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1 **Exploring dissatisfaction with treatment of hypothyroidism:**
2 **coexistent diseases and treatment preferences**

3
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40 **ABSTRACT**

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Context: Levothyroxine (LT4) monotherapy is the standard of care for treating hypothyroidism. However, some patients do not feel well and express interest in other therapies.

Objective: To inform the discussion at a symposium addressing treatment for hypothyroidism, we wished to determine perceptions of patients regarding their treatment for hypothyroidism.

Design: An online survey was created to obtain patient’s perceptions. Respondents were asked to rank satisfaction with their treatment for hypothyroidism, satisfaction with their treating physician, perceived physician knowledge about hypothyroidism treatments, perceived need for new treatments for hypothyroidism, and perceived life impact of hypothyroidism on a scale of 1 to 10. Respondents were asked to report the type of thyroid hormone they were taking, which was categorized as LT4, LT4 and liothyronine (LT4 + LT3), or desiccated thyroid extract (DTE). They also reported sex, age, cause of hypothyroidism, duration of treatment, medical history, and prevalence of symptoms or side effects.

Participants: A convenience sample of survey respondents with self-reported hypothyroidism.

Results: A total of 12,146 individuals completed the survey. Among respondents without self-reported depression, stressors or medical conditions (n=3670), individuals taking DTE reported a higher median treatment satisfaction of 7 (interquartile range (IQR): 5,9) and a higher physician satisfaction of 7 (IQR: 4,9) compared to other treatments. For LT4 treatment, satisfaction was 5 (IQR: 3,7) and physician dissatisfaction was 6 (IQR: 3,8). For LT4 + LT3 treatment, satisfaction was 6 (IQR: 3,8) and physician satisfaction was 6 (IQR: 3,8). Respondents taking DTE were also less likely to report hypothyroidism-associated side effects related to weight management, fatigue/energy levels, mood, and memory/other cognitive problems, compared to those taking LT4 or LT4 + LT3. The study design does not permit investigation of why patients taking DTE reported best perceived outcomes.

Conclusions: Despite the limitations of the study and the potential for sampling bias, data from this large convenience sample of hypothyroid individuals revealed generalized dissatisfaction with treatment and physicians; patients taking DTE reported best perceived outcomes. Future studies into what constitutes euthyroidism and what determines satisfaction with therapy are needed.

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INTRODUCTION

Hypothyroidism is a common endocrine problem that results from insufficient secretion of thyroid hormones due to an underactive thyroid gland; it requires lifelong treatment with thyroid hormone replacement therapy.¹ Currently, the standard of care to treat hypothyroidism is daily administration of levothyroxine (LT4), at doses that normalize serum thyroid stimulating hormone (TSH).^{2,3} Even though thyroxine (T4) is intrinsically active in some settings⁴, many tissues have deiodinases that activate T4 to triiodothyronine (T3), the biologically active thyroid hormone. The prevailing viewpoint is that a dosage of LT4 that normalizes serum TSH also normalizes serum and tissue T3 levels.⁵ Endocrinologists' offices are frequently visited by hypothyroid patients that remain symptomatic despite being "appropriately" treated, complaining of sluggishness, lethargy, sleepiness, memory problems, depression, cold intolerance, hoarseness, dry skin, body weight gain, and constipation.¹ Anecdotally, we know that these patients switch physician multiple times and many use unconventional therapies, such as dietary supplements, nutraceuticals and over-the-counter products.

Most patients with hypothyroidism experience resolution of their symptoms with standard therapy. However, 10 to 15% more of LT4-treated patients have poor quality of life compared with control individuals.⁶ The existence of patients with hypothyroidism who are symptomatic despite LT4 treatment that has normalized their TSH values has led to questions regarding the efficacy of monotherapy with LT4 for all patients.^{3,7} We now know objectively that in LT4-treated patients that exhibit a normal serum TSH there is a 15-20% decrease in the ratio of circulating T3/T4⁸; and about 15% of these patients do not maintain normal serum T3 levels.⁹ This is hypothesized to be the result of differences in D2 regulation between the hypothalamus and peripheral tissues, as has been shown in a hypothyroid rat model.¹⁰ That replacement with LT4 does not fully restore all aspects of euthyroidism is supported by the observation that females taking LT4 have lower energy expenditure compared to euthyroid women with similar age and body mass index.¹¹ In addition, NHANES data 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, report lower physical activity levels, and are more often taking statins, beta-blockers, and antidepressants compared to euthyroid participants matched by age, gender and race/ethnicity.⁸ They also report increased frequency of episodes of memory problems/confusion and are less likely to report being in excellent/good health.¹²

Few physicians are willing to prescribe combination LT4 plus liothyronine (LT3) to manage residual symptoms;¹³ and minimal information is available to describe prescription patterns of desiccated thyroid extract (DTE, a porcine-derived thyroid hormone replacement containing both T4 and T3). However, it is not clear that combination therapy is superior to monotherapy in managing hypothyroidism. A total of 14 double blind placebo controlled trials provided heterogeneous results with respect to health-related quality of life and mood and neurocognitive functioning; but there was a patient preference for combination therapy in some of the trials.^{6,14-26} 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.²⁷

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The objective of the current study is to analyze the results of an online survey conducted in the spring of 2017 which assessed perceptions of hypothyroid patients regarding treatment effectiveness and their satisfaction with physicians. Approximately 12,000 individuals taking LT4 monotherapy, combination therapy with LT4 and LT3, or desiccated thyroid extract, completed the survey which was posted on the American Thyroid Association (ATA)'s web site.

MATERIALS AND METHODS

Study participants

A convenience sample of hypothyroid individuals was solicited 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 the Spring of 2017 in Orlando FL. The program committee members deemed it important to describe the patient perspective regarding hypothyroidism treatment and 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 gender, age (categorized as under 40, 41-50 years old, 51-60 years old, 61-70 years old, or over 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 less than one year, 1-5 years, 6-10 years, more than 10 years). To recognize confounding conditions that may contribute to symptoms overlapping with those of hypothyroidism, participants were asked if 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], levothyroxine and LT3 [liothyronine, Cytomel], natural thyroid or desiccated thyroid extract [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 levothyroxine (LT4), levothyroxine and LT3 (LT4+LT3), and desiccated thyroid extract (DTE). Perception regarding treatment was examined by asking participants to rank, on a scale of 1 to 10, their satisfaction with treatment and with the current physician treating their hypothyroidism (1=not satisfied, 10=completely satisfied), the perceived knowledge of their physician about treatment of hypothyroidism (1=not at all knowledgeable, 10=very knowl-

166 edgeable), their assessment of the need for new treatments for hypothyroidism (1=no need,
167 10=strong need), and the impact of hypothyroidism on their life (1=not affected, 10=strongly af-
168 fected). In addition to reporting the median, 25th, and 75th percentile of the responses, the distri-
169 bution of the responses was also presented in graphic form. Additional questions were added to
170 assess participant's experiences with their medical care for hypothyroidism; respondents were
171 asked to categorize the number of times they changed physician because they were not satisfied
172 with their hypothyroidism treatment (categorized as none, 1 time, 2-4 times, 5-9 times, or 10 or
173 more times), identify relevant aspects of their life affected by hypothyroidism/thyroid hormone
174 treatment (categorized as weight management, fatigue or energy levels, mood, and memory or
175 other problems with thinking), and prevalence of seeking alternative form of hypothyroidism
176 treatment, not prescribed by your doctor (yes/no).

177
178 The survey (available in the Supplemental Materials and Methods) was available online from
179 1/28/2017 to 3/30/2017. A link to the survey was posted on the ATA website and distributed via
180 email to patients within the ATA database and to the members of the ATA Alliance for Thyroid
181 Patient Education. Members of the ATA were encouraged to further distribute the survey by
182 sharing on group websites and social media. Additionally, the link was included in the Signal
183 eNews, a monthly newsletter emailed to ATA members. No identifying or protected health in-
184 formation was collected from participants. Only IP address was recorded for the purpose of elim-
185 inating duplicate responses.

186
187 Initial analysis was conducted on the total sample (comprised of respondents taking LT4, LT4 +
188 LT3, or DTE). In addition, four subgroups were created based on disease characteristics in order
189 to further analyze perceptions regarding treatment of hypothyroidism according to the 3 treat-
190 ments. These groups were as follows: **Subgroup-1:** respondents without self-reported depres-
191 sion, stress or medical conditions; **Subgroup-2:** due to difference in age, gender, and hypothy-
192 roid treatment between respondents taking LT4, LT4 + LT3, and DTE a matched subgroup of
193 females was created - those taking LT4 and DTE (the tw largest groups of respondents) were
194 matched 2:1 by age, hypothyroidism treatment, etiology of hypothyroidism, and treatment dura-
195 tion to individuals taking LT4+LT3 (the smallest group of respondents) to account for baseline
196 differences; **Subgroup-3:** respondents with depression but no reported life-stressors or medical
197 conditions; and **Subgroup-4:** respondents with thyroid cancer but no self-reported depression,
198 life-stressors or medical condition.

199 **Statistical methods**

201 Analyses were completed with IBM SPSS Statistics (version 22.0). Both frequency (percent) and
202 median (interquartile range [25th, 75th percentile]) were used to describe the data. The Kruskal
203 Wallis test was used to compare difference in ranked median perception across the three medica-
204 tion treatment groups (LT4 vs LT4+LT3 vs DTE). If a significant difference was observed, the
205 Mann-Whitney U test was used to perform between group analyses. The chi-square test of asso-
206 ciation was utilized to determine difference in categorical variables across the three medication
207 treatment groups (LT4 vs LT4+LT3 vs DTE). Due to the multiple comparisons performed, a
208 conservative p value of <0.001 was utilized to identify statistically significant differences be-
209 tween groups. This rigorous p value was chosen in order to avoid over-interpreting results in the
210 setting of a survey-based dataset.

211

212 RESULTS

213

214 A total of 12,146 respondents completed the survey and all subsequent analyses were performed
215 based on the self-reported responses to questions about medical history and hypothyroidism
216 treatment. We excluded 53 respondents that were not taking medication for hypothyroidism. Of
217 the remaining 12,093 individuals (Supplement Table 1), 485 were excluded because they were
218 taking a medication for hypothyroidism other than LT4, LT4 + LT3, or DTE. An additional 442
219 were excluded due to survey completion from the same IP address and concern that the data rep-
220 resented duplicate surveys. As a result, the total sample of respondents that was further analyzed
221 comprised 11,166 individuals (Figure 1).

222

223 The female/male ratio of respondents was approximately 21:1 and age was relatively evenly dis-
224 tributed across the four age categories (Table 1). The most prevalent cause of hypothyroidism
225 was Hashimoto's/autoimmune disease (43%); however, 34% of respondents identified another
226 cause other than Hashimoto's/RAI/surgery or were unsure of hypothyroidism etiology (Table 1).
227 Only 7% of individuals were treated for hypothyroidism for less than one year; the majority
228 (63%) had been on treatment for more than 6 years. One-third of patients stated that their current
229 stress level could be contributing to hypothyroid-related symptoms; another third reported co-
230 existing medical conditions, with the most common one being depression (27%). Only 6% of
231 respondents self-reported depression without any other comorbidities (Table 1).

232

233 Within the total sample, 6,949 individuals were taking LT4 monotherapy, 978 reported taking
234 combination LT4+LT3, and 3,239 received DTE (Table 1). When considering perceptions re-
235 garding their treatment for hypothyroidism, the median response indicating treatment satisfaction
236 was 5 (25th-75th percentile interval: 3, 8) (Table 1). Among those who were frustrated with their
237 hypothyroidism treatment, the relevant areas identified as causing dissatisfaction were weight
238 management (69%), fatigue or energy level (77%), mood (45%), and memory or other problems
239 thinking (58%). The median response describing satisfaction with the patient's current physician
240 was 6 (25th-75th percentile interval: 3,6) and assessment of the doctor/physician knowledge re-
241 garding hypothyroidism treatment was 5 (25th-75th percentile interval: 3, 8); 54% of the sample
242 reported changing physicians more than twice because of dissatisfaction with treatment. Almost
243 all respondents believed that there was a strong need for new treatments for hypothyroidism
244 (median 10 (25th-75th percentile interval: 8,10)) and perceived a significant influence of hypothy-
245 roidism on life (median 10 (25th-75th percentile interval: 8,10)) (Table 1).

246

247 Next, multiple analyses were utilized to compare the responses within the total sample according
248 to their specific treatment (Table 2). When examining the three treatment sub-groups, the distri-
249 bution of gender, age, etiology and treatment duration were significantly different. Individuals
250 treated with DTE had the highest median satisfaction with treatment (7 (25th-75th percentile in-
251 terval: 4,8)) compared to those taking LT4 (5 (25th-75th percentile interval: 3,7)) or LT4+LT3 (5
252 (25th-75th percentile interval: 3,7)). In particular, as shown in the graphic representations, the dis-
253 tribution of responses was markedly different between those taking DTE versus LT4 (Table 2);
254 individuals on DTE predominately responded positively with an upward trend, such that re-
255 sponses were more frequent at the positive end of the scale. Conversely, individuals on LT4 were
256 more likely to respond negatively, exhibiting a distribution with a downward trend, such that re-
257 sponses were more frequent at the negative end of the scale (Table 2). This varied distribution

258 between groups can also be described by examining the number of patients who ranked satisfaction
259 with treatment as not satisfied (ranked 1 or 2) or completely satisfied (ranked 9 or 10); approxi-
260 mately 20% of respondents taking LT4 and LT4+LT3 were not satisfied with treatment while
261 14% of DTE users were not satisfied. In comparison, 22% of DTE users were completely satis-
262 fied compared to 10% of LT4 and LT4+LT3 respondents (Supplementary Figure 1). Individuals
263 taking DTE were less likely to report problems with weight management, fatigue/energy level,
264 mood, or memory when compared to those taking LT4 or LT4+LT3 (Table 2). Individuals taking
265 DTE had a higher median satisfaction with their current physician (7 (25th-75th percentile inter-
266 val: 4,9)) compared to those taking LT4 (5 (25th-75th percentile interval: 3,8)) or LT4+LT3 (6
267 (25th-75th percentile interval: 3-8)); perceived physician knowledge was slightly higher in the
268 DTE subgroup, compared with the LT4 subgroup (Supplementary Figure 2 and 3). Of note, 29%
269 and 21% of individuals taking DTE and LT4+LT3 changed doctors ≥ 5 times because they were
270 not satisfied with their treatment, compared to only 7% of respondents taking LT4. Those taking
271 DTE or LT4+LT3 were more likely to have tried alternative treatment forms not prescribed by
272 their doctor and thought their lives had been more affected by hypothyroidism (10 (25th-75th per-
273 centile interval: 9-10)), although this latter parameter was very high in all three subgroups (Table
274 2 and Supplementary Table 4).

275 276 **Analyses of Subgroups-1-4**

277
278 **Subgroup-1** (Supplement Table 2, n=3,670) captures respondents without self-reported depres-
279 sion, life-stressors or medical conditions. Those taking LT4 had a median reported treatment sat-
280 isfaction of 5 (25th-75th percentile interval: 3,7) (Table 3). Their perception regarding treatment
281 of hypothyroidism were as follows: physician satisfaction of 5 (25th-75th percentile interval: 3,8)
282 and physician knowledge of 5 (25th-75th percentile interval: 3,8). Individuals taking combination
283 therapy with LT4+LT3 experienced slightly higher treatment satisfaction (6 (25th-75th percentile
284 interval: 3,8), with similar physician satisfaction and perceived physician knowledge. Respond-
285 ents taking DTE had the highest scores in treatment satisfaction (7 (25th-75th percentile interval:
286 5,9)) and physician satisfaction (7 (25th-75th percentile interval: 4,9)). Regardless of treatment
287 modality, all respondents ranked at the highest level (9-10) the need for new treatments and the
288 perception of how much their lives had been affected by hypothyroidism (Table 3). Addition-
289 ally, respondents taking DTE were less likely to report weight management concerns, fatigue/low
290 energy levels, mood issues, or memory problems compared to those on LT4 or LT4+LT3 (Table
291 4).

292
293 **Subgroup-2** (Supplement Table 3, n=1535) is a matched subset of **Subgroup-1** with the re-
294 spondents taking LT4 and DTE being matched 2:1 by gender (only female respondents), age,
295 etiology of hypothyroidism, and treatment duration to individuals taking LT4+LT3. The match-
296 ing resulted in the size of the groups being reduced to 1535 respondents (Table 3). Despite the
297 matching, the results obtained in **Subgroup-2** remained very similar to **Subgroup-1** (Table 3 and
298 Table 4).

299
300 **Subgroup-3** (Supplement Table 4, n=679) respondents, who reported depression, but did not
301 report stressors or other medical conditions, in general ranked lower on all parameters when
302 compared to other subgroups. The median perception of those taking LT4 regarding treatment
303 satisfaction was 4 (25th-75th percentile interval: 1,6), physician satisfaction was 5 (25th-75th per-

304 centile interval: 2,7) and physician knowledge was 4 (25th-75th percentile interval: 2,6) (Table 3).
305 Individuals on LT4+LT3 reported similar perceptions (Table 3). Respondents taking DTE had
306 the highest scores for: treatment satisfaction 5 (25th-75th percentile interval: 3,7)) and physician
307 satisfaction 6 (25th-75th percentile interval: 3,8), albeit lower than Subgroups 1-2. Perception of
308 physician knowledge remained low (4 (25th-75th percentile interval: 2,8)), similar to other treat-
309 ment groups. Respondents using all treatment modalities ranked at the highest level (10) the need
310 for new treatments and the perception of how much their lives had been affected by hypothyroid-
311 ism (Table 3). Within this group, respondents taking DTE were less likely to report fatigue/low
312 energy levels and memory problems compared to those on LT4 or LT4+LT3, though the differ-
313 ence did not reach the statistical significance criterion of $p < 0.001$ (Table 4).
314

315 **Subgroup-4** (Supplement Table 5, n=346) respondents (those with thyroid cancer, but no other
316 reported co-morbidities) exhibited a similar upward trend in treatment satisfaction with DTE,
317 although not reaching statistical significance (Table 3); perceptions about physician satisfaction
318 also did not exhibit statistical significance between treatments. Notably, physician knowledge
319 exhibited a downward trend, with patients on DTE ranking the lowest (4 (25th-75th percentile in-
320 terval: 3,7). As before, the need for new treatments and impact of hypothyroidism on their lives
321 were ranked at the highest level (Table 3). Within this group, there was a trend toward respond-
322 ents taking LT4+LT3 being more likely to report weight management as a relevant area affected
323 by hypothyroidism compared to LT4 users. There was a trend towards those taking DTE being
324 less likely to report fatigue/low energy levels and mood issues compared to those on LT4 or
325 LT4+LT3 (Table 4). Respondents taking DTE exhibited a trend towards being less likely to re-
326 port memory problems compared to LT4+LT3 users (Table 4).
327

328 **DISCUSSION**

329
330 The present study reports the results of a large-scale assessment of patients' perceptions about
331 hypothyroidism. The results suggest that dissatisfaction with hypothyroidism treatment and treat-
332 ing physicians are important problems for patients. Furthermore, a strong need for development
333 of new treatments for hypothyroidism was identified. These are dramatic findings, as among
334 physicians treatment of hypothyroidism is considered to be straightforward. The fact that the
335 median reported satisfaction with treatment in the entire group is only 5 on a scale of 1-10 is re-
336 markable, and even if this only reflects the situation in a small portion of patients, this is very
337 concerning. Given that hypothyroidism is a common disease, this could translate into a signifi-
338 cant burden of unsuccessfully resolved symptoms within the entire population. At face value,
339 these results indicate that, although physicians believe that hypothyroidism is an eminently treat-
340 able condition, a large number of hypothyroid patients believe their lives have been greatly af-
341 fected by the disease, are profoundly unhappy with their treatment, and are unhappy with their
342 physicians. Almost universally, they believe there is a need for the development of new treat-
343 ment forms. It is also remarkable that there is a clear preference for DTE in the whole group as
344 well as when the group was broken down in multiple subgroups. Of course, the study is limited
345 by the potential intrinsic sample bias. However, the suggestion that something "real" is being
346 captured is bolstered by the finding that our survey did not demonstrate a clear positive patient
347 response to synthetic combination therapy with LT4+LT3.
348

349 The present study is based on responses provided by a convenience sample that is unlikely to
350 represent the more than 10 million Americans being treated for hypothyroidism. For example, it
351 is likely that there is selection bias, with underrepresentation of LT4-treated patients that are not
352 symptomatic who are less likely to be reached by thyroid-related social media. However, these
353 results corroborate recent findings obtained from NHANES data, a population-based survey rep-
354 resentative of individuals within the United States (a computer algorithm randomly selects
355 households from representative regions throughout the country). Notably, the NHANES LT4-
356 treated individuals struggled with the very same issues identified by the current sample, i.e.
357 weight management, low energy levels, depression and poor cognition compared to age, gender
358 and race/ethnicity matched euthyroid controls.^{8,12} These differences, however, were not signifi-
359 cantly associated with serum T3 levels, again highlighting the need to gain a better understand-
360 ing of underlying mechanisms.

361
362 The focus of prior research into combination therapy has been using synthetic LT4+LT3, rather
363 than DTE. The fourteen trials of synthetic LT4+LT3 that have been completed thus far show
364 some patient preference for combination therapy, but have failed to show obvious superiority of
365 LT4+LT3.^{6,14-20,22-26,28} Thyroid-related symptoms were generally not improved with combina-
366 tion therapy, other than when TSH suppression was achieved. Parameters such as quality of life,
367 mood, and neurocognitive performance were only improved in a minority of studies. These stud-
368 ies have multiple limitations (e.g. once daily dosing, short duration study, small study size, dis-
369 parate TSH values between study groups) that have been previously reviewed extensively.^{2,29}
370 Failure to demonstrate superiority of LT4+LT3 could be due to any combination of these short-
371 comings in study design or the drug formulation. However, it is also possible that synthetic com-
372 bination therapy is simply not superior to LT4. The one double blind, randomized, placebo con-
373 trolled trial of DTE versus LT4 also failed to show that DTE resulted in improvement in a num-
374 ber of neuropsychological measures.²⁸ There was a preference for DTE, which was associated
375 with the very modest, short-term weight loss of 3lbs that was associated with DTE. However,
376 long-term, outcome data were not reported, and it is not known if the weight loss was sustained.
377 A preference for LT4+LT3 has also been shown to be associated with the weight loss achieved
378 during therapy, although TSH suppression was a confounding factor.¹⁴

379
380 If the clinical trials conducted up to now have not shown benefits of either LT4+LT3 or DTE,
381 but uncontrolled patients surveys²⁷ or online patient forum opinions suggest that combination
382 therapy is preferred, this could simply reflect biased data, or it is also possible that the appropri-
383 ate patient group has not yet been formally studied. Prospective clinical trials of combination
384 therapy have not yet been conducted that have specifically recruited dissatisfied patients, patients
385 with the lowest circulating T3 levels; few trials have considered deiodinases or thyroid hormone
386 transporters polymorphisms. Certainly, retrospective data suggest that patient preference may be
387 linked to a patients' complement of thyroid hormone metabolism-associated polymorphisms.^{30,31}

388
389 If DTE actually does provide more satisfactory therapy for patients with hypothyroidism, it is
390 possible that this is due to (i) patient preference for higher treatment doses ii) patients being ren-
391 dered T3-thyrotoxic, (iii) the presence of some other orally active substance other than T4 and
392 T3 within the DTE, or (iv) a confounding factor such as use of other complementary or alterna-
393 tive medicine in users of DTE, or (v) an as yet unidentified aspect of thyroid physiology. It is
394 important to keep in mind though that DTE, like LT4, does not restore normal thyroid hormone

395 homeostasis. Circulating levels of T3 are increased during DTE therapy and may transiently ex-
396 ceed the upper limits of normal, while the average blood levels of T4 are below the lower limit
397 of normal. High levels of T3 are known to enhance mood in studies of patients with depression
398 and it is possible that patient preference for DTE reflects a positive effect of supra-physiologic
399 T3 levels on mood. At the same time, it is unknown whether transient supra-physiologic T3 lev-
400 els are safe or whether they could promote arrhythmias, especially in older or susceptible pa-
401 tients. With respect to patients potentially preferring higher doses, it has recently been shown in
402 a randomized blinded trial that patients preferred the LT4 dose that they believed was the highest
403 dose, even if they had not identified the relative dose correctly.³²
404

405 A major strength of this study is the large sample size. However limitations of the study include
406 probable sampling and/or recall bias, subjectivity, a lack of an external control (e.g. patients
407 treated for other endocrine disorders or other chronic medical conditions), and the use of an non-
408 validated survey instrument. With respect to the first limitation, we acknowledge the increased
409 likelihood that patients with significant dissatisfaction with their therapy for hypothyroidism are
410 more likely to have been motivated to complete the survey than those who feel unaffected by
411 their hypothyroidism, or even those who feel very happy about their treatment. To highlight this
412 50% of our survey respondents had changed their physician twice or more. It is anticipated, alt-
413 though not verified, that this questionnaire attracted dissatisfied patients or was preferentially
414 publicized among groups of dissatisfied patients. We therefore anticipate that we have captured
415 one, or possibly both, ends of the spectrum of opinion about treatment. If we assume that approx-
416 imately 15% of treated patients feel worse than individuals without thyroid disease, and if we
417 have captured a subset of these patients, our results, despite the inherent bias, nevertheless indi-
418 cate a significant unmet need among patients. We also seem to have captured predominately fe-
419 males in our survey. We know that hypothyroidism affects women/men with a ratio of 9:1, and
420 yet our respondents exhibited a ratio of 21:1.
421

422 With respect to the third and fourth limitations, because the diagnosis of hypothyroidism is self-
423 reported, we cannot be sure that the respondents do not include a significant number of individu-
424 als who are taking thyroid hormone because of a misdiagnosis of hypothyroidism or for a condi-
425 tion other than hypothyroidism, for example fibromyalgia . Additionally, hypothyroid patients
426 may also mistakenly attribute unrelated symptoms or decreased quality of life to their thyroid
427 condition. Once a patient has been diagnosed with a chronic condition such as hypothyroidism,
428 there is a natural tendency for a patient to associate their spectrum of symptoms with this condi-
429 tion. The attribution of these symptoms may be mistaken. If there is mis-attribution of symp-
430 toms, then these symptoms would not be expected to resolve with adjustment of therapy for hy-
431 pothyroidism. It is well known that patients with hypothyroidism have a greater disease burden
432 than the general population^{6,33}, and that hypothyroid patients treated to achieve a normal TSH
433 remain symptomatic.^{34,35} However, not only does manipulation of thyroid status in these individ-
434 uals fail to resolve symptoms,^{25,32} but also treatment of euthyroid individuals with hypothyroid-
435 like symptoms does not resolve symptoms.³⁶ We attempted to mitigate these particular limita-
436 tions by requesting that respondents report co-existent medical conditions and examining sub-
437 groups who did not have these conditions. In general, our findings remained generally unaltered
438 in these subgroup analyses. However, we do not know if we have fully captured other medical
439 conditions that might be the major source of some of the symptoms reported.
440

441 In conclusion, it is clear that a subset of patients with hypothyroidism are not satisfied with their
442 current therapy, nor their physicians. This is unexpected. These findings highlight the need for
443 high quality research to study treatments for hypothyroidism. Such treatments may include hor-
444 monal therapies, supportive care interventions, lifestyle modification interventions (e.g. exercise,
445 diet), or complementary/alternative treatments. Definitive trials need to be adequately statistical-
446 ly powered to detect clinically significant changes in important patient outcomes, attempt to pro-
447 vide steady levels of T3, and specifically target individuals who are symptomatic. Failure to con-
448 duct well-designed studies to advance our understanding in this area promotes reliance on anec-
449 dotal case reports/series, self-report survey studies (such as this one), and observational registry
450 data. In the absence of a better understanding of hypothyroidism treatment patients will continue
451 to experience unresolved symptoms and be exposed to the risks and expenses of treatments with
452 unproven benefits and possible harm.³⁷

453

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460

461

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Table 1: Demographic data, hypothyroid disease characteristics and perceptions regarding hypothyroid treatment for the total sample (n=11,166)

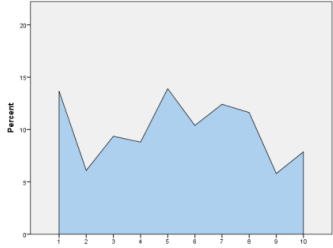
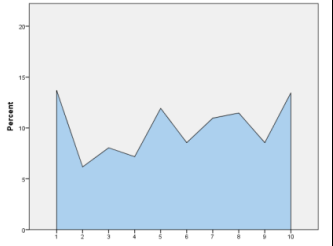
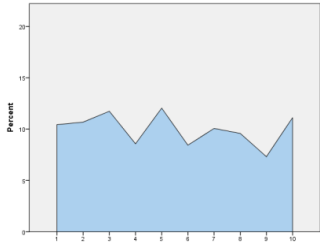
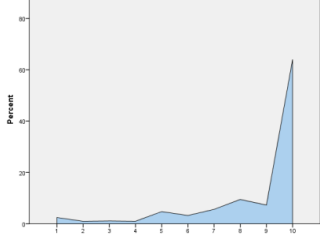
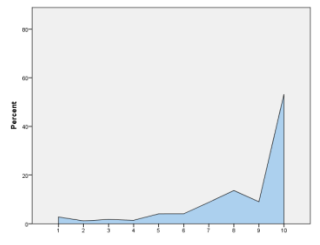
| Survey section | Survey question | Possible response | Respondents |
|--|---|--|---|
| Demographics | Gender* | Female Male | 10664 (96%) 502 (4%) |
| | Age* | 31-40 years 41-50 years 51-60 years ≥61 years | 2464 (22%) 3217 (29%) 2830 (25%) 2655 (23%) |
| Hypothyroid etiology and treatment | Etiology of hypothyroidism* | Hashimoto/autoimmune Radioactive iodine Surgery Other/Not known | 4812 (43%) 858 (8%) 1694 (15%) 3802 (34%) |
| | What thyroid hormone are you currently taking?* | LT4 LT4 + LT3 DTE | 6949 (62%) 978 (9%) 3239 (29%) |
| | Hypothyroid treatment duration* | Less than 1 year 1-5 years 6-10 years More than 10 years | 814 (7%) 3337 (30%) 2486 (22%) 4529 (41%) |
| Self-reported medical history | Is a condition not related to thyroid hormone causing your symptoms? | Current stress levels Other medical problem No condition identified | 3727 (33%) 3578 (32%) 3,861 (34%) |
| | Do you have any of these medical problems? | Heart disease Lung disease Diabetes Bone/Muscle disease GI disease Cancer (non-thyroid) Depression | 510 (5%) 312 (3%) 681 (6%) 868 (8%) 1506 (14%) 243 (2%) 2965 (27%) |
| Perception regarding hypothyroid treatment | How satisfied are you with the treatment you receive? + | 1= not satisfied 10=very satisfied | 5 (3,8)  |
| | 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? + | 1= not satisfied 10=very satisfied | 6 (3,8)  |

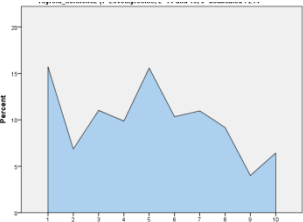
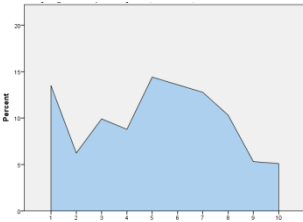
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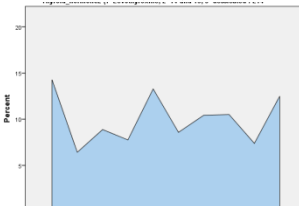
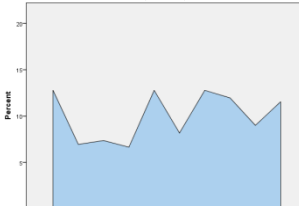
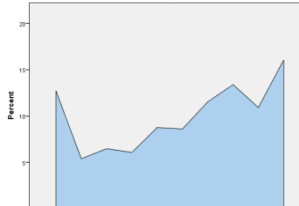
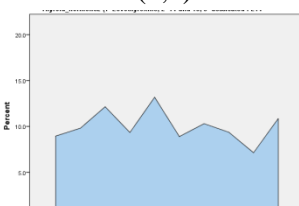
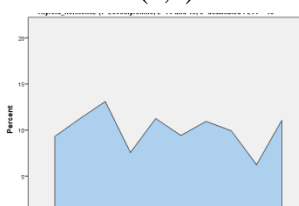
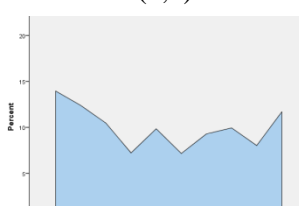
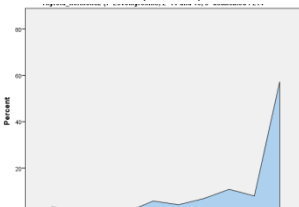
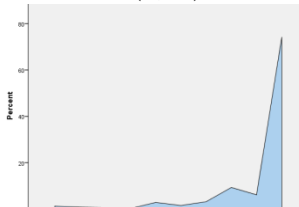
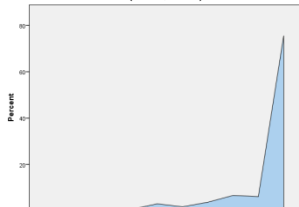
| | | | |
|--|--|---|--|
| | How knowledgeable is your doctor and/or physicians in general about hypothyroid treatment? ⁺ | 1=not knowledgeable 10= very knowledgeable | 5 (3,8)  |
| | How many times have you changed doctors because you were not satisfied with the treatment you were receiving? * | Never 1 time 2-4 times 5-9 times More than 10 | 3185 (29%) 1944 (17%) 4375 (39%) 1349 (12%) 313 (3%) |
| | How would you rate the need for new treatments for hypothyroidism? ⁺ | 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)  |

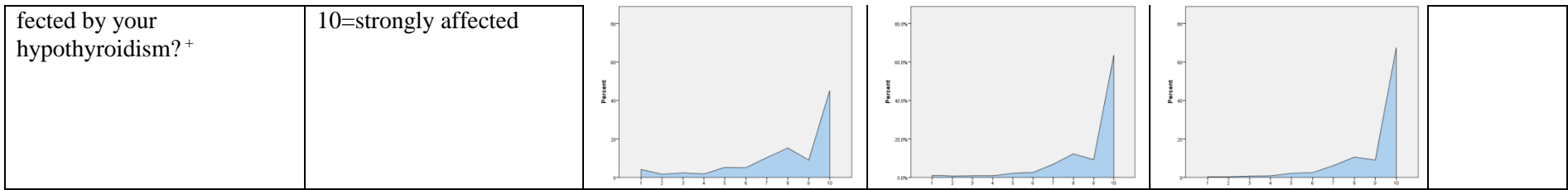
* Summarized as frequency (percent)

⁺ Summarized as median (25th percentile, 75th percentile)

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 |
|--|---------------------------------------|---|---|---|---------|
| Gender* | Female | 6546 (94%) | 944 (97%) | 3174 (98%) | <0.0001 |
| | Male | 403 (6%) | 34 (3%) | 65 (2%) | |
| Age* | 31-40 years | 1553 (22%) | 230 (23%) | 681 (21%) | <0.0001 |
| | 41-50 years | 1857 (27%) | 286 (29%) | 1074 (33%) | |
| | 51-60 years | 1709 (25%) | 258 (27%) | 863 (27%) | |
| | ≥61 years | 1830 (26%) | 204 (21%) | 621 (20%) | |
| Etiology of hypothyroidism* | Hashimoto/autoimmune | 2587 (37%) | 475 (49%) | 1750 (54%) | <0.0001 |
| | Radioactive iodine | 629 (9%) | 67 (7%) | 162 (5%) | |
| | Surgery | 1149 (17%) | 185 (19%) | 360 (12%) | |
| | Other | 2587 (38%) | 251 (12%) | 967 (30%) | |
| Hypothyroid treatment duration* | Less than 1 year | 609 (9%) | 32 (3%) | 173 (5%) | <0.0001 |
| | 1-5 years | 2012 (29%) | 268 (27%) | 1057 (33%) | |
| | 6-10 years | 1507 (22%) | 245 (25%) | 734 (23%) | |
| | More than 10 years | 2821 (41%) | 433 (44%) | 1275 (39%) | |
| Is a condition not related to thyroid hormone causing your symptoms? | | | | | |
| Do you have any of these medical problems? | | | | | |
| How satisfied are you with the treatment you receive? + | 1= not satisfied 10=very satisfied | 5 (3, 7)  | 5 (3,7)  | 7 (4,8)^#  | <0.0001 |
| | | | | | |
| If you are not satisfied, indicate relevant areas you feel are affected by your thyroid treatment* | Weight management | 4889 (70%) | 704 (72%) | 2136 (65%) | <0.0001 |
| | Fatigue or energy levels | 5547 (80%) | 793 (81%) | 2257 (70%) | <0.0001 |
| | Mood | 3369 (49%) | 458 (47%) | 1232 (38%) | <0.0001 |
| | Memory | 4150 (60%) | 612 (63%) | 1671 (52%) | <0.0001 |

| | | | | | |
|---|--|--|--|---|-------------------|
| <p>How satisfied are you with your current physician who treats you for your thyroid condition? ⁺</p> | <p>1= not satisfied 10=very satisfied</p> | <p>5 (3,8)</p>  | <p>6 (3,8)</p>  | <p>7 (4,9) ^{^#}</p>  | <p><0.0001</p> |
| <p>Table 2, continued</p> | | | | | |
| <p>How knowledgeable is your doctor and/or physicians in general about hypothyroid treatment? ⁺</p> | <p>1=not knowledgeable 10= very knowledgeable</p> | <p>5 (3,8)</p>  | <p>5 (3,8)</p>  | <p>5 (2,8)</p>  | <p>0.012</p> |
| <p>How many times have you changed doctors because you were not satisfied with the treatment you were receiving? [*]</p> | <p>Never 1 time 2-4 times 5-9 times More than 10</p> | <p>2775 (39%) 1476 (21%) 2408 (33%) 456 (6%) 92 (1%)</p> | <p>163 (16%) 156 (15%) 481 (48%) 176 (17%) 37 (4%)</p> | <p>372 (11%) 407 (12%) 1636 (48%) 783 (23%) 190 (6%)</p> | <p><0.0001</p> |
| <p>How would you rate the need for new hypothyroid treatments? ⁺</p> | <p>1=no need 10=strong need</p> | <p>10 (8,10)</p>  | <p>10 (9,10) [^]</p>  | <p>10 (10,10) [^]</p>  | <p><0.0001</p> |
| <p>Tried alternative hypothyroid treatment not prescribed by doctor* Yes No</p> | <p>Yes No</p> | <p>1316 (19%) 5633 (81%)</p> | <p>309 (32%) 669 (68%)</p> | <p>1483 (46%) 1756 (54%)</p> | <p><0.0001</p> |
| <p>How has your life been af-</p> | <p>1=not affected</p> | <p>9 (7,10)</p> | <p>10 (8,10) [^]</p> | <p>10 (9,10) [^]</p> | <p><0.0001</p> |



* Summarized as frequency (percent)

⁺ Summarized as median (25th percentile, 75th percentile), differences between groups determined by Kruskal-Wallis test

[^] Significantly different from respondents taking LT4 by Mann Whitney U test (p<0.0001)

[#] Significantly different from respondents taking LT4+T3 by Mann Whitney U test (p<0.0001)

569

Table 3: Comparison median perception of satisfaction regarding hypothyroid treatment by self-reported medication.

| <i>SUBGROUP-1:</i> Respondents without depression, stressors, or medical conditions | LT4 (n=2206) | LT4 +LT3 (n=316) | DTE (n=1148) | p-value |
|--|---|-------------------------|-------------------------|----------------------|
| | How satisfied are you with the treatment you receive? | 5 (3,7) | 6 (3,8) | 7 (5,9) [#] |
| How satisfied are you with your current physician who treats you for your thyroid condition? | 5 (3,8) | 6 (3,8) | 7 (4,9) [^] | <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) [^] | 10 (10,10) [^] | <0.0001 |
| How has your life been affected by your hypothyroidism? | 9 (7,10) | 10 (9,10) [^] | 10 (8,10) [^] | <0.0001 |
| <i>SUBGROUP-2:</i> Respondents without depression, stressors, or medical condition matched by gender, age & hypothyroid treatment | LT4 (n=614) | LT4 +LT3 (n=307) | DTE (n=614) | p-value |
| | How satisfied are you with the treatment you receive? | 5 (3,7) | 6 (3,8) | 7 (5,9) [#] |
| How satisfied are you with your current physician who treats you for your thyroid condition? | 5 (3,8) | 6 (3,8) [^] | 7 (3,9) [^] | <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) [^] | 10 (10,10) [^] | <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:</i> Respondents with depression, but without stressors or medical conditions | LT4 (n=457) | LT4 +LT3 (n=42) | DTE (n=180) | p-value |
| | How satisfied are you with the treatment you receive? | 4 (1,6) | 4 (2,6) | 5 (3,7) [^] |
| How satisfied are you with your current physician who treats you for your thyroid condition? | 5 (2,7) | 5 (2,8) | 6 (3,8) [^] | 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) [^] | <0.0001 |
| How has your life been affected by your hypothyroidism? | 10 (8,10) | 10 (10,10) | 10 (10,10) [^] | <0.0001 |
| <i>SUBGROUP-4:</i> Thyroid cancer without depression, stressors, or medical conditions | LT4 (n=224) | LT4 +LT3 (n=48) | DTE (n=74) | p-value |
| | How satisfied are you with the treatment you receive? | 5 (3,8) | 6 (4,8) | 7 (3,8) |
| 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) [^] | <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) [^] | 10 (9,10) | <0.0001 |

[^] Significantly different from respondents taking LT4 by Mann Whitney U test (p<0.0001)

[#] Significantly different from respondents taking LT4+T3 by Mann Whitney U test (p<0.0001)

Table 4: Comparison of hypothyroid side-effects that are a primary concern to respondents by self-reported medication

| <i>SUBGROUP-1:</i> Respondents without depression, stressors, or medical conditions | LT4 (n=2206) | LT4 +LT3 (n=316) | DTE (n=1148) | p-value |
|--|-------------------|---------------------|-------------------|-------------------|
| | Weight management | 69% | 74% | 64% [#] |
| Fatigue/energy levels | 75% | 76% | 64% ^{^#} | <0.0001 |
| Mood | 42% | 40% | 30% ^{^#} | <0.0001 |
| Memory or other problems with thinking | 55% | 59% | 44% ^{^#} | <0.0001 |
| <i>SUBGROUP-2:</i> Respondents without depression, stressors, or medical condition matched by gender, age & hypothyroid treatment | LT4 (n=614) | LT4 +LT3 (n=307) | DTE (n=614) | p-value |
| | Weight management | 71% | 74% | 59% ^{^#} |
| Fatigue/energy levels | 81% | 77% | 62% ^{^#} | <0.0001 |
| Mood | 47% | 40% | 29% ^{^#} | <0.0001 |
| Memory or other problems with thinking | 62% | 59% | 43% ^{^#} | <0.0001 |
| <i>SUBGROUP-3:</i> Respondents with depression, but without stressors or medical conditions | LT4 (n=457) | LT4 +LT3 (n=42) | DTE (n=180) | p-value |
| | Weight management | 77% | 71% | 75% |
| 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:</i> Thyroid cancer without depression, stressors, or medical conditions | LT4 (n=224) | LT4 +LT3 (n=48) | DTE (n=74) | p-value |
| | Weight management | 59% | 79% | 64% |
| 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 |

[^] Significantly different from respondents taking LT4 by Chi-square test (p<0.0001)

[#] Significantly different from respondents taking LT4+T3 by Chi-square test (p<0.0001)

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