NHS
Greater Glasgow and Clyde

CLINICAL GUIDELINE

Liothyronine (T3) in combination with levothyroxine (T4) for adults with hypothyroidism

A guideline is intended to assist healthcare professionals in the choice of disease-specific treatments.

Clinical judgement should be exercised on the applicability of any guideline, influenced by individual patient characteristics. Clinicians should be mindful of the potential for harmful polypharmacy and increased susceptibility to adverse drug reactions in patients with multiple morbidities or frailty.

If, after discussion with the patient or carer, there are good reasons for not following a guideline, it is good practice to record these and communicate them to others involved in the care of the patient.

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Lead Author:	Robbie Lindsay
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LIOTHYRONINE IN COMBINATION WITH LEVOTHYROXINE FOR ADULTS WITH HYPOTHYROIDISM

AIM/OBJECTIVE OF GUIDELINE

This guideline advises on the place in therapy of liothyronine (T3) as an add-on therapy in combination with levothyroxine (T4) in the treatment of **hypothyroidism only**.

INTRODUCTION/BACKGROUND

This guidance does not apply to the following patient groups

1. Patients with thyroid cancer who need T3 as part of investigation/treatment
2. Women who are planning or undergoing pregnancy (T3 not recommended - such patients need specialist care/advice).
3. Patients prescribed T3 for mental health indications such as treatment resistant depression on the recommendation of a psychiatrist.
4. Liothyronine monotherapy for treatment of hypothyroidism is out-with the scope of this guide. Monotherapy with T3 is not recommended in hypothyroidism; prescribing would be in exceptional circumstances only, such as an absolute specific intolerance e.g. extremely rare cases of levothyroxine induced liver injury, or for patients who are unable to metabolise levothyroxine to liothyronine[2].

Levothyroxine replacement therapy (T4) is the standard treatment of hypothyroidism and results in normalisation of biochemistry and symptoms in the vast majority of patients. It is included in the NHSGGC Adult Formulary as the preferred treatment of hypothyroidism in adults.

The British Thyroid Association (BTA)[1] advises that a small proportion of patients treated with levothyroxine continue to suffer with symptoms despite adequate biochemical correction. Additional treatment with liothyronine (T3) may be considered in these cases - reflecting that while the majority of thyroid hormone secreted by the thyroid naturally is T4, a small proportion (~7%) is secreted as T3 .

In very rare situations patients experience continuing symptoms of hypothyroidism severe enough to have a material impact on day to day functioning despite treatment with levothyroxine[2]. Where other potential causes have been investigated and eliminated, NHSGGC supports a 3 month trial with additional liothyronine initiated by a consultant NHS endocrinologist.

The decision to prescribe a trial of combination T3/T4 should be reached following an open and balanced discussion between an endocrinologist and the patient. This should include an explanation of the uncertain benefits, likely risks of over-replacement, lack of long-term safety data and the possibility of not continuing if the trial shows no benefit.

Liothyronine tablets are included in the NHSGGC Total Formulary (Adult) for use in combination with levothyroxine (T4) restricted to initiation by an endocrinologist.

Licensed 5 microgram, 10microgram and 20 microgram tablets of liothyronine are now available in the UK. NHSGGC does not support the use of unlicensed products and thyroid extracts (eg. Armour thyroid, ERFA Thyroid), compounded thyroid hormones, iodine containing preparations, and dietary supplements. The safety, quality and efficacy of these products cannot be assured.

SCOPE

- This guidance is written for primary and secondary care prescribers. It refers to adults only.
- The use of liothyronine for indications other than hypothyroidism is out-with the scope of this guidance.
- The guidance relates to use of liothyronine in combination with levothyroxine (not as monotherapy).

- Exclusions apply as detailed above.

ROLES/RESPONSIBILITIES

Secondary care / endocrinologist responsibilities

1. Ensure the patient fulfils all criteria for a trial of treatment
2. Ensure all alternative causes of symptoms are excluded - See Table 1 below for factors to be considered/investigated (this will have been initiated in primary care for many of these).
3. Prescribe combination therapy after full discussion of risks/benefits with patient.
4. Achieve a stable dose combination according to TFT – biochemical monitoring to be undertaken at 6-8 weeks.
5. Assess physical and psychological response to treatment after at least 3 months of stable dosing.
6. Supervise discontinuation of therapy if trial is unsuccessful.
7. Advise GP on ongoing monitoring requirements and follow-up arrangements if the intention is to continue on therapy
8. If discharging patient to care of GP, advise GP of criteria for re-referral to endocrinology if review is needed.

Primary care responsibilities

1. Investigate for alternative causes before referral as far as possible
2. Agree to prescribe T3 in line with local guidance once a stable dosing regimen has been determined by secondary care along with a decision to continue combination therapy indefinitely.
3. Check TFT annually once doses are stable or 6-8 weeks after a dose change; aim for TSH of 0.35-2.5 mU/L.
4. Seek advice from endocrine specialist on any aspect of patient care which is of concern and may affect treatment. Note: 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. Patient should be re-referred to endocrinology if necessary.

GUIDELINE

Considering T3 therapy in individual patients

1. There is **no** strong evidence that combination therapy with T4 and T3 has benefits over T4 monotherapy and **no** national guideline group recommends routine use.
2. Long term effects and side effects of combination T4 and T3 therapy are not known
3. Measurement of T3 is not considered helpful in the clinical decision whether to add T3 on an individual basis and should not be a routine part of monitoring of hypothyroid patients on T4.
4. Currently no genetic testing is recommended (or clinically available) to guide therapy

Indications

Where the patient has continuing symptoms not explained by another diagnosis (see Table 1 below) after full evaluation and, if necessary, a retrospective review of the original diagnosis of hypothyroidism, then a trial of T3 may be considered. This should be initiated by an endocrinology specialist.

T3 should only be used in combination with T4 and not as monotherapy.

Table 1 – Possible causes of persistent symptoms in euthyroid patients[2]

Category of Problem	Examples which can be ruled out by GP (prior to endocrinology referral)	Examples which can be ruled out by endocrinologist (prior to addition of T3)
Endocrine / Autoimmune factors	Diabetes mellitus: Coeliac disease: Pernicious anaemia	Adrenal insufficiency: Hypopituitarism:
Haematological	Anaemia: Multiple myeloma	
End organ damage	Chronic liver disease: Chronic kidney disease: Congestive cardiac failure	
Nutritional	Deficiency of any of the following - Vitamin B12: Folate: Vitamin D: Iron	
Metabolic	Obesity: Hypercalcaemia: Electrolyte imbalance	
Drug treatments	Betablockers: Statins: Opiates	
Lifestyle/patient factors	Poor adherence with T4 therapy: Stressful life events: Poor sleep pattern: Work related exhaustion: Alcohol excess	
Other	Obstructive sleep apnoea: Depression and anxiety: Polymyalgia rheumatic:	Carbon monoxide poisoning: Also consider possibility of - Viral and post-viral syndromes: Chronic fatigue syndrome: Fibromyalgia.

Contraindications

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

Dose and monitoring response

A reduction in T4 dose will be required when T3 is commenced and, ideally, this requires an individualised approach. Typically, for every 10 micrograms T3, the T4 dose should be reduced by 25-50 micrograms. T3 has a short half-life and requires twice or three times daily dosing. A typically starting dose would be 10 micrograms twice daily (resulting in a reduction of T4 by 50-100 micrograms).

Biochemical monitoring is done by specialist 6-8 weeks after commencing treatment and/or dose changes. TFT are best done prior to morning medication with a target TSH of 0.35-2.5 mU/L. Suppression of TSH to values below 0.1 mU/L is not recommended particularly in groups at greater risk of atrial fibrillation and/or osteoporosis.

Clinical response requires subjective evaluation by the patient and physician after at least 3 months of treatment with a stable combination regimen.

If continuing on maintenance therapy TFTs should be conducted annually.

Safety considerations

Increases in serum free T3 levels arising from liothyronine administration may provoke cardiac arrhythmias in susceptible individuals. T3 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.

REFERENCES

1. Okosieme O, Gilbert J, Abraham P, Boelaert K, Dayan C, Gurnell M, et al. Management of primary hypothyroidism: statement by the British Thyroid Association Executive Committee. Clin Endocrinol (Oxf) 2016 Jun;84(6):799-808.

2. Regional Medicines Optimisation Committee (RMOC). Guidance - Prescribing of Liothyronine (v 2). Nov 2018. Available here. Accessed 15/07/2020

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