

Supplementary 1: Survey on Current Use of Levothyroxine in Europe

Article title: Use of thyroid hormones in hypothyroid and euthyroid patients: A 2020 THESIS* questionnaire survey of members of the Danish Endocrine Society, * *Treatment of Hypothyroidism in Europe by Specialists: An International Survey*

Journal name: J Endocrinol Invest

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Introduction

Over the past several years, various levothyroxine (LT4) formulations (generic or branded, in tablet form, soft-gel capsules, or liquid solution), have become commercially available for clinical use in European Countries. Approved LT4 formulations, whether generic or branded, are generally reported as effective in the treatment of hypothyroidism (Scavone et al, 2016), though differences in bioavailability have been noted (Carswell et al, 2013). Yet pricing and cost vary vastly from \$ 5.00 to \$ 122 per month for 100 mcg (Wouters et al, 2017; <https://www.drugs.com/price-guide/tirosint>), and anecdotal claims by patients and some practitioners of widely varying efficacy and tolerance are abundant (Faasse et al, 2009; Casassus, 2018; <https://www.restartmed.com/tirosint/>). Different LT4 preparations are prescribed with variable frequency by endocrinologists and practitioners. Furthermore, regional differences in prescribing of LT4 (up to 3.5-fold) and a continuing upward trend across time, suggestive of lowering thresholds employed by physicians in initiating treatment, have been noted (Frank et al, 2014; Taylor et al, 2014, Razvi et al, 2019). Switching from one LT4 preparation to another (Ernst et al, 2017; Elmor et al, 2017) appears to incur a significant economic cost. Understanding physician prescribing preferences is important as it impacts on health care costs and the patient experience. A recent survey focusing on the controversial topic of use of T3 in hypothyroidism revealed that physician choice of treatment was powerfully influenced by ongoing patient symptoms and characteristics independently of biochemical control of hypothyroidism (Jonklaas et al, 2018). This is a concerning trend given the evidence against objective superiority of T3 treatment and the risks of subclinical hyperthyroidism. LT4 only preparations have the advantage (over T3) of restoring physiological levels of thyroid hormones without the potentially hazardous fluctuations in serum T3 concentration. However, physician prescribing choices among different LT4 preparations has not been studied in the context of persisting patient symptoms. A questionnaire survey was recently piloted in members of the Italian Association of Clinical Endocrinologists and yielded some interesting results (Negro

et al, 2019). It will therefore be of some considerable interest to know whether there are differences in experiences and practices between European countries.

Aim

This questionnaire is intended to identify attitudes of European physicians relating to the treatment of hypothyroidism focusing on available formulations of LT4 in clinical practice.

Individual responses will remain anonymous.

A: ABOUT YOU

A1. Sex

- a) Female
- b) Male

A2. Age (years) *[dropdown menu]*

- a) 20-30
- b) 31-40
- c) 41-50
- d) 51-60
- e) 61-70
- f) 70+

A3. Years in medical practice *[dropdown menu]*

- a) 0-10
- b) 11-20
- c) 21-30
- d) 31-40
- e) More than 40

A4. Specialty *[check all that apply]*

- a) Endocrinology
- b) Internal Medicine
- c) Pediatric Endocrinology
- d) Nuclear Medicine
- e) Surgery
- f) Family Medicine
- g) Gynecology
- h) Other

A5. Member of... *[check all that apply]*

- a) ETA (European Thyroid Association)
- b) ATA (American Thyroid Association)
- c) LATS (Latin American Thyroid Association)
- d) AOTA (Asian and Oceanian Thyroid Association)
- e) National Endocrine Societies
- f) None of the above

A6. Where do you practice? *[check all that apply]*

- a) University center
- b) Regional hospital

- c) Private clinic
- d) General Practice
- e) Basic researcher

A7. Do you treat thyroid patients on a regular basis (daily or weekly)?

- a) Yes, daily
- b) Yes, weekly
- c) No, I rarely treat thyroid patients

A8. Do you treat patients with hypothyroidism?

- a) Yes, from 10 to 50 patients/year
- b) Yes, from 51 to 100 patients/year
- c) Yes, > 100 patients/year
- d) No, I rarely treat hypothyroid patients

B. HYPOTHYROIDISM

B1. Thyroid hormones may be indicated in biochemically euthyroid patients with: [check all that apply]

- 1) unexplained fatigue
- 2) obesity resistant to life-style interventions
- 3) severe hypercholesterolemia, as a complementary treatment
- 4) depression resistant to anti-depressant medications
- 5) female infertility with high level of thyroid antibodies
- 6) simple goiter growing over time
- 7) no, treatment is never indicated for these patients

B2. Which thyroid hormones available for substitution therapy should be the first choice for the treatment of hypothyroid patients?

- 1) LT4
- 2) LT3
- 3) Desiccated thyroid
- 4) LT4 and LT3 combination

B3. Which of the following drugs are you prescribing in clinical practice? [check all that apply]

- 1) LT4
- 2) LT3
- 3) Desiccated thyroid
- 4) LT4 and LT3 combination

B4. How much control do you have over the formulation of LT4 dispensed for your patients? Please choose the option the best applies to your practice

- 1) most of my patients are dispensed the type of LT4 that I recommend
- 2) I have control over the type of LT4, but I have to justify it to the regulatory authorities every time I recommend it
- 3) the type of dispensed thyroxine is mostly chosen by general practitioners
- 4) for most of my patients I have no control over the type of LT4 that they are dispensed

B5. Interfering drugs may influence the stability of therapy. Which LT4 preparation is in your experience least likely to be subject to variable absorption?

- 1) tablets
- 2) soft-gel capsules
- 3) liquid solution
- 4) I expect no major changes with different formulations

B6. Which of the following preparations of LT4 would you prescribe in case of first diagnosis of hypothyroidism when the patient self-reports intolerance to various foods raising the possibility of celiac disease, malabsorption, lactose intolerance, or intolerance to common excipients

- 1) tablets
- 2) soft-gel capsules
- 3) liquid solution
- 4) I expect no major changes with the different formulations

B7. Which of the following preparations of LT4 would you prescribe for a patient established on LT4 who has unexplained poor biochemical control of hypothyroidism?

- 1) tablets from another manufacturer
- 2) soft-gel capsules
- 3) liquid solution
- 4) I expect no major changes with the different formulations

B8. Which of the following preparations of LT4 would you prescribe for a patient with poor biochemical control who is unable (due to busy lifestyle) to take LT4 fasted and separate from food/drink?

- 1) tablets
- 2) soft-gel capsules
- 3) liquid solution
- 4) I expect no major changes with the different formulations

B9. Which of the following preparations of LT4 would you prescribe for a patient established on LT4 tablets who has good biochemical control of hypothyroidism but continues to have symptoms?

- 1) tablets
- 2) soft-gel capsules
- 3) liquid solution
- 4) I expect no major changes with the different formulations

B10. After the start of LT4 replacement therapy, when would you re-check serum TSH:

- 1) after 2 weeks
- 2) after 4 – 6 weeks
- 3) after 8 weeks
- 4) no, I mostly rely on clinical evaluation

B11. In case of a switch to a different formulation or change from one manufacturer's LT4 tablet to another, when do you recommend that the serum TSH should be re-checked:

- 1) after 4 to 6 weeks
- 2) after 8 weeks
- 3) on the basis of clinical evaluation
- 4) no, there is no need of TSH control after preparation changes if the dosage is the same

B12. Dietary supplements (such as selenium or iodine) are proposed for patients with thyroid disease. Do you think that they may be used in addition to thyroid hormone replacement in hypothyroidism?

- 1) when there is coexisting autoimmune thyroiditis
- 2) in subclinical hypothyroidism
- 3) at the patient's request or as a complementary treatment
- 4) no, dietary supplements should never be used

B13. The use of combined replacement therapy, with administration of both LT4 and LT3, is generally not recommended. Do you think that may be considered:

- 1) for a short period, in patients recovering from protracted hypothyroidism
- 2) in patients with normal serum TSH who still complain of symptoms suggestive of hypothyroidism
- 3) in hypothyroid patients with normal serum TSH who complain of unexplained weight gain
- 4) due to the low quality of available evidence, combined therapy should never be used.

B14. It has been reported that some patients with hypothyroidism treated with levothyroxine continue to experience persistent symptoms despite normal serum TSH. The following three questions refer to such patients.

In your clinical practice how common is this phenomenon?

- 1) less than 5% of patients
- 2) 6-10%
- 3) 11-30%
- 4) More than 30%
- 5) Not sure

B15. It has been reported that some patients with hypothyroidism treated with levothyroxine continue to experience persistent symptoms despite normal serum TSH.

In your experience what has been the trend over the past 5 years?

- 1) I am seeing more such cases
- 2) I am seeing fewer such cases
- 3) No change
- 4) Not sure

B16. In most patients treated with levothyroxine who achieve normal serum TSH, persistent symptoms are due to:

- 1) inability of levothyroxine to restore normal physiology
strongly disagree/disagree/neutral/agree/strongly agree
- 2) psychosocial factors
strongly disagree/disagree/neutral/agree/strongly agree
- 3) comorbidities
strongly disagree/disagree/neutral/agree/strongly agree
- 4) chronic fatigue syndrome
strongly disagree/disagree/neutral/agree/strongly agree
- 5) patient unrealistic expectation
strongly disagree/disagree/neutral/agree/strongly agree
- 6) presence of underlying inflammation due to autoimmunity
strongly disagree/disagree/neutral/agree/strongly agree
- 7) the burden of chronic disease
strongly disagree/disagree/neutral/agree/strongly agree
- 8) the burden of having to take medication

strongly disagree/disagree/neutral/agree/strongly agree

B17. Using your experience with patients treated with levothyroxine who achieve normal serum TSH, but continue to experience symptoms like fatigue, please rank them from 1-8, where 1 is the most likely and 8 the least likely explanation in your opinion. [Double-click or drag-and-drop items in the left list to move them to the right - your highest-ranking item should be on the top right, moving through to your lowest ranking item].

- | | Rank (1-8) |
|--|--------------------------|
| 1) the burden of having to take medication | <input type="checkbox"/> |
| 2) patient unrealistic expectations | <input type="checkbox"/> |
| 3) inability of levothyroxine to restore normal physiology | <input type="checkbox"/> |
| 4) psychosocial factors | <input type="checkbox"/> |
| 5) presence of underlying inflammation due to autoimmunity | <input type="checkbox"/> |
| 6) comorbidities | <input type="checkbox"/> |
| 7) chronic fatigue syndrome | <input type="checkbox"/> |
| 8) the burden of chronic disease | <input type="checkbox"/> |

B18. Do you, yourself have a diagnosis of hypothyroidism requiring thyroid hormone treatment?

1. Yes
2. No

B19. (it will appear only in respondents who answered "yes" to question B18) Do you experience excessive tiredness/fatigue?

1. Yes
2. No

B20. (it will appear only in respondents who answered "yes" to question B18) Have you tried L-T4 and L-T3 combination treatment?

1. Yes
2. No

B21. (it will appear only in respondents who answered "yes" to question B18) Have you tried desiccated thyroid treatment?

1. Yes
2. No

B22. (it will appear only in respondents who answered "yes" to question B20 or B21) If you have tried of L-T4 and L-T3 combination treatment or desiccated thyroid, please describe your experience (e.g. how effective compared with L-T4 monotherapy, whether you continue to take it, side-effects, long-term concerns).

(Space for free text)

B23. (it will appear only in respondents who answered "No" to question B18) Would you consider L-T4 and L-T3 combination treatment or desiccated thyroid for yourself if you were to develop hypothyroidism?

1. Yes
2. No

B24. Please add comments (e.g., why you would or would not choose to take L-T4 and L-T3 combination treatment or desiccated thyroid for yourself)

(Space for free text)

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE

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