



PE1463 EFFECTIVE THYROID AND ADRENAL TESTING, DIAGNOSIS AND TREATMENT

This petition was lodged on 19 December 2012. A full history of the petition, including written submissions, links to the Official Report of the Committee's meetings and evidence sessions and a narrative timeline can be found on the petition webpage [here](#).

Whilst the petition is drafted in broad terms to cover all adrenal and thyroid disorders, the Public Petitions Committee's scrutiny of the issues has focused on a subset of these diseases – hypothyroidism.

The petition raises a number of issues with existing guidance, diagnosis (including testing procedures), treatment (including alternative medications) and the need for further research. The Committee has gathered a wide range of views and evidence on these issues from patients, stakeholders and health officials since the petition was lodged.

At its meeting on [29 September 2016](#), the Committee agreed to ask SPICe to produce a briefing on the issues raised by the petition. This briefing provides background on hypothyroidism and an overview of the evidence gathered on each of the key issues.

This briefing is not intended to be a fully comprehensive analysis of the research, data or information available about hypothyroidism. It seeks to provide some background, and to summarise some of the material made available to the Committee over the last three years.

(i) Brief overview of hypothyroidism

A [SPICe briefing](#) on the petition provides a brief outline of hypothyroidism dated 11 January 2013.

Symptoms

According to the [British Thyroid Foundation](#), the most common signs or symptoms of hypothyroidism are:

- fatigue and tiredness
- increased awareness of the cold
- dry and coarse skin
- dry and thinning hair
- hoarse or croaky voice

- constipation
- muscle weakness, cramps and aches
- pins and needles in the fingers and hands (carpal tunnel syndrome)
- heavier and longer periods
- fertility problems
- low libido
- weight gain
- puffy face and bags under the eyes
- slow speech, movements and thoughts
- low mood or depression
- memory problems
- difficulty in concentration
- slow heart beat
- slightly raised blood pressure
- raised cholesterol
- slowed growth (in children)

Types

The [NICE Clinical Knowledge Summary¹](#) (updated in April 2016) provides an overview of the types of hypothyroidism:

- Hypothyroidism is the result of reduced production of thyroid hormones (thyroxine [T4] and tri-iodothyronine [T3]). Thyroid hormones are released from the thyroid gland when it is stimulated by thyroid-stimulating hormone (TSH) from the pituitary gland.
- Primary hypothyroidism (95% of cases) occurs when the thyroid gland is unable to produce thyroid hormones because of iodine deficiency or an abnormality within the gland itself. It presents as:
 - Overt hypothyroidism — TSH levels are above the normal reference range (usually above 10 mU/L) and free T4 is below the normal reference range.
 - Subclinical hypothyroidism — TSH levels are above the normal reference range and T3 and T4 are within the reference range.

¹ NICE is the National Institute of Care and Health Excellence and is an English Non Departmental Public Body which provides national guidance and advice to improve health and social care.

- Secondary or central hypothyroidism is the result of insufficient production of TSH due to a pituitary or hypothalamic disorder.
- Postpartum thyroiditis is the development of thyrotoxicosis and/or hypothyroidism, within a year of giving birth in women had normal thyroid function prior to pregnancy.
- In the UK, hypothyroidism is most commonly caused by autoimmune disease or thyroid damage as a result of surgery or radioiodine therapy.

The most common cause of hypothyroidism is the autoimmune condition, [Hashimoto's thyroiditis](#). Both hyper- and hypothyroidism can also be caused by thyroiditis (thyroid inflammation), thyroid cancer, and excessive or deficient production of TSH.

Incidence

According to [NHS Choices](#), both men and women can have an underactive thyroid, although it's more common in women. In the UK, it affects 15 in every 1,000 women (1.5%) and 1 in 1,000 (0.1%) men. Children can also develop an underactive thyroid. ISD collected data for [numbers of consultations for hypothyroidism up till 2013](#) via the Practice Team Information.

Similarly, according to NICE, the prevalence of spontaneous hypothyroidism in areas where there is adequate iodine in the diet (such as in Scotland) is 1–2%. It is up to ten times more common in women than in men.

(ii) Overview of the Committee's scrutiny

The Committee has conducted many forms of evidence gathering since its consideration of the petition began. This includes:

- Evidence session with the Scottish Government on [25 June 2013](#), at which the following witnesses attended:

Alex Neil MSP, then Cabinet Secretary for Health and Wellbeing; Lesley Metcalf, Policy Manager, Clinical Priorities Team; and Alpana Mair, Deputy Chief Pharmaceutical Officer, Scottish Government;

- Round-table with stakeholders on [1 October 2013](#), at which the following witnesses attended:

Michael Matheson MSP, then Minister for Public Health; Professor Graham Leese CMO Specialty Adviser for Endocrinology; Sinéad Power, Policy Team Leader; Lesley Metcalf, Policy Manager, Clinical Priorities Team, Scottish Government; Sandra Whyte, Marian Dyer, and Lorraine Cleaver (the petitioners); Tara Wilmott, Head of Approvals, Education and Standards Directorate, General Medical Council; Dr Anthony Toft, Consultant Physician, Spire Murrayfield Hospital, Edinburgh; Lyn Mynott, Chair/Chief Executive, Thyroid UK; Professor Graham Williams, President, British Thyroid Association and Treasurer, Society for Endocrinology;

- Evidence session with the Scottish Intercollegiate Guidelines Network (SIGN) on [25 November 2014](#) at which the following witnesses attended:

John Kinsella, Chair, Sara Twaddle, Director, and Roberta James, Programme Lead, Scottish Intercollegiate Guidelines Network

- Evidence session with the Scottish Government on [9 February 2016](#), at which the following witnesses attended:

Maureen Watt MSP, then Minister for Public Health, Alpana Mair, Deputy Chief Pharmaceutical Officer, Scottish Government, and from Professor Graham Leese, Consultant and Honorary Professor in Diabetes and Endocrinology, NHS Tayside and CSO Speciality Adviser

- Oral evidence sessions with the petitioner on [5 February 2013](#) and [1 December 2015](#)
- Written evidence from patients and professionals

A number of challenges in addressing the issues raised by the petition have become apparent in the course of the Committee's evidence gathering:

- The complex technical issues regarding the biochemistry involved, testing and treatment options
- The conflict of opinion of some with the mainstream medical view
- The acknowledgement that further research is needed on this area of endocrinology
- The shift of natural thyroid extract being the standard treatment up to the 1980s to it now being an unlicensed product and not recommended for use in treatment by guidance.
- The apparent lack of awareness in primary care of all the possible presentations of hypothyroidism, their diagnosis and treatment
- A lack of understanding around the licensing and supply of medicines in UK

The petitioner has done much to raise awareness of the issues through her own work, not only lodging the petition and keeping the issue live, but through other means such as setting up a Facebook group, 'Thyroid Petition Scotland'. Her work has been supported by Thyroid UK, a national charity.

Since the petition was first lodged there has been a range of activities undertaken by different bodies in reviewing current advice, evidence and practice. These include:

- The [British Thyroid Association position statement](#) – clarification and expansion of previous positions on management
- Ongoing research into the complex relationships involved in thyroid hormone production and related metabolic processes
- Reassessments of the available evidence to ensure best clinical management
- Discussions with the [Scottish Intercollegiate Guidelines Network](#) (SIGN) led to the petitioner working with the Network and the Royal College of General

Practitioners to create a best practice document for treating patients who do not respond to standard treatment. This is in progress

- The NICE [Clinical Knowledge Summary](#) for primary care practitioners has been revised. It is based on updated, evidence-based guidance
- Healthcare Improvement Scotland – [Technologies Scoping Report](#)
- Scottish Government patient listening exercise undertaken by Thyroid UK

The [Scottish Government](#) and organisations such as the British Thyroid Association, the Thyroid Foundation, the Royal College of Physicians and the Society for Endocrinology state that current protocols are based on the current evidence and international guidelines that are available.

The Committee's scrutiny of the key issues presented by the petition is considered in more detail under the respective headings below.

(iii) Guidance framework

Management of hypothyroidism in the UK

When the petition was lodged there were no formal UK guidelines. However, guidance did exist prior to the petition being lodged. In July 2006, following a consultation process, a joint working group comprising representatives from the Association of Clinical Biochemistry, The British Thyroid Association and British Thyroid Foundation published "[UK Guidelines for the Use of Thyroid Function Tests](#)". There was also a statement from the Royal College of Physicians on the [Diagnosis and Management of Primary Hypothyroidism, revised in 2011](#). The absence of more formal, national guidance was a key concern of the petitioner in bringing her petition. The Public Petitions Committee has scrutinised this issue and, since the petition was lodged, guidance has been revised and developed:

1. The British Thyroid Association(BTA) published [a 'position statement' on 25 June 2015](#). This statement includes comparative recommendations from both the European Thyroid Association and the American Thyroid Association. It has been endorsed by the Association for Clinical Biochemistry and Laboratory Medicine, British Thyroid Foundation, Royal College of Physicians (RCP) and the Society for Endocrinology.
2. As referred to above, the National Institute for Care and Health Excellence (NICE) has produced a [Clinical Knowledge Summary](#) for hypothyroidism. This was revised in April 2016. Clinical Knowledge Summaries are concise, accessible summaries of current evidence for primary care professionals. The topics focus on the most common and significant presentations in primary care. They give information to support safe decision-making and improve standards of patient care.

This NICE summary appears to be very comprehensive in discussing areas including diagnosis, management, prescribing, misleading thyroid function tests, assessment of symptoms and other possible conditions' for example. It is in line with, and makes reference to, the BTA Statement and the RCP guidelines of 2011.

3. There is no SIGN guideline on thyroid and adrenal treatment, diagnosis and testing. The Committee therefore held an evidence session with SIGN on [25 November 2014](#) to discuss the process of submitting a topic for guideline development. On [9 December 2014](#), the Committee agreed to forward the evidence it had received to SIGN, including patient testimonies. It invited SIGN to work with the petitioner in the area of diagnosis and treatment of thyroid conditions and formulating the necessary questions. On [1 December 2015](#), the Committee took evidence from the petitioner who informed it that she is working with SIGN and the Royal College of General Practitioners in Scotland to produce a best practice document.

Management of hypothyroidism outside the UK

4. The [American Thyroid Association](#), a not-for-profit professional organisation 'devoted to thyroid biology and to the prevention and treatment of thyroid disease through excellence in research, clinical care, education, and public health', produced [guidelines for the treatment of hypothyroidism](#) in 2014.

The [European Thyroid Association](#) (ETA), a membership organisation whose 'aims are to promote knowledge in the thyroid field (fundamental and clinical) and improve knowledge of the thyroid gland and its diseases' has also produced a number of guidelines which have been compiled and peer-reviewed by clinicians who are expert in the field of endocrinology. These are summarised within the position statement by the British Thyroid Association, along with those from the American Thyroid Association.²

Guidance internationally now appears to be relatively uniform. The British Thyroid Association, in its position statement of 2015 cross-referenced its advice with both the ETA and ATA guidance.

² The following are examples of some of the specific guidance produced by the ETA
[2013 Guideline on Management of Subclinical hypothyroidism](#)
[2015 Editorial: Guidance in Subclinical Hyperthyroidism and Subclinical Hypothyroidism: Are We Making Progress?](#)
[2012 ETA Guidelines: The Use of L-T4 + L-T3 in the Treatment of Hypothyroidism](#)

GUIDANCE				
Petitioner's position	Updated guidance on mainstream diagnosis and treatment	Areas of contention in the evidence presented	Body or bodies responsible for effecting change in protocols	Action taken by Committee
<p>Seeking formal clinical guidelines on diagnosis and management of hypothyroidism. In relation to treatment, the petitioner is particularly seeking guidance for the treatment of patients who do not respond well to the standard medication (T4).</p> <p>The petitioner would also like to see guidance to ensure a more informed and holistic approach to initial testing and diagnosis, as well as the management of those who do not present with overt hypothyroidism</p>	<p>Current position statement by British Thyroid Association/review article in Clinical Endocrinology, published 25 June 2015.</p> <p>There is a statement about recommended management (with evidence ratings) along with guidance given by the European Thyroid Association and the American Thyroid Association.</p> <p>NICE has developed a Clinical Knowledge Summary (April 2016) for primary care practitioners</p> <p>The British Medical Journal has also produced Best Practice guidelines which were updated in April 2016</p>	<p>Guidance is piecemeal and variable across the world and even within the UK. Orthodox management is not taking account of recent, peer-reviewed research on the complex relationships between TSH, T3 and T4 and other metabolic processes.</p> <p>There appears to be a dearth of (good) research in key areas, which is essential for production of robust, safe national guidelines.</p>	<p>Scottish Intercollegiate Guidelines Network (SIGN).</p> <p>Royal Colleges, such as the RCGP could implement awareness-raising/training for GPs and other primary care staff in the limitations of current thyroid testing; the cases and outliers that are not captured by current testing, and to support primary care staff to consider disparate, chronic symptoms in a more holistic way (despite test results)</p> <p>Scotland could follow the lead from NICE if NICE were to produce a full Guideline, but would not be required to.</p> <p>Any guideline could take account of the significant minority of individuals who do not successfully convert T4 to T3 to suggest alternate treatment protocols (combined therapy, supplementing T3)</p> <p>Scottish Clinical Biochemistry Managed Diagnostic Network (SCBMDN) standardisation of clinical tests and testing protocols nationally.</p> <p>Revisit the most recent research to ascertain whether current guidance/orthodox position could be amended to reflect hormone testing parameters used elsewhere.</p>	<p>The Committee has engaged with SIGN which is taking forward the development of a best-practice document.</p>

(iv) Diagnosis and testing

The main concerns the petitioner has with diagnosis and testing are as follows:

Seeking more sensitive, thorough and informed diagnosis of hypothyroidism which:

- is not solely based on arbitrary, non-universal, under-researched measurement range of thyroid hormones
- recognises that hypothyroidism might be indicated even when initial biochemical testing might show normal function.

According to [NHS Inform](#), diagnosis is made in the first instance via a thyroid function test – TFT, as well as the clinical picture of presenting symptoms. It will be noted that these can be vague and wide-ranging, and can be similar to those of Chronic Fatigue Syndrome/Myalgic Encephalopathy.

This TFT test is used to test blood for levels of thyroid-stimulating hormone (TSH), as well as thyroxine (T4) and tri-iodothyronine (T3) (thyroid hormones).

TFTs include a measure of the amount of thyroid [hormones](#), Thyroxine (T4) or Tri-iodothyronine (T3) in the blood. These hormones are chemical substances that travel through the bloodstream and control or regulate the body's metabolism—how it functions and uses energy. Thyroid hormones are present in the blood in either protein bound forms (the majority) or the free and active form of the hormone. Currently, the majority of UK laboratories measure the free form of the hormones – [Free T4](#) (FT4) or [Free T3](#) (FT3). The petitioner also wishes to see reverse T3 (rT3) tested for, which is implicated in preventing T4 converting to T3. Current guidance and evidence does not appear to support testing for rT3.

[Thyroid Stimulating Hormone](#) (TSH) is produced by the [pituitary gland](#) and is part of the body's [feedback system](#) to maintain stable amounts of thyroid hormones in the blood. When thyroid hormone concentrations decrease in the blood, the pituitary gland is stimulated to release TSH, which in turn stimulates the production and release of T4 and T3 by the thyroid gland. When the system is functioning normally, TSH production turns on and off to maintain constant blood thyroid hormone concentrations.

In some laboratories, the initial blood test for thyroid disorders is a [TSH test](#). If TSH concentration is abnormal, it will usually be followed up with a FT4 measurement (or occasionally [total T4](#)). In some cases FT3 (or [total T3](#)) will also be performed. The petitioner would like to see that testing for FT3 or total T3 is always done as a matter of course, not only at diagnosis, but when treatment with T4 is ongoing and symptoms persist.

If the thyroid gland fails and the concentrations of thyroid hormones fall, a [feedback system](#) will result in increased TSH release from the pituitary gland. Similarly, if the thyroid gland becomes overactive and increased amounts of thyroid hormones are released, TSH production will be suppressed. If the feedback mechanism is not functioning properly, as can occur with a variety of illnesses not directly affecting the thyroid, the release of TSH may be reduced and the concentration of thyroid hormones in the blood may fall as a result. Very rarely, TSH concentrations may increase, due to a tumour of the pituitary, when the thyroid will make and release inappropriate amounts of T4 and T3, and the patient may experience symptoms

associated with hyperthyroidism. If there is decreased production of thyroid hormones, the patient may experience symptoms of hypothyroidism.

Typical reference ranges for normal thyroids

Test	From	To	Units
TSH	0.4	4/4.5	mU/L
FT4	9.0	25	pmol/L
FT3	3.5	7.8	pmol/L

Source: [British Thyroid Foundation](#)

These ranges are only a guide and will often vary according to laboratory because different tests or methodologies might be used. Variation in 'reference ranges' was raised in some of the evidence presented. As can be seen from the information below, arriving at a reference range is not an exact science.

A large number of individuals from a group who are thought to represent a "normal" population, will be tested for a particular laboratory test. The reference range is then derived mathematically by taking the average value for the group and allowing for natural variation around that value (plus or minus 2 standard deviations from the average). In this way, ranges quoted by labs will represent the values found in 95% of individuals in the chosen 'reference' group. In other words, even in a "normal" population, a test result will lie outside the reference range in 5% of cases (1 in 20). This is why the term "reference range" is preferred over "normal range".

Source: [Lab Tests Online and NHS Choices](#)

There are different reference ranges for pregnant women and for testing babies and young children, and many transient factors including other medications and other conditions can affect thyroid function test results.

The following table summarises test results and their potential meaning, depending on other presenting clinical features:

TSH	T4	T3	INTERPRETATION
High > 4.5 (UK, US)	Normal	Normal	Mild (subclinical) hypothyroidism
High > 4.5	Low	Low or normal	Hypothyroidism

(Source: [Lab Tests Online and NHS Choices](#))

Healthcare Improvement Scotland produced a [Technologies Scoping Report](#) on diagnostic testing for hypothyroidism in February 2014.

The following questions were scoped by the report:

1. In patients with symptoms suggestive of hypothyroidism, what is the evidence on the clinical and cost effectiveness of adding tests for serum total tri-iodothyronine (TT3), serum free T3 (FT3) and serum reverse T3 (rT3) to routine hypothyroid testing (TSH + T4)?

2. What is the evidence on the clinical and cost effectiveness of adding adrenal testing or the adrenal stress index test to routine hypothyroid testing (TSH + T4)?

This report concludes, with regards to testing and diagnosis:

‘An American non-systematic literature review reported that serum T3 measurement has little specificity or sensitivity for diagnosing primary hypothyroidism, since enhanced T4 to T3 conversion maintains T3 concentrations until hypothyroidism becomes severe.

No systematic reviews were identified assessing the clinical or cost effectiveness of routine adrenal function testing in the context of primary hypothyroidism. UK guidelines state that tests of adrenal function are mandatory in patients with a high index of suspicion of hypopituitarism. No studies were identified on the diagnostic validity or clinical utility of the adrenal stress index test/ adrenal stress profile.’

The [Scottish Clinical Biochemistry Managed Diagnostic Network \(SCBMDN\)](#) consists of all staff working in clinical biochemistry laboratories in all 14 NHS Scotland Health Boards. It is hosted by NHS, National Services Scotland and its stated purpose is to:

‘Bring together professionals from across Scotland to work in a coordinated manner to ensure the provision of high quality, clinically effective biochemistry services. By facilitating and fostering cooperation between clinical biochemistry departments the MDN aims to enable sharing of best practice, improve the evidence base for diagnostic tests, achieve harmonisation where possible, and provide a forum for the introduction and evaluation of new concepts and technologies.’

It also states that it is dedicated to ensuring that the right patients receive the right tests at the right time in the right way via [Demand Optimisation](#)– part of the Scottish Government’s broader programme in improving healthcare science. In the context of the SCBMDN, it is about working to reduce or eliminate unnecessary testing and enhancing decision-making in patient care.

The Network is collaborative, national and works across health board boundaries, and, amongst other things, aims towards consistency of practice and protocols in clinical biochemistry.

This Network could be the appropriate body to investigate testing protocols in labs across Scotland, in the context of the Demand Optimisation agenda to ensure consistency of thyroid hormone testing protocols across Scotland. A single, national process with accompanying advice could be of assistance to primary care practitioners when assessing patients.

DIAGNOSIS

Petitioner's position	Current mainstream diagnosis and treatment	Areas of contention in the evidence presented	Body or bodies responsible for effecting change in protocols	For possible consideration by the Committee/ Action taken
<p>Seeking more sensitive and informed diagnosis of hypothyroidism which:</p> <ul style="list-style-type: none"> - is not solely based on arbitrary, non-universal measurement range of thyroid hormones - recognises that hypothyroidism might be indicated even when initial biochemical testing might show normal function. 	<p>By blood test. Testing levels of TSH in first instance, in the context of presenting symptoms.</p> <p>Further testing can be requested and referral to endocrinologist maybe appropriate.</p>	<p>GPs are not well enough informed and/or not responsive to the presenting symptoms when a test result suggests 'normal' thyroid function.</p> <p>Too much emphasis is placed on arguably 'crude' testing for diagnosis, and during treatment leading to inappropriate or no treatment</p> <p>Patients who have symptoms (that are consistent with hypothyroidism) but whose TSH level is less than 10 are told that this means that their symptoms are not due to a thyroid problem and are not treated.</p> <p>Orthodox opinion is that in most cases mild or subclinical hypothyroidism (SCH) is not due to a chronic thyroid problem and will resolve itself, or that the raised TSH has another cause, not related to hypothyroidism. (however it is acknowledged that 20 – 50% will go on to develop hypothyroidism). It could be harmful to treat someone with SCH when their thyroid hormones are recorded as normal.</p>	<p>British Thyroid Association</p> <p>SIGN</p> <p>Scottish Clinical Biochemistry Managed Diagnostic Network (SCBMDN)</p>	<p>Thyroid testing is examined by the Scottish Clinical Biochemistry Managed Diagnostic Network (SCBMDN) in the context of the Demand Optimisation programme to ensure the standardisation of testing protocols across all labs in Scotland and the Network has not considered thyroid testing protocols in recent years.</p> <p>The Committee has already engaged with SIGN which is now working on a best-practice document with the petitioner.</p>

(v) Treatment

The petitioner wants to see natural desiccated thyroid (NDT) – extracted from porcine thyroid glands - available again. Up until the 1980s, this was the standard treatment prior to synthetics being available, but was phased out and removed from the National Formulary. It is not licensed for use in the UK.

The petitioner and others (Thyroid UK) believe that NDT provides effective treatment when levothyroxine (standard treatment) doesn't work, or when they do not receive a positive diagnosis of hypothyroidism due to testing alone recording normal function.

The petitioner would also like to see Liothyronine (also known as "L-T3") used more. This is licensed for use in the UK but is expensive and there is only one manufacturer, and there have been problems with supply in the past.

Standard treatment for hypothyroidism is with synthetic L-T4 (levothyroxine) and is appropriate for the majority of patients with primary hypothyroidism.

Levothyroxine (T4) is broken down by most people into T3, which is the active form of the hormone. It is argued that for some, this does not happen successfully, so continue to suffer symptoms.

It is important to note that most T3 production (80%) occurs via other metabolic processes and is associated with other organs – chiefly the liver and kidneys, **not** the thyroid gland. For this reason, treating with T3 is not deemed appropriate/relevant if someone has hypothyroidism – other conditions could be indicated.

Patients will, in many circumstances, require annual blood tests to check hormone levels. In exceptional circumstances, many of which have been described in the evidence presented to the Committee, such as persistent symptoms, would indicate referral to an endocrinologist, and possible treatment with Liothyronine (L-T3).

With regards to treatment, the HIS Technologies Scoping Report addressed the following questions:

- In patients diagnosed with hypothyroidism what is the evidence on the clinical and cost effectiveness of combined L-T4 + Liothyronine (L-T3) therapy?
- In patients diagnosed with hypothyroidism what is the clinical and cost effectiveness of treatment with natural desiccated thyroid extract?
- What is the evidence on the clinical and cost effectiveness of treatment of subclinical hypothyroidism?
- What is the evidence on the clinical and cost effectiveness of a trial of L-T4 in patients with symptoms suggestive of hypothyroidism but where thyroid function tests do not indicate hypothyroidism?

It concluded:

'A meta-analysis found no statistically significant differences between the clinical effectiveness of combined L-T4+L-T3 therapy and L-T4 monotherapy. In an analysis

of patient preference based on five crossover trials, 48% of study participants preferred combined therapy, compared with 27% who preferred L-T4 monotherapy.

Only one small trial comparing effectiveness of DTE with L-T4 was identified. There was no evidence of a difference between study periods on symptoms, general wellbeing and cognitive function.

A meta-analysis of studies of L-T4 treatment in patients with subclinical hypothyroidism reported no benefit to symptom scores or quality of life. Some small improvements in cardiac function tests were identified although the clinical significance of these is unclear. There was significant heterogeneity across studies and the study authors concluded that treatment should be based on clinical judgment and patient preference.

One small trial of L-T4 treatment in patients with symptoms consistent with hypothyroidism but with thyroid function tests within the reference range was identified. Across a battery of tests, clinical benefit of treatment was identified only in a test which assesses memory for non-verbal visual stimuli.'

This suggests that there is a need for further clinical studies to be conducted to test the questions posed.

The petitioner wants to see natural desiccated thyroid also known as thyroid extracts to be available as a treatment option. The standard clinical opinion across all the guidance (BTA, ETA, ATA) does not support the use of natural thyroid extracts. [The ATA position is as follows:](#)

'levothyroxine should remain the standard of care for treating hypothyroidism. We found no consistently strong evidence for the superiority of alternative preparations (e.g., levothyroxine – Liothyronine combination therapy, or thyroid extract therapy, or others) over monotherapy with levothyroxine, in improving health outcomes.'

On the issue of [combination therapy and the use of NDT](#) the ETA states:

'All these combination tablets (including those containing animal thyroid extract) are potentially harmful as due to their relatively high T3 content they carry a risk of inducing symptoms of thyroid hormone excess.'

The BTA 2015 statement concludes the following:

'There is no convincing evidence to support routine use of thyroid extracts, L-T3 monotherapy, compounded thyroid hormones, iodine containing preparations, dietary supplementation and over the counter preparations in the management of hypothyroidism.'

The NICE Clinical Knowledge Summary does not recommend the use of either combination therapy or NDT in primary care.

There appeared to be some confusion about the ability to influence the licensing of medicines in the UK. It was made clear that no authorities solicit applications to supply any medicine or product. It is solely a commercial decision taken by a pharmaceutical company or supplier if they wish to apply for a licence to supply a medicine or product for sale in the UK. Doctors are free to prescribe unlicensed medicines. The [GMC offers guidance](#) on this, which acknowledges that it is sometimes appropriate to prescribe unlicensed medicines and that a doctor's registration is not necessarily at greater risk if they do so:

'You are responsible for all prescriptions you sign and your decisions and actions when supplying and administering medicines and devices (or when they authorise or instruct others to do so).

Contrary to recent suggestions, GMC guidance does not include reference to any extra personal liability in relation to prescribing unlicensed medicines.

Importantly, prescribing unlicensed medicines will not put your registration at risk any more than other areas of practice covered by our guidance.'

The MHRA warns some caution:

'The responsibility that falls on healthcare professionals when prescribing an unlicensed medicine or a medicine off-label may be greater than when prescribing a licensed medicine within the terms of its licence.'

Licensing:

According to NHS Choices:

Before a medicine can be widely used in the UK, it must first be granted a licence.

While no medicine is completely risk free, a licence indicates all the proper checks have been carried out and the benefits of a medicine are believed to outweigh the risks.

This licence is also known as a marketing authorisation.

Licences are only granted if high standards of safety and quality are met during the whole development and manufacture of a medicine.

The product must also work for the purpose it is intended for if it is to be licensed.

In the UK, licences can be granted by:

- the [Medicines and Healthcare Products Regulatory Agency \(MHRA\)](#) – which can grant licences for medicines only in the UK
- the [European Medicines Agency \(EMA\)](#) – which can grant licences for medicines in the European Union (EU)

Before a licence can be granted, the medicine needs to be developed and tested.

Up to date information [from Medicines and Healthcare Products Regulatory Agency](#) MHRA regarding natural thyroid extracts and Liothyronine (as at 31 October 2016) states:

Currently :-

- There is no authorised medicinal product that contains natural thyroid extract
- There is only one authorised medicinal product of Liothyronine tablets: PL 00039/0432 TETROXIN TABLETS 20MCG (LIOTHYRONINE SODIUM BP 20MCG/TABLET), marketed by MERCURY PHARMA GROUP LIMITED

- MHRA held four scientific advisory meetings with companies who have enquired about submitting a proposed application for Liothyronine.
- MHRA has not received any enquiries from companies (or submissions) about the supply of natural thyroid extract.

The Scottish Government's listening exercise undertaken by Thyroid UK revealed that many patients who do not respond well to T4 had difficulty agreeing alternative treatment options with their GP. Some people feel their only option is to resort to private hormone testing and self-medication with unregulated, unlicensed products.

SIGN, the Royal College of General Practitioners and the petitioner are working on a best-practice document for treating patients who do not respond to T4 treatment.

TREATMENT

Petitioner's position	Current mainstream diagnosis and treatment	Areas of contention in the evidence presented	Body or bodies responsible for effecting change in protocols	Issues for Committee consideration
<p>The petitioner wants to see natural desiccated thyroid (NDT) available again. (Up until the 1980s, this was the standard treatment prior to synthetics but was phased out and removed from the National Formulary). It is not licensed for use in the UK.</p> <p>The petitioner and others (Thyroid UK) believe that NDT provides effective treatment when levothyroxine (standard treatment) doesn't work, or when they do not receive a positive diagnosis of hypothyroidism due to testing alone recording normal function.</p> <p>She would also like to see Liothyronine (also known as "L-T3") used more. This is licensed for use in the UK but is expensive and there is only one manufacturer, and there have been problems with supply in the past.</p>	<p>Standard treatment with synthetic L-T4 is appropriate for the majority of patients with primary hypothyroidism.</p> <p>Annual blood tests are indicated in many instances</p> <p>In exceptional circumstances (persistent symptoms) referral to endocrinologist, possible treatment with Liothyronine (T3) is also indicated</p> <p>The BTA guidance says of alternative treatments, including thyroid extracts: 'There is no convincing evidence to support routine use of thyroid extracts, L-T3 monotherapy, compounded thyroid hormones, iodine containing preparations, dietary supplementation and over the counter preparations in the management of hypothyroidism'</p>	<p>GPs might be reluctant to prescribe unlicensed medicines or products such as NDT.</p> <p>T3 is supplied by one company and is expensive.</p> <p>There appear to be very limited treatment options for those patients experiencing symptoms despite being prescribed L-T4</p> <p>Natural desiccated thyroid is not licensed, and therefore not regulated in the UK (and no company has sought to license it in the UK)</p> <p>GPs and Endocrinologists are able to prescribe NDT for individual patients, but in doing so accept responsibility for the health of the patient – as they do with whatever treatment they prescribe.</p> <p>Clinicians might fear accusations of malpractice and GMC involvement if they do prescribe, although the GMC has issued clear guidance that this is not the case, simply for prescribing an unlicensed product. However, they would be prescribing outwith the context of the quality and safety assurances of the UK and/or EU licensing authorities (MHRA and EMA) (see: Jerome Burne, "A cure for thyroid problems the NHS ignores – or quack doctor's poison? <i>Daily Mail Online</i>, 3/11/14).</p>	<p>Medicine and Healthcare Products Regulatory Agency (MHRA)</p> <p>Amdipharm Mercury Company Ltd. is the only licensed producer and distributor of Liothyronine (L-T3) in the UK. Neither the SG nor the MHRA can influence whether or not other manufacturers seek a licence to supply the medicine in the UK. This is a commercial decision for pharma companies</p> <p>SIGN best practice document is in progress with RCGP and petitioner</p> <p>Option for petitioner to lobby other pharmaceutical companies to consider application for licence to supply Liothyronine (L-T3) to UK to ensure more stable supply/introduce greater competition (and lower price)</p> <p>The petitioner could also lobby pharmaceutical companies or suppliers to apply for a licence to supply natural thyroid extract preparations to the UK</p>	<p>The Committee has no authority to influence applications to supply medicines or products – it is a commercial decision.</p> <p>Members could consider if it would be expected that a parliamentary committee would have the appropriate level of clinical and technical expertise to make clinical recommendations with regard to treatment options</p>

(vi) Research

There appears to be a consensus that continuing research is required to fully understand all the biochemical processes involved with thyroid function and the interaction between all the respective hormones, which are also associated with many processes and organs in the body.

The Scottish Government provided a copy of the randomised clinical trials in its submission dated [19 February 2016](#) and existing resources for diagnosis and treatment are informed by this research, such as the BTA position statement.

The petitioner believes that the research does not yet take full account of people who do not respond to standard (T4) treatment.

The Scottish Government advised that in Scotland, the Chief Scientist Office has responsibility with Government for the funding of clinical research (see submission dated [2 August 2016](#)). However, any research is dependent upon a proposal being brought forward and this has not occurred to date.

The ATA has made suggestions regarding future research:

‘Some examples of future research needs include the development of superior biomarkers of euthyroidism to supplement thyrotropin (TSH) measurements, mechanistic research on serum triiodothyronine levels (including effects of age and disease status, relationship with tissue concentrations, as well as potential therapeutic targeting), and long-term outcome clinical trials testing combination therapy or thyroid extracts (including subgroup effects). Additional research is also needed to develop thyroid hormone analogs with a favorable benefit to risk profile.’

Research is commissioned by a range of bodies and organisations such as:

- Commercial funders, including industry and private companies e.g. pharma
- Non-commercial funders, such as government departments, research councils, charities, National Institute of Health in USA (NIH) and the European Commission.

Below are links to some possible sources of further information regarding research routes (note this is not an exhaustive list):

- **Association of Medical Research Charities (AMRC)**
<http://www.amrc.org.uk/>
- **Chief Scientist Office (CSO)**
<http://www.cs.scot.nhs.uk/about/funding-2/>
- **Medical Research Council (MRC)**
www.mrc.ac.uk/Fundingopportunities/index.htm
- **National Institute for Health Research (NIHR)**
www.nihr.ac.uk/research/Pages/default.aspx

- **NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC)**
www.netscc.ac.uk/
- **UK Clinical Research Collaboration (UKCRC)**
<http://www.ukcrc.org/research-coordination/> [
- **UK Research Office (UKRO)**
<https://www.ukro.ac.uk/>

RESEARCH

Petitioner's position	Current research	Areas of contention in the evidence presented	Body or bodies responsible for effecting change	For possible consideration by the Committee
<p>Existing research is poorly designed to investigate the treatment needs of patients who do not respond to T4 (standard treatment) and safety concerns about natural desiccated thyroid need further investigation to see how these concerns can be addressed.</p>	<p>This link is to information on clinical trials as supplied by the Scottish Government on 2 August 2016</p> <p>A search of websites supplied in the narrative will provide some further information on other research and how research is commissioned.</p> <p>Information and links to hypothyroidism research since 2012</p>	<p>Lack of research/ lack of robust research internationally, particularly with patients who do not respond well to the standard treatment with L-T4</p>	<p>International research community, Pharma, Chief Scientists Office Scotland</p> <p>The petitioner could work with national third sector organisations such as Thyroid UK to work towards shaping and funding necessary research</p>	<p>The Committee could consider highlighting that there is potential need for further research into thyroid function and symptoms that persist despite standard treatment being followed etc.</p>

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SPICe Research

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