East Surrey CCG, Guildford & Waverley CCG, North West Surrey CCG, Surrey Downs CCG, Surrey Heath CCG, North East Hampshire & Farnham CCG, Crawley CCG, Horsham & Mid-Sussex CCG

Evidence review for Surrey Prescribing Clinical Network

Medicine and proposed indication	Liothyronine (L-Tri-iodothyronine sodium, T3) use as augmentation for treatment resistant depression in adults.
Requested by	Simon Whitfield Chief Pharmacist – Surrey and Borders Partnership NHS Foundation Trust

SUMMARY

Clinical Effectiveness

The British Association of Psychopharmacology in their 'Evidence-based guidelines for treating depressive disorders with antidepressants' (revised in 2015) summarised that augmentation or combination treatment can be considered by adding quetiapine, aripiprazole and lithium as first-line treatments and risperidone, olanzapine, tri-iodothyronine or mirtazapine as second-line treatments, although there should be increased awareness that the evidence derives mainly from studies in which lithium and tri-iodothyronine were added to TCAs and the other drugs added to SSRI/SNRIs[1]. It should also be noted that the recommendation for tri-iodothyronine is directly based on evidence from small, non-replicated, randomised controlled trials.

The National Institute for Health and Care Excellence (NICE) in the clinical guidelines for 'Depression in adults: recognition and management' state that augmentation of an antidepressant with thyroid hormones should not routinely be used as there is inconsistent evidence of effectiveness[2].

In the United States, in the Clinical Practice Guideline for the management of Major Depressive Disorder 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[3].

Safety

Rosenthal et al. suggest that there is good evidence to suggest T3 administration in the treatment of depressive states but limited data available on long-term safety[4]. Effects on thyroid levels and potential effects in cardiac and bone disease should be weighed against risk to health and safety from partially or inadequately treated major depression.

Patient factors

Patients showed a greater tolerability towards Liothyronine augmentation in comparison to Lithium[5]. Although treatment with established augmentation strategies would be considered first line, since there was no statistical difference in efficacy, the availability of an alternative approach with a different side-effect profile in addition to the lack of drug level monitoring and risk of toxicity would allow this flexibility and would be considered an advantage for poorly responsive patients.

Cost implications

Liothyronine sodium 20micrograms x 28 tablets cost £152.18*
Recommended dose is 20- 50micrograms daily

20micrograms daily x 28 = £152.18 / month*
50micrograms daily x 28 = £380.45 / month*

Annual cost (20micrograms) = £152.18 x 13 prescriptions = £1978.34
Annual cost (50micrograms) = £380.45 x 13 prescriptions = £4945.85

Data ePACT search for last financial year 2014-15 for liothyronine preparations for **all** indications:

CCG	Total Items	Total Act Cost
EAST SURREY CCG	**227**	**£42,453.54**
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SURREY DOWNS CCG	**427**	**£83,995.64**
SURREY HEATH CCG	**73**	**£17,524.69**
Grand Total	**988**	**£199,142.70**

*Drug Tariff October 2015

Based on current usage the estimated annual number of patients per year who would receive liothyronine as a treatment for depression is 5.

Relevant guidance / reviews

- NICE guidelines: Depression in adults: recognition and management
- British Association of Psychopharmacology. Guidelines for treating depressive disorders with antidepressants
- American Psychiatric Association. Practice guidelines for the Treatment of patients with Major Depressive Disorder

Likely place in therapy relative to current treatments

The major strategies employed for patients not responding or responding partially to a monotherapy trial with an antidepressant include

1) switching to a new antidepressant
2) combining 2 antidepressants from different classes
3) combining the antidepressant with a psychotherapeutic intervention and
4) augmenting the antidepressant with other agents to enhance antidepressant efficacy.

The likely place in therapy for Tri-iodothyronine (T3) in this case would be for patients whose depression has failed to respond to several antidepressants and cannot tolerate the burden associated with the use of lithium as an augmenting agent (see STEP 4).

SABP- Depression and Anxiety Spectrum Disorders Care Pathway[6]

Treatment-resistant depression (Step 4)

Consider:

Treatments from STEP 3
Starting or re-introducing any treatments that were inadequately delivered or adhered to. Check patient choice and reasons for any non-adherence.

Venlafaxine
for patients who have failed two adequate trials of alternative antidepressants

Combination of antidepressants and individual CBT
When patient presents initially with severe depression a combination should be considered as it is more cost-effective than either treatment on its own.
Also consider for patients who have relapsed while taking, or after finishing, a course of antidepressants.

A trial of lithium augmentation
For patients whose depression has failed to respond to several antidepressants and who are prepared to tolerate the burdens associated with its use

Augmentation of an antidepressant with another antidepressant
There is evidence for benefits of adding mianserin or mirtazapine to SSRIs.
Consider second opinion if using other combinations

Phenelzine
For patients who have failed to respond to alternative antidepressants and who are prepared to tolerate the side effects and dietary restrictions.

Augmentation of antidepressant with carbamazepine, lamotrigrine, buspirone, pindolol, valproate or thyroid supplementation is **not recommended** in the routine management of treatment-resistant depression.
Dosulepin should not be used routinely.
There is insufficient evidence to recommend augmentation of antidepressants with benzodiazepines.

Pink	Primary and Secondary* Care	Medical Treatment
Blue	Secondary Care* with possible return to primary care	Specialist Care

Recommendation to PCN

Amber

- Liothyronine can be used as an augmentation agent in the treatment of treatment resistant depression in patients who are intolerant of Lithium augmentation.

Black

- Routine use of Liothyronine in addition to antidepressant alone in the treatment of non-refractory

depression.

Medicine details

Name and brand name	Liothyronine sodium BP 20mcg tablets.
Licensed indication, formulation and usual dosage	**Liothyronine sodium BP 20mcg tablets.**[7] 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 thyroxine sodium is normally the drug of choice for routine replacement therapy. Dosage: Adults: Starting dose of 10 or 20 micrograms every 8 hours, increasing after one week, if necessary, to the usual recommended daily dose of 60 micrograms in two or three divided doses. Myxoedema Coma: 60 micrograms given by stomach tube, then 20 micrograms every 8 hours. It is more usual to start treatment with intravenous liothyronine. Adjunct to carbimazole treatment of thyrotoxicosis: 20 micrograms every 8 hours. Elderly and Children Patients: 5 micrograms daily (Liothyronine sodium tablets can be crushed and triturated with lactose for administration as a powder).
Summary of mechanism of action, and relevant pharmacokinetics	The major thyroid hormone secreted by the thyroid gland is thyroxine, also called T4 because it contains four iodine atoms. To exert its effects, T4 is converted to tri-iodothyronine (T3) by the removal of an iodine atom. This occurs mainly in the liver and in certain tissues where T3 acts, such as in the brain. The amount of T4 produced by the thyroid gland is controlled by another hormone, thyroid stimulating hormone (TSH) which is made in the pituitary gland by negative feedback. Putative mechanisms of action in depression, As mentioned in the STAR*D trial, include 'desensitisation of 5-HT^{1A} inhibitory receptors, direct effects on nuclear receptors affecting gene expression and increased brain metabolism'.
Important drug interactions	Liothyronine sodium therapy may potentiate the action of anticoagulants. Phenytoin levels may be increased by liothyronine. Anticonvulsants, such as carbamazepine and phenytoin enhance the metabolism of thyroid hormones and may displace thyroid hormones from plasma proteins. Initiation or discontinuation of anticonvulsant therapy may alter liothyronine dose requirements. If co-administered with cardiac glycosides, adjustment of dosage of cardiac glycoside may be necessary.

	Colestyramine and colestipol given concurrently reduces gastrointestinal absorption of liothyronine. Liothyronine raises blood sugar levels and this may upset the stability of patients receiving antidiabetic agents. Liothyronine increases receptor sensitivity to catecholamines thus accelerating the response to tricyclic antidepressants. A number of drugs may affect thyroid function tests and this should be borne in mind when monitoring patients on liothyronine therapy. Co-administration of oral contraceptives may result in an increased dosage requirement of liothyronine sodium. Amiodarone may inhibit the deiodination of thyroxine to triiodothyronine resulting in a decreased concentration of triiodothyronine with a rise in the concentration of inactive reverse triiodothyronine. As with other thyroid hormones, Liothyronine may enhance effects of amitriptyline and effects of imipramine. Metabolism of thyroid hormones accelerated by barbiturates and primidone (may increase requirements for thyroid hormones in hypothyroidism). Requirements for thyroid hormones in hypothyroidism may be increased by oestrogens.[1]
Monitoring requirements	Recommended Safety Guidelines for T3 Augmentation of Antidepressant Medication[4] • **Thyroid hormones** Obtain baseline TSH, free T4, and free T3 levels prior to augmentation. Recheck thyroid indices at 3 months and then every 6 months, or at minimum annually. In the longer term, if the patient has a history of multiple episodes or significant treatment resistance, maintenance on T3 is reasonable as an open-ended treatment option. If there are no symptoms of hyperthyroidism and no known cardiac disease, consider maintenance T3 supplementation even if the TSH level is below the normal reference range, depending on clinical efficacy. • **Cardiac risk** Document a discussion of the risk-benefit profile of long-term T3 augmentation, including potential cardiac risk. ECG baseline monitoring can give a useful indication of impending ischemia and it is necessary as Liothyronine is contraindicated in patients with cardiovascular disorders or angina. Blood pressure and pulse rate monitoring at baseline and if symptoms of hyperthyroidism observed (tachycardia). • **Osteoporosis risk** In postmenopausal women, bone density should be monitored with densitometry every 2 years. If bone density is declining, referral for evaluation of osteoporosis should be made. Standard recommendations for all postmenopausal women also include calcium (1200 mg/day) and vitamin D (800–1000 IU / day) supplementation. • Periodically reevaluate the risks and benefits of T3 supplementation, focusing specifically on depressive symptoms or change in status of cardiovascular disease.

Prescribing considerations	**Amber** • Liothyronine can be used as an augmentation agent in the treatment of treatment resistant depression in patients who are intolerant of Lithium augmentation. **Black** • Routine use of Liothyronine in addition to antidepressant alone in the treatment of non-refractory depression.
Other considerations	

Potential patient group (if appropriate to include)	
Brief description of disease	Clinical Knowledge and Skills – Depression Available at: http://cks.nice.org.uk/depression Accessed <18.11.15> • Depression is characterised by persistent low mood and/or loss of pleasure in most activities and a range of associated emotional, cognitive, physical, and behavioural symptoms. In the UK, depression is the third most common reason for consultation in general practice in the UK. • Depression is diagnosed according to the DSM-5 classification by the presence of at least five out of a possible nine defining symptoms, present for at least 2 weeks, of sufficient severity to cause clinically significant distress or impairment in social, occupational, or other important areas of functioning **Treatment-resistant depression** (TRD) typically refers to inadequate response to at least one antidepressant trial of adequate doses and duration. TRD is a relatively common occurrence in clinical practice, with up to 50% to 60% of the patients not achieving adequate response following antidepressant treatment.
Potential patient numbers per 100,000	NHS Choices Available at: http://www.nhs.uk/Conditions/Depression/Pages/Introduction.aspx Accessed <10.01.16> In the UK, depression is quite common and affects about 1 in 10 of the population at some point. Only 25-45% of patients experience remission after one acute trial of antidepressant. Journal of Clinical Psychiatry Prevalence and management of treatment-resistant depression. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17640154 Accessed <10.01.16>

	'Treatment-resistant depression (TRD) is a major public health problem in terms of its prevalence and in terms of individual suffering and cost to society. Best estimates indicate 12-month prevalence rates of approximately 3% for Stage 1 TRD (failure to respond to 1 adequate trial of an antidepressant) and approximately 2% for Stage 2 TRD (failure to respond to 2 adequate trials).'
Outcomes required	The aim of treatment is to induce remission of depressive symptoms.

Summary of current treatment pathway

SABP- Depression and Anxiety Spectrum Disorders Care Pathway[6]

Treatment-resistant depression (Step 4)

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Venlafaxine
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Dosulepin should not be used routinely.
There is insufficient evidence to recommend augmentation of antidepressants with benzodiazepines.

NICE guidelines

Drug treatments
When reviewing drug treatment for a person with depression whose symptoms have not adequately responded to initial pharmacological interventions:

- check adherence to, and side effects from, initial treatment
- increase the frequency of appointments using outcome monitoring with a validated outcome measure
- be aware that using a single antidepressant rather than combination medication or augmentation (see 1.8.1.5 to 1.8.1.9) is usually associated with a lower side-effect burden
- consider reintroducing previous treatments that have been inadequately delivered or adhered to, including increasing the dose
- consider switching to an alternative antidepressant.

Combining and augmenting medications

'Augmentation' is when an antidepressant is used with a non-antidepressant drug and 'combination' is when two antidepressants are used together.

When using combinations of medications (which should only normally be started in primary care in consultation with a consultant psychiatrist):

- select medications that are known to be safe when used together
- be aware of the increased side-effect burden this usually causes
- discuss the rationale for any combination with the person with depression, follow GMC guidance if off-label medication is prescribed, and monitor carefully for adverse effects
- be familiar with primary evidence and consider obtaining a second opinion when using unusual combinations, the evidence for the efficacy of a chosen strategy is limited or the risk–benefit ratio is unclear
- document the rationale for the chosen combination.

If a person with depression is informed about, and prepared to tolerate, the increased side-effect burden, consider combining or augmenting an antidepressant with

- lithium or
- an antipsychotic such as aripiprazole*, olanzapine*, quetiapine* or risperidone* or
- another antidepressant such as mirtazapine or mianserin.

Evidence review

Studies on the use of liothyronine for augmentation in the treatment of refractory depression

1. A comparison of lithium and T3 augmentation following two failed medication treatments for depression: A STAR*D report

Nierenberg A.A.,Fava M.,Trivedi M.H.,Wisniewski S.R.,Thase M.E.,McGrath P.J.,Alpert J.E.,Warden D.,Luther J.F.,Niederehe G.,Lebowitz B.,Shores-Wilson K.,Rush A.J.

Citation: *American Journal of Psychiatry*, September 2006, vol./is. 163/9(1519-1530), 0002-953X (Sep2006)
Available at: http://ajp.psychiatryonline.org/doi/abs/10.1176/ajp.2006.163.9.1519

Abstract: Objective: More than 40% of patients with major depressive disorder do not achieve remission even after two optimally delivered trials of antidepressant medications. This study compared the effectiveness of lithium versus triiodothyronine (T3) augmentation as a third-step treatment for patients with major depressive disorder.

Method: A total of 142 adult outpatients with nonpsychotic major depressive disorder who had not achieved remission or who were intolerant to an initial prospective treatment with citalopram and a second switch or augmentation trial were randomly assigned to augmentation with lithium (up to 900 mg/day; N=69) or with T3 (up to 50 mug/day; N=73) for up to 14 weeks. The primary outcome measure was whether participants achieved remission, which was defined as a score <7 on the 17-item Hamilton Depression Rating Scale. Results: After a mean of 9.6 weeks (SD=5.2) of treatment, remission rates were 15.9% with lithium augmentation and 24.7% with T3 augmentation, although the difference between treatments was not statistically significant. Lithium was more frequently associated with side effects (p=0.045), and more participants in the lithium group left treatment because of side effects (23.2% versus 9.6%; p=0.027).

Conclusions: Remission rates with lithium and T3 augmentation for participants who experienced unsatisfactory results with two prior medication treatments were modest and did not differ significantly. The lower side effect burden and ease of use of T3 augmentation suggest that it has slight advantages over lithium augmentation for depressed patients who have experienced several failed medication trials.

2
Combined treatment with sertraline and liothyronine in major depression: a randomized, double-blind, placebo-controlled trial.

Author(s): Cooper-Kazaz R1, Apter JT, Cohen R, Karagichev L, Muhammed-Moussa S, Grupper D, Drori T, Newman ME, Sackeim HA, Glaser B, Lerer B.

Citation: *Arch Gen Psychiatry*. 2007 Jun;64(6):679-88. **Available at:** http://www.ncbi.nlm.nih.gov/pubmed/17548749

Abstract

Background:
Antidepressant treatments that achieve a higher remission rate than those currently available are urgently needed. The thyroid hormone triiodothyronine may potentiate antidepressant effects.
Objective:
To determine the antidepressant efficacy and safety of liothyronine sodium (triiodothyronine) when administered concurrently with the selective serotonin reuptake inhibitor sertraline hydrochloride to patients with major depressive disorder.
Design: Double-blind, randomized, 8-week, placebo-controlled trial.
Setting: Outpatient referral centers.
Patients: A total of 124 adult outpatients meeting unmodified DSM-IV criteria for major depressive disorder without psychotic features.

Interventions: Patients 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.
Main outcome measures: The primary outcome measure was categorical response to treatment (> or =50% decrease in scores on the 21-item Hamilton Rating Scale for Depression from baseline to study end point). Remission rate (final Hamilton Rating Scale for Depression score, < or =6) was a secondary outcome measure.
Results: 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.

3
Long term augmentation with T3 in refractory major depression

Author(s): Kelly T.F.,Lieberman D.Z
Citation: *Journal of Affective Disorders*, May 2009, vol./is. 115/1-2(230-233), 0165-0327 (May 2009)
Available at: http://www.sciencedirect.com/science/article/pii/S0165032708003716

Abstract

Background:
The addition of triiodothyronine (T3) is one of the most widely studied augmentation strategies for refractory depression. Despite this there are no long term studies or studies of doses above 100 mcg.

Method:
Long term and high dose augmentation with T3 for refractory unipolar major depression was studied. Seventeen patients were assessed for symptom improvement with the Clinical Global Impression of Improvement Scale.

Results:
Fourteen of 17 patients showed improvement. One patient saw no improvement and 2 dropped out due to side effects. The patients who benefited showed an average CGI improvement of 2.5 (SD: 0.52). The average dose used was 80 mcg (SD: 30.2, range: 25 mcg-150 mcg). The average length of time on T3 was 24.2 months (SD: 19.4, range: 11.8-86.7). This case series shows that **T3 may be successfully employed as a long term treatment augmentation of major depression if over time dosage levels are increased beyond the traditional 50 mcg.**

4
Triiodothyronine augmentation in the treatment of refractory depression: A meta-analysis
Citation: *Archives of General Psychiatry*, 1996, vol./is. 53/9(842-848), 0003-990X (1996)
Author(s): Aronson R., Offman H.J., Joffe R.T., David Naylor C.

Abstract

Background: Several trials have addressed the efficacy of liothyronine sodium therapy in euthyroid, nonpsychotic depressed patients refractory to tricyclic antidepressant therapy. We undertook a meta-analysis of these trials.

Methods: The MEDLINE database (1966 to May 1995) and published reference lists were examined for controlled clinical trials of triiodothyronine augmentation in euthyroid patients with refractory depression. Quality assessment and data abstraction were performed independently by two reviewers. Results were aggregated three ways: the relative response rate compared with controls, accepting each trial's definition of clinical response; absolute improvement in response rates; and improvements in depression scores, analyzed

as continuous variables without a prespecified threshold for clinical response.

Results: Aggregating eight studies with a total of 292 patients, patients treated with triiodothyronine augmentation were twice as likely to respond as controls (relative response, 2.09; 95% confidence interval [CI], 1.31 to 3.32; P=.002). This corresponded to a 23.2% absolute improvement in response rates (95% CI, 4.5% to 41.9%; P=.02). Improvements in depression scores were moderately large (standardized effect size, 0.62; P<.001). However, study quality was uneven, and results were statistically heterogeneous. Among the four randomized double-blind studies, pooled effects were not significant (relative response, 1.53; 95% CI, 0.70 to 3.35; P=.29), but one study with negative results accounted for most of the intertrial heterogeneity in results.

Conclusions: Triiodothyronine augmentation may be an effective empirical method of increasing response rates and decreasing depression severity scores in a subgroup of patients with depression refractory to tricyclic antidepressant therapy, but the total number of patients randomized was small, and additional placebo-controlled data are required for a definitive verdict. Since therapeutic trends now favor other drugs, future trials might usefully examine triiodothyronine augmentation with selective serotonin reuptake inhibitors or compare potentiation strategies, eg, lithium vs triiodothyronine, for managing refractory depression. Such trials would benefit from much larger sample sizes than those reviewed here.

5

A placebo-controlled comparison of lithium and triiodothyronine augmentation of tricyclic antidepressants in unipolar refractory depression.

Citation: Archives of general psychiatry, vol. 50, no. 5, p. 387-393, 0003-990X (May 1993)

Author(s): Joffe, R T,Singer, W,Levitt, A J,MacDonald, C

Abstract:

To directly compare the efficacy of lithium carbonate and liothyronine sodium (triiodothyronine) in the augmentation of therapeutic response in antidepressant nonresponders. A randomized, double-blind, placebo-controlled study of 2 weeks' duration. The Mood Disorders Program, Clarke Institute of Psychiatry and the University of Toronto, Ontario. Fifty outpatients, males and females, with unipolar, nonpsychotic major depression who had failed to respond to treatment with desipramine hydrochloride or imipramine hydrochloride. Both liothyronine and lithium were more effective than placebo in reducing scores on the Hamilton Rating Scale for Depression. However, the antidepressant augmenting effect of these two compounds did not differ from each other. When response was defined as a 50% or more reduction in the Hamilton Rating Scale for Depression scores and a final score less than 10, we found that 10 of 17 subjects responded to liothyronine, nine of 17 responded to lithium and three of 16 responded to placebo. Our study suggests that **both lithium and liothyronine may be considered as alternatives in augmenting antidepressant response in patients who do not respond to treatment with a tricyclic antidepressant**.

Equity / Stakeholder views (if relevant)

Decisions of local Trusts DTCs and neighbouring APCs	**Derbyshire Medicines Management** Liothyronine for treatment resistant depression Status **Amber** Decision Date August 2013 **Shared Care Agreement Framework available at:** http://www.derbyshiremedicinesmanagement.nhs.uk/assets/Clinical_Guidelines/Shared_Care_Guidelines/Liothyronine.pdf <accessed 16.11.2015> **Comments** Consultant initiation. Unlicensed use in euthyroid states as an adjunct to any antidepressant in managing unipolar treatment resistant depression (TRD). Liothyronine augmentation is recommended to be positioned behind Lithium augmentation for managing TRD. However, Liothyronine provides an alternative approach with a different side-effect profile in a body of patients hitherto poorly responsive to the more evidence-based ways of managing TRD. There is no recommended duration. Clinical efficacy should be assessed regularly on an individual basis and it is suggested that this be at least every 3 months.

	East Kent Prescribing Group: **Prescribing recommendations Liothyronine** 1. For patients who are currently stable on liothyronine: continue therapy and review in view of lack of evidence. 2. Requests for initiation of liothyronine should only be following recommendation from an endocrinologist. It is not routinely prescribed for maintenance but rather immediately post – total thyroidectomy for up to 3 weeks until histology results are obtained. This is should then be switched over to Levothyroxine. 3. For unstable patients currently taking liothyronine (+/- levothyroxine): refer to endocrinologist for advice/review. Please note: **In exceptional cases, liothyronine may be initiated by a mental health specialist to augment an antidepressant in resistant depression.** Please continue to prescribe for these patients. **North Essex Partnership NHS Foundation Trust** Liothyronine used for augmentation in depression Status **Yellow**-to be initiated by specialist mental health Place in therapy: Used as 4th line in the treatment of depression **Comments** **Augmentation with thyroid supplementation is not routinely recommended.** **Survey** Data from different CCGs indicate that Liothyronine is either non-formulary or reserved as second line treatment for its licensed indications in thyroid disease. In Sussex Partnership NHS Foundation Trust, Liothyronine is on the list of non-formulary items approved for named patients only and it would be retained in secondary care for prescribing, as it is not on the CCG formulary for its use in depression. In Somerset Partnership NHS Foundation Trust, although Liothyronine has been approved for TRD it has been considered as inappropriate for GP prescribing and so it is marked as 'red' for all licensed and unlicensed indications. However, a couple of 'near misses' have been reported where patients have relapsed following the lack of continuation of prescribing in primary care (indication being treatment-resistant depression) and the absence of referral or where referral was delayed. The small number of patients renders the prescribing in secondary care possible but it is questioned whether this is an appropriate use of specialist resources. Data from consultants in SABP indicate that Liothyronine is not routinely used as an augmentation strategy with only one consultant (AC) reporting an initiation of a trial over the last 5 years. However, it has been reported (JO) that on a few occasions there is need for continuation of prescribing when patients move over to the area from SLAM, where it is much more regularly used as a strategy.
Recommendations from national / regional decision making groups	**1** The National Institute for Health and Care Excellence (NICE) in the clinical guidelines for 'Depression in adults: recognition and management' state that **augmentation of an antidepressant with thyroid hormones should not routinely be used as there is inconsistent evidence of effectiveness**.[2] **2** The British Association of Psychopharmacology include in their review a meta-analysis of augmentation of TCAs with tri-iodothyronine (T3), 25–37.5 µg, in four small RCTs of

	treatment-resistant depression which found significant benefit with regard to improvement in HDRS score (ES 0.6) but a non-significant improvement in response rate (NNT 13) (Aronson et al., 1996). A small subsequent study found no difference between lithium, T3, the combination and placebo in a 2-week study in patients predominantly on SSRIs (Joffe et al., 2006). The STAR*D study found a non-significantly higher remission rate on T3 (25–50 µg) 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 (Nierenberg et al., 2006).[1] Summary: There is a lack of direct evidence for the efficacy of increasing the dose after initial treatment non-response. Indirect evidence suggests there is a dose response for TCAs, venlafaxine and escitalopram (II) but not for other SSRIs. **The best evidence of efficacy in augmentation of antidepressants is for quetiapine, aripiprazole, risperidone and lithium (I). Evidence is less robust for olanzapine, tri-iodothyronine, bupropion, mirtazapine and buspirone** (II). There are few direct comparisons between different augmentation strategies, but quetiapine is at least as effective as lithium (II). The combination of reuptake inhibitors with mianserin (I) and SSRIs with TCAs/noradrenaline reuptake inhibitors (II) does not appear to be effective. There is developing but preliminary evidence of efficacy for augmentation with modafinil, S-adenosyl methionine (SAMe), testosterone (in men with low testosterone levels) and oestrogen (in premenopausal women) (II). Tryptophan augmentation may be effective (III) although is not always widely available. Data supporting methylphenidate and lamotrigine are weak (II). Augmentation with lithium and atypical antipsychotics is associated with significant side effects (I–II). Management of the more unusual or complex medication regimens may best be undertaken in liaison with specialist services or clinicians with a special interest (III). In older people the evidence base is much smaller, but overall about 50% of patients respond to switching or augmentation. The best evidence is for lithium augmentation (II). There is also some evidence for venlafaxine and selegiline. **3** In the American Psychiatric Association practice guidelines[8] for the Treatment of patients with Major Depressive Disorder Liothyronine is included as part of the strategies to address incomplete response (augmenting and combining treatments) RECOMMENDATION **Thyroid hormone supplementation, even in euthyroid patients, may increase the effectiveness of antidepressant medication treatment, whether used as an augmentation agent or in combination with an antidepressant from the outset of therapy.** The dose typically used for this purpose is 25 mcg/day of triiodothyronine, increased to 50 mcg/day if the response is inadequate after about a week. The duration of treatment required has not been well studied.

Health economic considerations

Cost per year per patient

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SURREY DOWNS CCG	427	£83,995.64
SURREY HEATH CCG	73	£17,524.69
Grand Total	988	£199,142.70

Alternative treatments cost per patient per year

Augmentation strategies approved by NICE guidelines

1. Lithium Carbonate modified release tablets (Priadel)

400mg x 100 tablets cost £4.02*

Recommended maintenance dose 400-1200mg daily = £1.13 - £3.39/month

Annual cost (400mg) = £1.13 x 13 prescriptions = £14.69
Annual cost (1200mg) = £3.39 x 13 prescriptions = £44.09**

2. Aripiprazole tablets

5mg x 28 tablets cost £43.99*
10mg x 28 tablets cost £43.81*

Maintenance dose as per availability of tablets (5-20mg)= £43.99-£87.62/month

Annual cost (5mg) = £43.99 x 13 prescriptions = £571.87
Annual cost (20mg) = £87.62 x 13 prescriptions = £1139.06

3. Olanzapine tablets

2.5mg x 28 tablets cost £0.96*
20mg x 28 tablets cost £2.09*

Recommended maintenance dose 10-20mg daily = £12.48-£27.17/month

Annual cost (2.5mg) = £0.96 x 13 prescriptions = £12.48
Annual cost (20mg) = £2.09 x 13 prescriptions = £27.17

4. Quetiapine immediate release tablets

25mg x 60 tablets cost £1.44*
200mg x 60 tablets cost £3.26*
300mg x 60 tablets cost £4.34*

Recommended maintenance dose 25-800mg daily = £0.72 - £5.97/month

Annual cost (25mg) = £0.72 x 13 prescriptions = £9.36
Annual cost (800mg) = £5.97 x 13 prescriptions = £77.61

5. Risperidone tablets

0.5mg x 20 tablets cost £1.05*
1mg x 20 tablets cost £1.01*
2mg x 60 tablets cost £1.80*

Recommended maintenance dose 0.5-3mg daily = £1.47-£2.25/month

Annual cost (0.5mg) = £1.47 x 13 prescriptions = £19.11
Annual cost (3mg) = £2.25 x 13 prescriptions = £29.25

Comparative Table of alternative treatments cost per patient

Treatment	Dose	Cost per month	Cost per year
Aripiprazole tabs	5-20mg	£43.99 - £87.62	£571.87 - £1139.06
Lithium MR (Priadel) tabs	400-1200mg	£1.13 - £3.39	£14.69 - £44.09
Olanzapine tabs	2.5-20mg	£0.96 - £2.09	£12.48-£27.17
Quetiapine tabs	25-800mg	£0.72 - £5.97	£9.36 - £77.61
Risperidone tabs	0.5-3mg	£1.47 - £2.25	£19.11 - £29.25
Tri-iodothyronine tabs	20-50 micrograms	£152.18 - £380.45	£1978 - £4946

*Drug Tariff October 2015
**Costs do not include monitoring requirements

Other financial considerations (if relevant)	
Health economic data (if available)	

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Date: 26.01.16

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Declaration of interest: None

Reviewed by: Name, designation and organisation

VERSION CONTROL SHEET

Version	Date	Author	Status	Comment
1	26.01.16	A. Vrana	Draft	Sent out for clinician comment

East Surrey CCG, Guildford & Waverley CCG, North West Surrey CCG, Surrey Downs CCG, Surrey Heath CCG, North East Hampshire & Farnham CCG, Crawley CCG, Horsham & Mid-Sussex CCG

Comments on Evidence review for Surrey Prescribing Clinical Network

Please include any comments you have answers to any questions asked as well as any additional references you feel may need to be included in the review. If there are any other of your colleagues that you feel we need to engage with please also let us know their names and where/how they can be contacted.

Medicine and proposed indication	
Prepared by	Name, designation and organisation
Comments on evidence review	
Additional evidence and references for consideration	Include any additional evidence and references you would like to submit for inclusion in the evidence review
Specific clinical questions	Specific questions arising from review
Other colleagues who should be contacted	Include name, designation and contact details of any other colleagues who should be consulted about this evidence
Declaration of interests	For example – any teaching, training, grants, consultancy, research funding, stock holding, nurse funding, equipment

Signature …….. Date ……