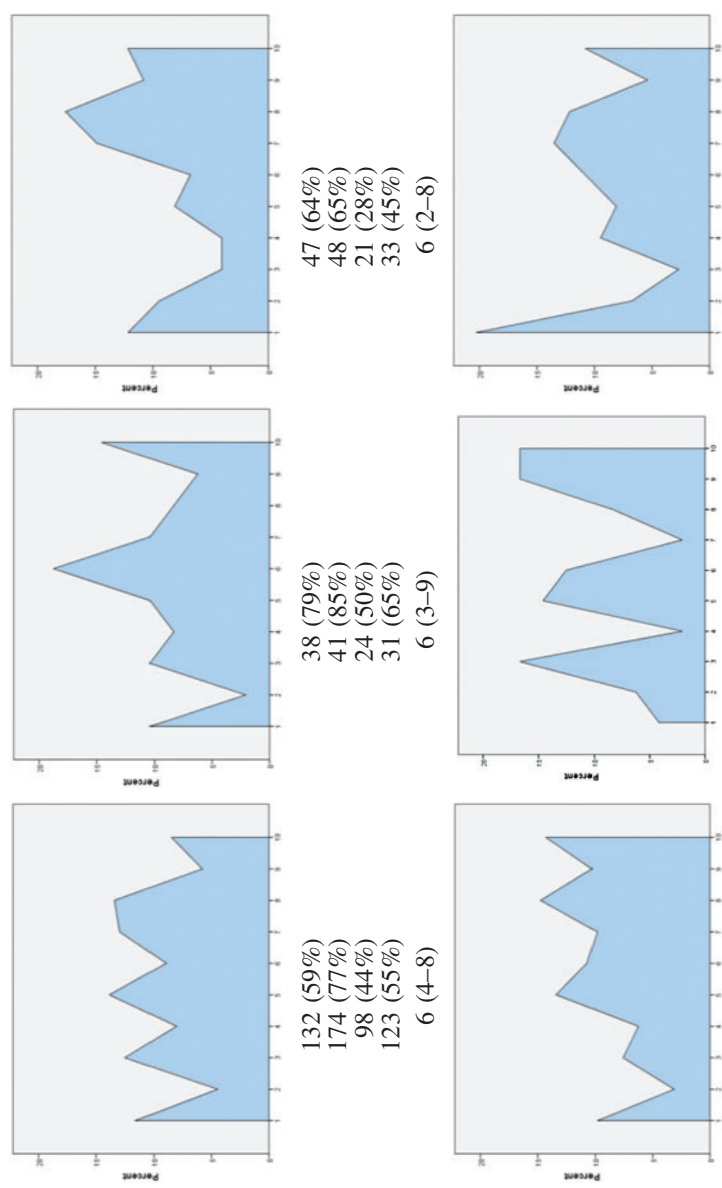
^aSummarized as frequency (%); differences between groups determined by chi-square analysis.

^bSummarized as median (IQR); differences between groups determined by Kruskal-Wallis test.

^cSignificantly different from respondents taking LT4 by Mann-Whitney U-test.

SUPPLEMENTARY TABLE S6. DEMOGRAPHIC DATA, HYPOTHYROID DISEASE CHARACTERISTICS, AND PERCEPTIONS REGARDING HYPOTHYROID TREATMENT FOR RESPONDENTS WITH A HISTORY OF THYROID CANCER BUT NO DEPRESSION, REPORTED LIFE STRESSORS, OR MEDICAL CONDITIONS (SUBGROUP 4, N = 346)

| Survey question | Possible response | LT4 (n = 224) | LT4 + LT3 (n = 48) | DTE (n = 74) | p-Value |
|--|--|---------------|--------------------|--------------|---------|
| Sex ^a | Female | 211 (94%) | 46 (96%) | 73 (99%) | 0.283 |
| | Male | 13 (6%) | 2 (4%) | 1 (1%) | |
| Age ^a | 31–40 years | 58 (26%) | 16 (27%) | 13 (18%) | 0.559 |
| | 41–50 years | 76 (34%) | 16 (33%) | 35 (47%) | |
| | 51–60 years | 51 (23%) | 12 (25%) | 16 (22%) | |
| | ≥61 years | 39 (17%) | 7 (15%) | 10 (14%) | |
| Etiology of hypothyroidism ^a | Hashimoto/autoimmune | 11 (5%) | 2 (4%) | 5 (8%) | 0.076 |
| | Radioactive iodine | 0 | 0 | 0 | |
| | Surgery | 198 (88%) | 37 (77%) | 60 (81%) | |
| Hypothyroid treatment duration ^a | Other | 15 (7%) | 9 (19%) | 8 (11%) | 0.065 |
| | <1 year | 29 (13%) | 4 (8%) | 5 (7%) | |
| | 1–5 years | 102 (46%) | 21 (44%) | 30 (41%) | |
| How satisfied are you with the treatment you receive? ^b | 6–10 years | 53 (24%) | 9 (19%) | 13 (18%) | 0.224 |
| | >10 years | 40 (18%) | 14 (29%) | 26 (35%) | |
| | 1 = not satisfied 10 = very satisfied | 5 (3–8) | 6 (4–8) | 7 (3–8) | |
| If you are not satisfied, indicate relevant areas you feel are affected by your thyroid treatment ^a | Weight management | 132 (59%) | 38 (79%) | 47 (64%) | 0.031 |
| | Fatigue or energy levels | 174 (77%) | 41 (85%) | 48 (65%) | |
| | Mood | 98 (44%) | 24 (50%) | 21 (28%) | |
| | Memory | 123 (55%) | 31 (65%) | 33 (45%) | |
| How satisfied are you with your current physician who treats you for your thyroid condition? ^b | 1 = not satisfied | 6 (4–8) | 6 (3–9) | 6 (2–8) | 0.117 |
| | 10 = very satisfied | | | | |



(continued)

SUPPLEMENTARY TABLE S6. (CONTINUED)

| Survey question | Possible response | LT4 (n = 224) | LT4 + LT3 (n = 48) | DTE (n = 74) | p-Value |
|--|-------------------------|--|--|---|---------|
| How knowledgeable is your doctor and/or physicians in general about hypothyroid treatment? ^b | 1 = not knowledgeable | 7 (4-9) | 6 (4-9) | 4 (3-7) ^{c,d} | <0.001 |
| | 10 = very knowledgeable | 97 (43%) 55 (25%) 62 (28%) 9 (4%) 1 (1%) | 11 (23%) 10 (21%) 20 (42%) 7 (15%) 0 | 5 (7%) 9 (12%) 43 (58%) 14 (19%) 3 (4%) | |
| How many times have you changed doctors because you were not satisfied with the treatment you were receiving? ^a | Never | 24 (11%) | 9 (19%) | 32 (43%) | <0.0001 |
| | Once | 200 (89%) | 39 (81%) | 42 (57%) | |
| Tried alternative hypothyroid treatment not prescribed by doctor ^a | Yes | 10 (7-10) | 10 (10-10) ^c | 10 (10-10) ^c | <0.001 |
| | No | | | | |
| How would you rate the need for new hypothyroid treatments? ^b | 1 = no need | 10 (8-10) | 10 (10-10) ^c | 10 (9-10) ^c | <0.001 |
| | 10 = strongly need | | | | |
| How has your life been affected by your hypothyroidism? ^b | 1 = not affected | | | | <0.001 |
| | 10 = strongly affected | | | | |

^aSummarized as frequency (%); differences between groups determined by chi-square analysis.

^bSummarized as median (IQR); differences between groups determined by Kruskal-Wallis test.

^cSignificantly different from respondents taking LT4 by Mann-Whitney U-test.

^dSignificantly different from respondents taking LT4 + T3 by Mann-Whitney U-test.

AUTHOR QUERY FOR THY-2017-0681-VER9-PETERSON 1P

AU1: Please check that author names appear correctly.

AU2: Please check that affiliations are correct

AU3: Please confirm keywords, taken from submission files..

AU4: Please clarify which table is being cited here.

AU5: Please check that correspondence details are correct and complete.

AU6: Footnote “#” was not cited in the table and has so been deleted. Please check.

AU7: Please clarify percentage “11 = 8”.

AU8: Please provide updated disclosure statement; please indicate which authors have nothing to disclose, if any.