PE1463/DDDD

Scottish Government letter of 2 August 2016

Thank you for your letter of 4 July 2016 regarding the Public Petitions Committee's continued consideration of petition PE1463 (Calling on the Scottish Parliament to urge the Scottish Government to take action to ensure GP's and endocrinologists are able to accurately diagnose thyroid and adrenal disorders and provide the most appropriate treatment).

I will deal with your questions in turn:

1. **What action will the Scottish Government take to address the issues raised by the petition in light of Thyroid UK's survey?**

   We are grateful to Thyroid UK for undertaking this listening exercise. It is, however, worth reiterating that this was not a scientific survey and is thus likely to have an over-representation of people with adverse symptoms. It may not therefore be truly representative of all people on thyroxine. Nonetheless, this is an important group and it is an on-going concern for clinicians (GPs and specialists alike) when people have on-going symptoms. The survey responses are available to see at Thyroid UK's website.

   Both anecdotal and clinical observation can be useful to raise scientific questions, but in the meantime we must rely on the evidence base.

2. **Has the Scottish Government extrapolated Scottish figures from the survey**

   An online method was used where respondents were invited to complete the listening exercise from a variety of sources including the Thyroid UK website forum, Facebook and Twitter pages, Thyroid UK E-news and Thyroid UK members' magazine as well as being advertised on other relevant forums and Facebook pages. Demographic information was not collected, therefore it is not possible to extrapolate data for Scotland. Thyroid UK has, we understand, written to the Committee and provided statistical percentages in relation to their membership - approximately 8.7% (448 out of 5159) of the membership is from Scotland. There is nothing in the findings that would suggest that Scotland is different from the rest of the UK.

3. **Does the Scottish Government intend to implement any of Thyroid UK's recommendations?**

   Thyroid UK was not commissioned by the Scottish Government to make recommendations but the position is as under, based on expert clinical advice on each recommendation.

   <u>Recommendation 1</u>
   Conducting full thyroid function tests to include TSH, Free T3, Free T4 and thyroid antibodies (TPO and TgAb) as standard in patients with symptoms of hypothyroidism or hyperthyroidism will ensure prompt and accurate diagnosis and fewer erroneous diagnoses. By not undertaking all the thyroid hormone tests (along with vitamin and mineral testing to check for deficiencies), the NHS is spending massive funds on searching for other causes for patients' symptoms.

   Response:

This range of tests is sometimes, but not always, needed. If the diagnosis and treatment is clear then these extra tests may not be needed, but if there is uncertainty they may be. Testing is thus personalised to the individual, which is less costly to the NHS than using a battery of tests for all individuals. The tests required for an underactive thyroid are different to an overactive thyroid. This is therefore an individual clinical decision in each case.

Recommendation 2

If a patient has subclinical hypothyroidism with symptoms of an underactive thyroid, the patient should be given a trial of levothyroxine. It is unfair and unethical to wait until a patient's TSH levels reach >10. We speak to many patients who have all the symptoms of hypothyroidism but their doctors will not diagnose them as having hypothyroidism until their TSH reaches 10. Some of these patients are eventually given levothyroxine and their symptoms improve.

Response:

Recommendations are that thyroxine is not started until the TSH is greater than 10mU/L for individuals who have no symptoms, as there is quite a high rate of the thyroid recovering back to normal if the TSH is <10mU/L in such circumstances. It is a primary duty of a doctor to do no harm. It would be undesirable to start an individual on thyroxine tablets possibly for the long-term if they did not need it, however, for people with symptoms, especially if they have positive thyroid antibodies, then thyroxine is often started earlier, but the individual needs a full clinical examination and assessment first. This is in accordance with European, American and British evidence-based guidelines. A TSH of 10 mU/L is not a cut off ("magic figure") for all individuals. There is published data to show that the average TSH when people start thyroxine is around 8mU/L, indicating that the majority of people start thyroxine when the TSH is <10mU/L. There is further evidence that the average TSH concentration when an individual starts thyroxine is decreasing as time goes by suggesting that thyroxine is getting started at an earlier stage.

It is worth noting that abnormal thyroid tests may not be due to thyroid disease. There are non-thyroid related reasons why thyroid function tests (especially free T3 but also TSH and free T4) may be abnormal, and can correct as the non-thyroidal illnesses are treated. In addition, recent evidence suggests that people over 65 with higher TSH and lower free T4 have increased life expectancy, and that the reference range of TSH should probably be higher e.g. up to 6mU/L, for older people. An individual clinical decision based on their particular circumstances is required in each case.

Recommendation 3:

Laboratories should not be refusing testing if a GP/endocrinologist has requested this. The clinician has all the history of the patient and is requesting for a reason. Laboratories should accept that clinicians need certain testing carried out to make informed decisions about their patients.

Response:

Laboratories usually undertake what is requested of them, but sometimes it is helpful for them to guide clinicians, as they are experts in the field of testing, and can help as to what extra tests may be useful and what tests may not be. Laboratory experts may help clinicians identify when abnormal thyroid tests are not due to thyroid disease and when results are problematic.

Recommendation 4:

If certain tests are refused, patients should be informed of the reasons why they are being refused. Under the terms of the NHS Constitution -patients should be given reliable and relevant information in a form they can understand, and support to use it. This will enable the patient to participate fully in their own healthcare decisions and help them in making choices.

Response:
The NHS Constitution is applicable in England. In Scotland, the Charter of Patient Rights and Responsibilities summarises what people can expect when they use NHS services and receive NHS care in Scotland: http://www.gov.scot/resource/0039/00390989.pdf. If a test is "refused" as opposed to a clinician being guided by the Biochemical experts that a test is unnecessary, then this should be and usually is discussed with the individual. Such a situation would be very rare.

Recommendation 5:
GPs should be educated on the use and implications of thyroid testing including FT3 and DIO2 testing. If they do not understand these tests they cannot give their patients information on the same.

Response:
DIO2 gene testing is available, but there is no expert consensus as what implications this has for people in clinical practice as more research is needed in this area, therefore, there is no agreed role for DIO2 testing which is not recommended in any guideline. We are also advised that this finding has not been replicated in other trials and there are potential methodological flaws in the original trial as outlined by the authors themselves. It would be unreasonable for GPs to know any detail on this, as it would be impossible for them to know about every single possible unproven genetic test in every disease area.

Recommendation 6:
Personalised medicine is crucial in hypothyroidism. Doctors should ensure that patients' hormone levels are restored to a level that is optimal for them rather than just bringing the patient to just inside the reference range.

Response:
The dose of thyroxine can be adjusted, such that the TSH concentration can change within the reference range. It is a balance between maximum gain for the person within limits that are generally agreed to be safe for the person. Unfortunately, what may feel optimal to a person from a symptomatic point of view may be harmful, and it is the obligation of the doctor to point this out and discuss the implications. It is a primary duty of a doctor to do no harm. All treatment decisions are a matter for discussion and agreement between the individual and the doctor concerned.

Recommendation 7:
Address the very high prescription rate of antidepressants when patients have symptoms remaining. Check for symptoms that are specific only to hypothyroidism and if the patient has subclinical hypothyroidism give a trial of levothyroxine.

Response:
Unfortunately there are no individual symptoms specific only to hypothyroidism and many of the symptoms (e.g. tiredness, weight gain) are extremely common in the general population, and are usually due to lifestyle reasons. That is why it is

important to interpret the biochemical tests in conjunction with the symptoms. All symptoms associated with hypothyroidism can have other causes, although it is agreed that the greater the number of symptoms associated with hypothyroidism, the more likely people are to respond to thyroxine. All treatment decisions are a matter for discussion and agreement between the individual and the doctor concerned.

Recommendation 8:

After titrating the dose upwards, if symptoms do not abate, test Free T4 and Free T3 levels, to ensure that the patient is converting T4 to T3 optimally, and also test for the DIO2 polymorphism. If the patient is found to have low levels of FT3 or the DIO2 polymorphism, treat with a combination of levothyroxine and liothyronine. If the patient continues to have symptoms after taking liothyronine consider a trial of Natural Desiccated Thyroid (NDT) as it's known that a percentage of patients do not improve unless they take NDT.

Response:

There are patient reports of benefits from liothyronine and NDT, but existing clinical trials do not support these findings. The risks of treating with liothyronine and NDT are unknown. Risks of osteoporosis and heart problems may take many years to become apparent. The comments assume that free T3 and DIO polymorphisms provides a "complete picture", but does not acknowledge the compensatory effects of other aspects of hormonal metabolism at cellular level such as membrane transportation, intracellular metabolism e.g. ubiquitination and nuclear transcription/translation. Research indicates that the science is much more complex than previously supposed. All treatment decisions are a matter for discussion and agreement between the individual and the doctor concerned.

Recommendation 9:

Since there is no provision for up to 16% of patients who do not do well on levothyroxine, new guidelines should be designed to help clinicians support these patients or the current guidelines should be updated to include this. At the moment many clinicians cannot help these patients because they are not aware of the possible next steps.

Response:

The British Thyroid Association (BTA), European and American Thyroid Association have produced guidelines. In addition the BTA have produced a document specifically aimed to help GPs, and the British Thyroid Foundation (BTF) have a FAQs document for people.

In places the Thyroid UK document suggests that 12.5% (645 out 5159) of respondents had adverse symptoms, but as noted in the response to question 1 above, this survey is likely to have had an over-representation of people with adverse symptoms.

Recommendation 10:

If clinicians are not prepared to prescribe alternative treatments for hypothyroid patients, they should be accepting of the patient's decision to self-treat, especially if the patient has improved their quality of life. If a clinician knows that a patient is self-treating, notes regarding self-treatment by the patient should be put on the patient's notes so that research is showing correct data regarding the incidence of this.

Response:
All treatment decisions are a matter for discussion and agreement between the individual and the doctor concerned. Doctors advise what they think is best for the individual before them, but individuals may choose not to take that advice. It seems reasonable to record self-medication in the same way other "over the counter" medication may be recorded in the notes, (provided the individual chooses to provide information on self-treatment with the doctor(s) concerned).

Recommendation 11
GPs should be educated on all the thyroid hormone replacements, since they should be monitoring patients who are taking liothyronine or NDT. Thyroid UK has heard of many instances of patients being more educated than clinicians in the use of these medications.

Response:
It is reasonable for GPs to have some awareness of, but not a full in depth understanding of unlicensed medications. It would be impossible for GPs to know about all unlicensed medications in all disease areas. Otherwise GPs will likely follow guidance as recommended and evaluated by experts in thyroid disease.

Recommendation 12
Patients should be kept on the brand of levothyroxine that suits them rather than being given the brand that is currently stocked by the pharmacist, as different brands can cause adverse effects in some patients. Any change of brand might also result in different bio-availability. At present pharmacies have control over which brands they purchase, dependent on price, and this is not good for patient outcomes.

Response:
There is strict regulation within UK pharmaceuticals ensuring that there is the same amount of thyroxine in each medication.

Recommendation 13
Health boards should consider the cost of further consultations with various specialists as well as further medications for patients who do not do well on levothyroxine. The reason patients are not given alternative thyroid hormone treatments are mostly due to the fact that benefit is not certain or due to cost. Keeping patients on a medication that makes them ill is a false economy.

Response:
If an individual is not doing well on thyroxine, then clinicians will usually investigate reasons for this. If that fails to identify a cause then the individual can be, and frequently is referred to an Endocrinologist. All treatment decisions are a matter for discussion and agreement between the individual and the doctor concerned.

Recommendation 14
Health boards should consider the ethics of refusing a particular treatment for a patient who is currently benefiting from this treatment. If a clinician can see evidence of a benefit for a patient, their current treatment should be continued.

Response:

All treatment decisions are a matter for discussion and agreement between the individual and the doctor concerned. This is an individual clinical decision in each case, bearing in mind a primary duty of a doctor to do no harm as noted above in recommendation 2.

Recommendation 15

Patients with hypothyroidism should be given key information about their condition to enable them to understand the effects of hypothyroidism, how to take their medication to allow for optimum absorption, how important it is to remember to take their medication daily and what the possible side effects may be if they take too much.

Response:

The British Thyroid Foundation patients' support group has a number of leaflets available for people available from their website

Recommendation 16

Clinicians should treat patients with dignity and respect, even if they disagree with the patient's requests for further testing or alternative medication.

Response:

We need to ensure that we foster mutually beneficial partnerships between patients, their families and those delivering healthcare services which respect individual needs and values and which demonstrate compassion, continuity, clear communication and shared decision making.

The Chief Medical Officer for Scotland reiterated the vital importance of this person-centred ethos in her 2015 annual report (http://www.gov.scot/Publications/2016/01/3745), describing the need to "deliver healthcare that focuses on true value to the patient"; the need to "place collaborative, relational decision-making and planning at the heart of our system" and the absolute imperative "to be focusing completely and relentlessly".

Recommendation 17

Clinicians should fully discuss the options and implications (benefits and harms) of all thyroid hormone replacement medications for hypothyroidism.

Response:

All treatment decisions are a matter for discussion and agreement between the individual and the doctor concerned. It is a primary duty of a doctor to do no harm (see also response to Recommendations 2, 6 14 and 16).

Recommendation 18

Clinicians should ensure that they have read the NHS Constitution and should abide by its principles.

Response:

The NHS Constitution applies in England. The Charter of Patient Rights and Responsibilities summarises what people can expect when they use NHS services and receive NHS care in Scotland: http://www.gov.scot/resource/0039/00390989.pdf

Recommendation 19

More research should be done on subclinical hypothyroidism, the polymorphic variants of DIO1 and/or DIO2 including how many patients have these polymorphisms, the use of liothyronine in patients who have low levels of FT3, the use of slow release liothyronine and the use of NDT.

Response:
There are some experts in the UK (and elsewhere) who are looking at many of these issues. DIO polymorphisms are only one small area of active research. Drugs looking into activation of specific thyroid receptor sub-types have also had a lot of attention, but as yet no useful outcome for clinical practice.

Recommendation 20
Research should be done to find out how many GPs are treating with T3/NDT and the reasons why and also how many GPs are monitoring patients who are self-treating with these medications.

Response:
That would be helpful information, although randomised controlled trials are more informative than such observational studies.

4. Is the Scottish Government minded to fund clinical research into treatment with L-T3 for patients who do not respond well to L-T4.

Within the Scottish Government, the Chief Scientist Office (CSO) has responsibility for the funding of clinical research. The CSO's research funding committees consider applications from all areas of medicine, the only stipulations being that the research is led by a Scottish-based clinician or scientist, and that it has the potential to improve the health and well-being of the people of Scotland. The CSO would welcome applications for research projects aimed at identifying optimum treatment modalities for hypothyroidism. These would go through the same rigorous independent review process as applications in any other clinical area.

You may also wish to be aware that the BTA has published a position statement, summarising the key points from the recently published American Thyroid Association (ATA) and European Thyroid Association (ETA) guidelines, and made recommendations on the management of primary hypothyroidism.

The BTA, the Association of Clinical Biochemistry (ACB), British Thyroid Foundation (BTF), The Royal College of Physicians (RCP) and the Society for Endocrinology (SFE) agreed the following statements in relation to treating people who do not respond well to L-T4:

- Synthetic L-T4 remains the treatment of choice in **hypothyroidism** with the aim of therapy being to restore physical and psychological well-being while maintaining normal laboratory reference range serum TSH levels (1/++0).

- It is acknowledged that a proportion of individuals on L-T4 are not satisfied with therapy and have persistent symptoms despite a normal serum TSH. Such symptoms should be given due consideration and patients should be thoroughly evaluated for other potential modifiable conditions.

- L-T4/L-T3 combination therapy in patients with hypothyroidism should not be used routinely, as there is insufficient evidence to show that combination therapy is superior to L-T4 monotherapy.

- If a decision is made to embark on a trial of LT4/L-T3 combination therapy in patients who have unambiguously not benefitted from L-T4, then this should be reached following an open and balanced discussion of the uncertain benefits, likely risks of over-replacement and lack of long-term safety data.

- 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.

I hope this information is helpful.

Yours sincerely

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