May 2016 (updated October 2019)

New Medicine Recommendation

Liothyronine 20microgram Tablets

Liothyronine as an add-on treatment for refractory hypothyroidism despite adequate monotherapy with levothyroxine

Liothyronine as monotherapy for the chronic management of hypothyroidism

Liothyronine for the management or resistant depression

Prescribing within Primary Care - Black

Liothyronine is **NOT recommended** for use by the NHS in Lancashire in the following setting:

- **as an add-on treatment for refractory hypothyroidism despite adequate monotherapy with levothyroxine**.

There is insufficient evidence to demonstrate efficacy in the above setting, availability of the drug is limited, adverse events are more prevalent than for levothyroxine monotherapy and there would be a considerable cost pressure to the health economy if prescribed for all patients with normal serum TSH levels and have persistent symptoms.

- **as monotherapy for the chronic management of hypothyroidism**

There is a paucity of evidence in the literature supporting the use of liothyronine monotherapy for the management of hypothyroidism. Liothyronine is not licensed for the long-term management of hypothyroidism. [1]

- **for the management of resistant depression**

There is a paucity of evidence in the literature supporting the use of liothyronine for the management of depression. Liothyronine is not licensed for the management of depression. [1]

Prescribing by secondary or tertiary care specialists for the treatment of acute conditions where thyroid replacement is needed rapidly, for a limited period and/or where a drug with shorter half-life is required **- Red**

Liothyronine **is recommended** for prescribing **by secondary or tertiary care specialists** in the following settings:

- preceding ablation therapy with radioactive iodine
- for the treatment of coma of myxedema, the management of severe chronic thyroid deficiency and hypothyroid states occurring in the treatment of thyrotoxicosis.*
- treating severe and acute hypothyroid states because of its rapid and more potent effect, thyroxine sodium is normally the drug of choice for routine replacement therapy.*

* = licensed indication

Specialist knowledge, intensive monitoring and specific dose adjustments are necessary. Liothyronine must be supplied by the hospital for the duration of the treatment course. Primary care initiation or continuation of treatment is not recommended unless in exceptional circumstances.

Summary of supporting evidence:

For the RED recommendations, liothyronine is either licensed or already being used in the specialist setting and choice of agent is driven by the drugs shorter half-life and more rapid onset of action. Therefore, the main body of the review focuses on liothyronine as an add-on treatment for refractory hypothyroidism despite adequate monotherapy with levothyroxine.

The clinical evidence for liothyronine as an add-on treatment for refractory hypothyroidism despite adequate monotherapy with levothyroxine is informed by 11 randomised controlled clinical trials, 9 of which fail to show a benefit for add-on treatment.

- Liothyronine is not licensed to be prescribed alongside levothyroxine as an add-on treatment for refractory hypothyroidism despite adequate monotherapy with levothyroxine
- In the UK it is estimated that the annual incidence of primary hypothyroidism is 3.5 per 1000 population for women and 0.6 per 1000 population for men. [2]
- In Lancashire the estimated prevalence of hypothyroidism is 5.9% (based on ePACT data).
- There is evidence to suggest that between 5 and 10% of patients that receive levothyroxine for hypothyroidism with normal serum TSH levels have persistent symptoms. [3]
- The potential cost pressure across the Lancashire health economy if all patients with refractory hypothyroidism receive combination treatment is between £4,035,672 and £18,840,080 per year.

Guidelines:

- The British Thyroid Association, the Royal College of Physicians, the European Thyroid Association and the National Institute Health and Care Excellence clinical knowledge summary either do not recommend combination therapy or mandate specialist use only and acknowledge that research needs to demonstrate greater efficacy before a more positive recommendation can be made. [3] [4] [5] [4] [6]

Efficacy:

- 11 randomised-controlled trials were identified that have investigated the use of a combination of levothyroxine and liothyronine in differing ratios compared to levothyroxine monotherapy. [7] [8] [9] [10] [11] [12] [13] [14] [15] [16] [17]
- There was one meta-analysis conducted in 2006 comparing combination therapy versus monotherapy. [18]
- Nine of the eleven RCTs conclude that the evidence does not indicate a positive effect of combined therapy on trial outcomes, including measures of quality of life, cognitive function, wellbeing, social functioning, mood, physical health measures or symptoms of hypothyroidism. [7] [8] [9] [10] [11] [12] [13] [14] [15]
- Subjective appreciation of liothyronine, associated with weight loss, was increased in one study [12]
- In a crossover group study of 28 patients, for patients in the add-on treatment analysis, compared with levothyroxine monotherapy:
    - levels of TSH decreased by 0.85mU/L (CI, 0.27 to 1.43mU/L) and
    - levels of free T3 increased by 0.8pmol/L (95% CI, 0.1 – 1.5pmol/L).
    - compared to monotherapy, patients performed better on the copies score of the Digit Symbol Substitution Test (increase 8.5points [95%CI, 3.0 – 14.0points]) and

on the time required to complete the Visual Scanning Test (decrease 10.0seconds [95%CI, 0.9 – 26.0 seconds]).

After cross-over, compared with levothyroxine monotherapy:

- serum levels of free T4 decreased by 3.9pmol/L (95% CI, 2.5 – 5.3pmol/L) after combination treatment,
- serum TSH levels increased slightly by 0.62mU/L (95% CI, 0.01 to 1.23mU/L)
- levels of free T3 remained unchanged.

12 patients preferred combination treatment, six preferred the add-on combination treatment, two preferred standard treatment and six had no preference (χ^2 value, 10.46; p = 0.015). [13]

- In one 68 patient study, the following were improved for combination therapy: general health (p = 0.01), social functioning (p = 0.02), vitality (p = 0.02) depression (p = 0.01), anxiety (p= 0.01), GSI (Global Severity Index; p = 0.01) and PST (Positive Symptoms Total; p = 0.02). There was also a significant improvement in quality of life and depression scores between baseline and control group data. 10 out of 11 parameters indicated a positive change. 49% of participants preferred combination treatment versus 15% preferring monotherapy. Those that preferred combination treatment had higher depression scores at baseline than patients without preference (35%). [17]
- In one 36 patient study, combination therapy showed favourable changes in serum lipid profile but higher activation of bone resorption. [15]
- The authors of a meta-analysis found no difference in the effectiveness of combination treatment versus monotherapy in any of the following symptoms: bodily pain, depression, anxiety, fatigue, QOL, bodyweight and serum lipid profile. [18]

Safety:

- There is evidence showing combination treatment is associated with more side effects than monotherapy. [15] [14] [10] [11] The SPC for levothyroxine has the same side effect profile as liothyronine with the following additions: angioedema, eosinophilia, liver dysfunction, nervousness, mania, menstrual irregularities. [19]
- In a 2009 study, 11% of the study population developed palpitations. [14]
- One study with 697 participants 109 participants taking combination treatment withdrew for the following reasons:
  - 41% (11/27) experienced symptoms of hyperthyroidism,
  - 64% (30/47) experienced symptoms of hypothyroidism and
  - 50% (3/6) experienced symptoms of both hypo- and hyperthyroidism [10]

Details of Review

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

Liothyronine

Strength(s) and form(s):

20microgram tablets (licensed preparation). Imported, unlicensed preparations are available in 5 and 25 microgram strengths.

Dose and administration:

Replacement therapy: by mouth, initially 10–20 micrograms daily gradually increased to 60 micrograms daily in 2–3 divided doses.

Recommended combination therapy (physiological replacement) [4]: levothyroxine monotherapy plus additional liothyronine at a ratio of between 20:1 and 13:1

BNF therapeutic class / mode of action

6.2.1 Thyroid hormones. Direct replacement of endogenous thyroid hormone triiodothyronine.

Licensed indication(s):

Liothyronine sodium tablets are qualitatively similar in biological action to thyroxine but the effect develops in a few hours and lasts for 24 to 48 hours after stopping the treatment.

Used 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 in the treatment of thyrotoxicosis as an adjunct to carbimazole to prevent sub-clinical hypothyroidism developing during treatment.

Liothyronine sodium may be preferred for treating severe and acute hypothyroid states because of its rapid and more potent effect, but levothyroxine sodium is normally the drug of choice for routine replacement therapy. [20]

Proposed use (if different from, or in addition to, licensed indication above):

Liothyronine as an add-on treatment for refractory hypothyroidism despite adequate monotherapy with levothyroxine (off-label use).

Course and cost (Licenced dose MIMS price March 2016) [21]**:**

Example regimen: Levothyroxine + Liothyronine (13:1 ratio) [1]

(Levothyroxine 200microgram o.d. and liothyronine 7.5microgram b.d.)

Levothyroxine 100microgram x 28 = £1.85

Liothyronine 20microgram x 28 = £198.62 (the 20 microgram tablet is used for the illustration as pricing is not available for other strengths)

Total annual medication cost = £669.57 - £1984.58 [21]

Current standard of care/comparator therapies:

Levothyroxine 50microgram – 200microgram o.d. annual cost of treatment = £26.26 – £105.04

Relevant NICE guidance

None

Background and context

Hypothyroidism is one of the commonest chronic conditions in western populations. In the UK has been estimated that the annual incidence of primary hypothyroidism is 3.5 per 1000 for women and 0.6 per 1000 for men. [2] Studies in Northern Europe, Japan and the USA have found the prevalence to range between 0.6 and 12 per 1000 women and between 1.3 and 4.0 per 1000 in men investigated. [22]

The commonest cause of hypothyroidism in developed countries is autoimmune thyroiditis. Surgical thyroidectomy as a treatment for hyperthyroidism or thyroid cancer is also a significant cause of hypothyroidism. [2]

Autoimmune thyroiditis generally causes a slow failure of hormone production; symptoms may develop over many years. Presentation ranges from mild symptoms such as fatigue to severe states such as myxoedema coma, although the latter is rarely now seen in developed countries. [2]

A diagnosis of primary hypothyroidism is confirmed by an increase in the serum thyroid stimulating hormone (TSH) above the upper limit of normal. If TSH is elevated and serum levothyroxine concentration is below the reference range patients are considered to have overt or symptomatic hypothyroidism. In these cases replacement therapy with synthetic levothyroxine is indicated. A starting dose of 50 – 100micrograms once a day in adults is currently recommended and the dose is adjusted by 25 – 50microgram every 3 – 4 weeks according to response. The aim of treatment is to render the patient back to a euthyroid state. [2] [23] [5]

There is evidence to suggest that between 5 and 10% of patients that receive levothyroxine for hypothyroidism with normal serum TSH levels have persistent symptoms related to the condition. Rationale for these symptoms include: awareness of chronic disease, presence of associated autoimmune diseases, extra-thyroid autoimmunity (not related to thyroid function) and inadequacy of levothyroxine therapy to restore serum levothyroxine and liothyronine levels. [3]

The use of combined levothyroxine and liothyronine has been suggested by the British Thyroid Association and the Royal College of Physicians as a potential alternative treatment for patients in this population despite acknowledging that further research is required. [3] [4] [5]

Liothyronine does have a place in the management of hypothyroidism. The shorter half-life (see below) and more rapid onset of action compared to levothyroxine make it more suitable for use in severe hypothyroid states. [20]

The British Thyroid Association Executive Committee published a statement regarding the management of hypothyroidism in 2015. [3] The statement recognises that a proportion of individuals continue to suffer with symptoms despite achieving adequate biochemical correction with levothyroxine monotherapy. The authors concluded that combination therapy should not be used routinely as there is insufficient evidence to show that combination therapy is superior to monotherapy. [3] Although the authors also state that if a decision is made to commence combination therapy for a patient that has unambiguously not benefitted from monotherapy, the risks and benefits of doing so should be fully discussed with the patient and documented. Such trials should only be supervised by a specialist endocrinologist. [3]

In 2012 the European Thyroid Association published guidelines on the use of combination treatment for the management of hypothyroidism. [4] The authors conclude that there is insufficient evidence that combination therapy is better than monotherapy. However, combination therapy might be considered as an experimental approach in compliant levothyroxine treated hypothyroid patients who are still symptomatic despite TSH levels within the reference range. Before a trial of combination therapy, support should be implemented for patients to deal with a chronic condition and the existence of any additional autoimmune disease should be excluded. [4] Where combination therapy is considered it must be implemented by a specialist endocrinologist and discontinued if there is no improvement after three months. The authors recommend a dose ratio of between 13:1 and 20:1 by weight (levothyroxine once a day and liothyronine daily dose in two divided doses). Combination preparations are not recommended. [4]

The Royal College of Physicians issued a statement about the diagnosis and management of primary hypothyroidism, concluding that the use of thyroid extracts or combination therapy without further research is not supported. Any use of combination therapy should be reserved for specialists on an individual patient basis. [5]

The National Institute Health and Care Excellence (NICE) published a clinical knowledge summary (CKS) in 2011 regarding the management of hypothyroidism. [6] The CKS explicitly states that prescribers should not use liothyronine (triiodothyronine) with levothyroxine. [6]

Pharmacokinetics and Pharmacology

Levothyroxine has an oral bioavailability of around 80%. Liothyronine has an oral bioavailability of 95%. Levothyroxine and liothyronine have half-lives of around 7 days and 1-2 days respectively in a euthyroid state. [20] [24] [19]

Levothyroxine and liothyronine undergo slower metabolic clearance in patients that have hypothyroidism compared to hyperthyroidism. In euthyroid patients, normal thyroid hormone concentrations are maintained as a result of compensatory hyperfunction of the thyroid. However, those patients receiving replacement therapy with levothyroxine may require increased doses to maintain clinical effectiveness. [24] Polypharmacy is an important factor to consider if hypothyroid patients remain symptomatic despite adequate replacement with levothyroxine as drug interactions could be influencing the patient's response to therapy.

Summary of evidence

Summary of efficacy data in proposed use:

There are 11 randomised-controlled trials in the literature that have investigated the use of a combination of levothyroxine and liothyronine in differing ratios compared to levothyroxine monotherapy. There was one meta-analysis conducted in 2006 comparing combination therapy versus monotherapy. The trials are of varied quality – the larger, better powered studies have their authors and publication dates in bold to aid with their identification.

Randomised Controlled Trials

The first, Bunevicius et al, 1999, was a double-blind, placebo-controlled, crossover study investigating the effects of levothyroxine as compared with levothyroxine plus liothyronine in patients with hypothyroidism. [16] 33 patients completed the study; 16 had autoimmune thyroiditis and 17 had near-total thyroidectomies secondary to cancer. Two groups were compared: participants' usual dose of levothyroxine in 50microgram capsules versus the usual dose of levothyroxine reduced by one 50microgram levothyroxine capsule substituted with 12.5microgram of liothyronine. The ratio by weight of levothyroxine to liothyronine was variable (between 10:1 and 5:1). Participants were randomised and the study was run for five weeks at which point the

treatment groups were switched and the study was run for another five weeks. [16] [4]

The primary endpoint of the study was not clear. Physiological and psychological measures were reported. Biochemical changes were unremarkable. Six measures pertaining to cognitive function and mood improved after participants had received combination treatment ($p<0.05$). The improved measures were: Digit Symbol Test (recall; $p = 0.04$), Digit Span Test (backwards recall; $p = 0.05$) and mood (fatigue, depression and anger; $p = 0.001$, 0.01 and 0.04 respectively). The authors concluded that partial substitution of liothyronine for levothyroxine may improve mood and neuropsychological function. [16]

The second, **Walsh et al, 2003**, was a double-blind, randomised, crossover study. [7] The study looked at the use of combined therapy in patients with primary hypothyroidism. 110 adult patients with primary hypothyroidism were randomised to two groups; 101 participants completed the study. At study entry all patients reduced their usual maintenance dose of levothyroxine by 50microgram and were randomised to one of two groups: levothyroxine 50microgram (control group) or liothyronine 10microgram (treatment group). The ratio by weight of levothyroxine to liothyronine was variable (between 15:1 and 5:1). Patients continued their reduced dose of levothyroxine. The study period was ten weeks after which participants resumed their usual dose of levothyroxine for four weeks and then switched to the opposite treatment group for a further ten weeks. [7] [4]

The primary endpoints of the study were: quality of life (QOL) and cognitive function. There was no significant difference between monotherapy and combined therapy for the short form (SF-36) health survey measures of physical and mental health. The general health questionnaire (GHQ-28) score was higher (indicating worse psychological wellbeing) for combined therapy (18.3+/- 1.0 for T4 vs. 21.2+/-1.0 for T4/T3; P=0.033). [7] Differences between scores derived from the thyroid symptoms questionnaire (TSQ) and visual analogue scale (VAS) scores were not significantly different between the groups. The only exception was the VAS score for anxiety which was higher for the combined group ($p=0.026$). Cognitive function tests also exhibited no difference between the groups. Patients preferred treatment was monotherapy ($n = 46$) although this was not statistically significant ($p = 0.32$). [7] The authors concluded that in the doses used in the study, combination treatment did not improve wellbeing, cognitive function or QOL compared to levothyroxine alone. [7]

The third RCT, **Sawka et al, 2003**, followed a double-blind, placebo-controlled design. [8] The authors compared the effect of a combination regimen on depressive symptoms against monotherapy plus placebo. 40 adult patients with primary hypothyroidism were randomised to study groups receiving one of two interventions: levothyroxine continued at maintenance dose plus a placebo b.d. or maintenance dose reduced by 50% and liothyronine commenced at 12.5micrograms b.d. The ratio by weight of levothyroxine to liothyronine was variable (mean ratio: 3.5:1). The study was continued for 15 weeks. [8] [4]; seven did not complete the study and were not included in the final analysis.

The primary endpoints of the study were mood and wellbeing. Combination therapy did not significantly affect self-assessed mood as measured by the CES-D scale or the SCL-90 subscales (depression, anxiety, global severity index, positive symptom total, positive symptom distress index) compared to levothyroxine plus placebo ($p > 0.05$ for all measures). [8] Combination therapy did not lead to a greater sense of wellbeing and social functioning as measure by the MOS subscales (physical role, bodily pain, general health, vitality, social functioning, emotional role, mental health, cognitive functioning, mental health index) than levothyroxine plus placebo ($p > 0.05$ for all measures). The authors concluded that the data did not support the routine use of combination therapy in hypothyroid patients with depressive symptoms. [8]

The fourth study, **Clyde et al, 2003**, was a randomised, double-blind, placebo-controlled trial. [9]

Combination therapy was compared with levothyroxine alone in primary hypothyroidism. 46 adult patients with at least a six month history of maintenance treatment with levothyroxine were randomised to one of two groups. Two participants did not complete the study and were not included in the final analysis. The treatment group had their usual maintenance dose of levothyroxine reduced by 50micrograms and was substituted with 7.5microgram of liothyronine taken twice a day. Similarly the control group had their maintenance reduced by 50micrograms and switched to 25microgram twice a day. The ratio by weight of levothyroxine to liothyronine was variable (mean ratio: 5.1:1). The study duration was four months. [9] [4]

The primary endpoints were scores from the hypothyroid specific health related quality of life questionnaire (HRQL) and measures of neurocognitive functioning. HRQL score decreased significantly across in both the control and treatment group ($p < 0.001$ and $p = 0.02$ respectively; higher scores suggest a more negative outcome). The decrease in score was greater in the control group but was not statistically significant ($p = 0.54$). Results of neurocognitive tests were not significantly different between the two groups with one exception. Those in the levothyroxine monotherapy group performed significantly better at the 'Grooved Peg Board' test ($p = 0.03$). The authors concluded that the treatment of hypothyroidism with combination therapy demonstrated no beneficial changes in hypothyroid symptoms or standard measures of cognitive performance. [9]

The fifth and largest study, **Saravanan et al, 2005**, was a randomised, double-blind study. The authors investigated the partial substitution of levothyroxine with liothyronine in patients on levothyroxine replacement therapy. [10] 697 patients were randomised to either treatment or control groups. The control group received their usual maintenance dose of levothyroxine open-label which was reduced by 50microgram and an additional blinded 50microgram tablet was added to treatment. The treatment group received the open-label maintenance dose again reduced by 50microgram and an additional 10microgram liothyronine tablet, indistinguishable from placebo (50microgram levothyroxine), was given. The ratio by weight of levothyroxine to liothyronine was variable (mean ratio: 7.7:1). 611 participants completed the study although all those that were randomised were included in the final analysis. 80 patients withdrew due to experiencing symptoms of either hypothyroidism or hyperthyroidism or both. The study lasted 12months. [10] [4]

The primary endpoints of the study were: QOL, cognition, mood and symptoms of hypothyroidism. At three months, GHQ scores improved in both control and treatment groups compared with baseline ($p < 0.001$ for both groups). The authors concluded that this was demonstration of a marked placebo effect, although improved compliance with medication in the control group may have accounted for the change as intragroup TSH levels fell (0.94 – 0.728mIU/ml, $p < 0.05$). Improvements in psychiatric and anxiety symptoms were also demonstrated in the treatment group at three months ($p = 0.01$ and $p = 0.033$ respectively). At 12 months GHQ scores had risen (worsened, $p = 0.0034$) and there was no significant difference ($p = 0.24$) between treatment and control groups. The authors concluded that the results may be consistent with a subgroup of patient experiencing transient improvement after partial substitution but does not provide conclusive evidence of specific benefit of combination treatment in patients on levothyroxine monotherapy. [10]

The sixth study, Rodriguez et al, 2005, was a randomised, double-blind, two-period, crossover study. [11] The study reviewed the effect of combination therapy (5:1 ratio of levothyroxine to liothyronine by weight) versus monotherapy on fatigue, symptoms of depression and working memory. The aim of the study was to replicate the findings of the 1999 study by Bunevicius et al. [16] 30 adult participants with primary hypothyroidism stabilised on levothyroxine were randomised and 27completed. All 30 were included in the final analysis. One participant withdrew due to an ADR associated with the study drug (the patient was receiving combination treatment; dizziness). The remaining two participants withdrew for reasons unrelated to the study. [11]

The primary endpoints were: fatigue, symptoms of depression and working memory; no significant differences in fatigue, depression and working memory scores were detected between treatment and control groups. [11]

The seventh study, **Appelhof et al, 2005**, was a double-blind, randomised controlled trial. [12] This study explored combination therapy in two ratios versus levothyroxine monotherapy in primary hypothyroidism. 141 adult patients with primary hypothyroidism were randomised to treatment and control groups. The treatment groups receiving a combination of levothyroxine and liothyronine in two ratios: 10:1 and 5:1by weight. Participants had their maintenance dose of levothyroxine reduced by 25microgram and liothyronine commence that provided one of either ratio. The control group received their usual dose of levothyroxine. All groups had their total daily dose administered in divided doses every 12hours (morning before food and night). The combination 10:1, 5:1 and control groups had group sizes of 46, 47 and 48 respectively at the start of the study. [12] 130 participants completed the 15 week study. Seven patients did not complete the study due to ADRs (four in the control group and three across the combination groups).

The primary outcome measure was a 'subjective appreciation' of the study medication rated on a five point scale. All those that withdrew from the study due to side effects were included in the final analysis and were considered not to prefer the study medication compared to their usual treatment. The primary outcome analysis shows that study medication was preferred to usual treatment by 14 patients in the levothyroxine group (29.2%), 19 of 36 patient (41.3%) in the 10:1 ratio group and 24 of 46 patients (52.2%) in the 5:1 ratio group (χ^2 test for trend, $p = 0.024$). The authors stated that the results suggested a linear increase in satisfaction with study medication with an increasing proportion of liothyronine. A secondary endpoint focussed on fatigue, although the result were not significant ($p = 0.55$) and will not be discussed. The authors concluded that decreased bodyweight was associated with satisfaction with study medication compared to control. [12]

The eighth study, Escobar-Morreale et al, 2005, followed a randomised, double-blind, crossover design. [13] Combination therapy was compared with levothyroxine monotherapy. 28 female participants with overt primary hypothyroidism were randomised to treatment and control groups; levothyroxine 75microgram and liothyronine 5microgram once a day versus levothyroxine 100microgram once a day for eight weeks. Participants then crossed over to the alternative treatment arm for another eight weeks. After this initial 16week study period all participants received an add-on treatment with levothyroxine 87.5microgram and liothyronine 7.5microgram for a final 8week period. Resulting in a fixed ratio by weight of 15:1. Two patients did not complete the study, one was receiving levothyroxine alone when withdrawn from the study and the second developed thyrotoxicosis after taking additional medication unrelated to the study. 26 participants were included in the final analysis. [13] [4]

The primary outcome measures were: serum thyroid hormone levels, profile of mood states (POMS), the Digit Symbol Substitution Test, the Digit Span Test, the Visual Scanning Test and patients' preference. The crossover part of the study yielded the following results:

- Compared with levothyroxine monotherapy, serum levels of free T4 decreased by 3.9pmol/L (95% CI, 2.5 – 5.3pmol/L) after combination treatment, whereas serum TSH levels increased slightly by 0.62mU/L (95% CI, 0.01 to 1.23mU/L) and levels of free T3 remained unchanged.
- No improvement after combination treatment was observed in any scale of the POMS, Digit Symbol Substitution Test or the Visual Scanning Test.
- Combination treatment slightly improved the backward and total scores of the Digit Span Test.

The add-on treatment group analysis showed the following:

- Levels of TSH decreased by 0.85mU/L (CI, 0.27 to 1.43mU/L) and levels of free T3 increased by 0.8pmol/L (95% CI, 0.1 – 1.5pmol/L) compared with levothyroxine monotherapy.
- No statistically significant differences were observed for the add-on combination treatment compared with monotherapy in any scale of the POMS and Digit Span Test.
- Compared to monotherapy, participants performed better on the copies score of the Digit Symbol Substitution Test (increase 8.5points [95%CI, 3.0 – 14.0points]) and on the time required to complete the Visual Scanning Test (decrease 10.0seconds [95%CI, 0.9 – 26.0seconds])

At the end of the study, 12 patients preferred combination treatment, six preferred the add-on combination treatment, two preferred standard treatment and six had no preference (χ^2 value, 10.46; p = 0.015). The authors concluded that combination treatment does not offer any objective advantage over levothyroxine monotherapy yet patients prefer combination treatment. [13]

A ninth study, **Valizadeh et al, 2009**, was a double-blind, randomised controlled trial. [14] The study looked at the efficacy of combined therapy compared to monotherapy in primary hypothyroidism. 71 adult patients with primary hypothyroidism that had been maintained on levothyroxine for at least six months were recruited. The treatment group received their usual dose of levothyroxine reduced by 50micrograms and substituted with liothyronine 6.25micrograms twice a day. The control group received their usual dose of levothyroxine which was reduced by 50micrograms and the patient received the equivalent dose at 25microgram twice a day. Participants had a TSH level taken after one month, those that had TSH levels outside the reference range had their T4 dose adjusted to compensate. 60 patients completed the study and were included in the final analysis; 10 patients did not complete the study due to ADRs. The study duration was four months after optimisation of TSH levels. [14]

The primary endpoints of the study were: psychosocial problems, bodyweight, heart rate, BP and serum lipid levels. No significant differences between groups after primary endpoint analysis were reported. The authors concluded that the data does not support the hypothesis that combined therapy improved well-being and general health of patients. [14]

The tenth study, **Nygaard et al, 2009**, was a double-blind, randomised, crossover trial. [17] The study concentrated on the effect of combination therapy versus levothyroxine monotherapy. 68 adult patients under the care of an endocrinology clinic and maintained on levothyroxine for at least six months were enrolled in the study. On entry to the study participants' levothyroxine dose was reduced by 50micrograms. Participants that entered the control group received 50microgram levothyroxine blinded. The ratio by weight of levothyroxine to liothyronine was variable (mean ratio: 3.85:1). The treatment group received 20microgram of liothyronine. The first phase of the study lasted 12 weeks at which point the groups were switched for a further 12 weeks. Of the 68 randomised to treatment, 59 completed the study and were included in the final analysis. The participants that withdrew did so for reasons not directly related to use of the study treatment. [17] Levothyroxine dose was decreased in some patients due to declining TSH levels; Ten patients had their open label levothyroxine dose reduced (seven in the combination groups and three in monotherapy groups). The levothyroxine dose was adjusted in order to achieve a stable TSH between treatment and control groups. [17] [4]

It was unclear what the primary endpoints of the study were; the study had multiple endpoints. The most prominent endpoints were: QOL and depression, preferred treatment and changes in thyroid function. The authors reported that, when comparing scores of QOL and depression on monotherapy versus combination groups, significant differences were seen in 7 out of 11 scores. The authors concluded that this indicated a positive effect relating to use of combination therapy. The 7 scores were: general health (p = 0.01), social functioning (p = 0.02), vitality (p = 0.02) depression (p = 0.01), anxiety (p= 0.01), GSI (Global Severity Index; p = 0.01) and PST (Positive Symptoms Total; p = 0.02). There was also a significant effect on quality of life and depression

scores between baseline and control group data, 10 out of 11 parameters indicated a positive change. [17] 49% of participants preferred combination treatment versus 15% preferring monotherapy; those that preferred combination treatment had higher depression scores at baseline than patients without preference (35%). No correlation between biochemical markers (T4, T3 and TSH) and changes in QOL and depression scores or patient preference were found. [17] The authors concluded that where morning TSH levels were constant between groups, combination therapy was superior to monotherapy when evaluating QOL and depression scores and patient preference. [17]

The eleventh study, Fadeyev et al, 2010, was a randomised controlled trial investigating combination therapy versus monotherapy in the treatment of primary hypothyroidism. [15] 36 premenopausal women with overt, untreated, primary hypothyroidism were enrolled in the study. The patients were allocated to a treatment or control group. The control group received levothyroxine at the dose 1.6microgram/kg/day. The treatment group received that same daily dose as the control group reduced by 25micrograms and substituted with 12.5micrograms of liothyronine. The treatment period lasted for six months. All participants completed the study. [15]

Primary endpoints were not clear. Prominent endpoints included: TSH levels, serum lipid profile and bone mineral density (DEXA scan) scan results. TSH levels were elevated in all patients at baseline, after six months of study medication there was no significant clinical difference in TSH levels between treatment and control groups. Total cholesterol levels were lower in in the treatment group compared to control (median 5.7 versus 4.6 respectively; $p < 0.05$). There was no significant difference in bone mineral density between the groups at six months, although urine deoxypyridinoline (a measure of bone resorption) was significantly elevated after combined therapy ($p < 0.05$). The authors concluded the combination therapy shows favourable changes in serum lipid profile but higher activation of bone resorption. [15]

Meta-Analyses and Systematic Reviews

One meta-analysis was identified, **Grozainsky-Glasberg et al, 2006**, investigating the use of combined treatment versus monotherapy for clinical hypothyroidism. [18] 11 randomised trials of 1,216 patients were included comparing the effectiveness of combination treatment and monotherapy for the treatment of clinical hypothyroidism in adults. The authors found no difference in the effectiveness of combination treatment versus monotherapy in any of the following symptoms: bodily pain, depression, anxiety, fatigue, QOL, bodyweight and serum lipid profile. The authors also stated that adverse effects did not differ between regimens. [18] The authors concluded that levothyroxine should remain the treatment of choice for patients with clinical hypothyroidism.

Table 1 Summary of RCT data. * Potential risk of bias grading derived from RCT summary table (see below).

Reference	Title	Primary endpoints	Potential risk of bias*	Evidence indicates a positive effect of combined treatment
[9]	Bunevicius et al, "Effects of Thyroxine as Compared with Thyroxine plus Triiodothyronine in Patients with Hypothyroidism," *The New England Journal of Medicine* , vol. 340, pp. 424 - 429, 1999.	Not clear. Prominent endpoints included: physiological and psychological measure were reported.	Medium	Yes
[10]	Walsh et al, "Combined Thyroxine/Liothyronine Treatment Does Not Improve Well-being, Quality of Life, or Cognitive Function Compared to Thyroxine Alone: A Randomised Controlled Trial in Patients with Primary Hypothyroidism," *The Journal of Clinical Endocrinology and Metabolism,* vol. 88, no. 10, pp. 4543-4550, 2003.	QOL and cognitive function.	Low	No
[11]	Sawka et al, "Does a Combination Regimen of Thyroxine (T4) and 3,5,3-Triiodothyronine Improve Depressive Symptoms Better than T4 Alone in Patients with Hypothyroidism? Results of a Double-Blind, Randomised, Controlled Trial.," *The Journal of Clinical Endocrinology and Metabolism,* vol. 88, no. 10, pp. 4551 - 4555, 2003.	Mood and wellbeing.	Medium	No
[12]	Clyde et al., "Combined Levothyroxine Plus Liothyronine Compared With Levothyroxine Alone in Primary Hypothyroidism A Randomised Controlled Trial," *Journal of the American Medical Association,* vol. 290, no. 22, pp. 2952 - 2958, 2003.	HRQL questionnaire and neurocognitive functioning.	Low	No
[13]	Saravanan et al. , "Partial Substitution of Thyroxine (T4) with Tri-Iodothyronine in Patients on T4 Replacement Therapy: Results of a Large Community-Based Randomised Controlled Trial.," The Journal of Clinical Endocrinology & Metabolism. , vol. 90, no. 2, pp. 805 - 812, 2005.	QOL, cognition, mood and symptoms of hypothyroidism.	Low	No
[14]	Rodriguez et al. , "Substitution of Liothyronine at a 1:5 Ratio for a Portion of Levothyroxine: Effect on Fatigue, Symptoms of Depression and Working Memory Versus Treatment with Levothyroxine Alone.," *Endocrine Practice,* vol. 11, no. 4, pp. 223 - 233 , 2005.	Fatigue, symptoms of depression and working memory.	Low	No
[15]	Appelhof et al., "Combined Therapy with Levothyroxine and Liothyronine in Two Ratios, Compared with Levothyroxine Monotherapy in Primary Hypothyroidism: a Double-Blind, Randomised, Controlled Clinical Trial.," *The Journal of Clinical Endocrinology & Metabolism* , vol. 90, no. 5, pp. 2666 - 2674, 2005.	Subjective appreciation of the study medication.	Low	Unclear. Author stated that satisfaction with study medication compared to control was related to decreased body weight.
[16]	Escobar-Morreale et al., "Thyroid Hormone Replacement Therapy in Primary Hypothyroidism: A Randomised Trial Comparing L-Thyroxine plus Liothyronine with L-Thyroxine Alone.," *Annals of Internal Medicine,* vol. 142, pp. 412-424, 2005.	serum thyroid hormone levels, profile of mood states (POMS), the Digit Symbol Substitution Test, the Digit Span Test, the Visual Scanning Test and patients' preference	Low	No
[17]	Valizadeh et al. , "Efficacy of Combined Levothyroxine and Liothyronine as Compared with Levothyroxine Monotherapy in Primary Hypothyroidism: A Randomised Controlled Trial.," *Endocrine Research,* vol. 34, no. 3, pp. 80-89, 2009.	Psychosocial problems, bodyweight, heart rate, BP and serum lipid levels.	Low/Medium	No
[18]	Nygaard et al. , "Effect of combination therapy with thyroxine (T4) and 3,5,3'-triiodothyronine versus T4 monotherapy in patients with hypothyroidism, a double-blind, randomised cross-over study," *European Journal of Clinical Endocrinology* , vol. 161, pp. 895-902, 2009.	Not clear. prominent endpoints included: QOL and depression, preferred treatment and changes in thyroid function.	Low	Yes. Improved QOL and depression scores compared to monotherapy if morning TSH levels remained constant
[19]	Fadeyev et al. , "Combined therapy with L-Thyroxine and L-Triiodothyronine compared to L-Thyroxine alone in the treatment of primary hypothyroidism," *Hormones* , vol. 9, no. 3, pp. 245-252, 2010.	Not clear. prominent endpoints included: TSH levels, serum lipid profile and bone mineral density.	Medium	No. Favourable changes in serum lipid profile but higher activation of bone resorption.

Other efficacy data:

There are two randomised controlled trials that investigate the bioequivalence of levothyroxine and liothyronine.

The first, Celi et al, 2010, was a randomised, double-blind, crossover trial. [25] The study focussed on the pharmacodynamic equivalence levothyroxine and liothyronine. 14 patients with a previous history of thyroidectomy were enrolled in to the study. Four patients withdrew from the study, three because of poor compliance with the study regimen. Control group participants received their usual dose of levothyroxine in three divided doses. Treatment group participants received half the calculated equivalent dose of levothyroxine as liothyronine. Half the dose was given initially to avoid hyperthyroidism. Liothyronine was then increased to achieve a TSH level of ≤ 1.0mU/L. The levothyroxine regimen was also 'adjusted' using a placebo when in fact the patient received a constant dose throughout. The study lasted at least 30 days. [25] The authors concluded that therapeutic substitution of liothyronine for levothyroxine was achieved at approximately 1:3 ratio. [25]

The second, Celi et al, 2011, was a double-blind, crossover trial that was an extension of the 2010 study by the same author. [26] The authors investigated the metabolic effects of liothyronine in hypothyroidism. 18 patients were randomised to treatment and 14 completed the study and were included in the final analysis. The first ten patients were discussed as part of the 2010 article. [26] Participants received either levothyroxine or liothyronine three times a day to achieve a target TSH form 0.5 – 1.5mU/L. The study lasted for six weeks. No difference was observed between TSH in treatment and control groups. The authors concluded that the substitution of liothyronine for levothyroxine at physiological doses reduced body weight and resulted in greater thyroid hormone action on lipid metabolism. [26]

Summary of safety data:

The Summary of Product Characteristics (SPC) for liothyronine lists side effects which are dose related. Patients that are receiving an excessive dose will experience side effects related to the drug itself. The SPC states that side effects would usually disappear on reduction of the dosage or withdrawal of treatment for a day or two. These side effects are: anginal pain, cardiac arrhythmias, palpitations, muscle cramps, tachycardia, diarrhoea, restlessness, excitability, headache, flushing, sweating, excessive loss of weight and muscular weakness, vomiting, tremor, insomnia, fever, heat intolerance, transient hair loss in children, hypersensitivity reactions including rash, pruritus and oedema also reported. [20] The SPC for levothyroxine has the same side effect profile as liothyronine with the following additions: angioedema, eosinophilia, liver dysfunction, nervousness, mania, menstrual irregularities. [19]

Six of the RCTs discussed comparing standard monotherapy and combination therapy (at different ratios) reported no significant side effects or differences in the side effects experienced by participants of control or treatment groups. [17] [18] [13] [12] [8] [7]

The two published studies comparing the bioequivalence of levothyroxine and liothyronine also reported no serious ADRs or significant side effects. The one exception being a case of general anxiety disorder reported in the 2011 study in a participant receiving levothyroxine. [25] [9]

Four of the RCTs comparing standard monotherapy and combination therapy (at different ratios) did report differences in side effects between control and treatment groups.

Fadeyev et al, 2010, concluded that combination treatment resulted in higher activation of bone resorption. [15] Valizadeh et al, 2009, described four patients that withdrew due to developing palpitations. 36 participants were randomised to the treatment group; 11% of the study population developed palpitations. [14] Saravanan et al, 2005, of 697 participants that were randomised to treatment, 109 taking combination treatment withdrew for the following reasons:

- 41% (11/27) experienced symptoms of hyperthyroidism,
- 64% (30/47) experienced symptoms of hypothyroidism and
- 50% (3/6) experienced symptoms of both hypo- and hyperthyroidism [10]

Rodriguez et al, 2005, stated the side effects were comparable between control (levothyroxine monotherapy) and treatment (combination therapy) groups except for the following symptoms: headache, difficulty sleeping and muscle weakness. The prevalence of these side effects was reported as being 10% higher in the treatment group. [11]

Strengths and limitations of the evidence:

Limitations

1. RCT treatment groups were small in some studies, with uncertainties about the studies being adequately powered.
2. Use of non-physiological ratios of levothyroxine and liothyronine (less than 13:1).
3. Dosing regimen of liothyronine in combined treatment groups may not always reflect typical liothyronine dosing regimens i.e. once a day compared to twice a day or three times a day as recommended. [23]
4. Some studies switched levothyroxine once daily dosing to partial twice daily dosing (i.e. 50micrograms of the maintenance dose given once a day switched to 25micrograms twice a day) the pharmacokinetic and subsequent pharmacodynamics consequences of doing this have not been mitigated in the studies reviewed.
5. Some of the studies randomised participants that had overt, untreated hypothyroidism whereas the remainder used participants that had previously been maintained on levothyroxine. Unsure what the physiological impact on results may have been due to this difference in study populations.

Strengths

1. Availability of 12 RCTs and one meta-analysis.
2. Two recent guidance articles published by recognised bodies. [3] [4]

Summary of evidence on cost effectiveness:

No cost-effectiveness analysis were identified. The evidence does not support the superiority of a physiologically comparable combination of levothyroxine and liothyronine over levothyroxine monotherapy for patients that remain symptomatic despite adequate replacement with levothyroxine. The prevalence of side effects and ADRs does not appear to be significantly higher when treated with combination therapy compared to monotherapy.

Cost-Minimisation Analysis (CMA)

A cost-minimisation analysis is completed where the outcome of the treatments being compared is the same. The least-costly option should be chosen. [27]

- Cost of maximal treatment with levothyroxine and additional liothyronine therapy at the ratio 13:1 (levothyroxine 200microgram o.d. and liothyronine 7.5microgram b.d.) for one year = £1984.58
- Cost of maximal treatment with levothyroxine as a monotherapy (levothyroxine 200microgram o.d.) for one year = £48.10
- Difference in cost is calculated using the above figures as follows: £1984.58 – £48.10 = £1936.48 additional cost per patient per year.

Based on the available evidence and CMA levothyroxine monotherapy should be used in preference to combination therapy for the population of patients with refractory hypothyroidism despite adequate replacement with levothyroxine.

Prescribing and risk management issues:

Additional TSH levels would likely to be required if combination therapy was recommended to be used routinely. Liothyronine is subject to supply issues. Not all liothyronine containing products are licensed in the UK; brands without a UK licence may not be bioequivalent. [23]

Commissioning considerations

Comparative unit costs

Drug	Example regimen	Pack cost	Cost per patient per course/ per year (ex VAT)
Levothyroxine + Liothyronine (13:1 ratio) [4]	Levothyroxine 200microgram o.d. and liothyronine 7.5microgram b.d.	Levothyroxine 100microgram x 28 = £1.85 Liothyronine 20microgram x 28 = £198.62	£1984.58
Levothyroxine + Liothyronine (13:1 ratio)	Levothyroxine 100microgram o.d. and liothyronine 3.75microgram b.d.	Levothyroxine 100microgram x 28 = £1.85 Liothyronine 20microgram x 28 = £198.62	£992.29
Levothyroxine + Liothyronine (20:1 ratio) [4]	Levothyroxine 200microgram o.d. and liothyronine 5microgram b.d.	Levothyroxine 100microgram x 28 = £1.85 Liothyronine 20microgram x 28 = £198.62	£1339.13
Levothyroxine + Liothyronine (20:1 ratio)	Levothyroxine 100microgram o.d. and liothyronine 2.5microgram b.d.	Levothyroxine 100microgram x 28 = £1.85 Liothyronine 20microgram x 28 = £198.62	£669.57
Levothyroxine (monotherapy)	Levothyroxine 200microgram o.d.	Levothyroxine 100microgram x 28 = £1.85	£48.10

Drug	Example regimen	Pack cost	Cost per patient per course/ per year (ex VAT)
Levothyroxine (monotherapy)	Levothyroxine 150microrgam o.d.	Levothyroxine 100microgram x 28 = £1.85 Levothyroxine 50microgram x 28 = £1.84	£47.97
Levothyroxine (monotherapy)	Levothyroxine 100microgram o.d.	Levothyroxine 100microgram x 28 = £1.85	£24.05
Levothyroxine (monotherapy)	Levothyroxine 50microgram o.d.	Levothyroxine 50microgram x 28 = £1.84	£23.92
Costs based on MIMS list prices 17/03/2016 [21] This table does not imply therapeutic equivalence of drugs or doses.			

Associated additional costs or available discounts:

All patients with refractory hypothyroidism would need an initial review by a specialist endocrinologist. Combination therapy should only be commenced and monitored by an endocrinologist. [3] [5] [4]

Productivity, service delivery, implementation:

There is a potential for significant additional demand from primary care on endocrinology outpatient clinics and associated time required for review by a specialist endocrinologist. Tariff price for an initial outpatient consultation with an endocrinologist = £187. Tariff price for a follow up appointment = £93. [28]

Additional biochemical monitoring may be required; TSH level monitoring may increase until patients are stabilised.

Additional demands on primary care appointments as there is a potential for patients receiving liothyronine to experience subclinical hyperthyroidism with associated weight loss.

Liothyronine is not licensed for use in combination with levothyroxine therefore such use would be 'off-label'.

Anticipated patient numbers and net budget impact:

Prevalence of patients with refractory hypothyroidism despite adequate replacement with levothyroxine is between 5 and 10% of patients receiving levothyroxine monotherapy. [4]

Using ePACT data, the estimated number of patients with hypothyroidism from all causes across Lancashire = 85,000 (5.9% of the population)

Estimated number of patients across Lancashire with refractory hypothyroidism = 4,250 - 8,500

Additional liothyronine cost incurred for one patient to receive combination therapy = £669.57 - £1936.48

Additional potential non-drug, endocrinology consultation costs incurred for one patient to receive combination therapy in first year of treatment assuming initial consultation plus one additional follow up consultation = £280.00

Total cost per patient in first year of treatment = £949.57 - £2,186.48

Potential cost pressure if all patients in Lancashire with refractory hypothyroidism received combination therapy in one year = £4,035,672.50 - £18,840,080.

Innovation, need, equity:

Liothyronine is not an innovative, new drug.

5 – 10% of patients with hypothyroidism that receive an adequate dose of levothyroxine may still be symptomatic. Combination therapy offers little or no advantage over current treatment options. Prescribing of combination therapy for patients with refractory hypothyroidism would be a significant cost pressures for the Lancashire health economy.

Combination therapy is not routinely offered in other regions.

References

[1] ADVANZ Pharma, "Liothyronine Sodium BP 20micrograms Tablets," Datapharm, 8th October 2019. [Online]. Available: https://www.medicines.org.uk/emc/product/5905/smpc. [Accessed 16th October 2019].

[2] Vaidya et al, "Management of hypothyroidism in adults," *The British Medical Journal,* vol. 337, no. a801, pp. 284-289, 2008.

[3] Okosieme et al., "Management of primary hypothyroidism: statement by the British Thyroid Association Executive Committee," *Clinical Endocrinology ,* vol. 0, pp. 1 - 10, 2015.

[4] Wiersinga et al. , "2012 ETA Guidelines: The Use of L-T4 + L-T3 in the Treatment of Hypothyroidism," *European Thyroid Jounrnal,* vol. 1, pp. 55-71, 2012.

[5] The Royal College of Physicians, "The Diagnosis and Management of Primary Hypothyroidism," Royal College of Physicians, London, 2009.

[6] National Institute for Health and Care Excellence, "Clinical Knowledge Summary: Hypothyroidism," National Institute for Health and Care Excellence, February 2011. [Online]. Available: http://cks.nice.org.uk/hypothyroidism#!scenariorecommendation:3. [Accessed 30 March 2016].

[7] Walsh et al, "Combined Thyroxine/Liothyronine Treatment Does Not Improve Well-being, Quality of Life, or Cognitive Function Compared to Thyroxine Alone: A Randomised Controlled Trial in Patients with Primary Hypothyroidism," *The Journal of Clinical Endocrinology and Metabolism,* vol. 88, no. 10, pp. 4543-4550, 2003.

[8] Sawka et al, "Does a Combination Regimen of Thyroxine (T4) and 3,5,3-Triiodothyronine Improve Depressive Symptoms Better than T4 Alone in Patients with Hypothyroidism? Results of a Double-Blind, Randomised, Controlled Trial.," *The Journal of Clinical Endocrinology and Metabolism,* vol. 88, no. 10, pp. 4551 - 4555, 2003.

[9] Clyde et al., “Combined Levothyroxine Plus Liothyronine Compared With Levothyroxine Alone in Primary Hypothyroidism A Randomised Controlled Trial,” *Journal of the American Medical Association,* vol. 290, no. 22, pp. 2952 - 2958, 2003.

[10] Saravanan et al. , “Partial Substitution of Thyroxine (T4) with Tri-Iodothyronine in Patients on T4 Replacement Therapy: Results of a Large Community-Based Randomised Controlled Trial.,” *The Journal of Clinical Endocrinology & Metabolism. ,* vol. 90, no. 2, pp. 805 - 812, 2005.

[11] Rodriguez et al. , “Substitution of Liothyronine at a 1:5 Ratio for a Portion of Levothyroxine: Effect on Fatigue, Symptoms of Depression and Working Memory Versus Treatment with Levothyroxine Alone.,” *Endocrine Practice,* vol. 11, no. 4, pp. 223 - 233 , 2005.

[12] Appelhof et al., “Combined Therapy with Levothyoxine and Liothyronine in Two Ratios, Compared with Levothyroxine Monotherapy in Primary Hypothyroidism: a Double-Blind, Randomised, Controlled Clinical Trial.,” *The Journal of Clinical Endocrinology & Metabolism ,* vol. 90, no. 5, pp. 2666 - 2674, 2005.

[13] Escobar-Morreale et al., “Thyroid Hormone Replacement Therapy in Primary Hypothyroidism: A Randomised Trial Comparing L-Thyroxine plus Liothyronine with L-Thyroxine Alone.,” *Annals of Internal Medicine,* vol. 142, pp. 412-424, 2005.

[14] Valizadeh et al. , “Efficacy of Combined Levothyroxine and Liothyronine as Compared with Levothyroxine Monotherapy in Primary Hypothyroidism: A Randomised Controlled Trial.,” *Endocrine Research,* vol. 34, no. 3, pp. 80-89, 2009.

[15] Fadeyev et al. , “Combined therapy with L-Thyroxine and L-Triiodothyronine compared to L-Thyroxine alone in the treatment of primary hypothyroidism,” *Hormones ,* vol. 9, no. 3, pp. 245-252, 2010.

[16] Bunevicius et al, “Effects of Thyroxine as Compared with Thyroxine plus Triiodothyronine in Patients with Hypothyroidism,” *The New England Journal of Medicine ,* vol. 340, pp. 424 - 429, 1999.

[17] Nygaard et al. , “Effect of combination therapy with thyroxine (T4) and 3,5,3'-triiodothyronine versus T4 monotherapy in patients with hypothyroidism, a double-blind, randomised cross-over study,” *European Journal of Clinical Endocrinology ,* vol. 161, pp. 895-902, 2009.

[18] Grozinsky-Glasberg et al , “Thyroxine-Triiodothyronine Combination Therapy Versus Thyroxine Monotherapy for Clinical HYpothyroidism: Meta-Analysis of Randomised Controlled Trials.,” *The Journal of Clinical Endocrinology and Metabolism ,* vol. 91, no. 7, pp. 2592 - 2599, 2006.

[19] Electronic Medicines Compendium, “Summary of Product Characteristics - Levothyroxine 25microgram tablets - Wockhardt UK Ltd,” 16 October 2015. [Online]. Available: www.emc.medicines.org.uk. [Accessed 10 March 2016].

[20] Electronic Medicines Compendium, “Summary of Product Characteristics - Liothyronine 20microgram

Tablets - Amdipharm Mercury Company Limited," 2014.

[21] Chloe Harman, MIMS, London: Haymarket Medical Media, 2016.

[22] M. Vanderpump, "The epidemiology of thyroid disease," *British Medical Bulletin,* vol. 99, no. 1, pp. 39-51, 2011.

[23] Royal Pharmaceutical Society, British National Formulary, vol. 70, London: Pharmaceutical Press, 2016.

[24] B. Katzung, Basic and Clinical Pharmacology, 11th Edition, New York : McGraw Hill Professional, 2009.

[25] Celi et al. , "The pharmacodynamic equivalence of levothyroxine and liothyronine. A randomised, double-blind, cross-over study in thyroidectomised patients," *Clinical Endocrinology,* vol. 72, no. 5, pp. 709-715, 2010.

[26] Celi et al. , "Metabolic Effects of Liothyronine Therpay in Hypothyroidism: A Randomised, Double-Blind, Crossover Trial of Liothyronine Versus Levothyroxine," *Journal of Endocrinology and Metabolism,* vol. 96, no. 11, pp. 3466-3474, 2011.

[27] Elliott et al, Essentials of Economic Evaluation in Healthcare, London: Pharmaceutical Press, 2004.

[28] NHS England, "2014/15 National Tariff Payment System: Annex 5A: National prices," NHS England, Leeds, 2014/15.

[29] Ferretti et al, "Evaluation of the Adequacy of Levothyroxine Replacemnet Therapy in Patients with Central Hypothyroidism.," *The Journal of Clinical Endocrinology and Metabolism,* vol. 84, pp. 924 - 929, 1999.

[30] Baisier et al, "Thyroid Insufficiency. Is Thyroxine the Only Valuable Drug?," *Journal of Nutritional and Environmental Mediicne,* vol. 11, pp. 159 - 166, 2001.

Table: Summary of key liothyronine combination RCTs relevant to use in refractory hypothyroidism

Reference	Trial design	Patients / subjects	Trial intervention and comparison	Outcomes: Primary endpoint (mITT)	Outcomes: Key secondary / exploratory endpoints	Grading of evidence / risk of bias
Bunevicius et al, "Effects of Thyroxine as Compared with Thyroxine plus Triiodothyronine in Patients with Hypothyroidism," The New England Journal of Medicine, vol. 340, pp. 424 - 429, 1999 [16]	Randomised controlled trial – double-blind, placebo-controlled, crossover design.	35 patients were enrolled, 33 completed the study. Sixteen patients had chronic autoimmune thyroiditis and 17 had thyroid cancer. One patient withdrew due to pregnancy and another patient withdrew due to anxiety.	Patients took their usual dose of levothyroxine on the first day of the study. Each patient was randomised to receive the usual dose of levothyroxine for 5/52 then levothyroxine plus liothyronine for 5/52 or visa-versa. Levothyroxine was given as 50microgram tablets for each patient's usual dose. Although 50microgram of the levothyroxine dose was replaced by a capsule. The capsule either contained 50microgram levothyroxine or 12.5microgram or liothyronine.	Not clear in method. Endpoints included: biochemical measurements, physiological and psychological assessments. Main outcomes reported in conclusion were improvements in mood and neuropsychological function.	Serum T3 and T4, serum cholesterol, pulse rate and BP, cognitive performance and mood scores.	Patient-oriented outcome measure? Yes. Allocation concealment? Yes Blinded if possible? Yes Intention to treat analysis? No Adequate power/size? No sample size calculation or power of sample size discussed. Adequate follow-up (>80%)? Yes, 33 out of 35 completed the study (94.3%). Level 2 evidence based on sample size and medium risk of bias. Risk of bias: medium. Base on the above.

Walsh et al, "Combined Thyroxine/Liothyronine Treatment Does Not Improve Well-being, Quality of Life, or Cognitive Function Compared to Thyroxine Alone: A Randomised Controlled Trial in Patients with Primary Hypothyroidism," The Journal of Clinical Endocrinology and Metabolism, vol. 88, no. 10, pp. 4543-4550, 2003. [7]	Randomised controlled trial – double-blind, randomised, crossover design.	110 adult patients with primary hypothyroidism were randomised to two treatment groups. Of the 110 enrolled, 101 completed the study.	At study entry, patients reduced their daily T4 dose by 50microgram and took the study medication (either levothyroxine 50microgram or liothyronine 10microgram) in addition to their reduced levothyroxine dose.	Well-being, QOL or cognitive function.	QOL scores, thyroid symptoms questionnaire, subjective satisfaction with treatment.	Patient-oriented outcome measure? Yes. Allocation concealment? No. Randomised in permuted block of 10 using sealed envelopes. Blinded if possible? Yes. Intention to treat analysis? Unsure if all patients that were randomised were included in the final analysis. Adequate power/size? Yes. Power was set at 80% and required sample size was 100. 110 were recruited to allow for withdrawals. Adequate follow-up (>80%)? Yes. 92% completed the study. Level 1 evidence based on adequate sized RCT with low risk of bias. Low risk of bias.

Sawka et al, "Does a Combination Regimen of Thyroxine (T4) and 3,5,3-Triiodothyronine Improve Depressive Symptoms Better than T4 Alone in Patients with Hypothyroidism? Results of a Double-Blind, Randomised, Controlled Trial," The Journal of Clinical Endocrinology and Metabolism, vol. 88, no. 10, pp. 4551 - 4555 [8]	Randomised controlled trial – double-blind, placebo-controlled.	40 adult patients were randomised to treatment groups. Seven did not complete the study.	Patient receiving T4 had their pre-study dose continued but also received a placebo b.d. those in the combination had their pre-study T4 dose reduced by 50% and T3 commenced 12.5micrograms b.d.	Mood and wellbeing scores	Symptom check-list (SCL-90), self-reported questionnaire, epidemiological screens for depression.	Patient-oriented outcome measure? Yes Allocation concealment? No, the method of randomisation was disclosed. Blinded if possible? Yes. Intention to treat analysis? Yes, ITT analysis stated that all individuals randomised would be included in the final analysis regardless of concordance. Not all patients that were randomised were included in the full analysis of results (7 in total across both groups). Adequate power/size? Sample size calculations and power were not discussed. Adequate follow-up (>80%)? 33/40 (82.5%) Level 1 evidence. Medium risk of bias no sample size calculations and power are not discussed.

Clyde et al., "Combined Levothyroxine Plus Liothyronine Compared With Levothyroxine Alone in Primary Hypothyroidism A Randomised Controlled Trial," Journal of the American Medical Association, vol. 290, no. 22, pp. 2952 - 2958, 2003. [9]	Randomised controlled trial – randomised, double-blind, placebo-controlled.	46 adult patients with at least a six month history of treatment with levothyroxine for primary hypothyroidism. Two participants that were randomised withdrew (one in each treatment group). They were not included in the final analysis.	The usual dose of levothyroxine or combination therapy: Usual levothyroxine dose was reduced by 50microgram and substituted with 7.5microgram liothyronine taken b.d. for 4/12.	Hypothyroid specific health related quality of life questionnaire (HRQL).	Body weight, serum lipid levels and 13 neuropsychological tests.	Patient-oriented outcome measure? Yes Allocation concealment? No. The method of randomisation was disclosed. Blinded if possible? Yes. Intention to treat analysis? Not obvious but of the 46 randomised, 44 were analysed. Adequate power/size? Power and sample sizes were discussed. Sample size calculations were not given but the authors stated that a sample size of 12 would detect a significant difference with 90% power between test and control groups on one aspect of the primary outcome measure. Adequate follow-up (>80%)? 44/46 (95.7%) Level 1 evidence based on the above criteria. Low risk of bias. Low risk of bias.

Saravanan et al. , "Partial Substitution of Thyroxine (T4) with Tri-Iodothyronine in Patients on T4 Replacement Therapy: Results of a Large Community-Based Randomised Controlled Trial.," The Journal of Clinical Endocrinology & Metabolism. , vol. 90, no. 2, pp. 805 - 812, 2005. [10]	Randomised controlled trial – double-blind.	697 adult patients with hypothyroidism were randomised to treatment. 611 were followed up at the conclusion of the trial; 573 were still receiving study medication.	The control group received their maintenance dose of levothyroxine open-label reduced by 50microgram and an additional blinded 50microgram tablets added to treatment. The treatment group received open-label maintenance dose reduced by 50microgram and an additional 10microgram liothyronine tablets indistinguishable from placebo (50microgram levothyroxine) given.	QOL, cognition, mood and symptoms of hypothyroidism.	Physical and biochemical measurements.	Patient-oriented outcome measure? Yes. Allocation concealment? No, method of randomisation disclosed. Blinded if possible? Yes. Intention to treat analysis? Yes. All those randomised were included in the final analysis – results adjusted and extrapolated if lost to follow up. Adequate power/size? Sample size give 80% power when detecting 0.7 differences on GHQ-12 Likert scale. Adequate follow-up (>80%)? 611/697 (87.7%) Level 1 evidence based on large group size and low risk of bias. Low risk of bias.

Rodriguez et al. , "Substitution of Liothyronine at a 1:5 Ratio for a Portion of Levothyroxine: Effect on Fatigue, Symptoms of Depression and Working Memory Versus Treatment with Levothyroxine Alone.," Endocrine Practice, vol. 11, no. 4, pp. 223 - 233 , 2005. [11]	Randomised controlled trial – double-blind, crossover design.	30 adult patients were randomised to treatment and 27 completed. All those that were randomised were included in the final analysis. One participant withdrew due to an ADR potentially due to the study medication. The other two participants withdrew for reasons unrelated to the study.	Levothyroxine maintenance dose plus placebo containing *Lactobacillus acidophilus* versus maintenance dose reduced by 50micrograms in one capsule and liothyronine 10micograms in a second. The subject received one of either treatment for 6/52 and then crossed over to receive the other treatment.	Fatigue, symptoms of depression and working memory.	Biometric variables and symptoms of hypothyroidism.	Patient-oriented outcome measure? Yes Allocation concealment? No. pharmacy computer system randomly assigned participants to study groups. Blinded if possible? Yes. Intention to treat analysis? Yes. All those that were randomised to treatment were included in the final analysis. Adequate power/size? Sample size analysis was conducted after 11 participants had completed the study. A sample size of 30 was chosen to provide a power of >0.99 to detect small incremental effects on measure of fatigue. Adequate follow-up (>80%)? 27/30 completed the study (90%) all were included in the final analysis. Level 1/2 evidence based on sample size, although power for detecting changes in fatigue are high. Low risk of bias.

Appelhof et al., "Combined Therapy with Levothyroxine and Liothyronine in Two Ratios, Compared with Levothyroxine Monotherapy in Primary Hypothyroidism: a Double-Blind, Randomised, Controlled Clinical Trial.," The Journal of Clinical Endocrinology & Metabolism , vol. 90, no. 5, pp. 2666 - 2674, 2005. [12]	Randomised controlled trial – double-blind	141 patients with primary autoimmune hypothyroidism were randomised. 130 completed the 15 week study. Seven patients discontinued due to ADRs (four in the T4 group and three in the combination group.	Treatment groups: Levothyroxine, levothyroxine and liothyronine (10:1) and levothyroxine and liothyronine (5:1). Group sizes were: 48, 46 and 47 respectively.	The primary outcome measure was subjective appreciation of the study medication rated on a 5 point scale.	Questionnaires including: mood states, multidimensional fatigue inventory, mental health and vitality subscales of the Rand-36 health survey and symptom checklist SCL-90.	Patient-oriented outcome measure? Yes. Allocation concealment? No, computer-generated list. For every six patients two were assigned to a treatment arm. Blinded if possible? Yes. Intention to treat analysis? Not all that were randomised were included in the final analysis. However, all those that withdrew due to ADRs were included in the final analysis (counted as not preferring the study medication). Last observations were carried forward where observations did not exist these were omitted from the final analysis. Adequate power/size? Sample size calculations and power were not discussed. Adequate follow-up (>80%)? 130/141 (92%) completed the study. Level 1/2 evidence – power of sample size was not discussed although low risk of bias. Low risk of bias.

Escobar-Morreale et al., "Thyroid Hormone Replacement Therapy in Primary Hypothyroidism: A Randomised Trial Comparing L-Thyroxine plus Liothyronine with L-Thyroxine Alone.," Annals of Internal Medicine, vol. 142, pp. 412-424, 2005. [13]	Randomised controlled trial – randomised, double-blind crossover trial.	28 female participants with over primary hypothyroidism. Two participants did not complete the study.	Levothyroxine 100micrgram/day vs. levothyroxine 75microgram and liothyronine 5microgram/day for 8/52. All patients the crossover to the alternative study group for 8/52. An add-on period where all participants received 87.5microgram of levothyroxine and 7.5microgram of liothyronine for 8/52 was completed after the initial two 8/52 periods.	Primary outcomes were: serum thyroid hormone levels, profile of mood states, the digit symbol substitution test, digital span test, the visual scanning test and patient's preference.	QOL and psychometric function and multiple biological thyroid hormone end-points were studied as secondary outcomes.	Patient-oriented outcome measure? Partially. Some biochemical primary outcomes. Allocation concealment? No. The method of randomisation was disclosed. Blinded if possible? Yes. Intention to treat analysis? 28 patients were recruited into the study. No obvious ITT analysis. Two did not complete the study. Adequate power/size? No sample size calculations were discussed. However, the authors stated that the sample gave 80% power. Adequate follow-up (>80%)? 26/28 (93%). Level 1/2 evidence – small sample size but low risk of bias. Low risk of bias.

Valizadeh et al. , "Efficacy of Combined Levothyroxine and Liothyronine as Compared with Levothyroxine Monotherapy in Primary Hypothyroidism: A Randomised Controlled Trial.," Endocrine Research, vol. 34, no. 3, pp. 80-89, 2009. [14]	Randomised controlled trial – double-blind	71 adult patients with primary hypothyroidism maintained on levothyroxine for at least six months were recruited. 60 patients completed.	Two treatment groups: usual treatment dose of levothyroxine vs. combination (usual treatment dose of levothyroxine reduced by 50microgram and replaced with 6.25microgram of liothyronine b.d.).	Psychosocial problems, bodyweight, heart rate, BP and serum lipid levels.	General health questionnaire, at baseline and 4months alongside: serum TSH, T3 and T4. Total cholesterol, LDL, HDL and triglycerides.	Patient-oriented outcome measure? Partly. Mainly biometrics. Allocation concealment? No, the method of randomisation was discussed. Blinded if possible? Both the physicians and participants were blind. Intention to treat analysis? No. 71 patients were randomised, 60 were included in the final analysis. 10 withdrew due to ADRs and one due to pregnancy. Adequate power/size? The authors did discuss power of the sample size. However, this appeared to be retrospective and stated that the sample size would detect a 20% difference at 80% power with an error rate of 5%. Adequate follow-up (>80%)? 60/71 (84.5%) Level 1/2 evidence. Small group sizes. High dropout rate, those that did not complete the study due to ADRs were not included in the final analysis. Low/medium risk of bias.

Nygaard et al. , "Effect of combination therapy with thyroxine (T4) and 3,5,3'-triiodothyronine versus T4 monotherapy in patients with hypothyroidism, a double-blind, randomised cross-over study," European Journal of Clinical Endocrinology , vol. 161, pp. 895-902, 2009. [17]	Randomised controlled trial – double-blind, randomised cross-over	68 adult hypothyroid patients were enrolled. All had been under the care of an endocrinology clinic and were maintained on T4 for at least 6/12. Nine did not complete the study. All did not complete the study for reasons unrelated to the study drug.	In the combined treatment group, the participant's levothyroxine dose was reduced by 50microgram and replaced with 20microgram liothyronine or 50microgram levothyroxine in the T4 only group. The participants received the intervention for 12/52 followed by a crossover for a further 12/52 period.	QOL and depression. Changes in thyroid function, weight, bioimpedance, waist-to-hip ratio before and after T4 therapy and T3/T4 combination therapy.	Serum thyroid levels and associated parameters i.e. TSH. Clinical parameters. Preferred treatment.	Patient-oriented outcome measure? Yes, QOL and depression alongside others. Allocation concealment? Method of randomisation was disclosed. Blinded if possible? Yes. Intention to treat analysis? Not discussed. Although not all patients that were randomised were included in the final analysis. Adequate power/size? The authors discussed sample size and power (80%). Error rate was set at 0.05%. Adequate follow-up (>80%)? 59/68 (87%) sample size was still above the minimum number required for 80% power for all outcomes. Level 1/2 evidence low sample size compared to other studies, Low risk of bias.

Celi et al, "The pharmacodynamic equivalence of levothyroxine and liothyronine. A randomised, double-blind, cross-over study in thyroidectomised patients," Clinical Endocrinology, vol. 72, no. 5, pp. 709-715, 2010. [25]	Randomised controlled trial – double-blind, cross-over	14 adult patients post thyroidectomy. Four patients withdrew. One reason was unrelated to the study drug and the remainder withdrew due to poor compliance with the study medication. Fourteen patients completed the study.	Study medication was available in the following strengths: levothyroxine – 5, 10 or 33micrograms and liothyronine – 2.5, 10 or 16micrograms. Study participants were randomised to either levothyroxine or liothyronine. No combination group was studied. Those receiving levothyroxine received their usual dose of levothyroxine t.d.s. participants randomised to T3 we treated with half the calculated equivalent dose of T4 to avoid hyperthyroidism .T3 was increased to achieve a TSH level of ≤ 1.0mU/l. T4 was also 'adjusted' using a placebo.	AUC of TSH from 0 – 60minutes and peak TSH concentration. Dose of T3 and T4 and ratio of T4/T3	Serial-sampling and TRH stimulation test: AUC of TSH from 0 – 60minutes and peak TSH concentration. Dose of T3 and T4 and ratio of T4/T3. The participants were monitored for the following symptoms: anxiety, palpitations, tremor, heat intolerance, depression, fatigue, constipation, dry skin, and heat or cold intolerance. Each was assessed and recorded by blind investigators.	Patient-oriented outcome measure? No Allocation concealment? Yes, the method of randomisation was not discussed. Blinded if possible? Yes. Intention to treat analysis? Not discussed. Unsure if all patients randomised were included in the final analysis. Adequate power/size? Very small sample size (14, 10 completed). No discussion of power of the sample size. Adequate follow-up (>80%)? No, 10/14 (71.4%) Level 2/3 evidence. High risk of bias. Sample size likely of insufficient power.

Fadeyev et al. , "Combined therapy with L-Thyroxine and L-Triiodothyronine compared to L-Thyroxine alone in the treatment of primary hypothyroidism," Hormones , vol. 9, no. 3, pp. 245-252, 2010. [15]	Randomised controlled trial	36 premenopausal women with untreated overt primary hypothyroidism. All patients completed the study.	The patients were divided in to two groups. One received levothyroxine at the dose 1.6microgram/kg. In the combination group patients had their dose of levothyroxine calculated and reduced by 25microgram and replaced with liothyronine 12/5microram. The treatment period lasted 6/12.	Not clear ?TSH Levels. DXA scans.	Free T4 and T3, lipid profile and osteocalcin. ECG and thyroid symptoms score.	Patient-oriented outcome measure? No Allocation concealment? No, the method of randomisation was disclosed. Blinded if possible? Unclear. Does not appear so. Intention to treat analysis? No. Adequate power/size? No sample size calculations or power of the sample size was discussed. Adequate follow-up (>80%)? 36/36 completed Level 2/3 evidence Medium risk of bias. No blinding, sample size was not justified and power was not discussed.

Celi et al. , "Metabolic Effects of Liothyronine Therapy in Hypothyroidism: A Randomised, Double-Blind, Crossover Trial of Liothyronine Versus Levothyroxine," Journal of Endocrinology and Metabolism, vol. 96, no. 11, pp. 3466-3474, 2011. [26] **Extension of 2010 study conducted by Celi et al 2010.**	Randomised controlled trial – double-blind, crossover	18 adult patients with hypothyroidism. Four patients withdrew from the study one because of relocation, three because of poor compliance with the medication regimen. Fourteen patients completed the study. Participants were studied as inpatients after six weeks on a stable dose and at the target TSH	T3 or T4 was administered t.d.s. to achieve a target TSH from 0.5 – 1.5.	Serum thyroid hormones, lipid parameters and indices of glucose metabolism	Physiological and body composition data. Serum TSH and serum T3.	Patient-oriented outcome measure? No. Allocation concealment? Method of randomisation not disclosed. Blinded if possible? Yes. Intention to treat analysis? Not discussed. Unsure if all patients randomised were included in the final analysis. Adequate power/size? Very small sample size, 14 out of 18 completed. Some of the results for the first 10 participants in the trial have been reported previously. Adequate follow-up (>80%)? No 14/18 (78%) Level 2/3 evidence – small sample size, medium possibility of bias. Medium risk of bias.

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

Midlands and Lancashire Commissioning Support Unit,

Jubilee House, Lancashire Business Park, Leyland, PR26 6TR

Tel: 01772 214 400 | www.midlandsandlancashirecsu.nhs.uk