5-2022

Combination Thyroid Hormone Therapy in the Treatment of Hypothyroidism

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by

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A Scholarly Project

Submitted to the Graduate Faculty of the University of North Dakota

in partial fulfillment of the requirements for the degree of

Master of Physician Assistant Studies

Grand Forks, North Dakota

May 2022

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Acknowledgments

I would like to thank my advisor, Professor Jay Metzger, MPAS, for his assistance in compiling this scholarly project. I would also like to thank Dr. Steven Case, PharmD, and Dr. Matthew Finke, MD, MPH, for their contributions to the pharmacological and statistical components of this endeavor. I would like to extend my gratitude to Dr. Heath Eggleston, MD, for graciously operating as my primary care preceptor, mentor, and lifelong colleague. Finally, I would like to extend my gratitude to my husband, Dr. Ross Johnson, DDS, MSD, for his deliberations of my scholarly project and infinite support of my journey to become a physician assistant.

Abstract

The nature of this systemic literature review and research is to explore the use of thyroxine (T4) monotherapy versus T4 and triiodothyronine (T3) (combination) therapy for the treatment of hypothyroidism. A literature review was conducted using electronic search databases which included PubMed, CINHAL, and Clinical Key. Mesh terms included hypothyroidism/drug therapy, hypothyroidism/diagnosis, thyroid hormones/physiology, and thyroxine. Filters applied to the search included clinical study, clinical trial, guideline, journal article, meta-analysis, randomized controlled study, and systematic review. The search was tapered by limiting results to the last ten years, human species, and adults 19+. The articles were further narrowed by excluding subclinical hypothyroidism and pregnancy. For this review, 21 resources were selected. The reviewed clinical studies resolved that combination and monotherapy are analogous in the general population despite commonly observed trends in those utilizing combination therapy: modest weight loss and subjective improved well-being. Regardless, most investigators deemed no benefit of implementing combination therapy over levothyroxine. Monotherapy remains the appropriate treatment for the general population of primary hypothyroid patients, as the majority experience positive outcomes with this regimen. Yet, combination therapy should not be entirely excluded and should be considered in patients who fail to respond appropriately to monotherapy. It also should be contemplated as a preliminary regimen in this population. Modest changes observed have often been considered trivial and clinically insignificant to investigators but can be substantial to modern patients. Though these perceived moderate improvements may only be observed in a select population, it does not yield them any less significant.

Keywords: desiccated thyroid hormone, hypothyroidism, thyroid hormone replacement, combination, DTE and liothyronine.

Introduction

Though small, the thyroid gland has a large impact on the metabolic processes of the body. Major contributions include metabolism, energy level, weight, regulation of other hormones, mood, fertility, temperature, heart rate, cognition, and the menstrual cycle. The main hormones, thyroxine (T4) and triiodothyronine (T3) are responsible for these processes. Unfortunately, millions of people around the world are affected by dysfunction of the thyroid. An overactive thyroid, more commonly known as hyperthyroidism, causes overproduction of thyroid hormones and subsequent heart rate acceleration, intolerance to heat, and unintentional weight loss. An underactive thyroid, termed hypothyroidism, occurs when the gland fails to produce adequate hormone levels, leading to symptoms such as cold intolerance, chronic constipation, and fatigue. This literature review focuses on the hypoactive spectrum of dysfunction. The etiologies of hypothyroidism are numerous and will be discussed later. Regardless of the cause, the mainstay of treatment consists of thyroid hormone replacement therapy. Although not curative, replacement therapy can relieve symptoms, normalize thyroid dysfunction and allow patients to live relatively normal lives. Typical treatment consists of supplementing the body with synthetic doses of T4. Thyroxine monotherapy has been utilized for decades and many patients have found success with this simple therapy to resolve symptoms. For those patients who remain symptomatic despite T4 supplementation, the addition of T3 has been proven to alleviate persistent hypothyroid symptoms. The nature of this literature review is to explore the use of T4 monotherapy versus T4 and T3 (combination) therapy for the treatment of hypothyroidism and to assist medical providers in offering optimal care to current and future hypothyroid patients.

Statement of the Problem

Thyroxine monotherapy has been the cornerstone of treatment for hypothyroidism for decades and is commonly prescribed as levothyroxine. Unfortunately, many patients continue to experience symptoms of hypothyroidism despite monotherapy supplementation. Current guidelines recommend that these patients be further supplemented with T3 in addition to T4. Despite these directives, many practitioners are hesitant or resistant to the option of combination therapy. Much of this opposition is due to the traditional focus on patients' serum thyroid hormone levels and thyroxine monotherapy instilled to medical professionals for decades. This has resulted in many hypothyroid patients being undertreated and left to continue to suffer from chronic malaise, altered cognition, depression, chronic constipation, and weight gain. It is imperative that clinicians be aware of and open to the indications and benefits of combination therapy in the treatment of hypothyroidism. Past and current research is available to assist medical professionals in providing tailored care when prescribing thyroid hormone replacement in such patients. Upon doing so, clinicians can implement best-practice guidelines, promote patient autonomy and be self-assured in their medical practice.

Research Question

Is the use of combination thyroid hormone therapy just as or more effective than the use of levothyroxine in the treatment of hypothyroidism?

Methods

A literature review was conducted using electronic search databases which included PubMed, CINHAL, and Clinical Key. The search criteria included the keywords desiccated thyroid hormone, hypothyroidism, thyroid hormone replacement, combination, DTE (desiccated thyroid extract), and liothyronine. Mesh terms included hypothyroidism/drug therapy,

hypothyroidism/diagnosis, thyroid hormones/physiology, and thyroxine. Filters applied to the search included clinical study, clinical trial, guideline, journal article, meta-analysis, randomized controlled study, and systematic review. The search was tapered by limiting results to the last ten years, human species and adults 19+. The articles were further narrowed by excluding subclinical hypothyroidism and pregnancy. Several articles were discovered while browsing through selected related articles and utilized despite being published greater than ten years ago. These were included to evaulate and compare several past and current publications. The articles were examined and evaluated for relevance to the chosen topic, bias, and quality of research.

Literature Review

Reviewed data has demonstrated that combination thyroid hormone therapy is beneficial for many hypothyroid patients and numerous studies have found it to be as effective as T4 monotherapy. As with any medication regimen, combination therapy has risks and benefits. Clinicians need to be aware of these, as well as current guidelines, in order to individualize and optimize treatment for each patient.

Pathophysiology of Hypothyroidism

The production and emission of thyroid hormones is regulated by the negative-feedback system of the hypothalamus, anterior pituitary, and thyroid gland, also referred to as the HPT axis. Each individual possesses an HPT axis set point that is determined genetically and is reflected by moderately consistent T3 and T4 levels throughout the lifespan. In response to low thyroid hormone levels, the hypothalamus will release thyrotropin releasing hormone (TRH) to the anterior pituitary gland. The pituitary will subsequently release thyroid stimulating hormone (TSH) to the thyroid gland, which will in turn produce, store and release thyroid hormones.

Triiodothyronine and thyroxine are the two main hormones produced by the thyroid (Bensenor et al., 2012).

T4 is considered inactive and must be converted to T3, the primary bioactive thyroid hormone. According to Biondi and Wartofsky (2012), biological accessibility to T3 is determined by deiodinases that cleave an iodine molecule from T4, designated type 1 (D1), type 2 (D2), and type 3 (D3). D1 is found in the thyroid, kidney, and liver and can activate or inactivate T4. It substantially contributes to the collection of circulating T3 in the body. D3 inactivates T3 and subsequently regulates the hormone by diminishing local concentrations in tissue. This mechanism protects areas from excess hormone binding. D2 is located in the thyroid gland, myocardium, anterior pituitary, brain, aortic smooth muscles, skeletal muscle, brown adipose tissue, and osteoblasts. D2 moderates the HPT axis and facilitates pituitary response to systemic T4 level changes. Accordingly, the fixed point at which TSH is secreted is subject to serum and pituitary T3 composed by D2. It also modulates intracellular T3 concentration.

Thyroid hormone receptors are found in practically all tissues. Thyroid hormones have been shown to signal changes in bone development and resorption by stimulating osteoblast and osteoclast activity. Thyroid hormones increase cardiac protein synthesis, blood volume, heart rate, and contractility and also decrease systemic vascular resistance, resulting in an overall increase in cardiac output. They also govern basal oxygen consumption, lipogenesis, lipolysis, and differentiation of brown and white adipose tissue in the liver. In addition, these hormones regulate the production and emission of other hormones of the pituitary (Yen, 2001).

Most of the thyroid hormone generated is T4, with about 3% unbound to carrier proteins (free) while the remaining T4 is joined to proteins. Roughly 30% of generated T3 is unbound, which enters target tissues and binds to thyroid hormone receptors inside the nucleus. This

binding regulates the transcription of target genes and subsequent protein synthesis within cells. The remaining T3 is sequestered to carrier proteins. The anterior pituitary regulates TSH levels based on feedback of free T4 (FT4) and free T3 (FT3) levels. Reductions in these thyroid hormone compositions stimulate secretion of TSH (Yen, 2001).

According to Almandoz and Gharib (2012), hypothyroidism is attributed to deficient thyroid hormone action in target tissues or insufficient thyroid hormone production and is most prevalent in ethnic groups, the elderly, and women. There are also several categories of hypothyroidism. Primary hypothyroidism occurs when the thyroid gland is impaired and there are subdivisions of primary hypothyroidism. Hashimoto's thyroiditis, or chronic autoimmune thyroiditis, is an autoimmune condition in which autoantibodies attack the thyroid gland. Particularly, antithyroid peroxidase (TPO) antibodies are the most frequently observed. Other commonly observed antibodies include thyroglobulin (Tg), TSH receptor, and TSH-blocking antibodies. These antibodies will cause lymphocyte infiltration of the gland, resulting in inflammation and impairment. This is the most common cause of primary hypothyroidism in areas where dietary iodine intake is sufficient. Iodine deficiency, however, is the most common cause of primary hypothyroidism around the world. Ironically, excess iodine intake can also lead to hypothyroidism. Other common causes of primary glandular failure include thyroid hormone resistance, radiation exposure, systemic illness, medications, gland agenesis, and thyroidectomy.

Secondary hypothyroidism occurs when there is insult to the pituitary gland. Potential causes include medications, infection, infiltrative disorders, surgery, trauma, and pituitary infarct. Tertiary hypothyroidism occurs when the hypothalamus is injured and causes are similar to those of secondary hypothyroidism. Secondary and tertiary hypothyroidism are also commonly referred to as central hypothyroidism (Almandoz and Gharib, 2012).

Preliminary Hypothyroidism Treatment

Initially, hypothyroidism treatment modalities were generally inadequate, supportive, and symptom-guided. One of the earliest therapies entailed patients receiving thyroid transplants into the abdominal cavity or tibia. These were harvested from preferably pregnant sheep or goats or human glands from those with goiter or Grave's disease. This treatment was considered successful as most of the patients experienced marked improvement in symptoms, but unfortunately, symptoms often returned, and the procedure was repeated up to four times. Despite the unknown quantities of thyroid hormones secreted from the transplants, it was considered to be the initial model of combination therapy in the treatment of hypothyroidism. Other early pharmacologic approaches included combination therapies of intravenous, subcutaneous, and oral extracts or ingestion of raw or cooked thyroid gland. These remedies were also considered successful but were not without adverse effects (McAninch & Bianco, 2019).

Thyroxine was initially crystallized by Edward Kendall in 1915 and subsequently administered via IV in 1925, efficaciously paving the way for synthetic T4 development. Serum T3 was then uncovered by Jack Gross and Rosalind Pitt-Rivers in 1952. Serum protein-bound iodine (PBI), basal metabolic rate (BMR), and clinical responsiveness to thyroid preparations became standard treatment parameters prior to the discovery of TSH. PBI evolved as the customary means of monitoring treatment response, indicating amounts of protein-bound and circulating T3 and T4. In spite of the conception of T4, combination therapy remained the favored remedy. Clinicians continued to utilize combination therapy due to the fear that T4 monotherapy would cause a deficiency in T3 (McAninch & Bianco, 2019).

Combination treatment was not without tribulations. Natural thyroid hormone producers promoted their products and assured double standardization methods that provided stable metabolic activity of all remedies. In spite of these, potency discrepancies in dispensed tablets were common. Although batches followed iodine content standards, many contained tablets of variable strength: some possessed nearly undetectable metabolic activity while others contained almost double potency. In addition, humidity restrained the shelf-life of desiccated tablets. Thus, many patients reported a failure in response to desiccated thyroid extraction (DTE) as the tablets they were consuming contained no active thyroid hormone. On the other end of the spectrum, many patients reported thyrotoxic effects, piloting claims of DTE to be dangerous, archaic, and without desirable properties. (McAninch & Bianco, 2019).

In 1982, Braverman et al. discovered the conversion of T4 to T3 in the periphery, introducing the theory that T4 monotherapy could replenish the prohormone collection and deiodinases govern the accessibility to active T3. It was soon discovered that T4 monotherapy could stabilize T4 and T3 levels at the expense of a high T4:T3 ratio. DTE, thyroglobulin, T3, and T3+T4 combination therapy produced low or low-normal T4 levels and raised T3 levels. An oral dose of T4 orally brought about apparent parallel biological and constant serum T3 and T4 levels through the day, which was assumed to be due to a consistent rate of T4 to T3 conversion. These findings persuaded many providers to promote T4 monotherapy as primary hypothyroidism treatment and shifted patients formerly treated with DTE to T4. In 1985, thyroid hormone replacement potency establishment was revised from iodine to T3 and T4 content. Subsequently, TSH radioimmunoassay became the pillar of treatment monitoring (McAninch & Bianco, 2019).

Hypothyroidism Diagnostics

The measurement of TSH levels is the foundation for detecting thyroid disease, with a reference range of 0.4-4.0 μIU/L (Papadakis and McPhee, 2020). It should be noted that these values vary with age and individual laboratory settings. Unbound T4 is frequently measured in concurrence with a TSH level to appraise thyroid function as a means of screening. TSH is increased in cases of primary hypothyroidism, as the anterior pituitary is attempting to stimulate the thyroid gland. FT4 will be low or near the low end of the reference range as the thyroid gland is unable to secrete adequate thyroid hormones. TSH will be low in secondary hypothyroidism while antibodies will be elevated in autoimmune thyroiditis. (p. 1156) According to Almandoz and Gharib (2012), serology analysis for evaluation of thyroid gland function should include TSH, total (bound and unbound) T3 and T4, free T4 and TPO antibodies. Serum T3 and T4 are considered biologically inactive as they are bound to proteins. Accordingly, total T3 and T4 levels should not be utilized as a sole means of thyroid disease evaluation. Clinicians should take into consideration that certain medications, illnesses, and pregnancy can affect protein-binding levels and may muddle serum results. Papadakis and McPhee (2020) assert that other potential laboratory anomalies of hypothyroidism include hyponatremia, hypoglycemia, anemia, and elevated liver enzymes, creatine kinase, low-density lipoprotein (LDL) cholesterol and triglycerides. (p. 1155) Two-dimensional ultrasound imagining can be utilized in evaluation of Hashimoto thyroiditis and goiter (Almandoz & Gharib, 2012).

The preceding paragraph demonstrates some discrepancies that exist between providers when it comes to thyroid disorder diagnostics. Garber et al. (2012) conducted a literature review in order to create updated evidence-based guidelines for providers for the diagnosis, treatment and maintenance of hypothyroidism. The American Association of Clinical Endocrinologists (AACE) and American

Thyroid Association (ATA) compiled a task force of expert providers that conducted an extensive literature review along with personal anecdotal experience to compile clinical recommendations and their respective rationale. Their endorsements are Grade A, B, and C (evidence-based) or Grade D (expert opinion-based due to lack of decisive clinical evidence). The literature review demonstrated that TSH levels should serve as the primary means of screening for thyroid dysfunction and monitoring ongoing hormone replacement (Grade A). However, interpretation should be utilized attentively as there are several shortcomings of the test, as TSH levels may be affected by other diseases, illnesses, and medications. Thus, TSH measurements alone are not adequate enough for evaluating suspected central hypothyroidism or the acutely ill.

Garber et at. (2012) also recommends that FT4 be obtained for the routine screening of thyroid disease or suspicion of hypothyroidism. Low FT4 confirms a hypothyroidism diagnosis. In the event of an elevated TSH, serum FT4 should be obtained in order to accurately correct the condition pharmacologically and be routinely monitored as TSH levels may take weeks or even months to return to normal. It should also be collected in patients with TSH levels in the standard or low range to assess for central hypothyroidism (Grade A). Total T4 is not routinely collected to monitor the condition of the thyroid or for screening purposes as approximately 99.97% of T4 is bound to proteins and, therefore, not metabolically active. Evaluation of total and free T3 serum levels have limited benefit in the assessment of hypothyroid dysfunction. This is because concentrations are frequently in the normal range due to elevated TSH levels and increased D2 activity in a hypothyroid state. T3 levels are also usually low in patients with severe illness devoid of thyroid disease due to increased thyroid hormone deactivation and reduced peripheral T4 to T3 conversion (Grade B).

It should be noted that many patients affected with autoimmune thyroiditis are biochemically euthyroid when a thyroid panel is collected. Thus, clinical judgment should be executed when

appropriate and thyroid gland and receptor antibodies obtained to assess for autoimmune disease (Grade B). Garber et al. (2012) also recommend that patient symptomology be taken into consideration for hypothyroidism diagnosis. Although many patient complaints may be subtle or attributed to other disease processes, the provider should not exclude this portion of the analysis. Detailed objective diagnostics include decreased metabolic rate, Achilles reflex time, and sleeping heart rate, and a noted increase in creatine kinase, total cholesterol, and low-density lipoprotein (LDL) cholesterol. These, however, should be utilized to support the diagnosis of hypothyroidism, not as a means of exclusive diagnosis (Grade B).

Levothyroxine Monotherapy Treatment

Modern treatment for hypothyroidism typically begins immediately after diagnosis and is commonly initiated when TSH levels exceed 10 μIU/L. Patients are generally treated with synthetic levothyroxine, which has a half-life of approximately one week. Levothyroxine monotherapy is commonly well-tolerated and safe when consumed appropriately and dosed individually (Biondi & Wartofsky, 2012). Levothyroxine should be administered on an empty stomach for at least one hour or four hours after the last meal. No other medications or supplements should be consumed within the hour of administration. Levothyroxine can also be dispensed in a once-weekly dose that is approximately seven times higher than a typical daily dose. Most patients are traditionally started on a small daily dose with gradual titration. Patients without significant comorbidities can be started on a weight-based dose of approximately 1.6 μg/kg/day (Chakera et al., 2012).

Dosing in geriatric patients (greater than 65 years of age) and those with cardiovascular disease should be utilized with caution and treatment should be initiated in the conventional manner. Dosing requirements generally decline progressively with age and standard doses can

trigger myocardial ischemia in elderly patients with silent heart disease. Therefore, treatment should be initiated at 25-50 μg/day with subsequent protracted titration. Patients with ischemic heart disease should be started on a dose of 12.5-25 μg/day with titrations every four to six weeks of similar dose increments until desired TSH levels are obtained. Goals of hormone replacement therapy include restoration of physiological euthyroidism as evidenced by observation of serum hormone quantities within normal limits and recession of hypothyroid manifestations (Chakera et al., 2012).

Historically, overtreatment with thyroid hormone replacement has been correlated with adverse effects on skeletal health, especially in the elderly. These consequences have been observed in suppression levels below 0.1 μIU/L, however. Thus, patients with primary hypothyroidism receiving levothyroxine supplementation should be treated to maintain TSH levels in their respective population reference ranges. It is not recommended that providers increase T4 doses in those who are asymptomatic with TSH levels in the upper limits of the normal reference range. The ATA and AACE recommend analyzing TSH levels four to six weeks after dose adjustments or a change in thyroid preparation (Almandoz and Gharib, 2012). Biondi and Wartofsky (2012) assert if symptoms persist despite seemingly adequate levothyroxine administration as evidenced by TSH levels in the normal reference range, the addition of T3 to the replacement regimen should be considered. Exclusive T3 administration is not utilized due to its short half-life, fluctuations in T3 and TSH levels and multiple daily dosing requirements. As the half-life of T3 is approximately one day, three daily doses of T3 are required to acquire biologically stable circulating T3 levels in the body, creating broad fluctuations in serum levels. Additionally, T3 has a higher degree of receptor binding, which amplifies metabolic activity.

Combination versus Monotherapy

Despite seemingly adequate therapy, many patients remain symptomatic while being treated with levothyroxine. According to McAninch and Bianco (2019), 10-15% of patients treated with T4 monotherapy continue to experience residual hypothyroid symptoms, particularly cognitive impairment. This has been documented as early as the 1970s when standard treatment doses contained 150 mcg of T4 and 45 mcg of T3. A subgroup of patients required additional T3 to replenish health. Although this could be due to confounding or disease misclassification, it could also imply inadequate hormone replacement with T4 monotherapy in a sizeable percentage of patients (Taylor et al., 2019).

Many clinical trials suggest that T4 monotherapy may in fact not exemplify a universal regimen for hypothyroidism. According to Chakera et al. (2012), many patients on levothyroxine supplementation fail to reach a biological FT3 and FT4 ratio regardless of a normal TSH level. Proposed hepatic and renal conversion of T4 to T3 impairment may explain this phenomenon. Other possible explanations include outstanding TSH levels within reference values, which can be indicative of subpar hormone replacement therapy, hypothyroidism and dysphoria symptom overlap, and inherent patient autoimmunity unrelated to thyroid status. Serum levels can also potentially misrepresent actual hormone concentration in target tissues. Taylor et al. (2019) report that levothyroxine is the most frequently prescribed medication in the United States and the third most regularly prescribed in the United Kingdom. Despite this, studies have consistently demonstrated that T4 monotherapy causes reduced FT3 and elevated FT4 levels in treated subjects in comparison to those with an undisturbed and intact HPT axis. Studies have also demonstrated that about 20% of T4 treated patients are “over-replaced,” as evidence by low

or repressed TSH levels. Interestingly, there is growing evidence that lower TSH levels tend to produce greater adverse effects as well as better patient satisfaction.

Patients subsidized with T4 monotherapy to attain TSH values within normal limits generally have a substantially increased T4:T3 ratio due to normal serum T3 and increased T4 quantities, according to Taylor et al. (2019). Trials of established hypothyroidism patients on monotherapy have confirmed that supra-physiological levels of T4 are mandatory to stabilize serum T3 quantities. A subset of goiter patients who were given T4 prior to thyroidectomy required a 33% increase in dosage after surgery to sustain pre-surgical TSH levels. Studies have also confirmed that T4 promotes the destruction and inhibits the activity of D2 in cell lines, allowing cells autonomy to protect themselves from T4 excess, and to increase local T3 production in areas of T4 deficiency. If this process occurs in the body, treating patients with subclinical hypothyroidism with T4 monotherapy may paradoxically worsen tissue hypothyroidism. Pituitary cells are less susceptible to autoregulation, proposing that TSH suppression occurs with T4 therapy in spite of T3 synthesis in peripheral tissues. This leads to a paradoxical decrease in local T3 synthesis and sole T4 will take place despite repressed or normal TSH levels. In cell line studies, pituitary cells are less prone to such “autoregulation,” suggesting that TSH will be effectively suppressed with T4 monotherapy despite inhibition of T3 generation within peripheral tissues. As a result, paradoxical reduction in local T3 generation on T4 alone occurs despite normalized or even suppressed TSH levels.

These findings have lead many to rethink T4 monotheraphy as the foundation of primary hypothyroidism therapy and revist the attributes of combination therapy. It has also brought into question combination therapy’s early production and clinical studies. McAninch & Bianco (2019) report that primitive trials conducted to evaluate dose correspondence and efficacy

between the various formulations of combination replacement therapy contained many shortcomings. Doses were substantially higher than utilized today and variable as mentioned previously. Outcome measures were based on normalization of PBI and/or BMR and the trials were not constructed as superiority trials. Because of this, it has brought into question whether any thyrotoxic effects observed were due to high dosages or type of agent utilized. In trials where congestive heart failure and angina were documented, T3 doses were 75-100 mcg/day, whereas in other trials, palpitations, irritability, nervousness, dizziness, perspiration, and tremor were observed in patients consuming 80 mcg of T4 plus 20 mcg of T3 on a daily basis. Reassuringly, these effects subsided with a modest dose reduction and combination therapy.

Growing interest in the subject has led to many studies about the effects of combination therapy in comparison to the traditional T4 monotherapy. Biondi and Wartofsky (2012) conducted an extensive systematic literature review on the effects and utilization of combination therapy in comparison to levothyroxine monotherapy. Eleven controlled trials that were randomized with 1,216 subjects determined that combination treatment was not superior to levothyroxine therapy in adverse events, total serum cholesterol, LDL, high-density lipoprotein (HDL) cholesterol, triglycerides, depression, anxiety, fatigue, body weight, body pain, and quality of life. A subsequent meta-analysis of 1,243 subjects indicated that combination therapy was advantageous to physical and psychological health, formerly supplemented with sole T4. However, another meta-analysis of nine controlled trials comparing T4 to T4/T3 treatment observed no substantial distinctions for psychiatric symptoms. Shortcomings of the studies included small sample sizes, substantial variation in combination dosing, low sensitivity of cognition and mood outcome measures and brief treatment duration. Only a minority of the trials investigated objective peripheral parameters of hormone action, there was a consistent lack of

homogeneity of the hypothyroid patient in the majority of trials and considerable disparity in the severity of hypothyroidism. This extensive literature review contained a large subject pool with ambiguous results.

Despite these findings, Biondi and Wartofsky (2012) recommend combination therapy be considered in four hypothyroidism groups of special interest: autoimmune thyroiditis, patients with thyroidectomy or radio-ablative procedures with inadequate gland function and lack of gland T3 production, patients with D2 genetic variations and hypothyroid patients with depression. Patients with autoimmune hypothyroidism have lingering T3 production from the gland, which may rationalize the necessary lower T4 doses in these patients in contrast to those without a thyroid gland. Nearly 20% of natural physiological T3 is secreted by the thyroid gland and ideally should be balanced out by rise in T4 deiodination in the periphery in patients who have undergone a thyroidectomy. Unfortunately, T4 supplementation has not exhibited the required amplification in deiodinase activity essential to synthesize physiological quantities of circulating T3 in these patients. This may be due to homeostatic changes, deiodinase activity and an altered HPT axis set point, resulting in a weaker feedback response of FT4 on TSH.

Hypothyroid patients with genetic D2 polymorphisms undergo fluctuations in the HPT axis set point, leading to a reduced negative feedback response of FT4 on TSH. Hypothyroid patients with resistive depression have demonstrated benefit with T3 supplementation in conjunction with tricyclic antidepressants. Noteably, adding T3 to Sertraline has augmented its antidepressant effects. Combination treatment in this population has yet to be investigated. The D2 Thr92Ala-12 polymorphism has been linked to HPT axis variation, cognition, bone remodeling and hormone replacement response. Thanks to the erraticism of the individual HPT axis set point, ascertaining a defined “normal” serum TSH level for all hypothyroid patients has

been problematic. Therefore, Biondi and Wartofsky (2012) assert it is necessary to stabilize not only TSH levels, but FT3 levels as well to bring about noteworthy effects of thyroid hormone in the periphery in hypothyroid patients. They do not, however, endorse T3 therapy in patients with cardiovascular disease or pregnancy.

The purpose of the randomized-controlled study conducted by Clyde et al. (2003) was to assess the advantages of levothyroxine monotherapy and levothyroxine plus liothyronine therapy in the treatment of primary hypothyroidism. The sample included 46 patients, aged 24-65 years old, who had been utilizing 50 µg/day levothyroxine therapy for at least three months and been treated for hypothyroidism for at least six months. Subjects were excluded from the study if they were pregnant, taking corticosteroids, amiodarone, sucralfate, cholestyramine, more than 325 mg/day of iron, had cardiovascular disease or medical issues affecting liver and/or renal function and were receiving suppressive doses of thyroid hormone. The study was double-blinded. Researchers utilized a control group, randomized the study sample, and applied an exclusion criterion to subject selection to address confounding variables.

Twenty-three of the subjects served as the control group and were given half of their usual levothyroxine dose (25 µg) in a capsule. In comparison, the other twenty-three served as the intervention group and were also given half their usual levothyroxine (25µg) plus a capsule of 7.5 µg of liothyronine, taken twice a day for a duration of four months. All subjects were given their usual 50 µg dose of levothyroxine and fasting TSH levels were obtained on day one of the study, followed by a neurocognitive examination, an interview, physical exam and symptom questionnaire. Study medications were administered on day two. TSH levels and previously described evaluations were repeated on the final day of the trial (Clyde et al., 2003).

Outcome measures contained neurocognitive function tests comprising of attention and working memory. Letter-number sequencing and spatial span subtests of the Wechler Memory Scale, Third Version (WMS-III), the Auditory Consonant Trigrams Test and Paced Auditory Serial Addition Test were utilized for these assessments. WMS-III and the Buschke Selective Reminding Test were used to assess learning and memory while the Thurstone Word Fluency Test measured written verbal memory. To measure manual dexterity and fine visual-motor coordination, the Grooved Peg Board test was employed. The Trail-Making Test Part B was used to evaluate attention, cognitive flexibility, visual scanning and visual-motor coordination. To measure depression symptom degree, the Beck Depressive Inventory (BDI) was employed. A health-related quality-of-life (HRQL) questionnaire was used to address primary outcome measures. Parametric (t test) or nonparametric (Mann-Whiney U test or Wilcoxon signed rank test) analysis was employed, depending on test results (Shapiro-Wilk test) assessing statistical model assumptions. A .05 2-tailed significance level was utilized for all parameters. The authors neglected to discuss what happened to the data of the dropped subjects and efforts made to avoid attrition bias (Clyde et al., 2003).

Clyde et al. (2003) reported analogous TSH levels in both groups at baseline and the end of the study. T3 levels increased ($P<.001$) and T4 levels decreased ($P<.001$) in the interventional group, but both levels persisted within normal limits. HRQL scores declined in both the control and intervention group ($P<.001$ and $P = .02$, respectively), but the reduction in scores was greater in the control group, although not statistically significant ($P = .54$). Twelve of the 13 neurocognitive exams reported no substantial difference between the two groups. The outstanding exam, the Grooved Peg test, demonstrated a decrease in performance in combination therapy subjects. Only 17 subjects from either group were given the BDI with no statistical

significance demonstrated (P = .21) when the group means of individual variations in scores were compared. A decrease in the mean BDI score of the control group (P = .005) was reported but not observed in the intervention group (P = .18).

The trial conducted by Clyde et al. (2003) concludes that there is no benefit of combination therapy over levothyroxine monotherapy in the treatment of primary hypothyroidism as evidenced by no advantageous variations in cognitive performances measures and HRQL results. The authors acknowledge the trial was not generalizable as the emphasis of the study was on patients with primary hypothyroidism. Outcome measures were not objective measures that are generally preferred for improvement with exogenous hormone replacement, such as basal metabolic rates. Finally, conductors failed to utilize suppressive doses of thyroid hormone, as many patients with primary hypothyroidism fail to attain succession of symptoms until on TSH suppressive doses of exogenous therapy, confining the intervention scope of the study.

Hennessey and Espaillat (2018) conducted a literature review in 2017 that included 72 non-review articles published within the last ten years. Seventeen were selected and accompanied by articles already known to the authors. The search included the terms “hypothyroid” or “hypothyroidism” and “triiodothyronine combination” or “T3 combination.” The authors compared patient treatment preference, mood and cognition outcomes and quality of life studies between combination and monotherapy. In all the examined trials, subjects treated with T4 monotherapy that reached TSH levels within the desired reference range generally had lower FT3 and higher mean FT4 levels than subjects in the controlled group. Many disparities in TSH levels, blood draw times, dosing and T4 ingestion were observed in the included studies, affecting thyroid panel quantities. One study utilized very high doses of T4 and combination

therapy and reported patients preferred monotherapy and demonstrated a more promising adverse effect profile. Of the four remaining 16 articles, four conveyed that combination therapy exhibited better outcomes in mood, cognition and quality of life and a subjective preference for T3/T4 treatment. The rest of the studies reported impartial results. Thus, the conclusion of this search yielded mixed and ambiguous results.

The authors then conducted a systematic review consisting of nine controlled trials with 1,056 subjects comparing the two therapies, which resulted in no observed advantage of combination therapy over monotherapy in mood, psychometric performance or quality of life. A meta-analysis was then conducted that entailed 11 randomized trials with 1,216 subjects comparing mono- versus combination replacement. This assessment observed no differences in quality of life, cognitive function, anxiety, depression, fatigue or body pain between the two. A third meta-analysis of 1,141 subjects in nine controlled trials reported no difference in therapies in terms of mood but demonstrated a preference for combination therapy. The fourth inquiry included a meta-analysis of 1,153 subjects in ten randomized, double-blind trials that reported intermittent improvements in cognitive function, mood, quality of life and adverse outcomes (Hennessey & Espaillat, 2018).

All trials utilized once-daily T3 dosing with combination therapy, which fails to sustain a steady-state biological concentration of the hormone. Application of alternative T3 preparations or three times a day dosing is necessary to evaluate combination therapy's effectiveness thoroughly. Trials were consistently short-term, with the lengthiest lasting one year. The authors then cited an observational study with a maximum of a 17-year follow-up that investigated 33,955 subjects treated with T4, 73 subjects treated with T3, and 327 patients treated with T3 and T4 therapy. There were no reported statistically significant differences in death, atrial

fibrillation, cardiovascular disease, fracture or diabetes outcomes in the therapies. The authors conclude from the above analyses that there are no or few differences in monotherapy and combination treatment and bolster there is no reproducible clinical proof to promote the value of combination therapy over lone levothyroxine (Hennessey & Espaillat, 2018).

According to Duntas and Jonklaas (2019), evidence is lacking to demonstrate an advantage of combination therapy over traditional levothyroxine in enhancing healthcare effects. The authors conducted a randomized, double-blind trial, consisting of 141 subjects aged 18-70 years of age, comparing levothyroxine supplementation to combination therapy with primary hypothyroidism. All identified an improvement in mood, fatigue, neurocognitive function and overall well-being. Of particular interest, patients demonstrated a preference for combination therapy. Subjects with combination partiality also noted a reduction in body weight, which could account for the preference. Regardless, these findings did not support combination treatment being superior to levothyroxine monotherapy.

Kamkinski et al. (2016) conducted a randomized, double-blind, crossover study in order to compare the effects of a specific T3/T4 dose (15 and 75 µg, respectively) in primary hypothyroidism treatment. Inclusion criteria included subjects aged 15-65 with an established primary hypothyroidism diagnosis and had previously received 125-150 µg/day of T4 monotherapy in the past six months. Exclusion criteria included pregnancy, hormonal contraception use, use of substances/drugs that alter TSH levels and pharmacokinetics of thyroid hormones, diabetes mellitus and serious comorbidities such as cardiovascular, renal and liver disease. Subjects diagnosed with depression were also included if they had received ample treatment with antidepressants in the past six months. Thirty-nine subjects were considered for participation, but seven were ultimately dismissed prior to randomization: one due to divorce,

one due to pregnancy, three due to increased TSH levels in the past six months and two due to diabetes mellitus onset.

Three of the subjects had radioiodine-induced gland dysfunction due to Grave's disease, six had thyroid cancer and subsequent thyroidectomies and 23 had idiopathic or autoimmune hypothyroidism. Thirty of the subjects were female. Participants were randomized to continue their T4 monotherapy (n = 17) or start the combination therapy (n = 15) for eight weeks (G1 and G2, respectively). The two groups then switched treatment for an additional eight weeks. Subject thyroid function, plasma glucose, lipid profile, body weight, vital signs, electrocardiogram, and quality of life (QoL) were assessed at weeks zero, eight, and 16. Clinical and biochemical data were comparable for both groups at baseline with the exception of basal TSH. Levels ranged from 0.001-4.5 μU/L in G1 and 0.001-8.425 μU/L in G2. Six subjects displayed suppressed TSH levels due to thyroid cancer treatment, while others had increased TSH levels at the time of randomization. Despite this, researchers kept all subjects in their statistical analysis because each crossover subject served as his or her own control (Kamkinski et al., 2016).

Medications were dispensed in identical capsules containing either 125 μg or 150 μg T4 or 75μg T4 plus 15 μg T3. The dispersion was conducted by one unblinded investigator, who did not participate in the result assessment. Adverse events were assessed by physical examination and patient history. Regimen adherence was evaluated by capsule counting and direct questioning during follow-up visits. Sample sizes were assessed using z-tests. Biochemical and clinical figures were evaluated via t-tests, one-way ANOVA, Dunn's multiple comparison test, and Mann-Whitney U test or Wilcoxon signed-range test for variables that lacked normal distribution. QoL scores were explored via Friedman rank-sum tests while hormone level and

QoL score associations were calculated via Pearson's or Spearman's correlation coefficients (Kamkinski et al., 2016).

At the conclusion of the study, Kamkinski et al. (2016) reported that FT4 levels were considerably lower in subjects while on combination treatment (G1 1.07 ± 0.29 at week 16 versus 1.65 ± .046 ng/dL at week eight; G2 0.97 ± 0.26 at week eight versus 1.63 ± 0.43 ng/dL at week 16, P<.001) while T3 and TSH levels were not affected by either therapy. TSH changes were insignificant in both G1 (P = 0.05) and G2 (P = 0.819). Five subjects experienced T3 levels greater than 180 ng/dL while taking combination therapy (mean 239 ± 57.1 ng/dL, highest 311.5 ng/dL) whereas only one subject taking monotherapy experienced increased T3 levels (298.5 ng/dL). From this data, the authors conclude that TSH and T3 levels were not affected by either type of therapy. Body weight, lipid profile and QoL were unaffected by either regimen. While on combination therapy, subjects experienced a slight increase in heartrate, but remained within normal limits. No considerable blood pressure or electrocardiogram changes (including arrythmias) occurred. All participants completed the study, and no substantial adverse effects were recounted.

No differences in global scores in QoL were noted between the two regimens (P = 0.888) and subgroup scores were also similar for both modalities (P>0.05). They did not report any associations between FT4 and T3 levels and global scores at baseline or while on mono- or combination therapy (all P>0.05), but a positive correlation was observed between global scores and TSH levels while on combination therapy (P = 0.018). Correlation evaluation comparing hormone levels and subgroup scores revealed associations between TSH levels and energy/general well-being while on combination therapy (P=0.019) and TSH levels and mood/emotions scores, also while taking combination therapy (P=0.023). The authors conclude that combination treatment produced no changes in TSH or T3 levels but

substantially lower FT4 levels. More subjects on combination therapy experienced elevated T3 levels than subjects on monotherapy but experienced no substantial changes in evaluated outcomes. Ultimately, Kraminski et al. (2016) infer no clear benefit from the studied combination preparation and recommend future trials to assess different formulations and the impact in those with genetic polymorphisms. Limitations of this study include short duration of treatment, non-standardization of monotherapy dosage, lack of blinding of investigator distributing capsules, lack of standardized TSH levels at baseline and consideration of T4 half-life when interchanging regimens.

Chakera et al. (2012) reported appraisal of a randomized, double-blind crossover study consisting of 14 subjects with primary hypothyroidism. The trial compared the effects of T3 versus T4 therapy in the participants. All received T3 or T4 three times a day and reached TSH levels between 0.5-1.5 μIU/L. Six weeks later, patients who received T3 therapy were found to have decreased lipid panel counts and weight loss, but no cardiovascular, insulin sensitivity or quality of life modifications. Chakera et al. (2012) subsequently conducted a meta-analysis of eleven randomized-controlled studies consisting of 1,846 subjects. The evaluation determined combination therapy failed to be any more efficacious than levothyroxine monotherapy. Despite these results, subjects in two of the eleven studies conveyed partiality towards combination treatment regardless of no objective change in overall welfare.

Dayan and Panicker (2018) performed a systematic literature review of studies comparing levothyroxine monotherapy and combination therapy. The authors discovered 13 randomized controlled trials that compared the efficacy of both drug therapies and one comparing levothyroxine to desiccated thyroid extract. In addition to the authors, there have been four other systematic reviews/meta-analyses of the studies, all of which assert there is no advantage of combination therapy over levothyroxine in cognition, quality of life and mood. This verifies thatyhe benefit of combination therapy over levothyroxine is lacking at a population

level. The trials, however, all had substantial differences in length of study, sample size, measured outcomes, T3 for T4 substitution methods, and doses. A rise in adverse events in subjects treated with combination therapy was not observed. Follow-up on subjects was also relatively short, varying between five to 52 weeks.

The TEARS study continued follow-up for a median of nine years after comparing 400 subjects who had ever been taking T3 to 33,955 who had only ever taken T4. This study found no escalation in fractures or cardiovascular disease in the T3 population. This was an observational study, the extent of T3 administration was not measured and the significant differences in comparison sizes generate bias. Despite its limitations, the TEARS study has been the longest and largest trial of its kind and offers encouragement that the dangers of T3 therapy are not as severe as previously understood. Other than the above-mentioned, little data on the safety and long-term effects of combination and T3 monotherapy exist (Dayan & Panicker, 2018).

There is also little safety data and no long-term studies present on DTE's long-term use. The preparations of DTE include unmeasured amounts of diiodothyronine and mono-triiodothyronine. Advocates of DTE uphold these contents offer a more appropriate hormone replacement, despite lack of evidence these are necessary for normal thyroid gland performance or their presence in noteworthy amounts in a euthyroid state. DTE also includes antigens and thyroid-associated proteins, which have not been studied to date. Thyroid and endocrine societies do not endorse habitual DTE use in hypothyroid patients due to the lack of safety data, longstanding studies, lack of trials demonstrating an advantage of DTE over T4 therapy and variability of DTE formulations (Dayan & Panicker, 2018).

Dayan and Panicker (2018) assert that despite the lack of recommendation from these significant associations, DTE use in hypothyroidism holds noteworthy usage. The authors stress the need for additional studies to better determine the safety and role of DTE. In the meantime, prescribers and patients currently utilizing DTE must be counseled on proper safety measures. The authors also prompt clinicians to note that when initiating combination therapy in patients taking sufficient T4 therapy, it is always necessary to remove part of the T4 dose to replace it with T3. The usual T3 dose will be between 5-20 mcg/day in a split dose. When initiating combination therapy, the trial should last approximately six months. If T3 and T4 therapy is shown to be advantageous, providers should continue therapy and validate the presence of benefit for a minimum of one year prior to arranging long-term treatment. They also assert that all patients being treated with thyroid hormone replacement therapy indeterminately be assessed for unfavorable bone, cardiovascular and psychological effects.

Hoang et al. (2013) conducted a study in order to evaluate levothyroxine and DTE efficacy in patients diagnosed with hypothyroidism. This was a randomized, double-blind, crossover study. Researchers assessed the cognitive function, sense of general well-being, and symptoms of involved patients. Seventy subjects, aged 18-65, diagnosed with primary hypothyroidism and on levothyroxine for at least six months were studied. Subjects were randomly selected to receive levothyroxine or DTE in indistinguishable capsules. TSH levels were obtained, and medications adjustments were performed after six weeks in order to sustain levels between 0.5-3.0 μIU/mL. Replacement therapy was continued for at least 12 weeks once subjects attained these levels. Treatment was then switched between the two groups for 16 weeks. TSH was tested at the six-week mark to ensure desired quantities, followed by a repeat examination at the end of the second treatment period.

All study subjects and investigators were blinded throughout the trial. Therapy compliance was confirmed by capsule counting and a physician that did not participate in randomization maintained a concealed randomization list. The randomization list was synthesized by a computer-generated random number table. Stable TSH levels were confirmed prior to testing. Exclusion criteria and sample randomization addressed confounding variables. At baseline and end of treatment, subjects experienced memory testing via the Wechsler Memory Scale, fourth edition (WMS-IV), thyroid symptom questionnaire (TSQ), quality of life general health questionnaire (GHQ-12), and Beck Depression Inventory (BDI). Subjects were also questioned about which treatment (first or second) they preferred. Drug diversities were studied via mixed linear modules and subgroup analyses were conducted for those who preferred T4 therapy, preferred DTE therapy or had no preference (Hoang et al., 2013).

Seventy-eight subjects were initially enrolled in the study, but only 70 completed. The authors did not disclose why eight of the subjects did not finish the trial. The subjects consisted of 53 females and 17 males, half of which were previously diagnosed with primary hypothyroidism while the other half was diagnosed with secondary. When initiating the trial and switching therapies, researchers failed to take the long half-life of T4 into consideration. Other limitations included lack of formal adjustment for multiple comparisons, no genetic testing for deiodinase polymorphisms, low sensitivity of several neurocognitive exams and biochemical measures, and small sample size. Strengths of the trial include a homogenous group of hypothyroid subjects without a history of thyroid cancer, measurement of subjective symptoms, adequate duration to explore potential effects, and measurement of subject preference and biochemical testing trial (Hoang et al., 2013).

Thirty-four subjects expressed DTE preference (49%), 13 conveyed T4 preference (19%) and 23 (33%) voiced no preference. DTE partiality was statistically significant (P = .002). The BDI increased (P = .057) and auditory memory was enhanced in all patients during DTE therapy (P = 0.041). In general, no variances were observed in general health questionnaires, neuropsychological testing or symptom scores. Still, a development towards improvement in auditory memory index (P = .081), TSQ (P = .121) and GHQ-12 (P = .098) in DTE treatment were noted. No differences were observed in delayed memory index, immediate memory index, visual working memory index or visual memory index between the two therapies. DTE therapy demonstrated a weight loss of an average of 2.86 pounds (P<.001) compared to T4 and those who demonstrated DTE preference experienced a four-pound average weight loss during DTE therapy when compared to the T4 period (P<.001). This group also demonstrated improvements in subjective symptoms, such as energy level, happiness, decision-making capability, memory, sleep and concentration (P<.001). No substantial changes in blood pressure or heart rate transpired during the trial (Hoang et al., 2013).

Hoang et al. (2013) assert that 88 µg of T4 is equal to 60 mg of DTE and DTE can be efficient if administered once daily, although the short half-life of T3 in DTE may not ensue maximal advantageous effects of the formulation. This can be remedied by administering the formulation twice daily. The authors concluded that thyroid hormone supplementation with DTE administered once daily in lieu of levothyroxine produces probable symptom and mental health improvement along with reasonable weight loss devoid of significant adverse effects. They recommend further studies of longer duration to refine DTE's effectiveness and safety.

Toloza et al. (2020) sought to better understand patient partiality towards DTE in the treatment of hypothyroidism and carried out a mixed-methods study by assessing online posts

from three hypothyroidism forums. Posts were composed by 673 patients currently undergoing hypothyroidism treatment with DTE. The authors obtained patient demographics and clinical features from the compositions. Analysis was initiated via searching the ten most common patient forums and included WebMD, Drugs.com, Endocrine Web, Topix, Health Questions, Spark People, Talk Health Partnership, Everyday Health, Patients Like Me, and Patients.info. The key terms Armour Thyroid, Nature Thyroid, desiccated thyroid extract or desiccated thyroid treatment, thyroid extract and hypothyroidism were utilized. From commencement of each website to March 2018, a sum of 1,235 posts were retrieved. Of those, 673 posts from WebMD, Patients Like Me and Drugs.com were assessed after preliminary screening. Posts were chosen based on hypothyroidism etiology, sex, DTE dose, age and quantitative description of perceived efficacy of DTE treatment. Content of these compositions were transferred to spreadsheets where three independent reviewers obtained data of the posts in duplicate. To evaluate the general frequency of patient attitudes and perceptions, Toloza et al. (2020) obtained treatment indications, age, gender, DTE dose, benefits and adverse effects of DTE, patient-perceived DTE treatment effectiveness, source of DTE initiation, DTE treatment duration, sources of obtaining DTE, sources of information about DTE and benefits, characteristics and side effects of any therapies utilized for the treatment of hypothyroidism prior to DTE from the chosen posts.

Toloza et al. (2020) reported that the most common indications for DTE were hypothyroidism or Hashimoto's (n = 257, 51%), post-surgical hypothyroidism (n = 126, 25%) and post-ablation hypothyroidism (n = 81, 16%). Duration of treatment fluctuated between two weeks to 45 years and 54.5% of posts asserted DTE use for a minimum of six months. Sixty-three percent of the doses (n = 109) ranged between 50-150 mg/day, with a mean dose of 84.1 ± 56.9 mg/day (n = 172). Providers introduced therapy in 46% of patients (n = 74) while patient

interest or request commenced treatment in 54% (n = 88) of patients. The chief source of DTE material included clinicians (n = 15, 9%), social networks (e.g., family, friends and coworkers) (n=84, 53%) and internet information sources (n = 60, 38%). Forty-five percent of patients (n = 300) asserted prior hypothyroidism treatment with T4 monotherapy (n = 279, 93%), T4 plus T3 (n = 15, 5%) and Liotrix (n = 6, 2%). Causes of transition from previous treatment to DTE included lack of change in overall well-being (n = 36, 22%), occurrence of adverse effects (n = 38, 24%), lack of improvement in symptoms (n = 75, 47%) and lack of changes in laboratory panels (n = 12, 7%), with 5% of posts stating any advantage of previous treatment use. The mean time on previous treatment was 10.3 ± 8.7 years.

Improvement in symptoms was the most frequently reported advantage of DTE (n = 155, 56%). Of these enhancements, fatigue (n = 43, 28%), weight gain (n = 26, 17%), neurocognitive symptoms (n = 8, 5%) dermatological symptoms (n = 8, 5%) and depression (n = 5, 3%) were reported. Other benefits included improvement in overall well-being (n = 94, 34%), potential to attain previous health status (n = 19, 7%) and low cost compared to previous therapy (n = 8, 3%). In regard to efficacy, 77% (n = 99) of the posts asserted DTE was more effective than previous treatment, 13% (n = 17) stated DTE was as effective as previous treatment and 10% (n = 13) states that DTE was less effective than previous treatment. Eighty-one percent of compositions asserted that DTE therapy demonstrated moderate to major overall effectiveness. The mean time of noticeable improvements with DTE therapy 29.7 ± 32.5 days, with a range of two days to four months. Reported adverse effects (n = 136, 20%) included weight loss (15%), fatigue (11%), heart palpitations (11%), intolerance to heat (11%), disturbances in sleep (10%), elevated blood pressure (7%), hair loss (5%), depression (4%), nervousness (4%), irritability (4%), tremors (3.7%) and miscellaneous (musculoskeletal, menstrual irregularities, etc., 15%). Mean time of

side effect perception was 64.5 ± 15.4 days. DTE sources included local pharmacies (n = 75, 63%), purchases outside of the United States (n = 37, 31 %) and online (n = 7, 6%). Seventy-seven posts expressed logistical issues with DTE including access/availability troubles (53%), effect variability between batches (22%), no actual prescription (22%) and no FDA approval (2.6%). Common trends observed in the study included persistent fatigue and neurocognitive symptoms with T4 monotherapy despite thyroid levels within reference ranges, improvement in multiple symptoms after DTE therapy initiation and frustration with attaining correct DTE dosing, as evidence by lack of efficacy or presence of adverse effects. Other trends included need for individualized treatment in hypothyroidism and barricades to DTE treatment, such as lack of supply, provider resistance and insurance coverage (Toloza et al., 2020).

Limitations of the study include selection bias, overrepresentation of positive or negative experiences, hypothyroidism diagnosis was self-reported, inability to determine if symptoms were related to other etiologies, lack of thyroid panel results prior to, during, or after treatment, inability to exclude the possibility that the same patient could post comments in multiple forums, medication compliance, chronic medications, body weight, physical activity, employment status, marital status and previous negative interaction with clinicians and misinformation. In spite of these shortcomings, Toloza et al. (2020) stress that the study represents a preliminary approach to attain patient perceptions, experiences and feelings in regard to DTE therapy in an unobserved and more realistic setting. This study concludes that patients utilizing DTE recurrently express an absence of individualized treatment for hypothyroidism and lack of feeling listened to by providers. The authors recommend the necessity of patient-centered care in congruence with current practice guidelines.

According to McAninch and Bianco (2019), a clinical study of combination therapy that was conducted in order to institute TSH levels within normal limits demonstrated an enhancement in psychological factors. Another 16-week trial compared DTE to T4 monotherapy, in which TSH levels were within normal limits in both regimens, exhibited a patient preference of 48% and 18.6% to DTE and T4 therapy, respectively. Subjects who expressed DTE partiality also underwent an average weight loss of four pounds. Numerous clinical trials have displayed subjective inclination for combination treatment despite absence of definitive objective outcomes when quality of life and/or thyroid-explicit inquiries are employed, proposing that conventional surveys may not obtain authentic factors augmented by combination therapy. Many trials have been unable to establish an advantage of combination therapy in comparison to levothyroxine monotherapy and not all studies have been able to duplicate combination therapy benefits in all populations. Much of this may be attributed to pharmacological properties of current oral T3 formulations. McAninch and Bianco (2019) reference a contemporary study of a slow-release oral T3 formula recently developed was administered to hypothyroid rats. The preparation bestowed stable serum T3 levels within normal limits. Human trials with the novel method are yet to come but provide optimism that high quality, controlled and randomized trials will ascertain if steady-dose combination therapy is superior to T4 monotherapy in the future.

Tariq et al. (2018) carried out a retrospective study over the course of six years consisting of 100 subjects treated with combination therapy. Subjects included five men and 95 women that were between the ages of 20 and 81 years old. The objective of the study was to measure biochemical and physical effects of the addition of T3 to T4 monotherapy as well as determine distinctions between T4 with synthetic T3 (synthetic therapy) and DTE with FT4 (natural therapy). The patients were selected from 2,400 hypothyroid subjects in an endocrinology clinic

treated with T4 monotherapy. Exclusion standards included fibromyalgia, long-lasting psychiatric disorders, vitamin B12 deficiency, vitamin D deficiency, depression and anemia. Subjects were also excluded if they were under the care of a primary care physician rather than an endocrinologist to avoid provider bias.

A year prior to the commencement of the study, the primary author contacted subjects in a blinded fashion via telephone and employed the Medical Outcomes Study Short From-20 questionnaire (SF-20) to assess everyday symptoms of hypothyroidism. Subjects were also questioned on their opinions of improvement on combination versus monotherapy treatment. A standardized hypothyroid (poor memory, depression, amenorrhea, dry skin, fatigue, cold intolerance, myxedema coma and weight gain) and hyperthyroid (tremor, arrhythmia, anxiety, and palpitations) symptom questionnaire was utilized to collect data for disease manifestations. Baseline laboratory tests prior to combination therapy initiation included TSH, FT3, FT4, T4, hemoglobin, vitamin B12 and vitamin D (Tariq et al., 2018).

According to Tariq et al. (2018), all subjects were deemed hypothyroid according to ATA criteria, as evidence by elevated TSH and normal or subnormal FT4 levels at the commencement of the study. Of the included subjects, 52% were diagnosed with Hashimoto's disease, 10% had ablation therapy following thyroid cancer or Grave's disease, 22% had surgical hypothyroidism and the remaining 16% had various etiologies. TSH measurements were obtained via third generation immunochemiluminescent assay, with a normal range of 0.3 to 5.1 μIU/L and a functional detection limit of 0.01 μIU/L, while FT3 and FT4 were quantified via enzyme immunoassay. Serum was collected from 8:00 a.m. to 4:00 p.m. Standard laboratory reference values were based on ATA and AACE endorsements as follows: TSH between 0.035-5.5 μIU/mL (euthyroid), TSH less than 0.01 μIU/mL and FT4 greater than 1.64 μIU/mL

(hyperthyroid), TSH greater than 5.5 μIU/mL and FT4 less than 0.56 μIU/mL (hypothyroid), FT3 2.5-4 μIU/mL (normal) and 24-hydroxyvitamin D greater than 30ng/mL (normal).

Tariq et al. (2018), reported that continuous variables were related as means and medians and categorical variables as proportions. The paired t-test was employed to manage before and after treatment comparisons while the student t-test was utilized to assess between-group differences. Fisher exact and χ^2 were applied for categorical variable comparisons. Principal outcomes of the trial measured if combination therapy was efficient in improving clinical manifestations of hypothyroidism, adverse effects of biochemical or clinical hyperthyroidism and hypothyroid symptom improvement by the SF-20 questionnaire.

Combination therapy was initiated in those who demonstrated continued hypothyroid manifestations despite ideal T4 therapy for a minimum of one year, reached normal TSH values and a sustained low normal FT3 level. The distribution of synthetic or natural therapy was selected due to physician and patient inclination. This study did not titrate T4 to supraphysiological quantities in which thyrotoxicosis is worrisome prior to initiating combination therapy. Select patients interchanged regimens contingent on manifestations and thyroid levels. The preliminary synthetic dose consisted of 5 mcg T3 with a decrease of 12.5 μg in T4 in order to reach average biochemical circulating FT4:FT3 ratio of 14:1. T3 was titrated to a limit of 12.5 μg dose to reach therapeutic and physiologic FT3 levels and symptomatic respite. No subjects were treated with T3 monotherapy. Initial DTE dosing, with an established 4:1 FT4:FT3 ratio, entailed 15 mg to achieve equivalent outcomes along with remedial TSH and FT4 levels. All subjects of either regimen were evaluated every three to six months to reach beneficial thyroid readings (Tariq et al., 2018).

Three men and 57 women utilized the natural regimen while two men and 38 women consumed the synthetic therapy during the study carried out by Tariq et al. (2018). The trial excluded six subjects due to cessation of therapy. Synthetic termination was due to preference, adverse effects and loss to follow-up while natural treatment cessation was due to lack of improvement in symptoms, pregnancy, and minimal adverse effects. The average follow-up interval was 27 months. The typical synthetic dose was 75 μg T4 and 5 μg T3 while the average natural therapy dose was 30 mg. Of the subjects who were given DTE therapy, 96.49% continued to exhibit TSH values within normal limits ($P<0.05$), FT4 persisted in the normal range also in 96.49% of patients ($P<0.05$) and T3 remained within normal limits in 93.62% of subjects ($P<0.005$). In the synthetic group, normal TSH levels endured in 89.47% ($P<0.05$), FT4 persisted within normal limits in 92.5% of subjects ($P>0.05$) and FT3 remained average in 90% of patients ($P<0.05$) in comparison to T4 monotherapy. Some subjects in both groups experienced abnormally low TSH levels for short intervals ($P>0.05$), but either regimen failed to yield higher than normal TSH values. Select patients who experienced abnormally low TSH levels were those with thyroid cancer and subsequently necessitated a lower TSH. None of those patients with low TSH or high FT3 and FT4 values required hospitalization for arrythmias or other adverse effects. Neither regimen demonstrated an advantage of better value with FT4, FT3 and TSH.

Tariq et al. (2018) also reported that twenty-six of the subjects utilizing synthetic therapy and 51 of those employing natural therapy partook in the SF-20 questionnaire, and 100% and 92% (respectively) responded with feeling “good, very good, or excellent” regarding self-health. Eighty to 100% on both therapies denied limitations with activities of daily living, such as strenuous sports, running, walking, climbing stairs, bathing, dressing, carrying groceries,

housework, eating). Of the subjects on synthetic therapy, 76.9% stated they felt “calm and peaceful” and 92.31% as “being a happy person.” Of those on natural therapy, 86.8% conveyed they felt “calm and peaceful,” and 88.2% related being “a happy person.” One hundred percent of natural regimen and 84.6% of synthetic users denied feelings of “hopelessness.”

The study conducted by Tariq et al. (2018) is one of few in the United States to assess the longstanding effects and safety of combination therapy. While past studies average a duration of 10-16 weeks, this study was carried out over the course of six years. Strengths of the study include extended T3 therapy, employment of endocrinologists to conduct the study, preservation of a physiological FT4:FT3 ratio of roughly 14:1, utilization of the SF-20 questionnaire and exclusion of similar hypothyroid-like symptom sources. Study shortcomings include retrospective nature, lack of pre-interventional data to compare prior to preliminary T3 therapy, lack of concurrent comparison to T4 therapy subjects, the SF-20 questionnaire was not compared to pretherapy status and variances in lab collection times.

Tariq et al. (2018) report that in the studied population, symptoms of hypothyroidism declined markedly, and subjects were devoid of an increase in hyperthyroidism. The transient elevations in FT3 and FT4 and reductions in TSH were attributable to dosing adjustments and differed among subjects. There were no reported variances in levels in subjects according to the source of hypothyroidism. Combination therapy is often condemned due to fears of hyperthyroidism instigation. This study reported that 6.7% of the 100 patients that expressed symptoms of anxiety and palpitations had TSH levels less than 0.35 μIU/mL and no arrythmias. Tariq et al. (2018) testify that combination therapy can be employed at the clinician’s discretion. In patients who continue to experience symptoms of hypothyroidism on adequate T4

supplementation, synthetic therapy is safe and advantageous in enriching the quality of life and alleviating symptoms.

Jonklass et al. (2014) performed a systematic review of treatment guidelines for hypothyroidism. Their intention was to assess current data gaps in treatment, treatment alternative evidence, the optional dosage of standard levothyroxine supplementation, goals of levothyroxine therapy, and sources of discontent with levothyroxine treatment. A task force, consisting of members of the ATA, distinguished 24 common questions relevant to the diagnosis and treatment of the disease. Literature associated with each question was examined and clinical reviews were accompanied with similar mechanistic and bench research literature reviews, when necessary. A bioethicist reviewed pertinent ethical matters. The following remedial categories were evaluated: levothyroxine therapy, non-levothyroxine-based thyroid hormone therapies, thyroid hormone analogs, thyroid extracts, synthetic combination therapy, T3 therapy and compounded thyroid hormones. Responses to each question were constructed into a formal recommendation statement. The task force utilized the American College of Physicians system to provide a grading system for clinical endorsements. Task members reported no conflict of interest at baseline or at the conclusion of the study. Members worked on a volunteer basis and received no funding from the ATA, did not collect gifts or funding for involvement of the document and paid for their own travel expenses. There were no funds obtained from commercial sources for the promotion of the document.

At the conclusion of the review, task members endorsed levothyroxine as optimal treatment for hypothyroidism due to its promising side effect profile, administration simplicity, effectiveness in reducing symptoms, long half-life, low cost, favorable intestinal absorption and longstanding knowledge of benefits (Strong recommendation, moderate-quality evidence). They

recommend clinicians prescribe brand name levothyroxine or generic formulations for maintenance therapy but advise against switching between the two products frequently (Weak recommendation, low-quality evidence (for general populations)). Members caution against levothyroxine doses in excess, as potential effects include osteoporosis and atrial fibrillation, and advise avoiding TSH levels below 0.1 μIU/L (Strong recommendation, moderate-quality evidence). The authors assert that when patients are treated with levothyroxine and attain TSH levels within the desired reference range, many experience T3 levels at the lower end or below the reference range. The clinical impact of this is not known at this time (Jonklass et al, 2014).

Jonklass et al. (2014) encourage when patients treated with T4 monotherapy remain symptomatic despite normal TSH levels, providers should assess for specific subgroups of the general population that benefit from combination therapy (Weak recommendation, low-quality evidence). Members prefer levothyroxine treatment as the standard of treatment for hypothyroidism in preference to thyroid extracts. Despite preliminary evidence from a short-term study that some patients may have a preference for thyroid extracts, long-term controlled trials to assert an advantage over T4 monotherapy and safety are lacking (strong recommendation, moderate-quality evidence). Participants advise against routine utilization of combination therapy with levothyroxine and liothyronine in primary hypothyroidism patients as there is a deficit in strong evidence of an advantage of combination treatment over T4 monotherapy (Weak recommendation, moderate-quality evidence).

The authors assert there is no strong evidence to support a standard trial of combination therapy (consisting of levothyroxine and liothyronine) in patients who continue to feel unwell in spite of normal TSH levels treated with levothyroxine monotherapy (insufficient evidence). Members endorse further research is warranted. They do not recommend genetic testing as a

guide for thyroid therapy selection (strong recommendation, moderate-quality evidence). Finally, task force members acknowledge that thrice-daily T3 administration may be associated with advantageous effects on lipid profiles and body weight, but clinical trials of longer duration are necessary prior to endorsement (Strong recommendation, moderate-quality evidence) (Jonklass et at., 2014).

According to Chiovata et al. (2019), the United Kingdom, European and American Thyroid Associations recommend trialing combination therapy in hypothyroid patients in particular circumstances. The Italian Thyroid Association, Italian Society of Endocrinology and European Thyroid Association recommend practitioners pilot combination therapy in patients with enduring symptoms despite normal TSH levels greater than six months in patients being treated with T4. Prior to instigating combination therapy, it is essential that autoimmune conditions, such as adrenal insufficiency, celiac disease, type one diabetes mellitus and vitamin B12 deficiency, be excluded. If an improvement in symptoms is not observed in three months, T4 monotherapy should be resumed.

The ATA and AACE recommend that hypothyroid patients be treated with levothyroxine only (Grade A) and assert there is not sufficient evidence to demonstrate that hypothyroid patients should be treated with T3 and T4 combinations (Grade B). They also state that there is a lack of evidence to promote DTE over T4 monotherapy and DTE should not be used to treat hypothyroid patients (Grade D). This is due to the lack of controlled trials endorsing DTE therapy over levothyroxine. The ATA and AACE stress the need for further research of combination and T3 monotherapy efficacy and safety. The authors cite one randomized, double-blind crossover intervention trial that compared T4 to T3 monotherapy in hypothyroid subjects. Both were administered three times a day and analogous TSH levels were obtained. Subjects taking T3 reported a greater decrease in body weight, total cholesterol and LDL cholesterol than

patients taking T4. There was no substantial difference in HDL cholesterol, exercise tolerance, insulin sensitivity, heart rate or blood pressure between the two remedies. There were only forteen subjects in the study and follow-up was limited to six weeks after initiation of treatment. Due to the limitations of this particular study, the authors do not endorse T3 monotherapy as a replacement for T4 (Garber et al., 2012).

Discussion

Despite treatment and TSH levels in the desired range, many monotherapy patients continue to exhibit manifestations of hypothyroidism. This observation has led some to question whether or not the biological synthesis of T3 from T4 is equivalent to thyroid T3 emission. Roughly 20% of T3 is secreted from the thyroid gland and the remaining is attributed to conversion from T4 to T3 in the peripheral tissues. It is believed that the transformation of T4 to T3 in the periphery supplies identical amounts of T3 required by each individual organ and tissue when patients are subsidized with levothyroxine. However, due to the fluctuations in tissue circulation and deiodinase distribution, many postulate that some tissues and organs may not be subjected to sufficient T3 distribution despite seemingly normal TSH levels (Biondi & Wartofsky, 2012).

Biological accessibility to T3 is determined by deiodinases that cleave an iodine molecule from T4. As mentioned previously, D2 is located in the thyroid gland, myocardium, anterior pituitary, brain, aortic smooth muscles, skeletal muscle, brown adipose tissue and osteoblasts. D2 modulates the HPT axis and facilitates pituitary response to systemic T4 level changes. Accordingly, the fixed point at which TSH is secreted is subject to serum and pituitary T3 generated by D2. It also modulates intracellular T3 concentration. Regulation of TSH at the HPT axis and at the intracellular levels by D2 offers explains why stabilization of TSH levels

during thyroxine monotherapy may not precisely reflect a state of euthyroidism in all organs and tissues (Biondi & Wartofsky, 2012). There is also an increase in evidence of tissue-specific hormone regulation by differential expression of hormone transporters and deiodinases, particularly in the brain. Sole T4 supplementation may fail to restore intracellular T3 levels in brain tissues in all subjects, accounting for the persistence of symptoms in some T4 monotherapy patients. In addition, recent evidence demonstrates that T4 inhibits deiodinases responsible for T4 to T3 conversion in target tissues, triggering a reduction in intracellular T3 levels despite a high circulating T4:T3 ratio (Taylor et al., 2019).

Many question the ability of serum thyroid hormone levels to accurately reflect intracellular hormone status, as cells can regulate T3 levels autonomously from circulating hormone levels via activation and metabolism of T4 and uptake variation. In addition, many modern T3 dosing tactics do not imitate T3 levels in euthyroid patients. In patients taking single daily doses, FT3 levels peak two to four hours after ingestion and wane around 12 hours. Similar FT3 reports have been observed in euthyroid patients taking T3, hypothyroid patients taking T3 monotherapy and combination therapy. Peak FT3 levels are frequently above reference range values. These conditions are substantially different from individuals without thyroid disease or medications (Taylor et al., 2019). Serum T3 level analysis and evaluation contain substantial difficulties due to the fact that other non-thyroidal ailments can produce low T3 levels. There are struggles in quantifying FT3 with standard clinical lab assays and serum T3 amounts do not reliably represent intracellular T3 levels because of intracellular deiodination (McAninch & Bianco, 2019). Nevertheless, T3 usage in hypothyroidism treatment continues to be disputed as it is believed T4 supplementation is competent in providing sufficient hormone to be broken down into T3. This is reinforced by the fact that circulating T4 quantities are approximately five times

that of T3, and intracellular quantities are not descendants of circulatory T3, but rather circuitously from T4 via D2 deiodinase action (Taylor et al., 2019).

With the preceding information, many have brought the entire diagnostic and treatment regimen of primary hypothyroidism into question, and growing interest has sparked in studies comparing monotherapy and combination therapy. A lingering debate regarding the standard TSH reference scale and desired target serum ranges with replacement therapy has been ongoing due to the discovery of individualized HPT axis set points along with the impact of race, gender and age on desired TSH values (Biondi & Wartofsky, 2012). Reliance only on TSH values to discern thyroid disease and management may be problematic, as reference values are not universally agreed upon. According to Taylor et al. (2019), many studies have demonstrated persistent hypothyroidism indicators in the liver, brain, and skeletal muscle with T4 monotherapy. The pituitary effect of T4 downregulation by D2 previously described may account for serum TSH standardization regardless of peripheral tissue hypothyroidism. These findings question serum TSH's ability to accurately display hormone quantities in all tissues in patients receiving T4 monotherapy. In comparison, consistent combination therapy has been proven to regulate factors dependent on thyroid hormones in the skeletal muscle, brain, and liver.

Many studies conducted on the matter have concluded that combination therapy is not more effective than T4 monotherapy. However, common outcomes are often mixed or ambiguous, including no variance in symptoms or laboratory findings or modest manifestation improvement. Some consecutive studies even demonstrate contradictory results. For example, as mentioned previously, Almandoz and Gharib (2012) conducted a meta-analysis that demonstrated no variance in lipids, body weight, mood, fatigue, or body pain between monotherapy or combination therapy. The same authors then conducted a subsequent systematic

literature review and reported that combination therapy demonstrated a decrease in LDL cholesterol, total cholesterol, and body weight in comparison to levothyroxine monotherapy. There was no variance observed in exercise tolerance, insulin sensitivity, heart rate or blood pressure. The systematic literature review performed by Biondi and Wartofsky (2012) determined that combination treatment was not superior to levothyroxine therapy in adverse events, cholesterol, mood, fatigue, body weight, body pain, and quality of life. A succesive meta-analysis conducted by the same authors indicated that combination therapy was advantageous to physical and psychological health to those formerly supplemented with sole T4. Nearly all studies such as these have demonstrated analogous outcomes in both regimens and moreover, have not demonstrated the superiority nor inferiority of combination to monotherapy. Nevertheless, levothyroxine has continued to be sanctioned as the standard of treatment. This can perhaps be attributed to the deficit in T3 research, side effect profile and preliminary poor studies rather than repeated comparable results.

A recurring theme in many of these studies is patient partiality for combination therapy. For example, all subjects, regardless of regimen studied by Duntas and Jonklaas (2019) identified an improvement in mood, fatigue, neurocognitive function and overall well-being. Despite these findings, patients demonstrated a preference for combination therapy. Most of this has been attributed to weight loss or improved subjective welfare, which has been credited to the placebo effect. Regardless of the cause, the recurrence is not without value. This emphasizes the necessity of patient-centered care in congruence with current practice guidelines. Combination therapy may not be of benefit over monotherapy in the general population, but patients that fall outside the bell curve may be more responsive for a variety of reasons. Whatever the cause, patient partiality towards combination treatment is a factor that should not be swiftly cast aside.

Rather, it should be taken into consideration by clinicians when compiling a regimen for the treatment of primary hypothyroidism.

Although many former and recent trials have failed to establish combination therapy dominance, other studies have exhibited notable benefits. The trial performed by Hoang et al. (2013) regarding DTE therapy demonstrated a weight loss of an average of 2.86 pounds ($P<.001$) compared to T4 and those who demonstrated DTE preference experienced a four-pound average weight loss during DTE therapy when compared to T4 ($P<.001$). This group also demonstrated improvements in subjective symptoms, such as energy level, happiness, decision-making capability, memory, sleep and concentration ($P<.001$). Tariq et al. (2018) carried out a retrospective study to determine distinctions between T4 with synthetic T3 (synthetic therapy) and DTE with FT4 (natural therapy). The most notable improvements were observed in mental health and overall welfare. Of the subjects on synthetic therapy, 76.9% stated they felt "calm and peaceful" and 92.31% as "being a happy person." Of those on natural therapy, 86.8% conveyed they felt "calm and peaceful" and 88.2% related being "a happy person."

These improvements are not always observed, as many other trials have yet to demonstrate benefit in body weight or temperament. For example, Kamkinski et al. (2016) compared the effects of a specific T3/T4 dose (15 and 75 µg, respectively) to monotherapy in primary hypothyroidism treatment. Body weight, lipid profile and quality of life were unaffected by either regimen. No differences in global scores in quality of life were noted between the two regimens ($P = 0.888$) and subgroup scores were also similar for both modalities ($P>0.05$). These opposing findings may reiterate that treatment for primary hypothyroidism needs to be individualized as some patients will show improvement in symptoms with combination therapy over monotherapy, while others may not.

Preference for combination therapy is frequently observed in the clinical setting. There are many speculations as to why this occurs. This could perhaps be attributed to a placebo effect. Another consideration is the collaborations between healthcare providers and patients. Clinicians should consider the interactions that have occurred between patients and healthcare providers and how they may have influenced a patient. This is especially important in those who have longstanding chronic conditions and are frequent to the healthcare environment. Patients have become more involved in their healthcare and engaged in researching personal health issues now more than ever. As a result, they often present to providers with regimen expectations. If providers are willing to placate patient requests, this may augment the placebo effect. Providers that are less amendable to these circumstances may also promote the placebo effect as patients will often seek out an affable clinician, who will then comply with patient requests. Tribulations in patient-provider relations is not an uncommon occurrence, and thyroid regimens are of no exclusion. For example, the study performed by Toloza et al. (2020) concluded that patients utilizing DTE recurrently express an absence of individualized treatment for hypothyroidism and lack of feeling listened to by providers. While patient autonomy is an important factor in treatment planning, it does not supersede evidence-based practice and clinician judgment. Conversely, patient subjectivity cannot completely be marginalized. These points affirm the necessity of patient-centered care in congruence with current practice guidelines.

Resistance to combination therapy is frequently due to the potential for thyrotoxic effects, particularly from T3. As earlier mentioned, preliminary regimens contained divergent methods of standardization than utilized today as well as substantially higher doses. Recent studies have been performed in order to re-evaluate the potential unfavorable side effects of T3 therapy. The TEARS study continued follow-up for a median of nine years found no escalation in fractures or

cardiovascular disease in the T3 population. No substantial changes in blood pressure or heart rate transpired during the trial carried out by Hoang et al. (2013). Subjects in the study conducted by Kamkinski et al. (2016) experienced a slight increase in heartrate, but remained within normal limits while on combination therapy. No considerable blood pressure or electrocardiogram changes (including arrhythmias) occurred. These novel studies suggest that the adverse effects of modern combination dosing may not be as dangerous as previously believed. However, it also does not alleviate the potential for thyrotoxic effects in certain patients or inappropriate doses.

Conclusion

Many uncertainties of the diagnosis and treatment of primary hypothyroidism remain, including limited data availabile on the safety of longstanding T3 administration and if serum TSH can be established primarily by circulating T4, not T3. Though TSH remains the mainstream method for the evaluation of thyroid function, the ongoing debate on standard reference values needs to be universally established prior to addressing additional inquiries. The appraisal of function reliant entirely on TSH and FT4 values is also of question. Until the foundation of diagnostics is more understood, current treatment guidelines and research will likely remain unchanged.

Combination therapy has been given a discouraging label and many clinicians are unwilling to reconsider its potential attributes to the hypothyroid population. Much of this is attributed to the lack of data on the side effect profile and long-term effects of T3 in comparision to levothyroxine and significantly higher dosing in preliminary use. These reservations have been challenged by recent studies and offer clinicians reassurance, as many adverse effects were not observed in combination remedies. Additional data is warranted and future trials will need suitable outcome evaluation and adequate power to identify modest effects that can significantly

affect the general population. Particular D2 polymorphisms, inclusion criteria to consider preliminary symptoms at time of diagnosis, co-morbidities and TSH levels at initiation, and near biological T3 supplementation adjusted to a physiological T4:T3 ratio are also warranted in future studies.

The aforementioned clinical studies have resolved that in the general population, combination and monotherapy are analogous. The trials, however, all had substantial differences in length of study, sample size, measured outcomes, T3 for T4 substitution methods and doses. Follow-up on subjects was also relatively short, varying between weeks to several years. While these trials are not flawless, results are consistently reproducible and compelling. A commonly observed trend included modest weight loss and subjective improved well-being with the utilization of combination therapy. Despite these positive outcomes, the majority of investigators deemed no benefit of implementing combination therapy over levothyroxine. Monotherapy remains the appropriate treatment for the general population of primary hypothyroid patients, as the majority experience positive outcomes with this regimen. Although combination therapy has not proved to be superior nor inferior to monotherapy, it's use should not be entirely excluded. This treatment should be considered in primary hypothyroid patients who fail to respond appropriately to monotherapy. It also should be contemplated as a preliminary regimen in this population. Like any other medication, the risks, benefits and patient individuality must be incorporated into clinician discernment, as well as patient symptomology and serum diagnostics on disease reassessment. The previously mentioned attributes of combination remedies may be considered trivial and clinically insignificant to investigators but substantial to trial participants and modern patients. Though these perceived moderate improvements may only be observed in a select population, it does not yield them any less significant.

Applicability to Clinical Practice

The evidence obtained and exhibited in this extensive literature review will supply medical professionals with evidence-based practice guidelines to extend optimal thyroid hormone replacement therapy to patients diagnosed with hypothyroidism. It will disclose the benefits and risks associated with combination therapy for clinicians to take into consideration and discussion with patients. This will allow patients and clinicians to make educated decisions for replacement therapy. It will provide literature on treatment guidelines, diagnostics/blood tests and symptomatology. A key purpose of this review is to promote patient autonomy, clinician free-thinking and individualized patient treatment.

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