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The Thyroid Patient Advocacy –UK (TPA-UK) response to the British Thyroid Association's (BTA) Statement on the Use of Combination Thyroxine/Triiodothyronine (Liothyronine) Therapy

Introduction

The Operating Framework for the NHS in England 2008/09 states: "This year, improving patient experience is an explicit priority rather than an assumption" and "underpinning our whole approach to these areas is the explicit understanding that raising the satisfaction of the patients who use our services, and increasing the confidence of the public who fund it, must be at the heart of all we do".¹

Thyroid Patient Advocacy-UK, also known as TPA-UK (a thyroid patient advocacy and support organisation), believes that the experience of patients is *not* being considered in the diagnosis and treatment of hypothyroidism, and NHS doctors fail to offer alternative therapy if L-thyroxine is ineffective in resolving symptoms or is poorly tolerated by patients. Although 'evidence based medicine' is to be applauded, much of the evidence base for the treatment of hypothyroidism is based on research that does *not* consider the patient's experience and may be flawed.^{2,3,4}

In a letter to the editor of the *British Medical Journal* (2003), Blanchard highlights why many studies fail to demonstrate the positive effects of combination therapy, which includes "the failure to keep the T4 tissue level up causes the beneficial effect of adding T3 to wane over time" and, on combination therapy studies by Walsh (2003)⁵ and Sawka (2003)⁶ he writes, ". . . these studies are flawed due to the incorrect dosages of T4 and T3".⁷

In a survey of 1500 hypothyroid patients undertaken by TPA-UK in 2005-2006, the dissatisfaction of many patients is highlighted. Of 1500 respondents, 93.8% (n=1407) had not been told of medicines other than L-thyroxine by their medical practitioner. 38.8% (n=768) felt they had "not been dealt with very well" or "not very well at all" by their doctor whilst seeking a diagnosis of their symptoms; 233 (15.5%) had given up paid employment; 300 (20%) had taken time off work as a result of thyroid illness; 500 (33.3%) felt their close relationships had been affected by thyroid illness and 632 (42.1%) had stopped or altered their exercise routines as a result of their symptoms. When asked of those patients undergoing L-thyroxine therapy, "Do you feel that you have fully regained your optimal state of health?", 1176 (78.4%) Answered "No".⁸

A further example of patients' dissatisfaction through lack of information and effective treatment for hypothyroidism was shown following an article on hypothyroidism in the Health Section of the *Daily Mail* (January 2008), which included information about the success of combination therapy (synthetic and natural) other than L-thyroxine alone therapy, and information about TPA-UK. The response from the general public requesting further information was so great that the *Mail's* switchboard was inundated with calls and they were unable to cope. A team of helpers was brought in to meet the demand.⁹

The International Hormone Society, currently the third largest international endocrine society with over 1800 physician members worldwide, has published a consensus on thyroid treatment that includes T4-only preparations, combinations of synthetic and natural (Armour) T3/T4 and T3-only therapy, whichever is in the best interest of the patient.¹⁰ The consensus is supported by much scientific evidence, and over 1600 signatures from physicians have been received supporting this consensus.¹¹

Further evidence of patients' dissatisfaction with T4 only therapy can be seen on the 'International Thyroid Patients' Petition for Better Diagnosis and Treatment Choice for Hypothyroid Patients'. Over 700 patients have signed this petition to date.⁵²

TPA-UK believes that the BTA's statement on the use of combination therapy does not consider the patient's experience and that this statement fails to present a balanced argument based on the available evidence. TPA-UK therefore provides herewith a response based on the literature and available research evidence not considered by the BTA.

BTA Statement:

A. There is no currently available tablet preparation containing thyroxine and tri-iodothyronine (T4/T3) in a combination that adequately reproduces the relative quantities of these hormones produced by the human thyroid gland. Neither is there a preparation that produces a sustained release of thyroid hormones in a pattern similar to that from the human thyroid gland.

Indeed, there is no tablet preparation that contains thyroxine (T4) and triiodothyronine (T3) in a combination that adequately reproduces the relative quantities of these hormones produced by the human thyroid gland. Most T3/T4 synthetic combinations contain a higher amount of T3 relative to T4 than the quantities produced by the human thyroid gland. Nevertheless, the T4/T3 combinations reproduce the human thyroid hormone production more closely than do thyroxine-only preparations, which contain only T4 and not T3, which is the most biologically active thyroid hormone. Thyroid extract, Armour Thyroid, USP, comes close to the ideal. There is no requirement for a synthetic preparation when natural thyroid extract has been used safely and effectively for over 100 years¹² and when synthetic preparations of T4/T3 can be titrated effectively.⁷

Whilst the ratio of T3:T4 in Armour® Thyroid is higher than that produced by the human thyroid gland, estimated to be secreted in a ratio of 15:1¹³ the ratio of these two hormones in the circulation does not represent the ratio secreted by the thyroid gland, since about 80% of peripheral T3 comes from monodeiodination of T4 hormones.¹⁴

In response to the second sentence of the aforementioned BTA statement 'A': Firstly, as the human thyroid hormone production is variable throughout the day and as it is not sustained naturally, there is no necessity for a sustained release preparation. Thyroxine continually circulates in the human body and as required is converted into the biologically available thyroid hormone T3. In some people, conversion of T4 to the active T3 is poor and many studies have demonstrated that additional T3 is beneficial for some hypothyroid patients.^{15, 16, 17, 18, 19, 20, 21, 22}

Secondly, in natural thyroid extract, the T4 and T3 are contained in larger thyroglobulin molecules that are more slowly absorbed and therefore release their T3 and T4 molecules at a slower rate. This enables more consistent availability of T4 and T3 over a 24-hour period than is provided by synthetic T4/T3 preparations or T4 alone.

BTA Statement:

B. Having been disregarded as a therapeutic approach to the treatment of hypothyroidism since the 1970s, interest in combination thyroxine/tri-iodothyronine (T4/T3) therapy was re-ignited by a study of 31 patients published in 1999.² Although this study showed promising results, with improvement in quality of life, well-being and brain (psychometric) function with combination therapy, the majority of the patients in the study had been treated previously for thyroid cancer. The relatively high doses of thyroxine that formed the routine treatment for thyroid cancer (compared to a lesser replacement dose that would be normal in hypothyroidism) could have confounded the results of the study.

C. Since this initial study, there has been a further seven rigorously conducted ("randomised, double-blind, placebo-controlled") studies, encompassing more than 900 hypothyroid patients (summarised in refs. 3 & 4). None of the subsequent studies showed a beneficial effect of combined T4/T3 therapy on measures of well-being, health and mental functioning. Three of the seven studies show harmful or undesirable effects of the T4/T3 combination.

The BTA statements 'B' and 'C' are considered, and responded to, together. In the study, BTA refer to in their statement 'B' (Bunevecius et al 1999) combined thyroxine / liothyronine treatment was shown to be superior to thyroxine mono-therapy in terms of mood and neuropsychological function in a group of 17 thyroid cancer patients and 16 chronic autoimmune thyroiditis patients.²¹ In a follow-up study²³ patients treated for thyroid cancer showed more mental improvement than those with autoimmune thyroiditis, possibly because

the thyroid cancer patients were more dependent on exogenous thyroid hormone and were therefore receiving higher dosages.

Subsequently a number of studies failed to reveal any benefit for combined therapy. However, it must be noted that the patients in these studies received low doses of thyroid hormone, titrated according to TSH level, a poor marker for thyroid hormone tissue response. Other studies have shown that treatment with T4 only does not succeed in achieving complete cellular euthyroidism in the target organs^{24, 25} and studies of thyroidectomized rats show that thyroxine alone does not ensure euthyroidism in all tissues but that combination T3/T4 therapy does.^{26, 27} and one study using T4 alone on patients with sub clinical hypothyroidism showed decrements in health status, psychological function, working memory, and motor learning.²⁸

In humans, T4/T3 treatments reduce serum cholesterol and increase the speed of the Achilles tendon reflexes better than T4 treatments alone.²⁹ Better prevention of goitre is obtained with T3/T4 combination therapy than with T4 only therapy, even if T4 is given at doses seven times higher those of T3/T4 treatments.³⁰

Prior to the introduction of modern thyroid function testing thyroid hormone titration was based primarily on patient signs and symptoms. The current TSH dominant approach produces lower levels of supplementation and significant morbidity.³¹

Considering the studies findings related to heart disease, it is interesting to note here that historically, hypercholesterolaemia was one of the clinical signs by which hypothyroidism was diagnosed. There has been no attempt to replicate the original Bunevicius research using adequate doses of thyroid hormone.

A further confounding issue is that this type of research is based on aggregated response. Thyroid hormone levels are not optimised for each patient. For a given titration strategy individual patients may be under or over medicated. Further research is needed on selected patient groups in order to determine the optimum supplementation strategy, according to the cause of hypothyroidism and individual patient response.

Other methodological issues affecting the quality of research are highlighted by Dr Lowe, who notes, in a critique of a paper by Kaplan et al, "as in other studies,^{2, 3, 4, 32, 33, 34, 35, 36} the thyroid cancer patients undoubtedly improved more because of their higher thyroid hormone dosages. Kaplan et al conjectured, however, that thyroid cancer patients improved more, not because of their higher dosages of thyroid hormone-but because they differed in some relevant but undetermined way from autoimmune thyroiditis patients.³⁷

There is further research evidence to support the use of T4/T3 combination therapy at the higher dosage levels which suppress the TSH, rather than a supplemental level dose, and in which the study results were not "confounded".^{32, 33, 34, 35, 36}

Other research has shown that patients report feeling better with TSH-suppressive dosages of thyroid hormone.^{38,39,40,41} Moreover, psychiatrists report that dosages of T3 higher than at only replacement level augment the depression-relieving effects of antidepressants.^{37, 32, 33, 34, 35, 36}

One double-blind, randomised, controlled trial studied 141 patients with primary autoimmune hypothyroidism who were randomised to groups treated with T4/T3 in a ratio of either 5:1 or 10:1, and a control group that continued with their previous T4-only treatment.⁴² After 15 weeks, the study showed a clear preference by patients for the combination treatments, and in particular, the 5:1 treatment featuring a higher level of T3, versus the T4-only treatment.

In another study in which patients were rendered hypothyroid by therapeutic destruction of the thyroid gland, some participants were given TSH-suppressive dosages of thyroid hormone and others given T4 replacement. Those on TSH-suppressive dosages did not gain excess weight; those on T4-replacement did. The researchers concluded that T4-replacement was the cause of the excess weight gain.⁴³ Other studies have shown that treatment of obesity using T3 alone with a very low calorie diet helps reduce weight,^{44, 45, 46, 47, 48, 49, 50, 51} and interestingly, a study published in the European Journal of Endocrinology (Ortega et al 2008) concluded that T3 concentrations might play a role in the regulation of insulin secretion.⁵²

These published reports are consistent with thousands of cases from thyroid patient support groups in the UK and worldwide where hypothyroid patients have recovered from their symptoms and other health problems with TSH-suppressive dosages of thyroid hormone *after* T4-replacement failed to help them.^{53, 54}

Therefore, there is much research evidence that demonstrates the beneficial effect of combination T4/T3 therapy. It is unfortunate that many of the studies undertaken have been small and often non-randomised. There is a lack of evidence from large-scale human clinical trials which demonstrate the safety and efficacy of using T3 or thyroid extract versus levothyroxine and which consider the patient's experience and preferences. Many doctors working in the field of thyroid disease have called for such clinical trials to be undertaken, but without success.

BTA Statement:

D. In three of the subsequent studies of combination treatment, the patients were asked which treatment they preferred, and in two of these three studies, more patients preferred the combination T4/T3 therapy. There is no obvious explanation for these observations, and it may or may not be a reproducible effect.

In fact, there have been numerous studies into combination T4/T3 therapy; including studies with significant superior effects of T4/T3 versus T4 alone⁵⁵ and studies with near significantly superior effects of T4/T3 versus T4 alone.⁵⁶ One study with globally no superior significant effects of T4/T3 versus T4 alone, except on one parameter where the patients on T4/T3 combinations did better.⁵⁷ Another, whilst not showing significantly superior effects of T4/T3 versus T4 alone, did show that the majority of patients preferred the T4/T3 combinations.⁵⁸

As these studies were done in a double-blind fashion, this would appear to demonstrate that the T3/T4 combination thyroid treatment was better on parameters, which the researcher did not study, but were the parameters considered important by patients in their experience of their medical condition?

BTA Statement:

E. The BTA keeps an open mind about whether using an appropriate formulation of T4/T3 combination tablet would, in the future, provide health and quality of life benefits in the treatment of hypothyroidism for a subgroup of patients. However, based on the current evidence from rigorous studies of large numbers of patients using the currently available formulations of synthetic thyroid hormones, combined T4/T3 cannot be recommended because of a lack of benefit and a small number of undesirable and harmful effects seen on combination treatment.

Some endocrinologists have opposed the use of products containing T3, claiming this is because of resulting brief peak blood level of T3, reaching the "thyrotoxic range" which may cause heart palpitations⁵⁹ or adversely affect the heart and that, by using levothyroxine, patients can avoid these problems. These claims are contradicted by researchers with extensive clinical experience with T3⁵⁹ and conversely there is much evidence to suggest that patients on T3/T4 combinations do not usually feel any discomfort caused by higher T3 peaks provided by the T3/T4 treatment. Rather there is evidence to show they may feel better.^{60, 61, 62}
^{63, 64 65, 66, 67} In addition, many studies comparing the effectiveness of T4 and T4/T3 replacement, did not report palpitations as an effect of the treatment.^{5, 6, 68, 69, 70, 66}

Considering the effects of T3 on the heart, a large community-based study of the health status of hypothyroid patients using T4-only replacement therapy was conducted in the UK. Compared to matched control patients, hypothyroid patients on "adequate" dosages of T4 had a higher reported incidence of four diseases: depression, hypertension, diabetes, and heart disease. Hypothyroid patients on inadequate T4 replacement (where TSH levels were elevated) also had a higher incidence of strokes.⁷¹ Hypothyroid patients chronically used more prescription drugs than those without hypothyroidism, especially for diabetes, cardiovascular disease, and gastrointestinal conditions.⁷² In the past, raised cholesterol was one of the clinical signs by which hypothyroidism was diagnosed.⁷³

Evidence in support of T3 monotherapy

A review of the available evidence suggests that T4 alone in many cases does not relieve all the patient's symptoms and also that some patients do not get relief from symptoms with combination synthetic T3 and T4 treatment. The evidence further supports the use of T3 alone to enable many patients to become free of symptoms, which may be due to the increased potency of T3 than T4^{74, 75} or because the effectiveness of T4 may be reduced in certain circumstances: for example, in conditions that reduce the conversion of T4 to T3 such as aging, obesity, disease, stress, exercise, malnutrition^{99, 15, 16, 17, 18, 19, 20, 21, 22}, where toxic substances such as phenols, cadmium, mercury, etc, or other medicines (e.g. propranolol, amiodarone) interfere by stimulating or inhibiting the T4 to T3 conversion^{76, 77, 15, 16, 17, 18, 19, 20, 21, 22, 79, 80}, hormone or trace element deficiencies or excess, (e.g. of T3, GH, insulin, melatonin, zinc, copper, selenium, glucocorticoids, ACTH, oestrogens etc) may inhibit the conversion of T4 to T3.^{81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95} In addition, the absorption of oral T4 can be variable (50% to 73%), contrasting with that of T3 which is more constant and efficient with an absorption of 95%.^{96, 97}

One interesting case is reported by Kaplan et al in 1981 of a patient who needed 500 mcgs of T3 daily to be free of hypothyroid symptoms. The patient's metabolism was normal and she had no tissue over-stimulation.⁹⁸ Another study demonstrated T3-induced recovery from fibromyalgia by a hypothyroid patient resistant to T4 and also to desiccated thyroid.⁹⁹

As with Kaplan's patient, many other patients have remained healthy for years on these supraphysiological dosages. None experienced adverse health affects, and none showed evidence of tissue over-stimulation upon serum and urine biochemical testing, electrocardiography, or bone densitometry. Most of these patients who recovered with T3 therapy, previously failed to benefit from the use of T4-only replacement.⁹⁸

No long term studies have shown that T3 is harmful, though despite this lack of evidence, endocrinologists warn of "*potential harm*"! This has generated irrational fear of T3 among other physicians. According to Doctors Honeyman-Lowe and Lowe, many patients asking their doctors for a trial of T3 are told, "If you take T3, you're going to have a heart attack and die!"¹⁰⁰

Other studies have demonstrated the positive effect of T3-only treatment, including psychiatric researchers whose patients use T3 and point out that it is generally well-tolerated.³³ Moreover, psychiatrists report that dosages of T3 higher than replacement dosages augment the depression-relieving effects of antidepressants.^{32, 33, 34, 35, 36} Case reports and open systematic clinical trials have showed improvement in euthyroid fibromyalgia patients treated with T3.^{101, 102, 103}

There is, however, a notable exception that some researchers neglect to consider regarding therapy using T3. Some critically ill cardiac patients can benefit from T3 treatment. Studies show that T3 improves these patients' heart function in a variety of ways. T3 also decreases the severity and incidence of their cardiac abnormalities, and increases their survival rate.^{104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 99} Endocrinologists might not recommend T3 for these heart patients, but some cardiologists and cardiac surgeons do. Rather than the BTA denouncing T3 therapy, they would better serve their patients' welfare by reading the relevant studies and then rectifying their judgment of T3 to reflect its safety and the potential benefits for select patients.

Consequences of the presumption that T4-replacement is invariably safe and effective

Professor A P Weetman, president of the BTA, writes that if patients complain of symptoms with TSH levels within the reference range, they are suffering from a "somataform disorder" and that they do not have a thyroid hormone deficiency.¹¹³ It is this false belief that has led to "new diseases" of the past 30 years. These new diseases are so-called "fibromyalgia" and "chronic fatigue syndrome." A vast amount of evidence indicates that inadequate thyroid hormone regulation is the major underlying causative factor in these supposed new disorders. For example, the only studies in which patients with these diagnoses have fully and lastingly recovered are those in which they underwent thyroid hormone therapy.^{114, 115, 116, 117, 118, 119, 120, 121, 39}

The BTA's view that levothyroxine is the "treatment of choice" for hypothyroidism brought to mind an article: "The Tomato Effect: Rejection of highly efficacious therapies" (*JAMA* 1984).¹²² New settlers in America refused to eat tomatoes as they belonged to the "nightshade family" and were thought to be poisonous despite evidence to the contrary! This article describes how highly effective therapies are abandoned due to paradigm shifts in the way physicians think about health and disease. An explanation of how 'the tomato effect' could influence the treatment of hypothyroidism is given in a *Lancet* editorial:¹²³

"Pharmaceutical companies influence medical decisions in a way that encourages the use of newer patentable therapies at the expense of older (but perhaps equally effective and less expensive) therapies...begins on the first day of medical school and lasts through to retirement. . . it starts slowly and insidiously, like an addiction, and can end up influencing the very nature of medical decision-making and practice . . . attempts to influence the judgment of doctors by commercial interests serving the medical industrial complex are nothing if not thorough."

There are many researchers, doctors, and patient advocates who believe that the BTA has been obstinate in its advocacy of thyroxine-only therapy. TPA-UK is concerned that the obduracy of the BTA may be linked, as they are now a registered charity, to the possibility that they may receive regular financial support from drug companies who profit from the prescribing of synthetic thyroxine. This suspicion of financial motivation is reinforced by the BTA's standard method of enforcing the practice of synthetic thyroxine-only therapy among doctors: dictatorship replacing scientific argument and debate. The suspicion will continue to mount if the BTA, despite the studies showing replacement therapies to be ineffective,^{5, 6, 68, 69, 55, 56} even harmful^{125, 71} for many sufferers, ignores the existing evidence demonstrated in this paper by TPA-UK.

The BTA, in partnership with the BTF and the ACB have drawn up, and maintain "The UK Guidelines for The Use of Thyroid Function Tests".¹²⁴ This imposes a great responsibility upon them to protect hypothyroid patients from adverse consequences. That responsibility is the compelling reason for the BTA to promptly reform its incorrect official position that thyroxine-only replacement is safe and effective for *all* hypothyroid patients.

To quote one patient: *"The ignorance, arrogance and incomprehension of the medical doctors I have been subjected to in my search for diagnosis and treatment leaves me incandescent with rage. Even as a qualified health professional working for a major DGH I remain powerless to prevent the cumulative long term health risks associated with lack of treatment; I am voiceless, neutered, patronised, and crawling day-to-day through what used to be my vital and colourful life. I would give everything I have for an open minded and creative diagnostician, and more for a little compassion, but this seems to be entirely beyond the capability of the modern medic. God help us all."*¹²⁶

Note: This paper should be read in conjunction with the TPA-UK's response to the BTA on Armour® Thyroid.

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