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Use of liothyronine (T3) in hypothyroidism: Joint British Thyroid Association/Society for endocrinology consensus statement

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Abstract

Persistent symptoms in patients treated for hypothyroidism are common. Despite more than 20 years of debate, the use of liothyronine for this indication remains controversial, as numerous randomised trials have failed to show a benefit of treatment regimens that combine liothyronine (T3) with levothyroxine over levothyroxine monotherapy. This consensus statement attempts to provide practical guidance to clinicians faced with patients who have persistent symptoms during thyroid hormone replacement therapy. It applies to non-pregnant adults and is focussed on care delivered within the UK National Health Service, although it may be relevant in other healthcare environments.

The statement emphasises several key clinical practice points for patients dissatisfied with treatment for hypothyroidism. Firstly, it is important to establish a diagnosis of overt hypothyroidism; patients with persistent symptoms during thyroid hormone replacement but with no clear biochemical evidence of overt hypothyroidism should first have a trial without thyroid hormone replacement. In those with established overt hypothyroidism, levothyroxine doses should be optimised aiming for a TSH in the 0.3–2.0 mU/L range for 3 to 6 months before a therapeutic response can be assessed. In some patients, it may be acceptable to have serum TSH below reference range (e.g. 0.1–0.3 mU/L), but not fully suppressed in the long term.

We suggest that for some patients with confirmed overt hypothyroidism and persistent symptoms who have had adequate treatment with levothyroxine and in whom other comorbidities have been excluded, a trial of liothyronine/levothyroxine combined therapy may be warranted. The decision to start treatment with liothyronine should be a shared decision between patient and clinician. However,

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individual clinicians should not feel obliged to start liothyronine or to continue liothyronine medication provided by other health care practitioners or accessed without medical advice, if they judge this not to be in the patient's best interest.

KEYWORDS

hypothyroidism, levothyroxine, liothyronine, subclinical hypothyroidism, tri-iodothyronine

1 | BACKGROUND

Primary hypothyroidism affects approximately 3% of the population, equivalent to about 2 million individuals in the United Kingdom.¹ The prevalence increases with age and is 10 times more common in women than in men. Most cases in adults are due to chronic autoimmune disease (Hashimoto's thyroiditis) or as a result of destructive treatment with either radioiodine or surgery for hyperthyroidism, benign nodular disease, or thyroid cancer.² Classical features of hypothyroidism include lethargy, weight gain, mental slowness, constipation, and cold intolerance but the clinical presentation is often nonspecific and the diagnosis ultimately rests on biochemical confirmation.^{2,3}

Levothyroxine is the standard treatment for hypothyroidism and 3% of the population in England are prescribed synthetic levothyroxine with the goal of therapy being to restore well-being and normalise serum TSH levels.^{2,3} Most patients respond satisfactorily within weeks of therapy, with striking improvement in typical symptoms. However, some levothyroxine-treated individuals continue to experience persistent symptoms despite adequate biochemical correction.^{4–7} The optimal approach to the management of such individuals remains controversial, largely because our understanding of why such patients have persistent symptoms remains poor. While a few practitioners would offer alternative thyroid therapies such as liothyronine and desiccated thyroid extracts (DTE) to such individuals, others would opt for an approach that is primarily focused on addressing lifestyle, alternative physical health-related or psychosocial explanations for persistent morbidity.⁸ These different approaches are based on the failure of numerous randomised controlled trials (RCT) to show the superiority of combination liothyronine/levothyroxine therapy over levothyroxine monotherapy alone^{9–12} (discussed below).

2 | METHODS

This consensus statement was developed following consultation within the executive bodies of the British Thyroid Association (BTA) and the Clinical Committee of the Society of Endocrinology (SfE). The remit and scope for the statement was agreed at the BTA executive meeting during the annual meeting of the SfE (British Endocrine Societies) in Edinburgh in November 2021. Further consultations were conducted virtually during which specific subject themes were

developed with nominated lead reviewers. Reviewers undertook a systematic search of the literature, summarised the subject based on the available evidence, and generated a position statement. Original publications, systematic reviews, and meta-analyses were referred to. Formal systematic reviews or meta-analyses were not repeated. An initial draft of the statement was sent round for consultation to the executives of the BTA and SfE in April 2022, and then further revisions were undertaken after feedback. Wider consultations were then held with other organisations, namely, the Royal College of Physicians, Edinburgh; Royal College of Physicians and Surgeons, Glasgow; the Association for Clinical Biochemistry and Laboratory Medicine; and the British Thyroid Foundation (BTF), a charity that supports patients with thyroid disorders, as well as primary care representatives. As this issue remains of concern to patients and National Health Service (NHS) endocrinologists, and new studies concerning both the safety of liothyronine and the efficacy of combined liothyronine/levothyroxine therapy have been published since the previous BTA statement in 2016, a revised statement was felt to be timely. Our emphasis remains on the evidence for use of combination therapy with liothyronine and levothyroxine or natural DTE in the management of overt primary hypothyroidism in the context of the UK NHS, where regional prescribing policies implemented owing to national cost pressures have created significant dissatisfaction. We have not addressed patients with secondary or central hypothyroidism and have not addressed other aspects of the management of hypothyroidism such as screening, management in pregnancy, children, or in patients with thyroid cancer.

3 | INTERPRETING RAISED THYROID STIMULATING HORMONE (TSH) LEVELS

The pituitary-derived TSH, due to its complex inverse association with the thyroid hormones (thyroxine and triiodothyronine), is the most sensitive and earliest biochemical marker of hypothyroidism.^{2,3} Throughout this paper, typical serum TSH concentrations are quoted, but several different TSH assays are in routine use and there are small differences in TSH reference range between these assays. Overt primary hypothyroidism is defined as TSH concentrations above the reference range (typically ≥ 10 mU/L) with FT4 levels below the reference range, while subclinical hypothyroidism is defined as TSH above the reference range (typically 5–10 mU/L), but FT4 levels within the reference range.^{2,3}

3.1 | Subclinical hypothyroidism

Subclinical hypothyroidism affects 5%–10% of the population, and around 5% will progress to overt hypothyroidism annually, if serum thyroid peroxidase antibodies (TPOAb) are positive.¹³ If TPOAb are negative, the rate of progression to overt disease is around 3% per year.¹³ Subclinical hypothyroidism (TSH: 5–10 mU/L), manifests as an isolated rise in TSH and resolves spontaneously in more than 50% of people,¹⁴ giving the potential for inappropriate treatment unless blood tests are repeated. In addition, large RCTs have shown no improvement in hypothyroid symptoms or quality of life (QoL) in older patients with subclinical hypothyroidism during treatment with levothyroxine.^{15–17} Therefore, improvement in symptoms with levothyroxine treatment may be an unrealistic expectation for most patients with subclinical hypothyroidism.

4 | INITIATING AND MONITORING LEVOTHYROXINE MONOTHERAPY

4.1 | Thresholds for initiating treatment

At present, the TSH threshold for levothyroxine initiation is contentious, as trials of treatment of subclinical hypothyroidism do not show evidence for improvement in symptoms or other benefits.^{15–18} Furthermore, a persistently abnormal TSH should be confirmed before initiation of levothyroxine, particularly in borderline cases (TSH: 5–10 mU/L) which make up the majority of people started on treatment.^{14,19} However, in reality, many patients with subclinical hypothyroidism (TSH: 5–10 mU/L) are now treated with levothyroxine,^{20,21} fuelling a rise in its use, such that it is now the third most frequently prescribed medication in the United Kingdom.²² In contrast, few patients are advised to seek lifestyle and exercise changes, despite the fact that there is positive evidence to support their benefits.²³

Thus, part of the rise in levothyroxine prescriptions is explained by overprescribing, as many healthy people sustain a transient rise in serum TSH following even a minor nonthyroidal illness. This has led to many patients being labelled as having hypothyroidism and started on levothyroxine inappropriately.^{20,21} In addition, the distribution of serum TSH reference interval is right-shifted with age,^{24–26} giving an upper 97.5% confidence interval of around 7.5 mU/L in healthy elderly people.²³ Studies from the United States and across Europe have shown that up to 30% of people prescribed levothyroxine may have had normal thyroid function tests beforehand,²¹ and conversely if levothyroxine therapy is stopped, 30%–50% will remain euthyroid.²⁷ Thus, it is unsurprising that many patients are dissatisfied with levothyroxine treatment, and this chimes with lack of symptomatic benefit in RCTs in subclinical hypothyroid patients, as well as overprescribing in patients who have no actual thyroid disease, but a transient elevation in serum TSH.

4.2 | Initiation and monitoring of levothyroxine monotherapy

Levothyroxine monotherapy remains the treatment of choice for hypothyroidism and has been since the 1970s. The optimal daily dose in overt hypothyroidism is 1.5–1.8 mcg/kg of bodyweight rounded to the nearest 25 mcg.^{2,3} A typical full replacement dose for overt hypothyroidism is around 100–150 mcg of levothyroxine. In younger patients with no significant comorbidities the full replacement dose can be given from the start.²⁸ Clinicians should consider starting levothyroxine at a dose of 25–50 mcg per day with subsequent titration in adults aged 65 and over and in those with history of cardiovascular disease.²³

Once started on levothyroxine, serum TSH is used to assess the response in primary hypothyroidism. The primary treatment goal is to normalise TSH levels.^{2,3} It is recommended that TSH levels are checked roughly every 3 months until stable (defined as two similar measurements within the reference range 3 months apart) and then once a year thereafter.²⁹ It needs to be acknowledged that nine studies over nearly 30 years across five different countries show that only 50%–70% of patients prescribed levothyroxine maintain serum TSH within reference range.^{20,30–34} One explanation for this is that small differences in thyroid hormone replacement (and corresponding serum TSH levels) may not make a difference to patient symptoms and QoL during treatment. Two studies which blinded patients to the strength of their levothyroxine replacement and performed detailed symptom and QoL analysis showed that patients cannot tell what dose of levothyroxine they are taking.^{35,36} However, in these blinded studies patients preferred higher perceived doses of levothyroxine, irrespective of the actual administered dose. Thus far, the common supposition that most patients are sensitive to small changes in their thyroid hormone replacement is not supported by objective data.

4.3 | Persistently raised TSH levels despite established levothyroxine monotherapy

Sometimes TSH levels remain persistently elevated despite adequate levothyroxine replacement. A summary of the most common causes is shown in Box 1. If symptoms of hypothyroidism persist despite normalisation of TSH, the dose of levothyroxine can be titrated further to place the TSH in the lower part of the reference range or even slightly below (i.e., TSH: 0.1–2.0 mU/L), but avoiding TSH < 0.1 mU/L. Use of alternate day dosing of different levothyroxine strengths may be needed to achieve this (e.g., 100 mcg for 4 days; 125 mcg for 3 days weekly). As noted above, the evidence base to support titration of levothyroxine doses to achieve “optimal” biochemical control of hypothyroidism is weak,^{35,36} nevertheless this is a safe and potentially effective intervention.

If medication adherence appears to be an issue, one potential strategy has been the use of once or twice weekly directly observed oral therapy, although successful studies to date have been small.^{37,38}

BOX 1 Causes of persistently elevated TSH despite apparently adequate levothyroxine replacement

Decreased bio-availability

- Insufficient replacement dose of levothyroxine.
- Poor medication adherence.
- Concomitant ingestion of iron tablets, calcium, cholestyramine, colessevalam, soy or caffeine.
- Malabsorption either due to hypochlorhydria (proton pump inhibitor therapy, *H. pylori* infection, autoimmune atrophic gastritis, gastrectomy, gastric by-pass) or coeliac disease.
- Inflammatory bowel disease.

Increased levothyroxine requirements

- Pregnancy, oral oestrogen.
- Weight gain.
- New medication prescribed which increases levothyroxine metabolism (e.g., rifampicin, carbamazepine, and phenytoin).
- Nephrotic syndrome with heavy proteinuria.

Other factors

- Addison's disease/primary adrenal insufficiency.
- TSH assay interference/macro-TSH.

5 | THE CHALLENGES WITH LEVOTHYROXINE MONOTHERAPY, LIOTHYRONINE/LEVOTHYROXINE COMBINED THERAPY AND DTE

For the majority of patients, levothyroxine provides a satisfactory replacement. However, a proportion of individuals have significant dissatisfaction with it, including ongoing significant impairment in psychological well-being compared to controls of similar age and sex.⁴⁻⁸ Typical persistent hypothyroid symptoms include lethargy, sleepiness, memory problems, cognitive difficulties ("brain fog") and weight gain.⁴⁻⁸ However, symptoms consistent with the presence of hypothyroidism are nonspecific and cannot be reliably used to differentiate those with hypothyroidism from euthyroid people.³⁹⁻⁴¹ For instance, 60% of unselected euthyroid individuals have one or more symptom that may be attributable to hypothyroidism.³⁹

Persistent and unresolved symptoms attributed to hypothyroidism have led some patients to utilise liothyronine or DTE. However, combination liothyronine/levothyroxine therapy has not been demonstrated to be superior to levothyroxine monotherapy in clinical trials.⁴² There have been at least 16 randomised controlled trials comparing the efficacy of combination liothyronine/

levothyroxine therapy versus levothyroxine monotherapy.^{9-12,42,43} Almost all these blinded RCTs showed that QoL improved during combined liothyronine/levothyroxine treatment, but that it also improved to the same degree during levothyroxine monotherapy, demonstrating the strong placebo effect of thyroid hormones. Furthermore, four systematic reviews/meta-analyses^{12,44-46} of these trials found no clear benefit of combination liothyronine/levothyroxine replacement over levothyroxine monotherapy in terms of mood, health-related QoL or cognitive function. This indicates that at the population level there is no benefit of using combination therapy regimens over levothyroxine monotherapy. Nevertheless, it should be noted that many of these studies were small, and none of the regimens used replicated physiological concentrations of circulating T3 in the euthyroid state. The noticeable improvement in QoL found in both combined liothyronine/levothyroxine and levothyroxine monotherapy groups during multiple blinded RCTs cautions against over-interpreting individual ("n = 1") therapeutic trials in everyday clinical practice.

At present in the United Kingdom, there is a 49-fold variation in the number of liothyronine prescriptions per 1000 levothyroxine prescriptions by local prescribing region.⁴⁷ A substantial driver of this has been the dramatic price rise in liothyronine in the United Kingdom, leading to local NHS medicine management policies, which have restricted prescriptions of liothyronine in some regions. However, even before this price rise, liothyronine use was less prevalent in more deprived areas, potentially reflecting exploitation by some private healthcare practitioners or more effective personal agency in affluent regions. Recently liothyronine prices have come down in the United Kingdom, although at the time of writing liothyronine remains around 50-fold more expensive in the United Kingdom than equivalent levothyroxine monotherapy.

The British National Formulary, published on behalf of the UK Medicines and Healthcare products Regulatory Agency (MHRA) and the UK Government Department of Health, does not list DTE as a recommended medicine for use in the NHS. Two randomised studies of DTE did not show benefits as compared to levothyroxine.^{43,48} Its use has not been endorsed by NICE or RMO.

5.1 | Possible reasons for dissatisfaction with levothyroxine monotherapy

5.1.1 | Comorbidities/inappropriate initiation of levothyroxine

Reasons for dissatisfaction with current practice are likely to be multifactorial. Having thyroid function tested is a marker of increased psychological morbidity.⁴⁹ In addition to borderline TSH levels at the initial prescription of levothyroxine,^{20,21} this raises the distinct possibility that, at least in a proportion of individuals, dissatisfaction may be due to other coexisting health problems and inappropriate initiation of thyroid hormones.

5.1.2 | Physiology and genetics

Hypothyroid patients treated with levothyroxine monotherapy tend to have lower serum T3 concentrations and higher T4 levels than healthy people.^{42,50} It has been proposed that this leads to tissue hypothyroidism in some people via inhibition of T4 activation by increased T4 levels.⁵¹ Unfortunately, tissue concentrations of thyroid hormones have not been measured in humans, in this context. We do not know whether the body's thyroid hormone regulatory system that allows each tissue to extract circulating thyroxine and convert it to T3 works in the same way for everybody.⁴² Two studies suggest that individuals with hypothyroidism with specific alleles of the *DIO2* or *MCT10* genes, involved in thyroid hormone activation and transport, may have a favourable response to liothyronine therapy.^{52,53} However, one involved a small patient cohort ($n = 45$) and neither provided robust statistical testing for multiple variants genotyped ($n = 16$ and $n = 4$ SNPs).^{52,53} To date, adequately powered studies have not been performed to confirm these genetic findings.

Furthermore, there are more than 50 known genes whose variations each have a small influence (e.g., 1%–3%) on blood thyroid hormone levels,⁵⁴ and this probably reflects a similarly complex situation for tissue thyroid hormone regulation. Thus, it is unlikely that one or two genetic variants could have a large effect on therapeutic response. It has been proposed that some people have a genetic inability to make sufficient T3,⁴² sometimes referred to as “poor converters.” A key question is why this putative genetic phenotype does not manifest in childhood or in euthyroid people. Further experimental validation of these theoretical possibilities may provide an explanation as to why some patients feel better on combined liothyronine/levothyroxine treatment than on levothyroxine alone.

6 | POTENTIAL ROLE OF LIOTHYRONINE AS COMBINATION OR MONOTHERAPY

Early position statements by the Royal College of Physicians (2011) did not support the use of DTE or liothyronine in the treatment of hypothyroidism.⁵⁵ In a departure from previous international society positions, the European Thyroid Association (ETA) published guidelines in 2012 on the use of combination therapy with liothyronine/levothyroxine which acknowledged the potential for combination therapy in individuals with primary hypothyroidism whose needs were not met by levothyroxine alone.⁵⁶ In addition, the American Thyroid Association (ATA) in 2014, while generally circumspect on the use of combination therapy, also acknowledged that combination therapy may be trialled in exceptional circumstances.⁵⁷ In 2016, the BTA published its position statement on the management of hypothyroidism.⁵⁸ In this statement, the situation of individuals who do not feel well on levothyroxine alone was acknowledged and it was recommended that such individuals should be carefully

assessed for various other conditions that could account for persistent symptoms. A trial of liothyronine/levothyroxine combination therapy could be considered in patients for whom no alternative cause for symptoms could be found after a thorough evaluation.⁵⁸

During 2019, both NICE²⁹ and Regional Medicines Optimisation Committee (RMOC)⁵⁹ published recommendations about liothyronine use, but these are not concordant, and objective criteria that support the initiation of liothyronine treatment in an NHS environment are lacking. The NICE guidelines did not recommend routine use of liothyronine either alone or in combination treatment based on the evidence available and cost considerations. Directives that liothyronine may be prescribed in “exceptional circumstances” are unhelpful, as almost any patient with persistent symptoms would see themselves as having exceptional need.⁵⁹ This has put NHS clinicians in a difficult situation. While neither NICE nor RMOC support routine liothyronine use, both leave the possibility open to some patients.

Since these publications, interest in the role of liothyronine has persisted, both in the biomedical literature as well as in the popular media. Recent surveys of the UK population have revealed significant variability in practice reflecting differences in local guidance, access to liothyronine across health authorities, and interpretations of existing guidelines.^{60,61} In addition, further trials of liothyronine/levothyroxine combination therapy, as well as the use of thyroid extracts, have recently been published, again with negative results.^{43,62} In addition, online surveys both in the United Kingdom and the United States show that most patients have persistent symptoms despite liothyronine/levothyroxine combination or DTE therapy.^{63,64} Acknowledging the need for more research in this area, an international consensus statement has recently been published by members of the ATA, ETA, and BTA, to guide the development of future trials of combination therapy,⁴² which are now underway.⁶⁵

7 | IS LIOTHYRONINE SAFE FOR THE TREATMENT OF HYPOTHYROIDISM?

There is extensive data gathered over many years regarding the safety and tolerability of synthetic levothyroxine as standard care for hypothyroidism.⁶⁶ At therapeutic doses, levothyroxine is safe, well-tolerated, with rarely reported serious side effects.⁶⁷ Levothyroxine has a narrow therapeutic index, however, and both under-treatment (TSH above the reference range) and over-treatment (TSH below the reference range) are common, with cross-sectional studies consistently showing that 30%–50% of patients on levothyroxine have TSH values outside of the laboratory reference range.^{20,30–34,65} Long-term over-treatment is associated with well-established risks of cardiac arrhythmia, stroke and osteoporosis, while under-treatment may be associated with impaired well-being, dyslipidaemia and cardiovascular disease.^{31,68} In contrast, data on the safety of liothyronine are

limited. Most randomised controlled trials have reported no difference in adverse event rates between individuals randomised to levothyroxine or combination liothyronine/levothyroxine therapy. Nevertheless, one study reported an excess of anxiety symptoms in patients taking combination liothyronine/levothyroxine therapy.¹⁰ However, these trials were of short duration, used varying liothyronine dosing schedules, and mostly measured only resting heart rate and blood pressure as safety endpoints.^{9–12}

Studies addressing long-term outcomes are few. A 17-year population-based study in Scotland, compared mortality, cardiovascular events, atrial fibrillation, diabetes, and fracture rates in patients who had ever used liothyronine ($n = 400$) and those who had only used levothyroxine ($n = 33,955$).⁶⁹ They found no

difference in any of these outcomes but reported a trend towards an increased risk of breast cancer in individuals taking liothyronine (odds ratio: 1.8, 95% confidence intervals (95% CI): 1.02–3.01, $p = .04$). A larger study of more than 1400 liothyronine users in the Korean population found an increased risk of stroke (incidence rate ratio: 1.8, 95% CI: 1.1–2.9; $p = .025$) and heart failure (1.7, 95% CI: 1.0–2.8; $p = .049$) compared to those taking levothyroxine alone, that was most marked in patients with more than a year of liothyronine exposure.⁷⁰ While these complications are consistent with adverse events expected from excessive thyroid hormone use, larger studies are still needed to clarify this. Neither this Korean study, nor another Swedish study have been able to confirm an association of breast or other cancers, or all-cause mortality with the use of liothyronine.^{70,71}

TABLE 1 Recommendations.

1	Most patients with hypothyroidism should be treated with levothyroxine alone.
2	We recommend monitoring of levothyroxine replacement therapy in individuals with primary hypothyroidism with serum TSH measurements, with additional free T4 measurements if TSH is outside the reference range.
3	Before considering a trial of liothyronine, we recommend confirming that a diagnosis of primary hypothyroidism is substantiated (documented TSH ≥ 10 mU/L; and/or low FT4 pretreatment with thyroid replacement hormones). If a diagnosis of overt hypothyroidism cannot be confirmed, consider a trial without levothyroxine with a repeat serum TSH after 6 weeks.
4	Before considering a trial of liothyronine, we recommend that comorbidities are excluded as the cause of the persistent symptoms (see Figure 1 for suggested investigations).
5a	Before considering a trial of liothyronine, we recommend adjusting levothyroxine dose to maintain serum TSH toward the lower end of the reference range (e.g., 0.3–2.0 mU/L) for 6 months
5b	When considering levothyroxine adjustment, it may be preferable to have a low but not suppressed serum TSH (e.g., 0.1–0.3 mU/L) during levothyroxine monotherapy if this improves symptoms, rather than starting on liothyronine.
6	While acknowledging the lack of benefit in numerous clinical trials and the placebo effect of thyroid hormone treatment, the authors note that some hypothyroid patients do experience benefit during a trial of treatment with liothyronine.
7	Before initiating liothyronine/levothyroxine combination therapy, we recommend that TSH levels are detectable and within reference range. Levothyroxine dose reduction should be considered before initiating liothyronine in individuals with undetectable TSH levels.
8	To initiate combination treatment, we recommend substituting liothyronine at about 1:17th of the current levothyroxine dose; and reducing levothyroxine dose by 3 \times liothyronine dose (see Figure 1 for sample regimens).
9	A minimum of 3–6 months of liothyronine/levothyroxine combination therapy while maintaining a TSH level within reference range, should be considered before determining the response to a trial.
10	To assess adequacy of replacement, monitoring with serum TSH only is recommended. In patients with a low or suppressed serum TSH, free T3 or free T4 should be measured to avoid over replacement. Interpretation of measured serum free T3 levels should be made in context of dosage, timing, and frequency of liothyronine therapy, and it should be stated on the laboratory request that the patient is taking liothyronine.
11	Where possible, we recommend use of a QoL questionnaire pre and post any trial of liothyronine, to assess response and confirm sustained benefit with combination therapy (preferably ThyPRO39; Watt et al. ⁷³).
12	We recommend that every patient considered for a trial of liothyronine should be assessed by an endocrinologist for initiation and confirmation of sustained response to treatment. However, we acknowledge that local policies around referral criteria for assessment and long-term monitoring for liothyronine therapy may vary.
13	Patients who feel well on combination liothyronine/levothyroxine with a serum TSH within the reference range should not be routinely deprescribed liothyronine. Following a discussion with an endocrinologist, some people stable on combination liothyronine/levothyroxine therapy may have a trial of levothyroxine monotherapy to see whether the liothyronine is still benefitting them.
14	Liothyronine should not be used as monotherapy except in the situation of confirmed allergy or intolerance to levothyroxine or its excipients.
15	Liothyronine should not be used in pregnancy.
16	We do not recommend use of desiccated thyroid extract.

8 | OBLIGATION TO INITIATE OR CONTINUE LIOTHYRONINE PRESCRIPTIONS

Doctors are not obliged to prescribe any medication that they believe is not in the patient's best interest. General Medical Council (GMC) guidance states: "Sometimes, patients will ask for treatment or care that you don't think is in their clinical interests. In these situations, you should explore the reasons for their request, their understanding of what it would involve and their expectations about the likely outcome. This discussion will help you take account of the factors that are significant to the patient and assess whether providing the treatment or care could serve the patient's needs. If, after discussion, you still think the treatment or care would not serve the patient's needs, you should not provide it. You should explain your reasons to the patient and explore other options that might be available, including their right to seek a second opinion".⁷² Hence while the challenges of persistent symptoms in some patients on levothyroxine alone are acknowledged, given the safety concerns and lack of efficacy with liothyronine use and in accordance with GMC guidance, doctors are able to decline a trial of liothyronine to patients.

In particular, doctors have no obligation to continue to provide NHS prescriptions for liothyronine or DTE that have been started by another medical practitioner (including private practice), or when purchased independently of medical advice or supervision from an online or overseas pharmacy. Many endocrinologists may not agree that a trial of liothyronine/levothyroxine combination therapy is warranted in these circumstances and their clinical judgement is valid given the current understanding of the science and evidence of the treatments.

9 | RECOMMENDATIONS

These recommendations are applicable to liothyronine (T3) prescribing in combination with levothyroxine or on its own, for noncancer-related thyroid hormone replacement therapy of primary hypothyroidism (see Table 1) (Box 2).

9.1 | Patient information and prescribing practicalities related to liothyronine

- Patients should be counselled regarding the risk of arrhythmias, accelerated bone loss and stroke associated with iatrogenic hyperthyroidism and the need for long-term monitoring.
- Liothyronine is available as licensed 5, 10, and 20 mcg preparations. For doses lower than 20 mcg, patients should use the 5 or 10 mcg preparation. Alternatively, a pill cutter may help with lower doses.
- Given the short half-life of liothyronine, splitting doses across 24 h is recommended for many people.

BOX 2 Consider a trial of combined liothyronine/levothyroxine in these circumstances:

- There is a proven diagnosis of overt primary hypothyroidism.
- Hypothyroid symptoms persist on levothyroxine alone.
- Levothyroxine has been administered appropriately in terms of duration, dose, and TSH response.
- Alternative comorbidities to explain persistent symptoms have been excluded.
- An endocrinologist is willing to initiate and supervise the trial.

If a 3–6 month trial of combined liothyronine/levothyroxine does not improve symptoms, it is recommended that the patient reverts to levothyroxine monotherapy.

- Patients established on stable doses of combined liothyronine/levothyroxine with serum TSH in the reference range may be safely discharged to primary care where the GP is willing to take on responsibility for TSH monitoring.

Information for patients and a summary of the recommendations for nonspecialist clinicians are available as supplements to this document.

9.2 | Deprescribing liothyronine or DTE

- Online surveys show that most patients have persistent symptoms despite liothyronine/levothyroxine or DTE therapy.^{63,64} In the presence of persistent symptoms, it is reasonable to stop liothyronine or DTE therapy. Furthermore, after a period of several years' stability on liothyronine or DTE therapy, many patients find that they can resume levothyroxine monotherapy with no change in symptoms or QoL.
- When reducing or stopping liothyronine therapy, 5 mcg of liothyronine should be replaced by about 15 mcg of levothyroxine (a 1:3 ratio).
- When reducing or stopping DTE therapy, one grain of DTE (e.g., Armour Thyroid) should be substituted by around 60 mcg of levothyroxine.
- Patients on larger doses of liothyronine may find it helpful to have a gradual change-over from liothyronine or DTE to levothyroxine monotherapy, whereas patients on a low dose of liothyronine may be able to stop immediately. We recommend repeat TSH blood testing 6–8 weeks following any change in prescription.

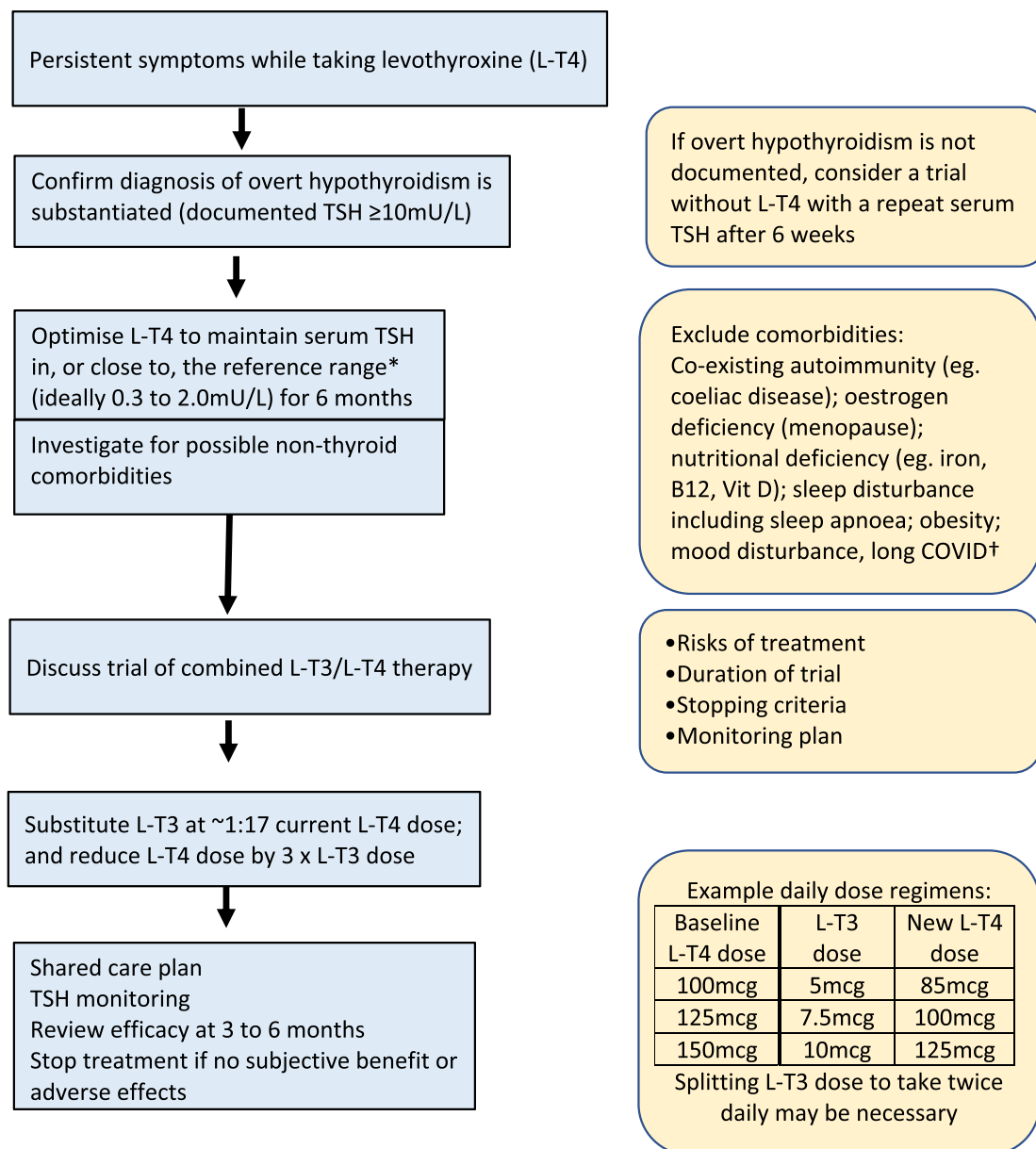


FIGURE 1 Flowchart to support joint BTA/SfE liothyronine (T3) use consensus statement. *Aim to keep TSH in the lower half of the reference range (0.3–2.0 mU/L) but if slight overtreatment with L-T4 resulting in a low TSH (0.1–0.3 mU/L) gives an improvement in symptoms, this may negate the need for a trial of L-T3. Serum TSH < 0.1 mU/L should be avoided. [†]Perform full physical examination. Suggested investigations include: FBC, U&E, LFT, Calcium, HbA1c, Ferritin, B12, vitamin D, Transglutaminase Abs. Consider 09:00 h cortisol if weight loss or other clinical suspicion of adrenal insufficiency. Sleep apnoea screening with Epworth score, Depression screening with HADS. [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1111/len.14935)]

10 | SUMMARY

Most patients with primary hypothyroidism respond well to levothyroxine replacement therapy.

For the small minority of patients who remain symptomatic despite adequate biochemical replacement with levothyroxine, a trial of liothyronine/levothyroxine combination therapy under specialist supervision may be appropriate. However, this should only be considered once the diagnosis of overt hypothyroidism is substantiated with appropriately raised TSH or a low FT4 level pretreatment.

Given limited efficacy and long-term safety data around use of liothyronine, long term prescription should be reserved for a very select group of patients with evidence of sustained response to combination therapy. Long-term serum TSH monitoring and avoidance of iatrogenic hyperthyroidism are recommended. Patients with persistent iatrogenic hyperthyroidism should be counselled regarding associated risks of stroke, cardiac arrhythmias and accelerated bone loss.

Both levothyroxine and liothyronine are currently overprescribed,^{20,21,27} including to people with a transient elevation in TSH

or to those with persistent subclinical hypothyroidism, where trials do not show a benefit from thyroid hormone replacement.^{12,15,16,44–46} Careful evaluation of the primary diagnosis of hypothyroidism and the sustained response to replacement therapy is recommended before considering dose titration or endorsement of ongoing use of liothyronine. Deprescription of relevant levothyroxine or liothyronine replacement therapy should be considered in symptomatic patients where symptoms appear to be driven by nonthyroid-related conditions. Clinicians should not continue to provide NHS prescriptions for liothyronine or DTE that have been started by a private practitioner or purchased independently of medical advice, if they do not believe it is in the patient's best interest.

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CONFLICT OF INTEREST STATEMENT

SHP has received speaker fees from IBSA, Merck, Quidel, Berlin Chemie, and has consulted for Apitope/Worg and Immunovant/Roivant on issues unrelated to T3. The remaining authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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