Liothyronine for hypothyroidism: A candidate for disinvestment or in need of further research?

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BMJ Open

Accepted/In press: 08/11/2021

Peer reviewed version

Title:

Liothyronine for hypothyroidism: A candidate for disinvestment or in need of further research? A value of information analysis

Short title:

Economic analysis of liothyronine

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Funding statement:

This work was supported by the All Wales Therapeutics and Toxicology Centre to develop the model. DAH is recipient of a senior research leader award by Health and Care Research Wales.

Declaration of competing interest:

DAH, KS, DF, PA, AH report no conflicts of interest.

Data availability statement:

Data are available upon reasonable request.

Word count: 3,973

Number of figures: 2

Number of tables: 5

Abstract

Objective: Medicines with limited evidence of effectiveness are prime candidates for disinvestment. However, investment in further research may be preferable to de-implementation, given that the absence of evidence is not evidence of absence, and research can inform formulary decisions. A case in point is liothyronine, which is sometimes prescribed to levothyroxine-treated patients who continue to experience hypothyroid symptoms. It is a putative low value medicine, associated with uncertainties in both clinical and cost effectiveness. The aim was to assess the cost-effectiveness of liothyronine in this context, and estimate the value of conducting further research.

Design: Cost utility and value of information analyses.

Setting: Primary care within the National Health Service in the UK.

Participants: Fifty-four levothyroxine-treated patients with persistent symptoms of hypothyroidism.

Interventions: Liothyronine plus levothyroxine versus levothyroxine alone.

Primary and secondary outcome measures: Incremental cost per quality-adjusted life year (QALY) gained, and the expected monetary value of sample information.

Results: 20/54 (37%) of patients who responded to the survey reported severe problems in carrying out usual activities of everyday living and 12/54 (22%) reported severe anxiety or depression symptoms. Mean (SD) utility was 0.53 (0.23). The differences in expected total, 10-year costs and QALYs between a treatment strategy of liothyronine/levothyroxine combination therapy, and levothyroxine alone, was £12,053 and 1.014, respectively. The incremental cost effectiveness ratio of £11,881 per QALY gained was sensitive to the price of

liothyronine. The probability of liothyronine/levothyroxine combination therapy being cost effective at a threshold of £20,000 per QALY was 0.56. The value of reducing uncertainty in the efficacy of treatment was £3.64m per year in the UK.

Conclusions: A definitive clinical trial to confirm clinical effectiveness may be preferable to immediate disinvestment, and would be justified given the value of the information gained far exceeds the cost.

Keywords:

Cost-effectiveness analysis, value of information analysis, disinvestment, liothryonine, hypothyroidism

Strengths and limitations of this study

- This first analysis of health utilities and costs relating to treatment-unresponsive hypothyroidism addresses a decision problem which is pertinent to the NHS across the UK
- The methods provide a framework for deciding whether investing in further research in order to reduce uncertainty in the clinical and cost-effectiveness of medicines presumed to be of low value, is preferable to formulary delisting
- Estimates of resource utilisation and treatment effectiveness were based on the opinions of a sample of general practitioners and endocrinologists
- The decision analytic model was a simple representation of what is a complex clinical management problem, often involving misdiagnosis, co-morbidities and multiple referrals, investigations and treatments

Introduction

Disinvestment from health care interventions and practices that are considered to offer no or low value is a strategy being used increasingly by healthcare systems around the world in response to unprecedented pressures on budgets [1]. Within the National Health Service (NHS) in the UK, there has been a specific focus on older medicines [2] – such as those which gained marketing authorisation in an era when the evidential standards were lower; or which have been largely supplanted by newer, more effective or safer medicines; or whose use has become marginalised resulting in variation in care, or monopoly of supply leading to price inflation. Health technology reassessment (HTR) describes the process of judging the value of such medicines, and determining whether they warrant continued use, more expanded use or disinvestment (deimplementation). HTR methods may also allow for an assessment of the value of conducting further research to reduce the uncertainty surrounding a medicine's clinical and cost-effectiveness. In such cases, continuing the *status quo* may be reasonably justified while new evidence accrues.

Liothyronine is an epitome, first licensed for the management of hypothyroidism in 1956, but replaced by levothyroxine which offers more favourable dosing and stable serum thyroid hormone concentrations. However, 5-10% of levothyroxine-treated patients continue to experience profound and sometimes disabling symptoms, such as fatigue, depression and impaired cognition, despite achieving thyroid hormone concentrations within reference range [3]. A proportion of these patients are prescribed liothyronine, usually in addition to levothyroxine [3].

Clinical guidelines advise against the routine prescribing of liothyronine. The European Thyroid Association recommends that liothyronine/levothyroxine combination therapy might be considered as an experimental approach in hypothyroidism for patients who are adherent

to levothyroxine, yet experience persistent symptoms despite serum thyroid stimulating hormone (TSH) values within the reference range [4]. The American Thyroid Association notes that there is currently insufficient evidence to support the routine use of combination therapy outside a formal clinical or *N-of-1* trial [5]; and largely based on these guidelines, the British Thyroid Association recommends that liothyronine/levothyroxine combination therapy may only be considered by endocrinologists for patients who have unambiguously not benefited from levothyroxine [6].

The use of liothyronine in the UK has been further discouraged because of significant price inflation due to monopoly status of the generic supplier since it was de-branded in 2007. The current price of 28 tablets of 20µg liothyronine is £165.18, compared with £26.15 in 2010. This resulted in the NHS listing liothyronine as a medicine that should not be prescribed routinely in primary care [7,8].

Clinical guidelines acknowledge the limited evidence-base for liothyronine. While thirteen trials of combination versus levothyroxine monotherapy therapy have been reported [9], the majority are underpowered, some are unlikely to have tested the correct dose of liothyronine, and none restricted recruitment to patients who did not feel significantly better on levothyroxine alone [3,9-12]. This latter point could explain why liothyronine/levothyroxine combination therapy has not demonstrated superiority, even in the larger trials. Walsh et al. [13] found no statistically significant difference in patient wellbeing, quality of life or cognitive function. Appelhof et al. [14] reported that patients preferred combination therapy but there were no differences in clinical endpoints; and Saravanan et al. [15] did not find a significant difference in General Health Questionnaire-12 scores.

The National Institute for Health and Care Excellence (NICE), in its clinical guideline on thyroid disease [16], recommended that further research should be undertaken on the clinical-

and cost-effectiveness of liothyronine/levothyroxine combination therapy compared with levothyroxine for people with hypothyroidism whose symptoms have not responded sufficiently to levothyroxine alone. However, a formal analysis of its clinical and cost-effectiveness was not undertaken.

The aim of the present study was to undertake an HTR focusing on the cost-effectiveness of liothyronine in this context and adopting the perspective of the NHS in the UK, to assess the value of conducting further research to ascertain the clinical effectiveness of liothyronine as a treatment for people with treatment-unresponsive hypothyroidism.

Methods

Overview

An economic model was developed to estimate the cost effectiveness (incremental cost per quality-adjusted life year, QALY gained) of liothyronine/levothyroxine combination therapy. Health utilities were obtained from a survey of hypothyroid patients. The likelihood of the addition of liothyronine in returning patients to age-matched population health was based on the survey of endocrinologists and general practitioners, who also provided estimates of patients' use of health care resources. The perspective of the NHS was adopted, with a 10-year time horizon of analysis. The economic analysis is reported in accordance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement [17].

Population

The model represented a population of patients diagnosed with primary hypothyroidism who remain actively symptomatic with levothyroxine despite being adherent with free T4 within normal ranges (9-25 pmol/l) and euthyroid serum TSH concentrations (0.4-4.0 mU/l). The

cohort represented adults aged 50 years upon entry to the model, consistent with the mean age of diagnosis of hypothyroidism [18]. The simulated cohort was followed for 10 years, a period considered to be sufficient to capture differences in costs and outcomes between the treatment strategies.

Intervention

In the model, patients could continue levothyroxine alone, representing usual care in the majority of cases, or alternatively trial a 3-month period of liothyronine in combination with levothyroxine [6]. Following the 3-month period, responders may continue liothyronine/levothyroxine combination therapy for the remainder of the 10-year time horizon of analysis. Non-responders discontinue liothyronine and revert to levothyroxine monotherapy. The base-case analysis assumed an average ratio of 1:3 [16], corresponding to a daily dose of 17μg of liothyronine and 50μg of levothyroxine. The dose of levothyroxine monotherapy was assumed to be 100μg/day.

Model structure

A decision tree was constructed (Figure S1, Supplementary appendix), in which 10-year expected costs and quality-adjusted life years (QALYs) were estimated, and discounted at 3.5% per annum [19].

Health utilities

Literature searches did not identify any relevant health utility data [20]. Self-selecting people who reported to be clinically unresponsive to levothyroxine alone despite being biochemically euthyroid were recruited to a survey that was advertisement via social media, and hosted on the website of the charity Thyroid UK. Consent was obtained within the online form, following a full explanation of the purpose and nature of the survey. Those who consented were invited to complete the online survey, which included the validated, multi-

attribute health utility instrument, the EuroQol EQ-5D-5L questionnaire and accompanying EQ-VAS (visual analogue scale) [21]. The EQ-5D-5L questionnaire asks about 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. EQ-5D-5L profiles were converted to EQ-5D-5L index values based on the EQ-5D-5L/3L cross walk value set for the UK [22] in line with current best practice [23]. Utility scores of 0 and 1 correspond to death and full health, respectively.

In the model, patients who responded to liothyronine/levothyroxine combination therapy were assumed to adopt age-matched population norm EQ-5D-3L utility values [24,25]. Patients entering the model, and remaining symptomatic to either levothyroxine monotherapy or in addition to liothyronine were assumed to experience the health utilities of the sample surveyed.

Mortality

The model applied standard mortality rates of the UK general population for 2016/18 [26], on the basis of no evidence of mortality differences in treated hypothyroid patients [18,27].

Resource use

There was no published data on NHS health care resource use and costs for the indication under consideration. Therefore, a survey of endocrinologists and general practitioners across Wales and the North West of England was conducted to estimate resource use in patients who were in each of the three branches of the decision analytic model. Clinicians recruited by one of the authors (AH) or the All Wales Therapeutic and Toxicology Centre were contacted and invited to complete the questionnaire. Categories of resource use included contacts with healthcare professionals (general practitioner GP surgery visits, endocrinologist outpatient appointments and phlebotomists), thyroid function and associated tests (including TSH, free

T4, free T3, TSH receptor antibodies TRAb, and thyroid peroxidase TPO antibody testing), and safety monitoring tests (including, electrocardiogram, echocardiogram, bone densitometry).

Unit costs

The unit costs of NHS care were derived from the NICE guideline [16] and from standard sources [25,28], based on a 2018/19 cost year (Table 1), and reported in British pounds (£).

Clinical effectiveness

Published clinical trials and systematic reviews [9,16] were assessed for relevant data on the clinical effectiveness of liothyronine/levothyroxine combination therapy. None of the trials restricted their inclusion criteria to (or performed a sub-group analysis of) the population of interest and were therefore not considered relevant to inform the decision problem. A survey was therefore undertaken, to elicit plausible estimates of treatment effect from endocrinologists and general practitioners experienced in prescribing liothyronine [29]. They were asked what proportion of patients would be expected to improve following a 3-month trial period with liothyronine/levothyroxine combination therapy. The mean of all responses was used in the base-case analysis.

Analysis

In the base-case deterministic analysis, the expected costs and QALYs were compared incrementally to estimate the incremental cost-effectiveness ratio (ICER):

$$\text{ICER} = \frac{\text{Cost}_{\text{LIOTHYRONINE + LEVOTHYROXINE}} - \text{Cost}_{\text{LEVOTHYROXINE}}}{\text{QALY}_{\text{LIOTHYRONINE + LEVOTHYROXINE}} - \text{QALY}_{\text{LEVOTHYROXINE}}}$$

Uncertainty analyses

A series of one-way sensitivity analyses was performed to assess the impact on the ICER of varying: the probability that patients respond following a 3-month trial of liothyronine/levothyroxine combination therapy; the time horizon of analysis; discount rates (0% and 6% per annum); the cost of liothyronine; the age of patients in the cohort; and of using EQ-VAS for utility in patients who remain symptomatic.

The extent to which the ICER changed when simultaneously varying the probability of patients responding to liothyronine/levothyroxine combination therapy, and the annual cost of liothyronine, was assessed in a two-way sensitivity analysis.

A probabilistic sensitivity analysis (PSA) was conducted for the simultaneous consideration of uncertainty in all model parameters (costs, QALYs and probability of treatment response). Uncertainties in these parameters were represented by relevant distributions and using Monte Carlo simulation with 10,000 replications to establish the probability of liothyronine/levothyroxine combination therapy being cost-effective for different threshold values of willingness to pay. Cost effectiveness acceptability curves [30] were constructed to represent this relationship and to facilitate comparison with the NICE thresholds of £20,000 to £30,000 per QALY operating in the UK [19].

For the PSA, the number of prescriptions and costs of medicines were assumed to be fixed. For other items of resource use, annual quantities (and the initial 3 months in the case of liothyronine) were sampled from gamma distributions with means and standard deviations (SD) based on responses to the survey. These were each multiplied by their respective unit costs. Utilities representing the general population norms were sampled from beta distributions with means and SD as reported by Kind et al [24]. EQ-5D utility values (U) from the sample of hypothyroid patients were transformed (1-U), and the parameters of a gamma distribution (α, β) were estimated via maximum likelihood for (1-U) ~ Gamma(α, β).

The probability of responding to liothyronine/levothyroxine combination therapy was sampled from a beta distribution fitted to the reported range of expert opinions.

Value of information analysis

In order to determine the value of conducting additional research to reduce uncertainties in the model, a value of information analysis was conducted using the Sheffield Accelerated Value of Information (SAVI) [31]. Value of information analysis aids understanding of the acceptability of the existing uncertainty compared with the investment needed to obtain the necessary evidence that would reduce that uncertainty, enabling a decision to be made with existing information or whether to invest in further research to inform decisions with more evidence. We calculated the Expected Value of Perfect Information (EVPI) per person and overall, the Expected Value of Partially Perfect Information (EVPPI) to identify those parameters that contribute most to the decision uncertainty, and the Expected Value of Sample Information (EVSI) to measure the potential value of a future clinical trial.

Software

The cost-effectiveness analysis and sensitivity analyses were performed in Microsoft Excel® 2016. Macros used to run simulations for the PSA were written in Visual Basic for Applications. The value of information analysis was conducted using SAVI [31].

Model validation

Validation checks were made in accordance with the AdViSHE tool [32]. Development and validation of the model structure was in consultation with endocrinologists, and based on best practice and clinical guidelines for trialling liothyronine prior to its long term prescribing. The face validity of data used as inputs to the model was both a function of findings from systematic review of the clinical literature, and the opinions of clinicians (endocrinologists and GPs) with expertise (internationally renowned in two cases) and /or experience in

treating patients with liothyronine. Extreme value testing and consistency checks were made to ensure there were no coding errors. The analysis and outputs were subject to review of external validity by members of the All Wales Prescribing Advisory Group, the All Wales Therapeutics and Toxicology Centre, and the All Wales Medicines Strategy Group.

Patient and Public Involvement

This research was designed and performed without active patient or public involvement.

Results

Health utilities

Responses were available from 54 people with hypothyroidism. Mean (SD, minimum, maximum) utility was 0.53 (0.23, 0.00, 0.84). 44/54 (81%) individuals reported having moderate problems (EQ-5D-5L level scores ≥3) in at least one attribute, most often their ability to perform usual activities, and anxiety or depression; 24/54 (44%) reported severe problems (level scores ≥4) in at least one attribute; and 9/54 (19%) reported extreme problems (level 5) in at least one attribute (Figure 1). Of note, 37% reported severe problems in carrying out usual activities of everyday living and 22% reported the regular occurrence of severe anxiety or depression symptoms. The mean (SD, minimum, maximum) EQ-VAS score was 49.3 (17.2, 5.0, 90.0).

Resource use and costs

Five endocrinologists and 3 GPs responded to the survey. They reported patients who remain symptomatic on levothyroxine monotherapy to visit their GPs on 5.5 instances a year on average, their endocrinologist 3.1 times, and receive 5.9 thyroid function tests annually (Table 1). For patients who respond to combination therapy, these frequencies were reported to reduce to 2.4, 2.6, and 4.8 times per year, respectively.

298 *Incremental analysis*

299 Total and disaggregated costs are reported in Table 2. The single largest cost item was
300 liothyronine, followed by hospital outpatient endocrinologist visits. The difference in
301 expected total, 10-year costs between a treatment strategy of liothyronine/levothyroxine
302 combination therapy, and levothyroxine alone, was £12,053, indicating that combination
303 therapy is more expensive overall. Patients were modelled to experience 5.559 discounted
304 QALYs following a decision to initiate a 3-month trial of liothyronine in addition to
305 levothyroxine (and continue treatment in those who respond). This compares with 4.545
306 QALYs for the current standard of care based on levothyroxine monotherapy. The resulting
307 incremental cost-effectiveness ratio is £11,881 per QALY gained (Table 3).

308 The ICER was insensitive to changes in several parameter estimates in one-way sensitivity
309 analyses (Table 4). However, there is considerable uncertainty in the probability of treatment
310 response, which translated to sensitivity in the ICER, increasing to £20,816 per QALY gained
311 if only 5% of patients respond. The key driver of cost-effectiveness was the price of
312 liothyronine. The multivariate sensitivity analysis (Figure S2, Supplementary appendix)
313 illustrates the combinations of prices and effectiveness probabilities of
314 liothyronine/levothyroxine combination therapy that result in ICERs that are cost-effective.
315 For example, based on a 5% chance of treatment response, liothyronine/levothyroxine is cost-
316 effective up to a cost of £3,245 per annum (which is marginally less than the current annual
317 cost of £3,366).

318 *Probabilistic sensitivity analysis*

319 Parameter estimates and specification of the probabilistic sensitivity analysis are presented in
320 Table 5, and the results are depicted as a cost-effectiveness plane and cost-effectiveness
321 acceptability curve in Figure 2. The PSA indicated the probabilities of

liothyronine/levothyroxine combination therapy being cost-effective at thresholds of £20,000 and £30,000 per QALY, as 0.557 and 0.642, respectively. The probabilities of being cost-saving is 0.060, and in generating QALY gains, is 0.939.

Value of information analysis

Based on a £20,000 per QALY threshold for cost-effectiveness, the overall EVPI per eligible patient is estimated at £2,521. This is equivalent to 0.126 QALYs per person when valuing uncertainty on the QALY scale. Assuming an annual number of patients potentially eligible for liothyronine of 10,000, the overall EVPI is £25,206,183 per year for the UK. If it is assumed that the relevance of the present analysis persists for 10 years, the overall expected value of removing decision uncertainty for the UK would in total be £252m. The EVPPI was highest for utilities in patients who remain symptomatic (£1,902 per person), followed by the probability of liothyronine combination therapy being clinically effective (£328 per person). A conservative, 1-parameter (probability of treatment response) population EVSI yielded an estimate of £3,644,000 per year for a clinical trial of 300 patients.

Discussion

Disinvestment of many medicines considered to be low in value has proven to be difficult to achieve in practice [1]. This is due to a number of reasons [33], including system factors such as a lack of funding or incentives for change, lack of skills in change management, and organisational challenges e.g. in relation to reimbursement. There is also patient and healthcare professional reluctance or consideration of it as a cost-saving exercise only; the belief that removal of a medicine will result in loss of benefit, or that deimplementation has greater disadvantage than to not accept a new medicine with similar value; and, in several cases, a lack of convincing evidence of no harm from withdrawal and no benefit.

In the case of liothyronine, there are disparate clinical views, high costs and a lack of robust evidence of clinical effectiveness. However, there is also a large unmet need with only unlicensed natural desiccated thyroid extract as an alternative [9], and a high demand from a significant minority of people with hypothyroidism who are seemingly unresponsive to levothyroxine with associated very low health-related quality of life compared to the general population [34]. Many report dissatisfaction with treatment and experience symptoms consistent with overt hypothyroidism, including fatigue, memory problems, cognitive dysfunction, feeling cold and weight gain [3,35]. Our survey indicated their mean utility value is 0.53 which makes these individuals comparable in terms of their health status, to patients with lung cancer, or acute cerebrovascular disease and would rank in the bottom decile of 100 chronic diseases [36].

The economic analysis suggests that liothyronine/levothyroxine combination therapy may represent a cost-effective treatment option for patients who remain symptomatic with levothyroxine alone despite achieving free T4 and TSH concentrations within the reference ranges. At £11,881 per QALY gained, the ICER fell below the NICE cost-effectiveness threshold of £20,000 per QALY. However, the probability of liothyronine/levothyroxine combination therapy being cost effective at this threshold was 0.557, reflecting the uncertainty that continued use results in positive net health benefit.

To address the uncertainty in the clinical effectiveness of liothyronine/levothyroxine combination therapy, the analysis quantified the value of conducting research, such as a definitive randomised controlled clinical trial. In monetary terms, and based on a population EVSI of £3.64m per year, the value of a clinical trial would be expected to exceed its cost within one year [37].

Literature searches did not identify any health utility measurement [20] or economic evaluations of liothyronine. Judgements on its cost-effectiveness in the UK appear to be made implicitly in policy guidelines, driven in large part by the significant difference in the current unit acquisition cost between liothyronine and levothyroxine. Guidelines either consider liothyronine/levothyroxine combination therapy to be non-inferior to levothyroxine alone (based on the available weak clinical evidence), or to be inferior because of the shorter pharmacokinetic elimination half-life and safety concerns. Neither perspective is fully justified, as the current evidence base is not targeted to the specific population in question, and inferiority has not been demonstrated. Certainly, the pharmacokinetics of levothyroxine support more convenient, once daily dosing, and stable concentrations of free T3. Liothyronine, by contrast, requires frequent daily dosing which causes fluctuations in free T3 that may have transient suppressive effects on TSH [38]. Although suppression of TSH (<0.03 mU/L) is associated with an increased risk of adverse cardiovascular outcomes [39] and mortality [18], a case-control study of patients taking long-term liothyronine found no evidence of additional risk of atrial fibrillation, cardiovascular disease or fractures, following adjustment for age [40]. The TSH concentrations of these patients were within normal range (median 1.07 mU/L).

Our analysis had strengths in addressing a decision problem which is pertinent to the NHS across the UK. Generalisability to other countries might be limited, however, as the cost of liothyronine is highly variable (for instance, 28 tablets costs €2.30 in Greece, €3.90 in Portugal and €36 in The Netherlands). The methods are nonetheless applicable in other jurisdictions in cases of price inflation because of monopoly supply of an off-patent medicinal product, or when medicines are presumed to be of low value because of uncertainty in their clinical effectiveness. A value of information analysis in these contexts will help inform whether there is value in reducing uncertainty (e.g. by investing in further

394 research), or whether disinvestment is more appropriate. In acknowledging the limited
395 evidence-base, we undertook a systematic approach to populate the model when direct
396 evidence was not available. In particular, the analysis of responses to the survey of clinicians
397 aimed to reflect the diversity of opinions in routine care, and not to achieve consensus,
398 consistent with accepted methods [29]. There is considerable polarity in the views of
399 prescribers with regards to the perceived benefits of liothyronine in the UK [41], and this was
400 reflected in our analysis. While the mean probability of treatment response was 0.40, 38% of
401 simulations had probabilities <0.1, and 20% >0.9.

402 However, there are caveats to our analysis. First, the model is a simple representation of what
403 is a complex clinical management problem. Patients may often be misdiagnosed or have co-
404 morbidities and experience multiple referrals, investigations and treatments. The decision
405 analysis assumes patients are identified and eligible at the point of entry to the model. We
406 further assumed that responders to liothyronine/levothyroxine combination therapy would
407 experience the same population norm health utilities as patients who are treated successfully
408 with levothyroxine. Second, we did not consider the influence of deiodinase 2 (DIO2) genetic
409 polymorphisms. The CC genotype (rs225014) is a purported predictor of response to
410 combination therapy [42]; however, this observation was based on a *post hoc* analysis, and
411 has not been replicated in further studies. Third, our reliance on clinical opinions for
412 estimates of resource utilisation may bias the analysis. Access to routine health
413 administration data or estimates from clinical trials may be preferred, but these were
414 unavailable. Responses to patient questionnaires may be biased for different reasons (e.g.
415 self-selection, recall bias, lack of understanding of medical procedures and terminology) [43].
416 Finally, our surveys of patients and clinicians were potentially limited in terms of selection
417 bias and alternative sampling methods may have been more reliable, although we are

418 unaware of any evidence to suggest that patient-reported resource use is more accurate than
419 clinician-reported [43].

420 In conclusion, health technology reassessment provides a basis for informing important
421 decisions concerning disinvestment, not only in relation to continued use, but also in relation
422 to the value of conducting further research. It is widely appreciated that the deimplemention
423 of low value medicines is more challenging than implementing new treatments, even when
424 there are significant uncertainties surrounding their clinical effectiveness. In the case of
425 liothyronine, our analysis suggests that while it might represent a cost-effective treatment
426 option for patients who remain symptomatic with levothyroxine alone, a definitive clinical
427 trial is necessary to confirm clinical effectiveness. This would be justified on the basis that
428 the value of the information gained far exceeds the cost of a trial.

429

430 **Author contributions:**

431 DAH conceived and designed the work, performed the analyses and drafted the manuscript.
432 DAH, KS and AH made substantial contributions to the acquisition of data. DAH, KS, DF,
433 PA, AH made substantial contributions to the interpretation of data for the work; revised the
434 manuscript critically for important intellectual content; gave their final approval of the
435 version to be published; and agree to be accountable for all aspects of the work in ensuring
436 that questions related to the accuracy or integrity of any part of the work are appropriately
437 investigated and resolved.

438

439 **Acknowledgments:**

The authors thank Kath Haines, Richard Boldero, Sara Pickett and Robert Bracchi from the All Wales Therapeutics and Toxicology Centre (AWTTC) for seeking approval for the survey of clinicians in Wales, and facilitating validation by the All Wales Prescribing Advisory Group; Cerian Harries for assistance with the analysis of the EQ-5D data; and Thyroid UK for facilitating the health utility survey. AWTTC had no involvement with this survey, and Thyroid UK received no funding for their part. The AWTTC did not input into the manuscript and are neutral with respect to the conclusions.

Ethical Approval Statement:

Recruitment to the utility survey was done following approval by the Research and Development Department at Salford Royal Hospital after confirmation with the Greater Manchester West Ethics Committee that this was a quality improvement exercise. The survey of health care professionals did not require ethical approval.

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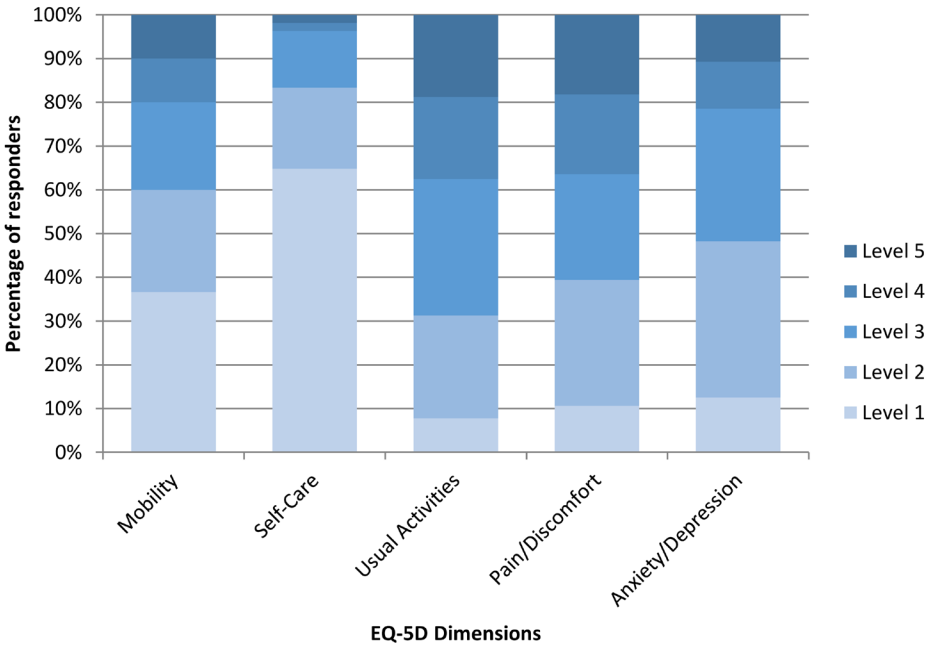
600 **Figure 1**. Distribution of responses to each dimension of the EQ-5D-5L. Levels 1-5

601 correspond to increasing severity in each of the domains from a rater point of view, 5 being

602 most severely affected



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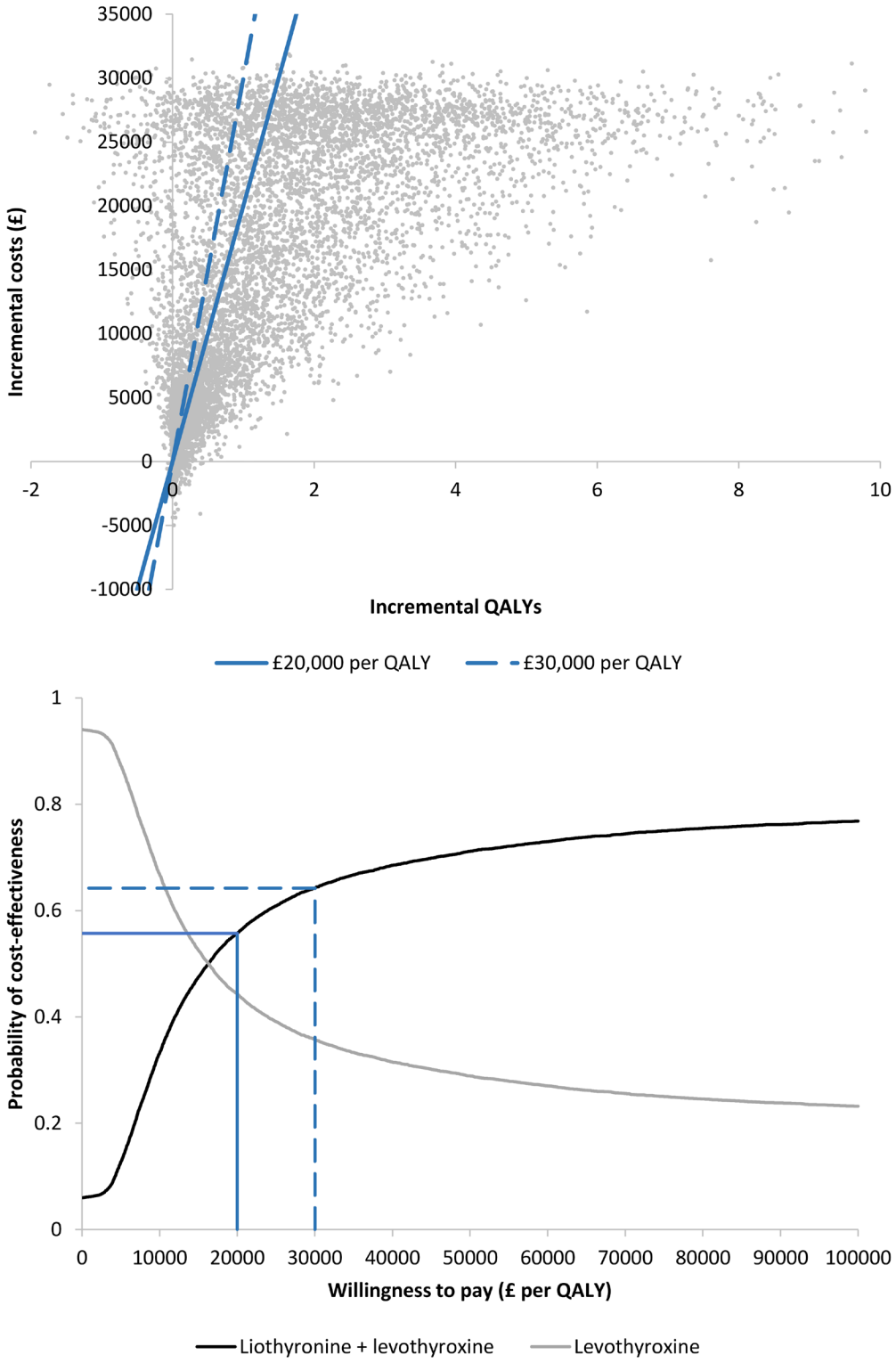
605 **Figure 2**. Cost-effectiveness plane (top) and cost effectiveness acceptability curve (bottom).
606 Blue lines indicate the willingness to pay thresholds of £20,000 per QALY (filled) and
607 £30,000 per QALY (dashed) and, in the cost effectiveness acceptability curve, the
608 corresponding probabilities of cost-effectiveness.


35000
30000
25000
20000
15000
10000
5000
0
-5000
-10000
Incremental costs (£)
-2
0
2
4
6
8
10
Incremental QALYs
£20,000 per QALY
£30,000 per QALY
1
0.8
0.6
0.4
0.2
0
Probability of cost-effectiveness
0
10000
20000
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40000
50000
60000
70000
80000
90000
100000
Willingness to pay (£ per QALY)
Liothyronine + levothyroxine
Levothyroxine

609

Table 1. Resource use and unit costs per intervention group, and according to treatment response

Resource item	**Number of units**			**Unit cost**	**Reference**
	Levothyroxine and Liothyronine + levothyroxine (non-responders >3 months) (per year)	Liothyronine + levothyroxine (First 3-month trial period)	Liothyronine + levothyroxine (Second and subsequent years in responders >3 months)		
Thyroid hormone					
Levothyroxine	100µg daily	50µg daily	50µg daily	£16.03 per year	16
Liothyronine		17µg daily	17µg daily	£3,365.82 per year	16
Healthcare professional					
Endocrinologist outpatient	3.13 (2.47)	2.38 (2.31)	2.56 (1.29)	£164 per visit	25
General practitioner	5.56 (3.11)	1.81 (1.85)	2.44 (1.24)	£37.40 per visit	28
Phlebotomist	5.94 (6.00)	4.88 (6.51)	5.00 (6.22)	£3.04 per sample	25
Thyroid tests					
TSH	5.94 (6.00)	4.88 (6.51)	4.81 (6.32)	£2.15 per test	16
Free T4	5.94 (6.00)	4.88 (6.51)	5.00 (6.22)	£2.10 per test	16
Free T3	1.25 (1.60)	2.50 (2.33)	2.56 (1.68)	£3.12 per test	16
TRAb antibody testing	0.25 (0.46)	0.38 (0.52)	0.56 (0.90)	£16.64 per test	16

TPO antibody testing	0.68 (0.70)	0.62 (0.74)	0.63 (0.74)	£12.32 per test	16
Safety monitoring					
Electrocardiogram	0.09 (0.08)	0.63 (0.52)	0.63 (0.52)	£58 per test	25
Echocardiogram	0.09 (0.08)	0.63 (0.52)	0.63 (0.52)	£97 per test	25
Bone densitometry	0.09 (0.08)	0.31 (0.46)	0.06 (0.07)	£77 per test	25

Values are means (standard deviation).

Table 2. Expected (mean) disaggregated 10-year costs (per patient)

Resource item	**Total 10-year costs**		
	Levothyroxine monotherapy	Liothyronine + levothyroxine (Response following 3-month trial period)	Liothyronine + levothyroxine (No response following 3-month trial period)
Thyroid hormone	£160.30	£33,818.50	£1,001.76
Healthcare professional			
Endocrinologist outpatient	£5,125.00	£4,202.50	£5,386.38
General practitioner	£2,080.38	£911.63	£2,096.15
Phlebotomist	£180.50	£152.00	£190.81
Thyroid tests			
TSH	£127.66	£103.47	£134.95
Free T4	£125.69	£105.00	£131.81
Free T3	£39.00	£79.95	£45.83
TRAb antibody testing	£41.60	£93.60	£46.80
TPO antibody testing	£84.70	£77.00	£90.28
Safety monitoring			
Electrocardiogram	£50.75	£362.50	£85.73
Echocardiogram	£84.88	£606.25	£143.38
Bone densitometry	£67.38	£48.13	£89.75
Total (undiscounted)	£8,166.82	£40,560.52	£9,443.52
Total (discounted at 3.5% per annum)	£7,029.74	£34,913.22	£8,306.54

Table 3. Incremental costs, QALYs and cost-effectiveness ratio

	Liothyronine + levothyroxine	**Levothyroxine**	**Increment (95% central range)**
Costs (deterministic)	£19,082.25	£7,029.74	£12,052.50
Costs (probabilistic)	£18,990.83	£7,098.58	£11,892.25 (-£878 to £28,939)
QALYs (deterministic)	5.559	4.545	1.014
QALYs (probabilistic)	5.638	4.556	1.083 (-0.11 to 5.32)
ICER (deterministic)			£11,880.65 per QALY
ICER (probabilistic)			£10,984.02 per QALY

Table 4. Results of one-way sensitivity analyses

Parameter	**Estimate***	**ICER (£ per QALY gained)**
Probability of response	0.05	£20,816.64
	0.1	£15,719.35
	0.2	£13,170.70
	0.6	£11,471.61
Discount rate (costs)	0%	£13,681.24
	6%	£10,838.31
Discount rate (QALYs)	0%	£10,300.84
	6%	£13,042.21
Discount rate (costs and QALYs)	0%	£11,862.00
	6%	£11,897.95
Time horizon (years)	1	£16,027.34
	5	£11,754.63
Cost of liothyronine (per annum)	£100	£179.10
	£1,000	£3,403.83
	£10,000	£35,651.14
Utility in symptomatic state based on EQ-VAS	0.493	£10,544.94

* Base-case vales are: probability of response 0.405, discount rate (costs and QALYs) 3.5% per annum, time horizon 10 years, cost of liothyronine £3,365.82 per year, and utility in symptomatic state 0.53.

Table 5. Parameter values for the probabilistic sensitivity analysis and value of information analysis

Parameter	**Mean (SD)**	**Distribution / notes**
Utility		
Asymptomatic (age 45-54)	0.85 (0.25)	~beta (1.626, 0.287)
Asymptomatic (age 45-54)	0.80 (0.26)	~beta (1.765, 0.441)
Symptomatic	0.53 (0.23)	1 – ~gamma (4.136, 0.114)
Survival probability		
Age 45-54	0.9846	Fixed
Age 55-64	0.9769	Fixed
Resource use (non-drug)	Mean (SD)*	~gamma (α, β) = ($Mean^2/SD^2$, $SD^2/Mean$)
Probability of response	0.405 (0.388)	~beta (0.242, 0.356)
Eligible incident population (per year)	100,000	Based on 3% of the UK population (66.65m) having hypothyroidism, and 5% of these not responding sufficiently to levothyroxine alone
Uptake of liothyronine (per year)	10%	Assumption
Size of future clinical trial (*n*)	300	Assumption

*See table 1 for values.