Guidance on the prescribing of Liothyronine (adapted from RMOC guidance)

1. Background

Spend for liothyronine in 2018/19 for OCCG was approximately £440k. There is a concern that many of the patients that are prescribed liothyronine in primary care is due to historical use. Discussions with the OUH Endocrinology team identified that there are specific groups of patients who should be taking this medication. Liothyronine is prescribed in post-thyroidectomy thyroid cancer patients prior to radioactive iodine therapy. There is also a small proportion of patients with primary hypothyroidism (~10%) who do not tolerate thyroxine replacement and/or are symptomatically better with liothyronine +/- levothyroxine.

Summary Advice

In most circumstances, the primary care prescribing of liothyronine (T3) is not supported for any patient. Initiation for patients with hypothyroidism should only be undertaken by consultant NHS endocrinologists. This advice applies to both liothyronine monotherapy and combination therapy with levothyroxine (T4).

As specified by the British Thyroid Association Executive Committee [(1)], 'clinicians have an ethical responsibility to adhere to the highest professional standards of good medical practice rooted in sound evidence. This includes not prescribing potentially harmful therapies without proven advantages over existing treatments'. The CCG, in line with the RMOC guidance, therefore recommends that strict criteria are applied to ensure that liothyronine is only prescribed in the very rare situations where alternative treatments have been found to be inadequate. In such circumstances, an ongoing shared care arrangement should be in place and if a patient is ever initiated on treatment, the prescribing responsibility should remain with the hospital consultant for at least 3 months.

TSH levels should be monitored during treatment to reduce the risk of over- or under-treatment, and free T4 / free T3 levels measured where clinically appropriate. The risks of over-treatment include atrial fibrillation, osteoporosis and bone fractures.

RMOC advice is summarised in the following table:

Indication and treatment regimen	Action for General Practitioners and NHS Consultants
Hypothyroidism • Patients currently receiving liothyronine monotherapy: See section 3.1.1 / 3.1.2 / 3.1.3 • Patients currently receiving liothyronine and levothyroxine combination therapy: See section 3.1.2 /3.1.3	Patients currently prescribed liothyronine, or levothyroxine and liothyronine combination therapy, for hypothyroidism should be reviewed to initiate switching to levothyroxine monotherapy where clinically appropriate. In some cases a retrospective review of the basis for the original diagnosis of hypothyroidism may be necessary. Arrangements should be made for switching to be undertaken by a consultant NHS endocrinologist, or by a General Practitioner with consultant NHS endocrinologist support. Patients who are currently obtaining supplies via private prescription or self-funding should not be offered NHS prescribing unless they meet the criteria in this guidance. The consultant endocrinologist must specifically define the reason if any patient currently taking liothyronine should not undergo a trial titration to levothyroxine monotherapy and this must be communicated to the GP
Hypothyroidism • Levothyroxine + liothyronine combination therapy for new patients: See section 3.1.2 / 3.1.4	In rare situations where patients experience continuing symptoms whilst on levothyroxine (that have a material impact upon normal day to day function), and other potential causes have been investigated and eliminated, a 3 month trial with additional liothyronine may occasionally be appropriate. This is only to be initiated by a consultant NHS endocrinologist. Following this trial the consultant NHS endocrinologist will advise on the need for ongoing liothyronine. Many endocrinologists may not agree that a trial of levothyroxine / liothyronine 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.
Oncology - Thyroid and parathyroid disease • Liothyronine monotherapy: See section 3.2	Prescribing of liothyronine in thyroid cancer, where it is used as an adjuvant to radioactive iodine treatment should only be addressed by specialists in secondary / tertiary care. Thyroid cancer patients who have completed their treatment usually need to take levothyroxine for life and should be managed in the same way as patients with hypothyroidism. .
Resistant depression • Liothyronine monotherapy or combination therapy: See section 3.3	All patients currently receiving liothyronine for a psychiatric indication should be reviewed by a consultant NHS psychiatrist, who should consider switching to an alternative treatment where clinically appropriate, or levothyroxine monotherapy where hypothyroidism is diagnosed. Patients continuing to receive ongoing liothyronine should be overseen by a consultant NHS psychiatrist.
Use of unlicensed thyroid extracts (e.g. Armour thyroid, ERFA Thyroid), plus compounded thyroid hormones, iodine containing preparations, dietary supplementation: See section 3.4	The prescribing of unlicensed liothyronine and thyroid extract products is not supported.

Part 1: Introduction

The national NHS England and NHS Clinical Commissioners' guidance: 'Items which should not routinely be prescribed in primary care: Guidance for CCGs' was published in November 2017. This is available at https://www.england.nhs.uk/wp-content/uploads/2019/08/items-which-should-not-routinely-be-prescribed-in-primary-care-v2.1.pdf
One of the products detailed in this guidance is the oral formulation of liothyronine.
The guidance published concerning liothyronine (in section 4.9 of the national guidance) is detailed in part 2 of this document.

Part 2: National Guidance Concerning Liothyronine

The NHS England and NHS Clinical Commissioners' guidance states the following:

Section 4.9
Liothyronine (including Armour thyroid and liothyronine combination products):

Background and Rationale
Liothyronine (sometimes known as T3) is used to treat hypothyroidism. It has a similar action to levothyroxine but is more rapidly metabolised and has a more rapid effect. It is sometimes used in combination with levothyroxine in products.

The price (NHS Drug Tariff) of liothyronine has risen significantly and there is limited evidence for efficacy above levothyroxine.

The British Thyroid Association, in their 2015 position statement, state "There is no convincing evidence to support routine use of thyroid extracts, L-T3 monotherapy, compounded thyroid hormones, iodine containing preparations, dietary supplementation and over the counter preparations in the management of hypothyroidism".

Due to the significant costs associated with liothyronine and the limited evidence to support its routine prescribing in preference to levothyroxine, the joint clinical working group considered liothyronine suitable for inclusion in this guidance. However during the consultation we heard and received evidence about a cohort of patients who require liothyronine and the clinical working group felt it necessary to include some exceptions based on guidance from the British Thyroid Association.

Recommendations

- *Advise CCGs that prescribers in primary care* ***should not initiate liothyronine for any new patient.***
- *Advise CCGs that individuals* ***currently prescribed liothyronine should be reviewed by a consultant NHS endocrinologist*** *with consideration given to switching to levothyroxine where clinically appropriate.*
- *Advise CCGs that a local decision, involving the Area Prescribing Committee (or equivalent) informed by National guidance (e.g. from NICE or the Regional Medicines Optimisation Committee), should be made regarding arrangements for on-going prescribing of liothyronine. This should be for individuals who, in exceptional circumstances, have an on-going need for liothyronine as confirmed by a consultant NHS endocrinologist.*

Exceptions and Further Recommendations

The British Thyroid Association (BTA) advise that a small proportion of patients treated with levothyroxine continue to suffer with symptoms despite adequate biochemical correction.

In these circumstances, where levothyroxine has failed and in line with BTA guidance, endocrinologists providing NHS services may recommend liothyronine for individual patients after a carefully audited trial of at least 3 months duration of liothyronine.

Liothyronine is used for patients with thyroid cancer, in preparation for radioiodine ablation, iodine scanning, or stimulated thyroglobulin test. In these situations it is appropriate for patients to obtain their prescriptions from the centre undertaking the treatment and not be routinely obtained from primary care prescribers

Part 3: RMOC Guidance – Prescribing of Liothyronine

The following RMOC guidance supports a consistent approach for the exceptional circumstances in which patients have an on-going need for liothyronine.

3.1 Prescribing of Liothyronine in Endocrinology: Hypothyroidism

3.1.1 Prescribing of Liothyronine in Endocrinology: Hypothyroidism Liothyronine Monotherapy

In accordance with the third recommendation of the national guidance (above), the RMOC has considered on-going prescribing of liothyronine and advises the following:

- Liothyronine monotherapy is not recommended in hypothyroidism; prescribing would be in exceptional circumstances only, such as clearly distinguishable specific levothyroxine medication intolerance including extremely rare cases of levothyroxine induced liver injury. Or potentially for patients who do not effectively metabolise levothyroxine to liothyronine, if a specialist assessing the patient according to these guidelines agrees
- In accordance with NHS guidance on 'Defining the Boundaries between NHS and Private Healthcare', patients who are currently obtaining supplies via private prescription or self-funding should not be offered NHS prescribing unless the guidelines in this document are met. Patients who have been seen privately retain the option of being referred back to the private service for private prescription.
- Individuals currently prescribed liothyronine for hypothyroidism are to be referred to a consultant NHS endocrinologist to consider transition to levothyroxine through a trial titration where clinically appropriate (see guideline 3.1.2 and 3.1.3 below).
- The consultant NHS endocrinologist must specifically define the reason if any patient currently taking liothyronine should not undergo a trial titration to levothyroxine, and this is to be communicated to the General Practitioner.
- If a previous trial titration has proved unsuccessful, the consultant endocrinologist should decide whether a further review is warranted and inform the General Practitioner accordingly.
- The review of NHS patients presently receiving liothyronine is to be managed locally and scheduled according to service capacity. Local commissioners should consider providing advice to General Practitioners to support the gradual conversion of current patients to levothyroxine, where clinically appropriate, with NHS endocrinologist support, and with appropriate arrangements for endocrinologist review.
- The abrupt withdrawal of liothyronine therapy from patients who have been stabilised on treatment for hypothyroidism is inappropriate.
- Treatment changes are to be under consultant NHS endocrinologist review or in circumstances where a General Practitioner is fully supported by a consultant NHS endocrinologist.
- Where liothyronine is prescribed, GP repeat prescribing would only be reasonable after completion of a 3 month or longer review by a consultant endocrinologist.
- Where liothyronine is so prescribed, prescribers and commissioners should consider the most appropriate means of meeting the patients' needs, and any arrangements for shared care are to be agreed within the local health economy.
- All shared care arrangements are to be authorised by the local commissioner.

3.1.2 Prescribing of Liothyronine in Endocrinology: Hypothyroidism Combination Levothyroxine and Liothyronine General Guidance:

- The guidance in 3.1.1 above for liothyronine monotherapy is also applicable when a patient converts to combination therapy.
- Combination levothyroxine / liothyronine should not be used *routinely* in the management of hypothyroidism as there is insufficient population based clinical evidence to show that combination therapy is superior to levothyroxine monotherapy.
- There is insufficient evidence at present to specify the quality of life measures to be adopted during a trial of combination levothyroxine and liothyronine, or during a trial titration from liothyronine to levothyroxine. Further work is ongoing to develop a validated quality of life measurement tool in advance of the NICE thyroid disease guidelines planned for release in 2019. In the interim, NHS consultant endocrinologists should document the range and severity of hypothyroid symptoms experienced by the patient prior to and during the assessment period.
- Specialist endocrinology oversight therefore requires review of both blood biochemistry and patient symptoms as recommended by the British Thyroid Association Executive Committee. (1)

3.1.3 Prescribing of Liothyronine in Endocrinology: Hypothyroidism Trial Titration to Levothyroxine:

- There is no defined conversion factor, and conversion of patients from liothyronine to levothyroxine monotherapy will require a reduction in the dose of liothyronine and an increase in levothyroxine. A reduction of dose of liothyronine by 10 micrograms will probably require an increase in dose of levothyroxine of 50 micrograms. Once on levothyroxine monotherapy, patients will need to have adjustment in the dose as per standard practice by monitoring of the TSH on a 6 weekly basis. Blood tests should not be undertaken more often than 6 weekly because the TSH will not have reached steady state until 6 weeks after any change. Free T4 / free T3 levels should also be measured where clinically appropriate.
- The withdrawal of liothyronine should occur gradually in line with NHS consultant endocrinologist recommendations, and may take many months to complete
- If ongoing treatment with liothyronine is required, any shared care arrangement for continuation (to be agreed with the local commissioner) must incorporate dosage guidance and monitoring arrangements. Strict control of prescribing is warranted with, at minimum, 3 months prescribing responsibility taken by the NHS consultant endocrinologist.

3.1.4 Prescribing of Liothyronine in Endocrinology: Hypothyroidism New Patients Whose Symptoms Persist on Levothyroxine Therapy:

- As noted by the British Thyroid Association Executive Committee [(1)], it is acknowledged that a proportion of individuals on levothyroxine are not satisfied with therapy and have persistent symptoms despite a serum TSH within the reference range. Such symptoms should be investigated and patients thoroughly evaluated for other potentially modifiable conditions (see box 1 below) before the potential commencement of liothyronine is considered. In some cases a retrospective review of the original diagnosis of hypothyroidism may be necessary. If there is no biochemical evidence of hypothyroidism a gradual withdrawal of all thyroid hormone preparations would be indicated.

Box 1: Some possible causes of persistent symptoms in euthyroid patients on levothyroxine:

Endocrine /autoimmune	Haematological	End organ damage	Nutritional	Metabolic	Drugs	Lifestyle	Other
Diabetes mellitus Adrenal insufficiency Hypopituitarism Coeliac disease Pernicious anaemia	Anaemia Multiple myeloma	Chronic liver disease Chronic kidney disease Congestive cardiac failure	Deficiency of any of the following: Vitamin B12 Folate Vitamin D Iron	Obesity Hypercalcaemia Electrolyte imbalance	Beta blockers Statins Opiates	Stressful life events Poor sleep pattern Work-related exhaustion Alcohol excess	Obstructive sleep apnoea Viral and postviral syndromes Chronic fatigue syndrome Carbon monoxide poisoning Depression and anxiety Polymyalgia rheumatic Fibromyalgia

- Levothyroxine dose titration and patient adherence should be fully assessed prior to consideration of combination therapy, as profound differences in response to small adjustments in levothyroxine dosage have been observed.
- It is recognised that a small number of patients may have persistent symptoms of hypothyroidism despite adequate replacement using levothyroxine, evidenced biochemically by serum Thyroid Stimulating Hormone (TSH) being between 0.4 - 1.5mU/L. As part of the overall holistic management of these patients, consultant NHS endocrinologists may start a trial of combination levothyroxine and liothyronine in order to restore wellbeing in circumstances where other potential causes of symptoms have been excluded and all other treatment options have been exhausted.
- As specified by the British Thyroid Association Executive Committee [(1)], 'If a decision is made to embark on a trial of levothyroxine and liothyronine combination therapy in patients who have unambiguously not benefited from levothyroxine then this should be reached following an open and balanced discussion of the uncertain benefits, likely risks of over-replacement and lack of long-term safety data. Such patients should be supervised by accredited endocrinologists with documentation of agreement after fully informed and understood discussion of the risks and potential adverse consequences. Many clinicians may not agree that a trial of levothyroxine / liothyronine combination therapy is warranted in these circumstances and their clinical judgement must be recognised as being valid given the current understanding of the science and evidence of the treatments'.
- Prescribing responsibility should remain with the endocrinologist until there is a formal assessment of the safety and benefit of treatment within 6 months of starting therapy, evidenced by quality of life improvements and biochemical markers.
- If there is no evidence of ongoing clinical benefit from combination levothyroxine and liothyronine, treatment with liothyronine is to be discontinued and the patient converted back to levothyroxine alone. It should be noted that the majority of randomised clinical trials have indicated a pronounced placebo effect.
- If ongoing combination treatment is warranted, any shared care arrangement (as detailed above) must incorporate regular monitoring and dose adjustment guidance, with referral to an endocrinologist if symptoms recur.

Note: Shared Care Agreements are to be prepared in accordance with 'Responsibility for Prescribing between Primary and Secondary/Tertiary Care, NHS England (2018) (https://www.england.nhs.uk/wpcontent/uploads/2018/03/responsibility-prescribing-between-primary-secondary-care-v2.pdf).

3.2 Prescribing of Liothyronine in Oncology: Thyroid and Parathyroid Disease

Liothyronine is recommended as part of the management of thyroid cancer in preparation for radioiodine remnant ablation (RRA) or radioiodine therapy (^{131}I).

The prescribing is considered for short term use as part of the endocrine management and therefore prescribing responsibilities should be retained by the specialist endocrine / oncology team involved with the management of the patient.

Short term use of liothyronine is sometimes also advised in preparation for a sestamibi parathyroid scan.

Prescribing in such situations should be addressed in the specialist hospital environment only.

Thyroid cancer patients who have completed their treatment usually need to take levothyroxine for life, so should be managed in the same way as patients with hypothyroidism (see section 3.1).

3.3 Prescribing of Liothyronine in Psychiatry: Resistant Depression

- Liothyronine is incorporated in some local treatment pathways for resistant severe depression, this being an off-label indication. Where this is the case, such pathways should be reviewed by the local prescribing committee to confirm that prescribing guidance is appropriate.
- It should be noted that the current (May 2018) draft NICE guideline 'Depression in adults: treatment and management' incorporates the augmentation of an antidepressant with thyroid hormones under 'strategies that should not be used routinely as there is inconsistent evidence of effectiveness'.
- Due to the very limited evidence for use of thyroid hormones in depression, a more holistic approach should be adopted when the initial treatment of depression is inadequate. Where thyroid hormones are considered necessary, treatment should be initiated with standard levothyroxine.
- Where liothyronine is used off-label for resistant severe depression, this must be initiated by a consultant NHS psychiatrist.
- All psychiatric patients currently receiving liothyronine should be reviewed by a consultant psychiatrist. A psychiatrist recommending ongoing treatment with liothyronine for depression should justify why an alternative treatment or levothyroxine is not appropriate.
- All patients receiving ongoing liothyronine should be overseen by a consultant NHS psychiatristt; consultant NHS endocrinology advice is also recommended for such patients.
- It is unlikely that ongoing treatment with liothyronine would be under a shared care arrangement, but if this is considered, it is to be agreed with the local commissioner as detailed in section 3.1 above.

3.4 Products that are Not Recommended for Prescribing

- Thyroid extracts (eg. Armour thyroid, ERFA Thyroid), compounded thyroid hormones, iodine containing preparations, and dietary supplementation are not recommended. The prescribing of unlicensed liothyronine and thyroid extract products are not supported as the safety, quality and efficacy of these products cannot be assured.

Part 4: Further RMOC Statements

Patient Safety

Increases in serum free T3 levels arising from liothyronine administration may provoke cardiac arrhythmias in susceptible individuals, and it is contraindicated in patients with angina of effort or cardiovascular disease.

TSH levels should be monitored during treatment, and also free T3 and free T4 levels where clinically appropriate, in order to reduce the risk of over- or under-treatment. The risks of over-treatment include atrial fibrillation, osteoporosis and bone fractures, and the risks of under treatment are also significant..

Liothyronine Supply

The current number of market authorisation holders may change. Patients should be informed that this is a rarely used product and there is the potential for instability in supply.

NICE Guideline

The National Institute for Health and Care Excellence is scheduled to publish a Clinical Guideline on ‘Thyroid disease: assessment and management’ in November 2019.

Patient Outcomes

This guidance focuses on the safe, appropriate and cost-effective use of medicines and should support patients to get the best outcomes from their medicines by enabling patients to make informed choices and agreeing treatment plans

Part 5: Useful Links

- British Thyroid Association Guidelines
- UKMI Medicines Q&A – What clinical evidence is there to support the use of armour thyroid or desiccated thyroid extract
- Royal College of Physicians: The diagnosis and management of primary hypothyroidism, 2011
- NICE Clinical Knowledge Summary: Hypothyroidism, June 2018
- Presqipp B121. Liothyronine (DROP-List) 2.2
- BTA Management of Primary Hypothyroidism 2015
- European Thyroid Association 2012 guidelines

Patient information leaflets:

- https://www.prescqipp.info/items-which-should-not-routinely-be-prescribed-patient-leaflets

References

1. Okosieme, Gilbert J, Abraham P, et al. Management of primary hypothyroidism: statement by the British Thyroid Association Executive Committee. Clin Endocrinol (Oxf). 2016;(84):799-808.

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