

# Evidence-Based Use of Levothyroxine/Liothyronine Combinations in Treating Hypothyroidism: A Consensus Document.

**Title:** Evidence-Based Use of Levothyroxine/Liothyronine Combinations in Treating Hypothyroidism: A Consensus Document.

**Publication year:** 2021

**Journal:** Thyroid : official journal of the American Thyroid Association

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**Society:** European Respiratory Society

**Origin country:** International (Europe)

**Target countries:** Europe

**DOI:** 10.1089/thy.2020.0720

**PMID:** 33276704

**Source:** <https://pubmed.ncbi.nlm.nih.gov/33276704/>

Thyroid Thyroid 1174 thy 9104317 thy Thyroid 1050-7256 1557-9077 SAGE Publications  
PMC8035928 PMC8035928.1 8035928 8035928 33276704 10.1089/thy.2020.0720  
10.1089/thy.2020.0720 1 Article Evidence-Based Use of Levothyroxine/Liothyronine Combinations  
in Treating Hypothyroidism: A Consensus Document Jonklaas et al. Combination Therapy  
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Thyroid Association (ATA)/British Thyroid Association (BTA)/European Thyroid Association (ETA)  
Symposium held in London, United Kingdom and Chicago, USA on Sunday, November 3, 2019.

This article is being co-published in the European Thyroid Journal (S. Karger AG; DOI;  
10.1159/000512970).

01 2 2021 February 2021 12 2 2021 31 2 375698 156 182 01 02 2022 01 02 2022 14 04 2021 01  
02 2022 Copyright 2021, Mary Ann Liebert, Inc., publishers © American Thyroid Association ©  
European Thyroid Association (Published by S. Karger AG, Basel) 2021 Mary Ann Liebert, Inc.,  
publishers Background: Fourteen clinical trials have not shown a consistent benefit of combination  
therapy with levothyroxine (LT4) and liothyronine (LT3). Despite the publication of these trials,  
combination therapy is widely used and patients reporting benefit continue to generate patient and  
physician interest in this area. Recent scientific developments may provide insight into this  
inconsistency and guide future studies.

**Methods:** The American Thyroid Association (ATA), British Thyroid Association (BTA), and European Thyroid Association (ETA) held a joint conference on November 3, 2019 (live-streamed between Chicago and London) to review new basic science and clinical evidence regarding combination therapy with presentations and input from 12 content experts. After the presentations, the material was synthesized and used to develop Summary Statements of the current state of knowledge. After review and revision of the material and Summary Statements, there was agreement that there was equipoise for a new clinical trial of combination therapy. Consensus Statements encapsulating the implications of the material discussed with respect to the design of future clinical trials of LT4/LT3 combination therapy were generated. Authors voted upon the Consensus Statements. Iterative changes were made in several rounds of voting and after comments from ATA/BTA/ETA members.

**Results:** Of 34 Consensus Statements available for voting, 28 received at least 75% agreement, with 13 receiving 100% agreement. Those with 100% agreement included studies being powered to study the effect of deiodinase and thyroid hormone transporter polymorphisms on study outcomes, inclusion of patients dissatisfied with their current therapy and requiring at least 1.2 µg/kg of LT4 daily, use of twice daily LT3 or preferably a slow-release preparation if available, use of patient-reported outcomes as a primary outcome (measured by a tool with both relevant content validity and responsiveness) and patient preference as a secondary outcome, and utilization of a randomized placebo-controlled adequately powered double-blinded parallel design. The remaining statements are presented as potential additional considerations.

**Discussion:** This article summarizes the areas discussed and presents Consensus Statements to guide development of future clinical trials of LT4/LT3 combination therapy. The results of such redesigned trials are expected to be of benefit to patients and of value to inform future thyroid hormone replacement clinical practice guidelines treatment recommendations.