

Stability, Effectiveness, and Safety of Desiccated Thyroid vs Levothyroxine: A Rebuttal to the British Thyroid Association

Dr. John C. Lowe*

*Director of Research, Fibromyalgia Research Foundation
Contact: Dr. John C. Lowe drlowe@drlowe.com

Received: February 16, 2009

Accepted: February 23, 2009

Abstract. In 2007, an Executive Committee (the Committee) of the British Thyroid Association (BTA) published a document in which it concluded that levothyroxine is safer, more stable, and more effective than Armour Thyroid. By extension, the conclusion also applies to other natural desiccated thyroid (NDT) products, such as Nature-Throid and Westhroid. Enough evidence is available, however, to conclude that T_4/T_3 therapies with either synthetic hormones or NDT are safer and more effective than T_4 replacement, and that NDT is more stable than levothyroxine products. The Committee mentioned clinical trials that directly bear on its conclusions, but it did not include any of these in the reference section of its document. Instead, it referenced a review of the clinical trials by Escobar-Morreale et al. and a meta-analysis of the trials by Grozinsky-Glasberg et al. These two publications, however, deal with synthetic T_4/T_3 therapies, not NDT. Both publications contain factual errors and unbalanced presentations of data, excluding or limiting data favorable to T_4/T_3 therapies. Specific examples from the publications are included in this rebuttal. The unbalanced data presentations and factual errors of Escobar-Morreale et al. and Grozinsky-Glasberg et al. may have influenced the Committee's conclusions. Nonetheless, the Committee's document contains false statements and unbalanced presentations of data independent from those in the other authors' publications. Specific examples are included in this rebuttal. The Committee, the BTA, Escobar-Morreale et al., and Grozinsky-Glasberg et al. are all called upon to correct their false statements of fact as well as their unbalanced presentations of data relevant to their conclusions.

Keywords. Armour Thyroid • British Thyroid Association • FDA • Levothyroxine • Levoxyl • Natural desiccated thyroid • Nature-Throid • Synthroid • Westhroid

Attacks on Desiccated Thyroid

In February 2007, an Executive Committee of the British Thyroid Association (the Committee) published a document in which it denounced Armour Thyroid (Armour). Armour Thyroid is a brand of natural desiccated thyroid that contains four parts T_4 to one part T_3 , that is, a ratio of 4 to 1 (4:1). Whether the Committee intended it or not, its arguments against Armour also apply to other brands of desiccated thyroid, including Nature-Throid and Westhroid. Because the arguments apply to all these products, in this rebuttal I subsume and refer to all such brands as desiccated thyroid except when particular passages are specific to Armour. In its document, the Committee, as well as opposing the use of desiccated thyroid, also advocated T_4 replacement as the preferable treatment for hypothyroidism.

The basic issues raised by the Committee were

(1) the stability of desiccated thyroid, and (2) its safety and (3) effectiveness as a form of treatment for hypothyroid patients. Considerable evidence that bears on these issues is readily available. Yet the Committee cited virtually none of it. In this rebuttal, I cite the evidence they left out of their document. When faced squarely and considered without prejudice, that evidence leads to conclusions diametrically opposed to those of the Committee.

The medical literature contains at least twenty reports of studies in which researchers compared the effectiveness and safety of different thyroid hormone therapies.^{[7][10][15][16][22][23][24][25][26][29][31][32][33][36][39][40][41][42][44][45]} Among the therapies compared in the studies were T_4 alone, desiccated thyroid, and combined synthetic T_4/T_3 . Instead of referencing these studies, however, the Committee cited only two papers in which authors reviewed the most recent studies that

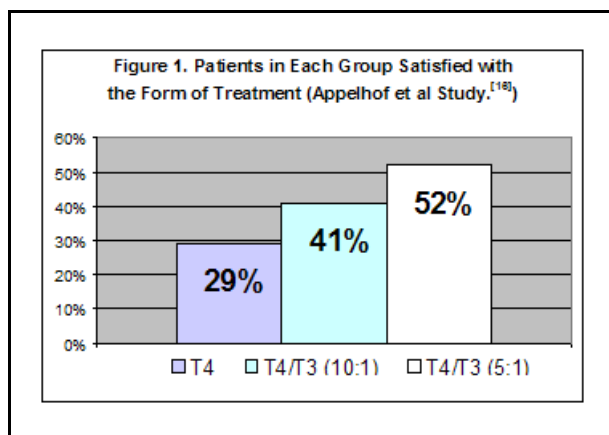
compared T₄ monotherapy to synthetic T₄/T₃. One of those papers is a review of the studies by Escobar-Morreale et al.,^[17] and the other is a report of a meta-analysis by Grozinsky-Glasberg et al.^[18]

In this paper, I critically dissect relevant parts of the two papers cited by the Committee. I also show that both papers contain errors that misinform readers who take the authors' statements at face value. Members of the Executive Committee appear to be among the misinformed. I include citations below that indicate that the Committee accepted without question and reiterated false statements of the authors of the two papers. Possibly as a result of this, but apparently for other reasons, the Committee's document contains falsehoods that I cite below. As will be obvious to readers, only if the falsehoods were true could the Committee validly deduce its conclusions about T₄ replacement and desiccated thyroid. But the evidence I present shows that the falsehoods are indeed false.

Issues Raised by the Committee of the British Thyroid Association (BTA)

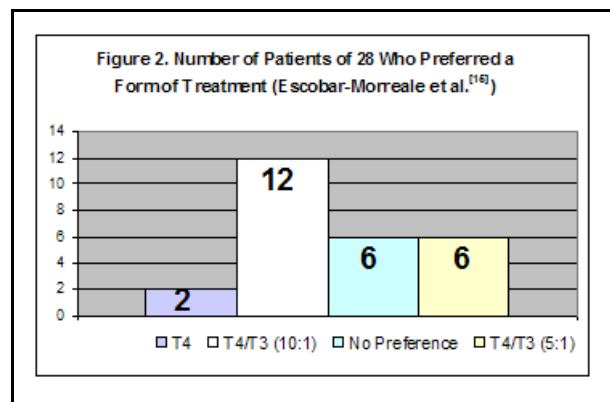
The Committee contends that T₄ is more stable, safer, and more effective than desiccated thyroid. This proposition, however, is a mere presumption, one that is refuted by evidence that I present below. The Committee bulwarks its proposition only with an unbalanced presentation of some evidence, and false claims about other relevant evidence.

As I document below, contrary to the conclusions of the Committee, the evidence actually shows that compared to desiccated thyroid, T₄ is less stable. Moreover, *replacement* therapies (dosages of thyroid hormone that keep the TSH level within its current—but often revised—reference range), including T₄ replacement and T₄/T₃ replacement, are ineffective



for many patients and potentially harmful to them.

Because of its documented ineffectiveness for many patients and its potential harm, T₄ replacement should be abandoned as the thyroid hormone therapy of choice. Clinicians should preferably typically prescribe desiccated thyroid or synthetic T₄/T₃ in dosages larger than replacement dosages. I base this recommendation on several findings: (1) hypothyroid patients have long used desiccated thyroid safely and effectively, (2) some studies show desiccated thyroid to be at least as effective as T₄ replacement, and (3) two studies showed that patients who used T₄/T₃ therapy in a 5:1 ratio—close to the 4:1 ratio in desiccated thyroid—had no adverse effects (while patients using T₄ alone did) and were more satisfied with the combination therapy than with T₄ alone (see Figures 1 and 2).



Invalid Conclusion

When Bunevicius et al. reported improvement in cognitive function after patients substituted 12.5 mcg of T₃ for 50 mcg of their T₄ dosage,^[7] other researchers quickly conducted four studies in which they compared the effectiveness of T₄ replacement to T₄/T₃ replacement. The ratio of T₄ to T₃ that patients in the studies used was far higher than the 4:1 ratio in Armour, Nature-Throid, and Westhroid desiccated thyroid. One aim in the studies was to keep patients' TSH levels within the reference range, which makes the tested T₄/T₃ treatments a form of "replacement."

No difference was found between the two types of replacement therapies. Based on this finding, the endocrinologists who conducted the studies,^{[23][24][25]} others,^[26] and endocrinologists who wrote editorials about the studies,^{[30][43]} made a logical error. By using incorrect universal propositions rather than correct singular ones, they sweepingly denounced as no more effective than T₄ replacement *all* T₄/T₃ ther-

apies—not just the T_4/T_3 replacement tested in the studies.

They did not bother to note that the T_4/T_3 therapy they studied was not the T_4/T_3 therapy long used by clinicians who have reported treatment results superior to those of T_4 replacement. That superior treatment was the use of desiccated thyroid and synthetic T_4/T_3 products with a T_4/T_3 ratio of 4:1 or lower. I first reported this logical error of the endocrinology researchers and editorialists in 2003 and again in 2006.^[8] But to this date none of them have responded. I hope that the British Thyroid Association (BTA) will not be similarly silent. (For a detailed description of the endocrinologists' logical error, see my critique of the first four T_4 vs T_4/T_3 studies that followed the 1999 Bunevicius study.^[8,pp.2-4])

The Committee made the same error as the researchers who conducted the T_4 replacement vs T_4/T_3 replacement studies and the endocrinologists who wrote editorials about them. I would like to remind the Committee of the words of one of their countrymen who was one of the greatest intellects in history, Lord Bertrand Russell: "I do like clarity and exact thinking, and I believe that very important to mankind. Because, when you allow yourself to think in exactly, your prejudices, your bias, your self interest come in in ways you don't notice, and you do bad things without knowing that you're doing them. Self deception is very easy. So I do think exact thinking immensely important."^[5]

Instability of T_4 Products

Eric P. Duffy, PhD is Director, Division of Post-Marketing Evaluation Office of New Drug Quality Assessment, OPS, FDA. In 2006, he presented a slide presentation titled "Stability Of Levothyroxine Sodium Products."^[2] On slide 8, Dr. Duffy wrote: "Levothyroxine Tablet Stability: Levothyroxine sodium (T_4) is labile to [prone to reduced potency by] the following: Heat, moisture, oxidative conditions, chemical reactions. These conditions typically occur during levothyroxine formulation, tableting, packaging, and storage." He then wrote, "*Many* levothyroxine drug products have exhibited: history of sub-optimal stability profile, significant loss of potency over shelf life, [and] inconsistent stability profiles within an individual manufacturer's drug product line." (Italics mine.)

Another FDA scientist, Steven B. Johnson, Pharm.D., is with the Division of Pharmaceutical

Evaluation II of the FDA. In a 2003 slide presentation, he said, "Levothyroxine degrades quickly with exposure to light, moisture, oxygen, and carbohydrate excipients."^[3,slide 5] He noted that over the years, companies worked to improve the stability of their levothyroxine products, and significant changes occurred.^[3,slide 6] Obviously, stability was a problem; why else would companies work to improve stability? In fact, the stability problem has been so substantial that until the FDA stopped the practice, many companies engaged in "stability overage"; that is, the companies would add more than 100% of the T_4 designated on the product label. They did so because they assumed that potency would be lost, and they compensated for the loss by packing extra T_4 into the tablets.^{[2,slide 9][3,slide 5]}

The instability of levothyroxine tablets is noteworthy, especially in view of the Committee's claim that levothyroxine products are more stable than desiccated thyroid products. Dr. Johnson cited the FDA recall record of levothyroxine: "Between 1990 and 1997: 10 recalls, 150 lots, and 100 million tablets."^[3,slide 5] (Italics mine.) The reasons for the FDA recalls are also noteworthy: "Content uniformity, sub-potency, and stability failures."^[3,slide 5]

Whether intentional or not, the BTA's Executive Committee painted a grossly imbalanced picture of the comparative stability of desiccated thyroid and levothyroxine. The Committee clearly cast an unfavorable light on desiccated thyroid by presenting the meager evidence against it, while failing to disclose the copious evidence against T_4 . The fact is that the stability of levothyroxine has been far more in question at the FDA than has that of desiccated thyroid.

Stability of Natural Desiccated Thyroid

According to the Committee: "The concentration of thyroid hormones in Armour Thyroid USP is regulated by the manufacturer to United States Food and Drug Administration (FDA) standards. Despite this, *there have been significant problems with the stability of Armour Thyroid in recent years*, prompting a massive recall of tablets." (Italics mine.) The Committee also wrote, "An FDA enforcement removed more than half a million bottles of Armour Thyroid from US pharmacies in 2005 due to unstable concentrations of thyroid hormone in the preparation."^[1] Indeed, batches of the product were recalled in 2005.^[9] But the Committee mentions "problems with the stability . . . in recent years."

(Italics mine.) This suggests that the FDA has repeatedly recalled Armour batches in two or more years. But the Committee cites only the 2005 recall; I cannot find documentation for others.

The Committee's purpose in citing the Armour recall appears to have been to implicitly argue that levothyroxine products (levothyroxine sodium, thyroxine, and T_4) are more stable than desiccated thyroid products. If so, the Committee engaged in card-stacking of evidence, as it failed to disclose a highly relevant fact: the T_4 products Synthroid and Levoxyl have been recalled far more often than Armour, Nature-Throid, or Westroid—all desiccated thyroid hormone products. In fact, Nature-Throid and Westroid have never been recalled for instability.

Anyone with Internet access can view the public record at www.fda.gov/search.html. Searches show that the many recalls of T_4 products dwarf the few recalls of desiccated thyroid.

Clinicians and patients interested in the relative merits and demerits of T_4 and desiccated thyroid should be aware that desiccated thyroid products are not carelessly produced. The Committee failed to note that manufacturers of desiccated thyroid take proper steps to ensure its potency before the products are shipped to pharmacies. For example, the manufacturer of Nature-Throid and Westroid Thyroid USP tablets takes appropriate steps to ensure consistent potency from tablet-to-tablet and lot-to-lot. The manufacturer not only performs analytical tests on the raw material (Thyroid USP powder), but also on the tablets (finished products) to measure actual T_4 and T_3 activity.^[11] As a result of this attention to quality, only two recalls—voluntary ones—have occurred in the past eight years. These recalls included fewer than one hundred bottles. The recalls were for a labeling problem, *not* for instability or potency variability as with levothyroxine products.

Ineffectiveness of T_4 Replacement for Many Patients

The endocrinology specialty has long claimed that T_4 replacement is effective for most hypothyroid patients, and that patients need no other treatment such as T_4/T_3 therapy. However, as I wrote in a 2006 review (and in 2003) of four T_4 vs T_4/T_3 studies published in 2003, T_4 replacement is ineffective for many hypothyroid patients.^[8,p.14] At that time, at least six studies had shown this to be true.^{[7][15][16][23][24][25][26][27][28]} As I said above, in the 1999 Bunevicius

study^[7] patients who had been on T_4 replacement substituted 12.5 μg of T_3 for 50 μg of their usual T_4 dosages. The neuropsychological function of patients who added T_3 to their treatment improved. It is obvious but worth emphasizing that from the patients' improved neuropsychological function, it follows that their previous T_4 monotherapy had failed to provide them the higher level of function that T_4/T_3 provided.

In a large, community-based questionnaire study in 2002,^[27] researchers evaluated the health status of hypothyroid patients using T_4 replacement therapy. Compared to matched control patients, hypothyroid patients on "adequate" dosages of T_4 had a higher reported incidence of four diseases: depression, hypertension, diabetes, and heart disease. Hypothyroid patients on inadequate T_4 replacement (their TSH levels were elevated) also had a higher incidence of strokes. In addition, hypothyroid patients chronically used more prescription drugs, especially for diabetes, cardiovascular disease, and gastrointestinal conditions. Patients on T_4 replacement had scores 21% higher (worse) than controls on the General Health Questionnaire. The researchers wrote, "This community-based study is the first evidence to indicate that patients on thyroxine replacement even with a normal TSH display significant impairment in psychological well-being compared to controls of similar age and sex."^[27,p.577]

In the study by Cassio et al.,^[26] researchers treated infants who had congenital hypothyroidism with either T_4 or T_4/T_3 replacement. The infants had scores on psychological tests that were lower than those of infants who were not hypothyroid. The two replacement therapies did not improve the scores of the hypothyroid infants, so their psychological impairment presumably persisted.

To take part in the Sawka et al. study,^[24] patients on T_4 replacement had to have test evidence of depression: that is, they had to have, ". . . evidence of depressive symptoms as defined by a score of more than 5 on the 30-item General Health Questionnaire . . . on 2 occasions, at least 2 wk apart."^[24,p.4551] The researchers found that replacement therapies were not effective for the patients and, again, presumably left them depressed.

In the Walsh et al. study,^[23] typical symptoms suffered by hypothyroid patients who were dissatisfied with their T_4 replacement included "tiredness, impaired well-being, or weight gain."^[23,p.4544] The study showed that replacement therapies were ineffective for these patients and left them suffering

from their symptoms.

In addition to the four studies I just mentioned, two other studies also showed the ineffectiveness of T₄ replacement.^{[15][16]} The study by Escobar-Morreale et al.^[15] is especially informative. The researchers reported that patients on both T₄ and T₄/T₃ replacement “performed worse than controls in the time score and Visual Scanning Test”^[15,p.420] But patients who used a 5:1 ratio of T₄ and T₃ did not perform worse than the healthy control subjects. Also, patients on T₄ and T₄/T₃ replacement therapies did worse than healthy controls on two other tests (isovolumic relaxation time and brainstem evoked potentials), but patients who used T₄ and T₃ in a 5:1 ratio did *not* do worse than controls.^[15,p.420] This positive result for 5:1 T₄/T₃ therapy is evidence from Escobar-Morreale et al. that the therapy was more effective than the two forms of replacement therapy.

False Reporting by the Committee, Escobar-Morreale et al., and Grozinsky-Glasberg et al.

In this rebuttal to the Committee of the BTA, I cite incidences of unbalanced presentation of data that deny readers an accurate understanding of the research concerning the relative stability, safety, and effectiveness of desiccated thyroid as compared to synthetic T₄ products. In the pursuit of scientific truth, these instances of unbalanced presentation are lamentable. However, the Committee, Escobar-Morreale et al., and Grozinsky-Glasberg et al. gave false reports concerning the research data that are an even more egregious departure from accurate reporting.

The Committee’s extrapolation that T₄/T₃ therapies provide no benefits

The Committee of the BTA wrote, “Since this initial study, [the 1999 Bunevicius et al. study^[7]] there have been a further [*sic*] seven rigorously conducted (‘randomized, double-blind, placebo-controlled’) studies *None of the subsequent studies showed a beneficial effect of combined T₄/T₃ therapy on measures of wellbeing, health and mental functioning.*” (Italics mine.) The Committee then concluded, “. . . combined T₄/T₃ cannot be recommended *because of a lack of benefit*” The studies of T₄/T₃ therapy the Committee referred to involved synthetic hormones, none of which were used in the 4:1 T₄/T₃ ratio as contained in desiccated thyroid. But in its document, the Committee implies by extrapolation

that desiccated thyroid, too, cannot be recommended because of a lack of benefit.

I request that the Committee reconcile its conclusion, at the very least, with the evidence I cite in this section. This evidence directly contradicts their conclusion. Older studies show that T₄/T₃ in the form of desiccated thyroid was at least as effective as synthetic T₄. As Cobb and Jackson wrote in a drug therapy review, desiccated thyroid products are equipotent to T₄ alone in treating hypothyroidism.^[19,p.53] This was determined by a study of the potency of desiccated thyroid using an antigoirogenic assay in rats.^[13] Most studies of T₄/T₃ therapy have not been of desiccated thyroid itself, although at least 12 studies did directly compare desiccated thyroid to T₄ alone.^{[4][29][31][32][33][35][37][38][39][40][42][45]} The Committee, however, did not cite these studies; instead, it extrapolated to desiccated thyroid from studies that compared synthetic T₄ to synthetic T₄/T₃ combinations. Reading the same studies the Committee referred to makes clear that its claim of a lack of benefit of desiccated thyroid is false.

First Bunevicius Study. In a study published in 1999, Bunevicius et al.^[7] included 26 hypothyroid women. Eleven had autoimmune thyroiditis and 15 had been treated for thyroid cancer. Patients either continued their usual dose of T₄, or they substituted 12.5 µg of T₃ for 50 µg of their usual dosage of T₄.

Bunevicius et al. later wrote that when patients were undergoing T₄/T₃ therapy, they had “clear improvements in both cognition and mood, the latter changes being greater.”^[21,p.167] The researchers also wrote, “The patients who had been treated for thyroid cancer showed more mental improvement than the women with autoimmune thyroiditis”^[21,p.167] However, *patients in both groups improved on some measures.*^[21,pp.169-171]

This is important to note because in the review paper that the Committee cited, Escobar-Morreale et al. falsely reported that *only* thyroid cancer patients improved. Specifically, they wrote, “. . . the presumed benefits of T₃ substitution were restricted to athyreotic thyroid cancer patients”^[17,p.4949] Consider, however, what Bunevicius and Prange actually reported: Referring to visual analog scales, they wrote, “The advantages [improvements] for combined treatment were statistically significant in the . . . [autoimmune thyroiditis] group on 4 scales, in the . . . [thyroid cancer] group on 6 scales.”^[21,p.170] Table 5 in Bunevicius and Prange’s report shows this

to be true.^[21,p.172] Escobar-Morreale et al., then, are guilty of false reporting.

Second Bunevicius Study. In the second Bunevicius study,^[22] patients were hypothyroid from thyroidectomy for Graves' disease. The patients substituted 10 µg of T₃ for 50 µg of their usual T₄ monotherapy dose. In their first study, Bunevicius et al. substituted 12.5 µg of T₃ for 50 µg of T₄.^[7] Despite the more modest substitution dose of 10 µg of T₃ in the second study, the results indicated that patients improved with T₄/T₃ therapy.

Compared to baseline scores when patients were using T₄ replacement, the patients had statistically significant improvement on three measures.^[22,p.130] Allowing for a slightly larger significance level ($p = 0.06$), the patients using T₄ also improved on one other measure—a total of four measures. Similarly, when patients used T₄ and T₃, they significantly improved on three measures. But allowing for slightly larger significance levels ($p = 0.06$ to 0.08), these patients also improved on four more measures—a total of seven measures. This means that with T₄ alone, patients improved on four measures, while on T₄/T₃, they improved on seven. With the slightly expanded significance levels, then, patients improved more with T₄ and T₃ combined than they did on T₄ alone.

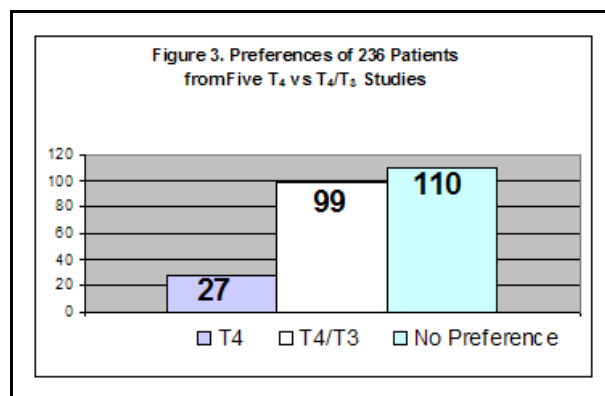
Bunevicius et al. wrote: “Thus, to a statistically significant degree, the substitution of 10 µg of T₃ reduced the concentration of free T₄, as well as the symptoms of hypothyroidism and subjective tension, while improving pairs recalled on the Digit Symbol Test. In addition, it tended to reduce the symptoms of hyperthyroidism, to improve mood on the Beck Depression Inventory, as well as feelings of confusion on the Visual Analog Scale, and to improve the raw score on the Digit Symbol Test and forward recall on the Digit Span Test.”^[22,pp.131-132]

In the 2005 Saravanan study,^[14] patients substituted 10 µg of T₃ for 50 µg of their T₄ dosages. The researchers wrote that patients on the different therapies had no differences in a number of test scores. However, patients who used T₄/T₃ had some improvements compared to patients who used T₄ alone. The researchers reported, “. . . a significantly greater reduction in psychiatric caseness [patients who met the criteria for different disorders] was seen in the T₃ group compared with T₄ alone . . . Improvement was also seen in the HADS anxiety score [the Hospital Anxiety and Depression questionnaire] at 3 months.”^[14,p.807] (Italics mine.)

Patients' Preference for T₄/T₃ Therapy. The

Committee wrote that in *two* studies in which researchers compared T₄ to T₄/T₃ therapy, patients preferred T₄/T₃ therapy. This is a factual error by the Committee. Actually, patients preferred or were more satisfied with T₄/T₃ therapy in *five* studies.^{[7][15][16][22][36]}

In each of the five studies, far more patients preferred T₄/T₃ therapy over T₄ replacement. Combining the preference data from the five studies, of 236 patients, 110 patients had no preference. Only 27 patients preferred T₄ replacement while 99 preferred some form of T₄/T₃ therapy. (See Figure 3.)

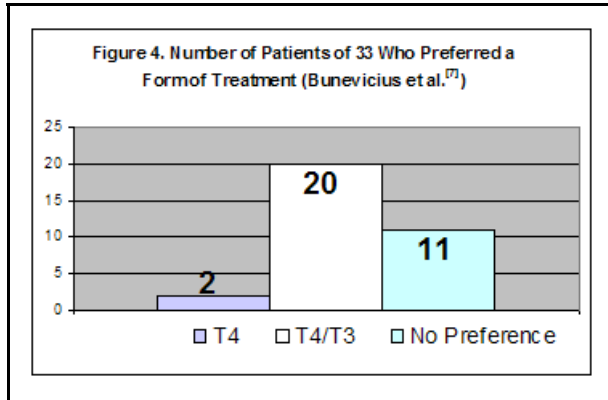


In two studies,^{[15][16]} patients used T₄/T₃ in a ratio of both 10:1 and 5:1. Of the 61 patients involved, 31 preferred the 10:1 ratio; 30 preferred the 5:1 ratio.

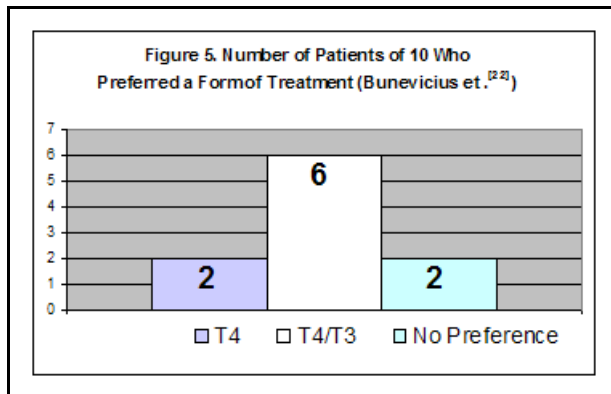
One of the five studies was published in 1999,^[7] another in 2002,^[22] and three other studies were published in 2005^{[15][16][36]}—all well before the 2007 Committee document published by the British Thyroid Association.^[1] Despite this, the Committee failed to mention that patients preferred T₄/T₃ therapies. Perhaps this neglect of the Committee was due to its dependence on the reviews by Escobar-Morreale et al.^[17] and Grozinsky-Glasberg et al.^[18] rather than the original study reports the reviewers purportedly analyzed. In any case, neglecting this important finding constitutes an unbalanced presentation of data that favors T₄ replacement over T₄/T₃ therapies.

The 1999 and 2002 studies that the Committee did not reference were the first and second Bunevicius et al. studies.^{[7][22]} At the end of the 1999 study, the researchers asked patients about their preferences for a particular form of treatment. The researchers wrote, “When asked at the end of the study whether they preferred the first or second treatment, 20 patients preferred thyroxine plus triiodothyronine, 11 had no preference, and 2 preferred thyroxine alone (p

= 0.001).^{»[7,p.427]} (See Figure 4.)



At the end of the 2002 study, the researchers asked patients about their preferences. “Six patients,” they wrote, “preferred combined treatment, reporting increased energy, better performance, and decreased ‘tension in the eyes.’ Two preferred monotherapy with T₄, and two found no difference.”^{»[22,p.132]} (See Figure 5.)



In the Applehof et al. study, patients who used T₄/T₃ therapy were more satisfied with the treatment. In fact, the researchers found a linear relationship between the use of T₃ and the number of patients preferring treatment: In the T₄ monotherapy group, only 29.2% were satisfied with the treatment; in the group who used T₄/T₃ therapy in a 10:1 ratio, 41.3% were satisfied; and in the group that used T₄/T₃ therapy in a 5:1 ratio, 52.2% were satisfied. (See Figure 1.)

Escobar-Morreale et al.^[15] and Rodriguez et al.^[36] also reported more satisfaction with T₄/T₃ therapies (see Figures 2 and 6). Unfortunately, Grozinsky-Glasberg et al., for all practical purposes, gave no attention to patients’ preference for T₄/T₃ therapies. To

their credit, Escobar-Morreale et al. did mention patients’ preference for T₄/T₃ in their abstract, the body of their review, and in their conclusion section.^[15]

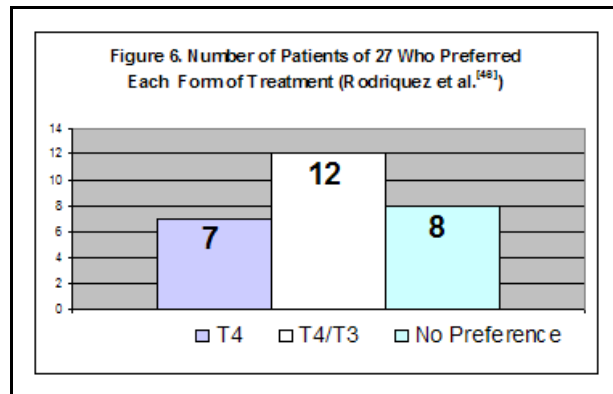
In some studies, researchers did not inquire about patients’ satisfaction with tested therapies. In the Walsh et al.^[23] study the researchers did inquire, and there was no difference in patients’ preferences.

The Committee’s parroting of false statements by Escobar-Morreale et al. and Grozinsky-Glasberg et al.

The Committee wrote, “There is no evidence to favour the prescription of Armour Thyroid in the treatment of hypothyroidism over the prescription of thyroxine sodium.”^[1] The Committee appears to have argued against desiccated thyroid by appropriately including it among T₄/T₃ therapies. Its claim of no benefit of these therapies over T₄ replacement, however, is false. It is possible that the source of the Committee’s erroneous conclusions are false statements by Escobar-Morreale et al. and Grozinsky-Glasberg et al. in their reviews of the studies testing T₄ alone vs T₄/T₃ therapies.

As Figures 1 through 6 show, patients’ satisfaction is a benefit often provided by T₄/T₃ therapies. In their meta-analysis of the T₄ vs T₄/T₃ studies, Grozinsky-Glasberg et al. side-stepped this important finding. They merely included the term “satisfaction” in a table,^[16,p.2594] and they briefly mentioned patients dissatisfied with T₄ replacement.^[16,p.2597] They did not include the words “prefer” or “preferred” in their paper, and they did not include the data from the five studies in which patients by far preferred T₄/T₃ therapies.

Keep in mind that Applehof et al. reported that weight loss with T₄/T₃ therapy correlated with patients’ satisfaction with the treatment.^[16,p.2672] But Grozinsky-Glasberg et al. were so dismissive of weight loss from T₄/T₃ therapy that they contradicted themselves on different pages of their report: In their results section under “Weight Changes” they wrote, “The weight in the combination group was lower at the end of the study, and *this difference reached statistical significance . . .*”^{»[18,p.2596]} (Italics mine.) Yet in their abstract they wrote, “No difference was found in . . . body weight . . .”^{»[18,p.2592]} And in their discussion section, they wrote “. . . there was no significant difference in terms of weight change.”^{»[18,p.2597]}



Grozinsky-Glasberg et al. also falsely reported the outcome of Bunevicius and Prange's reanalysis of their data from their 1999 study.^[21] Grozinsky-Glasberg et al. wrote: "Only one trial found significant benefit of combination therapy over the monotherapy. It was later suggested that this benefit was associated with the cause of hypothyroidism and that only athyreotic [without a thyroid gland or endogenously produced thyroid hormone] thyroid cancer patients benefited from the combination therapy, whereas patients with autoimmune thyroiditis did not."^[18,p.2597] (Italics mine.) Yet clearly, Bunevicius and Prange's report of their reanalysis shows this statement to be patently false. In Table 5 of Bunevicius and Prange's report, they showed improvement on visual analog scales among thyroiditis patients. Compared to the patients' baseline measures (when they were on T₄ replacement), testing when they were using T₄/T₃ therapy revealed *statistically significant* ($p=0.02$) reductions in sadness, confusion, fearfulness, and irritability.^[21,p.172]

In their report, Bunevicius and Prange wrote, "Table 5 shows results on the visual analogue scales. For each diagnostic group [thyroid cancer and autoimmune thyroiditis patients] on all 8 scales, there was at least a *tendency for improvement after T₄ plus T₃ compared to T₄ alone.*"^[21,p.170] They then wrote, "The advantages for *combined treatment were statistically significant in the AT [autoimmune thyroiditis] group on 4 scales, in the TC [thyroid cancer] group on 6 scales.*" (All italics mine.) These statements by Bunevicius and Prange and Table 5 in their report show that in their meta-analysis paper, Grozinsky-Glasberg et al. falsely reported the results of the Bunevicius and Prange reanalysis.

Maybe the mistake of Grozinsky-Glasberg et al. was in taking at face value what Escobar-Morreale et al. stated in a review of T₄ vs T₄/T₃ studies. (Grozin-

sky-Glasberg et al. cited the review paper at the end of their false statement about the result of the Bunevicius and Prange reanalysis.^[18,p.2597] Escobar-Morreale et al. wrote, "A subsequent reanalysis of the data, removing from the initial study the data from the two men, from four depressed women, and from a woman who presented with increased serum TSH levels at baseline, revealed that the findings originally reported were maintained only in the subset of athyreotic patients and not in women with autoimmune thyroiditis."^[17,p.4949] (Italics mine.) Thus, Escobar-Morreale et al. may be the source of false statements about Bunevicius and Prange's finding. Unfortunately, other researchers have reiterated the false statements.^[36]

Eleven Studies Have Compared T₄-Replacement to Natural Desiccated Thyroid: Factual Error of the Committee

Referring to T₄ and desiccated thyroid, the Committee wrote, "There has never been a direct comparison of these two treatments." (Italics mine.) When I read this, I immediately turned in my desk chair and pulled from a filing cabinet 12 published reports of "direct comparison" of these two forms of treatment.^{[4][29][31][32][33][35][37][38][39][40][42][45]} Researchers reported using Armour *per se* in three of the studies.^{[4][39][40]}

One study was published in 1972.^[39] The researchers wrote, "The present study was designed to compare the effects of desiccated thyroid and monosodium l-thyroxine [T₄], administered by mouth, on serum lipids in a group of hypothyroid patients." The researchers reported, ". . . a cholesterol-lowering effect was manifested by the time of first testing after institution of desiccated thyroid or l-thyroxine treatment." They wrote further, "The magnitude of the hypolipidemic [fat lowering] effects were [*sic*] similar when desiccated thyroid and l-thyroxine were give [*sic*] orally in therapeutic [*sic*] equivalent doses."^[39,p.1047]

Another "direct comparison" was published in 1978.^[40] The researchers wrote, "The biologic effect of the two therapies was compared by estimating by interpolation the dose of thyroid hormone that caused the peak serum TSH after TRH to fall to 5 μ U/ml."^[40,p.1518] They concluded, ". . . a daily dose of 100 mcg of T₄ was on average equal in biologic activity to 101 mg of desiccated thyroid; 60 mg of desiccated thyroid was equal to 60 μ g of T₄."^[40,p.1518]

Two other research groups showed that the 60 mg of desiccated thyroid had the effect of 100 mcg of T_4 in raising the basal metabolic rate.^{[29][42]} A number of other researchers have made "direct comparison" of desiccated thyroid and T_4 .^{[4][31][32][33][34][37][38]} These studies show that the Committee's statement that Armour (and by extension, similar desiccated thyroid products) has not been directly compared to T_4 was an *ex cathedra* pronouncement, one that is clearly false.

Necessity of Retractions. In the interest of precision and accuracy in the science of thyroidology—in fact, in the interest of its credibility—Escobar-Morreale et al., Grozinsky-Glasberg et al., and the Executive Committee of the BTA are compelled to correct their false reports of Bunevicius and Prange's actual study results. Also, the Committee is compelled to correct its false statement that no studies have compared T_4 to desiccated thyroid.

As the statements of these groups of authors stand, they drive the body of scientific information in clinical thyroidology away from the goal of accuracy and truth. Regarding Escobar-Morreale et al. and Grozinsky-Glasberg et al., we have to look no further than the Committee's document to confirm that their incorrect and inexact reports send ripples of falsehood through the sea of beliefs within the field of clinical thyroidology and of its decision-makers. Setting off such ripples is contrary to the traditional aims of science and is not a worthy legacy of these authors. On the grounds of science ethics, they are obligated to rectify their errors.

Harm Through the Ineffectiveness of T_4 Therapy

It appears that when the Committee was writing its document, it had the impression that research had unequivocally established the safety and effectiveness of T_4 replacement. The Committee wrote, "The BTA committee [*sic*] cannot recommend a treatment with possible side-effects [*sic*], [such as desiccated thyroid], *when a safe and equally-well established treatment [T_4 replacement] exists.*"^[11] (Italics mine.) The proposition that T_4 replacement is safe and effective for all patients, however, is simply false. Studies show that for many people, the therapy is harmful by virtue of its ineffectiveness.

In 2000, Bunevicius and Prange wrote: "It is conventional to provide replacement treatment with T_4 alone, in the belief that each tissue will make suffi-

cient quantities of T_3 (the more potent hormone) for its own needs. Nevertheless, *it has long been noted that after treatment with T_4 alone not all patients are entirely well.*"^[21,p.167] (Italics mine.) Here they reference a report by Taylor et al.^[44] *published in 1970.* Today, 39 years later, studies are still showing that T_4 replacement is ineffective for many patients, subjecting them to the ravages of deficient thyroid hormone regulation of cell function. This is indicated by patients who were "stable" on T_4 replacement: (1) still suffering from hypothyroid symptoms and having various abnormal test scores,^{[23][24][26][27]} (2) entering a study hoping they would feel better on another thyroid hormone therapy,^[25] (3) having disorders plausibly explained by too little thyroid hormone regulation,^{[10][16][27][36]} (4) gaining and not being able to lose weight,^{[12][20]} and (5) suffering potentially-fatal diseases associated with untreated or undertreated hypothyroidism and using more medications for those diseases.^[27]

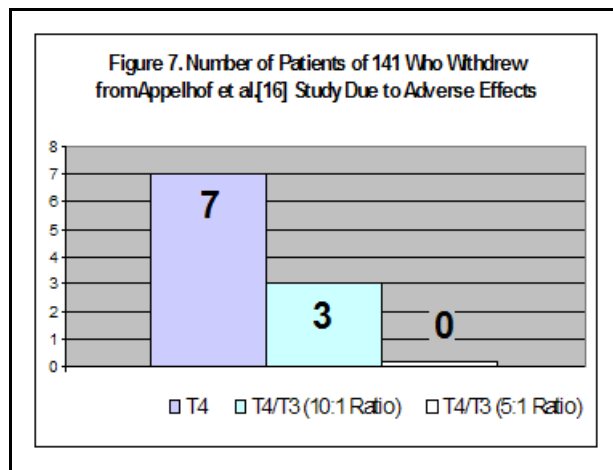
Inadequate regulation of cell function by thyroid hormone in patients using T_4 replacement can cause them to not only suffer, but to potentially die earlier than otherwise. It can also greatly increase medical and societal costs. Because of these harmful effects, it is reasonable to conclude that T_4 replacement—in which the TSH is kept within the reference range—is injurious to many hypothyroid patients and to society at large.

Adverse Effects in Studies of T_4 and T_4/T_3 Therapies. The Committee wrote in its document, "Three of the seven studies show harmful or undesirable effects of the T_4/T_3 combination."^[1] One might assume from the Committee's statement that desiccated thyroid and other T_4/T_3 therapies are likely to cause adverse effects. But it would have been obvious that this is not true had the Committee accurately reported what was found in the three studies.^{[15][16][22]}

In one of the studies, Escobar-Morreale et al. compared T_4 and T_4/T_3 replacement to T_4/T_3 therapy in a 5:1 ratio. After the study ended they wrote, "No adverse effects were reported with any of the treatments."^[15,p.420] They also reported the proportion of patients who had increased heart rates. They defined increased rates as higher than 120 beats/min in daytime and higher than 100 beats/min at night. Of 420 patients on T_4 replacement, 13 had raised heart rates. Of 376 patients using T_4/T_3 replacement, 13 had increased rates. But of 377 patients using T_4/T_3

therapy in a 5:1 ratio, only 7 had increased heart rates.^[15,p.420] The researchers reported, however, that the groups did not differ statistically.

In the study by Appelhof et al.,^[16] patients who used T₄/T₃ therapy in a 5:1 ratio had no adverse effects. In contrast, patients who used T₄ and T₄/T₃ replacement did have adverse effects. Appelhof et al. wrote of adverse effects in the study: “One participant (5:1 [T₄/T₃] group) withdrew because of unexpected travel abroad for family matters and was excluded from all analyses. Seven patients withdrew because of side effects, four in the LT₄ group and three in the 10:1 [T₄/T₃] group. Various side effects were mentioned (e.g. fatigue, muscle aches, dizziness, irritability), but no specific complaints could be identified for those on combination therapy.”^[16,p.2668] (see Figure 7).



In the second Bunevicius et al study,^[22] the researchers compared T₄ to T₄/T₃ replacement. More patients were satisfied with T₄/T₃ than with T₄ replacement. (Figure 5) Perhaps the lack of satisfaction of patients using T₄ replacement resulted from the adverse effects they experienced: two patients reported that they experienced “sensitiveness of the heart,” and one reported “hand tremor.”^[22,p.132]

Of most relevance to desiccated thyroid, studies of patients who used T₄/T₃ therapy in a ratio close to that of desiccated thyroid had no adverse effects. The Committee failed to report this, just as it failed to report that patients in studies of T₄ replacement have had adverse effects. By failing to report accurately, the Committee cast an unjustified shadow of doubt over T₄/T₃ therapies, including desiccated thyroid, and it flooded T₄ replacement with an indefensible light of safety.

Conclusions

In its document on desiccated thyroid and T₄/T₃ therapies, the Executive Committee of the British Thyroid Association presented a grossly unbalanced picture of the stability of levothyroxine sodium, Armour Thyroid, and by extension, other prescription desiccated thyroid products such as Nature-Throid and Westhroid. The Committee also reiterated false statements about T₄/T₃ therapies contained in reports by other researchers. Furthermore, the Committee did this without mentioning or accounting for the other researchers’ variances from the facts.

In addition, in its denouncement of desiccated thyroid, the Committee failed to account for the outcome of two highly relevant studies.^{[15][16]} In these studies, treatment with T₄ and T₃ in a 5:1 ratio (close to the 4:1 ratio in desiccated thyroid) was more effective in some ways than was T₄ replacement and T₄/T₃ replacement.

While warning of adverse effects from desiccated thyroid, the Committee failed to disclose the complete lack of adverse effects among patients who used T₄ and T₃ in a 5:1 ratio.^{[15][16]} It also failed to disclose that patients using T₄ replacement and T₄/T₃ replacement (in 10:1 to 15:1 ratios) had adverse effects.^[16]

Moreover, the Committee failed to account for three harmful effects from T₄ replacement. These are: (1) continued suffering from hypothyroid symptoms by patients who are restricted to T₄ replacement^{[7][15][16][23][24][25][26][27][28]}—in as high a percentage as 50%,^[27] (2) a higher incidence in these patients of diseases associated with hypothyroidism,^[27] and (3) the use of more drugs by the patients.^[27]

At the top of its homepage, the BTA once indicated that it is “Encouraging the Highest Standards [*sic*] of Research and Patient Care.” I trust that the BTA’s integrity is such that it will conduct itself in accord with this statement. Hence, I also expect that its Executive Committee will revise its document on desiccated thyroid based on a careful reading of the *original* reports of the studies to which they refer, taking note of the findings I have described. As the Committee does so, the scientific and humanitarian imperatives are that it abide by the advice of one of the United Kingdom’s—indeed, history’s—most eminent logicians: “When you are studying any matter or considering any philosophy, ask yourself *only* ‘what are the facts, and what is the truth that the facts bear out.’ Never let yourself be diverted either by what you wish to believe, or by what you think

would have beneficent social effects if it were believed. But look *only* and *surely* at *what are the facts*.”^[6]

References

1. The British Thyroid Association Executive Committee Armour Thyroid (USP) and combined thyroxine/ triiodothyronine as thyroid hormone replacement: a statement from February 2007. http://www.british-thyroid-association.org/armour_statement_2007.pdf
2. Duffy, E.P.: Stability of levothyroxine sodium products, 2006. <http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4228S1-01-04-Eric%20Duffy%20slides.pdf>
3. Johnson, S.B.: Endogenous substance bioavailability and bioequivalence: levothyroxine sodium tablets, March 13, 2003. http://www.fda.gov/ohrms/dockets/ac/03/slides/3926S2_07_Johnson.ppt
4. LeBoff, M.S., Kaplan, M.M., Silva, J.E., et al.: Bioavailability of thyroid hormones from oral replacement preparations. *Metabolism*, 31(9):900-905, 1982.
5. Russell, B.: 1959 Interview of Bertrand Russell by J.F. McDonald. <http://www.youtube.com/watch?v=LUaSO9WDcng>
6. Russell, B: Bertrand Russell, BBC interview, 1959. <http://www.youtube.com/watch?v=L719pgqiLo0&feature=related>
7. Bunevicius, R., Kazanavicius, G., Zalinkevicius, R., et al.: Effects of thyroxine as compared with thyroxine plus triiodothyronine in patients with hypothyroidism. *N. Engl. J. Med.*, 340:424-429, 1999.
8. Lowe, J.C.: Thyroid hormone replacement therapies: ineffective and harmful for many hypothyroid patients. *Thyroid Science*, 1(1):C1-21, 2006. <http://www.thyroidscience.com/Criticism/lowe.dec.2006/t4%20vs%20t4t3%20studies.htm>
9. FDA: Recalls and Field Corrections: Drugs—Class II, May 11, 2005. www.fda.gov/bbs/topics/enforce/2005/ENF00899.html
10. Siegmund, W., Spieker, K., Weike, A.I., et al.: Replacement therapy with levothyroxine plus triiodothyronine (bioavailable molar ratio 14:1) is not superior to thyroxine alone to improve well-being and cognitive performance in hypothyroidism. *Clin. Endocrinol. (Oxf)*, 60(6):750-757, 2004.
11. Western Research Labs, 2007. <http://www.wes-throid.com/vs.asp>
12. Tigas, S., Idiculla, J., Beckett, G., et al.: Is excessive weight gain after ablative treatment of hyperthyroidism due to inadequate thyroid hormone therapy? *Thyroid*, 10(12):1107-1111, 2000.
13. Mangieri, C.N. and Hund, M.H.: Potency of United States Pharmacopeia desiccated thyroid tablets as determined by the antigiotogetic assay in rats. *J. Clin. Endocrinol. Metab.*, 30:102-104, 1970.
14. Saravanan, P., Simmons, D.J., Greenwood, R., et al.: Partial substitution of thyroxine (T₄) with tri-iodothyronine in patients on T₄ replacement therapy: results of a large community-based randomized controlled trial. *J. Clin. Endocrinol. Metab.*, 90(2):805-812, 2005.
15. Escobar-Morreale, H.F., Botella-Carretero, J.I., Gómez-Bueno, M., et al.: Thyroid hormone replacement therapy in primary hypothyroidism: a randomized trial comparing L-thyroxine plus liothyronine with L-thyroxine alone. *Ann. Intern. Med.*, 142(6):412-424, 2005.
16. Appelhof, B.C., Fliers, E., Wekking, E.M., et al.: Combined therapy with levothyroxine and liothyronine in two ratios, compared with levothyroxine monotherapy in primary hypothyroidism: a double-blind, randomized, controlled clinical trial. *J. Clin. Endocrinol. Metab.*, 90(5):2666-2674, 2005.
17. Escobar-Morreale, H.F., Botella-Carretero, J.I., Escobar del Rey, F., et al.: Review: Treatment of hypothyroidism with combinations of levothyroxine plus liothyronine. *J. Clin. Endocrinol. Metab.*, 90(8):4946-4954, 2005.
18. Grozinsky-Glasberg, S., Fraser, A., Nahshoni, E., et al.: Thyroxine-triiodothyronine combination therapy versus thyroxine monotherapy for clinical hypothyroidism: meta-analysis of randomized controlled trials. *J. Clin. Endocrinol. Metab.*, 91:2592-2599, 2006.
19. Cobb, W.E. and Jackson, I.M.: Drug therapy reviews: management of hypothyroidism. *Am. J. Hosp. Pharm.*, 35(1):51-58, 1978.
20. Bastemir, M., Akin, F., Alkis, E., et al.: Obesity is associated with increased serum TSH level, independent of thyroid function. *Swiss. Med. Wkly.*, 137(29-30):431-434, 2007.
21. Bunevicius, R. and Prange, A.J.: Mental improvement after replacement therapy with thyroxine plus triiodothyronine: relationship to cause of hypothyroidism. *Int. J. Neuropsychopharmacol.*, 3(2):167-174, 2000.
22. Bunevicius, R., Jakubonien, N., Jurkevicius, R., et al.: Thyroxine vs thyroxine plus triiodothyronine in treatment of hypothyroidism after thyroidectomy for Graves' disease. *Endocrine*, 18(2):129-133, 2002.
23. Walsh, J.P., Shiels, L., Mun Lim, E.E., et al.: Combined thyroxine/liothyronine treatment does not improve well-being, quality of life, or cognitive function compared to thyroxine alone: a randomized controlled trial in patients with primary hypothyroidism. *J. Clin. Endocrinol. Metab.*, 88(10):4543-4550, 2003.
24. Sawka, A.M., Gerstein, H.C., Marriott, M.J., et al.: Does a combination regimen of thyroxine (T₄) and 3,5,3'-triiodothyronine improve depressive symptoms better than T₄ alone in patients with hypothyroidism? Results of a double-blind, randomized, controlled

- trial. *J. Clin. Endocrinol. Metab.*, 88(10):4551-4555, 2003.
25. Clyde, P.W., Harari, A.E., Getka, E.J., and Shakir, K.M.M.: Combined levothyroxine plus liothyronine compared with levothyroxine alone in primary hypothyroidism: a randomized controlled trial. *J.A.M.A.*, 290:2952-2958, 2003.
 26. Cassio, A., Cacciari, E., Cicgnani, A., et al.: Treatment of congenital hypothyroidism: thyroxine alone or thyroxine plus triiodothyronine? *Pediatrics*, 111(5): 1055-1060, 2003.
 27. Saravanan, P., Chau, W.F., Roberts, N., et al.: Psychological well-being in patients on 'adequate' doses of L-thyroxine: results of a large, controlled community-based questionnaire study. *Clin. Endocrinol. (Oxf.)*, 57(5):577-585, 2002.
 28. Walsh, J.P.: Dissatisfaction with thyroxine therapy: could the patients be right? *Curr. Opin. Pharmacol.*, 2:717-722, 2002.
 29. Lavietes, P.H. and Epstein, F.H.: Thyroid therapy of myxedema: A comparison of various agents with a note on the composition of thyroid secretion in man. *Ann. Intern. Med.*, 60:79-87, 1964.
 30. Cooper, D.S.: Combined T₄ and T₃ therapy—back to the drawing board. *J.A.M.A.*, 290:3002-3004, 2003.
 31. Gorowski, T., Pucilowska, J., and Wernic, K.: Comparative effects of desiccated thyroid gland and sodium salt of L-thyroxine in the treatment of hypothyroidism. *Pol. Tyg. Lek.*, 44(32-33):768-770, 1989.
 32. Krenning, E.P., Docter, R., Visser, T.J., et al.: Replacement therapy with L-thyroxine: serum thyroid hormone and thyrotropin levels in hypothyroid patients changing from desiccated thyroid to pure thyroxine substitution therapy. *Neth. J. Med.*, 28(1):1-5, 1981.
 33. Felt, V. and Nedvidkova, J.: Comparison of treatment with L-thyroxine and a dried thyroid gland preparation in patients with hypothyroidism. *Vnitr. Lek.*, 28 (11):1067-1073, 1982.
 34. Cobb, W.E. and Jackson, I.M.: Drug therapy reviews: management of hypothyroidism. *Am. J. Hosp. Pharm.*, 35(1):51-58, 1978.
 35. Wartofsky, L.: Combined levotriiodothyronine and levothyroxine therapy for hypothyroidism: are we a step closer to the magic formula? *Thyroid*, 14(4):247-248, 2004.
 36. Rodriguez, T., Lavis, V.R., Meininger, J.C., et al.: Substitution of liothyronine at a 1:5 ratio for a portion of levothyroxine: effect on fatigue, symptoms of depression, and working memory versus treatment with levothyroxine alone. *Endocr. Pract.*, 11:223-233, 2005.
 37. Kosowicz, J., Horst-Sikorska, W., Lacka, K., et al.: Outcome of treating hypothyroidism with thyreoidium. *Pol. Tyg. Lek.*, 48(27-28):599-602, 1993.
 38. Warszawie, C.M.K.P.: Treatment of hypothyroidism with L-thyroxine. *Pol. Tyg. Lek.*, 48(27-28):605-608, 1993.
 39. Singh, S.P., Feldman, E.B., and Carter, A.C.: Desiccated thyroid and levothyroxine in hypothyroidism: comparison in replacement therapy. *N.Y. State J. Med.*, 72(9):1045-1048, 1972.
 40. Sawin, C.T., Hershman, J.M., Fernandez-Garcia, R., et al.: A comparison of thyroxine and desiccated thyroid in patients with primary hypothyroidism. *Metabolism*, 27(10):1518-1525, 1978.
 41. Smith, R.N., Taylor, S.A., and Massey, J.C.: Controlled clinical trial of combined triiodothyronine and thyroxine in the treatment of hypothyroidism. *Brit. Med. J.*, 4:145-148, 1970.
 42. McGavack, T.H. and Reckendorf, H.K.: Therapeutic activity of desiccated thyroid substance, sodium L-thyroxine and D, L-triiodothyronine: a comparative study. *Am. J. Med.*, 20:774-777, 1956.
 43. Kaplan, M.M., Sarne, D.H., and Schneider, A.B.: Editorial: In search of the impossible dream? Thyroid hormone replacement therapy that treats all symptoms in all hypothyroid patients *J. Clin. Endocrinol. Metab.*, 88(10):4540-4542, 2003.
 44. Taylor, S., Kapur, M., and Adie, R.: Combined thyroxine and triiodothyronine for thyroid replacement therapy. *Brit. Med. J.*, 2:270-271, 1970.
 45. Baisier, W.V., Hertoghe, J., and Eeckhaut, W.: Thyroid insufficiency: is thyroxine the only valuable drug? *J. Nutr. Environ. Med.*, 11:159-166, 2001.