Thyroid UK Stakeholder Feedback to PrescQIPP Bulletin 121 in Regard to Liothyronine

Although the PrescQIPP Bulletin 121 is factually correct, Thyroid UK is very concerned about the impact that this document is having on patients.[1]

We have noticed that over the past year local Clinical Commissioning Groups have been informing doctors and endocrinologists that they should not be prescribing liothyronine (T3) to patients and this has led to many patients being switched from T3 to levothyroxine (T4), even if they have been extremely well on this drug for many years.

The PrescQIPP DROP-List is an accumulation of medicines that are regarded as low priority, poor value for money or medicines for which there are safer alternatives.

We assume that liothyronine would come under the poor value for money in this list since Thyroid UK believes it is neither a low priority (due to the fact that 5% - 15% of patients still have remaining symptoms on T4 alone[2-7]) nor a drug for which there are safer alternatives (there is no alternative for a patient who cannot convert T4 to T3 or who has had a thyroidectomy and is therefore missing the 20% of T3 that a normal thyroid produces.[8 9] Cost being the cause is certainly borne out by what doctors are telling patients who are being taken off T3.

In respect of the PrescQIPP recommendations, it is clear that PrescQIPP are supporting the practice of switching all patients from T4 to T3 without consulting any patients.

Thyroid UK is very concerned about the recommendations, *"Review all patients taking liothyronine (alone or in combination with levothyroxine) for suitability for switching to levothyroxine. Switch all suitable patients to levothyroxine. For patients under the care of a relevant specialist, involve them in the decision to switch to levothyroxine." and "It may be necessary in some cases to establish patient is genuinely hypothyroid before swapping (historically confirmed on biochemistry in accredited NHS lab or if not stop treatment and show thyroid stimulating hormone (TSH) rise). In these cases, start with standard dose of levothyroxine and titrate."*

What guidance is there for GPs on the "suitability" of patients who can be switched? From what we are seeing, there is no test that is being done for suitability. GPs are simply switching all patients to levothyroxine alone.

We believe it is unethical to take patients off of thyroid medication when they have been taking this for years and are extremely well. Your recommendation to establish the validity of the patient's hypothyroidism diagnosis may very well encourage GPs to take this step, even though it is not necessary, purely because the patient was initially diagnosed, for example, by a private GP rather than an NHS GP.

The recommendation, *"CCG Medicines Management Teams should liaise with local endocrinologists to ensure that prescribing is consistent across the interface between primary and secondary care."* is unclear.

It is assumed that this means that both clinicians in primary and secondary care should not prescribe T3 for their patients. This recommendation prevents clinicians from using their medical experience and autonomy to act in the patients' best interests since they know the patient and the medical history of the patient.

The last recommendation, *"As with all switches, these should be tailored to the individual patient."* will be ignored by GPs as in hypothyroidism there seems to be no individuality in treatment especially since T3 is now technically banned, even in specialist care.

In regard to your, *"Rationale for switching to levothyroxine*" we have the following comments:

- *Levothyroxine (L-T4) is a prodrug and is converted to liothyronine (L-T3) in the body.[3] Prior to the 1970s, synthetic combinations of levothyroxine and liothyronine or desiccated animal thyroid containing varying amounts of thyroid hormones were used, but these have now been replaced with the use of levothyroxine monotherapy.[4]*

  It is well known that 5% - 15% of patients have remaining symptoms on levothyroxine and doctors are frustrated by this.[2-7] According to patients who have contacted us, without the current BTA statement and the PrescQIPP Bulletin 121 many doctors would be treating patients with the addition of T3 or with natural desiccated thyroid (NDT) and these patients would be well with no symptoms remaining.[1]

  The PresCQIPP statement is misleading by suggesting implicitly that because NDT products were inconsistent originally they still are today. It omits to acknowledge the correction of the original variability in NDT content of T3 and T4, as found in much more tightly regulated and consistent products today, more closely and adequately controlled by appropriate Pharmacopeias.

- *Levothyroxine is the NHS thyroid hormone of choice as it is cost-effective, suitable for once daily dosing due to its long half-life and provides stable and physiological quantities of thyroid hormones for patients requiring replacement.[4]*

  It may be *cost effective* but it is not *effective* for 5% - 15% of patients.2-7

  Cost in these circumstances cannot ethically override clinical effectiveness.

- *Liothyronine is not routinely recommended for prescribing as it has a much shorter half-life and steady-state levels cannot be maintained with once daily dosing.[4]*

  Patients are extremely happy to dose two or three times a day.[1] Sustained-release T3 is available which would negate the use of two to three times a day dosing.[10]

- *The combination of levothyroxine and liothyronine, in both non-physiological and physiological proportions, has not consistently been shown to be more beneficial than levothyroxine alone with respect to cognitive function, social functioning and wellbeing. The variation in hormonal content and large amounts of liothyronine may lead to increased serum concentrations of L-T3 and subsequent thyrotoxic symptoms, such as palpitations and tremor.*[4]

  Although not consistently shown to be more beneficial in studies, patients in some of the studies preferred the use of T3 with their levothyroxine – *"Overall, of the 27 study subjects who completed the trial, 7 preferred standard treatment, 8 perceived no difference, and 12 preferred substitution treatment"*[11] Unfortunately, patients are never listened to.[1]

  If the dose of T3 is titrated slowly and the patient is monitored closely, increased serum concentrations of L-T3 and subsequent thyrotoxic symptoms, such as palpitations and tremor, should not be seen.

  The Safety review of liothyronine use: a 20 year observational follow up study by Prof Graham Leese and Enrique Soto-Pedre showed *"No increased risk of fractures or atrial fibrillation in patients taking liothyronine compared to L-thyroxine was demonstrated. There was an increased risk of mental health disorders if liothyronine was used alone."* (http://www.endocrine-abstracts.org/ea/0038/ea0038OC5.6.htm)

  The argument is inconsistent and misleading. So long as the content of T3 is known in a preparation there is no need, and certainly no inevitability, for overdosing. It is not clear as to which medication your comment, "The variation in hormonal content —" refers but actually does not apply to either pure T3 preparations or to natural desiccated thyroid extracts, both of which are now closely equivalent source-to-source.

- *There is currently insufficient evidence of clinical and cost effectiveness to support the use of liothyronine (either alone or in combination) for the treatment of hypothyroidism.*[5,6]

  We note that most studies on T3 + T4 state that more research needs to be done. At what point will there be enough research on this topic? How many studies will there need to be that shows some patients prefer T3 added to their T4? Perhaps this statement could be added to your recommendations.

  As appropriate and well-designed trials have not as yet been carried out and there seems to be no intention to do this, patients will continue to be ill on levothyroxine alone.

- *Evidence supports the use of thyroxine alone in the treatment of hypothyroidism, with this usually being prescribed as levothyroxine.*[2]

  It seems that the evidence that a significant number of people do not do well on levothyroxine and that the European Guidelines state that an experimental trial of T3 for patients can be actioned has been ignored.

- *Liothyronine (available as licensed 20 microgram tablets and unlicensed [5] microgram tablets) is considerably more expensive than levothyroxine.[6] Many other liothyronine-containing preparations (such as Armour Thyroid) are also unlicensed, therefore the safety and quality of these products cannot be assured.*

  Thyroid UK believes that this is the real reason that patients are being switched to levothyroxine. Time and time again, patients are told by their doctor that they can't prescribe it because it is too expensive.

- *Liothyronine is subject to supply issues and the amount of active ingredient may not be standardised so can vary from batch-to-batch, providing variable control.*

  There has been supply issues in the past but not for a few years. This is because there is only one manufacturer of this medication in the UK. There are several brands of T3 in Europe that are easily accessible (and, indeed, much cheaper than the UK brand) should there be any supply issues by the UK manufacturer in the future.

  The issue of one licenced manufacturer in the UK who has severely inflated the cost of liothyronine to the NHS should be addressed rather than restricting a life-saving hormone due to cost. For parity, NHS Scotland patients cannot be refused a medication on cost basis and this should therefore not be happening in England.

  There have also been supply issues with certain brands of levothyroxine which causes problems for patients who prefer a particular brand.[12] Levothyroxine also varies from batch to batch (90.0-105.0% of the declared amount of levothyroxine sodium in each tablet)[13] and, indeed, there have been withdrawals of this medication.[14] The T3 content of tablets are standardised in the same way as levothyroxine.

  Thyroid UK feels that this statement should therefore be removed from this bulletin as it is not a balanced statement.

- *UK and international guidelines[5,8,9] found no consistently strong evidence for the superiority of alternative preparations (L-T4 + L-T3 combination therapy or thyroid extract therapy – preparations containing dried animal thyroid extracts, such as Armour Thyroid) over monotherapy with levothyroxine in improving health outcomes. It is recognised that some patients on levothyroxine remain symptomatic despite treatment leading to TSH levels in the therapeutic range. The reasons for this are not fully understood and such patients should be under the care of an endocrinologist.[2]*

  The European Thyroid Association guidelines (2012 ETA Guidelines: The use of LT4+LT3 in the Treatment of Hypothyroidism) recommended the following:

  - (12) As the currently available L-T4 + L-T3 combination preparations contain a L-T4/L-T3 dose ratio lower than 13: 1, it is recommended to use

separate L-T4 and L-T3 tablets in L-T4 + L-T3 combination therapy (1/+00).

- (13) It is recommended that L-T4 + L-T3 combination therapy should be monitored by thyroid function tests in blood samples withdrawn before morning medication has been taken, aiming at normal serum TSH, free T4, free T3 and free T4/free T3 ratio (1/++0).

- (14) If dose adjustment of L-T4 + L-T3 combination therapy is necessary to achieve a normal serum TSH, free T4, free T3 and free T4/free T3 ratio, it is suggested the dose of just one of the components is changed, preferably of L-T3 (2/+00).

- (15) It is suggested that treatment of hypothyroidism by the combination of L-T4 and L-T3 should be supervised by accredited internists/endocrinologists (2/++0).

The conclusion of the ETA guidelines was, "L-T4 + L-T3 combination therapy should be considered solely as an experimental treatment modality. The present guidelines are offered to enhance its safety and to counter its indiscriminate use."

We believe the PrescQIPP bulletin should state this to clarify things for GPs and for transparency.

- *The BTA does not recommend the routine prescribing of additional liothyronine in any presently available formulation, including Armour Thyroid, as it is inconsistent with normal physiology, has insufficient evidence to show that combination therapy is superior to L-T4 monotherapy, and may be harmful.[2] There is no evidence to support the use of L-T3 monotherapy.[2]*

  The BTA states that it does not recommend the **routine** use of T3. This should not be construed as **do not ever use.**

  If NDT is inconsistent with normal physiology, so then is levothyroxine alone since the human body produces both T3 and T4 in a normal state. Medicine is assuming that the body will easily take up the strain by making more T3, which plenty of recent evidence shows is not the case for a strong minority of patients.

- *However, the BTA statement advises that some patients, who have "unambiguously not benefited from L-T4, may benefit from a trial of L-T4/L-T3 combination therapy. They should be supervised by accredited endocrinologists with documentation of agreement after fully informed and understood discussion of the uncertain benefits, likely risks of over-replacements and potential adverse consequences and lack of safety data.[2] The statement goes on to say that many clinicians may not agree that a trial of L-T4/L-T3 combination may be warranted in these circumstances and their clinical judgement must be recognised as being valid given the current*

understanding of the science and evidence of treatments.[2] A set of questions and answers relating to the statement that may help support discussion with patients is available here: http://www.btf-thyroid.org/images/documents/FAQ_for_BTA_Hypothyroidism_Statement.pdf"

Unfortunately, the clinical judgement of doctors and endocrinologists does not seem to enter into the picture. Local CCGs along with pharmacists now seem to have the right to control what a doctor or endocrinologist does, something that Thyroid UK finds alarming.

- *The symptoms of an underactive thyroid are not specific to the thyroid and may be due to many other conditions. If the TSH is within the reference range and dose adjustment has not helped, then the doctor should look for other causes of these symptoms. The list of possible alternative conditions is long but includes pernicious anaemia, coeliac disease, vitamin D deficiency, sleep apnoea, poor lifestyle and lack of sleep, depression, fibromyalgia, chronic fatigue syndrome and side-effects of medications.*

  Thyroid UK suggests that once a doctor has ruled out these conditions as a cause of leftover symptoms, T3 should be prescribed on an experimental trial basis. Unfortunately, many patients are automatically being diagnosed with depression, fibromyalgia or CFS/ME rather than the clinician look into T3 levels.

  This statement relies on the now discredited idea that TSH normalisation proves adequacy of treatment. This idea has been completely refuted in recent papers. Such a position encourages consideration of alternative problems far too easily.

- *Desiccated thyroid products (such as Armour Thyroid, ERFA) are unlicensed products in the UK, derived from pig thyroid, and contain an excessive amount of L-T3 in relation to L-T4*

  Whilst the ratio of T4 to T3 in NDT differs from a human thyroid, we know that many people resolve all of their symptoms on this medication. There has been some research in this regarding NDT that shows patients improve on this medication.[15-18]

  However, this different ratio of T4 and T3 is unimportant if the patient is dosed according to the T3 content, disregarding the T4 as an inactive prohormone.

- *Over-treatment with L-T4, when given alone, has similar risks to over-treatment with L-T3, e.g. palpitations and tremor, atrial fibrillation, strokes, osteoporosis and fracture. It is difficult to get dosing of L-T3 right and therefore the risk of over-treatment is high.[2]*

  We know from what patients have told us that doctors are increasing the dosage of levothyroxine to try to relieve symptoms in patients which is causing palpitations and tremor etc so there is the same risk as treatment with

T3. However, a careful trial of T3 could eliminate this risk. The Safety review of liothyronine use: a 20 year observational follow up study by Prof Graham Leese and Enrique Soto-Pedre showed *"No increased risk of fractures or atrial fibrillation in patients taking liothyronine compared to L-thyroxine was demonstrated. There was an increased risk of mental health disorders if liothyronine was used alone."* (http://www.endocrine-abstracts.org/ea/0038/ea0038OC5.6.htm)

It seems that many doctors are working towards individualised treatment for hypothyroidism[19] but the NHS are trying to maintain a one size fits all strategy for patients with hypothyroidism.

What needs to be remembered is that the BTA statement refers to primary hypothyroidism. There are no guidelines specifically for secondary (central) hypothyroidism and we believe that many people actually have secondary hypothyroidism, possibly due to things such as previous head injury or the DIO2 polymorphism.[20, 21, 22] However, secondary hypothyroidism can often be missed because only the TSH test is done.[21]

We believe that our Hypothyroid Patient Experiences Survey will be useful for you to read, especially since it includes recent research regarding deiodinases including the polymorphism DIO2 which is not mentioned in your bulletin but which is very relevant for people who have this gene as it means that they cannot convert T4 to T3 and therefore require T3 treatment.[1] Unfortunately, the NHS does not routinely test for this and therefore symptomatic patients are being denied liothyronine which consigns these patients to decades of ill health.

We notice that you include the Health Improvement Scotland Technologies Scoping Report of 22nd February 2014 in your list of research. In this document it states, "UK guidelines for the use of thyroid function tests published in 2006[2] were based on a nonsystematic review of generally poor quality evidence from the United States (US) National Academy of Clinical Biochemistry (now archived)[8]. This begs the question, "If the TSH test was derived from poor quality evidence, how can we be sure that patients are being treated safely and adequately?

There are some very pertinent research studies found here: http://www.thyroidchange.org/related-research.html#Additional

In conclusion, Thyroid UK feels that PrescQIPP Bulletin 121 should be looked at again and changed to include more research which will make it a more balanced document. Clinicians should be made more aware that a trial of T3 of slow release T3 is a possibility for patients who have remaining symptoms on levothyroxine.[22 23]

One point that we would like to make is that there are no NICE guidelines for primary or secondary hypothyroidism. Statements and Guidelines do not have to be adhered to if the doctor feels something different would be in the best interests of his patient.[24] (http://www.bmj.com/content/350/bmj.h841/rapid-responses)

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