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LETTER

Hypothyroidism: A Small Clinical Trial Will Quickly Resolve the Combination Therapy Controversy

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Hypothyroidism is an extremely common condition. More than 100 million prescriptions for thyroxine (T4) are processed in the USA each year. T4 is the recommended treatment for hypothyroidism. But 5-15% of patients treated to target with T4 continue to have symptoms. Some of these patients respond dramatically to the addition of triiodothyronine (T3) as first reported 20 years ago [1]. Surprisingly there have been 18 clinical trials involving more than 1500 patients that have attempted to confirm a positive response to combination therapy (T4 + T3), but none showed any convincing benefit [2]. The reason is simple-very poor patient selection-*all* hypothyroid patients taking T4 were studied rather than confining the trials to the dissatisfied ones.

Twelve experts representing the American, British and European Thyroid Associations have recommended further clinical trials to assess combination therapy using thyroxine and triiodothyronine (T4 + T3) as compared with thyroxine monotherapy in hypothyroid patients [3]. They state that future trials must include patients who are *dissatisfied* with the current thyroxine treatment and take at least 1.2 mcg/kg of T4 daily - patient outcomes must be a primary endpoint. The group also advocates a randomised placebo-controlled, double-blinded parallel design and that such trials should be adequately powered to assess the effects of deiodinase and thyroid hormone transporter polymorphisms.

We suggest that the benefits of combination therapy could be studied in a very small number of patients over a short timeframe by using a disease-specific clinical sign as an entry criterion.

Patients dissatisfied with T4 monotherapy are a diverse group [4]. Those cases with relative T3 deficiency require precise clinical selection for inclusion in a trial. They have residual symptoms and suggestive trends in their thyroid function tests, and importantly a highly specific clinical sign of intracellular T3 deficiency - delayed relaxation of tendon reflexes, particularly the ankle jerks. Clinical experience indicates that *all* of these patients will show a dramatic improvement with the introduction of T3 [4], and their reflexes will become normal within weeks. This was first reported 10 years ago [5], but it appears that clinicians and even the experts can overlook clinical signs, and many cannot accept that slow reflexes occur when Thyrotropin (Thyroid Stimulating Hormone or TSH) levels are normal. Thyroxine (T4) is essentially a circulating pro-hormone and T3 is the active substrate at an intra-cellular level. Circulating T4 is part of the negative feedback loop

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Table 1: Numbers required in a trial.

Statistical Power	Treatment Sample Size	Placebo Sample Size	Total Sample Size	Treatment Response	Placebo Response	Level of Significance
90%	8	8	16	90%	20%	P < 0.01
90%	6	6	12	95%	20%	P < 0.01

controlling pituitary TSH secretion. This explains why a patient can have normal T4 and TSH levels in the presence of intra-cellular T3 deficiency.

There are other categories of "unhappy hypothyroid patients" that should be excluded from a trial of combination therapy. Patients with Hashimoto Disease with autoimmune symptoms and extremely high levels of thyroid antibodies (anti-TPO antibody titres of > 1000 IU/ml, normal < 100 IU/ml) improve after total thyroidectomy [6]. To include such cases in a trial of combination therapy would obscure the results.

The remaining patients with unexplained symptoms, absence of clinical signs, and completely normal thyroid biochemistry and antibodies require supportive care [4]. Rare cases of true thyroxine allergy can be identified and treated. None of these categories is likely to show benefit in a trial of combination therapy apart from placebo responsiveness.

The Table 1 shows the numbers required in a trial with a 90% power to detect a significant difference using conservative estimates of 90% and 95% for the efficacy of combination therapy and allowing a placebo response rate of 20% in the control group [7]. This long-standing controversial issue could be resolved by studying a small sample size of 16 patients over a period of 3 to 6 months in a randomized double-blind placebo controlled study. The investigating team will require careful training to identify abnormal ankle jerks with confidence. Alternatively the Burdick photomotogram could be used. A positive outcome will immediately benefit patients and it will inform revised clinical guidelines which are long overdue.

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