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New Treatments And Lt3 (Liothyronine) Combinations / Alternative Therapies

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Abstract: This article reviews new approaches to the treatment of hypothyroidism, specifically the combination of levothyroxine (LT4) and liothyronine (LT3), as well as alternative therapies. The article provides an in-depth review of the limitations of LT4 monotherapy, the rationale for the addition of LT3, clinical trial results, safety issues, and future developments. The aim is to highlight more effective treatment options for patients with persistent symptoms and to emphasize the importance of personalized medicine.
Keywords: Hypothyroidism, LT4 monotherapy, LT3 combination, triiodothyronine, thyroxine, deiodinase polymorphism, desiccated thyroid extract, slow-release LT3, personalized medicine, thyrotoxicosis, clinical trials.

Hypothyroidism, a disease caused by the thyroid gland not producing enough thyroid hormones, is successfully treated in modern medicine with levothyroxine (LT4) monotherapy, but in some patients, despite the achievement of biochemical euthyroidism (normal TSH levels), symptoms may persist. These symptoms include chronic fatigue, depression, cognitive impairment (memory and attention deficit), impaired physical function, and a general decrease in quality of life, the occurrence of which may be associated with an insufficient supply of the thyroid hormones triiodothyronine (T3) and thyroxine (T4) in the tissues, which are the main functions of the thyroid gland. Standard LT4 monotherapy provides mainly T4, which is converted to active T3 by deiodinase enzymes (especially type 2 deiodinase – DIO2), but in some patients, especially those with polymorphisms in the DIO2 gene (such as Thr92Ala rs225014), this conversion is inefficient, which can lead to T3 deficiency in tissues (especially brain and muscle). Therefore, in recent years, especially in studies conducted in 2023-2025, the combination of LT4 and liothyronine (LT3) has been intensively studied as a new treatment option. This method has been shown to be effective in improving the quality of life of patients, restoring cognitive functions and reducing physical pain, especially in patients who have not fully responded to LT4 monotherapy and who have persistent symptoms.

The rationale for LT3 combinations is thyroid lies in the natural secretion of the gland: in a healthy person, the ratio of T4 to T3 is approximately 14:1, but with LT4 monotherapy this ratio may be disturbed, since peripheral conversion is not always optimal and in some cases T3 levels remain low. The latest Systematic reviews and randomized trials suggest that the combination of LT4 + LT3 is safe and superior to LT4 monotherapy in terms of patient preference, but results are inconsistent – some studies (e.g., parallel-group trials in 2024-2025) reported a reduction in symptoms, improved physical function, and reduced pain, while others reported no statistically significant differences but higher subjective patient ratings. For example, in randomized clinical trials, serum LT4 + LT3 was It has been shown to be effective in preventing cholesterol levels (especially LDL) and weight gain, but these results depend on individual patient characteristics, including genetic factors. Among the new approaches, sustained-release or extended-release LT3 preparations deserve special attention - for example, poly-zinc-liothyronine (PZL) or LT3-sulfate-based formulations, which maintain stable serum T3 levels, eliminate the need for multiple daily doses, and approximate the pharmacokinetic profile to the natural state. In phase 1 and 2 trials, which are being conducted in 2024-2025, these drugs have prevented sharp peaks in T3 and improved patients' physical function, pain levels, and quality of life, but long-term safety (e.g., effects on the cardiovascular system and bone density) is still being fully studied, and new protocols (e.g., trials on the IRCT list) are ongoing.
Desiccated in the context of alternative therapies thyroid extract (DTE, e.g. Armour Thyroid), which contains natural T4 and T3 (in a ratio of approximately 4:1), is not recommended as a first choice by most professional guidelines because of its uncertain dosage and difficulty in standardization. However, recent In comparative studies (2021-2024), switching to DTE has improved symptoms and weight loss and mood in some patients,

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but overall efficacy is similar compared to the synthetic combination of LT4 + LT3, and long-term safety and standardization are questionable. New developments include liver- selective T3-like molecules (thyromimetics, e.g., resmetirom – MGL-3196), which have a metabolic used in dysfunction- related fatty liver disease (NAFLD/MASLD, NASH) and was approved by the FDA in 2024. These drugs activate THR-β receptors in liver cells, reducing fat accumulation and improving fibrosis, but they have not yet been approved as a primary treatment for hypothyroidism and are mainly used in comorbid conditions. In addition, genetic factors, particularly the DIO2 polymorphism (Thr92Ala), may predict patients' response to LT3 combinations – this polymorphism may be associated with LT4 monotherapy in patients with symptoms It is stronger and gives better results when combined with LT3, so the personalized (precision) medicine approach will be important in the future.

the use of LT4 + LT3 is Signs of toxicosis (heart rhythm disturbances, osteoporosis, muscle weakness) may be observed, but with the correct dosage (LT4:LT3 ratio 13-20:1, TSH within the normal range) this risk is minimal and the last meta -analyses and long-term follow-up (up to 9 years) show no increase in cardiovascular risk. British Thyroid Association, European In the 2023-2025 consensus documents of organizations such as the Thyroid Association and the American Thyroid Association, the addition of LT3 is recommended on an experimental basis in patients with persistent symptoms, but this should be done under the supervision of a specialist (endocrinologist), after excluding other comorbid conditions (e.g. heart disease), and based on genetic testing. The design of clinical trials is important: crossover studies, thyroid-specific patient -reported outcomes (e.g., ThyPRO39), use of slow-release LT3 preparations, and genetic stratification may lead to consistent results in future studies. Overall, LT3 combinations, slow-release formulations, and alternative therapies are opening up new horizons in the treatment of hypothyroidism, but their efficacy depends on individual factors (genetics, severity of symptoms, comorbidities), and more phase 2b/3 trials and long-term follow-up are needed. In the future, a personalized medicine approach—therapy selected based on genetic testing and biomarkers — may revolutionize the treatment of this disease.

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