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Levothyroxine overuse: time for an about face?

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Despite the fairly low prevalence (about 0·2–2·0%) and stable incidence of overt hypothyroidism, use of levothyroxine is increasing. In the USA, the number of prescriptions for levothyroxine increased from 97 million in 2007 to 120 million in 2014, and in the UK from 2·8 million in 1998 to 19 million in 2007 and 29 million in 2014 (figure). Levothyroxine has become the most prescribed drug in the USA and the third most prescribed drug in the UK.[1,2] What factors are driving the prescription and possible overuse of levothyroxine? What is the evidence? And what can be done to improve the quality of levothyroxine prescription.

Subclinical hypothyroidism affects up to 12% of the adult population or roughly 1 billion adults worldwide. Some evidence supports use of levothyroxine to improve cardiovascular events, quality of life, and cognitive function in patients with subclinical hypothyroidism, but the evidence of benefit is scant (appendix).[3] Guidelines, however, indicate treatment with levothyroxine for people with subclinical hypothyroidism with thyroid-stimulating hormone concentration of 10 mIU/L or higher and people with thyroid-stimulating hormone between 5·5 mIU/L and 10 mIU/L who have symptoms attributable to hypothyroidism, positive autoantibodies, or cardiovascular disease (appendix). Accordingly, nine of every ten women with subclinical hypothyroidism with a thyroid-stimulating hormone concentration between 5·5 mIU/L and 10 mIU/L could receive levothyroxine.[4] As a result, the prevalence of untreated subclinical hypothyroidism in Norway has decreased by 64% in women and 54% in men between 1995–97 and 2006–08.[5] Additionally, people in the UK with thyroid-stimulating hormone concentration of 10·0 mIU/L or lower were prescribed levothyroxine 1·3 times more in 2009 than in 2001,[6] and 31% of treated patients in this cohort had a thyroid-stimulating hormone concentration of 10 mIU/L or less, normal thyroxine values, and no symptoms of hypothyroidism or abnormal cardiovascular risk factors.

See Online for appendix

The American Thyroid Association recommends screening asymptomatic men and women older than 35 years for thyroid dysfunction every 5 years, which translates into testing about 3·5 billion adults worldwide. Expert panels, however, disagree about the criteria for screening the general population for hypothyroidism and have proposed different cutoffs (appendix). Despite the counterarguments, the enthusiasm for this practice has resulted in a surge of thyroid tests in otherwise healthy non-pregnant people. In the UK, about 25% of the adult population are estimated to have their thyroid function measured every year.[6]

In a population-based study, 62% of thyroid-stimulating hormone values between 5·5 mIU/L and 10 mIU/L normalised without intervention.[7] Thyroid-stimulating hormone pulsatility, concomitant transient illness, drugs, environmental and stress factors, and other factors might explain this reversal. Thus, the prescription of levothyroxine should require evidence of persistently abnormal levels of thyroid-stimulating hormone. Current practice, however, places one of every three patients with subclinical hypothyroidism on levothyroxine treatment with only one abnormal thyroid-stimulating hormone test result.[6] Additionally, healthy elderly people might generally have increased thyroid-stimulating hormone levels. Some researchers have suggested increasing the upper boundary of the normal range of thyroid-stimulating hormone to 7·5 mIU/L or 8·5 mIU/L in normal adults aged 65 years and older. Ideally, to avoid misclassification and overtreatment, clinicians should receive population-specific reference limits.

Dry skin, hair loss, constipation, myalgia, fatigue, menstrual irregularities, low energy, and weight gain are all challenging but non-specific symptoms of subclinical and overt hypothyroidism. The probability of hypothyroidism in the presence of one of these symptoms is about 10%. In fact, 20–25% of people with normal thyroid hormone levels report one or two hypothyroidism-related symptoms.[8] Therefore, symptoms might not reliably identify those who can benefit from levothyroxine treatment. Evidence supporting levothyroxine treatment for patients with subclinical hypothyroidism with non-specific symptoms is lacking. In selected cases, patients and clinicians might consider a brief therapeutic trial with levothyroxine with the goal of improving symptoms with reassessment and discontinuation of treatment if proven ineffective. Such explorations, however, can be affected by clinician and patient expectation, including the placebo effect.

Levothyroxine 3-month out-of-pocket cost to patients in the USA varies considerably, from US$4 to US$100. Synthroid, with 21·5 million annual prescriptions, is the leading prescribed brand-name medication in the USA, with revenues greater than US$1 billion annually.[1] In the UK, the annual amount of thyroid replacement therapy has tripled from 1998 to 2007 and the cost per day increased from less then £5000 to more than £40 000. In assessments of the economic effects of current practice, the costs to patients and other payers of thyroid testing, clinical follow-up of abnormal test results, clinical visits, and possible lifelong monitoring, follow-up, and levothyroxine use must be taken into account.

In the past few decades, the incidence of thyroid cancer has tripled in the USA. Additionally, screening of pregnant women for thyroid dysfunction has also increased the number of thyroid function tests. Whereas in patients with cancer there is a definite need for levothyroxine use (eg, as replacement in patients undergoing total thyroidectomy), in pregnant women, at least in those with small increases in thyroid-stimulating hormone levels, there is still substantial uncertainty.[9]

The safety of levothyroxine is also an issue. In a study of patients older than 65 years taking levothyroxine, 40–50% had a thyroid-stimulating hormone concentration of less than 0·45 mUI/L.[10] At these concentrations, patients can exhibit hyperthyroidism, increasing the risk for arrhythmias, angina pectoris, bone loss, and fractures. As well as the potential harms, levothyroxine contributes to treatment burden. Once started, about 90% of patients continue levothyroxine therapy in the long term.[6] Taking this drug often demands modification of daily habits—eg, dosing 30–60 min before a meal, monitoring of effects, and clinic and laboratory visits—as well as financial costs to the patient.

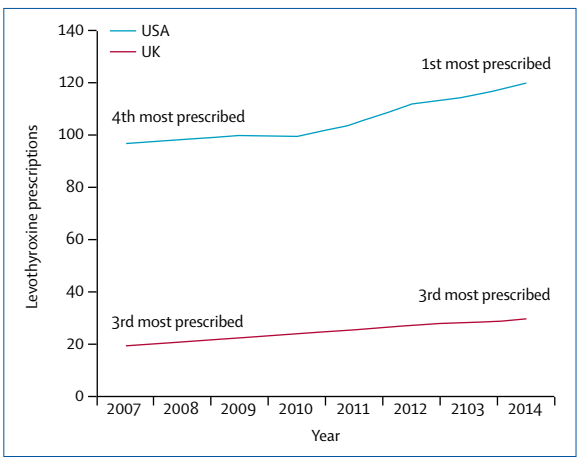

Figure: **Levothyroxine prescriptions from 2007 to 2014 in the USA and the UK**

The question is how to start doing better? In the consultation, clinicians and patients must deliberate together, armed with the evidence to determine whether thyroid-stimulating hormone testing followed by levothyroxine treatment is the best way to address their situation.[11] In view of the existing evidence, we propose several strategies to improve the quality of levothyroxine use. First, the reason to explore the possibility of subclinical hypothyroidism should be determined with each patient individually. If symptoms are non-specific, physicians and patients should carefully consider the potential benefit versus the burden of treatment. Second, for people with abnormally high thyroid-stimulating hormone concentrations consistent with subclinical hypothyroidism (based on age-dependent thyroid-stimulating hormone cutoff values), the thyroid-stimulating hormone test should be repeated, ideally in the same laboratory, 3–6 months after the abnormal test, before treatment is considered. Third, clinicians need to recognise that patients with non-specific symptoms and normal thyroid function tests do not benefit from levothyroxine therapy. Finally, if subclinical hypothyroidism is confirmed and the patient agrees with a treatment trial, the lowest dose of a generic levothyroxine preparation should be used

(to achieve an on-range thyroid-stimulating hormone concentration) at first, and reassessed periodically (eg, once or twice a year) to determine the efficacy of levothyroxine use. Treatment should be discontinued if ineffective (ie, no response to symptoms), and the dose lowered if toxic effects become evident.

There is substantial uncertainty and complexity associated with the technical aspects of identifying otherwise healthy people affected by mild, non-specific symptoms, who would benefit from levothyroxine. This uncertainty and complexity calls for policies that invite patients and clinicians to enrol in clinical trials to assess the effectiveness of levothyroxine use, rather than to the routine, expanding, and prolonged use of a treatment of uncertain value.

In conclusion, there is evidence of substantial overuse of levothyroxine. The treatment of individuals with mild, non-specific symptoms and the overdiagnosis of subclinical hypothyroidism, imprecise screening recommendations, and misinterpretation of normal thyroid-stimulating hormone variability could be contributing to levothyroxine overuse, imposing a substantial economic and treatment burden on millions of people. A prudent and patient-centred approach[11] might mitigate the effect of the prevailing uncertainty on the quality of levothyroxine prescription, while much needed research accrues.

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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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SUPLEMENTARY APPENDIX

1. Table S1
2. Table S2
3. Table S3
4. Further Reading References

Table S1. Summary of evidence for levothyroxine effectiveness in patients with subclinical hypothyroidism

Outcome	Risk of bias	Indirectness	Inconsistency	Imprecision	Magnitude of effect	N= (treated/ not treated)	Treatment effect	Point estimate (in case of differences between groups)	Quality of the evidence
Cardiovascular events[a]	2 Obs. studies (no significant limitation)	No	Yes	Yes	Small	4936/12011	One study favoring the treatment group in the younger population (< 70 years). No difference between groups in the older population (both studies)	Younger population (<70 years): HR: 0.61 (0.39-0.95)[b]	Low-quality
All-cause mortality	2 Obs. studies (no significant limitation)	No	Yes	Yes	Small	4936/12011	No difference between groups	ND	Low-quality
Quality of life	5 RCTs (2 cross over studies)	No	Yes	Yes	Small	275/256	No difference between groups, with different scales used among studies	ND	Low-quality
Cognitive function	3 RCTs	No	Yes	Yes	Small	106/94	One study favored the treatment group, in the memory composite score. No difference between groups with different scales used among studies	Memory composite score, difference between group changes 0.58 (0.14, 1.03) P= 0.01	Low-quality

HR, hazard ratio; Obs, observational; RCT, randomized clinical trial; N, number of patients; ND, no difference between groups.

[a] One study used a composite outcome of fatal and non-fatal events of ischemic heart disease; second study evaluated myocardial infarction.

[b] Composite outcome of fatal and non-fatal ischemic heart disease

Table S2. Clinical scenarios where treatment of subclinical hypothyroidism may be considered

Clinical Scenario	**Evidence**
TSH >10 mIU/L	The risk of progression to overt hypothyroidism is ~70-80%. (**Diez**)
TSH 5-10 mIU/L + positive anti-thyroperoxidase antibodies + symptoms suggestive of hypothyroidism in individuals less than 65 years of age without cardiovascular disease.	The OR (95% CI) of developing overt hypothyroidism: (a) Raised serum TSH alone 8 (3-20) for women and 44 (19-104) for men. (b) Positive anti-thyroid antibodies alone 8 (5-15) for women and 25 (10-63) for men. (c) Both raised serum TSH and positive anti-thyroid antibodies 38 (22-65) for women and 173 (81-370) for men. The 20-year risk of overt hypothyroidism has been reported 4.3% annually and 55% cumulative.
TSH 5-10 mIU/L + patients that received radio-iodine therapy, high-dose external neck radiation, or subtotal thyroidectomy.	Hypothyroidism occurs in approximately 80% of patients receiving high-dose therapy (160 microCi/g). Radiation of 2500-4000 rads (>25-40 Gy) or more is associated with a ~20-50% rate of overt hypothyroidism. After subtotal thyroidectomy ~80-90% of patients develop overt hypothyroidism.
TSH above reference for trimester during pregnancy + positive anti-thyroperoxidase antibodies TSH >2.5 mIU/L during 1st Trimester TSH >3.0 mIU/L during 2nd and 3rd trimester.	Some studies have reported an increased risk of preeclampsia, placental abruption, gestational hypertension, gestational diabetes, preterm delivery, and decreased Intellectual coefficient n the offspring and/or miscarriage. Higher rate of pregnancy loss (~15%) has been reported with concomitant positive anti-thyroperoxidase antibodies. An RCT (only abstract published) recently reported no difference in terms of IQ, preterm delivery, gestational diabetes, gestational hypertension, and preeclampsia.
TSH 5-10 mIU/L and Infertility	Despite the lack of evidence of efficacy, the potential even though small benefit may justify the transient and cautious use of L-T4 therapy until further data is available

Table S3. Recommendations from different organizations for thyroid disfunction in asymptomatic adults.

Organization	**Recommendation/Level of Evidence**
American Thyroid Association	Women and men > 35 years of age should be screened every 5 years
U.S. Preventive Services Task Force	Insufficient evidence for or against screening
Royal College of Physicians of London	Screening of the healthy adult population unjustified
American College of Physicians	Women >50 years of age with an incidental finding suggestive of symptomatic thyroid disease should be evaluated
American Association of Clinical Endocrinologists	Older patients, especially women, should be screened
American Academy of Family Physicians	Patients >60 years of age should be screened

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