# New Medicine Assessment

# Liothyronine for the treatment of resistant depression

**Recommendation:**

**Red RAG rating.**

- Medicine is supplied by the hospital for the duration of the treatment course.
- Primary care initiation or continuation of treatment is not recommended unless exceptional circumstances such as specialist GP.

  Red medicines are those where primary care prescribing is not recommended. These treatments should be initiated by specialists only and prescribing retained within secondary care. They require specialist knowledge, intensive monitoring, specific dose adjustments or further evaluation in use. If however, a primary care prescriber has particular specialist knowledge or experience of prescribing a particular drug for a particular patient it would not always be appropriate for them to expect to transfer that prescribing responsibility back to secondary care. There should be a specific reason and a specific risk agreement, protocol and service set up to support this.

  Primary care prescribers may prescribe RED medicines in exceptional circumstances to patients to ensure continuity of supply while arrangements are made to obtain on going supplies from secondary care.



Date: December 2024

## Details of Review

**Name of medicine** (generic & brand name)**:** Liothyronine

**Strength(s) and form(s):** 5mcg, 10mcg, 20mcg tablets and capsules

**Dose and administration:** Dose 20–50µg/day[1]

**BNF therapeutic class / mode of action: Thyroid hormones**

Thyroid hormone is postulated to exert antidepressant efficacy through multiple mechanisms.[2] Depression is associated with neuronal death, so decreasing neuronal stress, atrophy, and death should be associated with an antidepressant effect. Liothyronine has been shown to increase gene expression by increasing levels of thyrotropin-releasing hormone, corticotrophin releasing factor, and brain derived neurotrophic factor. There are changes in sensitivity and transcription of serotonin (5-HT) receptors and possibly a net increase in serotonin signalling after liothyronine administration. Administration of liothyronine has also led to increased basal 5-HT levels in the frontal cortex. There is a possible but unclear association between liothyronine and adrenergic transmission and activity of second-messenger systems. It has not been demonstrated to increase concentrations of monoamine metabolites, even in patients whose depression improved after treatment with liothyronine.

**Licensed indication(s):**

- Liothyronine is indicated in adults and children for the treatment of coma of myxoedema, the management of severe chronic thyroid deficiency and hypothyroid states occurring in the treatment of thyrotoxicosis.
- Liothyronine sodium can be used also as an adjunct to carbimazole to prevent sub-clinical hypothyroidism developing during carbimazole treatment of thyrotoxicosis.
- Liothyronine sodium may be preferred for treating severe and acute hypothyroid states because of its rapid and more potent effect, but thyroxine sodium is normally the drug of choice for routine replacement therapy.

**Proposed use** (if different from, or in addition to, licensed indication above): Refractory / resistant depression (unlicensed use)

**Course and cost:[3]**

- 28 x 5 µg capsules = £55
- 28 x 5 µg tablets = £123.38
- 28 x 10µg capsules = £65.00
- 28 x 10µg tablets = £152.44
- 28 x 20µg capsules = £55.00
- 28 x 20 µg tablets = £40.10

**Current standard of care/comparator therapies:**

Lamotrigine 100mg x 56 = £2.12

Buspirone 30mg tablets x 30 = £30.38

Venlafaxine 225mg modified release capsules x 28 = £16.27

**Relevant NICE / OTHER guidance:**

**NICE (2022) Depression in adults: treatment and management NG222**[4] -If a person with depression wants to try a combination treatment and is willing to accept the possibility of an increased side-effect burden, consider referral to a specialist mental health setting or consulting a specialist. Treatment options include: …. triiodothyronine (liothyronine)

**NHSE guidance**[5] states: Treatment of depression should follow the NICE guideline Depression in adults: treatment and management. Where liothyronine is prescribed for the treatment of depression only, this should be under the advice of an NHS consultant psychiatrist.

**Maudsley Prescribing Guide**1 - Listed as a second choice for refractory depression

**AWMSG**[6] - 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 liothyronine should be overseen by a consultant NHS psychiatrist.

In the **Clinical Practice Guideline for the management of Major Depressive Disorder (USA)**[7] prepared by the American VA/DoD, Liothyronine is included alongside Lithium as established augmentation strategies for SSRIs and TCAs, with Lithium being considered the best-studied augmentation strategy

## Background and context

Liothyronine for the treatment of resistant depression currently holds a BLACK RAG rating on LSCMMG (2019). NICE have since published NG222 (2022) which lists liothyronine as a treatment option for this condition and this is also supported by both NHSE (2023) and the Maudsley prescribing guide (2021).

LSCFT have requested that the current RAG rating be reviewed and changed to RED.

LSCFT anticipate that this change to the colour classification will not have any significant impact on prescribing rates as numbers of patients treated are likely to be small.

## Summary of evidence

**Summary of efficacy data in proposed use:**

A meta-analysis of augmentation of TCAs with tri-iodothyronine (T3), 25–37.5 µg, in four small RCTs of treatment-resistant depression found significant benefit with regard to improvement in HDRS score (ES 0.6) but a non-significant improvement in response rate (NNT 13).[8]

A small subsequent study found no difference between lithium, liothyronine, the combination and placebo in a 2-week study in patients predominantly on SSRIs (Joffe et al., 2006).[9]

The STAR*D study found a non-significantly higher remission rate on liothyronine (25–50µg) than lithium (23% vs. 16%, NNT 14) with significantly fewer patients discontinuing due to side effects (10% vs. 23%, NNH 8), although it should be noted that lithium levels were not consistently monitored in this study.[10]

A review and meta – analysis of six double-blind, placebo-controlled studies (2001)[11] assessing the concomitant administration of thyroid hormone and antidepressant to accelerate clinical response in patients with nonrefractory depression were conducted with liothyronine and a tricyclic antidepressant. Five of the six studies found liothyronine to be significantly more effective than placebo in accelerating clinical response. The pooled, weighted effect size index was 0.58, and the average effect was highly significant. Further, the effects of liothyronine acceleration were greater as the percentage of women participating in the study increased. Conclusions: This meta-analysis supports the efficacy of liothyronine in accelerating clinical response to tricyclic antidepressants in patients with nonrefractory depression. Furthermore, women may be more likely than men to benefit from this intervention.

A double-blind, randomized, 8-week, placebo-controlled trial of 124 adult outpatients with major depressive disorder without psychotic features, were randomized to receive sertraline hydrochloride (50 mg/d for 1 week; 100 mg/d thereafter) plus liothyronine sodium (20-25 microg/d for 1 week; 40-50 microg/d thereafter) or sertraline plus placebo for 8 weeks.[12] Intent-to-treat Hamilton Rating Scale for Depression response rates were 70% and 50% in the sertraline-liothyronine and sertraline-placebo groups, respectively (P = .02; odds ratio, 2.93; 95% confidence interval, 1.23-7.35); remission rates were 58% with sertraline-liothyronine and 38% with sertraline-placebo (P = .02; odds ratio, 2.69; 95% confidence interval, 1.16-6.49). Baseline T(3) values were lower in patients treated with sertraline-liothyronine who had remissions than in those without remissions (t(48) = 3.36; P<.002). Among patients treated with sertraline-liothyronine, remission was associated with a significant decrease in serum thyrotropin values (F(1,73) = 4.00; P<.05). There were no significant effects of liothyronine supplementation on frequency of adverse effects. Conclusions: These results demonstrate enhancement of the antidepressant effect of sertraline by concurrent treatment with liothyronine without a significant increase in adverse effects. The antidepressant effect of liothyronine may be directly linked to thyroid function.

In an open trial, the efficacy of liothyronine adjuvant to selective serotonin reuptake inhibitors (SSRIs) in subjects with major depressive disorder (MDD) resistant to SSRI treatment was investigated.[13] Twenty subjects who had failed to respond to a course of treatment of at least 8 weeks with an SSRI antidepressant were enrolled in a 4-week open-label augmentation treatment with liothyronine 50 microg/day. During liothyronine augmentation, the severity of depression decreased from an initial mean +/- SD HAM-D-17 score of 20.5 +/- 3.6 to a final HAM-D-17 score of 14.0 +/- 7.1 (p < .001). Seven subjects (35.0%) were treatment responders (HAM-D-17 reduction >or= 50%), and 6 subjects (30.0%) achieved clinical remission (final HAM-D-17 <or= 7). The 5 subjects with atypical depression experienced significantly (p < .01) greater clinical improvement (final HAM-D-17 scores 6.6 +/- 1.8 vs. 16.4 +/- 4.5), and higher rates of treatment response (100% [5/5] vs. 13.3% [2/15]) and remission (80.0% [4/5] vs. 13.3% [2/15]), compared to subjects with nonatypical MDD. The 8 subjects with melancholic MDD experienced significantly (p < 0.05) greater depression severity at the end of the study compared to non melancholic MDD subjects (final HAM-D-17 scores = 18.3 +/- 6.6 vs. 11.1 +/- 6.1). Conclusion: Triiodothyronine augmentation of SSRIs may be a promising treatment strategy in SSRI-resistant MDD, particularly in subjects with the atypical MDD subtype.

**Summary of safety data:**

Patients who are started on liothyronine augmentation for a psychiatric disorder should be

monitored in the same manner as patients with hypothyroidism.[14] TSH, free T4, and free T3 levels should be measured regularly, as well as whenever there is a report of increased anxiety, tremor, palpitations, insomnia, or other symptoms suggestive of hyperthyroidism. Patients should also be monitored for other conditions that could be exacerbated by T3 supplementation, including hypertension, tachycardia, osteopenia or osteoporosis, atrial arrhythmias, and hyperglycaemia. Finally, it should be borne in mind that some beta-blockers influence thyroid hormone metabolism and plasma levels.

The following effects are indicative of excessive dosage and usually disappear on reduction of dosage or withdrawal of treatment for a day or two.[15]

The undesirable effects are listed below by organ class and the following frequency convention:

| **System Organ Class** | **Frequency** | **Adverse events** |
|---|---|---|
| Cardiac disorders | Not known | Anginal pain, cardiac arrhythmias, palpitations, tachycardia |
| Gastrointestinal disorders | Not known | Diarrhoea, vomiting |
| General disorders and administration site conditions | Not known | Fever, flushing, fever and heat intolerance |
| Immune system disorders | Not known | Hypersensitivity reactions including rash, pruritus and oedema also reported. |
| Metabolism and nutrition disorders | Not known | Excessive loss of weight |
| Musculoskeletal and connective tissue disorders | Not known | Muscle cramps, muscular weakness |
| Nervous system disorders | Not known | Headache, tremor, |
| Psychiatric disorders | Not known | Restlessness, excitability, insomnia, |
| Skin and subcutaneous tissue disorders | Not known | Sweating |
| Vascular disorders | Not known | Flushing |

Liothyronine sodium treatment may result in an increase in insulin or anti-diabetic drug requirements. Care is required for patients with diabetes mellitus and diabetes insipidus.

TSH levels should be monitored during treatment to reduce the risk of over- or undertreatment. The risks of over-treatment include atrial fibrillation, osteoporosis and bone fractures.

Baseline ECG is recommended prior to commencement of liothyronine treatment in order to detect changes consistent with ischaemia. Patients should undergo cardiovascular monitoring, including periodic ECGs, during liothyronine treatment. Liothyronine is contraindicated in established myocardial ischaemia

Safety during pregnancy is not known. The risk of foetal congenital abnormalities should be weighed against the risk to the foetus of untreated maternal hypothyroidism.

Breast-feeding - Liothyronine sodium is excreted into breast milk in low concentrations. This may interfere with neonatal screening programmes.

**Strengths and limitations of the evidence:**

**Strengths –** Multiple studies**,** most have shown that liothyronine is an efficacious enhancement

and augmentation strategy for depression in combination with antidepressants, primarily tricyclic antidepressants and selective serotonin reuptake inhibitors

**Limitations –** Majority of studies published more than 10 years ago, small patient numbers, limited data available for liothyronine's efficacy with newer antidepressants, short study duration.

**Summary of evidence on cost effectiveness:**

28 x 20µg tablets = £40.10

Recommended dose is 20- 50µg daily

Potential Monthly cost = £40.10 - £100.25,

Potential Annual cost = £1,303.25 / patient.

Costs more than current treatments but this could offset hospital admissions, etc.

Clinical and biochemical TFT monitoring required.

Prices may fluctuate – have varied considerably over time.

**Prescribing and risk management issues:**

TSH, free T4, and free T3 levels should be measured regularly, as well as whenever there is a report of increased anxiety, tremor, palpitations, insomnia, or other symptoms suggestive of hyperthyroidism. Patients should also be monitored for other conditions that could be exacerbated by T3 supplementation, including hypertension, tachycardia, osteopenia or osteoporosis, atrial arrhythmias, and hyperglycemia.

**References**


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[4] NICE NG222 https://www.nice.org.uk/guidance/ng222

[5] NHS England (2023) Liothyronine – advice for prescribers, https://www.england.nhs.uk/long-read/liothyronine-advice-for-prescribers/#liothyronine-for-depression

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